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SUMMARY WITH CRITICAL APPRAISAL

Cyclosporine for Moderate to Severe Plaque Psoriasis in Adults: A Review of Clinical Effectiveness and Safety

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Context and Policy Issues

Psoriasis is a T-cell mediated skin disease that causes excessive growth of skin cells and accumulation of psoriatic lesions.[1] The focus of this review is on plaque psoriasis, which is the most common form of disease, characterized by erythematous plaques covered with silvery, flaking scales.[2] The other, less common, forms of psoriasis (i.e. guttate, inverse, pustular, and erythrodermic) are not addressed in this review. The prevalence of plaque psoriasis in Canada, based on age-specific prevalence rates from outpatient practices in the United Kingdom from 1987 to 2002 and Canadian consensus data of 2006, is estimated at about 1.7% (more than 500 000 Canadians).[3,4] The disease adversely impacts patients on multiple dimensions of life, with physical, social, and psychological implications.[3]

Plaque psoriasis is classified as mild, moderate, or severe based on the percentage of body affected: <3% (mild), 3 to10% (moderate), and >10% severe.[1] Other classifications combine percentage of body affected with disease severity (i.e. erythema, induration, and desquamation), such as the Psoriasis Area and Severity Index (PASI). A PASI score of less than 10 is mild disease and a score of 10 or greater is moderate to severe disease.[5]

The management strategy for plaque psoriasis is tailored based on its classification of mild, moderate, or severe. For mild forms, topical agents may be sufficient, whereas moderate to severe forms often require systemic agents, of which there are several choices (i.e. traditional systemic treatments and biologics). Among the traditional systemic treatments, cyclosporine is a polypeptide calcineurin inhibitor that was first recognized for clinical efficacy against psoriasis over 30 years ago.[6] Cyclosporine administration for psoriasis is limited to short courses (>1-2 years avoided) due to concerns about adverse effects, such as nephrotoxicity and hypertension.[7]

The biologic agents are a more recent introduction to the management strategy for psoriasis. These agents block specific components of the immune system, such as tumour necrosis factor-α (e.g. infliximab, etanercept) and interleukin-12/23 (e.g. ustekinumab).[7] They are reserved for more severe or refractory forms of disease and patients must meet certain criteria for provincial reimbursement. For example, Ontario Drug Benefits will reimburse infliximab in adults with severe plaque psoriasis only if there has been failure, intolerance, or a contraindication to adequate trials of several standard therapies, including at least two systemic oral agents (i.e. methotrexate, acitretin, or cyclosporine).[8] Given the side effect profile and limitations in the use of cyclosporine, this review evaluates the clinical effectiveness and safety of this treatment for moderate to severe plaque psoriasis in adults.

Research Questions

1. What is the clinical effectiveness of cyclosporine for moderate to severe plaque psoriasis in adults?
2. What is the short and long-term safety of cyclosporine for moderate to severe plaque psoriasis in adults?

Key Findings

Three systematic reviews, two randomized-controlled trials (RCTs), and nine non-randomized studies of safety outcomes formed the evidence base for this review.[9-22] The systematic reviews and RCTs assessed outcomes at 12-16 weeks, while the non-randomized studies provided follow-up of several years. Few studies conducted head-to-head comparisons of cyclosporine with traditional systemic treatments or biologics. Only one RCT had a head-to-head comparison between cyclosporine and biologics.[13]

A well conducted systematic review and network meta-analysis found no difference between cyclosporine and methotrexate (direct comparison) in Psoriasis Area and Severity Index (PASI) 90, PASI 75, or Physician Global Assessment (PGA) of 0 or 1.[9] In the network meta-analysis, cyclosporine was inferior to some biologics on these outcomes.[9] In two RCTs not included in the systematic reviews, no statistically significant differences were observed in PASI score with cyclosporine versus methotrexate, or cyclosporine versus etanercept or ustekinumab.[12,13] These studies had a sample size of 34 and 150 respectively, and may have been underpowered.

In a network meta-analysis, no statistically significant differences in adverse events were observed between cyclosporine and biologics or traditional systemic treatments. The same was observed for serious adverse events, although this data must be interpreted with caution due to small event rates.[9] The non-randomized studies provided insights into long-term safety outcomes, such as infections, cardiovascular events, and discontinuation.[14-22] All non-randomized studies were conducted in European centers and the generalizability to Canadian settings is unclear.

The choice of the optimal initial treatment modality for moderate to severe plaque psoriasis remains uncertain. Given the lack of long-term efficacy data, safety data in the Canadian context, and head-to-head comparisons for cyclosporine and biologics, the evidence base is limited.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases and a focused Internet search. No methodological filters were applied to limit the retrieval by study type. The search was limited to English language documents published between January 1, 2013 and March 5, 2018.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed. The final selection of full-text articles was based on the inclusion criteria presented in Table 1. For the clinical effectiveness outcomes, evidence from health technology assessments, systematic reviews, meta-analyses, and RCTs were considered. For safety outcomes, non-randomized primary studies were additionally evaluated.

Table 1: Selection Criteria

Population	Adults with moderate to severe plaque psoriasis.
Intervention	Cyclosporine (e.g., Neoral, Sandimmune)
Comparator	Traditional systemic drugs (e.g., acitretin, apremilast, methotrexate, tofacitinib); Biologics (e.g., adalimumab, brodalumab, certolizumab, etanercept, guselkumab, infliximab, ixekizumab, ustekinumab, secukinumab)
Outcomes	Q1: Clinical effectiveness (e.g., Psoriasis Area and Severity Index [PASI] response, health-related quality of life, and functional outcomes [e.g., Dermatology Life Quality Index, Physician Global Assessment]) Q2: Safety (e.g., mortality, adverse events, infection, hypertension, malignancies, nephrotoxicity, and other short and long-term harms)
Study Designs	Q1: Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials Q2: Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2013. Studies of other forms of psoriasis (i.e. pustular, erythrodermic, and nail) and psoriatic arthritis were excluded (please note: psoriasis vulgaris, which is another term for plaque psoriasis, was included). Studies that compared cyclosporine with topical therapies or phototherapy were also excluded. Data from figures were not used unless data points were explicitly labelled.

