Appendix Table C-1. Evidence tables for randomized controlled trials and observational studies

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomesa | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Atsumi et al., 2016-713, 153  C-OPERA  Country, Clinical Setting:  Japan, multicenter  Study Design:  RCT  Overall N:  316  Study Duration:  2 yrs | Adults (aged 20-64) who are MTX naïve with RA fulfilling 2010 ACR/EULAR classification criteria, ≤ 12 months of persistent arthritic symptoms, DAS28-ESR ≥ 3.2, ≥ 3x upper limit of normal anti-CCP antibody, and positive rheumatoid factor and/or radiographic evidence of bone erosions | Interventions, dose:  G1:   * CZP: 400 mg at wks 0, 2, and 4, 200 mg every 2 wks thereafter (subcutaneous) * MTX: 8 mg/wk, increased to 12 mg/wk at wk 4, 16 mg/wk at wk 8, 16 mg/wk thereafter (oral)   G2:   * Placebo * MTX: 8 mg/wk, increased to 12 mg/wk at wk 4, 16 mg/wk at wk 8, 16 mg/wk thereafter (oral)   Those in either arm with DAS28-ESR > 3.2 at/after wk 24 for ≥ 4 wks were eligible for rescue treatment with open-label CZP after discontinuing the double-blind period  In the post-treatment period (wks 52-104) all patients received MTX alone. Patients who flared could receive rescue treatment with open-label CZP  N:  G1: 159  G2: 157 | Mean disease duration, mos:  4.0-4.3  Baseline DAS28-ESR, mean:  5.4-5.5  Baseline HAQ-DI, mean: Baseline HAQ-DI, mean:  1.0-1.1  Prior csDMARD use, %:  18.5-19.5  MTX naive:  100  MTX inadequate responders:  NR  Biologic non-responders:  NR  Prior CS use, %:  16.4-19.7 | At 2 yrs  DAS28-ESR LDA, %:  G1: Figure only (Sup. Figure S1)  G2: Figure only (Sup. Figure S1)  P = 0.003  ACR20 response, %:  NR  ACR50 response, %:  NR  ACR70 response, %:  NR  DAS28-ESR remission, %:  G1: 41.5  G2: 33.1  P = 0.132  SDAI remission, %:  G1: 41.5  G2: 29.3  P = 0.026  HAQ remission (HAQ ≤5), %:  G1: 73.0  G2: 63.7  P = 0.09  mTSS score  Change from baseline, mean:  G1: 0.66 (SD, 5.38)  G2: 3.01 (SD, 9.66  P = 0.001 | At 2 yrs  Overall AEs:  G1: 96.9  G2: 95.5  SAEs:  G1: 10.7  G2: 11.5  Overall discontinuation:  G1: 53.5  G2: 63.7  Discontinuation due to AEs:  G1: 6.3  G2: 3.8  Discontinuation due to lack of efficacy:  G1: 0.0  G2: 0.6  Patient adherence:  NR  Specific AEs:  Deaths  G1: 0.0  G2: 0.0  Malignancy  G1: 1.3 (cervix carcinoma)  G2: 0.0 | Medium (24 weeks); High (1-2 years) |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomesa | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Atsumi et al., 2016-713, 153  C-OPERA  (continued) |  | Mean age, yrs:  49 (range 21-64)  Sex, % female:  81.0  Race, % white:  NR  Race, % black:  NR |  | No radiographic progression (change ≤ 0.5), %:  G1: 84.2  G2: 67.5  P<0.001  SF-36:  NR  At 1 year  DAS28-ESR disease activity:  NR  ACR20 response, %:  G1: 78.6  G2: 68.8  p<0.055  ACR50 response, %:  G1: 73.0  G2: 51.6  p<0.001  ACR70 response, %:  G1: 57.2  G2: 34.4  p<0.001  DAS28-ESR remission, %:  G1: 57.2  G2: 36.9  p<0.001  mTSS score  Change from baseline, mean:  G1: 0.36 (SD, 2.70)  G2: 1.58 (SD, 4.86)  p<0.001 | Interstitial lung disease  G1: 4.4  G2: 0.6  Nausea/Vomiting/Decreased appetite  G1: 27.0  G2: 24.2  Hepatic disorders  G1: 45.9  G2: 46.5  Tuberculosis  G1: 0.0  G2: 0.0  Pneumonia  G1: 5  G2: 6.4  Serious Infections  G1: 3.1  G2: 5.1  Infections and infestations  G1: 71.7  G2: 59.2  Injection site reaction  G1: 3.1  G2: 1.3  At 1 yr  Overall AEs:  G1: 96.2  G2: 94.3  SAEs:  G1: 8.2  G2: 8.9 |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomesa | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Atsumi et al., 2016-713, 153  C-OPERA  (continued) |  |  |  | No radiographic progression (change ≤ 0.5), %:  G1: 82.9  G2: 70.7  p=0.011  HAQ:  NR | Overall discontinuation:  G1: 30.2  G2: 53.5  Discontinuation due to AEs:  G1: 5.7  G2: 3.8  Discontinuation due to lack of efficacy:  G1: 0.0  G2: 0.6  Patient adherence:  NR  Specific AEs:  Deaths  G1: 0.0  G2: 0.0  Malignancy  G1: 0.6 (cervix carcinoma)  G2: 0.0  Interstitial lung disease  G1: 3.1  G2: 0.6  Nausea/Vomiting/Decreased appetite  G1: 24.5  G2: 20.4  Hepatic disorders  G1: 42.8  G2: 44.6 |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomesa | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Atsumi et al., 2016-713, 153  C-OPERA  (continued) |  |  |  |  | Tuberculosis  G1: 0.0  G2: 0.0  Pneumonia  G1: 4.4  G2: 5.1  Serious Infections  G1: 3.1  G2: 4.5  Infections and infestations  G1: 61.0  G2: 55.4  Injection site reaction  G1: 3.1  G2: 1.3 |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Atsumi et al., 201613  C-OPERA  (continued) |  | Ethnicity, % Latino:  NR | RF seropositive, %:  93.0-96.2  anti-CCP seropositive, %:  100  Baseline mTSS score, mean:  5.2-6.0  Bone erosion judged by physician, %:  49.7-51.0 | SF-36:  NR  At 24 wks  DAS28-ESR remission, %:  G1: 52.8  G2: 30.6  p<0.001  **mTSS score, mean change from baseline:**  G1: 0.26 (SD, 1.55)  G2: 0.86 (SD, 2.37)  p=0.003 | Hepatic disorders  G1: 42.8  G2: 44.6  Tuberculosis  G1: 0.0  G2: 0.0  Pneumonia  G1: 4.4  G2: 5.1  Serious Infections  G1: 3.1  G2: 4.5  Infections and infestations  G1: 61.0  G2: 55.4  Injection site reaction  G1: 3.1  G2: 1.3 |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Bakker et al., 2012;94  CAMERA-II  Country, Clinical Setting:  Netherlands, 7 hospital outpatient rheumatology clinics  Study Design:  RCT  Overall N:  239  Study Duration:  2 years | Patients meeting 1987 revised ACR criteria for RA with disease duration <1 yr, who were DMARD and glucocorticoid naïve | Interventions, dose:  G1: MTX + Prednisone 10 mg/d tight-control strategy  G2: MTX + Placebo tight-control strategy  Both arms received initial dose of oral MTX 10 mg/wk, plus folic acid 0.5 mg/d, bisphosphonate (alendronate or risedronate) and cholecalciferol.  Strategy steps based on >20% improvement in SJC and at least 2 of the following: TJC, ESR, and VAS for general well-being at each monthly visit, compared with previous visit.  Steps to achieve >20% improvement could include MTX dose escalation, switch to subcutaneous MTX, addition of cyclosporine or adalimumab, or switch to different medication (the latter leading to dropout)  N:  G1: 118  G2: 121  Mean age, yrs:  53-54  Sex, % female:  60-61 | Mean disease duration, mos:  NR  **Baseline DAS, mean:**  5.5-5.8  **Baseline HAQ, mean:**  1.0-1.2  **MTX naive:**  100  **Prior csDMARD use, %:**  0  **MTX inadequate responders:**  NA  **Biologic non-responders:**  NA  Seropositive (RF or CCP) (%):  RF+: 55-61  Baseline Sharp score, median:  0  Erosive disease, %:  12-17 | At 2 years  Mean DAS28 score (SD)  G1: 2.30 (0.34)  G2: 2.49 (0.25)  Mean difference (95% CI): -0.26 (-0.68 to 0.16) (p=0.21)  ACR20 response, %  G1: 65  G2: 61  Mean difference (95% CI): 3.6  (-8.7 to 15.9) (p=0.56)  ACR50 response, %  G1: 53  G2: 42  Mean difference (95% CI): 11.0 (-1.7 to 23.6) (p=0.091)  ACR70 response, %  G1: 38  G2: 19  Mean difference (95% CI): 18.3 (7.0 to 29.6) (p=0.002)  Remission, %  G1:72  G2:61  Mean difference (95% CI): 10.5 (-1.5 to 22.4) (p=0.089)  Median total SHS score (IQR)  G1:0 (0 to 3)  G2:0 (0 to 4) (p=0.32)  Mean difference (95% CI): 0.0 (-1.1 to 1.1) | **Overall:**  G1: 74  G2: 79  SAEs  G1: 2  G2: 4  Overall discontinuation  At 2 years  G1: 28.0  G2: 29.8  At 1 year  G1: 16.1  G2: 13.2  Discontinuation because of AEs  At 2 years  G1: 13.6  G2: 16.5  At 1 year  G1: 8.5  G2: 7.4  Patient adherence  At 2 years  G1: 94.9  G2: 96.6  At 1 year  G1: 95.7  G2: 97.5 | Medium |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Bakker et al., 2012;94  CAMERA-II  (continued) |  | Race, % white:  NR |  | Sensitivity analyses for observed data showed no statistical differences  Median SHS erosive joint damage score (IQR)  G1:0 (0 to 0)  G2:0 (0 to 2) (*P* =0.022)  Mean difference (95% CI): 0.0 (-0.1 to 0.0)  Linear mixed-model analysis found that erosion score was, on average, 0.87 SHS units lower in G1 than G2  Linear mixed-model regression coefficient (95% CI): -0.87 (-1.31 to -0.43) (p=0.001)  Erosion-free as measured by SHS, %  G1:78  G2:67 (p=NR)  Mean HAQ score (SD)  G1: 0.5 (0.13)  G2: 0.7 (0.13)  Mean difference (95% CI): -0.18 (-0.34 to -0.02) (p=0.027)  At 18 months  Mean DAS28 score (SD)  Figure only data (p=0.183)  Mean HAQ score (SD)  Figure only data; p=0.014 | **Mortality**  G1: 1  G2: 0  Hospitalization  G1: 1  G2: 4  Nausea  G1: 19.65  G2: 36.1 (p=0.006)  ALT >ULN  G1: 12.8  G2: 27.7 (p=0.006)  AST >ULN  G1: 6.8  G2: 17.6 (p=0.016)  Infections requiring antibiotics  G1: 0.01  G2: 0  Pneumonitis  G1: 0.01  G2: 0  Headache  G1: 19.6  G2: 26  Weight gain (kg, mean [SD])  G1: 2.9 (4.2)  G2: 1.3 (5.3) (p=0.028) |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Bakker et al., 2012;94  CAMERA-II  (continued) |  |  |  | At 1 year  Mean DAS28 score (SD)  G1: 2.45 (0.29)  G2: 2.59 (0.29)  Mean difference (95% CI): -0.21 (-0.52 to 0.11) (p=0.194)  ACR20 response, %  G1: 70  G2: 66  Mean difference (95% CI): 4.5 (-7.4 to 16.4) (p=0.45)  ACR50 response, %  G1: 56  G2: 43  Mean difference (95% CI): 13.6 (0.9 to 26.2) (p=0.037)  ACR70 response, %  G1: 27  G2: 26  Mean difference (95% CI): 1.3 (-10.0 to 12.6) (p=0.82)  Mean HAQ score (SD)  G1: 0.5 (0.11)  G2: 0.7 (0.13)  Mean difference (95% CI): -0.18 (-0.34 to –0.02) (p=0.027)  At 6 months  Mean DAS28 score (SD)  Mean difference (95% CI): -0.89 (-0.52 to -0.11) (p<0.001)  Mean HAQ score (SD)  Figure only data (p=0.001) |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Bakker et al., 2012;94  CAMERA-II  (continued) |  |  |  | At 3 months  Mean DAS28 score (SD)  Mean difference (95% CI): -1.56 (-1.88 to -1.25) (p<0.001)  Mean HAQ score (SD)  Figure only data (p<0.001) |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr:  Bathon et al., 200014; Genovese et al., 2002110;  Genovese et al., 2005112;  Bathon et al., 2006111  Enbrel ERA  Country, Setting:  US, clinics  Study Design:  RCT  Overall N:  424 eligible (of 632 total)  Study Duration:  12 mos (1 year open label extension) | Patients with early, aggressive RA with disease duration <3 years and who were MTX-naïve | Interventions, dose:  G1: MTX 7.5 mg/wk to 20 mg/wk dose escalation  (19 mg/wk mean dose)  G2: ETN  (25 mg twice wkly, subcutaneous)  N:  G1: 217  G2: 207  Mean age, yrs:  49-51  Sex, % female:  74-75  Race, % white:  84-88 | Mean disease duration, mos:  11-12  Median disease duration, mos:  0.3-0.8  Baseline Sharp score, mean:  2.4-12.9  **MTX naïve, %:**  100  Prior csDMARD use, %:  23-25  Prior CS use, %  39-42  MTX inadequate responders, %:  0  Biologic non-responders, %:  NR  Seropositive (RF or CCP) (%):  RF+: 87-89 | At year 2 (open-label extension)  ACR20, %  G1:59  G2:72 (p=0.005)  **ACR50, %**  G1:42  G2:49 (p=NS)  **ACR70, %**  G1:24  G2:29 (p=NS)  Subgroup analysis for ACR20/50/70  Ages ≥65, events per patient-year  ACR20, %  G1: 44  G2: 54  ACR50, %  G1: 31  G2: 22  ACR70, %  G1: 13  G2: 14  Ages <65, events per patient-year  ACR20, %  G1: 58  G2: 77  ACR50, %  G1: 43  G2: 54 | At year 2  Overall discontinuation  G1: 40.55  G2: 25.6 (p=NR)  Discontinuation because of AEs  G1: 12.4  G2: 7.25 (p=NR)  Discontinuation because of lack of efficacy  G1: 3.7  G2: 4.8  Patient adherence  NR  SAEs  G1: 12  G2: 12 (p=NR)  Subgroup analysis for SAEs  Ages ≥65, events per patient-year  G1: 0.417  G2: 0.321  Ages <65, events per patient-year  G1: 0.072  G2: 0.046  Rates similar in elderly vs. non-elderly patients, but P=NR | Medium |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr:  Bathon et al., 200014; Genovese et al., 2002110;  Genovese et al., 2005112;  Bathon et al., 2006111  Enbrel ERA  (continued) |  |  | Baseline DAS, mean:  NR  Erosive disease, %:  85-88 | ACR70, %  G1: 25  G2: 32  **HAQ improvement of at least 0.5 units, %:**  G1:37  G2:55  G2 > G1 (p<0.001)  Subgroup analysis for mean change in HAQ from baseline (SD)  Ages ≥65, events per patient-year  G1: 0.61 (0.78)  G2: 0.46 (0.66)  Both groups showed improvements exceeding MCID  Ages <65, events per patient-year  NR, but improvements mirrored those of ages ≥65  **Change in total modified Sharp score, mean**  G1: 3.2  G2: 1.3 *(*p=0.001)  **Erosion score change, mean**  G1: 1.9  G2: 0.7 *(*p=0.001) | Mortality  G1: 0  G2: 1 (p=NR)  Serious infections  G1: 4.15  G2: 3.4 (p=NR)  Subgroup analysis for serious infections  Ages ≥65, events per patient-year  G1: 0.074  G2: 0.095  Ages <65, events per patient-year  G1: 0.016  G2: 0.01  Rates higher in elderly patients, but P=NR  Injection site reaction  G1: 9  G2: 39  G1 < G2 (*P* ≤0.05)  Nausea  G1: 31  G2: 20  G1 > G2 (*P* ≤0.05) |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr:  Bathon et al., 200014; Genovese et al., 2002110;  Genovese et al., 2005112;  Bathon et al., 2006111  Enbrel ERA  (continued) |  |  |  | At 1 yr  ACR20 response rates, %:  G1: 65  G2: 72 *(*p=0.16)  **Increase in Sharp score, mean**  G1: 1.59  G2: 1.00 *(*p=0.11)  **Erosion score change, mean**  G1: 0.47  G2: 1.03 *(*p=0.002)  **Mean HAQ scores**  No significant difference in HAQ scores between MTX and ETN 25 mg arms, with ~55% in each arm having at least a 0.5-unit improvement  **At 6 months**  Significantly more pts on ETN (25 mg) than on MTX achieved ACR20, ACR50, ACR70 responses (data NR, p<0.05) | Dizziness  G1: 12  G2: 15  Vomiting  G1: 9  G2: 10  Alopecia  G1: 12  G2: 6  G1 > G2 (*P* ≤0.05)  Mouth ulcer  G1: 17  G2: 5  G1 > G2 (*P* ≤0.05)  Cancer  G1: 3  G2: 4 (p=NR)  Subgroup analysis for cancer  Ages ≥65, events per patient-year  G1: 0.049  G2: 0.057 |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr:  Bathon et al., 200014; Genovese et al., 2002110;  Genovese et al., 2005112;  Bathon et al., 2006111  Enbrel ERA  (continued) |  |  |  |  | Ages <65, events per patient-year  G1: 0.004  G2: 0.003  At year 1  Overall discontinuation  G1: 22.1  G2: 14.5 (p=NR)  Discontinuation because of AEs  G1: 10.1  G2: 4.8 (p=NR)  Patient adherence  NR  Mortality  G1: 0  G2: 1  URTI  G1: 39  G2: 35 |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr:  Bathon et al., 200014; Genovese et al., 2002110;  Genovese et al., 2005112;  Bathon et al., 2006111  Enbrel ERA  (continued) |  |  |  |  | Infections at other respiratory tract sites, events per patient-year  G1: 1.3  G2: 1.0 (p=0.006)  Injection site reaction  G1: 7  G2: 37  G1 < G2 (p <0.05)  Nausea  G1: 29  G2: 17  G1 > G2 (p<0.05)  Rash  G1: 23  G2: 12  G1 > G2 (p <0.05)  Alopecia  G1: 12  G2: 6  G1 > G2 (p <0.05)  Mouth ulcer  G1: 14  G2: 5  G1 > G2 (p<0.05) |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Bejarano et al., 2008;16 Emery et al., 2016152  PROWD  Country, Clinical Setting:  United Kingdom, “Multicenter”  Study Design:  RCT  Overall N:  148  Study Duration:  56 wks | Patients aged ≥18 years with RA according to ACR criteria, <2 yrs symptom duration, MTX/biologic naïve, who were in paid employment, and had self-reported RA-related work impairment | Interventions, dose:  G1: ADA (40 mg every other wk + MTX (7.5 mg/wk, max 25 mg/wk)  G2: Placebo + MTX (7.5 mg/wk, max 25 mg/wk)  MTX: Dosage reached 25 mg/wk by wk 12 in the presence of remaining synovitis. Mean dose at 56 wks was 15.5 mg/wk in G1 and 16.2 mg/wk in G2  ADA: Administered via subcutaneous injection  N:  G1: 75  G2: 73  Mean age (SD), yrs:  47 (SD, 9.0)  Sex, % female:  53.4-58.4  Race, % white:  NR | Mean symptom duration, mos:  7.9-9.5  Baseline DAS, mean:  5.9-6.0  Baseline HAQ, mean (SD):  1.3 (SD, 0.6)  MTX naïve, %:  100  Prior csDMARD use:  Mean: 0.2 per patient  MTX inadequate responders:  0  Biologic non-responders:  0  RF seropositive (%):  95-96  Anti-CCP antibody positive (%):  63-64  Baseline Sharp score, mean:  NR  Erosive disease, %:  NR | At week 56  DAS disease activity  G1: 3.0 (SD, 1.8)  G2: 3.8 (SD, 2.1, p=0.013)  ACR20 response, %  G1: 71.6  G2: 54.8 (p=0.034)  ACR50 response, %  G1: 56.0  G2: 45.2 (p=0.189)  ACR70 response, %  G1: 50.7  G2: 37.5 (p=0.108)  Remission (DAS28 <2.6), %  G1:48.0  G2:36.1 (p=0.145)  SHS  NR  HAQ change from baseline  G1:-0.7 (SD, 0.6)  G2:-0.4 (SD, 0.7) (p=0.005)  Job loss, %  G1: 18.6  G2: 39.7 (p<0.005)  SF-36 outcome  NR  At week 16  Job loss, %  G1: 16  G2: 27.3 (p=0.092) | Overall:  G1: 90.7  G2: 87.7  SAEs  G1: 17.3  G2: 15.1  Overall discontinuation  G1: 25  G2: 37  Discontinuation because of AEs  G1: 8  G2: 11  Discontinuation because of lack of efficacy  G1: 17.3  G2: 35.6  Patient adherence  NR  Abdominal pain (Serious)  G1: 1.4  G2: 0  Nausea  G1: 21.3  G2: 32.9  Diarrhea  G1: 10.7  G2: 8.2  Headache  G1: 10.7  G2: 6.8 | Medium (16 week data);  High (56 week data) |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Bijlsma et al., 2016;33  Teitsma et al., 2017135  U-Act-Early  Country, Clinical Setting:  The Netherlands,  Outpatient departments  Study Design:  RCT  Overall N:  317  Study Duration:  2 yrs | Patients were diagnosed with RA within 1 year before inclusion, DMARD-naïve, aged ≥18, met current RA classification criteria, and had a DAS28 score of ≥2.6 | Interventions, dose:  G1: TCZ 8 mg/kg intravenously every 4 wks (max 800 mg/dose) + MTX 10 mg/wk orally (max 30 mg/wk)  G2: TCZ 8 mg/km intravenously every 4 wks (max 800 mg/dose) + placebo MTX  G3: MTX 10 mg/wk orally (max 30 mg/wk) + placebo TCZ  MTX: dose increased stepwise every 4 weeks by 5 mg up to the max dose  N:  G1: 106  G2: 103  G3: 108  Mean age, yrs:  54.0 | Median disease duration, days (IQR):  26 (IQR, 16.0-43.0)  Baseline DAS, mean:  5.2 (SD, 1.1)  Baseline HAQ, mean:  1.2 (SD, 0.64)  MTX naïve, %:  100  **Prior csDMARD use, %:**  0  MTX inadequate responders:  NA  Biologic non-responders, %:  NA | At 2 yrs  DAS disease activity, decrease from baseline, median (min, max)  G1: 3.3 (-0.73, 6.07)  G2: 3.3 (0.1, 6.8)  G3: 3.2 (-0.79, 7.52)  p=0.66  ACR20 response, %  G1: 63  G2: 65  G3: 61  ACR50 response, %  G1: 49  G2: 55  G3: 48  ACR70 response, %  G1: 36  G2: 39  G3: 35 | Overall:  G1: 99.1  G2: 96.1  G3: 98.1  p=0.32  SAEs  G1: 16.0  G2: 18.4  G3: 12.0  p=0.44  Overall discontinuation  G1: 26.4  G2: 21.4  G3: 27.8  Discontinuation because of AEs  G1: 8.5  G2: 9.7  G3: 7.4  p=0.82  Discontinuation because of lack of efficacy  G1: 8.5  G2: 3.9  G3: 12.0 | Medium |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Bijlsma et al., 2016;33  Teitsma et al., 2017135  U-Act-Early  (continued) |  | Sex, % female:  67  Race, % white:  96 | Seropositive (RF or anti-CCP) (%):  RF: 72  anti-CCP: 70  Combined RF and anti-CCP: 79  Baseline Sharp score, median (IQR):  0.0 (IQR, 0.0-1.0)  Erosive disease, %:  NR | DAS remission, %, sustained during entire study  G1: 86  G2: 88  G3: 77  G2 vs. G3: p=0.0356  G2 vs. G1: p=0.59  G3 vs. G1: p=0.06  SHS change from baseline, mean (SD)  G1: 1.18 (SD, 3.919)  G2: 1.45 (SD, 4.272)  G3: 1.53 (SD, 2.421)  median (IQR)  G1: 0.00 (IQR, 0.00-1.00)  G2: 0.00 (IQR, 0.00-2.00)  G3: 0.00 (IQR, 0.00-2.56)  G2 vs. G3: p=0.0381  G2 vs. G1: p=0.53  G3 v G1: p=0.0207  HAQ mean change from baseline  G1: 0.48 (SD, 0.55)  G2: 0.61 (SD, 0.61)  G3: 0.62 (SD, 0.50)  p=0.06  FACIT-F Score, mean (SD)  G1: 39.2 (10.1)  G2: 38.4 (10.6)  G3: 37.9 (10.0)  FACIT-F change from BL, mean (SD)  G1: 6.3 (10.3)  G2: 6.4 (11.1)  G3: 6.6 (11.4) | Patient adherence, %  The full 104 wk study was completed by 75% of all participants  G1: 73.6  G2: 78.6  G3: 72.2  Specific AEs  G1: NR  G2: NR  G3: NR |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Bijlsma et al., 2016;33  Teitsma et al., 2017135  U-Act-Early  (continued) |  |  |  | SF-36 PCS, mean (SD)  G1: 64.9 (15.5)  G2: 65.0 (19.1)  G3: 63.6 (16.4)  SF-36 PCS change from BL, mean (SD)  G1: 15.3 (18.9)  G2: 16.0 (19.1)  G3: 14.1 (16.1)  SF-36 MCS, mean (SD)  G1: 73.5 (14.3)  G2: 73.6 (15.2)  G3: 73.2 (15.2)  SF-36 MCS change from BL, mean (SD)  G1: 11.6 (12.6)  G2: 6.9 (16.1)  G3: 8.6 (16.2)  EQ-5D Score, mean (SD)  G1: 0.85 (0.15)  G2: 0.83 (0.19)  G3: 0.82 (0.15)  EQ-5D change from BL, mean (SD)  G1: 0.18 (0.24)  G2: 0.22 (0.27)  G3: 0.16 (0.22)  EQ-VAS, mean (SD)  G1: 73.8 (16.7)  G2: 76.6 (18.2)  G3: 71.2 (17.3)  EQ-VAS change from BL, mean (SD)  G1: 12.6 (20.6)  G2: 14.0 (21.0)  G3: 12.3 (21.4) |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Bijlsma et al., 2016;33  Teitsma et al., 2017135  U-Act-Early  (continued) |  |  |  | At 52 weeks  DAS disease activity, decrease from baseline, median (min, max)  G1: 3.3 (-1.02, 7.48)  G2: 3.4 (0.28, 7.66)  G3: 3.3 (-0.74, 6.13)  p=0.09  ACR20 response, %  G1: 75  G2: 72  G3: 69  ACR50 response, %  G1: 62  G2: 59  G3: 51  ACR70 response, %  G1: 44  G2: 44  G3: 33  DAS remission, %  NR  SHS change from baseline, mean (SD)  G1: 0.50 (SD, 1.495)  G2: 0.79 (SD, 3.242)  G3: 0.96 (SD, 2.870)  median (IQR)  G1: 0.00 (IQR, 0.00-0.00)  G2: 0.00 (IQR, 0.00-0.00)  G3: 0.00 (IQR, 0.00-1.00)  G2 vs. G3: p=0.06  G2 vs. G1: p=0.49  G3 v G1: p=0.0164 |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Bijlsma et al., 2016;33  Teitsma et al., 2017135  U-Act-Early  (continued) |  |  |  | HAQ mean change from baseline  G1: 0.46 (SD, 0.50)  G2: 0.48 (SD, 0.55)  G3: 0.55 (SD, 0.51)  p=0.14  FACIT-F Score, mean (SD)  G1: 39.5 (8.8)  G2: 40.5 (9.3)  G3: 37.1 (11.0)  FACIT-F change from BL, mean (SD)  G1: 7.2 (9.6)  G2: 8.0 (11.8)  G3: 6.7 (12.0)  SF-36 PCS, mean (SD)  G1: 68.5 (16.5)  G2: 70.5 (19.1)  G3: 64.2 (17.2)  G2 vs. G3, P<0.05  SF-36 PCS change from BL, mean (SD)  G1: 19.2 (16.3)  G2: 21.5 (17.0)  G3: 14.3 (16.1)  G2 vs. G3, P<0.05  SF-36 MCS, mean (SD)  G1: 74.7 (13.9)  G2: 76.0 (14.9)  G3: 73.8 (15.7)  SF-36 MCS change from BL, mean (SD)  G1: 12.0 (13.8)  G2: 11.8 (16.4)  G3: 10.7 (16.9)  EQ-5D Score, mean (SD)  G1: 0.85 (0.13)  G2: 0.84 (0.15)  G3: 0.84 (0.14) |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Bijlsma et al., 2016;33  Teitsma et al., 2017135  U-Act-Early  (continued) |  |  |  | EQ-5D change from BL, mean (SD)  G1: 0.20 (0.27)  G2: 0.22 (0.23)  G3: 0.20 (0.24)  EQ-VAS, mean (SD)  G1: 74.0 (16.6)  G2: 74.1 (18.2)  G3: 72.6 (20.7)  EQ-VAS change from BL, mean (SD)  G1: 13.8 (23.3)  G2: 12.6 (19.4)  G3: 14.2 (21.2)  At 24 weeks  DAS disease activity, median decrease from baseline  G1: 3·6 (0·75, 7·48)  G2: 3·6 (0·45, 7·64)  G3: 2·1 (-1·67, 5·11)  p <0.0001  ACR20 response, %  G1: 75  G2: 75  G3: 59  G2 vs. G3: p=0.0343  G3 vs. G1: p=0.0099  ACR50 response, %  G1: 64  G2: 59  G3: 34  G2 vs. G3: p=0.0009  G3 vs. G1: p<0.0001 |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Bijlsma et al., 2016;33  Teitsma et al., 2017135  U-Act-Early  (continued) |  |  |  | ACR70 response, %  G1: 44  G2: 37  G3: 15  G2 vs. G3: p=0.0003  G3 vs. G1: P <0.0001  DAS remission, %  NR  SHS change from baseline, mean (SD)/median IQR)  G1: NR  G2: NR  G3: NR  HAQ mean change from baseline  G1: 0.50 (SD, 0.55)  G2: 0.63 (SD, 0.66)  G3: 0.65 (SD, 0.54)  p=0.0275  FACIT-F Score, mean (SD)  G1: 39.1 (9.8)  G2: 39.0 (9.4)  G3: 36.0 (8.9)  G1 and G2 vs. G3, p=0.038 each  FACIT-F change from BL, mean (SD)  G1: 7.4 (9.5)  G2: 7.3 (10.9)  G3: 4.7 (9.4)  G1 and G2 vs. G3, p<0.05 each  SF-36 PCS, mean (SD)  G1: 64.9 (18.5)  G2: 63.0 (18.9)  G3: 60.2 (16.5)  G1 vs. G3, p<0.05 |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Bijlsma et al., 2016;33  Teitsma et al., 2017135  U-Act-Early  (continued) |  |  |  | SF-36 PCS change from BL, mean (SD)  G1: 15.6 (16.8)  G2: 14.5 (16.7)  G3: 9.2 (14.7)  G1 vs. G3, p<0.05    SF-36 MCS, mean (SD)  G1: 73.8 (16.4)  G2: 71.8 (15.1)  G3: 69.5 (14.1)  G1 vs. G3, p<0.05  SF-36 MCS change from BL, mean (SD)  G1: 10.3 (15.0)  G2: 6.8 (16.4)  G3: 5.7 (14.0)  G1 vs. G3, p<0.05  EQ-5D Score, mean (SD)  G1: 0.84 (0.17)  G2: 0.80 (0.20)  G3: 0.77 (0.17)  G1 vs. G3, p<0.05  EQ-5D change from BL, mean (SD)  G1: 0.19 (0.22)  G2: 0.17 (0.29)  G3: 0.13 (0.23)  G1 vs. G3, p<0.05  EQ-VAS, mean (SD)  G1: 72.8 (19.3)  G2: 72.8 (17.7)  G3: 69.7 (17.7) |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Bijlsma et al., 2016;33  Teitsma et al., 2017135  U-Act-Early  (continued) |  |  |  | EQ-VAS change from BL, mean (SD)  G1: 12.6 (21.9)  G2: 11.7 (20.5)  G3: 10.7 (20.8)  **At 12 weeks**  FACIT-F Score, mean (SD)  G1: 35.7 (10.8)  G2: 38.2 (9.4)  G3: 35.1 (10.7)  G2 vs. G3, p=0.023  FACIT-F change from BL, mean (SD)  G1: 4.8 (9.0)  G2: 6.0 (10.5)  G3: 4.0 (10.0)  SF-36 PCS, mean (SD)  G1: 59.7 (18.7)  G2: 61.6 (15.8)  G3: 57.6 (15.9)  G2 vs. G3, p<0.05  SF-36 PCS change from BL, mean (SD)  G1: 10.2 (13.9)  G2: 13.6 (14.8)  G3: 6.6 (12.7)  G2 vs. G3, p<0.05  SF-36 MCS, mean (SD)  G1: 70.1 (15.8)  G2: 72.7 (14.7)  G3: 69.4 (14.1) |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Bijlsma et al., 2016;33  Teitsma et al., 2017135  U-Act-Early  (continued) |  |  |  | SF-36 MCS change from BL, mean (SD)  G1: 7.6 (13.6)  G2: 7.3 (13.7)  G3: 4.7 (13.6)  EQ-5D Score, mean (SD)  G1: 0.79 (0.20)  G2: 0.80 (0.14)  G3: 0.74 (0.21)  G1 vs. G3, p=0.041  G2 vs. G3, p=0.009  EQ-5D change from BL, mean (SD)  G1: 0.14 (0.24)  G2: 0.18 (0.24)  G3: 0.08 (0.26)  G1 and G2 vs. G3, p<0.05 each  EQ-VAS, mean (SD)  G1: 72.4 (15.9)  G2: 69.5 (16.4)  G3: 63.9 (17.9)  G1 vs. G3, p=0.001  G2 vs. G3, p=0.039  EQ-VAS change from BL, mean (SD)  G1: 12.6 (20.8)  G2: 8.8 (19.0)  G3: 3.9 (19.7)  G1 and G2 vs. G3, p<0.05 each |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Bili et al., 201411  Country, Clinical Setting:  United States, 4 hospitals  Study Design:  Observational (Retrospective cohort)  Overall N:  2,101  Study Duration:  10 yrs | Patients had RA diagnosis made with the International Classification of Diseases, Ninth Revision (ICD-9), twice by a GHS rheumatologist (definition was validated against 1987 ACR criteria). Patients with CVD prior to initiation of RA medication, and those who were DMARD naïve were excluded | Interventions, dose:  G1: TNFa inhibitors alone or in combination with MTX medication exposure  G2: MTX alone or in combination with other nonbiologic DMARDs  G3: Non-MTX, nonbiologic DMARDs  G1 details: TNFa inhibitors include: ETN, ADA, IFX, GOL, and certolizumab. Other concomitant nonbiologic DMARDs permitted  G2 details: Nonbiologic DMARDs include: MTX, HCQ, LEF, Azathioprine, SSZ, and Minocycline. Could not also use TNFa inhibitors or other biologic medicines  Note: in all groups, Corticosteroids were considered non-DMARDs and (along with NSAIDs) were allowed in each group. Dose information for all groups not available. Additionally, Patients could contribute time to different groups according to medication exposure. Therefore, exposure is reported as “exposure periods” and one patient can contribute to multiple periods | Median disease duration, mos (IQR):  0.99-9.0 mos  Baseline DAS, mean:  NR  Baseline HAQ, median:  NR  MTX naive:  NR  Prior csDMARD use, %:  100  MTX inadequate responders:  NR  Prior CS use, %  89.3-94.4  Biologic non-responders:  NR  Seropositive (RF or CCP) (%):  62.5 | NA | Overall:  Coronary artery disease (CAD) events (n)  G1: 12  G2: 16  G3: 18  CAD event incidence rate (95% CI)  G1: 5.0 (CI 2.8-8.8)  G2: 5.0 (CI 3.0-8.1)  G3: 10.9 (CI 6.9-17.3)  CAD hazard ratio, fully adjusted, (95% CI)  G1: 0.45 (CI 0.21-0.96)  G2: 0.54 (CI 0.27-1.09)  G3: Reference  Cardiovascular disease (CVD) events (n)  G1: 26  G2: 32  G3: 24  CVD event incidence rate (95% CI)  G1: 11.1 (CI 7.5-16.3)  G2: 10.0 (CI 7.1-14.2)  G3: 14.7 (9.9-22.0) | High |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Bili et al., 201411  (continued) |  | N:  G1: 879  G2: 1447  G3: 898  Mean age, yrs:  51.7-56.9  Sex, % female:  73  Race, % white:  96 | Baseline Sharp score, mean:  NR  Erosive disease, %:  NR |  | CVD hazard ratio, fully adjusted, (95% CI)  G1: 0.79 (CI 0.44-1.41)  G2: 0.85 (CI 0.49-1.46)  G3: Reference |  |
| Author, yr, Study Name:  Bliddal et al., 201577  Country, Clinical Setting:  Denmark, Information from national prescription register | Patients aged ≥18 at first diagnosis/contact, who had filled ≥1 MTX prescription between Jan 1998-Dec 2012. The cohort was constructed from the Danish population of | Interventions, dose:  Adherence to MTX: 32.9% took <5 mg MTX per week of followup, and 43.5% took <7.5 mg of MTX per week of followup. Median time from diagnosis to first MTX prescription was 0.66 (IQR, 0.26–1.80) years  N:  18,703  Mean age, yrs:  59.8 (SD, 14.4) | Median time from diagnosis to first MTX prescription, yrs (IQR)  0.66 yrs (IQR, 0.26-1.80)  Baseline DAS, mean:  NR  Baseline HAQ, median:  NR | N/A | Overall:  NR  SAEs  NR  Overall discontinuation  After an initial loss of adherence, the remainder Danish RA patients slowly but steadily dropped out of treatment over the following years. After 10.9 years, 50 percent discontinued. | N/A |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Bliddal et al., 201577  (continued)  Study Design:  Observational (only single arm eligible)  Overall N:  18,703  Study Duration:  Followed for mean of 7.8 yrs | approx. 5.4 million inhabitants | Sex, % female:  72  Race, % white:  NR | MTX naive:  100  Prior csDMARD use, %  NR  Prior CS use, %  61  Biologic non-responders:  NR  Seropositive (RF or CCP) (%):  NR  Baseline Sharp score, mean:  NR  Erosive disease, %:  NR |  | Discontinuation because of AEs  NR  Patient adherence  The main determinants of non-adherence were female gender, younger age, and tie from diagnosis to initiation of MTX.  No difference in adherence to MTX was present between those managed in private practice (1,925 (IQR, 467–3,056) days) versus 1,892 (IQR, 452–3,316) days for patients treated in hospital. In those who filed more than one MTX prescription, the mean adherence time for 7.5mg MTX per week was 2,245 (IQR, 986–3,407) days.  Specific AEs  NA (specific AEs for head-to-head trials only) |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr:  Boers et al., 199724; Landewe et al., 2002100;  Tuyl et al., 2010141  COBRA study  Country, Setting:  Netherlands and Belgium, multicenter  Study Design:  RCT  Overall N:  155  Study Duration:  5 yrs | Adults (aged 18 to 69 yrs) fulfilling ACR criteria for RA with disease duration < 2 yrs; active disease defined as ≥ 6 actively inflamed joints (located at ≥ 3 sites) and ≥ 2 of the following: ≥ 9 tender joints (irrespective of site), morning stiffness for ≥ 45 mins, Westerren’s ESR ≥ 28 mm in first hour; NSAID treatment for ≥3 mos; no prior use of csDMARDs (other than antimalarials) or corticosteroids | Interventions, dose:  G1:   * MTX:7.5 mg/wk with 1 mg/day folic acid until wk 40 when weaned off * SSZ: 500 mg/day, increased to 2,000 mg/day over 3 wks (oral) * PNL: 60 mg in wk 1, 40 mg in wk 2, 25 mg in wk 3, 20 mg in wk 4, 15 mg in wk 5, 10 mg in wk 6, 7.5 mg/wk thereafter until wk 28 when weaned off (oral)   G2:   * Placebo with 1 mg/day folic acid * SSZ: 500 mg/day, increased to 2,000 mg/day over 3 wks (oral) * Placebo   NSAIDs and simple analgesics were allowed, but discontinuation was actively pursued; ≤ 2 intra-articular steroid injections were allowed in 2 periods after wk 38 (not in 6-wk period preceding independent assessment); any other intervention with parenteral or oral corticosteroids was not allowed  N:  G1: 76  G2: 79 | Median disease duration, mos:  4 (range: 1-24)  Baseline DAS, mean:  NR  Baseline HAQ, mean:  NR  Prior csDMARD use, %:  0  MTX naive, %:  100  MTX inadequate responders, %:  NA  Biologic non-responders, %:  NA  RF seropositive, %:  74.4  Baseline Sharp score, median:  G1: 3 (range 0-58)  G2: 5 (range: 0-48)  Overall: NR  Radiographic evidence of erosions, %:  73.1 (of 149) | At 5 yrs  DAS28 disease activity, mean change per yr:  G1: -0.02 (95% CI, -0.12 to 0.08)  G2: -0.13 (95% CI, -0.24 to -0.02)  p=0.265  Time-averaged DAS28 disease activity, mean change per yr:  G1: -0.07 (95% CI, -0.11 to -0.03)  G2: -0.17 (95% CI, -0.23 to --0.11)  p=0.014  ACR response, %:  NR  DAS remission, %:  NR  Sharp score, mean change per yr:  G1: 5.6 (95% CI, 4.3 to 7.1)  G2: 8.6 (95% CI, 6.2 to 11)  p=0.033  HAQ, mean change per yr:  G1: 0.01 (95% CI -0.03 to 0.05)  G2: 0.01 (95% CI -0.03 to 0.05)  p=0.875  SF-36:  NR  At 80 wks  Sharp score, median:  G1:4 (range: 0-80)  G2:12 (range: 0-72)  p<0.01 | Overall AEs:  G1: 72.3  G2: 62.0  SAEs:  G1: 2.6  G2: 7.6  Overall discontinuation:  G1: 8.0  G2: 29.1  p=0.0008  Discontinuation due to AEs:  G1: 2.6  G2: 7.6  Discontinuation due to lack of efficacy:  G1: 5.3  G2: 15.2  Patient adherence (satisfactory compliance):  G1: 84.2  G2: 84.8  Specific AEs:  Rash:  G1: NR  G2: 5.1  GI complaints:  G1: 14.5  G2: 12.7 | Medium (56 week, 5 year, and most 11 year outcomes)  High (11-year radiographic outcomes) |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr:  Boers et al., 199724; Landewe et al., 2002100;  Tuyl et al., 2010141  COBRA study  (continued) |  | Mean age, yrs:  G1: 49.5 (SD, 11.9)  G2: 49.4 (SD, 12.3)  Overall: NR  Sex, % female:  58.3  Race, % white:  98.7  Race, % black:  0.0  Ethnicity, % Latino:  0.0 |  | At 56 wks  DAS28 disease activity, mean change:  G1: -1.4 (SD, 1.2)  G2: -1.3 (SD, 1.4)  p=0.78  Pooled index, mean change:  G1: 1.1 (SD, 0.8)  G2: 0.9 (SD, 0.8)  p=0.20  Persisting ACR-defined remission, %:  G1: 1.3  G2: 4.0  Sharp score, median:  G1: 2 (range: 0-43)  G2: 6 (range 0-54)  p=0.004)  HAQ, mean change:  G1: -0.8 (SD, 0.8)  G2: -0.6 (SD, 0.7)  p<0.06  Pain (visual analogue scale), mean change:  G1: -23 (SD, 29)  G2: -25 (SD, 28)  p<0.66 | Dyspnea (final diagnosis exacerbation of chronic bronchitis):  G1: 1.3  G2: NR  Thrombocytopenia (diagnosis preleukaemic disease):  G1: NR  G2: 1.3 |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr:  Boers et al., 199724; Landewe et al., 2002100;  Tuyl et al., 2010141  COBRA study  (continued) |  |  |  | At 28 wks  DAS28 disease activity, mean change:  G1: -2.1 (SD, 1.2)  G2: -1.3 (SD, 1.2)  p<0.0001  Pooled index, mean change:  G1: 1.4 (SD, 0.7)  G2: 0.8 (SD, 0.7)  (p<0.0001)  ACR20 response, %:  G1: 72.4  G2: 49.4  p=0.006  ACR50 response, %:  G1: 48.7  G2: 26.6  p=0.007  ACR-defined probable or definite remission, %:  G1: 27.6  G2: 16.5  p=0.14  Sharp score, median:  G1: 1 (range: 0-28)  G2: 4 (range: 0-44)  p<0.0001  HAQ, mean change:  G1: -1.1 (SD, 0.8)  G2: -0.6 (SD, 0.6)  p<0.0001 |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr:  Boers et al., 199724; Landewe et al., 2002100;  Tuyl et al., 2010141  COBRA study  (continued) |  |  |  | Pain (visual analogue scale), mean change:  G1: -34 (SD, 25)  G2: -20 (SD, 30)  p<0.002 |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Breedveld et al., 200615;  Kimel et al., 2008103;  van Vollenhoven et al., 2010149;  van der Heijde et al., 2010115;  Strand et al., 2012116;  Smolen et al., 2013117;  Keystone et al., 2014118;  Landewe et al., 2015119  PREMIER  Country, Clinical Setting:  Multinational (Europe, North America, Australia),  multicenter (133)  Study Design:  RCT | Adults (aged ≥ 18 yrs) fulfilling ACR criteria for RA with disease duration <3 yrs, ≥8 swollen joints, ≥10 tender joints, ESR ≥28 mm/hr or CRP ≥1.5 mg/dl, and either rheumatoid factor positivity or ≥1 joint erosion; patients were MTX, cyclophos-phamide, cyclosporine and azathioprine naïve, but could have prior treatment with ≤2 other DMARDs | Interventions, dose:  G1:   * MTX: Initiated at 7.5 mg/wk, increased to 15 mg/wk for wks 4-8, and increased to 20 mg/wk at wk 9 (oral) * ADA: 40 mg every other wk (subcutaneous) * Folic acid: 5-10 mg/wk   G2:   * Placebo * ADA: 40 mg every other wk (subcutaneous) * Folic acid: 5-10 mg/wk   G3:   * MTX: Initiated at 7.5 mg/wk, increased to 15 mg/wk for wks 4-8, and increased to 20 mg/wk at wk 9 (oral) * Placebo * Folic acid: 5-10 mg/wk   For patients who did not achieve ACR20 response at wk 16, the injectable medication (ADA or placebo) was increased to weekly after the oral medication (MTX or placebo) was optimized | Mean disease duration, yrs:  0.7-0.8  Baseline DAS28, mean:  6.3-6.4  Baseline HAQ-DI, mean:  1.5-1.6  Prior csDMARD use, %:  32.4  MTX naïve, %:  100  MTX inadequate responders, %:  0 | At 2 yrs  DAS28 (CRP) disease activity, mean change:  G1: -3.8  G2: -3.1  G3: -3.1  ACR20 response, %:  G1:69  G2:49  G3:56  G1 vs. G2: p<0.001  G1 vs. G3: p=0.002  ACR50 response, %:  G1:59  G2:37  G3:43  G1 vs. G2/3: p<0.001  ACR70 response, %:  G1:47  G2:28  G3:28  G1 vs. G2/3: p<0.001  DAS28 remission (< 2.6), %:  G1: 49  G2:25  G3:25  G1 vs. G2/3: p<0.001 | Overall AEs:  G1: 97.8  G2: 95.6  G3: 95.3  SAEs:  G1: 18.5  G2: 21.1  G3: 15.9  p=0.192  Overall discontinuation:  G1: 24.3  G2: 39.1  G3: 34.2  p<0.001  Discontinuation because of AEs:  G1: 11.9  G2: 9.5  G3: 7.4  p=0.21  Discontinuation because of lack of efficacy:  G1: 4.9  G2: 19.0  G3: 17.9  Patient adherence:  NR | Medium |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Breedveld et al., 200615;  Kimel et al., 2008103;  van Vollenhoven et al., 2010149;  van der Heijde et al., 2010115;  Strand et al., 2012116;  Smolen et al., 2013117;  Keystone et al., 2014118;  Landewe et al., 2015119  PREMIER  (continued)  Overall N:  799  Study Duration:  2 yrs |  | N:  G1: 268  G2: 274  G3: 257  Mean age, yrs:  G1: 51.9 (SD, 14.0)  G2: 52.1 (SD, 13.5)  G3: 52.0 (SD, 13.1)  Overall: NR  Sex, % female:  74.5  Race, % white:  NR  Race, % black:  NR  Ethnicity, % Latino:  NR | Biologic non-responders, %:  NR  Prior CS use, %:  35.9  RF or CCP seropositive, %:  NR  Baseline mTSS, mean:  18.1-21.9  Erosive disease, %:  NR | Modified Sharp score  Mean change:  G1:1.9  G2:5.5  G3: 10.4  G1 vs. G2/3: p<0.001  G2 vs. G3: p<0.001  No radiographic progression (change ≤ 0.5), %:  G1: 61  G2: 45  G3: 34  G1 vs. G2/3: p<0.01  G2 vs. G3: p<0.01  HAQ-DI, mean change:  G1: -1.0 (SD, 0.7)  G2: -0.9 (SD, 0.7)  G3: -0.9 (SD, 0.6)  G1 vs. G2: p=0.058  G1 vs. G3: p<0.05  HAQ-DI response (change ≥ 0.22), %:  G1: 72  G2: 58  G3: 63  G1 vs. G2/3: p<0.05  HAQ-DI score of 0 (no functional impairment), %:  G1: 33  G2: 19  G3: 19  G1 vs. G2/3: p<0.001 | Specific AEs  Infections, n (per 100 patient yrs):  G1: 123  G2: 110  G3: 119  Serious infections, n (per 100 patient yrs):  G1: 2.9  G2: 0.7  G3: 1.6  G1 vs. G2: p<0.05  G1 vs. G3: Not significant  Malignancies, n (per 100 patient yrs):  G1: 0.4  G2: 0.9  G3: 0.9 |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Breedveld et al., 200615;  Kimel et al., 2008103;  van Vollenhoven et al., 2010149;  van der Heijde et al., 2010115;  Strand et al., 2012116;  Smolen et al., 2013117;  Keystone et al., 2014118;  Landewe et al., 2015119  PREMIER  (continued) |  |  |  | SF-36  Mental component, mean:  G1: 51.8 (SD, 8.8)  G2: 49.8 (SD, 8.1)  G3: 52.4 (SD, 8.4)  G1 vs. G3: p=0.7609  G2 vs. G3: p=0.0148  Physical component, mean:  G1: 48.8 (SD, 8.3)  G2: 44.7 (SD, 8.0)  G3: 45.9 (SD, 7.8)  G1 vs. G3: p<0.0001  G2 vs. G3: p=0.3912  Pain (visual analog scale), mean:  G1: 9.6 (SD, 14.9)  G2: 19.6 (SD, 16.5)  G3: 12.5 (SD, 15.8)  G1 vs. G2: p<0.0001  G2 vs. G3: p=0.1571  Retained or gained employment, %:  G1: 57.6 (of 210)  G3: 47.6 (of 210)  Missed work days, mean:  G1: 17.4 (for 130 employed)  G3: 36.9 (for 110 employed)  p<0.0001 |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Breedveld et al., 200615;  Kimel et al., 2008103;  van Vollenhoven et al., 2010149;  van der Heijde et al., 2010115;  Strand et al., 2012116;  Smolen et al., 2013117;  Keystone et al., 2014118;  Landewe et al., 2015119  PREMIER  (continued) |  |  |  | At 76 wks  SF-36  Mental component, mean:  G1: 51.4 (SD, 8.7)  G2: 49.3 (SD, 8.1  G3: 51.7 (SD, 8.4)  Physical component, mean:  G1: 47.5 (SD, 8.8)  G2: 43.9 (SD, 7.8)  G3: 44.7 (SD, 8.0)  Pain (visual analog scale), mean:  G1: 13.1 (SD, 15.0)  G2: 22.2 (SD, 16.9)  G3: 18.4 (SD, 16.1)  At 1 yr  DAS28 (CRP) disease activity, mean change:  G1: -3.6  G2: -2.8  G4: -2.8  ACR20 response, %:  G1:73  G2:54  G3:63  G1 vs. G2: p<0.001  G1 vs. G3: p=0.022  ACR50 response, %:  G1:62  G2:41  G3:46  G1 vs. G2/3: p<0.001 |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Breedveld et al., 200615;  Kimel et al., 2008103;  van Vollenhoven et al., 2010149;  van der Heijde et al., 2010115;  Strand et al., 2012116;  Smolen et al., 2013117;  Keystone et al., 2014118;  Landewe et al., 2015119  PREMIER  (continued) |  |  |  | ACR70 response, %:  G1:46  G2:26  G3:28  G1 vs. G2/3: p<0.001  DAS28 remission (< 2.6), %:  G1: 43  G2: 23  G3: 21  G1 vs. G2/3: p<0.001  Modified Sharp score  Mean change:  G1:1.3  G2:3.0  G3: 5.7  G1 vs. G2: p=0.002  G1 vs. G3: p<0.001  G2 vs. G3: p<0.001  No radiographic progression (change ≤ 0.5), %:  G1: 64  G2: 51  G3: 37  G1 vs. G2/3: p<0.01  G2 vs. G3: p<0.01  HAQ-DI, mean change:  G1: -1.1 (SD, 0.6)  G2: -0.8 (SD, 0.7)  G3: -0.8 (SD, 0.7)  G1 vs. G2, p=0.002  G1 vs. G3: p<0.001 |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Breedveld et al., 200615;  Kimel et al., 2008103;  van Vollenhoven et al., 2010149;  van der Heijde et al., 2010115;  Strand et al., 2012116;  Smolen et al., 2013117;  Keystone et al., 2014118;  Landewe et al., 2015119  PREMIER  (continued) |  |  |  | SF-36  Mental component, mean:  G1: 50.7 (SD, 8.7)  G2: 49.1 (SD, 8.2)  G3: 51.3 (SD, 8.5)  Physical component, mean:  G1: 46.6 (SD, 8.2)  G2: 42.5 (SD, 7.9)  G3: 43.5 (SD, 8.1)  Pain (visual analog scale), mean:  G1: 16.8 (SD, 15.7)  G2: 26.6 (SD, 17.1)  G3: 23.4 (SD, 16.1)  At 6 months  Modified Sharp scores, mean change:  G1:0.8  G2:2.1  G3: 3.5  G1 vs. G2/3: p<0.001  G2 vs. G3: p<0.001  SF-36  Mental component, mean:  G1: 50.3 (SD, 8.6)  G2: 48.6 (SD, 8.0)  G3: 51.8 (SD, 8.5)  Physical component, mean:  G1: 45.3 (SD, 8.2)  G2: 41.1 (SD, 8.0)  G3: 42.2 (SD, 8.1) |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Breedveld et al., 200615;  Kimel et al., 2008103;  van Vollenhoven et al., 2010149;  van der Heijde et al., 2010115;  Strand et al., 2012116;  Smolen et al., 2013117;  Keystone et al., 2014118;  Landewe et al., 2015119  PREMIER  (continued) |  |  |  | Pain (visual analog scale), mean:  G1: 20.9 (SD, 16.5)  G2: 30.6 (SD, 17.2)  G3: 29.4 (SD, 16.5)  At 3 mos  SF-36  Mental component, mean:  G1: 49.7 (SD, 8.7)  G2: 47.9 (SD, 8.2)  G3: 550.1 (SD, 8.8)  Physical component, mean:  G1: 44.8 (SD, 8.0)  G2: 39.9 (SD, 7.8)  G3: 41.0 (SD, 8.1)  Pain (visual analog scale), mean:  G1: 23.2 (SD, 16.5)  G2: 34.2 (SD, 17.9)  G3: 33.8 (SD, 17.9) |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Burmester et al., 2016-732, 134  FUNCTION  Country, Clinical Setting:  Multiple countries, 237 sites  Study Design:  RCT  Overall N  1162  Duration of study  2 yrs | Patients aged ≥18 years with moderate to severe active RA classified by ACR criteria, ≤2 years duration, and MTX or DMARD naïve. | Interventions, dose:  G1: TCZ 4 mg/kg + MTX  G2: TCZ 8 mg/kg + MTX  G3: TCZ 8 mg/kg + placebo  G4: Placebo + MTX  TCZ/placebo: administered intravenously every 4 wks  MTX/placebo: Initiated at 7.5 mg/wk, increased to 20 mg/wk (max) by wk 8 in patients with ongoing swollen or tender joints  Patients not receiving 8 mg/kg TCZ and not achieving DAS-28 ≤3.2 at wk 52 switched to escape (8 mg/kg TCZ+MTX) | Median disease duration, yrs:  0.2-0.3 yrs  Baseline DAS, mean:  6.6-6.7  Baseline HAQ, median:  1.50-1.75  MTX naïve, %:  100  Prior csDMARD use, %:  0 | At 2 yrs  DAS28-ESR LDA, %  G1: 34.4  G2: 55.5  G3: 51.4  G4: 21.3  ACR20 response, %  G1: 39.6  G2: 65.2  G3: 61.6  G4: 25.4  ACR50 response, %  G1: 36.5  G2: 57.6  G3: 53.1  G4: 22.0  ACR70 response, %  G1: 31.6  G2: 46.6  G3: 39.4  G4: 17.4  DAS28-ESR remission, %  G1: 28.1  G2: 47.6  G3: 43.5  G4: 16.0  Change in modified total Sharp score, mean (SD)  G1: 1.43 (SD 11.7)  G2: 0.19 (SD 2.1)  G3: 0.62 (SD 4.8)  G4: 1.88 (SD 6.2)  HAQ  NR | Overall adverse and serious adverse events were only reported as N of total events at 104 weeks, rather than as individuals experiencing events.  