Critical Appraisal of Individual Studies

The included systematic reviews were evaluated using the AMSTAR II checklist.[23] Additional considerations relevant to network meta-analysis were evaluated based on the credibility, analysis, and reporting quality & transparency criteria of Jansen 2014 et al.[24] The RCTs were assessed with the Cochrane Risk of Bias Tool and non-randomized studies with the Downs and Black checklist.[25,26] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

Summary of Evidence

Quantity of Research Available

A total of 299 citations were identified in the literature search. Following screening of titles and abstracts, 267 citations were excluded and 32 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved form the grey literature search. Of these potentially relevant articles, 19 were excluded for various reasons, while 14 publications (13 from electronic databases and 1 from grey literature) met the inclusion criteria and were included in this report. The included reports consisted of three systematic reviews, two additional RCTs that were not included in

the three systematic reviews, and nine non-randomized studies of safety outcomes.[9-22] Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest are in Appendix 5.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

The systematic reviews were published between 2014 and 2017. Sbidian et al.[9] searched for RCTs up to December 16, 2016 and included 109 studies, 74 of which were analyzed in a network meta-analysis. Schmitt et al.[11] searched for RCTs up to October 18, 2012 and included 48 studies. Schmitt et al. conducted both direct and indirect comparisons, however no network meta-analysis was presented. There was overlap in the studies included by Sbidian et al. and Schmitt et al., however the methods of synthesis were different and Schmitt et al. presented absolute risk differences whereas Sbidian et al. presented relative risks. The objective of the review by Zweegers et al.[10] was to examine the effectiveness of treatments for plaque psoriasis in real-life practice settings; therefore, RCTs were excluded and safety data were not analyzed. Zweegers et al.[10] searched for database registries and cohorts from 1990 to May 2014 and included 32 studies, of which one study was relevant to cyclosporine.

The two RCTs were published in 2017.

The nine non-randomized safety studies were retrospective or prospective cohorts, published in between 2013 and 2017.[14-22]

Country of Origin

For the systematic reviews, the countries of origin for the first author were France,[9] the Netherlands,[10] and Germany.[11]

The RCTs were from Korea[12] and Greece[13].

Of the non-randomized studies, three were from Spain[14,15,18], two from Germany[16,20], three from Italy[17,21,22], and one from Denmark[19].

Patient Population

The systematic review of Sbidian et al.[9] included studies of adults over 18 years of age, with moderate to severe plaque psoriasis or psoriatic arthritis whose skin had been clinically diagnosed with moderate to severe psoriasis and who were at any stage of treatment. The mean sample size of the studies was 366 (range: 10 to 1881). The participants were between 27.0 and 56.5 years of age (mean: 44 years) and men were more highly represented than women (26 902 vs. 12 384). All studies recruited participants from a hospital setting and baseline mean PASI score was 20 (range: 9.5 to 39).

Zweegers et al.[10] included studies of adults over 18 years of age and excluded studies that administered two or more traditional systemic treatments (i.e. combination treatment). At baseline, the mean PASI score was greater than 10 (range: 11.6 to 26.5).

Schmitt et al.[11] included studies in adult patients (age not specified) with at least 75% diagnosed with moderate to severe plaque psoriasis. Studies of combination treatments were excluded. A total of 16,696 patients were included, of which 1,120 were randomized to cyclosporine.

The RCT by Choi et al.[12] included adult patients with psoriasis lesions with 5% or greater of body surface area, although the type of psoriasis was not specified. Forty patients were originally enrolled and 34 completed the study. The RCT by Ikonomidis et al.[13] enrolled 150 adult patients with plaque psoriasis with a median PASI score of 13.3.

The patient populations in the non-randomized studies were heterogeneous, as they were recruited from different countries and over different time periods. However, all non-randomized studies included adult patients, the majority with plaque psoriasis. One non-randomized study did not report the percentage of patients with plaque psoriasis.[20] Piaserico et al.[21] recruited elderly patients (>65 years) with plaque psoriasis and examined the risk of adverse events and infections over five years.

Interventions and Comparators

The network meta-analysis of Sbidian et al.[9] compared cyclosporine with other conventional systemic agents (fumaric acid esters, methotrexate, acitretin), small molecules (tofacitinib, apremilast, ponesimod), and biologics (ixekizumab, secukinumab, brodalumab, guselkumab, certolizumab, ustekinumab, tildrakizumab, adalimumab, itolizumab, infliximab, etanercept, and alefacept). The analysis of Schmitt et al.[11] included comparisons of cyclosporine with methotrexate, alefacept, and etretinate. In Zweegers et al.,[10] no direct comparisons were available, although PASI 75 responses were presented for cyclosporine relative to other treatments from different studies. In the single cyclosporine study included in Zweegers et al., the mean cyclosporine dose was 3.5 mg/kg/d. In the current review, only data for those treatments available in Canada are discussed, and the conventional systemic agents and small molecules have been classified under traditional systemic therapies, in accordance with the PICO table.

Choi et al.[12] compared cyclosporine with methotrexate. The initial dose of cyclosporine was 150 mg/d for women and 200 mg/d for men. The initial dose of methotrexate was 10 mg/week plus 1 mg/d folic acid, increasing by 2.5 mg every two weeks up to a maximum of 15 mg/week. Treatment was administered for 16 weeks. In the only head-to-head comparison available for cyclosporine and biologics, Ikonomidis et al.[13] compared cyclosporine with ustekinumab and etanercept. Cyclosporine was administered at a dose of 2.5 to 3 mg/kg/d for 16 weeks. The biologics were administered as ustekinumab 45 mg subcutaneous at baseline, 4, and 16 weeks, and etanercept 50 mg subcutaneous two days per week up to 16 weeks.

Although the majority of non-randomized safety studies did not directly compare cyclosporine with other treatments, effect estimates (e.g. rate of adverse events) were provided by treatment group, which included traditional systemic agents and biologics. Two studies[15,22] provided a direct comparison of cyclosporine with methotrexate or all other treatments combined [etanercept, adalimumab, infliximab, efalizumab, acitretin, methotrexate, and psoralen plus ultraviolet A light (PUVA)]. Most of the studies did not report details of administration, such as dose and frequency. Carpentieri et al.[17] indicated an initial mean cyclosporine dose of 4.5 mg/kg/d, with allowance of dose adjustments. The mean cyclosporine dose in Piaserico et al.[21] was 3.5 mg/kg and the median staring dose in Gisondi et al.[22] was 3 mg/kg/d.

Outcomes

The primary outcomes in Sbidian et al.[9] were the proportion of patients who reached PASI 90 (i.e. proportion of patients who achieved ≥90% reduction in baseline PASI) and serious adverse events, defined as death, life-threatening events, initial or prolonged hospitalisation, and adverse events requiring intervention to prevent permanent impairment or damage. Secondary outcomes included proportion of patients who reached PASI 75 (i.e. proportion of patients who achieved ≥75% reduction in baseline PASI), Physician Global Assessment (PGA) of 0 or 1 (the PGA is a six-point measure of psoriasis, with 0=no clinical signs and 1=minimal), quality of life [Dermatology Life Quality Index (DLQI), Skindex, Psoriasis Disability Index (PDI), or Psoriasis Symptom Inventory (PSI)], adverse events, and relapse in the maintenance phase (between 52 to104 weeks after randomization). No data were available on quality of life or relapse. The primary outcome in Schmitt et al.[11] was the proportion of patients reaching PASI 75, and secondary outcomes were PASI 50, PASI 90, adverse events, and withdrawals. No data for PASI 50 and PASI 90 were available for cyclosporine. In Zweegers et al.[10], the primary outcome was the proportion of patients who reached PASI 75 at week 12 to 16. Secondary outcomes were PASI 75 at intermediate and long-term follow-up, PASI 50, PASI 90, PASI 100, mean PASI, and PGA. However, data on intermediate, long-term, and secondary outcomes were not available for cyclosporine.

The outcomes in the RCTs were PASI score[12,13], modified PASI 75 (exclusion of head area)[12], time required to achieve modified PASI 75[12], and laboratory abnormalities[12].

The non-randomized studies included the following safety outcomes: adverse events leading to discontinuation of therapy,[14,17] infections,[15,20,21] drug survival (interval between first and last dose) and reasons for treatment discontinuation,[16,18] adverse events and serious adverse events,[18,21] cardiovascular events,[19,20] all-cause mortality,[19] malignancies,[20] liver enzymes and kidney function,[22] and metabolic disorders (hypercholesterolemia, hypertriglyceridemia, diabetes mellitus, and hypertension).[22] Most non-randomized studies provided long-term safety data (4 to >11 years).

Summary of Critical Appraisal

Systematic Reviews

Of the three systematic reviews, Sbidian et al. had the most rigourous and transparent methods, satisfying all AMSTAR II criteria.[9] The search was comprehensive without language restrictions and all systematic treatments for plaque psoriasis were considered. The network meta-analysis provided effect estimates for cyclosporine compared with all other conventional systemic treatments, small molecules, and biologics. Given the lack of head-to-head comparisons available for cyclosporine, the ranking of treatments for plaque psoriasis based on the network is informative, although it must be pointed that head-to-head comparisons are preferable to indirect comparisons if available. The network meta-analysis was otherwise well conducted, according to the criteria of Jansen et al.[24] A drawback of this review is that it has limited generalizability to general practices because all patients were from hospital settings and evidence was available only for short-term follow-up of 12 to 16 weeks.

In the network meta-analysis[9], cyclosporine compared with biologics demonstrated no statistically significant differences for serious adverse events, however the confidence intervals for all comparisons were wide. This evidence, therefore, was based on small event

rates and must be interpreted with caution. The same considerations applied to cyclosporine versus tofacitinib, apremilast, and acitretin.[9] Similarly, the confidence intervals presented in the network-meta-analysis for PASI 90 and PGA of 0 or 1, comparing cyclosporine with certolizumab, were wide and must be interpreted with caution.

The publication by Schmitt et al.[11] was of lower quality compared with Sbidian et al. However this review presented absolute risk differences, which offers a different perspective of efficacy than relative risks. Schmitt et al. examined published studies only, in English or German, and the search date was less recent than Sbidian et al.

The review of non-randomized effectiveness studies by Zweegers et al.[10] offered a unique perspective of real world psoriasis practice settings. However, only one study relevant to cyclosporine was included and this study did not have a comparator. Although the review presented PASI 75 response of cyclosporine relative to other treatments from different studies, these are naïve comparisons and must be interpreted with caution. The studies were identified by searching two databases only and there was no assessment of the grey literature.

Randomized-Controlled Trials

The study by Choi et al.[12] was presented as a research letter and there was insufficient information to assess any of the risk of bias domains of the Cochrane Risk of Bias tool.[25] This study was small (N=34) and may have been underpowered. The study by Ikonomidis et al. (N=150)[13] reported proper procedures of randomizing patients to cyclosporine, ustekinumab, or etanercept groups using a random numbers table. The primary objective of this study was not to examine the efficacy of treatments for plaque psoriasis, but rather to examine the effect of ustekinumab on vascular and myocardial function relative to etanercept and cyclosporine; the reporting of PASI score was secondary and not a focus of the paper. Twelve percent (N=18) of patients were excluded due to inadequate outcome assessment or loss to follow-up, and patients were not blinded to treatment received. The generalizability of findings to general practice is limited because follow-up was short-term (16 weeks).

Non-randomized Studies

The main strength of these studies is the long-term follow-up data of several years, which could not be provided by the RCT evidence. In addition, many of these studies were based on registries that included data on several thousands of patients. Some studies adjusted for important baseline differences, such as PASI score[16] and different times of inclusion[19]. However, in other studies it was difficult to determine baseline comparability of groups due to poor reporting of patient characteristics, or baseline differences were not adjusted. Given the more recent introduction of biologic agents to the market, it is possible that follow-up times were shorter in patients receiving biologics than conventional systemic treatments, however the handling of this in analyses was often unclear. Few studies reported cyclosporine dosing and none described compliance with treatment regimens. All non-randomized studies were from European centers and the generalizability to North American practice setting is unclear.

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Summary of Findings

1. What is the clinical efficacy/effectiveness of cyclosporine for moderate to severe plaque psoriasis in adults?

The findings for this question are based on three systematic reviews (follow-up: up to 16 weeks) and two RCTs (follow-up: 16 weeks).[9-13]

PASI Score:

Choi et al. reported no statistically significant difference in PASI score between cyclosporine and methotrexate at 2, 4, 8, 12, and 16 weeks of treatment.[12] Ikonomidis et al. also reported no significant difference in PASI score from baseline to 16 weeks among cyclosporine, etanercept, and ustekinumab.[13]

PASI 90:

In Sbidian et al.,[9] direct head-to-head evidence for cyclosporine versus methotrexate was available from two studies with a total of 172 patients. A random-effects meta-analysis of these studies found no statistically significant difference between treatment groups. In the network meta-analysis, cyclosporine was statistically inferior to the following biologics: ixekizumab, secukinumab, brodalumab, guselkumab, ustekinumab, adalimumab, infliximab, and etanercept. However, no statistically significant difference was found between cyclosporine and certolizumab, tofacitinib, apremilast, methotrexate, or acitretin.