Overall at 52 wks:  G1: 88.6  G2: 88.3  G3: 85.6  G4: 83.3  SAEs at 52 wks  G1: 10.0  G2: 10.7  G3: 8.6  G4: 8.5  Overall discontinuation at 104 wks  G1: 32.4  G2: 29.6  G3: 29.1  G4: 30.4  Discontinuation because of AEs at 104 wks  G1: 13.5  G2: 16.3  G3: 17.1  G4: 7.8 | Medium;  High (2 years) |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Burmester et al., 2016-732, 134  FUNCTION  (continued) |  |  |  | SF-36  NR  At 1 yr  DAS28-ESR, LDA, %  G1: 47.6  G2: 57.9  G3: 50.3  G4: 30.0  ACR20 response, %  G1: 65.3  G2: 67.9  G3: 65.4  G4: 58.5  ACR50 response, %  G1: 54.9  G2: 56.2  G3: 50.7  G4: 41.5  ACR70 response, %  G1: 37.8  G2: 43.4  G3: 37.0  G4: 29.3 |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Burmester et al., 2016-732, 134  FUNCTION  (continued)  Overall N:  1162  Study Duration:  2 yrs |  | N:  G1: 290  G2: 291  G3: 292  G4: 289  Mean age, yrs:  49.5-51.2  Sex, % female:  78.1  Race, % white:  NR | MTX inadequate responders:  0  Biologic non-responders:  0  **Prior CS use, %:**  NR  RF seropositive, %:  89.5  Baseline Sharp score, mean:  5.66-7.72  Erosive disease, %:  100 | DAS remission, % (95% CI)  G1: 34.0 (28.6 to 39.5)  G2: 49.0 (43.2 to 54.7)  G3: 39.4 (33.8 to 45.0)  G4: 19.5 (14.9 to 24.1)  p<0.0001  Change in total mTSS, mean (SD)  G1: 0.42 (2.93)  G2: 0.08 (2.09)  G3: 0.26 (1.88)  G4: 1.14 (4.03)  G2 vs. G4: p=0.0001  HAQ-DI, mean change from baseline  G1: -0.75  G2: -0.81  G3: -0.67  G4: -0.64  G2 vs. G4: p=0.0024  SF-36 change from baseline  Figure only;  G2 > G4: p=0.0066  Significantly greater change in SF-36 PCS scores in the TCZ 8 mg/kg + MTX group than in the MTX group (p=0.0066).  No differences in SF-36 PCS scores between the TCZ 4 mg/kg + MTX group and the MTX group or between TCZ and MTX group.  No differences in SF-36 MCS scores. | Overall discontinuation at 52 wks  G1: 20.3  G2: 22.0  G3: 19.2  G4: 21.8  Discontinuation because of AEs at 52 wks  G1: 12.1  G2: 20.3  G3: 11.6  G4: 7.4  Patient adherence  NR  Specific AEs  NR |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Burmester et al., 2016-732, 134  FUNCTION  (continued) |  |  |  | At 24 weeks  DAS disease activity  Figure only  ACR20 response, %  Figure only  ACR50 response, %  Figure only  ACR70 response, %  Figure only |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Burmester et al., 2016-732, 134  FUNCTION  (continued) |  |  |  | DAS remission, %  G1: 31.9  G2: 44.8  G3: 38.7  G4: 15.0  p=0.0001  Change in modified total score, mean (SD)  Figure only  HAQ-DI change from baseline  Figure only  SF-36 change from baseline  Figure only;  G2 > G4: p=0.0014  Significantly greater change in SF-36 PCS scores in the TCZ 8 mg/kg + MTX group than in the MTX group (p=0.0014).  No differences in SF-36 PCS scores between the TCZ 4 mg/kg + MTX group and the MTX group or between TCZ and MTX group.  No differences in SF-36 MCS scores. |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Choy et al., 200893  CARDERA  Country, Clinical Setting:  England/ Wales, outpatient clinics  Study design  RCT  Overall N  232 (out of 467 total)  Duration of study  2 yrs | Adults (aged ≥ 18 yrs) with active RA as determined by ACR criteria of <24 mos and three of the following: ≥3 swollen joints, ≥ 6 tender joints, ≥45 min morning stiffness, ESR ≥28 mm/h | Interventions, dose:  G1:   * MTX: 7.5 mg/wk, increasing incrementally to target dose of 15 mg/wk (open-label) * Ciclosporin placebo * PNL placebo   G2:   * MTX: 7.5 mg/wk, increasing incrementally to target dose of 15 mg/wk (open-label) * Ciclosporin placebo * PNL: step-down initiated with MTX, initial dose of 60 mg/day and reduced to 7.5 mg at wk 6, 7.5 mg/day from wks 6 to 28, stopped by wk 34 | Mean disease duration, mos:  2.7-5.1  Baseline DAS28, mean:  5.6-5.9  Baseline HAQ, mean:  1.5-1.7 | At 2 yrs  DAS28 disease activity, mean change:  G1: -1.42 (SE 0.17)  G2: -1.37 (SE 0.15)  ACR response, %:  NR  DAS28 remission (< 2.6), %:  G1: 17.9  G2: 20.0  Sharp score:  NR | Overall AEs:  SAEs:  G1: 17.9  G2: 16.5  Overall discontinuation:  G1: 16.2  G2: 47.0  NNH for any adverse event leading to discontinuation was and 14 (95% CI, 6 to 65) with added PNL | Medium |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Choy et al., 200893 (continued) |  | N:  G1: 117  G2: 115  Mean age, yrs:  54  Sex, % female:  69.6  Race, % white:  NR | Prior CS use, %:  NR  MTX naive:  NR  Prior csDMARD use, %:  13.9  MTX inadequate responders:  NR  Biologic non-responders:  NR  RF seropositive, %:  66.8  Baseline Sharp score, mean:  NR  Baseline Larsen score, median:  G1: 7 (IQR, 3, 15)  G2: 6 (IQR, 2, 20)  Erosive damage, %:  33.0 | Cases with new erosions (primary outcome), %:  G1: 29  G2: 16  Larsen score, mean change:  G1: 7.41 (SE 0.99)  G2: 4.70 (SE 0.69)  **HAQ, mean change:**  G1: -0.29 (SE 0.07)  G2: -0.28 (SE 0.07)  SF-36  Physical component, mean change:  G1: 5.8 (SE 1.0)  G2: 3.5 (SE 1.0)  Mental component:  “No differences” | Discontinuation due exclusively to toxicity:  G1: 6.8  G2: 12.2  Toxicity implicated in discontinuation:  G1: 10.3  G2: 19.1  Discontinuation due exclusively to lack of efficacy:  G1: 11.1  G2: 8.7  Lack of efficacy implicated in discontinuation:  G1: 16.2  G2: 11.3  Patient adherence:  NR |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Choy et al., 200893 (continued) |  | Race, % black  NR  Ethnicity, % Latino  NR |  | EuroQol:  “No differences” at 6 mos  DAS28 disease activity, mean change:  G1: -1.14  G2: -1.81  DAS28 remission (< 2.6), %:  G1: 9  G2: 36  HAQ, mean change:  G1: -0.21  G2: -0.53 | Specific AEs  Death:  G1: 0.9  G2: 0.9  Malignancies:  G1: 4.3  G2: 0.0  Myocardial infarctions, angina, strokes:  G1: 0.9  G2: 1.7  Upper GI:  G1: 0.9  G2: 0.0  Infections  G1: 6.0  G2: 3.5  Transient creatine elevation:  G1: 4.3  G2: 3.5  **Tuberculosis:**  Overall: 0.4 |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Choy et al., 200893 (continued) |  |  |  |  | Pneumonia:  Overall: 0.6  Respiratory tract infection:  G1: 46.1  G2: 42.6  Nausea or vomiting:  G1: 12.8  G2: 17.4  Abdominal pain:  G1: 6.0  G2: 7.8  Mouth ulcer:  G1: 4.3  G2: 3.5  Headache:  G1: 5.1  G2: 8.7  Dizziness:  G1: 3.4  G2: 5.2 |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Choy et al., 200893 (continued) |  |  |  |  | Diarrhea:  G1: 4.3  G2: 8.7  Paresthesia:  G1: 2.6  G2: 6.9  Cough:  G1: 6.0  G2: 9.6  Elevated blood pressure:  G1: 0.8  G2: 6.9 |  |
| Author, yr, Study Name:  Conaghan et al., 201629  Country, Clinical Setting:  Multiple countries,  24 centers  Study Design:  RCT | Patients aged ≥18 with active RA (defined as >6 tender/painful joints and >6 swollen joints), ≤2 years duration, ESR >28 mm/h, or CRP >7 mg/L. | Interventions, dose:  G1: Tofacitinib 20 mg/d + MTX (starting at 10 mg/wk, max 20 mg/wk)  G2: Tofacitinib 20 mg/d + placebo  G3: MTX (starting at 10 mg/wk, max 20 mg/wk) + placebo  Tofacitinib: Administered orally as 2 5mg capsules, twice daily | Mean disease duration, yrs:  0.6-0.8  Baseline DAS, mean:  6.3-6.5  Baseline HAQ, mean:  1.5 | At 12 months  DAS28-4(ESR) ≤3.2 disease activity  G1: 58.8 (SE 8.4, p<0.001)  G2: 30.6 (SE 7.7)  G3: 18.9 (SE 6.4)  ACR20 response, %  G1: 82.9 (SE 6.4)  G2: 66.7 (SE 7.9)  G3: 56.8 (SE 8.1) | Overall:  G1: 69.4  G2: 86.1  G3: 81.1  SAEs  G1: 5.6  G2: 2.8  G3: 5.4 | Medium |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Conaghan et al., 201629  (continued)  Overall N:  109  Study Duration:  1 yr | Patients were generally MTX and biological DMARD naive | MTX: Starting at 10 mg/wk, to 15 mg/wk at end of month 1, and 20 mg/wk at end of month 2. Administered orally and titrated if tolerated  N:  G1: 36  G2: 36  G3: 37  Mean age, yrs:  47.8-50.8  Sex, % female:  82.6  Race, % white:  NR | MTX naïve, %:  94.5  Prior CS use, %  52.3  MTX inadequate responders:  0  Biologic non-responders:  0  Seropositive (%):  RF:  75.5  Anti-CCP:  79.4  Baseline Sharp score, mean:  12.6-13.7  Erosive disease, %:  100 | ACR50 response, %  G1: 65.7 (SE 8.0, p<0.01)  G2: 50.0 (SE 8.3)  G3: 35.1 (SE 7.8)  ACR70 response, %  G1: 28.6 (SE 7.6)  G2: 33.3 (SE 7.9)  G3: 24.3 (SE 7.1)  DAS28-4(ESR) <2.6 remission, %  G1: 35.3 (SE 8.2, p<0.05)  G2: 19.4 (SE 6.6)  G3: 13.5 (SE 5.6)  mTSS mean change from baseline  G1: 0.85 (SE 0.51)  G2: -0.15 (SE 0.52, p<0.05)  G3: 1.36 (SE 0.54)  HAQ-DI improvement vs. baseline ≥0.22  G1: 73.5 (SE 7.6)  G2: 72.2 (SE 7.5)  G3: 73.0 (SE 7.3)  SF-36  NR  At 6 months  DAS28-4(ESR) ≤3.2 disease activity  G1: 41.2 (SE 8.4)  G2: 27.8 (SE 7.5)  G3: 21.6 (SE 6.8) | Overall discontinuation  G1: 22.2  G2: 25.0  G3: 43.2  Discontinuation because of AEs  G1: 11.1  G2: 5.6  G3: 13.5  Patient adherence  NR  Rash  G1: 2.8  G2: 11.1  G3: 0.0  Headache  G1: 8.3  G2: 5.6  G3: 5.4  URTI  G1: 8.3  G2: 5.6  G3: 5.4  Bronchitis  G1: 8.3  G2: 0.0  G3: 0.0  Diarrhea  G1: 2.8  G2: 5.6  G3: 2.7 |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Conaghan et al., 201629  (continued) |  |  |  | ACR20 response, %  G1: 77.1 (SE 7.1, P <0.05)  G2: 72.2 (SE 7.5)  G3: 54.1 (8.2)  ACR50 response, %  G1: 57.1 (SE 8.4, p<0.01)  G2: 52.8 (SE 8.3, p<0.05)  G3: 27.0 (SE 7.3)  ACR70 response, %  G1: 34.3 (SE 8.0)  G2: 30.6 (SE 7.7)  G3: 24.3 (SE 7.1)  DAS28-4(ESR) <2.6, disease remission  G1: 29.4 (SE 7.8)  G2: 13.9 (SE 5.8)  G3: 13.5 (SE 5.6)  SHS, modification of total score, mean change from baseline  G1: 0.44 (SE 0.50)  G2: -0.14 (SE 0.51)  G3: 0.93 (SE 0.52)  HAQ-DI improvement vs. baseline ≥0.22  G1: 76.5 (SE 7.3)  G2: 75.0 (SE 7.2)  G3: 70.3 (SE 7.5) |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Conaghan et al., 201629  (continued) |  |  |  | SF-36  NR  At 3 months  DAS28-4(ESR) ≤3.2 disease activity  G1: 32.4 (SE 8.0)  G2: 30.6 (SE 7.7)  G3: 16.2 (SE 6.1)  ACR20 response, %  G1: 77.1 (SE 7.1)  G2: 66.7 (SE 7.9)  G3: 56.8 (SE 8.1)  ACR50 response, %  G1: 48.6 (SE 8.4)  G2: 55.6 (SE 8.3, p<0.05)  G3: 29.7 (SE 7.5)  ACR70 response, %  G1: 25.7 (SE 7.4)  G2: 27.8 (SE 7.5)  G3: 13.5 (SE 5.6)  DAS28-4(ESR) <2.6, disease remission  G1: 23.5 (SE 7.3)  G2: 2.8 (SE 2.7)  G3: 13.5 (SE 5.6)  SHS, modification of total score, mean change from baseline  NR |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Conaghan et al., 201629  (continued) |  |  |  | HAQ-DI improvement vs. baseline ≥0.22  G1: 73.5 (SE 7.6)  G2: 75.0 (SE 7.2)  G3: 81.1 (SE 6.4)  SF-36  NR |  |  |
| Author, yr, Study Name:  Cummins et al., 20155  Country, Clinical Setting:  Australia, Public teaching hospital  Study Design:  Observational (only single arm eligible)  Overall N:  181 (119 began triple therapy)  Study Duration:  104 wks median followup | Patients, referred by practitioners to the Early Arthritis Clinic (EAC), who met 1987 ACR criteria for RA with disease duration >2 yrs | Interventions, dose:  At diagnosis, patients were offered initial triple therapy:   * MTX, 10 mg/wk, up to 25 mg/wk max * SSZ 1 g b.i.d. (up titrated over 4 wks) * HCQ 200 mg b.i.d. (up titrated over 2 wks)   Details: According to the EAC’s response driven step-up protocol:  Every 4 wks increase MTX by 5 mg/wk as needed. If poor response after at least 4 mo, change to LEF, MTX (15 mg/wk) and HCQ (stop SSZ). If poor response after taking LEF for 3 mo, apply for bDMARD if meets criteria.  If intolerant to MTX, change MTX to LEF (in addition to SSZ and HCQ).  If intolerant to SSZ or HCQ, use 2 drugs for 3 mo then add LEF for 3 mo. | Median disease duration, mos (IQR):  6 mos (IQR, 4-10.5)  Baseline DAS, mean:  4.62 (SD, 1.37)  Baseline HAQ, median:  NR  MTX naive:  NR  MTX inadequate responders:  NR  Prior csDMARD use, %  NR  Prior CS use, %  NR  Biologic non-responders:  NR | N/A | Overall:  Of the 119 patients who commenced triple therapy, 23.5% remained on MTX, HCQ, and SSZ at last followup  SAEs  NR  Overall discontinuation  76  Discontinuation of first DMARD because of AEs  37.8  Patients who discontinued first DMARD due to non-adherence  4  Specific AEs  NA (specific AEs for head-to-head trials only) | N/A |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Cummins et al., 20155  (continued) |  | If multiple intolerances to MTC, LEF, SSZ or HCQ, use AZA/CYC/Gold for 3 mo. If poor response, apply for bDMARD if meets criteria.  N:  119  Mean age, yrs:  52.8 (SD, 13.1)  Sex, % female:  67.2  Race, % white:  NR | RF Seropositive (%):  74.8  Baseline Sharp score, mean:  NR  Erosive disease, %:  NR |  |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  de Jong et al., 20134  de Jong et al., 2014146  Kuijper, et al., 2016;147  De Jong et al., 2016148  tREACH  Country, Clinical Setting:  The Netherlands,  Clinical  Study Design:  RCT  Overall N:  515 randomized, 281 selected  Study Duration:  1 yr | Patients age ≥18 years, arthritis ≥1 joint(s) and symptom duration <1 year. Patients were not included if they were diagnosed with a crystal arthropathy, (post)infectious arthritis, or autoimmune disorder other than RA, were receiving DMARDs or corticosteroids, or had contraindications for initial study medication | Interventions, dose:  G1: MTX (25 mg/wk, dosage reached after 3 wks) + SSZ (2 g/d) + HCQ (400 mg/d) + GCs intramuscularly  G2: MTX (25 mg/wk, dosage reached after 3 wks) + SSZ (2 g/d) + HCQ 400 mg/d) + GC oral tapering scheme  G3: MTX (25 mg/wk, dosage reached after 3 wks) + GC oral tapering scheme  MTX: Doses delivered orally  GCs: Tapering scheme was 15 mg/d, wks 1-4; 10 mg/d, wks 5-6; 5 mg/d, wks 7-8; 2.5 mg/d wks 9-10)  For all groups: If DAS was ≥ 2.4, medication was intensified  N:  G1: 91  G2: 93  G3: 97  Mean age, yrs:  53.2  Sex, % female:  68  Race, % white:  NR | Median disease duration, mos:  166  Baseline DAS, mean:  3.36 (SD, 0.96)  Baseline HAQ, mean:  1.00 (SD, 0.66)  **Baseline EQ-5D, mean**  0.60 – 0.65  MTX naive:  NR  MTX inadequate responders:  NR  Biologic non-responders:  NR  RF-Seropositive (%):  81  Baseline Sharp score, median (IQR):  0 (IQR, 0-0)  Erosive disease, %:  17.1 | At 2 years  DAS sustained LDA (%)  G1 + G2: 80  G3: 78  ACR response, %  NR  DAS sustained remission, %  G1 + G2: 59  G3: 53  SHS  NR  HAQ  NR  EQ-5D  NR  SF-36  NR  At 1 year  DAS disease activity, mean  G1: 1.40 (SD, 0.68)  G2: 1.61 (SD, 0.87)  G3: 1.68 (SD, 0.89)  DAS disease activity, mean change from baseline  G1: -1.83 (SD, -1.03)  G2: -1.75 (SD, -1.14)  G3: -1.69 (SD, -1.27) | Overall, patients with ≥1 AE(s):  G1: 84  G2: 88  G3: 79  SAEs  G1: 5  G2: 11  G3: 10  Overall discontinuation  G1: 15  G2: 9.7  G3: 10.3  Discontinuation because of AEs  G1: 1.1  G2: 0.0  G3: 2.1  Patient adherence  At 1 yr, 1.1% of patients were listed under “protocol violations” for “no compliance”  Headache  G1: 11  G2: 14  G3: 13 | Medium |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  de Jong et al., 20134  de Jong et al., 2014146  Kuijper, et al., 2016;147  de Jong et al., 2016148  tREACH  (continued) |  |  |  | Good EULAR response, %  G1: 70  G2: 62  G3: 66  Moderate EULAR response, %  G1: 17  G2: 23  G3: 10  No EULAR response, %  G1: 13  G2: 15  G3: 24  DAS<1.6 remission, %  G1: 61  G2: 54  G3: 51  Change in total mTSS, median (IQR)  G1: 0.13 (IQR, 0-1)  G2: 0 (IQR, 0-1)  G3: 0 (IQR, 0-1)  HAQ mean, SD  G1: 0.38 (SD, 0.46)  G2: 0.51 (SD, 0.55)  G3: 0.63 (SD, 0.57)  HAQ mean change from baseline, SD  G1: -0.48 (SD, -0.63)  G2: -0.42 (SD, -0.59)  G3: -0.47 (SD, -0.53)  EQ-5D  G1: 0.80 (SD 0.12)  G2: 0.79 (SD 0.11)  G3: 0.77 (SD 0.17) |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  de Jong et al., 20134  de Jong et al., 2014146  Kuijper, et al., 2016;147  de Jong et al., 2016148  tREACH  (continued) |  |  |  | SF-36  NR  Paid work, %  G1: 79  G2: 76  G3: 65  Unemployed, %  G1: -2  G2: -8  G3: 11  G2 vs. G3: p=0.015  Working hrs/wk, median  G1: 32 (IQR 4-40)  G2: 24 (IQR 12-40)  G3: 25 (IQR 4-36)  Took sick leave, %  G1: 89  G2: 81  G3: 81  Took long-term sickness, %  G1: 19  G2: 9  G3: 30  Days absent, median  G1: 3 (IQR 1-8)  G2: 5 (IQR 2-11)  G3: 4 (IQR 1-8)  Occurrence of reduction in contract hours, %  G1: 32  G2: 38  G3: 39 |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  de Jong et al., 20134  de Jong et al., 2014146  Kuijper, et al., 2016;147  de Jong et al., 2016148  tREACH  (continued) |  |  |  | Decrease in contract hours, median  G1: 18 (IQR 4-37)  G2: 5 (IQR 1-11)  G3: 29 (IQR 10-36)  Occurrence of increase in contract hours, %  G1: 15  G2: 13  G3: 16  Increase in contract hours, median  G1: 8 (IQR 4-11)  G2: 10 (IQR 2-17)  G3: 10 (IQR 4-20)  Days of lost productivity, median  G1: 17 (IQR 3-100)  G2: 14 (IQR 4-51)  G3: 28 (IQR 4-179)  At 9 mos  DAS disease activity, mean (SD)  G1: 1.50 (SD 0.77)  G2: 1.63 (SD 0.89)  G3: 1.78 (SD 0.90)  **HAQ, mean (SD)**  G1: 0.51 (SD 0.59)  G2: 0.50 (SD 0.55)  G3: 0.67 (SD 0.63)  **EQ-5D mean, (SD)**  G1: 0.78 (SD 0.13)  G2: 0.78 (SD 0.15)  G3: 0.76 (SD 0.18) |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  de Jong et al., 20134  de Jong et al., 2014146  Kuijper, et al., 2016;147  de Jong et al., 2016148  tREACH  (continued) |  |  |  | **At 6 mos**  DAS disease activity, mean (SD)  G1: 1.74 (SD 0.94)  G2: 1.80 (SD 0.95)  G3: 2.02 (SD 0.91)  HAQ, mean (SD)  G1: 0.45 (SD 0.53)  G2: 0.53 (SD 0.56)  G3: 0.69 (SD 0.55)  **EQ-5D mean, (SD)**  G1: 0.77 (SD 0.16)  G2: 0.76 (SD 0.17)  G3: 0.74 (SD 0.16)  At 3 mos  DAS disease activity, mean  G1: 1.86 (SD, 0.96)  G2: 1.82 (SD, 0.86)  G3: 2.21 (SD, 1.04)  G1 vs. G3: p=0.021  G2 vs. G3: p=0.007  DAS disease activity, mean change from baseline  G1: -1.39 (SD, 1.0)  G2: -1.54 (SD, 0.98)  G3: -1.19 (SD, 1.02)  Good EULAR response, %  G1: 53  G2: 48  G3: 43  Moderate EULAR response, %  G1: 27  G2: 34  G3: 26 |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  de Jong et al., 20134  de Jong et al., 2014146  Kuijper, et al., 2016;147  de Jong et al., 2016148  tREACH  (continued) |  |  |  | No EULAR response, %  G1: 20  G2: 18  G3: 31 |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  de Jong et al., 20134  de Jong et al., 2014146  Kuijper, et al., 2016;147  de Jong et al., 2016148  tREACH  (continued) |  |  |  | DAS<1.6 remission, %  G1: 44  G2: 43  G3: 31  SHS  NR  HAQ mean, SD  G1: 0.51 (SD, 0.54)  G2: 0.52 (SD, 0.55)  G3: 0.68 (SD, 0.64)  HAQ mean change from baseline, SD  G1: -0.41 (SD, 0.50)  G2: -0.40 (SD, 0.53)  G3: -0.37 (SD, 0.57)  EQ-5D  G1: 0.75 (SD 0.18)  G2: 0.76 (SD 0.16)  G3: 0.73 (SD 0.17)  SF-36  NR |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr:  den Uyl et al., 201425; ter Wee et al., 2015105;  COBRA-light study  Country, Setting:  Netherlands  multicenter  Study Design:  RCT  Overall N:  164  Study Duration:  1 yr (and 1 yr followup) | Adults aged ≥18 yrs, fulfilling ACR criteria for RA with disease duration < 2 yrs; active disease defined as ≥ 6 swollen and tender joints and ESR of ≥28 mm/h or a global health score of ≥20 mm on a 0-100 mm VAS. All patients were glucocorticoid (GC) or DMARD naïve (other than antimalarials)  More exclusion criteria: uncontrolled diabetes mellitus, heart failure, uncontrolled hypertension, ALT or AST level >3x the upper limit of normal, reduced renal function, | Interventions, dose:  G1: COBRA   * PNL: 60 mg/d, tapered to 7.5 mg/d in 6 wks * MTX: 7.5 mg/wk * SSZ: 1 g/d, increased to 2 g/d after 1 wk * ETN intensification required for patients who did not reach DAS <1.6 at wk 26 or 39: 50 mg/wk subcutaneously   G2: COBRA-Lite   * PNL, 30 mg/d tapered to 7.5 mg/d in 9 wks * MTX, 10 mg/d with stepwise increments in all patients to 25 mg/wk in 9 wks * ETN intensification required for patients who did not reach DAS <1.6 at wk 26 or 39: patients received ETN until wk 52   Details:  Concomitant treatment with NSAIDs and intra-articular injections with GCs were permitted | Median disease duration, mos (IQR):  16 wks (IQR: 8-30)  Baseline DAS, mean:  3.95-4.13  Baseline DAS28, mean:  5.45-5.67  Baseline HAQ, mean:  1.36-1.37  MTX naive:  100  MTX inadequate responders:  NR  Prior csDMARD use (%):  NR  Prior CS use, %:  NR  RF Seropositive (%):  58 | At 1 yr  DAS score, mean (SD)  G1: 1.70 (SD, 1.0)  G2: 1.88 (SD, 1.0)  B (95% CI): 0.19 (CI -0.07 to 0.45)  p=0.15  DAS28 score, mean (SD)  G1: 2.49 (SD, 1.3)  G2: 2.71 (SD, 1.3)  B (95% CI): 0.24 (−0.08 to 0.57)  p=0.15  Change in DAS, mean (SD)  G1: -2.41 (SD, 1.2)  G2: -2.02 (SD, 1.1)  B (95% CI): 0.21 (CI -0.09 to 0.52)  p=0.17  ACR20, but not ACR50, %  G1: 15  G2: 18  ACR50, but not ACR70, %  G1: 25  G2: 17  ACR70 response, %  G1: 31  G2: 35 | At 52 wks  Overall, ≥1 AE  G1: 96  G2: 96  SAEs  G1: 11.1  G2: 19.8  Overall discontinuation  G1: 3.7  G2: 4.9  Discontinuation because of AEs  NR  Patients with ≥1 protocol violation /deviation  G1: 60.5  G2: 58.0  Patients with ≥1 major protocol violation  G1: 58.0  G2: 40.7 | Medium |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr:  den Uyl et al., 201425; ter Wee et al., 2015105;  COBRA-light study  (continued) | Contraindi-cations for GCs and a positive tuberculin skin test | PNL:  G1:   * wk 1, 60 mg/d * wk 2, 40 mg/d * wk 3, 30 mg/d * wk 4, 20 mg/d * wk 5, 15 mg/d * wk 6, 10 mg/d * wk 7-28 7.5 mg/d   Total: 2327.5 mg  G2:   * wk 1, 30 mg/d * wk 2, 20 mg/d * wk 3, 15 mg/d * wk 4-8, 10 mg/d * wk 9-28, 7.5 mg/d   Total: 2012.5 mg  MTX  G1:   * wk 2: 7.5 mg/wk   G2:   * wk 2-4: 10 mg/wk * wk 5-8: 17.5 mg/wk * wk 9-26: 25 mg/wk   Note: If DAS was >1.6 after 13 wks, in G1, protocol required increase of MTX dose to 25 mg/wk; in G2, physician was required to consider parenteral MTX  SSZ:  G1:   * wk 2: 1000 mg/d * wk 3-26: 2000 mg/d   G2: NA | Anti-CCP Seropositive (%):  62-66  Baseline Sharp score, mean:  1.61-2.66  Erosive disease, %:  10-17 | ACR Non-Responders, %  G1: 23  G2: 25  OR: 1.03 (0.71 to 1.49)  p=0.73  DAS clinical remission (DAS <1.6), %  G1: 47  G2: 38  RR: 0.85 (0.64 to 1.13)  p=0.18  ACR/Boolean remission, %  G1: 15  G2: 17  RR: 1.03 (0.90 to 1.18)  p=0.67  Mean change in SHS  G1: 0.49 (SD, 1.6)  G2: 0.59 (SD, 1.4)  B (95% CI): 0.18 (−0.27 to 0.63)  p=0.42  HAQ, mean  G1: 0.57 (SD, 0.5)  G2: 0.61 (SD, 0.6)  B (95% CI): 0.07 (−0.08 to 0.21)  p=0.35  SF-36  NR | Specific AEs  Leukopenia  G1: 1  G2: 4  At 26 wks  Overall, ≥1 AE  G1: 94  G2: 90  SAEs  G1: 3.7  G2: 7.4  Overall discontinuation  G1: 1.2  G2: 1.2  Discontinuation due to AEs  G1: 1.2  G2: 1.2  Protocol violations  G1: 24  G2: 7  Major protocol violations  G1: 7.4  G2: 2.5  Specific AEs  AEs are listed, but categories are too broad to determine specifics (i.e. “skin problems” but not rash) |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr:  den Uyl et al., 201425; ter Wee et al., 2015105;  COBRA-light study  (continued) |  | ETN:  In both groups, ETN use stopped at 52 wks  N:  Baseline:  G1: 81  G2: 81  Followup:  G1: 80  G2: 80  Mean age, yrs:  51-53  Sex, % female:  67-70  Race, % white:  NR |  | At 26 wks  DAS score, mean (SD)  G1: 1.62 (SD, 0.96)  G2: 1.78 (SD, 1.13)  Change in DAS, mean (SD)  G1: -2.50 (SD, 1.12)  G2: -2.18 (SD, 1.10)  G1 vs. G2: 0.21 (95% CI -0.11 to 0.53)  ACR 20 response, %  G1: 74  G2: 72  ACR50 response %  G1: 57  G2:62  ACR70 response, %  G1: 38  G2: 49  Good EULAR response, %  G1: 75  G2: 65  Fulfilled EULAR Non-Response Criteria, %  G1: 6  G2: 11  “Minimal disease activity” (DAS <1.6), %  G1: 49  G2: 41 p=NS, NR |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr:  den Uyl et al., 201425; ter Wee et al., 2015105;  COBRA-light study  (continued) |  |  |  | Remission “according to ACR/ELUAR Boolean remission criteria,” %  G1: 16  G2: 20  SHS or Larsen score  NR  HAQ, mean change from baseline  G1: -0.8 (SD, 0.6)  G2: 0.8 (SD, 0.7)  95% CI (adjusted): 0.1 (CI -0.1 to 0.2)  p=0.49  SF-36  NR |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Detert, 201334  HIT HARD  Country, Clinical Setting:  Germany,  Private practice, hospitals, university departments  Study Design:  RCT  Overall N:  172  Study Duration:  48 wks, (open label 24-48 wks) | Patients aged 18-75 meeting ACR criteria for RA with disease duration of up to 1 year. Included patients had ≥6 of 66 joints swollen, ≥6 of 68 tender, morning stiffness lasting ≥30 minutes, and ESR of ≥28 mm/h or CRP concentration of ≥1.0 mg/dl. All DMARD and biologic naïve. | Interventions, dose:  G1: ADA 40 mg subcutaneously every other wk for 24 wks + open label subcutaneous MTX (15 mg/wk)  G2: Placebo subcutaneously every other wk for 24 wks + open label subcutaneous MTX (15 mg/wk)  MTX: Administration of ADA and placebo were discontinued after wk 24, and MTX open-label monotherapy continued until wk 48  N:  G1: 87  G2: 85  Mean age, yrs:  47.2-52.5  Sex, % female:  68.6  Race, % white:  NR | Median disease duration, mos:  1.6-1.8  Baseline DAS28, mean:  6.2-6.3  Baseline HAQ-DI score, 1-3 scale, mean:  1.3-1.4  MTX naïve, %:  100  MTX inadequate responders:  0  Biologic non-responders:  0  Seropositive (RF or CCP) (%):  66.3  Baseline Sharp score, mean:  6.3-11.4  Erosive disease, %:  SHS erosion score, 0-280 scale, mean  2.2-4-4 | At 48 wks  DAS disease activity  G1: 3.2 (SD, 1.4)  G2: 3.4 (SD, 1.6, p=0.41)  ACR20 response, %  G1: 66.0  G2: 74.9 (p=0.21)  ACR50 response, %  G1: 52.6  G2: 51.4 (p=0.88)  ACR70 response, %  G1: 40.5  G2: 34.0 (p=0.40)  DAS remission, %  G1: 42.4  G2: 36.8 (p=0.47)  SHS score  G1: 2.6  G2: 6.4 (p=0.01)  HAQ-DI, mean  G1: 0.61 (SD, 0.6)  G2: 0.66 (SD, 0.6, p=0.40)  SF-36, mean score  Mental  G1: 50.0 (SD, 9.6)  G2: 47.9 (SD, 9.6, p=0.37))  Physical  G1: 41.4 (SD, 12.4)  G2: 42.0 (SD, 10.3, p=0.79) | Overall:  G1: NR  G2: NR  SAEs  G1: 13.7  G2: 19.5  Overall discontinuation  G1: 12.6  G2: 32.9  Discontinuation because of AEs  G1: 4  G2: 7  Patient adherence  G1: 87.4  G2: 67.1  Specific AEs here  G1: NR  G2: NR | Medium (DAS28, ACR response, HAQ-DI, SF-36, attrition);  High (mTSS, SHS erosion score) |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| **Author, yr, Study Name:**  Detert, 201334  HIT HARD  (continued) |  |  |  | At 24 wks  DAS disease activity  G1: 3.0 (SD, 1.2)  G2: 3.6 (SD, 1.4, p=0.009)  ACR20 response, %  G1: 79.0  G2: 67.6 (p=0.10)  ACR50 response, %  G1: 63.8  G2: 48.7 (p=0.049)  ACR70 response, %  G1: 48.0  G2: 26.8 (p=0.006)  DAS remission, %  G1: 47.9  G2: 29.5 (p=0.021)  SHS score  G1: Figure only  G2: Figure only  HAQ-DI, mean  G1: 0.49 (SD, 0.6)  G2: 0.72 (SD, 0.6, p=0.0014)  SF-36, mean score  Mental  G1: 48.8 (SD, 9.8)  G2: 48.9 (SD, 8.8, p=0.51)  Physical  G1: 44.0 (SD, 11.1)  G2: 39.8 (SD, 9.9, p=0.0002) |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr:  Dougados et al., 1999;21  Maillefert et al., 2003104  Country, Setting:  Finland, France, Germany (France only for 5 yr), multicenter  Study Design:  RCT  Overall N:  209  Study Duration:  5 years | Patients meeting 1987 ACR criteria for RA with disease duration <1 yr, who were corticosteroid and DMARD-naïve | Interventions, dose:  G1: SSZ + placebo  G2: MTX + placebo  G3: SSZ + MTX  MTX: 7.5 mg wkly (2.5 mg 3 times per wk). After wk 16, could be increased to 15 mg wkly if efficacy inadequate  SSZ: increased to 2 grams daily by day 9. Could be increased to 3 grams daily after wk 16 of study if efficacy was inadequate  SSZ + MTX: same regiments for each drug as described above  N:  D1: 68  D2: 69  D3: 72  Mean age, yrs:  50-52  Sex, % female:  71-77  Race, % white:  NR | Mean disease duration:  G1: 2.9 mos  G2: 2.3 mos  G3: 3.4 mos  Prior csDMARD use, %:  0  Prior CS use, %:  0  MTX naive, %:  100  Baseline DAS, mean:  4.13-4.24  Baseline HAQ, mean:  1.25-1.38  MTX inadequate responders:  0  Biologic non-responders:  0  Seropositive (RF or CCP) (%):  RF+: 62-75  Baseline Sharp total damage score, mean:  6.11-8.91 | At 1 year  Mean DAS change:  G1: -1.15  G2: -0.87  G3: -1.26 (p=0.019 from inter-group comparisons using analysis of variance)  ACR20 response, %:  G1:59  G2:59  G3:65 (p=NR)  Mean change from baseline in SHS erosion score  G1: 2.38  G2: 2.38  G3: 1.85 (p=NS)  Mean change from baseline mTSS  G1: 4.64  G2: 4.50  G3: 3.46 (p=NS)  Any detectable radiological progression in SHS erosion score, %  G1: 13  G2: 10  G3: 7 (p=NS)  Any detectable radiological progression in mTSS, %  G1: 14  G2: 16  G3: 9 (p=NS) | Overall:  G1: 75  G2: 75  G3: 91 (p=0.025)  SAEs  G1: 0  G2: 2  G3: 1  Overall discontinuation  At 1 year  G1: 30.9  G2: 21.7  G3: 29.2  Discontinuation because of AEs  G1: 14.7  G2: 10.1  G3: 12.5  Patient adherence  NR  Nausea  G1: 32  G2: 23  G3: 49 (p=0.007)  Erythema  G1: 4.4  G2: 0  G3: 0 (p=0.047)  Increased AST  G1: 0  G2: 4.3  G3: 0 (p=0.05) | Medium |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr:  Dougados et al., 1999;21  Maillefert et al., 2003104  (continued) |  |  | Baseline Sharp total radiological score, median:  0 (0-3)  Erosive disease, %:  NR | At 5 years  Txt of pts with early RA with combination therapy of MTX and SSZ during first yr did not result in any long term differences in disease activity, quality of life, or structural damage compared with monotherapy with either drug used alone  Mean DAS (SD):  G1 or G2:2.2 (1.1)  G3:2.2 (1)  Overall: (p=0.9)  Mean HAQ (SD):  G1 or G2:0.6 (0.6)  G3:0.6 (0.7)  Overall: (p=0.9)  Median mTSS (IQR)  G1 or G2: 8.5 (1.5-17.2)  G3: 7.5 (1.1-27.3) (p=0.7) |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Durez et al., 2007;18  Country, Clinical Setting:  Belgium, hospitals  Study Design:  RCT  Overall N:  44  Study Duration:  1 yr | Patients fulfilling ACR criteria for RA < 1 yr, ≥ 6 swollen joint count, and ≥ 8 tender joint count, no prior MTX or methyl-PNL use or prior treatment with >2 DMARDs, prior treatment with glucocorticoids < 3 mos (and not during 1 mo prior to study) | Interventions, dose:  G1:   * IFX: 3 mg/kg at wks 0, 2, 6 and then every 8 wks until wk 46 (intravenous) * MTX: initiated 7.5 mg/wk, increased to max 20 mg/wk by wk 14   G2:   * Methyl-PNL: 1 gm at wks 0, 2, 6 and then every 8 wks until wk 46 (intravenous) * MTX: initiated 7.5 mg/wk, increased to max 20 mg/wk by wk 14   G3:   * MTX: initiated 7.5 mg/wk, increased to max 20 mg/wk by wk 14   IFX and methyl-PNL stopped after 1 yr as patients continued MTX treatment only  N:  G1: 15  G2: 15  G3: 14  Mean age, yrs:  G1: 50.0 (SD 9.9)  G2: 50.3 (SD 14.2)  G3: 53.8 (SD 15.2)  Sex, % female:  G1: 67  G2: 60  G3: 71  Race, % white:  NR | Mean disease duration, yrs:  G1: 0.36 (SD 0.31)  G2: 0.25 (SD 0.33)  G3: 0.45 (SD 0.29)  DAS28-CRP, mean:  G1: 5.3 (SD 1.1)  G2: 5.3 (SD 1.3)  G3: 5.2 (SD 0.8)  HAQ, mean:  G1: 1.5 (SD 0.8)  G2: 1.2 (SD 0.7)  G3: 1.3 (SD 0.6)  MTX naïve, %:  100  MTX inadequate responders, %:  NA  Biologic non-responders, %:  NR  RF seropositive, %:  G1: 67  G2: 100  G3: 64  Sharp score, mean:  NR  Radiographic evidence of erosions, %:  G1: 13  G2: 33  G3: 36 | At 1 yr  **DAS28-CRP disease activity, mean:**  G1: 2.79 (SD 0.77)  G2: 2.77 (SD 1.09)  G3: 3.26 (SD 1.31)  Significant within group improvement (G1: P < 0.0001, G2: P < 0.0001, G3: P = 0.005); no between-group differences  **ACR20 response, %:**  See ACR70 response below  **ACR50 response, %:**  See ACR70 response below  **ACR70 response, %:**  “A similar trend [improvement] was observed at week 52 (Figure 4B) but without statistically significant differences between groups (as determined by Fisher’s exact test)”  **DAS remission, %:**  G1/2: 70  G3: 40  **Sharp score, mean:**  NR; primary outcomes were MRI based  **HAQ, mean:**  “HAQ scores improved significantly over time in the IV Methyl-PNL (G2) and IFX group (G1) (P < 0.001 by Friedman’s test), with patients receiving IV Methyl-PNL experiencing significantly more improvement | Overall AEs (n):  G1: 15  G2: 15  G3: 19  SAEs:  G1: 0.0  G2: 0.0  G3: 6.7  Overall discontinuation:  G1: 6.7  G2: 6.7  G3: 14.3  Discontinuation due to AEs:  G1: 6.7  G2: 0.0  G3: 0.0  Discontinuation due to lack of efficacy:  G1: 0.0  G2: 6.7  G3: 0.0  Patient adherence:  NR  Specific AEs:  Benign infection (n)  G1: 80.0 (12)  G2: 80.0 (12)  G3: 93.3 (14)  Mild hepatotoxicity (n)  G1: 14.3 (2)  G2: 20.0 (3)  G3: 33.5 (5) | Medium |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Durez et al., 2007;18  (continued) |  | Race, % black:  NR  Ethnicity, % Latino:  NR |  | compared with patients receiving MTX…from baseline to week 52 (P = 0.019, respectively, by Mann-Whitney U test) (Figure 4C)”  **SF-36:**  NR  At 22 wks  **DAS28-CRP disease activity, mean:**  G1: 5.57 (SD 1.03)  G2: 5.39 (SD 1.22)  G3: 4.85 (SD 0.96)  No between group differences at wk 22 or another intermediate timepoint (unclear)  **ACR20 response, %:**  See ACR70 response below  **ACR50 response, %:**  See ACR70 response below  **ACR70 response, %:**  “Clinical responses assessed by the ACR 20% improvement criteria (ACR20), the ACR50, and the ACR70 at week 22 were significantly better in the IV Methyl-PNL and IFX groups compared with the MTX group (Figure 4A)” |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Durez et al., 2007;18  (continued) |  |  |  | HAQ, mean:  “HAQ scores improved significantly over time in the IV Methyl-PNL (G2) and IFX group (G1) (P < 0.001 by Friedman’s test), with patients receiving IV Methyl-PNL experiencing significantly more improvement compared with patients receiving MTX from baseline to week 22… (P = 0.006…by Mann-Whitney U test) (Figure 4C)” |  |  |
| Author, yr, Study Name:  Emery et al., 200812;  Anis et al., 2009154;  Emery et al., 2010108;  Kekow et al., 2010109;  Dougados et al., 2014156;  Zhang et al., 2012155  COMET | Adults (aged ≥ 18 yrs) with diagnosis of adult-onset RA per ACR criteria; disease duration 3-24 mos, DAS28 ≥ 3.2; either Westergren ESR ≥ 28 mm/h or CRP ≥ 20 mg/L; no | Interventions, dose:  G1:   * MTX: 7.5 mg/wk (oral); dose was titrated up over 8 wks to a max of 20 mg/wk for those with tender or swollen joints * ETN: 50 mg/wk (subcutaneous)   G1a: Continue MTX + ETN in yr 2  G1b: Switch to ETN only in yr 2 | Mean disease duration, mos:  9.0 (SE 0.3)  Baseline DAS28, mean:  6.5 (SD, 1.0)  Baseline HAQ, mean:  1.7 (SD, 0.7)  Prior CS use, %:  49.1 | At yr 2  DAS28 disease activity, change in mean from yr 1:  G1a: 0.00  G1b: 0.5 (p<0.05 vs. G1a)  G2a: -0.5 (p<0.001 vs. G2b)  G2b: 0.1  ACR 20 response, %:  G1a: 86 (p<0.001 vs. G2b)  G1b: 80  G2a: 81 (p=0.004, vs. G2b)  G2b: 61 | Overall AEs:  yr 1  G1: 89.8  G2: 89.9  yr 2  G1a: 82.0  G1b: 80.2  G2a: 78.9  G2b: 78.8  SAEs:  yr 1  G1: 12.0  G2: 12.7 | Medium |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Emery et al., 200812;  Anis et al., 2009154;  Emery et al., 2010108;  Kekow et al., 2010109;  Dougados et al., 2014156;  Zhang et al., 2012155  COMET  (continued)  Country, Clinical Setting:  Multinational,  Study design  RCT  Overall N  542  Duration of study  2 yrs | prior MTX, ETN, or other TNF antagonist use; and no treatment with DMARDs or corticosteroid injections 1 mo prior to baseline visit | G2:   * MTX: 7.5 mg/wk (oral); dose was titrated up over 8 wks to a max of 20 mg/wk for those with tender or swollen joints * Placebo   G2a: Switch to MTX + ETN (50 mg/wk subcutaneous) in yr 2  G2b: Continue MTX only in yr 2  N:  G1: 274 (a: 111, b: 111)  G2: 268 (a: 90, b: 99)  Mean age, yrs:  51.4 (SD, 0.6)  Sex, % female:  73.3  Race, % white  87.7  Race, % black  NR  Ethnicity, % Latino  NR | Prior csDMARD use, %:  20.8  MTX naïve, %  100  MTX inadequate responders:  NR  Biologic non-responders:  NR  anti-CCP seropositive, %:  66.9  Baseline Sharp score, mean:  NR  Erosive disease, %:  NR | ACR50 response, %:  G1a: 70 (p<0.001 vs. G2b)  G1b: 64  G2a: 66 (p=0.007 vs. G2b)  G2b: 46  ACR70 response, %:  G1a: 57 (p<0.001 vs. G2b)  G1b: 44  G2a: 48 (p=0.034 vs. G2b)  G2b: 32  DAS28 remission (< 2.6), %:  G1a: 57.4 (of 108, p=0.002 vs. G2b)  G1b: 50.0 (of 108)  G2a: 58.0 (of 88, p=0.003 vs. G2b)  G2b: 35.1 (of 94)  **mTSS score**  Change from yr 1, mean:  G1a: -0.02 (95% CI, -0.32 to 0.29;p=0.006 vs. G1b)  G1b: 0.11 (95% CI, -0.54 to 0.77)  G2a: 0.78 (95% CI, -0.06 to 1.61)  G2b: 2.07 (95% CI, 0.42 to 3.72)  No radiographic progression (change ≤ 0.5), %:  G1a: 89.9 (of 99, p=0.008 vs. G1b, p=0.009 vs. G2a, p<0.001 vs. G2b)  G1b: 74.7 (of 99)  G2a: 74.7 (of 79)  G2b: 67.5 (of 83) | yr 2  G1a: 7.2  G1b: 9.0  G2a: 12.2  G2b: 12.1  Overall discontinuation:  yr 1  G1: 19.3  G2: 29.5  yr 2  G1a: 6.3  G1b: 16.2  G2a: 17.8  G2b: 23.2  Discontinuation due to AEs:  yr 1  G1: 10.2  G2: 12.7  yr 2  G1a: 2.7  G1b: 4.5  G2a: 7.8  G2b: 9.1  Discontinuation due to lack of efficacy:  Yr 1  G1: 3.3  G2: 9.0  Yr 2  G1a: 0.0  G1b: 6.3  G2a: 1.1  G2b: 7.1 |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Emery et al., 200812;  Anis et al., 2009154;  Emery et al., 2010108;  Kekow et al., 2010109;  Dougados et al., 2014156;  Zhang et al., 2012155  COMET  (continued) |  |  |  | HAQ-DI:  Mean change from yr 1:  G1a: Not significant/NR  G1b: Not significant/NR  G2a: 0.17 (SD, 0.42, p=0.0007)  G2b: Not significant/NR  Response (≤ 0.5), %:  G1a: 62 (p=0.011 vs. G2b)  G1b: NR  G2a: NR  G2b: 44  SF-36:  NR  At yr 1  DAS28 LDA (≤3.2), %:  G1: 64.2 (of 265, 95% CI, 58 to 70)  G2: 41.4 (of 263, 95% CI, 35 to 47)  p<0.0001  DAS LDA (≤2.4), %:  G1: 73.2 (of 265, 95% CI, 67 to 79)  G2: 48.7 (of 263, 95% CI, 43 to 55)  p<0.0001  ACR 20 response, %:  G1: 85.9 (of 256, 95% CI, 82 to 90)  G2: 67.1 (of 243, 95% CI, 61 to 73)  p<0.0001  ACR50 response, %:  G1: 70.7 (of 256, 95% CI, 66 to 76)  G2: 49.0 (of 243, 95% CI, 43 to 55)  p<0.0001 | Patient adherence:  NR  Specific AEs:  Death  yr 2  G1: 0.4  G2: 0.0  yr 2  G1a: 0.0  G1b: 0.0  G2a: 0.0  G2b: 1.0  Malignancies  yr 1  G1: 1.5 (leukemia [1], skin cancer [3])  G2: 1.5 (breast cancer [3], prostate cancer [1])  yr 2  G1a: 0.0  G1b: 0.9 (basal cell cancer)  G2a: 5.6 (GI cancer, bladder cancer, rectal melanoma, prostate cancer, basal cell cancer)  G2b: 3.0 (pancreatic cancer, cancer of the chest wall and lungs, basal cell cancer)  Serious infections:  yr 1  G1: 1.8  G2: 3.0 |  |