PASI 75:

In Sbidian et al.,[9] direct head-to-head evidence for cyclosporine versus methotrexate was available from two studies with a total of 172 patients. A random-effects meta-analysis of these studies found no statistically significant difference between treatment groups. In the network meta-analysis, cyclosporine was statistically inferior to the following biologics: ixekizumab, secukinumab, brodalumab, guselkumab, ustekinumab, adalimumab, and etanercept. However, no difference was found between cyclosporine and certolizumab, infliximab, tofacitinib, apremilast, methotrexate, or acitretin.

Schmitt et al.[11] synthesized the same two studies of direct head-to-head comparisons between cyclosporine and methotrexate, as Sbidian et al., however reported an absolute risk difference rather than relative risk. In agreement with Sbidian et al., no statistically significant difference was found between cyclosporine and methotrexate.

In the review of non-randomized effectiveness studies by Zweegers et al.[10], no direct comparisons between cyclosporine and other treatments were available. In naïve comparisons, the proportion of patients achieving PASI 75 in the single cyclosporine study was similar to methotrexate and higher than acitretin. The upper limit of response for biologics was higher than cyclosporine.

In the small (N=34) RCT by Choi et al.[12], no difference was found in modified PASI 75 (exclusion of head area assessment), or the time to reach modified PASI 75, between cyclosporine and methotrexate.

Patient Global Assessment 0 or 1:

In Sbidian et al.[9], direct head-to-head evidence for cyclosporine versus methotrexate was available from one study with 88 patients, which found no statistically significant difference.

In the network meta-analysis, cyclosporine was statistically inferior to the following biologics: ixekizumab, secukinumab, brodalumab, guselkumab, ustekinumab, adalimumab, and certolizumab. However, no difference was found between cyclosporine and infliximab, etanercept, tofacitinib, apremilast, methotrexate, or acitretin.

2. What is the short and long-term safety of cyclosporine for moderate to severe plaque psoriasis in adults?

The findings for this question are based on three systematic reviews (follow-up: up to 16 weeks), two RCTs (follow-up: 16 weeks), and nine non-randomized studies (follow-up: 16 weeks to >11 years).[9-22]

Adverse Events:

In Sbidian et al.[9], direct head-to-head evidence for cyclosporine versus methotrexate was available from two studies with a total of 172 patients. A random-effects meta-analysis of these studies found no statistically significant difference between treatment groups. In the network meta-analysis, no statistically significant differences were observed between cyclosporine and biologics or traditional systemic treatments.

In a retrospective cohort of 187 elderly patients (N=36 cyclosporine) from Italy, with follow-up of 5 years, cyclosporine was associated with a higher rate of adverse events compared with methotrexate.[21] The rate for cyclosporine was also numerically higher than acitretin and biologics. The adverse events of cyclosporine were primarily hypertension and renal insufficiency. The authors indicated that cyclosporine should be used with extreme caution in the elderly, given the higher risk for baseline renal impairment and cardiovascular comorbidities in this population.

Serious Adverse Events:

In a network meta-analysis,[9] cyclosporine compared with biologics, tofacitinib, apremilast, acitretin, or methotrexate demonstrated no statistically significant differences. Based on relative ranking of treatments for serious adverse events, methotrexate was associated with the most favourable safety profile, followed by cyclosporine, certolizumab, and infliximab.

In a prospective cohort of 1,956 patients (N=356 cyclosporine) from Spain, with median follow-up of 3.3 years, the hazard ratio for cyclosporine verses methotrexate was statistically higher.[18]

Infection

In a prospective cohort of 1,352 patients from Spain (N= 472 cyclosporine), with follow-up of greater than 7 years, the risk of overall infection and serious infection were higher with cyclosporine compared with methotrexate.[15] Serious infection was defined as infection that resulted in death, was life-threatening, required prolonged hospitalization, or caused persistent disability. Effect estimates for other treatments compared with methotrexate are also presented in Appendix 4, Table 10. No statistically significant difference for recurrent infection was found between cyclosporine and methotrexate.

A prospective cohort of 2,444 patients from Germany (N=229 cyclosporine), with follow-up of 4 years, classified infections as severe if an antibiotic prescription was required, and as serious if the infection was life-threatening or resulted in an in-patient stay.[20] No significant differences in severe or serious infections for cyclosporine, biologics, or methotrexate were found.

Malignancy

A prospective cohort of 2,444 patients from Germany (N=229 cyclosporine), with follow-up of 4 years, found no significant differences in the rate of malignancies for cyclosporine, methotrexate, or biologics.[20]

Cardiovascular Outcomes

A prospective cohort of 2,444 patients from Germany (N=229 cyclosporine), with follow-up of 4 years, found no significant differences in the rate of severe cardiovascular events for cyclosporine, methotrexate, or biologics.[20] This study also reported MACE (malignancies and major cardiac events) and found no differences.

In a retrospective cohort of 6,902 patients from Denmark (N=244 cyclosporine), with maximum follow-up of 5 years, the incidence rate of a composite cardiovascular endpoint, defined as cardiovascular death, myocardial infarction, and stroke, was assessed.[19] The incidence rate per 1000 patient-years was numerically higher for retinoids compared with cyclosporine, methotrexate, or biologics.

Metabolic Outcomes

In a prospective cohort of 10,539 patients from Italy (N=2,309 cyclosporine), with follow-up of 16 weeks, the incidence (i.e. new cases) of hypercholesterolemia, hypertriglyceridemia, diabetes mellitus, and arterial hypertension were monitored.[22] Hypercholesterolemia was defined as serum total cholesterol levels ≥250 mg⁄dL, hypertriglyceridemia as serum triglycerides levels ≥200 mg⁄dL, diabetes mellitus as taking hypoglycemic medication or when a physician's diagnosis was available, and arterial hypertension as taking antihypertensive medications, if a diagnosis by a physician was available, or if systolic blood pressure >140 mmHg and diastolic blood pressure >90 mmHg were documented on two separate occasions. Compared with all other treatments combined (i.e. etanercept, adalimumab, infliximab, efalizumab, acitretin, methotrexate, and PUVA), cyclosporine was associated with a statistically significant, higher risk of hypercholesterolemia and diabetes mellitus. Cyclosporine was also associated with a statistically significant higher risk of arterial hypertension. The risk of hypertriglyceridemia was not statistically significant. According to the authors, cyclosporine should be used with caution in patients with cardio-metabolic comorbidities.

Liver Enzymes and Kidney Function

In a prospective cohort of 10,539 patients from Italy (N=2309 cyclosporine), with follow-up of 16 weeks, increases in liver enzymes and serum creatinine were evaluated.[22] A clinically relevant increase in liver enzymes was defined as alanine amino transferase (ALT) or aspartate amino transferase (AST) levels ≥2 times the upper reference normal value. Hypercreatininemia was defined as serum creatinine level ≥1.5 mg/dL. Compared with all other treatments combined (i.e. etanercept, adalimumab, infliximab, efalizumab, acitretin, methotrexate, and PUVA), cyclosporine was associated with lower risk of AST increase ≥2 times, no statistically significant difference in ALT increase ≥2 times, and no significant difference in hypercreatinemia.

Treatment Discontinuation

Reasons for treatment discontinuation were evaluated in a prospective cohort of 1,938 patients from Spain, with follow-up of over 7 years.[14] More discontinuations were due to ineffectiveness or loss of effectiveness (22%) and remission (20%) than adverse events

(11%). The incidence of adverse events leading to discontinuation of treatment were higher for cyclosporine compared with methotrexate, acitretin, infliximab, adalimumab, etanercept, and ustekinumab (note: no statistical test conducted). The incidence of serious adverse events leading to discontinuation were higher for cyclosporine compared with methotrexate, acitretin, adalimumab, etanercept, and ustekinumab, but lower than infliximab (note: no statistical test conducted). In regards to individual adverse events, the authors stated that infection was the most common cause of discontinuation (highest risk: infliximab; among traditional systemic agents highest risk: cyclosporine). Cyclosporine had the highest rate of adverse events related to hypertension, nervous system disorders, and gastrointestinal tract disorder, and the second highest rate of adverse events related to skin disorders.

In a retrospective cohort of 373 patients from Germany (N=19 cyclosporine), with follow-up greater than 11 years, the percentage of patients who stopped treatment due to adverse events was highest for cyclosporine, followed by methotrexate, acitretin, infliximab, adalimumab, etanercept, and ustekinumab.[16] This study also measured drug survival (i.e. interval between the first and last dose) and found that it was highest for ustekinumab and lowest for cyclosporine.

In a retrospective cohort of 100 patients (N=72 cyclosporine) from an Italian dermatology clinic, with follow-up of 7 years, adverse events leading to discontinuation of therapy was higher for cyclosporine than methotrexate, and similar to acitretin.[17] In a cohort from Spain, no difference was observed in discontinuations due to adverse events in patients receiving cyclosporine or methotrexate, although the probability of drug survival during the first year, based on discontinuation due to adverse events, was lower for cyclosporine compared with methotrexate.[18]

Mortality

In a retrospective cohort of 6,902 patients from Denmark (N=244 cyclosporine), with maximum follow-up of 5 years, the rate of all-cause mortality was numerically higher for retinoids compared with cyclosporine, methotrexate, and biologics.[19]

Appendix 4 presents tables of the main study findings and authors' conclusions.

Limitations

The main limitation of the evidence base for cyclosporine in moderate to severe plaque psoriasis is the lack of head-to-head comparisons of efficacy with other conventional systemic treatments and biologic agents. Only one RCT, conducted in Greece, was identified that directly compared cyclosporine with two different biologics, etanercept and usekinumab.[13] The primary objective of this study, however, was not to compare treatments with respect to efficacy and it may have been underpowered to detect differences in PASI scores. The systematic review by Sbidian et al.[9] attempted to fill the gap in head-to-head comparisons by conducting a network meta-analysis of anti-psoriatic treatments. The network meta-analysis made use of the placebo-controlled trials to estimate comparative effects for cyclosporine versus all other treatments individually. Although this analysis demonstrated that some biologics may have superior efficacy to cyclosporine, the results must be interpreted cautiously because they were based on a small number of cyclosporine studies. Head-to-head comparisons from well conducted RCTs are preferred for the highest rigour of evidence on treatment efficacy. In addition, the patients in the network meta-analysis were younger (mean age: 44 years), with a high baseline PASI score (mean: 20), and were from hospital settings. According to the authors, "This young age and the high

level of disease severity may not be typical of patients seen in daily clinical practice, especially for patients who need a first-line systemic treatment."[9] (p69)

Plaque psoriasis is a chronic condition that requires long-term, ongoing, management. The systematic reviews of RCTs and the two RCTs subsequently published, provided data on short-term follow-up of 12 to 16 weeks only.[9-13] The lack of data on long-term efficacy outcomes is an important limitation. The review of non-randomized effectiveness studies of anti-psoriatic treatments also only provided follow-up to 12 weeks.[10] Although this review posed a relevant clinical inquiry (i.e. to assess the effectiveness of treatments in real-life practice), the information gleaned from this review was limited, as it included only one study on cyclosporine and omitted several other, potentially relevant, non-randomized studies of effectiveness.

The non-randomized safety studies followed large numbers of patients over several years and provided data on many outcomes that were not available in the RCTs.[14-22] These studies have the limitations of non-randomized designs (e.g. baseline comparability of treatment groups, potential for selection bias, and incomplete reporting of treatment doses, compliance, and characteristics of patients excluded). In addition, all non-randomized studies were from European centers or registries, and the applicability of the findings to the Canadian context is unclear. With the exception of one study in elderly patients,[21] all studies were in middle-aged patients (average age between 40 and 50 years). Safety data in young adults, the elderly, and those with specific comorbidities, such as cardiovascular disease, are spare or not available.