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| Author, yr, Study Name:  Emery et al., 200812;  Anis et al., 2009154;  Emery et al., 2010108;  Kekow et al., 2010109;  Dougados et al., 2014156;  Zhang et al., 2012155  COMET  (continued) |  |  |  | ACR70 response, %:  G1: 48.4 (of 256, 95% CI, 41 to 55)  G2: 28.4 (of 243, 95% CI, 22 to 34)  p<0.0001  DAS28 remission (< 2.6), %:  G1: 49.8 (of 265, 95% CI, 44 to 56)  G2: 27.8 (of 263, 95% CI, 23 to 33)  p<0.0001  DAS remission (< 1.6), %:  G1: 51.3 (of 265, 95% CI, 45 to 57)  G2: 27.8 (of 263, 95% CI, 23 to 33)  p<0.0001  mTSS score  Change from baseline, mean:  G1: 0.27 (95% CI, -0.13 to 0.68)  G2: 2.44 (95% CI, 1.45 to 3.43)  No radiographic progression (change ≤ 0.5), %:  G1: 79.7 (of 246, 95% CI, 75 to 85)  G2: 58.7 (of 230, 95% CI, 53 to 65)  p<0.0001  HAQ, mean change:  G1: -1.02  G2: -0.72  p<0.0001  Normal function (HAQ-DI <0.5), %  G1: 55  G2: 39 (p=0.0004)  SF-36  Mental component, mean change:  G1: 6.8  G2: 6.1 (p=NS) | yr 2  G1a: 0.9  G1b: 1.8  G2a: 1.1  G2b: 2.0  Cardiovascular events, n:  yr 1  G1: 2  G2: 2  yr 2  NR  Hepatotoxicity/ elevated liver enzymes, n:  yr 1  G1: 0  G2: 3  Respiratory events  yr 1  Tuberculosis:  G1: 0.0  G2: 0.0  Pneumonia, n:  G1: 1  G2: 1  Upper respiratory infection, n:  G1: 45  G2: 44 |  |

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| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Emery et al., 200812;  Anis et al., 2009154;  Emery et al., 2010108;  Kekow et al., 2010109;  Dougados et al., 2014156;  Zhang et al., 2012155  COMET  (continued) |  |  |  | Physical component, mean change:  G1: 13.7  G2: 10.7  p=0.003  Stopped working at least once, %:  G1: 8.6 (of 105)  G2: 24.0 (of 100)  p=0.004  Absenteeism  Missed workdays, mean:  G1: 14.2  G2: 31.9 | yr 2  Tuberculosis:  G1a: 0.0  G1b: 0.0  G2a: 0.0  G2b: 0.0  yr 1  Nausea or vomiting, n:  G1: 53  G2: 50  Not specified, n:  G1: 1  G2: 4  yr 2  NR  Infusion/injection site reactions, n:  yr 1  G1: 1  G2: 2  yr 2  NR  Demyelination or multiple sclerosis:  yr 1  G1: 0.0  G2: 0.0  yr 2  G1a: 0.0  G1b: 0.0  G2a: 0.0  G2b: 0.0 |  |

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| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Emery et al., 200812;  Anis et al., 2009154;  Emery et al., 2010108;  Kekow et al., 2010109;  Dougados et al., 2014156;  Zhang et al., 2012155  COMET  (continued) |  |  |  |  | Worsening of RA, n:  yr 1  G1: 2  G2: 5  yr 2  NR  Cholelithiasis, n:  yr 1  G1: 2  G2: 0  yr 2  NR  Intervertebral disc protrusion, n:  yr 1  G1: 2  G2: 0  yr 2  NR  Osteoarthritis, n:  yr 1  G1: 0  G2: 2  yr 2  NR  Any other AEs:  Yr 1  Interstitial lung disease (2 incombined-treatment group) and hip arthroplasty (2 in MTX group).  yr 2  NR |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Emery et al., 20157  AVERT  Country, Clinical Setting:  Multinational  Study Design:  RCT  Overall N:  351  Study Duration:  2 yrs | Adults (aged ≥ 18 yrs) with persistent symptoms for ≤ 2 yrs, active clinical synovitis of ≥ 2 joints for ≥ 8 wks, DAS (CRP) ≥ 3.2, and anti-CCP-2 antibody positivity; patients were either MTX-naïve at study entry or had previous exposure of ≤ 10 mg/wk for ≤ 4 wks but not within 1 mo prior to enrollment | Interventions, dose:  G1:   * ABA: 125 mg/wk (subcutaneous) * MTX: 7.5 mg/wk, titrated to 15-20 mg/wk within 6-8 wks * Folic acid   G2:   * ABA: 125 mg/wk (subcutaneous) * Folic acid   G3:   * MTX: 7.5 mg/wk, titrated to 15-20 mg/wk within 6-8 wks * Folic acid   N:  G1: 119  G2: 116  G3: 116  Mean age, yrs:  47.0 (SD, 12.6) | Mean disease duration, yrs:  0.56  Baseline DAS28 (CRP), mean:  5.4  Baseline HAQ-DI, mean:  1.4  MTX naïve, %:  NR  MTX inadequate responders, %:  NR  Biologic non-responders, %:  NR  RF seropositive, %:  95.2 | At 1.5 yrs  (6 mos after withdrawal)  DAS28 (CRP) disease activity:  NR  ACR20 response, %:  G1: 21.8  G2: 16.4  G3: 15.5  ACR50 response, %:  G1: 16.0  G2: 14.7  G3: 9.5  ACR70 response, %:  G1: 9.2  G2: 10.3  G3: 6.0  DAS28 (CRP) remission (< 2.6), %:  G1: 14.8 (of 115)  G2: 12.4 (of 113)  G3: 7.8 (of 115) | 12month Overall AEs:  G1: 84.9  G2: 80.2  G3: 82.8  SAEs:  G1: 6.7  G2: 12.1  G3: 7.8  Overall discontinuation:  G1: 13.4  G2: 21.6  G3: 17.2  Discontinuation because of AEs:  G1: 4.2  G2: 6.9  G3: 4.3  Discontinuation because of SAEs:  G1: 1.7  G2: 4.3  G3: 2.6 | Medium |

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| Author, yr, Study Name:  Emery et al., 20157  AVERT  (continued) |  | Sex, % female:  77.8  Race, % white:  84.6  Race, % black:  NR  Ethnicity, % Latino:  NR | anti-CCP-2 positive, %:  100  Baseline Sharp score, mean:  NR  Erosive disease, %:  NR | Sharp score:  NR  HAQ-DI response (≥ 0.3), %:  G1: 21.8  G2: 16.4  G3: 10.3  SF-36:  NR  At 1 yr (before withdrawing treatment)  DAS28 (CRP) disease activity:  Difference in change from baseline  G1 vs. G3: -0.52 (95% CI, -0.74 to -0.30)  G2 vs. G3: -0.26 (95% CI, -0.11 to -0.48)  ACR20 response, %:  G1: 74.8  G2: 63.8  G3: 65.5  ACR50 response, %:  G1: 63.0  G2: 53.4  G3: 46.6 | Discontinuation due to lack of efficacy:  G1: 4.3  G2: 5.2  G3: 9.5  Patient adherence:  NR  Specific AEs at 12mo:  Death  G1: 0.0  G2: 0.0  G3: 0.0  2 died during withdrawal phase in G3: uterine neoplasm, renal failure  Serious infection  G1: 0.8  G2: 3.4  G3: 0.0 |  |

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| Author, yr, Study Name:  Emery et al., 20157  AVERT  (continued) |  |  |  | ACR70 response, %:  G1: 52.1  G2: 38.8  G3: 34.5  DAS28 (CRP) remission (< 2.6), %:  G1: 60.9 (of 115)  G2: 42.5 (of 113)  G3: 45.2 (of 115)  p=0.01 for G1>G3  HAQ-DI response (≥ 0.3), %:  G1: 65.5  G2: 52.6  G3: 44.0 |  |  |
| Author, yr, Study Name:  Emery et al., 201738, 39  C-EARLY  Country, Clinical Setting:  Europe, Australia, North America, and Latin America (181 sites)  Study Design:  RCT  Overall N:  879b  Study Duration:  1 yr | Adults who are DMARD naïve with moderate-to-severe RA fulfilling 2010 ACR/EULAR classification criteria, diagnosed ≤1 year before randomization, and with poor prognostic factors (RF or anti-CCP seropositive) | Interventions, dose:  G1: CZP + MTX   * CZP: 400 mg at wks 0, 2, and 4, 200 mg every 2 wks thereafter (subcutaneous) * MTX: 10-25 mg/wk (increased by 5 mg every 2 wks to 25 mg or max tolerated dose by wk 8); max tolerated dose continued through wk 52 (oral)   G1a: CZP + MTX patients with very early RA (≤4 mos)  G1b: CZP + MTX patients with early RA (>4 mos)  G2:   * Placebo * MTX: 10-25 mg/wk (increased by 5 mg every 2 wks to 25 mg or max tolerated dose by wk 8); max tolerated dose | Mean disease duration, mos:  2.9  Baseline DAS28-ESR, mean:  6.7  Moderate disease activity (DAS28-ESR >3.2 to ≤5.1), %:  3.5  High disease activity (DAS28-ESR >3.2 to ≤5.1), %:  96.5  Baseline HAQ-DI, mean:  1.6  Prior CS use, %:  32.6 (systemic) | At wk 52c  DAS28-ESR disease activity score  Change from baseline, mean:  G1: -3.6 (SE, 0.1)  G2: -3.0 (SE, 0.1)  P<0.001  Timepoint score, mean:  G1: 3.11 (SD, 1.58)  G2: 3.77 (SD, 1.68)  P<0.001  LDA (DAS28-ESR ≤3.2), %:  G1: 54.7  G2: 39.4  P<0.001  ACR20 response, %:  G1: 69.0  G2: 61.5  P=NS  ACR50 response, %:  G1: 61.8  G2: 52.6  p=0.023 | Overall AEs (≥5% in any system organ class):  G1: 79.7  G2: 72.8  p=NS  SAEs:  G1: 10.6  G2: 9.2  p=NS  Overall discontinuation:d  G1: 24.2  G2: 34.7  Discontinuation due to AEs:d  G1: 7.7  G2: 7.8  P=NS | Medium  High (KQ 2 WPS-RA work productivity outcomes) |

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| Author, yr, Study Name:  Emery et al., 201738, 39  C-EARLY  (continued) |  | continued through wk 52 (oral)  Those in either arm with DAS28-ESR >3.2 at wks 20 and 24 were withdrawn to allow them to switch to a complementary medication  N:  G1: 660  G2: 219  Mean age, yrs:  50.6  Sex, % female:  76.8  Race, % white:  NR  Race, % black:  NR  Ethnicity, % Latino:  NR | Prior csDMARD use, %:  0  MTX naive:  100  MTX inadequate responders:  0  Biologic non-responders:  0  RF seropositive, %:  96.8  anti-CCP seropositive (%):  83.9  Baseline Sharp score:  Median (range): 3.0 (0 to 161);  Mean: 7.5  Erosive disease, %:  77.8 | ACR70 response, %:  G1: 51.3  G2: 39.9  p<0.001  Sustained LDA (DAS28-ESR ≤3.2 at both wks 40 and 52), %  G1: 43.8  G2: 28.6  OR (95% CI): 2.0 (1.4 to 2.8)  p<0.001  Sustained remission (DAS28-ESR <2.6 at both wks 40 and 52), %  G1: 28.9  G2: 15.0  OR (95% CI): 2.3 (1.5 to 3.5)  p<0.001  DAS28-ESR remission (DAS28-ESR <2.6), %:  G1: 42.6  G2: 26.8  OR (95% CI): 2.0 (1.4 to 2.9)  p<0.001  mTSS score  Change from baseline, mean:  G1: 0.2  G2: 1.8  p<0.001  No radiographic progression (change from baseline mTSS ≤ 0.5), %:  G1: 70.3  G2: 49.7  OR (95% CI): 2.4 (1.7 to 3.4)  p<0.001 | Patient adherence:  NR  Specific AEs:e  Rates for most frequently reported AEs (see below) described as “similar for both treatment arms”.  Nausea:  G1: 12.6  G2: 10.1  p=NR  URTI  G1: 10.9  G2: 5.1  p=NR  UTI  G1: 7.3  G2: 7.4  p=NR  Nasopharyngitis  G1: 7.0  G2: 6.0  p=NR  Headache  G1: 6.8  G2: 3.7  p=NR    Deaths resulting from AEse,f  G1: 0.3  G2: 0.5  P=NR |  |

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| Author, yr, Study Name:  Emery et al., 201738, 39  C-EARLY  (continued) |  |  |  | HAQ-DI change from baseline, mean  G1: -1.00  G2: -0.82  p<0.001  **Normative function (HAQ-DI ≤0.5) (%)**  G1: 48.1  G2: 35.7  p=0.002  **Fatigue: BRAF-MDQ change from baseline, meang**  G1: -17.8 (SE 0.6)  G2: -15.6 (SE 1.0)  p=NR  **WPS-RA: Number of work days missed in last month for employed patients, meanh**  G1: 0.6 (SD 2.6)  G2: 0.9 (SD 2.5)  p=NR  **WPS-RA: Number of work days with reduced productivity in last month, meanh**  G1: 1.0 (SD 3.4)  G2: 1.8 (SD 4.7)  p=NR  **WPS-RA: Interference with work productivity in last month, meanh,i**  G1: 1.4 (SD 2.0)  G2: 1.9 (SD 2.3)  p=NR | Active tuberculosis  G1: 0.2  G2: 0.0  p=NR  **Latent tuberculosis**  G1: 0.15  G2: 0.9  p=NR  Serious Infections and Infestations  G1: 3.0  G2: 3.2  P=NR  General disorders and administration site conditions  G1: 16.4  G2: 12.4  p=NR |  |

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| Author, yr, Study Name:  Emery et al., 201738, 39  C-EARLY  (continued) |  |  |  | WPS-RA: Number of days with no household work in last month, meanh  G1: 1.9 (SD 5.1)  G2: 3.0 (SD 6.7)  p=NR  **WPS-RA: Number of days with reduced household work productivity in last month, meanh**  G1: 2.1 (SD 5.3)  G2: 3.0 (SD 6.6)  p=NR  **WPS-RA: Number of days with hired outside help in last month, meanh**  G1: 0.6 (SD 3.2)  G2: 0.7 (SD 3.3)  p=NR  **WPS-RA: Number of days missed of family/social/leisure activities in last month, meanh**  G1: 0.9 (SD 3.6)  G2: 0.9 (SD 3.1)  p=NR  **WPS-RA: Interference with household work productivity in last month, meanh,i**  G1: 1.9 (SD 2.5)  G2: 2.5 (SD 2.8)  p=NR  At wk 40c  LDA (DAS28-ESR ≤3.2), %:  G1: 49.2  G2: 32.9  p<0.001 |  |  |

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| Author, yr, Study Name:  Emery et al., 201738, 39  C-EARLY  (continued) |  |  |  | HAQ-DI change from baseline, mean  G1: -0.98  G2: -0.83  p≤0.05  At wk 36c  LDA (DAS28-ESR ≤3.2), %:  G1: 45.5  G2: 31.5  P<0.001  HAQ-DI change from baseline, mean  G1: -0.95  G2: -0.82  p≤0.05  At wk 24  DAS28-ESR disease activity score, mean:  G1: 3.54 (SD, 1.47)  G2: 4.07 (SD, 1.44)  P<0.001  LDA (DAS28-ESR ≤3.2), %:  G1: 39.7  G2: 30.5  p≤0.05  HAQ-DI change from baseline, mean  G1: -0.92  G2: -0.83  p≤0.05  At wk 20c  LDA (DAS28-ESR ≤3.2), %:  G1: 40.5  G2: 28.2  p≤0.05 |  |  |

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| Author, yr, Study Name:  Emery et al., 201738, 39  C-EARLY  (continued) |  |  |  | HAQ-DI change from baseline, mean  G1: -0.90  G2: -0.79  p≤0.05  At wk 12c  DAS28-ESR disease activity score, mean:  G1: 3.88 (SD, 1.44)  G2: 4.43 (SD, 1.46)  P<0.001  LDA (DAS28-ESR ≤3.2), %:  G1: 31.6  G2: 18.5  P<0.001  HAQ-DI change from baseline, mean  G1: -0.85  G2: -0.69  P<0.001 |  |  |

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| Goekoop-Ruiterman, 200579;  Allaart et al., 200691;  Goekoop-Ruiterman, 200785;  van der Kooij, 200983;  van der Kooij, 200986  Dirven et al., 201280;  Dirven et al., 201382;  Klarenbeek et al., 201081;  Markusse et al., 201687;  Klarenbeek et al., 201190  Klarenbeek et al., 201189  Markusse et al., 201488  BeSt study  Country and setting  The Netherlands  18 peripheral and 2 university hospitals  Study design  RCT | Non-pregnant patients aged ≥18 yrs with active (≥6 of 66 swollen joints, ≥6 of 68 tender joints and ESR rate ≥28 mm/hr or global health score of ≥20 mm on 0-100 mm VAS) early RA according to revised 1987 criteria, disease duration ≤2 yrs. No prior use of DMARDs (other than antimalarials) or concomitant treatment with an experimental drug | **Note:** BeST protocol uses thrice-monthly DAS calculations and aims at achieving low DAS, with a protocol that requires treatment adjustments if DAS is >2.4, but stable (after 6 mos tapering off) medication as long as the DAS is ≤2.4  **G1:** **Sequential monotherapy**: MTX (15 mg/wk, increased to 25-30 mg/wk if DAS >2.4)  **G2: Step-up combination therapy:** MTX (15 mg/wk, increased to 25-30 mg/wk if DAS >2.4). If response still insufficient, SSZ was added, followed by the addition of hydroxychloroquine (HCQ) and then by PRED  **G3: Initial combination therapy with PRED**: MTX (7.5 mg/wk) + SSZ (2,000 mg/d) + PRED (60 mg/d, tapered in 7 wks to be 7.5 mg/d)  **G4: Initial combination therapy with IFX:** MTX (25-30 mg/wk) + IFX (3 mg/kg) at weeks 0, 2, 6, and every 8 weeks thereafter)  **G5: Initial Monotherapy group (iMono):** Combined G1 + G2 for post-hoc analysis  G5a: poor prognosis patients from G5  G5b: non-poor prognosis patients from G5 | Median symptom duration, wks  23-26 wks  Prior CS use, %  NR  Prior csDMARD use, %  0  MTX naïve, %  100  Baseline DAS score, mean  4.3-4.5  Baseline D-HAQ score, mean  1.4  RF seropositive, %  64-67  Baseline mTSS score, mean:  5.9-7.3  Erosions on hand/foot radiograph, %:  70-73 | At 10 yrs  Low DAS (≤2.4), %  G1: 84  G2: 77  G3: 83  G4: 84  ACR20/50/70 or EULAR response, %  NR  DAS (<1.6) remission, %  G1: 51  G2: 49  G3: 53  G4: 53  Achieved drug-free remission during at least 1 visit, %  G1: 27  G2: 24  G3: 22  G4: 29  In drug-free remission during at 10 yrs, %  G1: 8.7  G2: 9.1  G3: 9.0  G4: 10.2  Increase in mTSS, median (IQR)  G1: 2.0 (IQR, 0 to 11.0)  G2: 2.5 (IQR, 0 to 13.5)  G3: 3.0 (IQR, 0.3 to 11.3)  G4: 1.5 (IQR, 0.0 to 6.0) | At 10 yrs  Overall:  Overall, 89% of patients reported AEs (74 AEs per 100 patient years). These were equally distributed between the 4 groups (p=0.159) at 10 year followup  Patients who reported SAEs  Overall, 47% of patients reported SAEs (12 SAEs per 100 patient-years) at 10 year followup  SAEs per 100 patient-years, yrs 6-10  G1: 13.2  G2: 10.9  G3: 12.1  G4: 13.4  CVD adverse events per 100 patient years, yrs 6-10  G1: 5.5  G2: 6.4  G3: 7.8  G4: 5.7  Mortality, at 10 yr followup  G1: 12.7  G2: 12.4  G3: 15.8  G4: 15.6 | Low  Medium (for 10 year outcomes) |

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| Goekoop-Ruiterman, 200579;  Allaart et al., 200691;  Goekoop-Ruiterman, 200785;  van der Kooij, 200983; van der Kooij, 200986  Dirven et al., 201280;  Dirven et al., 201382;  Klarenbeek et al., 201081;  Markusse et al., 201687;  Klarenbeek et al., 201190  Klarenbeek et al., 201189  Markusse et al., 201488  BeST Study  (continued) |  |  |  | Improvement in HAQ compared with baseline, mean (SD)  G1: 0.8 (SD, 0.6)  G2: 0.7 (SD, 0.8)  G3: 0.8 (SD, 0.8)  G4: 0.8 (SD, 0.8)  p=0.64  SF-36 Physical and Mental Component scores  Figure only  At 3 years  DAS disease activity  NR  ACR20/50/70 or EULAR response, %  NR  DAS remission, %  Figure only  SHS  Figure only  Improvement in in HAQ compared with baseline, mean (SD)  G1: 0.8 (SD, 0.7)  G2: 0.7 (SD, 0.7)  G3: 0.8 (SD, 0.8)  G4: 0.9 (SD, 0.7)  p=0.66  SF-36 Physical and Mental Component scores  Figure only | Overall discontinuation  G1: 8.7  G2: 16.5  G3: 10.5  G4: 7.0  Overall: 11  Adherence  G1: 15.1  G2: 12.4  G3: 18.8  G4: 8.6  Overall: 14  Cardiovascular, yrs 3-4  G1: 4  G2: 6  G3: 10  G4: 9  p=0.25  Dermal/mucosal, yrs 3-4  G1: 13  G2: 13  G3: 14  G4: 9  p=0.72 |  |