Conclusions and Implications for Decision or Policy Making

Three systematic reviews, two RCTs, and nine non-randomized studies were evaluated in this review.[9-22] Few studies conducted head-to-head comparisons of cyclosporine with traditional systemic treatments or biologics. Only one RCT had a head-to-head comparison between cyclosporine and biologics.[13] A network meta-analysis found no difference between cyclosporine and methotrexate in PASI 90, PASI 75, or PGA of 0 or 1.[9] However cyclosporine was inferior to some biologics on these outcomes.[9] In two small RCTs, no statistically significant differences were observed in PASI score with cyclosporine versus methotrexate, or cyclosporine versus etanercept or ustekinumab.[12,13] The non-randomized studies provided insights into long-term safety outcomes, such as infections, cardiovascular events, and treatment discontinuation.[14-22] There were no statistically significant differences in adverse events between cyclosporine and biologics or traditional systemic treatments in the network meta-analysis.[9]

The efficacy data is all short-term and lacks sufficient head-to-head comparisons for cyclosporine and biologics. The long-term data on safety outcomes come from non-randomized studies in European countries and the applicability to the Canadian context is unclear. Although the network meta-analysis suggested that some biologics may be superior to cyclosporine on efficacy outcomes, this level of evidence is lower in hierarchy than head-to-head comparisons.

Based on the evidence reviewed, more direct head-to-head comparison studies on the long-term efficacy and safety of cyclosporine versus biologics are needed, that are applicable to the Canadian context. Such evidence will provide greater insights about the proper place of these agents in the management of patients with moderate to severe plaque psoriasis.

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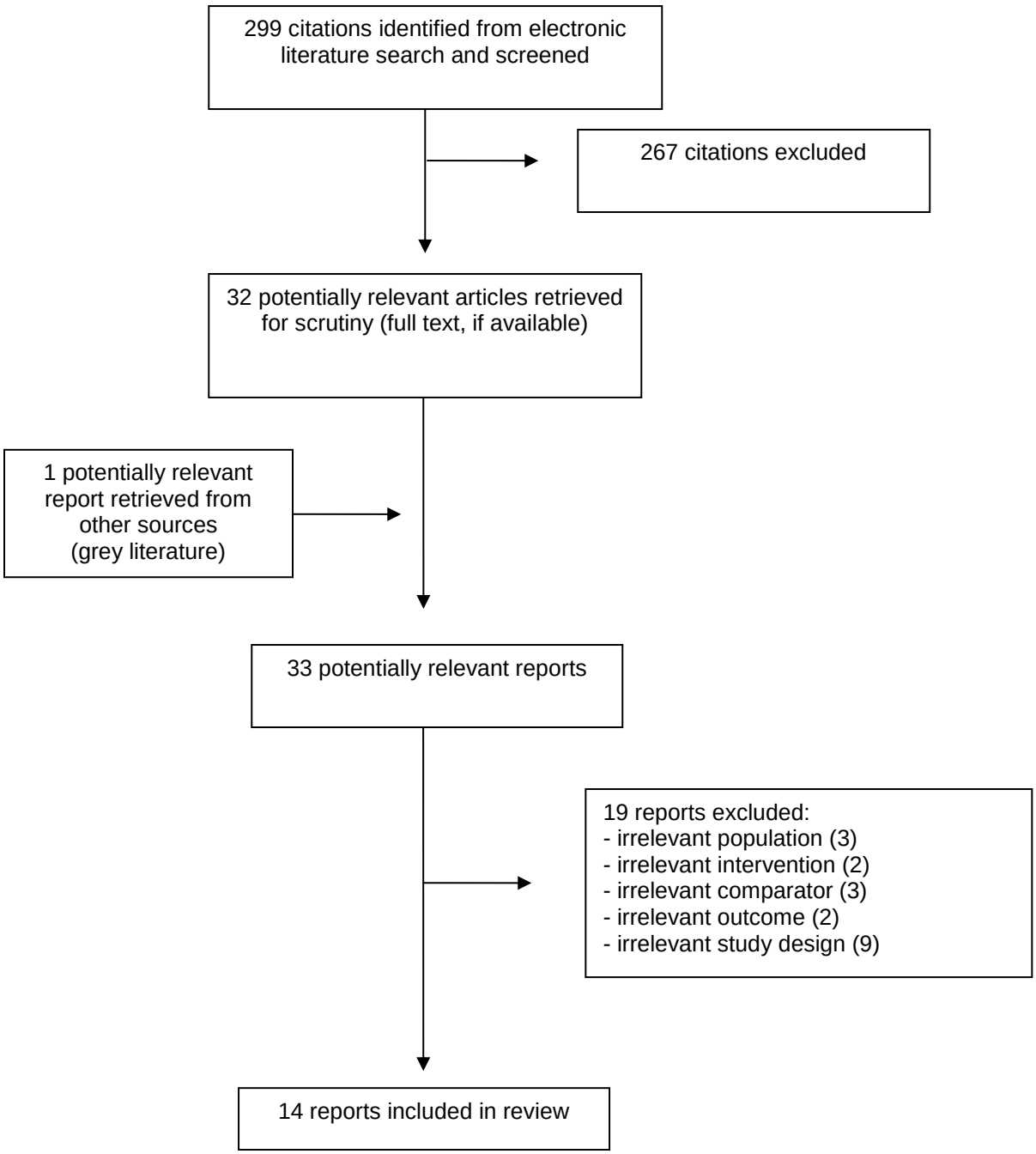
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