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| Goekoop-Ruiterman, 200579;  Allaart et al., 200691;  Goekoop-Ruiterman, 200785;  van der Kooij, 200983; van der Kooij, 200986  Dirven et al., 201280;  Dirven et al., 201382;  Klarenbeek et al., 201081;  Markusse et al., 201687;  Klarenbeek et al., 201190  Klarenbeek et al., 201189  Markusse et al., 201488  BeST Study  (continued) |  |  |  | HAQ score, mean  Figure only  HAQ score, improvement from BL, mean  G1: 0.7 (SD, 0.7)  G2: 0.8 (SD, 0.7)  G3: 0.9 (SD, 0.7)  G4: 0.9 (SD, 0.7)  p=0.257  Progression of SHS from baseline, mean (SD)  G1: 9.0 (SD, 17.9)  G2: 5.2 (SD, 8.1)  G3: 2.6 (SD, 4.5)  G4: 2.5 (SD, 4.6)  p=0.005  G1 & G2 vs. G3 & G4: p<0.050  Progression of SHS from baseline, median (IQR)  G1: 2.0 (IQR, 0.0 - 8.6)  G2: 2.0 (IQR, 0.3 - 7.0)  G3: 1.0 (IQR, 0.0 - 2.5)  G4: 1.0 (IQR, 0.0 - 3.0)  Change in SHS  Figure only  Relative risk for SHS Progression, RR (95% CI)  G1: 1.0  G2: 0.91 (CI 0.73-1.12)  G3: 0.74 (CI 0.61-0.89)  G4: 0.73 (CI 0.61-0.88) | Patient adherence  Overall, 5% discontinued adherence to protocol because of noncompliance, but not all were lost to followup, and all available data were included in the ITT analysis  Skin rash or other mild dermal or mucosal events  G1: 10  G2: 12  G3: 9  G4: 6  Infections (mainly upper respiratory tract)  G1: 4  G2: 7  G3: 8  G4: 8  Cardiovascular events in year 1, %  G1: 2  G2: 2  G3: 6  G4: 2  CVD adverse events per 100 patient years, yrs 1-2  G1: 2.9  G2: 3.0  G3: 7.0  G4: 5.2 |  |

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| --- | --- | --- | --- | --- | --- | --- |
| Author, yr:  Haagsma, 199723  Country, Setting:  Netherlands, 1 academic and 6 peripheral clinics  Study Design:  RCT  Overall N:  105 | Patients meeting ACR criteria for RA with symptom duration <1 yr, who were DMARD-naïve | Interventions, dose:  G1: SSZ (1 g/day; max 3 g/day)  G2: MTX (7.5 mg/wk; max 15 mg/wk)  G3: MTX (7.5 mg/wk; max 15 mg/wk) + SSZ (1 g/day; max 3 g/day)  N:  G1: 34  G2: 35  G3: 36  Mean age, yrs:  54.9-57.0 | Mean disease duration, mos:  2.6-3.1  Prior csDMARD use, %:  0  Prior CS use, %  0  MTX naive, %:  100  Baseline DAS, mean:  4.6-5.0 | No significant differences in efficacy between combination (MTX, SSZ) and single therapy (MTX or SSZ), only a trend favoring combination therapy, MTX and SSZ were comparable  At 1 yr  DAS mean change:  G1: -1.6 (95% CI, -2.0 to -1.2)  G2: -1.7 (95% CI, -2.0 to -1.4)  G3: -1.9 (95% CI, -2.2 to -2.3) | Overall:  G1: 88.2  G2: 77.1  G3: 88.9  SAEs:  G1: 8.8  G2: 0  G3: 0  Overall discontinuation  G1: 35.3  G2: 5.7  G3: 16.7  Time to discontinuation in G1 > G2, G3 (p=0.006) | Medium |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr:  Haagsma, 199723  (continued)  Study Duration:  1 yr |  | Sex, % female:  61.8-66.7  Race, % white:  NR | Baseline HAQ:  0.92-1.20  Seropositive (RF or CCP) (%):  RF+: 94.2-97.1  Baseline Sharp score, mean:  NR  Erosive disease, %:  NR | HAQ change from baseline:  G1:-0.32 (95% CI, -0.53 to -0.10)  G2: -0.46 (95% CI, -0.68 to -0.25)  G3: -0.51 (95% CI, -0.76 to -0.26)  N of pts with a response according to ACR criteria at end of study:  G1: 25  G2: 25  G3: 28 | Discontinuation because of AEs  G1: 26.5  G2: 5.7  G3: 13.9  Discontinuation because of lack of efficacy  G1: 8.8  G2: 0.0  G3: 2.8  Patient adherence  >90% for all patients  AEs possibly/probably related to treatment  **G1: 47.1**  **G2: 31.4**  **G3: 63.9**  G3 > G1, G2 (p=0.023)  Cardiovascular Events (Dyspnea):  G1: 5.9  G2: 0  G3: 5.6  Nausea:  G1: 29.4  G2: 25.7  G3: 63.9  URTI  G1: 17.6  G2: 20.0  G3: 27.8 |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Heimans et al., 2013;9  Heimans et al., 2014;158  Heimans et al., 2016120  IMPROVED  Country, Clinical Setting:  Netherlands, multicenter (12 hospitals)  Study Design:  RCT | Adults (aged ≥ 18 yrs) RA (fulfilling ACR and EULAR criteria for RA with symptom duration ≤ 2 yrs) or UA (≥ 1 joint with clinical synovitis and ≥ 1 other painful joint, clinically suspected as due to early RA regardless of symptom duration), DAS ≥ 1.6, no prior antirheumatic therapy, and for whom MTX 25 mg/wk with PRED: 60 mg/day tapered to 7.5 mg/day had not lowered their DAS28 to ≤ 1.6 during the first 4 mos of disease treatment | Interventions, dose:  G1:   * MTX: 25 mg/wk * PRED: 7.5 mg/day * HCQ: 400 mg/day * SSZ: 2000 mg/day * PRED, HCQ, SSZ stopped if remission achieved at 8 mos; switched to 25 mg/wk MTX and 40 mg/every other wk ADA if remission not achieved at 8 mos (12 mos of treatment) * MTX stopped if remission remained at 12 mos (16 mos of treatment)   G2:   * MTX: 25 mg/wk * ADA: 40mg every other wk   ADA tapered if remission achieved at 8 mos; ADA increased to 40 mg/wk if remission not achieved at 8 mos (12 mos of treatment) non-MTX drugs were stopped/tapered in patients who achieved remission after 8 mos; MTX was stopped if remission remained 4 mos later. Patients in G1 that did not achieve remission at 8 mos received G2 therapy instead. Patients in G2 that did not achieve remission at 8 mos received an increased dose of 40 mg/wk of ADA. | Median disease duration, wks:  G1: 22 (IQR, 9-40)  G2: 21 (IQR, 8-29)  Overall: NR  4-mos DAS, mean:  G1: 2.49 (SD, 0.63)  G2: 2.57 (SD, 0.68)  Overall: NR  4-mos HAQ, mean:  G1: 0.86 (SD, 0.57)  G2: 0.88 (SD, 0.57)  Overall: NR  MTX naïve, %:  0.0  MTX inadequate responders, %:  100  **Prior DMARD use, %:**  100  Biologic non-responders, %:  NR  ACPA positive, %:  G1: 48.2  G2: 46.2  Overall: NR | At 2 yrs  (20 mos after randomization)  DAS disease activity, mean:  G1: 2.02 (SD, 0.70)  G2: 1.92 (SD, 0.85)  p=0.45  ACR response, %:  NR  DAS remission (< 1.6), %  G1: 26.5  G2: 30.8  p=0.76  mTSS score, progression (increase ≥ 0.5), %:  G1: 10.8  G2: 6.4  p=0.31  HAQ, mean:  G1: 0.90 (SD, 0.66)  G2: 0.83 (SD, 0.67)  SF-36:  NR  12 mos  (8 mos after randomization)  DAS disease activity, mean:  G1: 2.07 (SD, 0.89)  G2: 1.77 (SD, 0.90)  p=0.04 | Overall AEs in yr 2:  G1: 63.9  G2: 66.7  SAEs in yr 2:  G1: 6  G2: 10.2  Overall discontinuation:  NR  Discontinuation because of AEs:  NR  Discontinuation because of lack of efficacy:  NR  Patient adherence:  NR  Specific AEs:  Increased liver enzymes:  G1: 8.4  G2: 3.8  **Between 4 mos (randomization) and yr 1**  **Overall AEs, %:**  G1: 74  G2: 68  P = 0.41  **SAEs, %:**  G1: 8.4  G2: 9 | High |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Heimans et al., 2013;9  Heimans et al., 2014;158  Heimans et al., 2016120  IMPROVED  (continued) |  |  |  |  | Overall discontinuation, %:  NR  **Discontinuation because of AEs, %:**  NR  **Discontinuation because of lack of efficacy, %:**  NR  **Patient adherence:** NR  **Specific AEs:**  Increased liver enzymes:  G1: 6  G2: 11.5  Rash:  G1: 6  G2: 7.7  URTI:  G1: 4.8  G2: 10.2  Nausea:  G1: 7.2  G2: 6.4  Headache:  G1: 8.4  G2: 0  Dizziness:  G1: 1.2  G2: 0 |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Heimans et al., 20139;  Heimans et al., 2016120  IMPROVED  (continued)  Overall N:  161  Study Duration:  2 yrs |  | N:  G1: 83  G2: 78  Mean age, yrs:  49 -51  Sex, % female:  74-77  Race, % white:  NR  Race, % black:  NR  Ethnicity, % Latino:  NR | Baseline mTSS score, median:  G1: 0 (IQR, 0-0.5)  G2: 0 (IQR, 0-0)  Erosive disease, %:  G1: 12.0  G2: 16.7  Overall: NR | DAS remission (< 1.6), %  G1: 25.3  G2: 41.0  p=0.01  **Total SHS, median (IQR):**  G1: 0 (0.0-0.5)  G2: 0 (0-0)  **SHS progression median (IQR):**  G1: 0 (0-0)  G2: 0 (0-0)  HAQ, mean:  G1: 0.87 (SD, 0.66)  G2: 0.81 (SD, 0.66)  p=0.60  SF-36:  Mental component, mean:  G1: 50.5 (SD, 10.3)  G2: 50.5 (SD, 10.1)  p=0.97  Physical component, mean:  G1: 39.9 (SD, 10.3)  G2: 43.0 (SD, 11.4)  p=0.10  Pain (visual analog scale), mean:  G1: 38 (SD, 28)  G2: 28 (SD, 25)  p=0.02  **VAS global health (mm), mean:**  G1: 33 (SD 23)  G2: 27 (SD 20) | Pneumonia or bronchitis  G1: 3.6  G2: 1.3 |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Heimans et al., 20139;  Heimans et al., 2016120  IMPROVED  (continued) |  |  |  | Erosive, %  G1: 15  G2: 15  8 mos  (4 mos after randomization)  DAS disease activity, mean:  G1: 1.97 (SD, 0.87)  G2: 2.01 (SD, 0.91)  p=0.77  HAQ, mean:  G1: 0.74 (SD, 0.61)  G2: 0.81 (SD, 0.64)  p=0.51  SF-36:  Mental component, mean:  G1: 46.6 (SD, 17.9)  G2: 48.7 (SD, 10.3)  p=0.85  Physical component, mean:  G1: 42.8 (SD, 10.9)  G2: 42.5 (SD, 11.0)  p=0.10  Pain (visual analog scale), mean:  G1: 35 (SD, 26)  G2: 31 (SD, 25)  p=0.36 |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Hellgren et al., 2017;76  SRQ Register analysis  Country, Clinical Setting:  Sweden, outpatient  Study Design:  Single-arm study  Overall N:  12,656  Study Duration:  15 years | Patients meeting 1987 revised ACR criteria for RA between 1997 and 2012 with disease duration <1 yr between first RA symptom and diagnosis | Interventions, dose:  G1: Patients developing lymphomas   * G1a: Patients receiving initial therapy with MTX in first year after diagnosis AND developing lymphomas * G1b: Patients receiving oral corticosteroids during first year of follow-upj AND developing lymphomas * G1c: Patients receiving TNFi (i.e., TNF biologic) therapy everj AND developing lymphomas   G2: Rest of RA patient cohort   * G2a: Rest of RA patient cohort receiving initial therapy with MTX in first year after diagnosis * G2b: Rest of RA patient cohort receiving oral corticosteroids during first year of follow-upj * G2c: Rest of RA patient cohort receiving TNFi therapy everk   **N:**  G1: 55   * G1a: 40 * G1b: 22 * G1c: 12 | Mean disease duration:  NR, but <1 yr in entire sample  **Baseline DAS, median:**  5.2  **Baseline HAQ:**  NR  **MTX naive:**  100  **Prior csDMARD use, %:**  0  **MTX inadequate responders:**  NA  **Biologic non-responders:**  NA  **Prior CS use, %:**  0  RF seropositive, %:  66  Baseline Sharp score:  NR  Erosive disease, %:  NR | NR | Lymphoma  Proportion with MTX use  G1a: 72  G2a: 75  HR (95% CI): 0.9 (0.8 to 1.0) adjusted for age, sex, and inflammatory activity during first year after RA diagnosis  HR (95% CI): 0.9 (0.9 to 1.0) adjusted for age, sex, inflammatory activity during first year after RA diagnosis, and concomitant use of corticosteroids or TNFi  Proportion with oral CS use  G1b: 40  G2b: 63  HR (95% CI): 0.5 (0.3 to 0.9) adjusted for age, sex, and inflammatory activity during first year after RA diagnosis  HR (95% CI): 0.5 (0.3 to 0.9) adjusted for age, sex, inflammatory activity during first year | N/A |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Hellgren et al., 2017;76  SRQ Register analysis  (continued) |  | G2: 11,638   * G2a: 8,739 * G2b: 7,339 * G2c: 3,072   Mean age, yrs:  58  Sex, % female:  69 |  |  | after RA diagnosis, and concomitant use of MTX or TNFi  Proportion with TNFi use  G1c: 19  G2c: 24  HR (95% CI): 0.9 (0.4 to 1.9) adjusted for age, sex, and inflammatory activity during first year after RA diagnosis  HR (95% CI): 1.2 (0.6 to 2.4) adjusted for age, sex, inflammatory activity during first year after RA diagnosis, and concomitant use of MTX or corticosteroids |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Horslev-Petersen et al., 2014;36  Axelsen et al., 2015;161  Ørnbjerg et al., 2017;163  Horslev-Petersen et al., 2016;162  Ammitzboll et al., 2013160  OPERA  Country, Clinical Setting:  Denmark, multiple outpatient clinics  Study Design:  RCT  Overall N:  180  Study Duration:  2 yrs | Adults (aged ≥ 18 yrs) fulfilling ACR criteria for RA with disease duration < 6 mos, moderate to severe RA defined as DAS28 CRP > 3.2, no prior DMARD use, and no treatment with glucocorticoids within last 4 wks | Interventions, dose:  G1:   * MTX: 7.5 mg/wk, increased to 15 mg/wk after 1 mo and 20 mg/wk after 2 mos * ADA: 40 mg every other wk (subcutaneous)   G2:   * MTX: 7.5 mg/wk, increased to 15 mg/wk after 1 mo and 20 mg/wk after 2 mos * Placebo   ≤ 4 swollen joints observed at each visit (total 7) were injected with triamcinolone hexacetonide (40 mg/ml, 0.5-2 ml/joint); if unacceptable disease activity persisted at 3 mos or thereafter (defined as either DAS28 CRP ≥ 3.2 and ≥ 1 swollen joint or intra-articular injection of 4 ml triamcinolone was given monthly for 3 consecutive mos), 200 mg/day HCQ and 2,000 mg/day SSZ were added; if LDA was not achieved within an additional 3 mos, | Mean disease duration, days:  83-88  Baseline DAS28 CRP, mean:  5.5-5.6  Baseline HAQ, median:  1.0-1.1  MTX naive:  100  Prior csDMARD use, %: 0  MTX inadequate responders:  NA  Biologic non-responders:  NA  Prior CS use, %:  0  RF seropositive, %:  72.0 | At 2 yrs  (1 yr after stopping ADA)  DAS28 CRP disease activity, median change:  G1: -3.1 (5/95% range: -1.0 to 5.7)  G2: -3.1 (5/95% range: -1.3 to 5.1)  p=0.72  ACR20 response, %:  G1: 86  G2: 81  p=0.52  ACR50 response, %:  G1: 74  G2: 69  p=0.55  ACR70 response, %:  G1: 58  G2: 63  p=0.65  DAS28 CRP remission (< 2.6), %:  G1: 66  G2: 69  p=0.79 | Overall AEs:  NR  SAEs:  At 1 yr (%)  G1: 15.7  G2: 11.0  During yr 2 (n)  G1: 4  G2: 11  Overall discontinuation:  At 1 yr  G1: 9.0  G2: 12.1  At 2 yrs  G1: 10.1  G2: 16.5  Discontinuation because of AEs:  At 1 yr  G1: 2.2  G2: 1.1  At 2 yrs  No discontinuations due to AEs | Medium |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Horslev-Petersen et al., 2014;36  Axelsen et al., 2015;161  Ørnbjerg et al., 2017;163  Horslev-Petersen et al., 2016;162  Ammitzboll et al., 2013160  OPERA  (continued) |  | ADA/placebo was discontinued, and the patient was considered a non-responder and prescribed open-label non-ADA biologics  N:  G1: 89  G2: 91  Mean age, yrs:  G1: 56.2 (25.8-77.6)  G2: 54.2 (29.3-76.7)  Overall: NR  Sex, % female:  66.0  Race, % white:  NR  Race, % black:  NR  Ethnicity, % Latino:  NR | anti-CCP seropositive, %:  65.1  Baseline Sharp score, median:  4.3-4.5  Erosive disease, %:  53 | Sharp score  Median change:  G1: 1.05  G2: 2.63  p=0.12  No radiographic progression (change ≤ 0), %:  G1: 64  G2: 51  p=0.81  HAQ  Median change:  G1: -0.9 (5/95% range: 0.3 to -2.5)  G2: -0.6 (5/95% range: 0.5 to -1.9)  p=0.10  Response (< 0.5), %:  G1: 70  G2: 64  p=0.43  SF-36  Mental component, median:  G1: 56 (5/95% range: 36 to 62)  G2: 56 (5/95% range: 34 to 64)  p=0.96  Physical component, median:  G1: 46 (5/95% range: 23 to 57)  G2: 45 (5/95% range: 22 to 56)  p=0.30  Pain (VAS), median change:  G1: -36 (5/95% range: 13 to -88)  G2: -31 (5/95% range: 6 to -80)  p=0.68 | Discontinuation because of lack of efficacy:  At 1 yr  G1: 3.4  G2: 2.2  At 2 yrs  No discontinuations due to lack of efficacy  Discontinuation due to patient request/non-compliance:  At 1 yr  Overall: 4.4  Specific AEs  Bronchitis:  At 1 yr  G1: 1.1  G2: 1.1  Subcutaneous atrophy:  At 1 yr  G1: 1.1  G2: 0.0  Leucopoenia:  At 1 yr  G1: 0.0  G2: 1.1 |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Horslev-Petersen et al., 2014;36  Axelsen et al., 2015;161  Ørnbjerg et al., 2017;163  Horslev-Petersen et al., 2016;162  Ammitzboll et al., 2013160  OPERA  (continued) |  |  |  | Fatigue (VAS), median change:  G1: -32 (5/95% range: 2 to -79)  G2: -22 (5/95% range: 34 to -75)  p=0.25  At 1 yr  DAS28 CRP disease activity, median:  G1: 2.0 (5/95% range: 1.7 to 5.2)  G2: 2.6 (5/95% range: 1.7 to 4.7)  p=0.009  ACR20 response, %:  G1: 86  G2: 78  p=0.21  ACR50 response, %:  G1: 80  G2: 63  p=0.020  ACR70 response, %:  G1: 65  G2: 45  p=0.012  DAS28 CRP remission (< 2.6), %:  G1: 74  G2: 49  p=0.0008  Sharp score  Median change:  G1: 0.27  G2: 1.64  p=0.008 |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Horslev-Petersen et al., 2014;36  Axelsen et al., 2015;161  Ørnbjerg et al., 2017;163  Horslev-Petersen et al., 2016;162  Ammitzboll et al., 2013160  OPERA  (continued) |  |  |  | No radiographic progression (change ≤ 0), %:  G1: 67  G2: 52  p=0.07  HAQ, median change:  G1: -0.88 (5/95% range: -2.46 to 0.13)  G2: -0.63 (5/95% range: -1.82 to 0.38)  p=0.012  SF-36  Mental component, median change:  G1: 5.5 (5/95% range: -8.5 to 20.1)  G2: 4.3 (5/95% range: -9.3 to 27.4)  p=0.83  Physical component, median change:  G1: 13.2 (5/95% range: -2.3 to 33.0)  G2: 10.6 (5/95% range: -11.2 to 22.7)  p=0.015  Pain (visual analogue scale), median:  G1: 7 (5/95% range: 0 to 64)  G2: 20 (5/95% range: 0 to 71)  p=0.007  Fatigue (visual analogue scale), median:  G1: 16 (5/95% range: 0 to 81)  G2: 20 (5/95% range: 0 to 84)  p=0.10 |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Horslev-Petersen et al., 2014;36  Axelsen et al., 2015;161  Ørnbjerg et al., 2017;163  Horslev-Petersen et al., 2016;162  Ammitzboll et al., 2013160  OPERA  (continued) |  |  |  | EQ-5D, median change from baseline (5th/95th percentile ranges)  G1: 0.22 (-0.05 to 0.67)  G2: 0.20 (-0.06 to 0.56) (p=0.095) |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Kavanaugh et al., 2013;37  Smolen et al., 2014;151  Emery et al., 2016152  OPTIMA  Country, Clinical Setting:  Multiple countries, 161 sites (Academic hospitals, research centers, private practices and rheumatology clinics)  Study Design:  RCT  Overall N:  1032  Study Duration:  78 wks (open label after 26 wks) | Patients aged ≥18 years with RA diagnosis based on ACR criteria, with disease duration <1 yr. All patients were MTX and biological DMARD naïve | Interventions, dose:  G1: ADA 40 mg/every other wk + MTX 7.5 mg/wk (maximum of 20 mg/wk by wk 8)  G1a: Randomized to placebo + MTX (ADA withdrawal)  G1b: Randomized to ADA + MTX (ADA continuation)  G1c: Open-label ADA + MTX (ADA carry-over)  G2: Placebo + MTX  G2a: Continued masked placebo + MTX monotherapy  G2b: Open-label ADA + MTX (ADA rescue)  MTX: Initiated at 7.5 mg/wk, increased by 2.  N:  G1: 515 (a: 102, b: 105, c: 259)  G2: 517 (a: 112, b: 348)  Mean age, yrs:  50.4-50.7  Sex, % female:  74  Race, % white:  89.5 | Mean disease duration, mos:  4.0-4.5 mos  Baseline DAS, mean:  6.0  Baseline HAQ-DI (0-3), mean:  1.60-1.61  MTX naïve, %:  100  MTX inadequate responders:  0  Biologic non-responders:  NR  RF Seropositive (%):  88.3  Sharp score (modified total), mean:  11.2-11.8  Patients with ≥1 erosion, %:  83.4 | At 78 wks  DAS28 <3.2 % achieving LDA  G1a: 81.2  G1b: 91.4  G1c: NR  G2a: 81.3  G2b: 60  ACR20 response, %  G1a: 94.1  G1b: 95.2  G1c: NR  G2a: 91.1  G2b: 83  ACR50 response, %  G1a: 80.4  G1b: 88.6  G1c: NR  G2a: 76.8  G2b: 63  ACR70 response, %  G1a: 64.7  G1b: 77.1  G1c: NR  G2a: 61.6  G2b: 43  DAS28 (CRP) <2.6 remission, %  G1a: 66.3  G1b: 85.7  G1c: NR  G2a: 67.9  G2b: 44 | Overall:  Period 1  G1: 73.6  G2: 71.2  Period 2  G1a: 77.5  G1b: 71.4  G1c: 76.8  G2a: 74.1  G2b: 77.6  SAEs  Period 1  G1: 7.2  G2: 6.2  Period 2  G1a: 10.8  G1b: 11.4  G1c: 6.9  G2a: 8.0  G2b: 9.2  Overall discontinuation  G1 total: 22.3  G2 total: 24.2  Period 1:  G1: 10  G2: 11  Period 2:  G1a: 12.7  G1b: 9.5  G1c: 16.6  G2a: 13.4  G2b: 15.2 | Low |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Kavanaugh et al., 2013;37  Smolen et al., 2014;151  Emery et al., 2016152  OPTIMA  (continued) |  |  |  | Change from baseline in mTSS ≤0.5 (%)  G1a: 80.6  G1b: 89.3  G1c: NR  G2a: 78.0  G2b: Figure only  HAQ-DI (0-3), mean (95% CI)  G1a: 0.38 (CI 0.27 to 0.50)  G1b: 0.35 (CI 0.25 to 0.45)  G1c: 0.89 (CI 0.81 to 0.98)  G2a: 0.39 (CI 0.29 to 0.48)  G2b: 0.76 (CI 0.69 to 0.83)  SF-36  NR  At 26 wks  DAS, % achieving LDA target  G1: 47  G2: 26 (p<0.001)  ACR20 response, %  G1: 70  G2: 57 (p<0.001)  ACR50 response, %  G1: 52  G2: 34 (p<0.001)  ACR70 response, %  G1: 35  G2: 17 (p<0.001) | Discontinuation because of AEs  Overall:  G1: 8.9  G2: 7.9  Period 2  G1a: 6.9  G1b: 2.9  G1c: 6.6  G2a: 5.4  G2b: 5.7  Patient adherence  NR  Bronchitis  G1a: 0  G1b: 0  G1c: 0  G2a: 0.9  G2b: 0  Dizziness  G1a: 1.0  G1b: 0  G1c: 0  G2a: 0  G2b: 0 |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Kavanaugh et al., 2013;37  Smolen et al., 2014;151  Emery et al., 2016152  OPTIMA  (continued) |  |  |  | DAS <2.6 remission, %  G1: 34  G2: 17 (p<0.001)  mTSS mean change  G1: 0.15  G2: 0.96 (P <0.001)  HAQ-DI, mean value  G1: 0.7  G2: 0.9 (P <0.001)  Normal function (HAQ-DI <0.5), %  G1: 40  G2: 28 (p<0.001)  SF-36  NR  WPAI activity impairment, mean % change from baseline  G1: 32.0  G2: 23.7 (p=0.0071)  WPAI presenteeism (performance while at work owing to RA), mean % change from baseline  G1: 24.6  G2: 17.1 (p=0.0253)  WPAI overall work impairment, mean % change from baseline  G1: 27.3  G2: 18.3 (p=0.0105) |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Kavanaugh et al., 2013;37  Smolen et al., 2014;151  Emery et al., 2016152  OPTIMA  (continued) |  |  |  | At 22 wks  DAS, % achieving LDA target  G1: 44  G2: 24 (P <0.001)  ACR20 response, %  NR  DAS remission, %  NR  SHS, mean change in modified total score  G1: 0.15  G2: 0.96 (P <0.001)  HAQ-DI, mean value  G1: 0.7  G2: 0.9 (P <0.001)  SF-36  NR |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Kellner et al., 201019  Country, Clinical Setting:  Germany, 174 centers  Study Design:  Observational (only single arm eligible)  Overall N:  334  Study Duration:  25.5 wks observance on average | Adult patients with early RA (defined by a max disease duration of 1 year since diagnosis) were eligible if the investigator was convinced that they might profit from treatment with LEF and if they did not show any contraindi-cations. The physician’s decision for LEF treatment was based on patient’s condition and independent of study documenta-tion | Interventions, dose:  Recommended loading dose was LEF, 100 mg/d. Maintenance dose was LEF 20 mg/d in 91.6% of patients and 10 mg/d in 8.4% of patients.  61.7% were concomitantly treated with corticosteroids, and in 27.5% of patients additional DMARDs (most often MTX, 22.2%) were used.  N:  334  Mean age, yrs:  55.8 (SD, 13.2)  Sex, % female:  73.0  Race, % white:  NR | Median time since RA diagnosis, mos:  4.0  Mean disease duration, mos (SD):  7.5 (SD, 15.8)  Baseline DAS, mean:  5.7 (SD, 1.2)  Baseline HAQ-DI, mean:  1.37 (SD, 0.7)  MTX naive:  58.1  MTX inadequate responders:  NR  Prior csDMARD use, %  47.9  Prior CS use, %  NR  Biologic non-responders:  NR  RF seropositive (%):  73.1 | N/A | Overall:  10.8  SAEs (“Serious adverse drug reactions”)  1.2  Overall discontinuation  11.1  Discontinuation because of AEs  6.3  Patient adherence  NR  Specific AEs  NA (specific AEs for head-to-head trials only) | N/A |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Kellner et al., 201019  (continued) |  |  | CCP seropositive (%):  60.9  Baseline Sharp score, mean:  NR  Erosive disease, %:  45.6 |  |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Leirisalo-Repo et al, 201340  Rantalaiho et al., 2014128  Kuusalo et al., 2015127  NEO-RACo  Country, Clinical Setting:  Finland,  15 rheumatology centers  Study Design:  RCT  Overall N:  99  Study Duration:  2 yrs (5 yrs followup) | Patients aged 18-60, fulfilling ACR criteria for RA, DMARD naïve, and not permanently work disabled or retired. All had active disease (≥6 swollen joints/≥6 tender joints) and either early morning stiffness ≥45 min, ESR rate ≥30 mm/h or CRP ≥20 mg/l | Interventions, dose:  G1: “FIN-RACo” (MTX + SSZ + HCQ + PRED) + IFX (3 mg/kg from wks 4-26)  G2: “FIN-RACo” (MTX + SSZ + HCQ + PRED) + Placebo (from wks 4-26)  FIN-RACo: Regimen consisting of:   * MTX: Starting at 10 mg/wk, 15 mg/wk at wk 4, 20 mg/wk at wk 10, 25 mg/wk from wk 14 * SSZ: Starting at 1 g/d, 2 g/d at 2 wks, 1-2 g/d from wk 4 * HCQ: 35 mg/kg/wk from start through study duration * PRED: 7.5 mg/d from start through study duration * Acid folic with MTX (5 mg/wk), Calcium (1000 mg/d), and Vitamin D3 (800 IU/d) throughout study   IFX: Received at wks 4, 6, 10, 18, and 26  N:  G1: 50  G2: 49  Mean age, yrs:  46-47 | Median disease duration, mos (IQR):  4 (IQR, 2, 6)  Baseline DAS, mean:  5.5-5.6  Baseline HAQ, mean:  0.9-1.1  MTX naive:  100  MTX inadequate responders:  0  Biologic non-responders:  NR  RF seropositive (%):  76  Baseline Sharp score, mean:  2.0-2.8  Erosive disease, %:  37 | At 5 years followup  DAS disease activity, mean (SD)  G1: 2.0 (SD, 1.2)  G2: 1.7 (SD, 0.9)  p=0.33  ACR20 response, %  NR  ACR50 response, %  NR  ACR70 response, %  NR  ACR strict remission, % (95% CI)  G1: 60 (CI 44 to 74)  G2: 61 (CI 45 to 75)  p=0.93  DAS remission, % (95% CI)  G1: 84 (CI 71 to 94)  G2: 89 (CI 76 to 96)  p=0.51  SHS scores, mean (SD)  G1: 4.3 (SD, 7.6)  G2: 5.3 (SD, 7.3)  p=0.54  HAQ, median (IQR)  G1: 0 (IQR, 0.0-0.1)  G2: 0 (IQR, 0.0-0.0)  p=0.39  SF-36  NR | Overall:  Year 5:  G1: 91.3  G2: 97.9  Year 2:  G1: 90  G2: 96  SAEs  Year 5:  G1: 8.7  G2: 10.6  p=0.99  Year 2:  G1: 6  G2: 8  Overall discontinuation  Year 5  G1: 10  G2: 6.1  Year 2  G1: 8  G2: 8.2  Discontinuation because of AEs  Year 2:  G1: 2  G2: 0 | Low |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Leirisalo-Repo et al, 201340  Rantalaiho et al., 2014128  Kuusalo et al., 2015127  NEO-RACo  (continued) |  | Sex, % female:  67  Race, % white:  NR |  | At 2 years  DAS disease activity  NR  ACR20 response, %  NR  ACR50 response, % (95% CI)  G1: 96 (CI 86 to 100)  G2: 92 (CI 80 to 98)  p=0.436  ACR70 response, % (95% CI)  G1: 86 (CI 73 to 94)  G2: 71 (CI 57 to 83)  p=0.090  ACR modified remission, % (95% CI)  G1: 66 (CI 51 to 81)  G2: 53 (CI 38 to 67)  p=0.19  DAS28 remission, % (95% CI)  G1: 82 (CI 72 to 93)  G2: 82 (CI 71 to 93)  SHS score, mean change from baseline (95% CI)  G1: -0.2 (CI -1.2 to 0.4)  G2: 1.4 (CI 0.8 to 2.3)  p=0.0058 | Patient adherence  Year 2:  95% of patients sufficiently complied with the study protocol  **Year 5:**  NR  Specific AEs  GI symptoms: 56% vs. 61%  Respiratory: 56% vs. 67%  Elevated liver enzymes 12% vs. 16% |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Leirisalo-Repo et al, 201340  Rantalaiho et al., 2014128  Kuusalo et al., 2015127  NEO-RACo  (continued) |  |  |  | HAQ, mean (95% CI)  G1: Figure only (Fig 2C)  G2: Figure only (Fig 2C)  SF-36  NR  Note: there are some figure-only data available for months 3, 6, 12, and 18 (see Figure 2) |  |  |
| Author, yr, Study Name:  Lie et al., 201228  NOR-DMARD analysis  Country, Clinical Setting:  Norway  Study Design:  register-based longitudinal observational study  Overall N:  1,102  Study Duration:  3 yrs | Patients with an RA diagnosis, disease duration ≤ 1 yr, and no prior DMARD use who were enrolled in the NOR-DMARD register and starting treatment with SSZ or MTX as monotherapies | Interventions, dose:  G1: SSZ (median dose of 2.0 g [IQR 2.0-2.0] at all timepoints)  G2: MTX (median dose of 10 mg [IQR 7.5-15.0] at baseline, 15 mg [IQR 12.5-15.0] at 3 mos, 15 mg [IQR 12.5-20.0] at 6 mos)  N:  G1: 175  G2: 927  Mean age, yrs:  G1: 49.9 (SD, 14.8)  G2: 55.9 (SD, 13.6)  Overall: NR  Sex, % female:  66.9  Race, % white:  NR  Race, % black:  NR  Ethnicity, % Latino:  NR | Median disease duration, mos:  NR  Baseline DAS28, mean:  G1: 4.38 (SD, 1.35)  G2: 5.00 (SD, 1.34)  Overall: NR  Baseline modified HAQ, median:  G1: 0.50 (IQR, 0.13-0.75)  G2: 0.63 (IQR, 0.25-1.00)  Corticosteroid (PNL) use, %:  G1: 32.0  G2: 55.6  MTX naïve, %:  100  MTX inadequate responders, %:  0.0 | At 6 months  Mean DAS28 change from baseline (SD) – LOCF  G1: -1.04 (1.64)  G2: -1.52 (1.6) (p=0.003 from t-test; p=0.36 from ANCOVA adjusted for propensity score quintile; p=0.71 from ANCOVA adjusted for propensity score quintile and physician global VAS)  ACR20 response, % - LUNDEX  G1: 20.8  G2: 44.5 (p=NA)  ACR50 response, % - LUNDEX  G1: 9.1  G2: 21.6 (p=NA)  ACR70 response, % - LUNDEX  G1: 5.2  G2: 14.3 (p=NA)  DAS28 remission (<2.6), % - LUNDEX  G1: 25.1  G2: 27.9 (p=NA) | Overall AEs:  G1: 62.9  G2: 71.4  NR  Overall discontinuation:  G1: 78.9  G2: 48.1  Discontinuation because of AEs:  G1: 36.0  G2: 15.4  Discontinuation because of lack of efficacy:  G1: 27.4  G2: 21.7  Patient adherence:  NR  Specific AEs  Infections:  G1: 20.0  G2: 34.1  p<0.001 | High |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Lie et al., 201228  NOR-DMARD analysis  (continued) |  |  | Biologic non-responders, %:  NR  RF seropositive, %:  G1: 50.3  G2: 61.4  Overall: NR  Baseline Sharp score, mean:  NR Erosive disease, %:  NR | Mean modified HAQ (MHAQ) change from baseline (SD)  G1: -0.13 (0.45)  G2: -0.26 (0.48) (p=0.002 from t-test; p=0.05 from ANCOVA adjusted for propensity score quintile; p=0.13 from ANCOVA adjusted for propensity score quintile and physician global VAS)  Mean SF-36 PCS change from baseline (SD)  G1: 4.0 (8.5)  G2: 5.4 (9.8) (p=0.11 from t-test; p=0.26 from ANCOVA adjusted for propensity score quintile; p=0.42 from ANCOVA adjusted for propensity score quintile and physician global VAS)  Mean SF-36 MCS change from baseline (SD)  G1: 2.4 (11.4)  G2: 2.8 (11.2) (p=0.67 from t-test; p=0.78 from ANCOVA adjusted for propensity score quintile; p=0.74 from ANCOVA adjusted for propensity score quintile and physician global VAS) | Nausea:  G1: 13.1  G2: 18.9  p<0.07  Abdominal pain:  G1: 8.0  G2: 4.1  p<0.03  Rash:  G1: 9.1  G2: 2.7  p<0.001  Hair loss:  G1: 1.1  G2: 5.1  p<0.02  Stomatitis:  G1: 0.6  G2: 4.4  p<0.01 |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Lie et al., 201228  NOR-DMARD  (continued) |  |  |  | Mean Pain VAS change from baseline (SD)  G1: -9.2 (23.6)  G2: -14.7 (26.9) (p=0.02 from t-test; p=0.24 from ANCOVA adjusted for propensity score quintile; p=0.41 from ANCOVA adjusted for propensity score quintile and physician global VAS)  Mean Fatigue VAS change from baseline (SD)  G1: -0.4 (28.2)  G2: -4.4 (29.6) (p=0.13 from t-test; p=0.21 from ANCOVA adjusted for propensity score quintile; p=0.24 from ANCOVA adjusted for propensity score quintile and physician global VAS)  Data not abstracted for patient matching analysis (according to RF status and baseline DAS28) because only unadjusted comparisons of their data were performed.  At 3 months  ACR20 response, % - LUNDEX  G1: 18.3  G2: 47.4 (p=NA)  ACR50 response, % - LUNDEX  G1: 5.9  G2: 21.3 (p=NA) |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Lie et al., 201228  NOR-DMARD analysis  (continued) |  |  |  | ACR70 response, % - LUNDEX  G1: 3.2  G2: 14.0 (p=NA)  DAS28 remission (<2.6), % - LUNDEX  G1: 14.6  G2: 25.6 (p=NA) |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Marcora et al., 2006113  Country, Clinical Setting:  United Kingdom, hospital outpatient rheumatology clinic  Study Design:  RCT  Overall N:  26  Study Duration:  6 mos | Adults (aged ≥18 yrs) fulfilling ACR criteria for RA < 6 mos, DAS28 > 3.2, no prior DMARD or CS use | Interventions, dose:  G1:   * ETN: 25 mg twice/wk (subcutaneous)   G2:   * MTX: 7.5 mg/wk for 1 mo, increased to max 15 mg/wk in mo 2 and 20 mg/wk in mo 4 if necessary (oral), with 10 mg/wk folic acid   N:  G1: 12  G2: 14  Mean age, yrs:  G1: 54 (SD 11)  G2: 50 (SD 15)  Sex, % female:  75.0 (of 24)  Race, % white:  NR  Race, % black:  NR  Ethnicity, % Latino:  NR | Mean disease duration, mos:  NR  DAS28, mean:  G1: 6.1 (SD 0.7)  G2: 5.8 (SD 1.1)  Overall: NR  HAQ, mean:  G1: 1.9 (SD 0.6)  G2: 1.2 (SD 0.7)  Overall: NR  MTX naïve, %:  100  MTX inadequate responders, %:  NA  Biologic non-responders, %:  NA  RF seropositive, %:  58.3 (of 24)  Sharp score, mean:  NR  Erosive disease, %:  NR | At 24 wks  **DAS28 disease activity, mean:**  G1: 3.2 (SD 1.5)  G2: 3.1 (SD 1.4)  Treatment x time: P = 0.53  Time: P < 0.01  **ACR response, %:**  NR  **EULAR response, %:**  G1: 25.0  G2: 16.7 (of 12)  **DAS remission, %:**  NR  **Sharp score, mean:**  NR  **HAQ, mean:**  G1: 1.0 (SD 0.9)  G2: 0.6 (SD 0.6)  Treatment x time: P = 0.38  Time: P < 0.01  **SF-36:**  NR  At 12 wks  **DAS28 disease activity, mean:**  G1: 3.8 (SD 1.5)  G2: 3.4 (SD 1.2)  **HAQ, mean:**  G1: 1.2 (SD 0.8)  G2: 0.6 (SD 0.7) | Overall AEs:  NR  SAEs:  G1: 0.0  G2: 0.0  Overall discontinuation:  G1: 0.0  G2: 0.0  Discontinuation due to AEs:  NA  Discontinuation due to lack of efficacy:  NA  Patient adherence:  NR  Specific AEs:  Injection site reaction  G1: 8.3  G2: 0.0 | Medium |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  McWilliams et al., 2013137  ERAN  Country, Clinical Setting:  UK and Eire, 22 outpatient centers  Study Design:  Observational, (Retrospective cohort)  Overall N:  766  Study Duration:  2 yrs | Patients recruited after diagnosis of RA by rheumatologist. People whose diagnosis subsequently changed were removed from study database. Data were analyzed for patients who had been recruited prior to July 2009, ≥ 2 years before data retrieval for this analysis, and who had commenced DMARDs before visit 4 | Interventions, dose:  G1: Initial DMARD regimen of SSZ monotherapy  G2: Initial DMARD regimen of MTX monotherapy  G3: Initial DMARD regimen of MTX + SSZ + HCQ triple therapy  N:  G1: 273  G2: 336  G3: 52  Mean age, yrs:  56-58  Sex, % female:  65-72  p<0.05  Race, % white:  NR | Median disease duration, mos (IQR):  6 mos (IQR, 4-12)  Baseline DAS28, median (IQR):  5.8 (IQR, 4.6-7.0)  Baseline HAQ, median (IQR):  1.1 (IQR, 0.6-1.8)  MTX naive:  100  MTX inadequate responders:  NR  Prior csDMARD use, %  0  Prior CS use, %  16-17  Biologic non-responders:  NR  Seropositive (%):  61-62 | NA | **Note:** sensitivity analyses only including participants who satisfied ACR 1987 classification criteria for RA did not affect statistical associations between baseline factors and DMARD change (data not shown).  Changed DMARD, %  G1: 43  G2: 36  G3: 4  Heat-to-head analysis, comparing G1 and G2:  MTX is favored as initial DMARD (aOR (95% CI)=0.41 (0.28-0.60), p<0.001  Changed DMARD due to adverse drug reaction, %  G1: 59  G2: 23  G3: 2 | High |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  McWilliams et al., 2013137  ERAN  (continued) |  |  | Baseline Sharp score, mean:  NR  Erosions, %:  26-47 |  | Likelihood of DMARD change, aOR (95% CI)  G1: 1.09 (CI 0.57-2.12)  G2: 0.56 (CI 0.29-1.06)  G3: 0.30 (CI 0.12-0.79, p=0.014)  Risk of adverse drug reaction, aOR (95% CI)  G1: 1.92 (CI 0.85-4.37)  G2: 0.38 (CI 0.16-0.94, p<0.05)  G3: 0.33 (CI 0.08-1.38) |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Montecucco et al., 20123  Country, Clinical Setting:  Italy, University hospital clinic  Study Design:  RCT  Overall N:  220  Study Duration:  1 year | Patients met RA classification criteria, aged >18 years, symptom duration <12 mos, and had active disease according to the disease activity score. | Interventions, dose:  G1: MTX 10 mg/wk (max 25 mg/wk) + PRED 12.5 mg/d for 2 wks  G2: MTX 10 mg/wk (max 25 mg/wk)  PRED: dose tapered to 6.25 mg/d for the followup period  MTX: After starting at the baseline dosage, if patients did not reach LDA state at following visits, dose was increased (if tolerated) to 15 mg/wk, then 20 and 25 mg/wk  N:  G1: 110  G2: 110  Mean age, yrs:  57-62  p=0.06  Sex, % female:  63.6  Race, % white:  NR | Median disease duration, mos:  2.97-3.48  Baseline DAS, median:  5.0-5.2  Baseline HAQ, median:  1.0-1.1  MTX naive:  NR  MTX inadequate responders:  NR  Biologic non-responders:  NR  Seropositive (RF or CCP) (%):  NR  Baseline Sharp score, mean:  NR | At 12 months  DAS disease activity  Figure only data  ACR20 response, %  NR  LDA  G1: 80.2%  G2: 75.5%  p=0.44  DAS remission, %  G1: 44.8  G2: 27.8  p=0.02  SHS  NR  HAQ  NR  SF-36  NR  VAS pain  Figure only data  Mean difference: -8.8 (95% CI, -17.5 to -0.1); p=0.04  At 9 months  VAS pain  Figure only data; p=NS  At 6 months  VAS pain  Figure only data; p=NS | Overall:  NR  SAEs  NR  Overall discontinuation  G1: 8.2  G2: 10.9  Discontinuation because of AEs  G1: 5.5  G2: 9.1  p=0.29  Patient adherence, RR  Patients in G1 were less likely to adhere to protocol  RR=0.82 (95% CI 0.69, 0.96)  Specific AEs  NR | Medium |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Montecucco et al., 20123  (continued) |  |  | Erosive disease, %:  NR | At 4 months  VAS pain  Figure only data  Mean difference: -10.8 (95% CI, -19.1 to -2.5); p=0.01 |  |  |
| Author, yr, Study Name:  Moreland et al., 201220;  O’Dell et al., 2013159  TEAR  Country, Clinical Setting:  United States, Multicenter  Study Design:  RCT  Overall N:  755  Study Duration:  2 yrs | Adults (aged ≥18 yrs) fulfilling ACR criteria for RA with disease duration < 3 yrs, active RA defined as ≥ 4 swollen joints and 4 tender joints (using a 28-joint count), rheumatoid factor or anti-CCP antibody positivity, ≥2 erosions on radiographs of hands/wrists/ feet, prior CS use limited to ≤ 10 mg/day of PRED and stable ≥ 2 wks prior to | Interventions, dose:  G1 (immediate):   * MTX: Escalated to 20 mg/wk, or lower dose if no active tender/painful or swollen joints at wk 12 (oral) * SSZ: 500 mg twice/day and, if tolerated, escalated to 1,000 mg twice/day * HCQ: 200 mg twice/day * Folic acid: 1 mg/day   G2 (immediate):   * MTX: Escalated to 20 mg/wk, or lower dose if no active tender/painful or swollen joints at wk 12 (oral) * ETN: 50 mg/wk (subcutaneous) * Placebo * Folic acid: 1 mg/day   G3 (step-up):   * MTX: Escalated to 20 mg/wk, or lower dose if no active tender/painful or swollen joints at wk 12 (oral) | Mean disease duration, mos:  2.9-4.5  Baseline DAS28-ESR among completers, mean:  5.8-5.9  Baseline modified HAQ among completers, mean:  1.0-1.1 | At 102 wks  DAS28-ESR disease activity, mean:  G1: 2.9 (SD, 1.5)  G2: 3.0 (SD, 1.4)  G3: 2.8 (SD, 1.3)  G4: 3.0 (SD, 1.4)  DAS28-ESR disease activity, mean change from wk 48 (primary outcome):  By arm: p=0.28  G1/2 vs. G3/4: p=0.55  G2/4 vs. G1/3: p=0.48  ACR20 response, %:  Figure only data; p=NS  ACR50 response, %:  Figure only data; p=NS | Overall AEs:  G1: 76.5  G2: 79.1  G3: 74.2  G4: 73.3  p=0.47  SAEs:  G1: 13.6  G2: 14.3  G3: 12.9  G4: 12.5  p=0.94  Overall discontinuation:  G1: 42.4  G2: 34.8  G1/2: 32.4  G3: 39.5  G4: 34.9  G3/4: 19.0  Discontinuation because of AEs:  G1/2: 1.9  G3/4: 1.3 | High |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Moreland et al., 201220;  O’Dell et al., 2013159  TEAR  (continued) | screening, and no prior biologic therapy | * SSZ: 500 mg twice/day if DAS28-ESR ≥ 3.2 at wk 24; if tolerated, escalated to 1,000 mg twice/day (otherwise, placebo) * HCQ: 200 mg twice/day if DAS28-ESR ≥ 3.2 at wk 24 (otherwise, placebo) * Folic acid: 1 mg/day   G4 (step-up):   * MTX: Escalated to 20 mg/wk, or lower dose if no active tender/painful or swollen joints at wk 12 (oral) * ETN: 50 mg/wk (subcutaneous) if DAS28-ESR ≥ 3.2 at wk 24 (otherwise, placebo) * Placebo * Folic acid: 1 mg/day   N:  G1: 132  G2: 244  G3: 124  G4: 255  Mean age, yrs:  G1: 48.8 (SD, 12.7)  G2: 50.7 (SD, 13.4)  G3: 49.3 (SD, 12.0)  G4: 48.6 (SD, 13.0)  Overall: NR  Sex, % female:  72.2 | Low-dose CS treatment at screening, %:  41.7  Prior csDMARD use, %:  23.6  MTX naive:  79.2  MTX inadequate responders:  NR  Biologic non-responders, %:  0.5 (protocol exceptions)  RF seropositive, %:  89.7  RF negative/anti-CCP seropositive, %:  3.3  Baseline mTSS among completers, mean:  4.1-6.5 | ACR70 response, %:  Figure only data;  G2/4 > G1/3: p=0.0109  DAS remission (< 2.6), %:  G1: 59.1  G2: 56.6  G3: 56.5  G4: 52.9  p=0.93  G1/2 vs. G3/4: p=0.36  G2/4 vs. G1/3: p=0.43  mTSS score, mean:  G1: 7.3 (SD, 13.3)  G2: 7.0 (SD, 16.6)  G3: 6.2 (SD, 8.9)  G4: 4.8 (SD, 7.2)  Change in G1/2 vs. G3/4: p=0.74  Change in G2/4 vs. G1/3: 0.64 vs. 1.69; p=0.047  No radiographic progression (mTSS change < 0.5), %:  G1: 64.9  G2: 79.4  G3: 68.3  G4: 71.1  p=0.33  G1/2 vs. G3/4: p=0.56  G2/4 vs. G1/3: p=0.02 | Discontinuation because of SAEs:  G1/2: 2.7  G3/4: 1.1  Discontinuation because of lack of efficacy:  G1/2: 3.7  G3/4: 2.9  Patient compliance:  G1/2 vs. G3/4: p=0.74  G2/4 vs. G1/3: p=0.76  Specific AEs:  NR |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Moreland et al., 201220;  O’Dell et al., 2013159  TEAR  (continued) |  | Race, % white:  79.6  Race, % black:  11.3  Ethnicity, % Hispanic:  11.3 | Erosive disease, %:  NR | Modified HAQ, mean:  G1: 1.0 (SD, 0.3)  G2: 1.0 (SD, 0.3)  G3: 0.9 (SD, 0.3)  G4: 0.9 (SD, 0.3)  SF-36:  NR  At wk 48  No difference in HAQ functional capacity among groups (p=NR)  At wk 24 (prior to initiating step-up)  DAS28-ESR disease activity, mean change:  G1/2: 3.6  G3/4: 4.2  p<0.0001  ACR20 response, %:  G1: Figure only  G2: Figure only  G3: Figure only  G4: Figure only  G1/2 > G3/4: p<0.0001  ACR50 response, %:  G1: Figure only  G2: Figure only  G3: Figure only  G4: Figure only  G1/2 > G3/4: p<0.0001  ACR70 response, %:  G1: Figure only  G2: Figure only  G3: Figure only  G4: Figure only  G1/2 > G3/4: p<0.0001 |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Mottonen et al., 199922;  Puolakka et al., 2004102;  Korpela et al., 2004;101  Makinen et al., 2007;144  Rantalaiho et al., 2010142;  Karstila et al., 2012145**;**  Rantalaiho et al., 2013143  FIN-RACo  Country, Clinical Setting:  Finland, multicenter | Adults (aged 18-65 yrs) fulfilling ACR criteria with symptom duration < 2 yrs, active disease defined as ≥ 3 swollen joints and ≥ 3 of the following: ESR ≥ 28mm/h, CRP > 19 mg/L, morning stiffness ≥ 29 mins, > 5 swollen joints and > 10 tender joints; patients had no prior DMARD use and no glucocorticoid therapy within previous 2 wks | G1:   * MTX: Initiated at 7.5 mg/wk and increased to 10 mg/wk if patient did not achieve clinical improvement at 3 mos; could be tapered and then discontinued at 18 mos if remission achieved during first yr with initial combo * HCQ: 300 mg/day * SSZ: 500 mg/twice daily * PNL: Initiated at 5 mg/day and increased to 7.5 mg/day if patient did not achieve clinical improvement at 3 mos; could be tapered and then discontinued at 9 mos if remission achieved during first yr with initial combo   G2:   * SSZ: Initiated at 2 g/day and increased to 3 g/day if clinically indicated at 3 mos * Patients switched to 7.5-15 mg/wk MTX at 6 mos if an AE ocurred or clinical response < 25% | Mean disease duration, mos:  G1: 7.3 (range 2-22)  G2: 8.6(range 2-23)  Baseline DAS, mean:  NR  Baseline HAQ, mean:  G1: 0.9 (SD, 0.6)  G2: 0.9 (SD, 0.6)  Overall: NR  MTX naïve, %:  100  MTX inadequate responders, %:  0.0  Biologic non-responders, %:  NR  RF seropositive, %:  68.2  Baseline Sharp score, mean:  NR  Larsen score, median:  G1: 2 (IQR, 0-4)  G2: 2 (IQR, 0-8)  Overall: NR | At 5 years  DAS28 remission, %:  G1: 28  G2: 22  P = NS  At 2 years  DAS28 disease activity:  NR  ACR20 response, %:  G1: 78 (95% CI, 69 to 80)  G2: 84 (95% CI, 75 to 90)  ACR50 response, %:  G1:71.1  G2:58.1  p=0.058  ACR70 response, %:  NR  DAS28 remission, %  G1: 68  G2: 41  Sustained DAS28 remission, % (95% CI)  G1: 51 (95% CI 39 to 62)  G2: 16 (95% CI 10 to 24)  P < 0.001  OR: 5.58 (95% CI 2.60-11.55)  ACR remission, %  G1: 42  G2: 20 | Overall AEs:  G1: 70.1  G2: 71.4  SAEs:  G1: 3.1  G2: 5.1  Overall discontinuation:  G1: 10.3  G2: 7.1  Discontinuation due to AEs:  G1: 23.7  G2: 22.4  Discontinuation due to lack of efficacy:  G1: 1.0  G2: 0.0  Patient adherence:  NR  Specific AEs  AAT and AP > 2x normal:  G1: 11.3  G2: 23.5  p=0.026 | Medium |

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| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Mottonen et al., 199922;  Puolakka et al., 2004102;  Korpela et al., 2004;101  Makinen et al., 2007;144  Rantalaiho et al., 2010142;  Karstila et al., 2012145**;**  Rantalaiho et al., 2013143  FIN-RACo  (continued) |  |  |  | Sustained ACR remission, % (95% CI)  G1: 14 (95% CI 7 to 23)  G2: 3 (95% CI 1 to 9)  P = 0.013  OR: 4.61 (95% CI 1.17-16.99)  Clinical remission, %:  G1: 37.1  G2: 18.4  p=0.003  Sharp score:  NR  Larsen score medain:  G1:4 (IQR, 0-14)  G2:12 (IQR, 4-20)  p=0.002  Median increase in Larsen Score:  G1:1.5  G2:2.0 (p<0.001) |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Mottonen et al., 199922;  Puolakka et al., 2004102;  Korpela et al., 2004;101  Makinen et al., 2007;144  Rantalaiho et al., 2010142;  Karstila et al., 2012145**;**  Rantalaiho et al., 2013143  (continued)  Study Design:  RCT  Overall N:  199  Study Duration:  2 yrs |  | N:  G1: 97  G2: 98  Mean age, yrs:  G1: 47 (range 23-65)  G2: 48 (range 20-65)  Overall: NR  Sex, % female:  62.1  Race, % white:  NR  Race, % black:  NR  Ethnicity, % Latino:  NR | Radiographic evidence of erosions, %:  48.2 | HAQ, mean change:  G1:-0.6 (95% CI, -0.7 to -0.4)  G2:-0.6 (95% CI, -0.8 to -0.5)  Median work disability per pt-observation yr, days:  G1:12.4  G2:32.2 (p=0.008)  At 1 yr  ACR50 response, %:  G1: 70.1  G2: 57.1  p=0.028  Clinical remission, %:  G1: 24.7  G2: 11.2  p=0.011  DAS28 remission, %  G1: Figure only (Fig. 2)  G2: Figure only (Fig. 2)  **Sustained DAS28 remission, %**  G1: 57.0  G2: 23.3  ACR remission, %  G1: Figure only (Fig. 2)  G2: Figure only (Fig. 2)  Sustained ACR remission, %  G1: 16.5  G2: 3.3  At 6 mos  ACR20 response, %:  G1: 80 (95% CI, 71 to 88)  G2: 78 (95% CI, 69 to 86) | Cardiovascular Events:  G1: 1 MI  G2: 2 MIs  Malignancies:  1 prostate cancer; 1 multiple myeloma  URTI:  1 pneumonia |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Mottonen et al., 199922;  Puolakka et al., 2004102;  Korpela et al., 2004;101  Makinen et al., 2007;144  Rantalaiho et al., 2010142;  Karstila et al., 2012145**;**  Rantalaiho et al., 2013143  (continued) |  |  |  | DAS28 remission, %  G1: 66  G2: 37  **Sustained DAS28 remission, %**  NA  ACR remission, %  G1: 25  G2: 12  Sustained ACR remission, %  NA |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Nam et al., 201496  IDEA  Country, Clinical Setting:  United Kingdom,  4 clinical sites  Study Design:  RCT  Overall N:  112  Study Duration:  78 wks (1-26 wks blinded, 26-78 wks open-label) | Patients aged 18-80, meeting ACR criteria for RA, with 3-12 mos symptom duration, active disease (DAS>2.4) and DMARD naive | Interventions, dose:  G1: MTX (10 mg/wk to max tolerated dose) + IFX (3 mg/kg)  G2: MTX (10 mg/wk to max tolerated dose) + Intravenous Methyl-PNL (250 mg single dose) + Placebo  MTX: 10 mg/wk to 20 mg or max tolerated dose by wk 6  IFX: Max dose 1000 mg, delivered via infusion at wks 0, 2, 6, 14, 22  Methyl-PNL/Placebo: Delivered via infusion at wk 0; placebo delivered at wks 2, 6, 14, 22, 26, 38, 50, 68 and 78  N:  G1: 55  G2: 57  Mean age, yrs:  52.9-53.7  Sex, % female:  68.8  Race, % white:  NR | Median disease duration, mos:  1.2  Baseline DAS, mean:  3.56-4.05  Baseline HAQ-DI, mean:  1.34-1.43  MTX naive:  100  Prior csDMARD use, %  0  MTX inadequate responders:  100  Biologic non-responders:  NR  **Prior CS use, %:**  0  RF seropositive (%):  55  Baseline mTSS score, mean:  6.05-9.23  Erosion disease:  NR | At week 78 (Open Label)  DAS disease activity  NR  ACR20 response, %  G1: 70.7  G2: 71.1  ACR50 response, %  G1: 64.3  G2: 63.4  ACR70 response, %  G1: 46.2  G2: 50.1  DAS28 remission, %  G1: 54.3  G2: 65.3  **DAS remission, %**  G1: 47.7  G2: 50.0  p=0.792  mTSS total score, mean (SD)  G1: 1.69 (SD, 3.28)  G2: 3.19 (SD, 7.75)  p=0.253  Adjusted difference (95% CI): −1.31 (CI −3.59 to 0.96)  Mean change in HAQ-DI, mean (SD)  G1: -0.85 (SD, 0.60)  G2: -0.79 (SD, 0.54)  p=0.826  SF-36  NR | Overall  G1: 98.2  G2: 94.7  SAEs  G1: 36.4  G2: 15.8  Overall discontinuation  G1: 20  G2: 24.6  Discontinuation because of AEs  G1: 5.5  G2: 1.8  Patient adherence  NR  Infection – pulmonary/upper respiratory  G1: 3.6  G2: 1.8 | Medium |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Nam et al., 201496  IDEA  (continued) |  |  |  | At week 50 (Open Label)  DAS disease activity  NR  ACR 20/50/70, %  NR  EULAR remission, %  G1: 16.5  G2: 19.4  DAS28 remission, %  G1: 55.7  G2: 49.6  mTSS total score, mean (SD)  G1: 1.20 (SD, 2.27)  G2: 2.81 (SD, 6.88)  p=0.132  Adjusted difference (95% CI): −1.45 (CI −3.35 to 0.45)  HAQ  NR  SF-36  NR  At week 26  % achieving LDA score, DAS28 ≤3.2  G1: 64.4  G2: 66.6  ACR20 response, %  G1: 71.0  G2: 75.2 |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Nam et al., 201496  IDEA  (continued) |  |  |  | ACR50 response, %  G1: 54.0  G2: 55.1  ACR70 response, %  G1: 32.7  G2: 31.8  Remission, (DAS28 <1.6), %  G1: 40.6  G2: 50.8  mTSS total score, mean (SD)  G1: 0.83 (SD, 1.69)  G2: 1.52 (SD, 4.25)  p=0.291  Adjusted difference (95% CI): −0.59 (CI −1.70 to 0.52)  Mean change in HAQ-DI, mean (SD)  G1: -0.70 (SD, 0.56)  G2: -0.61 (SD, 0.47)  SF-36  NR  At week 14  % achieving LDA score, DAS28 ≤3.2  G1: 55.4  G2: 54.1  ACR20 response, %  NR  ACR50 response, %  NR |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Nam et al., 201496  IDEA  (continued) |  |  |  | ACR70 response, %  NR  DAS28 remission, %  G1: 42.3  G2: 40.0  mTSS total score, mean (SD)  NR  Mean change in HAQ-DI, mean (SD)  NR  SF-36  NR |  |  |
| Author, yr, Study Name:  Porter et al., 20168  ORBIT  Country, Clinical Setting:  United Kingdom, multicenter (Rheumatology departments)  Study Design:  RCT, open label, noninferiority  Overall N:  329  Study Duration:  1 yr | Patients were aged >18, met 1987 ACR criteria for RA, and had a DAS28 score >5.1. All had previously attempted treatment with ≥2 csDMARDs, were seropositive for RF or CCP, and were biological treatment naïve. All patients were not pregnant, breastfeeding, or of childbearing potential. | Interventions, dose:  G1: RTX 1 g on days 1 and 15 with premedication 30 min before of methylprednisolone 100mg IV, paracetamol 1gram, chlorphenamine 10mg, and after 26 wks if patient responded to treatment but had persistent disease activity (DAS>3.2). If flare (>1.2 increase in DASESR), early retreatment >20 weeks was allowed  G2: TNF inhibitor – ADA 40 mg every other week subcutaneously, or ETN 50 mg/wk subcutaneously  TNF inhibitor (either ADA or ETAN provided according to patient’s and rheumatologist’s choice | Mean disease duration, mos:  G1: 8.0  G2: 6.7  Baseline DAS, mean:  G1: 6.2 (0.9)  G2: 6.2 (1.1)  Baseline HAQ, mean:  G1: 1.7  G2: 1.8  MTX naïve, %:  0  MTX inadequate responders, %:  NR  MTX intolerance, %:  G1: 26  G2: 25 | At 1 yr (primary outcome)  DAS disease activity, mean change  G1: -2.6 (SD, 1.4)  G2: -2.4 (SD, 1.5)  p=0.24  ACR20 response, %  G1: 66  G2: 71  OR (95% CI)=0.8 (0.5-1.4)  ACR50 response, %  G1: 49  G2: 45  OR (95% CI)=1.2 (0.7-1.9)  ACR70 response, %  G1: 23  G2: 26  OR (95% CI)=0.8 (0.5-1.5) | Overall:  G1: 95  G2: 95  SAEs  G1: 25.7  G2: 17.2  Overall discontinuation  G1: 18.8  G2: 17.7  Discontinuation because of AEs  G1: 1.4  G2: 1.3  Patient adherence  See comment | High |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Porter et al., 20168  ORBIT  (continued) |  | N:  G1: 165  G2: 164  Mean age, yrs:  57  Sex, % female:  72  Race, % white:  NR | Prior csDMARD use, %:  100  Biologic non-responders, %:  0  Seropositive (RF or CCP) (%):  100  Baseline Sharp score, mean:  NR  Erosive disease, %:  NR | DAS28 remission (DAS28 ESR <2.6), %  G1: 23  G2: 21  OR (95% CI)=1.1 (0.6-2.1)  SHS  NR  HAQ mean change from baseline  G1: -0.49 (SD, 0.6)  G2: -0.38 (SD 0.5)  p=0.0391  SF-36  NR  EQ-5D mean change from baseline  G1: 0.2 (SD, 0.4)  G2: 0.3 (SD, 0.3)  p=0.9048  At 6 months  DAS disease activity  NR  ACR20 response, %  G1: 61  G2: 65  OR (95% CI)=0.8 (0.5-1.4)  ACR50 response, %  G1: 37  G2: 41  OR (95% CI)=0.9 (0.5-1.4) | Specific AEs  Infections:  G1: 53.5  G2: 70.9  Injection site reactions: p=0.003  Death:  G1: 1 (elbow prosthesis infection)  G2: 1 (myocardial infarction) |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Porter et al., 20168  ORBIT  (continued) |  |  |  | ACR70 response, %  G1: 15  G2: 17  OR (95% CI)=0.8 (0.5-1.5)  DAS28 remission, %  G1: 14  G2: 16  OR (95% CI)=0.9 (0.4-1.8)  SHS  NR  HAQ mean change from baseline  G1: -0.44 (SD, 0.6)  G2: -0.31 (SD, 0.6)  p=0.0391  SF-36  NR  EQ-5D mean change from baseline  G1: 0.2 (SD, 0.4)  G2: 0.3 (SD, 0.4)  p=0.9048 |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Quinn et al., 200541  Country, Clinical Setting:  NR  Study Design:  RCT  Overall N:  20  Study Duration:  2 yrs | Patients with RA diagnosis meeting 1987 ACR criteria for RA with <1 yr symptoms, no prior treatment with DMARDs or oral corticosteroids, MCP joint involvement, stable dosage of NSAIDs for 2 wks prior to screening, and poor prognosis according to PISA scoring system | Interventions, dose:  G1:   * MTX: Beginning at 7.5 mg/wk, rapidly increased to 25 mg/wk in the presence of remaining synovitis * IFX: 3 mg/kg infusion at wks 0, 2, 6 and every 8 wks thereafter for 46 wks   G2:   * MTX: Beginning at 7.5 mg/wk, rapidly increased to 25 mg/wk in the presence of remaining synovitis | Mean disease duration, mos:  6.0-7.4 mos  Baseline DAS28, median:  G1: 6.3 (IQR, 5.6-6.5)  G2: 6.9 (IQR, 6.1-7.9) | At 2 yrs (followup)  ACR20 response, %  G1: 70  G2: 50  ACR50 response, %  G1: 70  G2: 50  ACR70 response, %  G1: 67  G2: 30  p<0.05  DAS28-4<2.6 remission, %  G1: 70  G2: 20  SHS, mean change in total score from baseline  G1: 10  G2: 12 | Overall AEs:  Overall: 15  SAEs:  NR  Overall discontinuation:  NR  Discontinuation because of AEs:  Overall: 5  Discontinuation because of lack of efficacy:  NR  Patient adherence:  NR  Specific AEs:  NR | Medium |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Quinn et al., 200541  (continued) |  | * Placebo   N:  G1: 10  G2: 10  Mean age, yrs:  52  Sex, % female:  66.7  Race, %:  NR | Baseline HAQ, median (IQR):  G1: 1.3 (IQR, 0.88)  G2: 1.3 (IQR, 0.97)  MTX naïve, %:  100  MTX inadequate responders, %:  0  Biologic non-responders:  NR  RF seropositive, %:  65  Baseline Sharp score, mean:  NR  Erosive disease, %:  Figure only | At 54 weeks  DAS28 disease activity score median change (IQR)  G1: Figure only (Fig 2)  G2: Figure only (Fig 2)  ACR20 response, %  G1: 80  G2: 60  ACR50 response, %  G1: 78  G2: 40  p<0.05  ACR70 response, %  G1: 67  G2: 30  p<0.05  DAS28-4<2.6 remission, %  G1: Figure only (Fig 6)  G2: Figure only (Fig 6)  SHS  NR  HAQ, % change in median functional score  Figure only, but significant functional benefit favoring G1>G2 (p=0.05)  SF-36  NR  At 14 weeks  DAS28 disease activity score median change (IQR)  G1: Figure only (Fig 2)  G2: Figure only (Fig 2) |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Quinn et al., 200541  (continued) |  |  |  | ACR20 response, %  G1: 60  G2: 20  ACR50 response, %  G1: 60  G2: 0  ACR70 response, %  G1: 60  G2: 0  DAS28 disease remission  G1: Figure only (Fig 2)  G2: Figure only (Fig 2)  HAQ, % change in median functional score  G1: Figure only (Fig 4)  G2: Figure only (Fig 4)  SF-36  NR  Sharp score, mean change from baseline  NR |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, year, study name, if applicable  Schipper et al., 200926  Nijmegen RA Inception Cohort  Country and setting  Netherlands, outpatient clinics  Study design  Observational (prospective cohort)  Overall N  230  Duration of study  1 yr | Adults age ≥18 yrs with RA of <1 yr duration diagnosed according to 1987 ACR revised criteria who had attempted SSZ treatment as first or second DMARD but were otherwise DMARD-naïve | Comparisons (dosage and frequency)  G1: MTX (7.5 mg/wk; max 30 mg/wk)  G2: SSZ (750 mg/d; max 3 g/d) + MTX (7.5 - 30 mg/wk)  N:  G1: 124  G2: 106  Mean age (years)  61.8-63.8  Sex, % female  70-74  Race, % white  NR | Median disease duration, wks:  14-47  Baseline DAS28, mean  4.9-5.1  Baseline HAQ:  NR  Prior CS use, %:  8-9  Prior csDMARD use, %:  Other than SSZ:  13-15  MTX naïve, %:  NR  MTX inadequate responders:  0  Biologic non-responders:  100 (to SSZ)  Seropositive (RF or CCP), %:  RF(+): 73-81  Baseline Sharp score:  NR  Erosive disease, %:  NR | At 1 yr  DAS28, mean difference in change from baseline (SD):  G1: -1.1 (1.3)  G2: -0.9 (1.2)  Adjusted between-group difference (SE): 0.05 (0.15); *P*=0.756  Sub-analysis for SSZ + MTX group only  DAS28, mean difference in change from baseline  SSZ + MTX completers: 1.0  SSZ discontinuers: 0.7 (P=0.158)  ACR 20/50/70, %:  NR  EULAR good or moderate response, %:  G1: 53  G2: 51 (P=NS)  At 6 mos  DAS28, mean difference in change from baseline (SD):  G1: -0.9 (1.3)  G2: -0.8 (1.3)  Adjusted between-group difference (SE): -0.05 (0.16); *P*=0.737 | At 52 weeks  Overall discontinuation  G1: 33.9  G2: 50 (P=0.013, mainly driven by events during first 6 months)  Discontinuation because of AEs  G1: 18.5  G2: 11.3  At 6 months  Overall discontinuation  G1: 18.5  G2: 31.1  Discontinuation because of AEs  G1: 14.5  G2: 8.5 | High |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Soubrier et al., 2009;92  GUEPARD  Country, Clinical Setting:  France, multicenter  Study Design:  RCT  Overall N:  65  Study Duration:  1 yr | Adults (aged ≥18 yrs) fulfilling ACR criteria for RA < 6 mos, DAS28-ESR ≥ 5.1, no prior MTX or biologic use | Interventions, dose:  G1:   * ADA: 40 mg every other wk; stopped at wk 12 if DAS28 < 3.2; restarted for 12 wks if relapse occurred, and then increased to 40 mg/wk if DAS28 remained > 3.2 after 12 wks and tapered then stopped if successful, otherwise ETN (25 mg twice/wk) initiatied for 12 wks; ETN stopped if successful after 12 wks and restarted if relapse occurred; if ETN failed, LEF initatied for 12 wks * MTX: initiated with 0.3 mg/kg/wk (adjusted to max 20 mg/wk); tapered to 7.5 mg/wk if DAS 28 < 2.6 for ≥ 6 mos; initial dose reintroduced if disease activity flared up after tapering   G2:   * MTX: initiated with 0.3 mg/kg/wk (adjusted to max 20 mg/wk); tapered to 7.5 mg/wk if DAS 28 < 2.6 for ≥ 6 mos; initial dose reintroduced if disease activity flared up after tapering; ADA (40 mg every other wk or 40 mg/wk), ETN (25 mg twice/wk), or LEF added if insuffient response at wk 12 or later | Median disease duration, mos:  4.4  DAS28, mean:  6.2 (SD 0.8)  HAQ, mean:  1.4-1.7  MTX naïve, %:  100  Prior csDMARD use, %: 0  MTX inadequate responders, %:  NA  Biologic non-responders, %:  NA  Prior CS use, %:  15.4  RF seropositive, %:  73.8  anti-CCP seropositive, %:  73.1  Sharp score, mean:  2.4-7.5  Erosive disease, %:  34.4 | At 1 yr (change from wk 12)  **DAS28-ESR disease activity, mean:**  G1:  G2:  **ACR20 response, %:**  G1: 85  G2: 81  Not statistically significant (P = NR)  **ACR50 response, %:**  G1: 67  G2: 68  Not statistically significant (P = NR)  **ACR70 response, %:**  G1: 42  G2: 58  Not statistically significant (P = NR)  **DAS remission, %:**  G1: 39.4  G2: 59.4  *P = 0.15*  **mTSS, mean change:**  G1: 1.9 (SD 4) among 27  G2: 1.8 (SD 4.7) among 29  P = 0.18  **HAQ, mean change:**  G1: -1.02 (95% CI -1.24, -0.81)  G2: -0.93 (95% CI -1.17, -0.69)  P = 0.79  **SF-36:**  Improvement in physical and mental components did not reach statistical significance (data NR) | Overall AEs:  NR  SAEs:  G1: 15.2  G2: 15.6  Overall discontinuation:  G1: 15.2  G2: 9.4  Discontinuation due to AEs:  NR  Discontinuation due to lack of efficacy:  NR  Patient adherence:  NR  Specific AEs:  NR | Medium (12 wks)  High (52 wks) |