Author (Year)	Objective	Study Designs Included, No. Studies & Follow-up	Population	Direct Comparators (for CSA)	Outcomes
Sbidian (2017)[9]	To compare the efficacy and safety of conventional systemic agents, small molecules, and biologics in patients with moderate-severe psoriasis.	RCTs (search: until Dec. 16, 2016) Total No. = 109 No. NMA = 74 CSA studies = 10 Induction (<24 wks) & Maintenance (between 52-104 wks after randomization)	Adults (> 18 years) with moderate-severe plaque psoriasis or psoriatic arthritis with clinical diagnosis of moderate-severe psoriasis.	CSA vs. Acitretin CSA vs. MTX CSA vs. Placebo *Network meta-analysis conducted*	**Primary:** PASI 90 SAE **Secondary:** PASI 75 PGA 0 or 1 QoL AE Relapse in maintenance phase
Zweegers (2016)[10]	To review the evidence on the effectiveness of conventional systemic treatments and biologics in patients with plaque psoriasis, in daily, real-life practice settings.	Database registries and cohorts (search: 1990-May 2014, safety studies were excluded) Total No. = 32 CSA studies = 1 Short-term: (12-16 wks) Intermediate-term: (<16-≤28 wks) Long-term: (≥1 yr)	Adults (≥ 18 years) with plaque psoriasis (severity not indicated).	No direct comparison of CSA with other treatments in the single study available. PASI 75 responses presented relative to other treatments.	**Primary:** PASI 75 at wk 12-16 **Secondary:** PASI 75 (intermediate & long-term) PASI 50 PASI 90 PASI 100 PASI mean PGA BSA
Schmitt (2014)[11]	To review the efficacy and safety of systemic treatments for moderate-severe or severe psoriasis.	RCTs (search: until Nov. 4 2009, RCTs from the German S3-psoriasis guidelines & from Jan 1. 2009-Oct. 18 2012, database searches) Total No. 48 CSA studies = 10	Adults (age not specified) with moderate-severe or severe psoriasis	CSA vs. MTX CSA vs. Placebo *Indirect comparisons conducted (based on placebo-controlled trials)*	**Primary:** PASI 75 **Secondary:** PASI 50 PASI 90 AE Withdrawals

AE = adverse effect; BSA = body surface area; CSA = cyclosporine; MTX = methotrexate; NMA = network meta-analysis; No. = number; PASI = Psoriasis Area and Severity Index; PGA = Physician Global Assessment; QoL = quality of life; RCT = randomized controlled trial; SAE = serious adverse event; wk = week; yr = year

Table 3: Characteristics of Included Randomized Controlled Trials

Author (Year)	Objective	Follow-up	Population	Comparator	Outcomes
Choi (2017) (pilot study)[12]	To compare the clinical effectiveness of CSA and MTX using a new objective severity assessment method.	16 wks	Adult patients with psoriasis lesions ≥ 5% of body surface area. N = 34 (40 initially enrolled)	CSA vs. MTX	PASI score Modified PASI 75 (head area assessment was excluded) Time required to achieve modified PASI 75 Laboratory abnormalities
Ikonomidis (2017)[13]	To examine the effect of IL-12 inhibition on vascular and myocardial function, compared with TNF-α inhibition or CSA treatment.	16 wks	Adult patients with plaque psoriasis. Baseline median PASI score 13.3. N=150 (50 per group)	CSA vs. Ustekinumab vs. Etanercept	PASI score

CSA = cyclosporine; IL = interleukin; MTX = methotrexate; wk = week; PASI = Psoriasis Area and Severity Index; TNF = tumour necrosis factor

Table 4: Characteristics of Included Non-Randomized Studies of Safety Outcomes

Author (Year)	Study Design & Location	Follow-up	Population	Comparators	Outcomes
Belinchon (2017)[14]	Prospective Cohort Spain (12 dermatology departments in hospitals)	>7 years: Jan. 2008 to Nov. 2015 CSA: 304.8 person-years	BIOBADADERM Registry No. treatment cycles: CSA = 529 Baseline mean PASI: 12 % with plaque psoriasis: 100	Etanercept Infliximab Adalimumab Ustekinumab Acitretin MTX	Adverse events leading to discontinuation of therapy Individual adverse events (MedDRA) *This data was not extracted*
Davila-Seijo (2017)[15]	Prospective Cohort Spain (12 dermatology departments in hospitals)	>7 years Jan. 2008 to Nov. 2015 CSA: 250.6 person-years	BIOBADADERM Registry N=1352 (CSA 472 & MTX 880) Baseline median PASI: CSA 7.1 & MTX 4.1 % with plaque psoriasis: CSA 90.3% & MTX 93.3%	CSA vs. MTX	Infection Serious Infection Recurrent Infection
Arnold (2016)[16]	Retrospective Cohort Germany (outpatient, tertiary care psoriasis clinic)	>11 years: Jan. 2003 to May 2014	N = 373 (CSA 19) Baseline mean PASI: CSA 12 % with plaque psoriasis: Total 80.5% & CSA 78.9%	Adalimumab Etanercept Infliximab Ustekinumab Acitretin MTX	Drug survival (interval between first and last dose) Reasons for treatment discontinuation
Carpentieri (2016)[17]	Retrospective Cohort Italy (dermatology clinic)	7 years: 2007 to Jul. 2014	N = 100 (CSA 72) Baseline median PASI: 10 % with plaque psoriasis: Total 52% % with scalp psoriasis: Total 30% CSA dose: initial mean dosage 4.5 mg/kg/d with dose adjustments allowed	Acitretin MTX	Adverse events leading to discontinuation of therapy
Davila-Seijo (2016)[18]	Prospective Cohort Spain (12 dermatology departments in hospitals)	>5 years Jan. 2008 to Oct. 2013 Median follow-up: 3.3 years	N = 1956 (CSA 356) Baseline mean PASI: CSA 13 (Other groups 9-18) % with plaque psoriasis: CSA 89%	Etanercept Infliximab Adalimumab Usekinumab Acitretin MTX	Drug survival for adverse events SAE

Table 4: Characteristics of Included Non-Randomized Studies of Safety Outcomes

Author (Year)	Study Design & Location	Follow-up	Population	Comparators	Outcomes
Ahlehoff (2015)[19]	Retrospective Cohort Denmark (linkage of administrative databases)	Recruitment: 2007 to 2011 Follow-up until Dec. 2011 Max. follow-up: 5 years	N = 6902 (CSA 244) Baseline mean PASI: NR (patients classified as having severe psoriasis) Patients diagnosed with psoriasis vulgaris (ICD, 10th revision, L40)	Biologics Retinoids MTX	CV events All-cause mortality
Reich (2015)[20]	Prospective Cohort Germany (251 dermatology centers)	4 years: Jan. 2008 to Dec. 2012	PsoBest Registry N = 2444 (CSA 229) Baseline mean PASI: 14.7 % with plaque psoriasis: NR	Adalimumab Etanercept Infliximab Ustekinumab MTX	Infections (severe and serious) CV events (severe) Malignancies MACE
Piaserico (2014)[21]	Retrospective Cohort Italy (dermatology departments)	5 years: Sept. 2005 to Sept. 2010	N = 187 (elderly >65 years) (CSA 36) Baseline mean PASI: 14.2 (CSA 17) % with plaque psoriasis: 100 CSA dose (mean): 3.5 mg/kg	Etanercept Adalimumab Infliximab Ustekinumab Acitretin MTX	Adverse events Infections
Gisondi (2013)[22]	Prospective Cohort Italy (155 dermatology centers)	Recruitment began Sept. 2005. Patients with at least 16 wks follow-up by Sept. 2009 were included.	Psocare Registry N = 10 539 (CSA 2309) Baseline mean PASI: 17.4 % with plaque psoriasis: 100 CSA starting dose (median): 3 mg/kg/d	CSA vs. all other treatments combined (etanercept, adalimumab, infliximab, efalizumab, acitretin, MTX, and PUVA)	Cholesterol and Triglycerides Liver enzymes (ALT, AST) Creatinine Diabetes mellitus Arterial HTN