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| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Soubrier et al., 2009;92  GUEPARD  (continued) |  | Decision to adjust treatment made every 3 mos for patients not achieving DAS28 ≤ 3.2  N:  G1: 33  G2: 32  Mean age, yrs:  G1: 46.3 (SD 16.3)  G2: 49.3 (SD 15.2)  Sex, % female:  80.0  Race, % white:  14  Race, % black:  NR  Ethnicity, % Latino:  NR |  | **Pain (visual analogue scale):**  No difference (data NR)  **Fatigue (visual analogue scale):**  No difference (data NR)  **Patient global assessment (visual analogue scale):**  No difference (data NR)  At 12 wks  **ACR20 response, %:**  G1: 84  G2: 50  Statistically significant (P = NR)  **ACR50 response, %:**  G1: 66  G2: 27  Statistically significant (P = NR)  **ACR70 response, %:**  G1: 44  G2: 19  Statistically significant (P = NR)  **DAS remission, %:**  G1: 36.4  G2: 12.5  P = 0.02  **HAQ, mean change:**  G1: -0.82 (95% CI -1.11, -0.52)  G2: -0.51 (95% CI -0.72, -0.30)  P = 0.26 |  |  |

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| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Soubrier et al., 2009;92  GUEPARD  (continued) |  |  |  | Pain (visual analogue scale):  No difference (P = 0.19)  Fatigue (visual analogue):  No difference (P = 0.20)  **Patient global assessment (visual analogue scale):**  P = 0.13 |  |  |
| Author, yr:  St. Clair et al., 2004;17  Smolen et al., 2006;107  Smolen et al., 2009;106  Janssen Research and Development, 2017157  ASPIRE  Country, Setting:  Multinational, unversity hospitals  Study Design:  RCT  Overall N:  1049  Study Duration:  54 wks | Patients meeting ACR criteria for RA with symptom duration ≥3 months and ≤3 yrs and who were MTX naïve | Interventions, dose:  G1: MTX (20 mg/wk) + placebo  G2: MTX + IFX  (3 mg/kg/wk)  G3: MTX + IFX  (6 mg/kg/wk)  N:  G1: 298  G2: 373  G3: 378  Mean age, yrs:  50  Sex, % female:  71.1  Race, % white:  NR | Mean disease duration, yrs:  0.9  Baseline DAS28-ESR, mean:  6.67 (1.04)  Baseline HAQ, mean:  1.5  MTX naive:  100  MTX inadequate responders:  NA  Biologic non-responders:  NR  Seropositive (RF or CCP) (%):  RF+: 71-73  Baseline Sharp score, mean:  11.2-11.6 | At 54 weeks  DAS disease activity  % remission (DAS28-ESR <2.6):  G1: 12.3  G2&G3: 21.3  P<0.001  ACR20, %:  G1:53.6  G2:62.4  G3:66.2  (G2 vs. G1; p=0.028)  (G3 vs. G1; p<0.001)  ACR50, %:  G1:32.1  G2:45.6  G3:50.4  (G2 vs. G1; p<0.001)  (G3 vs. G1; p<0.001)  ACR70, %:  G1:21.2  G2:32.5  G3:37.2  (G2 vs. G1; p=0.002)  (G3 vs. G1; p<0.001) | Overall:  NR  SAEs:  G1: 11  G2: 14  G3: 14  Serious Infections (≥1 infection):  G1: 2.1  G2: 5.6  G3: 5.0  p=0.02  Overall discontinuation  G1: 25.5  G2: 21.4  G3: 23.8  Discontinuation because of AEs  G1: 3.2  G2: 9.5  G3: 9.6  Discontinuation due to lack of efficacy:  G1: 9.1  G2: 1.9  G3: 3.2 | Medium |

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| Author, yr:  St. Clair et al., 2004;17  Smolen et al., 2006;107  Smolen et al., 2009;106  Janssen Research and Development, 2017157  ASPIRE  (continued) |  |  | Erosive disease, %:  80-84 | mTSS score change:  G1: 3.7  G2: 0.4  G3: 0.5  (G1 vs. G2, G3:p<0.001)  Changes in TSS by disease activity (remission, low, moderate, high)  G1: 1.1, 2.2\*\*, 3.9\*\*, 5.8\*\*  G2: -0.2, -0.4, 0.6, 2.1.  [COMPARED WITH G2: \*p=0.05, \*\*p=0.01]  HAQ > 0.22, %:  G1:65.2  G2:76.0  G3:75.5 (G2 vs. G1; p=0.003)  (G3 vs. G1; p<0.004)  SF-36 PCS scores  G1: 10.1  G2: 11.7  G3: 13.2  G3 vs. G1, p=0.003  G3 vs. G2; p=0.10  Employability:  IFX + MTX (OR 2.4 [95% CI 2.23 to 2.61], p<0.001)  MTX (p=0.56)  Combo has higher probability of improvement than MTX alone  Net increase in employability, %:  MTX + IFX: 8  MTX-only: 2 | Patient adherence  NR  Infusion or injection reaction:  G1: 7  G2: 21  G3: 15  TB:  G1: 0  G2: 0.8  G3: 0.3 |  |

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| --- | --- | --- | --- | --- | --- | --- |
| Author, yr:  St. Clair et al., 2004;17  Smolen et al., 2006;107  Smolen et al., 2009;106  Janssen Research and Development, 2017157  ASPIRE  (continued) |  |  |  | Net change in actual employment, %:  MTX + IFX: -0.5  MTX-only: -1.3 (p=NS)  Employability status changed from employable to unemployable, %:  IFX: 8  MTX-only: 14 (p=0.05)  At weeks 30 to 54  HAQ:  G1:0.68  G2:0.80  G3:0.88;  (G2 vs. G1; p=0.03)  (G3 vs. G1; p<0.001) |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr:  Svensson et al., 200327  BARFOT Study #1 (1992-1995)  Country, Setting  Sweden, multicenter  Study Design:  RCT  Overall N:  245  Study Duration:  2 yrs | Patients with active RA diagnosed according to 1987 ACR revised criteria who were DMARD and glucocorticoid-naïve. Patients not included if not seen within 1 yr of symptom or sign of RA | Interventions, dose:  G1: PRED 7.5-15 mg/d for 1-3 months + MTX (if needed) 5-15 mg/wk, dosages NR)  G2: SSZ 2-3 g/day + PRED (if needed) up to 10 mg/d  N:  G1: 113  G2: 108  Median age, yrs:  54  Sex, % female:  63  Race, % white:  NR | Mean disease duration, mos:  6 mos  Prior csDMARD use, %:  0  Prior CS use, %:  0  MTX naive, %:  100  RF seropositive, %:  56 (between-group difference, p=0.0005)  Baseline DAS, mean:  4.9-5.0  **DAS score >3.2, %:**  92  HAQ, median score:  0.9  Larsen score, median  4.0 | At 2 yrs:  DAS disease activity  NR  Good EULAR response, %  G1: 30  G2: 33  Moderate EULAR response, %  G1: 40  G2: 30  No EULAR response, %  G1: 30  G2: 37  Remission, DAS28 <2.6, %  G1: 29  G2: 19 (p=0.095)  Larsen score, mean change from baseline  G1: 6.2 (SD, 12.2)  G2: 4.1 (SD, 10.9, p=0.298)  HAQ mean change from baseline  G1: -0.35 (SD, 0.61)  G2: -0.38 (SD, 0.55, p=0.752)  SF-36 outcome  NR  At 3 months  Figure only (Figure 2) | Overall:  NR  SAEs  NR  Overall discontinuation  G1: 19.5  G2: 47.2  Discontinuation because of AEs  G1: 11.5  G2: 33.3  Patient adherence  Patients who stayed on the allocated treatment for 2 yrs called “completers”. Overall, one-third of patients were non-completers (19% from G1 and 47% from G2)  Specific AEs  NR | High |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr:  Svensson et al., 2005;78  Hafstrem et al., 2009;97  Ajeganova et al., 2014;140  Hafstrom et al., 2014138  BARFOT Study #2 (1995-1999)  Country, Setting  Sweden, multicenter (6 centers)  Study Design:  RCT | Adults ages 18 to 80 yrs with active RA of ≤ 1 yr duration diagnosed according to 1987 ACR revised criteria who were DMARD and glucocorticoid-naive   * Excluded for previous fragility fractures, pts < 65 yrs | Interventions, dose:  G1: PNL (7.5 mg/d) + DMARD (SSZ 2 g/day, or MTX mean dose 10 mg/wk)  G1a: Subset of G1 (PNL + DMARD) participants who agreed to participate in 4 year followup  G1b: Subset of G1a participants in remission  G1c: Subset of G1a participants not in remission  G1d: Subset of G1 (PNL + DMARD) who had radiographs of hands and feet at baseline and 2 yr followup | Mean disease duration, mos:  5.8-6.5  DMARD naive, %:  100  Corticosteroid naive, %:  100  MTX naive, %:  100  Baseline DAS, mean:  5.3-5.4  HAQ:  0.98-1.01 | At 4 years (followup)  DAS disease activity  NR  ACR20/50/70 or EULAR response, %  NR  DAS remission  According to longitudinal analysis investigating the relationship between DAS remission and radiographic damage in patients randomized to G1a and G21:  DAS remission during followup=10.5 (Wald x^2), p<0.001 | Overall:  NR  SAEs  NR  Overall discontinuation  G1: 11.8  G2: 19.8  Discontinuation because of AEs  G1: 1.7  G2: 0 | Medium (High for 4 year outcomes) |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr:  Svensson et al., 2005;78  Ajeganova et al., 2014;140  Hafstrom et al., 2014;138  BARFOT Study #2 (1995-1999) (continued)  Overall N:  259  Study Duration:  2 yrs (4 and 10 yr followup) | with T score <-2.5 on bone mineral densitometry, and patients ≥65 yrs with Z score >-1 | G1e: Subset of G1 (PNL + DMARD), only including patients who had no history of prior CV events  G2: DMARD only (SSZ 2 g/day, or MTX mean dose 11 mg/wk)  G2a: Subset of G2 (DMARD only) participants who agreed to participate in 4 year followup  G2b: Subset of G1a participants in remission  G2c: Subset of G1a participants not in remission  G2d: Subset of G2 (DMARD only) who had radiographs of hands and feet at baseline and 2 yr followup  G2e: Subset of G2 (DMARD only), only including patients who had no history of prior CV events  N:  G1: 119 (a: 64, b: 35, c: 29, d: 108, e: 112)  G2: 131 (a: 86, b: 26, c: 60, d: 117, e: 111) | RF Seropositive, %:  66  Baseline Sharp score, mean:  4.1-4.8  Erosion score at baseline, mean:  1.9 | mTSS, median (IQR)  G1a: Figure only  G1b: 7.0 (IQR, 2.0-10.0)  G1c: 16.0 (IQR, 8.9-28.5)  G2a: Figure only  G2b: 7.5 (IQR, 4.0-16.0)  G2c: 13.0 (IQR, 2.0-20.0)  G1b vs. G1c: p=0.001  G2b vs. G2c: p=0.644  mTSS change from baseline, median (IQR)  G1a: NR  G1b: 4.5 (IQR, 2.0-7.5)  G1c: 12.0 (IQR, 4.0-24.5)  G2a: NR  G2b: 6.5 (IQR, 1.5-12.0)  G2c: 10.5 (IQR, 1.0-20.0)  G1b vs. G1c: p=0.006  G2b vs. G2c: p=0.466  HAQ score improvement  G1a: NR  G1b: NR  G1c: NR  G2a: NR  G2b: NR  G2c: NR  G1a vs. G2a: p=0.034  SF-36  NR | Patient adherence  NR  Specific AEs:  Nausea  G1: 0  G2: 0.8  Leukopenia  G1: 0.8  G2: 2.3  Rash  G1: 5.0  G2: 6.9  At 10 yrs (followup)  Total incident CV event, %  G1e: 15.2  G2e: 13.5 (p=0.72)  Incident ischaemic coronary event, %  G1e: 6.2  G2e: 9.0 (p=0.44)  Incident ischaemic cerebrovascular event, %  G1e: 8.9  G2e: 4.5 (p=0.19)  Death, %  G1e: 8  G2e: 8 (p=0.98) |  |

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| Author, yr:  Svensson et al., 2005;78  Ajeganova et al., 2014;140  Hafstrom et al., 2014;138  BARFOT Study #2 (1995-1999) (continued) |  | Mean age, yrs:  51-59  Sex, % female:  64  Race, % white:  NR |  | At 3 years (followup)  DAS disease activity  NR  ACR20/50/70 response, %  NR  DAS remission, %  NR  mTSS, mean (SE)  G1a: Figure only  G1b: NR  G1c: NR  G2a: Figure only  G2b: NR  G2c: NR  HAQ  NR  SF-36  NR  At 2 yrs:  DAS28 score, mean  G1: 2.7 (SD, 1.3)  G2: 3.2 (SD, 1.4, p=0.005)  ACR or EULAR  NR | Risk of CV-related death in patients with DAS remission compared with those not in remission, HR (95% CI)  G1e: 0.30 (CI 0.07 to 1.1, p=0.087)  G2e: 0.42 (CI 0.09 to 2.03, p=0.28)  Risk of CV-related death in patients with good EULAR response compared with those without good response, HR (95% CI)  G1e: 0.45 (CI 0.12  to 1.70, p=0.24)  G2e: 0.28 (CI 0.07 to 1.13, p=0.074) |  |

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| --- | --- | --- | --- | --- | --- | --- |
| Author, yr:  Svensson et al., 2005;78  Ajeganova et al., 2014;140  Hafstrom et al., 2014;138  BARFOT Study #2 (1995-1999) (continued) |  |  |  | DAS28 < 2.6 disease remission, % achieved  G1: 55.5  G1a: 55  G2: 32.8  G2a: 30  G1 vs. G2: p=0.0005  G1a vs. G2a: p=0.003  HAQ mean score  G1: Figure only  G2: Figure only (p=0.003)  HAQ, mean decrease from baseline:  G1: 0.5 (SD, 0.5)  G2: 0.7 (SD, 0.6)  **Change from baseline in mTSS, median (IQR)**  G1d: 1.8 (IQR, 0.5-6.0)  G2d: 3.5 (IQR, 0.5-10.0)  (p=0.019)  Change from baseline in mTSS, mean (SD)  G1d: 5.2 (SD, 9.0)  G2d: 9.1 (SD, 14.3)  SF-36  NR  At 18 mos:  DAS28 score, mean  G1: Figure only  G2: Figure only (p=0.001) |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr:  Svensson et al., 2005;78  Ajeganova et al., 2014;140  Hafstrom et al., 2014;138  BARFOT Study #2 (1995-1999) (continued) |  |  |  | ACR20/50/70 or EULAR  NR  DAS28 < 2.6 disease remission, % achieved  G1: NR  G1a: 53  G2: NR  G2a: 34  G1a vs. G2a: p=0.020  HAQ mean score  G1: Figure only  G2: Figure only (p=0.0005)  SHS outcome  NR  SF-36  NR  At 1 yr:  DAS28 score, mean  G1: 2.7 (SD, 1.5)  G2: 3.3 (SD, 1.5, p=0.001)  ACR20/50/70 or EULAR  NR  DAS28 < 2.6 disease remission, % achieved  G1: 51.3  G1a: 49  G2: 39.2  G2a: 42  G1 vs. G2: p=0.006)  G1a vs. G2a: p=0.36 |  |  |

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| --- | --- | --- | --- | --- | --- | --- |
| Author, yr:  Svensson et al., 2005;78  Ajeganova et al., 2014;140  Hafstrom et al., 2014;138  BARFOT Study #2 (1995-1999) (continued) |  |  |  | HAQ mean score  G1: Figure only  G2: Figure only (p=0.002)  HAQ, mean decrease from baseline:  G1: 0.4 (SD, 0.5)  G2: 0.6 (SD, 0.6)  mTSS change from baseline, median (IQR)  G1d: 1.0 (IQR, 0-3.0)  G2d: 2.0 (IQR, 0-5.0)  (p=0.035)  mTSS change from baseline, mean (SD)  G1d: 2.4 (SD, 4.6)  G2d: 5.3 (SD, 9.3)  SF-36  NR  At 6 months  DAS28 score, mean  G1: Figure only  G2: Figure only (p=0.0005)  ACR20/50/70 or EULAR  NR  DAS28 < 2.6 disease remission, % achieved  G1: NR  G1a: 48  G2: NR  G2a: 22  G1a vs. G2a: P =0.001 |  |  |

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| --- | --- | --- | --- | --- | --- | --- |
| Author, yr:  Svensson et al., 2005;78  Ajeganova et al., 2014;140  Hafstrom et al., 2014;138  BARFOT Study #2 (1995-1999) (continued) |  |  |  | **HAQ mean score**  G1: Figure only  G2: Figure only (p=0.0005)  SHS outcome  NR  SF-36  NR  At 3 months  DAS28 score, mean  G1: Figure only  G2: Figure only (p=0.0005)  ACR20/50/70 or EULAR  NR  DAS28 < 2.6 disease remission, % achieved  G1: NR  G1a: 35  G2: NR  G2a: 9  G1a vs. G2a: p=0.0005  HAQ mean score  G1: Figure only  G2: Figure only (0.0005)  SHS outcome  NR  SF-36  NR |  |  |

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| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Tak et al., 2011;30  Rigby et al., 2011;133  Tak et al., 2012;132  IMAGE  Country, Clinical Setting:  Multinational, multicenter  Study Design:  RCT  Overall N:  755  Study Duration:  2 yrs | Adults (aged 18 to 80 years) fulfilling ACR criteria for RA with disease duration between 8 wks and 4 yrs, active disease defined as swollen and tender joint counts ≥ 8 each and CRP ≥ 1 mg/dl, radiographic evidence of erosive damage attributable to RA if rheumatoid factor negative, and no prior MTX use | Interventions, dose:  G1:   * MTX: 7.5 mg/wk escalated up to 20 m/wk by wk 8 (oral) * RIT: 1,000 mg on days 1 and 15 (intravenous; infusions premedicated with 100 mg methylprednisolone)   G2:   * MTX: 7.5 mg/wk escalated up to 20 m/wk by wk 8 (oral) * RIT: 500 mg on days 1 and 15 (intravenous; infusions premedicated with 100 mg methylprednisolone)   G3:   * MTX: 7.5 mg/wk escalated up to 20 m/wk by wk 8 (oral) * Placebo   Concomitant glucocorticoids (≤ 10 mg/day PNL or equivalent) and non-steroidal anti-inflammatory drugs were allowed with stable doses while intravenous or -muscular glucocorticoids and additional DMARDs were not allowed; repeat courses were permitted from wk 24 for patients with DAS28 ESR ≥ 2.6 | Mean disease duration, yrs:  0.91-0.99  Baseline DAS28 ESR, mean:  7.0-7.1  Baseline HAQ, mean:  1.7-1.8  Concomitant CS, %:  46.4 (of 748)  Prior csDMARD use, %:  29.9 (of 748)  MTX naïve, %:  100  MTX inadequate responders, %:  0.0  Biologic non-responders, %:  NR | At wk 104  DAS28 LDA, %:  G1: 48  G2: 45  G3: 25  G1/2 vs. G3: p<0.0001  ACR response, %:  NR  DAS28 remission (< 2.6), %:  G1: 32  G2: 34  G3: 13  G1/2 vs. G3: p<0.0001  Genant-modified Sharp score  Total score, mean change:  G1: 0.41  G2: 0.76  G3: 1.95  G1 vs. G3: p<0.0001  G2 vs. G3: p=0.0041  No radiographic progression (change ≤ 0), %:  G1: 57  G2: 49  G3: 37  G1 vs. G3: p<0.0001  G2 vs. G3: ex-p=0.0059 | Overall AEs:  G1: 86.8  G2: 82.7  G3: 86.3  SAEs:  G1: 13.2  G2: 14.9  G3: 16.9  Overall discontinuation:  G1: 15  G2: 15  G3: 29  Discontinuation because of AEs:  G1: 2.8  G2: 3.2  G3: 6.8  Discontinuation because of lack of efficacy:  NR (Lack of efficacy and refusal of treatment were the most common reasons for withdrawal)  Patient adherence:  NR | Low |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Tak et al., 2011;30  Rigby et al., 2011;133  Tak et al., 2012;132  IMAGE  (continued) |  | N:  G1: 251  G2: 252  G3: 252  Mean age, yrs:  G1: 47.9 (SD, 13.3)  G2: 47.9 (SD, 13.4)  G3: 48.1 (SD, 12.7)  Overall: NR  Sex, % female:  81.1 (of 748)  Race, % white:  NR  Race, % black:  NR  Ethnicity, % Latino:  NR | RF seropositive, %:  86.4 (of 748)  Baseline Genant-modified Sharp score, mean:  6.9-7.7  Erosive disease, %:  NR | HAQ-DI response (decrease ≥0.22), %:  G1: 86  G2: 84  G3: 77  G1 vs. G3: p<0.05  SF-36:  NR  At 1 yr  DAS28 ESR disease activity  Mean change:  G1: -3.21  G2: -3.05  G3: -2.06  G1/2 vs. G3: p<0.0001  LDA, %:  G1: 43  G2: 40  G3: 20  G1/2 vs. G3: p<0.0001  ACR20 response, %:  G1: 80  G2: 77  G3: 64  G1 vs. G3: p<0.0001  G2 vs. G3: p<0.05  ACR50 response, %:  G1: 65  G2: 59  G3: 42  G1/2 vs. G3: p<0.0001 | Specific AEs  Infusion-related reaction:  G1: 18.4  G2: 14.1  G3: 12.4 |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Tak et al., 2011;30  Rigby et al., 2011;133  Tak et al., 2012;132  IMAGE  (continued) |  |  |  | ACR70 response, %:  G1: 47  G2: 42  G3: 25  G1/2 vs. G3: p<0.0001  DAS28 ESR remission, %:  G1: 31  G2: 25  G3: 13  G1 vs. G3: p<0.0001  G2 vs. G3: p<0.001  Genant-modified Sharp score  Total score, mean change:  G1: 0.359  G2: 0.646  G3: 1.079  G1 vs. G3: p<0.001 No radiographic progression (change ≤ 0), %:  G1: 64  G2: 58  G3: 53  G1 vs. G3: p<0.05  HAQ-DI  Mean change:  G1: -0.916  G2: -0.905  G3: -0.628  G1/2 vs. G3: p<0.0001 |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Tak et al., 2011;30  Rigby et al., 2011;133  Tak et al., 2012;132  IMAGE  (continued) |  |  |  | Response (decrease ≥ 2.2), %:  G1: 88  G2: 87  G3: 77  G1/2 vs. G3: p<0.05  SF-36  Mental component, mean change:  G1: 6.662  G2: 6.181  G3: 4.848  Physical component, mean change:  G1: 10.763  G2: 10.073  G3: 7.237  G1 vs. G3: p<0.0001  G2 vs. G3: p<0.001  Pain (visual analogue scale), mean change:  G1: -40.0  G2: -36.2  G3: -27.8  G1/2 vs. G3: p<0.0001  FACIT-F, mean change:  G1: 10.282  G2: 9.362  G3: 6.830  G1 vs. G3: p<0.0001  G2 vs. G3: p<0.05 |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Tak et al., 2011;30  Rigby et al., 2011;133  Tak et al., 2012;132  IMAGE  (continued) |  |  |  | At wk 24  DAS28 ESR disease activity:  NR  Genant-modified Sharp score  Total score, mean change:  G1: 0.328  G2: 0.580  G3: 0.701  G1 vs. G3: p<0.05  No radiographic progression (change ≤ 0), %:  G1: 70  G2: 63  G3: 59  G1 vs. G3: p<0.05 |  |  |
| Author, yr, Study Name:  Takeuchi et al., 201435;  Yamanaka et al., 2014150  HOPEFUL 1  Country, Clinical Setting:  Japan  Study Design:  RCT  Overall N:  334  Study Duration:  26 wks (with 6 month open label) | Adults (aged ≥ 20 yrs) fulfilling ACR criteria for RA with disease duration ≤ 2 yrs, tender joint count ≥ 10, swollen joint count ≥ 8, CRP level ≥ 1.5 mg/dl or ESR ≥ 28 mm/h, and ≥ 1 joint erosion or rheumatoid factor positivity; no prior treatment | Interventions, dose:  G1:   * MTX: 6 mg/wk and increased to 8 mg/wk if ≥ 20% decrease in tender or swollen joint counts not achieved on/after wk 8 (oral) * ADA: 40 mg every other wk (subcutaneous) * Folic acid: 5 mg/wk   G2:   * MTX: 6 mg/wk and increased to 8 mg/wk if ≥ 20% decrease in tender or swollen joint counts not achieved on/after wk 8 (oral) * Placebo * Folic acid: 5 mg/wk | Mean disease duration, yrs:  0.3  Baseline DAS28-ESR, mean:  6.6  Baseline DAS28 (CRP), mean:  5.8-5.9  Baseline HAQ-DI, mean:  1.1-1.3 | At 26 wks  DAS28-ESR disease activity, change in mean:  G1: -2.9  G2: -1.7  DAS28 (CRP) disease activity, change in mean:  G1: -2.9  G2: -1.7  ACR20 response, %:  G1: 75.4  G2: 56.4  ACR50 response, %:  G1: 64.3  G2: 38.7  ACR70 response, %:  G1: 47.4  G2: 22.7 | Overall AEs:  G1: 80.7 (376 events)  G2: 71.8 (302 events)  SAEs:  G1: 0.6  G2: 0.6  Overall discontinuation:  G1: 15.2  G2: 22.1  Discontinuation because of AEs:  G1: 4.1  G2: 2.5  Moved to rescue:  G1: 8.2  G2: 17.2  Patient adherence:  NR | Medium |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Takeuchi et al., 201435;  Yamanaka et al., 2014150  HOPEFUL 1  (continued) | with MTX or LEF or >2 other DMARDs | Those experiencing > 20% increase in tender and swollen joint counts at wks 12, 16, or 20 were eligible for open-label rescue treatment with 40 mg ADA every other week; those completing the 26 wk double-blind period were eligible for open-label ADA + MTX for an additional 26 wks  N:  G1: 171  G2: 163  Mean age, yrs:  G1: 54.0 (SD, 13.1)  G2: 54.0 (SD, 13.2)  Overall: NR  Sex, % female:  81.4  Race, % white:  NR  Race, % black:  NR  Ethnicity, % Latino:  NR | Prior CS use, %:  32.0  Prior csDMARD use, %:  48.2  MTX naïve, %:  100  MTX inadequate responders, %:  NR  Biologic non-responders, %:  NR  RF seropositive, %:  84.4  anti-CCP seropositive, %:  84.1  Baseline mTSS score, mean:  G1: 13.6 (SD, 22.3)  G2: 13.6 (SD, 17.4)  Overall: NR  Erosive disease, %:  NR | DAS28-ESR remission (< 2.6), %:  G1: 31.0  G2: 14.7  p<0.001  Association of LDA at baseline with no radiographic progression (subgroup analysis – multivariate regression)  G1: Not associated (p=NS)  G2: Significantly associated (p=0.02)  DAS28 (CRP) remission (< 2.6), %:  G1: 52.0  G2: 26.4  p<0.001  mTSS score  Change from baseline, mean:  G1: 1.5  G2: 2.4  p<0.001  No radiographic progression, %:  G1: 62.0  G2: 35.4 (of 161)  p<0.001  Association of LDA at baseline with no radiographic progression (subgroup analysis – multivariate regression)  G1: Not associated (p=NS)  G2: Significantly associated (p=0.01) | Specific AEs :  Injection-site reaction  G1: 10.5  G2: 3.7  p=0.02 |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Takeuchi et al., 201435;  Yamanaka et al., 2014150  HOPEFUL 1  (continued) |  |  |  | HAQ-DI:  Change in mean:  G1: -0.6 (SD, 0.6)  G2: -0.4 (SD, 0.6)  p<0.001  Response (< 0.5), %:  G1: 60.2  G2: 36.8  p<0.001  SF-36:  NR  At 20 wks  DAS28-ESR disease activity, change in mean:  G1: -2.6  G2: -1.7  DAS28 (CRP) disease activity, change in mean:  G1: -2.8  G2: -1.7  ACR20 response, %:  G1: 78.9  G2: 62.0  ACR50 response, %:  G1: 62.0  G2: 37.4  ACR70 response, %:  G1: 36.3  G2: 16.0 |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Takeuchi et al., 201435;  Yamanaka et al., 2014150  HOPEFUL 1  (continued) |  |  |  | At 16 wks  DAS28-ESR disease activity, change in mean:  G1: -2.6  G2: -1.6  DAS28 (CRP) disease activity, change in mean:  G1: -2.6  G2: -1.7  ACR20 response, %:  G1: 74.8  G2: 54.0  ACR50 response, %:  G1: 59.6  G2: 31.9  ACR70 response, %:  G1: 31.0  G2: 14.7 |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Takeuchi et al., 201435;  Yamanaka et al., 2014150  HOPEFUL 1  (continued) |  |  |  | At 12 wks  DAS28-ESR disease activity, change in mean:  G1: -2.5  G2: -1.4  DAS28 (CRP) disease activity, change in mean:  G1: -2.5  G2: -1.4  ACR20 response, %:  G1: 76.6  G2: 54.6  ACR50 response, %:  G1: 53.2  G2: 26.4  ACR70 response, %:  G1: 25.7  G2: 8.0 |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Todoerti et al., 20106  Country, Clinical Setting:  Italy, early RA clinic  Study Design:  RCT  Overall N:  210  Study Duration:  2 yrs | Patients meeting ACR criteria for RA with symptom duration <12 mos | Interventions, dose:  G1: Low-dose oral PRED + MTX  G2: MTX only  Both treatments were DAS driven step-up protocols  MTX:  10 mg/wk;  Increased to 15 mg/wk and then to 20 mg/wk if LDA (DAS ≤2.4) not reached during followup visits  Low-dose PRED:  12.5 mg/d for wks 1-2 then 6.25 mg/d  N:  G1: 105  G2: 105  Mean age, yrs:  58-61  Sex, % female:  G1: 78.1  G2: 70.5  Race, % white:  NR | Median disease duration, mos (IQR):  3 (1.93-5.4)  Baseline DAS, mean:  3.74 (SD, 0.88)  Baseline HAQ, median:  1.19 (IQR, 0.63-1.88)  MTX naive:  NR  MTX inadequate responders:  NR  Biologic non-responders:  NR  Seropositive (RF or CCP) (%):  RF+: 41.9-46.7  CCP+: 28.6-29.7  Baseline Sharp score, mean:  NR  Erosive disease, %:  NR | DAS remission, %  At 18 mos  G1: 76.7  G2: 33.3 (p=0.01)  OR (95% CI) for probability of still being in remission over first 6 mos after first year of txmt: 4.480 (1.35-14.82) (p=0.014)  P based on GEE analysis <0.001  At 1 yr  G1: 39.7  G2: 30.6 (p=0.290)  OR (95% CI): 1.965 (1.214 to 3.182) (p=0.006) for probability of being in remission within 1 yr  DAS more suppressed in G1 than G2 (P <0.001, based on GEE analysis)  At 9 mos  G1: 35.2  G2: 25.9 (p=0.239)  At 6 mos  G1: 26.3  G2: 16 (p=0.082)  At 4 mos  G1: 25.5  G2: 8 (p=0.001)  At 2 mos  G1: 14.9  G2: 7 (p=0.112) | NR | Medium |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, year, study name, if applicable  van Vollenhoven et al., 200910;  Eriksson et al., 2013;121  van Vollenhoven et al., 2012;122  Rezaei et al., 2013123  Eriksson et al., 2016;124  Levitsky et al., 2015;125  Karlsson et al., 2013;126  Levitsky et al., 2017168  SWEFOT  Country and setting  Sweden; multicenter  Study design  RCT  Overall N  258  Duration of study  12 mos (2 yr followup) | Adults (aged ≥ 18 yrs) fulfilling ACR criteria for RA with symptom duration < 1 yr, DAS28 > 3.2, no prior DMARD use, no oral glucocorticoid or stable glucocorticoid therapy for ≥ 4 wks of ≤ 10 mg/day PRED (or equivalent), and for whom MTX ≤ 20 mg/wk had not lowered their DAS28 to ≤ 3.2 during the first 3 mos of disease treatment | Comparisons (dosage and frequency)  G1:   * MTX: 20 mg/wk (oral) * SSZ: 2000 mg/day (oral) * HCQ: 400 mg/day (oral)   G1a: Obese (BMI ≥ 30) subpopulation of G1  G1b: Overweight (BMI <25-29.9) subpopulation of G1  G1c: Normal (BMI <25) subpopulation of G1  G2:   * MTX: 20 mg/wk (oral) * IFX: 3 mg/kg at wks 0, 2, 6 and every 8 wks thereafter (intravenously)   G2a: Obese (BMI ≥ 30) subpopulation of G2  G2b: Overweight (BMI <25-29.9) subpopulation of G2  G2c: Normal (BMI <25) subpopulation of G2  N:  G1: 130  G1a: 20  G1b: 22  G1c: 52  G2: 128  G2a: 12  G2b: 26  G2c: 53  Mean age, yrs:  G1: 52.9 (SD, 13.9)  G2: 51.1 (SD, 13.3)  Overall: NR | Mean disease duration, mos:  6.2-6.3  3-mo DAS28, mean:  4.79-4.91  Baseline HAQ, mean:  1.27-1.32  Prior CS use, %  7.0  MTX naïve, %:  0  Prior csDMARD use, %:  100  MTX inadequate responders, %:  100  Biologic non-responders, %:  NR  RF seropositive, %:  67.1  3-mo Sharp score, mean:  NR | At 2 yrs  ACR20 response %  G1: 33  G2: 40 (p=0.259)  ACR50 response%  G1:22  G2:30 (p=0.124)  ACR70 Response %  G1:14  G2: 16 (p=0.566)  **Good EULAR response, %**  G1a+G2a: 38  G1c+G2c: 66  OR: 3.2 (95% CI 1.4 to 7.3)  **Remission**  G1a+G2a: 15  G1c+G2c: 52  OR: 6.0 (95% CI 1.6 to 22.6)  **Multivariate baseline predictor of DAS28 non-remission: Obesity, OR (95% CI)**  G1a: 7.7 (95% CI 1.4 to 41.2)  G2a: 2.1 (95% CI 0.5 to 10.0)  At 12 mos  DAS27 disease activity:  NR  ACR20 response, %:  ITT population:  G1: 28.5  G2: 42.2  RR 1.48 (95% CI 1.06 to 2.08;p=0.0266) | Overall AEs, n:  G1: 48 (in 33 patients)  G2: 32 (in 26 patients)  SAEs:  G1: 0.8  G2: 0.8  Overall discontinuation:  G1: 31.5  G2: 18.0  p=0.014  Discontinuation due to adverse events:  G1: 10.8  G2: 7.8  Discontinuation due to lack of efficacy:  G1: 13.8  G2: 2.3  Patient adherence:  NR (5 in G1 never received allocated treatment and 5 switched treatment; 8 in G2 never received allocated treatment and 5 switced treatment) | Medium |

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| --- | --- | --- | --- | --- | --- | --- |
| Author, year, study name, if applicable  van Vollenhoven et al., 200910;  Eriksson et al., 2013;121  van Vollenhoven et al., 2012;122  Rezaei et al., 2013123  Eriksson et al., 2016;124  Levitsky et al., 2015;125  Karlsson et al., 2013126  SWEFOT  (continued) |  | Sex, % female:  76.7  Race, % white:  NR  Race, % black:  NR  Ethnicity, % Latino:  NR | Erosive disease, %:  NR | mITT population:  G1: 45.4  G2: 59.4  RR 1.31 (95% CI, 1.03 to 1.66;p=0.0257)  ACR50 response, %:  ITT population:  G1: 14.6  G2: 25.0  RR 1.71 (95% CI, 1.02 to 2.86;p=0.0424)  mITT population:  G1: 33.8  G2: 48.4  RR 1.43 (95% CI, 1.06 to 1.93;p=0.0226)  ACR70 response, %:  ITT population:  G1: 6.9  G2: 11.7  RR 1.69 (95% CI, 0.77 to 3.73;p=0.2044)  mITT population:  G1: 15.4  G2: 28.1  RR 1.83 (95% CI, 1.12 to 2.98;p=0.0156)  DAS28 remission, %:  NR | Specific AEs:  Respiratory system, %:  G1: 0.1  G2: 0.6  Other GI symptoms (not specified), %:  G1: 11.5  G2: 0.7  Skin and allergic reactions, %:  G1: 2.3  G2: 8.5 |  |

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| --- | --- | --- | --- | --- | --- | --- |
| Author, year, study name, if applicable  van Vollenhoven et al., 200910;  Eriksson et al., 2013;121  van Vollenhoven et al., 2012;122  Rezaei et al., 2013123  Eriksson et al., 2016;124  Levitsky et al., 2015;125  Karlsson et al., 2013126  SWEFOT  (continued) |  |  |  | Achieved remission at least 3 months after initiation, %:  G1a: 15  G1b+G1c: 32  G2a: 42  G2b+G2c: 35  Sharp score:  NR  HAQ:  NR  SF-36:  NR  **At 9 mos**  **Achieved remission at least 3 months after initiation %:**  G1a: 0  G1b+G1c: 27  G2a: 33  G2b+G2c: 41  G1a vs G2a, P = 0.021  G1a vs G1b+G1c, P = 0.017  **At 6 mos**  **Achieved remission at least 3 months after initiation %:**  G1a: 0  G1b+G1c: 28  G2a: 27  G2b+G2c: 26  G1a vs G2a, P = 0.045  G1a vs G1b+G1c, P = 0.009 |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Verschueren, et al., 201598  Verschueren, et al., 201595  Verschueren, et al., 201799  CareRA  Country, Clinical Setting:  Belgium,  rheumatology centers (academic, hospital, and private)  Study Design:  RCT  Overall N:  379  Study Duration:  2 yrs | Patients with RA defined by ACR criteria with disease duration ≤1 yr, and DMARDs/glucocorticoid naïve | Interventions, dose:  G1: COBRA Classic (high-risk patients)   * MTX (15 mg/wk) + SSZ (2 g/d) + PRED (60 mg/d tapered to 7.5 mg/d from wk 7)   G2: COBRA Slim (high-risk patients)   * MTX (15 mg/wk) + PRED (30 mg tapered to 5 mg from wk 6)   G3: COBRA Avant-Garde (high-risk patients)   * MTX (15 mg/wk) + LEF (10 mg/d) + PRED (30 mg tapered to 5 mg from wk 6)   G4: MTX tight step up (low-risk patients)   * MTX (15 mg/wk), no steroids allowed   G5: COBRA Slim (low-risk patients)   * MTX (15 mg/wk) + PRED (30 mg tapered to 5 mg from wk 6)   MTX: COBRA classic scheme has a higher MTX dose than the original COBRA schedule (other publication) | Mean disease duration, wks:  1.8-3.2  Baseline DAS28(CRP), mean:  4.5-5.0  Baseline HAQ, mean:  0.9-1.2  MTX naïve, %:  100  MTX inadequate responders:  0  Biologic non-responders:  NR  RF seropositive, %:  23.4-83.7  Baseline Sharp score, mean:  0.7-1.3  Erosive disease , %  0.0-34.4 | At 52 wks  DAS28 (CRP) disease activity, mean change (SD)  G1: 2.5 (SD, 1.5)  G2: 2.3 (SD, 1.4)  G3: 2.3 (SD, 1.5)  G4: 2.1 (SD, 1.7)  G5: 2.1 (SD, 1.9)  G1 vs. G2 vs. G3 p=0.329  G4 vs. G5 p=0.990  Good EULAR response, %  G1: 67.3  G2: 68.4  G3: 67.7  G4: 57.4  G5: 60.5  G1 vs. G2 vs. G3 p=0.995  G4 vs. G5 p=0.771  Moderate EULAR response, %  G1: 84.7  G2: 88.8  G3: 88.2  G4: 78.7  G5: 76.7  G1 vs. G2 vs. G3 p=0.654  G4 vs. G5 p=0.822  DAS28 <2.6 remission, %  G1: 64.3  G2: 60.2  G3: 62.4  G4: 57.4  G5: 67.4 | Overall:  G1: 67.3  G2: 66.3  G3: 78.5  G4: 63.8  G5: 51.2  SAEs  G1: 15.3  G1: 15.3  G3: 10.8  G4: 14.9  G5: 16.3  Overall discontinuation  G1: 8.2  G2: 9.2  G3: 8.6  G4: 6.4  G5: 11.6  Discontinuation because of AEs  NR  Patient adherence  69.4  Itch and Rash  G1: 4.1  G2: 3.1  G3: 1.1  G4: 6.4  G5: 4.7 | Medium |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Verschueren, et al., 201598  Verschueren, et al., 201595  Verschueren, et al., 201799  CareRA  (continued) |  | PRED: Dose tapered down wkly except for the lowest dose (7.5 mg in G1 and 5 mg in G2/3) which was maintained until wk 28. After that PRED was tapered. Mean PRED dose at 52 wks was 4.9 mg/d (SD, 1.6)  N:  G1: 98  G2: 98  G3: 93  G4: 47  G5: 43  Mean age, yrs:  51.2-53.2  Sex, % female:  64.3-80.9  Race, % white:  NR |  | Change in SHS from baseline, mean (SD)  G1: 0.3 (SD, 0.5)  G2: 0.4 (SD, 1.1)  G3: 0.3 (SD, 0.6)  G4: 0.2 (SD, 0.3)  G5: 0.3 (SD, 0.5)  G1 vs. G2 vs. G3 p=0.819  G4 vs. G5 p=0.257  HAQ change according to ITT analysis after LOCF imputation  G1: 0.7 (SD, 0.7)  G2: 0.5 (SD, 0.7)  G3: 0.6 (SD, 0.7)  G4: 0.5 (SD, 0.6)  G5: 0.6 (SD, 0.7)  G1 vs. G2 vs. G3 p=0.368  G4 vs. G5 p=0.832  SF-36  NR  At 16 wks  DAS disease activity, change from baseline  G1: 2.8 (SD, 1.2)  G2: 2.6 (SD, 1.2)  G3: 2.4 (SD, 1.3)  G4: 1.76 (SD, 1.68)  G5: 2.12 (SD, 1.41)  G1 vs. G2 vs. G3 p=0.140  G4 vs. G5 p=0.192  G1 v G2 difference (95% CI): 0.2 (-0.13 to 0.52)  G2 v G3 difference (95% CI): -0.2 (-0.49 to 0.21) |  |  |

| Study  Characteristics | Study Population Summary | Interventions and Patient Characteristics | Baseline Disease and Treatment Characteristics | Health Outcomes | Adverse Events (%) | ROB Rating |
| --- | --- | --- | --- | --- | --- | --- |
| Author, yr, Study Name:  Verschueren, et al., 201598  Verschueren, et al., 201595  Verschueren, et al., 201799  CareRA  (continued) |  |  |  | Good EULAR response, %  G1: 79.6  G2: 79.6  G3: 76.6  G4: 44.7  G5: 58.1  G1 vs. G2 vs. G3 p=0.844  G4 vs. G5 p=0.202  G1 v G2 difference (95% CI): 0.0% (−11.3% to 11.3%)  G2 v G3 difference (95% CI): −3.0% (−14.7% to 8.7%)  Moderate EULAR response, %  G1: 98.0  G2: 95.9  G3: 93.6  G4: 72.3  G5: 86.0  G1 vs. G2 vs. G3 p=0.320  G4 vs. G5 p=0.111  G1 v G2 difference (95% CI): 2.1% (−3.6% to 8.2%)  G2 v G3 difference (95% CI): −2.3% (−9.6% to 4.6%)  DAS remission, %  G1: 70.4  G2: 73.5  G3: 68.1  G4: 46.8  G5: 65.1  G1 vs. G2 vs. G3 p=0.713  G4 vs. G5 p=0.081  G1 v G2 difference (95% CI): -3.1% (-15.4% to 9.5%)  G2 v G3 difference (95% CI): -5.4% (-18.0% to 7.4%) |  |  |

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| Author, yr, Study Name:  Verschueren, et al., 201598  Verschueren, et al., 201595  Verschueren, et al., 201799  CareRA  (continued) |  |  |  | SHS  NR  HAQ mean change from baseline  G1: 0.8 (SD, 0.6)  G2: 0.6 (SD, 0.6)  G3: 0.7 (SD, 0.6)  G4: 0.40 (SD, 0.62)  G5: 0.58 (SD, 0.64)  G1 vs. G2 vs. G3: p=0.081  G4 vs. G5: p=0.267  G1 vs. G2 difference (95% CI): 0.2 (0.02 to 0.37)  G2 vs. G3 difference (95% CI):  0.1 (−0.17 to 0.19)  HAQ score of 0 (no functional impairment), %  G1: 45.9  G2: 42.9  G3: 48.9  G4: 23.4  G5: 51.2  G1 vs. G2 vs. G3: p=0.7  G4 vs. G5: p=0.006  SF-36  NR |  |  |

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| Author, yr, Study Name:  Westhovens et al., 200931;  Wells et al., 2011129;  Bathon et al., 2011130;  Smolen et al., 2015131  AGREE  Country, Clinical Setting:  Multinational,  Clinical Setting  NR  Study design  RCT  Overall N  509  Duration of study  1 yr (1-yr open label extension) | Adults (aged ≥ 18 yrs) with disease duration ≤ 2 yrs, at least 12 tender and 10 swollen joints, CRP ≥ 0.45 mg/dl, rheumatoid factor and/or anti-CCP-2 antibodies seropositivity, and radiographic evidence of bone erosions; patients were either MTX-naïve at study entry or had previous exposure of ≤10 mg/wk for ≤3 wks but not within 3 mos prior to consenting to participate | Interventions, dose:  G1:   * ABA: ~10 mg/kg on days 1, 15, 29, and every 4 wks thereafter (intravenous) * MTX: 7.5 mg/wk, 15 mg/wk at wk 4, and 20 mg/wk at wk 8 thereafter   G2:   * Placebo * MTX: 7.5 mg/wk, 15 mg/wk at wk 4, and 20 mg/wk at wk 8 thereafter   In yr 2, G1 continued treatment while ABA was initiated in G2N:  G1: 256  G2: 253  Mean age, yrs:  49.7-50.1 | Mean disease duration, mos:  6.2-6.7  DAS28 (CRP), mean:  6.3  HAQ-DI, mean:  1.7  Prior CS use, %:  49.0-51.2  Prior csDMARD use, %:  HCQ: 1.6-2.0  SSZ: 0-1 | At 1 yr  DAS28 (CRP) disease activity:  G1: -3.22 (SE 0.09)  G2: -2.49 (SE 0.09)  p<0.001  ACR20 response, %:  NR  ACR50 response, %:  G1: 57.4  G2: 42.3  p<0.001  ACR70 response, %:  G1: 42.6  G2: 27.3  p<0.001  DAS28 (CRP) remission (<2.6), %:  G1: 41.4  G2: 23.3  p<0.001 | Overall AEs:  G1: 84.8  G2: 83.4  SAEs:  G1: 7.8  G2: 7.9  Overall discontinuation:  G1: 9.4  G2: 10.3  Discontinuation due to AEs:  G1: 3.1  G2: 4.3  Discontinuation due to SAEs:  G1: 1.2  G2: 1.2  Discontinuation due to lack of efficacy:  G1: 0.0  G2: 3.2 | Low (ACR response, DAS28 remission, LDA, radio-graphic outcome, discontinuation, AEs);  Medium (HAQ-DI, SF-36) |

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| Author, yr, Study Name:  Westhovens et al., 200931;  Wells et al., 2011129;  Bathon et al., 2011130;  Smolen et al., 2015131  AGREE  (continued) |  | Sex, % female:  G1: 76.6  G2: 78.7  Overall: NR  Race, % white:  G1: 78.9  G2: 86.6  Overall: NR  Race, % black:  NR  Ethnicity, % Latino:  NR | HCQ  1.6-2.0  SSZ  0.0-0.4  MTX naïve, %:  98.0  MTX inadequate responders, %:  NR  Biologic non-responders, %:  NR  RF seropositive, %:  96.1-96.8  anti-CCP-2 positive, %:  85.8-92.2  Baseline Genant-modified Sharp score, mean:  7.1  Radiographic evidence of bone erosions %:  100 | Genant-modified Sharp score  Change in total score, mean:  G1: 0.63  G2: 1.06  p=0.040  **No radiographic progression (total ≤ 0):**  G1: 61.2% (95% CI, 55.0-67.3)  G2: 52.9% (95% CI, 46.6-59.2)  Difference: 8.3% (95% CI, -1.0 to 17.5)  HAQ-DI  Achieved change of ≥0.3 units, %:  G1: 71.9  G2: 62.1  p=0.024  Adjusted mean change from baseline:  G1: -0.96 (SE 0.04)  G2: -0.76 (SE 0.04)  SF-36  Mental component, mean change from baseline:  G1: 8.15 (SE 0.64)  G2: 6.34 (SE 0.64)  p=0.046  Physical component, mean change from baseline:  G1: 11.68 (SE 0.62)  G2: 9.18 (SE 0.63)  p=0.005 | Patient adherence:  NR  Specific AEs, n:  Death  G1: 2  G2: 4  Malignancies  G1: 1 (pancreatic)  G2: 0  Respiratory events  Tuberculosis  G1: 0  G2: 0  Pneumonia  G1: 1  G2: 3  Upper respiratory infection  G1: 26  G2: 26  Serious infections (not including pneumonia)  Gastroenteritis  G1: 1  G2: 1  Cellulitis  G1: 1  G2: NR  Pseduomonal lung infection  G1: 1  G2: NR |  |

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| Author, yr, Study Name:  Westhovens et al., 200931;  Wells et al., 2011129;  Bathon et al., 2011130;  Smolen et al., 2015131  AGREE  (continued) |  |  |  | At 6 mos  DAS28 (CRP) remission (< 2.6), %:  G1: 31.4  G2: 17.7  Genant-modified Sharp score  Change in total score, mean:  G1: 0.47  G2: 0.74  Change in erosion score, mean:  G1: 0.40  G2: 0.62  Change in joint-space narrowing, mean:  G1: 0.08  G2: 0.12 | Post operative lung infection  G1: 1  G2: NR  Breast cellulitis/ staphycoccal infection  G1: NR  G2: 1  Other infections (not specified)  G1: 132  G2: 139  Infusion/injection site reactions, n  G1: 16  G2: 5  Dizziness, n  G1: 5  G2: 2  Most frequently reported adverse events  G1:   * Nausea:> 10% pts * Upper respiratory tract infection: > 10% pts * Headache: > 10% pts   G2: NR |  |

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a Five of our included studies reported MRI progression as an outcome evaluating high-dose corticosteroids,18 csDMARDs,29 TNF biologics,18, 41 non-TNF biologics,7 and combinations and therapy strategies.36

b The C-EARLY study’s randomized sample was 879, but baseline characteristics reflect the full analysis set of 868 patients, except for the proportion of systemic CS users, which was based on the safety set of 876 patients, and radiographic data, which used the radiographic set of 691 patients.38

c Efficacy outcomes in the C-EARLY study were analyzed for the full analysis set of 868 patients, except for radiographic data which used the radiographic set of 691 patients.

d AE outcomes in the C-EARLY study were analyzed for the safety set of 876 patients, with the exceptions of overall discontinuation and discontinuation due to AEs, which were based on the randomized sample of 879 patients.38

e Arm-specific data for the C-EARLY study’s specific AEs presented in this appendix (e.g., nausea) were only available on ClinicalTrials.gov.39

f Of the two deaths occurring in the C-EARLY study’s CZP + MTX arm, one was caused by a stroke not considered related to study medication, and the other was a case of disseminated, non-characterized, mycobacterium infection primarily located in the peritoneum with acute respiratory distress, considered to be study medication related. The one death occurring in the MTX arm (respiratory failure) was not considered related to study medication.38

g BRAF-MDQ total score ranges from 0 to 70, with higher scores indicating worse fatigue. A negative value in BRAF-MDQ change from baseline indicates an improvement from baseline.39

h Data for the C-EARLY study’s measures of fatigue, work productivity, household work productivity, and family/social/leisure activity were available for fewer patients than the full analysis sets. For the BRAF-MDQ, 841 of 848 patients were analyzed (G1: 636, G2: 205). For all work productivity measures, 457 of 858 patients were analyzed (G1: 351, G2: 106). For all measures of household productivity, hired outside help, and family/social/leisure activity, 846 of 858 patients were analyzed (G1: 640, G2: 206).39

i In the C-EARLY study, measures of arthritis interference with work or household work productivity in the last month was measured on a scale that ranged from 0 (no interference) to 10 (complete interference).39

j In the SRQ Register analysis, only patients with ≥1 year of follow-up were included in the analysis of patients receiving corticosteroids.76

k Includes all patients in the SRQ Register analysis who started TNF treatment at any time during the entire study period (1997-2012).76

AAT = alanine aminotransferase; ABA = abatacept; ACR = American College of Rheumatology (20/50/70 = 20%/50%/70% improvement); ADA = adalimumab; AE = adverse event (S = serious); ALT = alanine transaminase; ANCOVA = analysis of covariance; aOR = adjusted odds ratio; AP = alkaline phosphatase; AST = aspartate aminotransferase; BRAF-MDQ = Bristol Rheumatoid Arthritis Fatigue – Multidimensional Questionnaire; CCP = cyclic citrullinated peptide; CI = confidence interval; CRP = C-reactive protein; CS = corticosteroid; csDMARD = conventional synthetic DMARD; CZP = certolizumab pegol; DAS = Disease Activity Score (based on 44 joints); DAS28 = Disease Activity Score based on 28 joints; DMARD = disease-modifying antirheumatic drug (cs = conventional synthetic); ESR = erythrocyte sedimentation rate; ETN = etanercept; EQ-5D = EuroQoL standardized instrument; EULAR = European League against Rheumatism; Fig. = figure; G = group; GOL = golimumab; HAQ = Health Assessment Questionnaire (DI = Disability Index); HCQ = hydroxychloroquine; IFX = infliximab; IQR = interquartile range; ITT = intention to treat; IV = intravenous; kg = kilogram; low disease activity = LDA; LEF = leflunomide; LOCF = last observation carried forward; MCP = metacarpophalangeal; Methyl-PNL = methylprednisolone; mg = milligram; mm = millimeters; mo = month; MRI = magnetic resonance imaging; mTSS = modified Total Sharp/van der Heijde score; MTX = methotrexate; N = number; NA = not applicable; NNH = number needed to harm; NR = not reported; NSAID = non-inflammatory ant steroidal drugs; OR = odds ratio (a = adjusted); PISA = Persistent Inflammatory Symmetrical Arthritis; PNL = prednisolone; PRED = prednisone; RA = rheumatoid arthritis; RCT = randomized controlled trial; RF = rheumatoid factor; RIT = rituximab; ROB = risk of bias; RR = risk ratio; SD = standard deviation; SE = standard error; SF-36 = Short-Form Health Survey 36-Item (PCS = physical component score; MCS = mental component score); SHS = Sharp/van der Heijde Score; SJC = swollen joint count; SRQ = Swedish Rheumatology Quality; SSZ = Sulfasalazine; Sup. = Supplemental; TCZ = tocilizumab; TJC = tender joint count; TNF = tumor necrosis factor; TNFa = TNF alpha; TNFi = TNF inhibitor; TOF = tofacitinib; ULN = upper limit of normal; URTI = upper respiratory tract infection; VAS = visual analog scale; wk = week; WPS-RA = Work Productivity Survey - Rheumatoid Arthritis; yr = year.