ALT = alanine amino transferase; AST = aspartate amino transferase; BIOBADADERM = Spanish Registry of Adverse Events for Biological Therapy in Dermatological Diseases; CSA = cyclosporine; CV = cardiovascular; HTN = hypertension; ICD = International Classification of Diseases; IR = incidence rate; MedDRA = Medical Dictionary for Regulatory Activities; MACE = malignancies and major cardiac events; MTX = methotrexate; NR = not reported; PASI = Psoriasis Area and Severity Index; PUVA = psoralen plus ultraviolet A light; SAE = serious adverse event; wks = weeks

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR II[23]

Strengths	Limitations
Sbidian (2017)[9]	
• The systematic review fulfilled all AMSTAR II criteria. • The population, intervention, comparators, and outcome (PICO) domains were clearly formulated and an *a priori* protocol was followed. • The literature search was comprehensive up to December 2016, included grey literature sources, and was without any language restrictions. • Study selection, data extraction, and quality assessment were conducted by multiple reviewers, and the included studies and analyses were clearly described. • All conventional systemic treatments and biologic agents for psoriasis were considered in the review and the network meta-analysis provided an informative ranking of treatments based on outcomes of efficacy and safety. • Both induction therapy (short-term remission) and maintenance therapy (long-term remission) were considered, although no data for the latter were available.	• The generalizability of the findings to general practices may be limited because all included studies recruited participants from hospital settings. • Evidence was available for only short-term remission (12-16 weeks) and, therefore, this review does not inform about long-term efficacy and safety of cyclosporine. • For additional limitations specific to the network meta-analysis, please see Table 2.
Zweegers (2016)[10]	
• This review provided a unique perspective of real-life management of patients with psoriasis by examining non-randomized studies of effectiveness. • The PICO domains were clearly specified. • Study selection and data extraction were conducted in duplicate. • The presence of heterogeneity among the included studies was addressed in qualitative interpretation. • Different time points (i.e. short, intermediate, and long-term) were considered.	• The review was not based on an *a priori* protocol. • The literature search included two databases, however there was no assessment of the grey literature or hand searching of reference lists; therefore, some studies may have been missed. • Additionally, 21 articles were excluded due to language, which may have resulted in the omission of relevant data from non-English sources. • The quality of included studies was not assessed and characteristics of the populations of the included studies were not provided.
Schmitt (2014)[11]	
• The PICO domains were provided. • Study selection, data extraction, and quality assessment were conducted in duplicate. • The included studies were described in adequate detail.	• The review was not based on an *a priori* protocol. • Only published studies in English or German were considered for inclusion. • Effect estimates were combined with random effects meta-analysis, however sources of heterogeneity and their effects on results were not accounted for. • The quality of included studies was not considered in meta-analyses. • There was no assessment of publication bias. • Industry affiliations were reported by authors, however no information was provided as to how these conflicts of interest were managed.

Table 5: Strengths and Limitations of Network Meta-Analysis using the Credibility Criteria of Jansen 2014[24]

Strengths	Limitations
Sbidian (2017)[9]	
• The authors attempted to identify and include all RCTs that were relevant to the network of interventions. • The trial data formed one connected network of RCTs from which both direct and indirect evidence could be obtained. • Although the analyses included studies of all levels of quality, a sensitivity analysis was conducted that examined the impact of bias on the results. • No naïve comparisons were conducted (i.e. treatment comparisons across studies were made based on the relative effects reported in each study). • The results of both direct and indirect comparisons were presented. • The analyses were based on a random-effects model to account for the presence of heterogeneity among studies. • The analysis process and results were transparent and clearly reported (e.g. a graphical representation of the network was provided, individual study results could be easily obtained, and a ranking of treatments by efficacy and safety was examined). • The authors' interpretation was supported by the results. • Author conflicts of interest were reported and addressed.	• The results of a network meta-analysis are valid only if the trials in the network are sufficiently similar in all respects, aside from the intervention. • Although the authors conducted meta-analysis only if the population, interventions, comparators, and outcomes were judged to be similar, a formal statistical evaluation of heterogeneity and the impact of effect modifiers on the results could not be made due to poor reporting by studies (i.e. the authors had planned to extract and examine the influence of effect modifiers, such as age, sex, body weight, duration and severity of psoriasis, baseline severity of psoriasis, and previous treatments, but could not perform subgroup or meta-regression analyses with the data available). • This is more a limitation of the underlying evidence base rather than the network meta-analysis itself.

Table 6: Strengths and Limitations of Randomized Controlled Trials using the Cochrane Risk of Bias Tool[25]

Strengths	Limitations
Choi (2017)[12]	
N/A	• This study was presented as a research letter and there was insufficient information presented to assess any of the risk of bias domains. • Randomization, allocation concealment, blinding, incomplete outcome data, and selective reporting were unclear.
Ikonomidis (2017)[13]	
• The study was properly randomized using a table of random numbers to assign patients to either cyclosporine, ustekinumab, or etanercept.	• The primary objective of this study was to examine the effect of ustekinumab on vascular and myocardial function, relative to etanercept and cyclosporine; the reporting of PASI score was secondary. • A total of 150 patients were included, with 50 patients in each treatment group; 18 patients were excluded from analyses, 16 due to inadequate echocardiography images and 2 due to absence at 4-month follow-up. The characteristics of excluded patients were not provided. • The procedures for concealing allocation to treatment group were not described. • Participants were not blinded to treatment received and it is unclear as to whether outcome assessors were blinded.

Table 7: Strengths and Limitations of Non-Randomized Safety Studies using Downs and Black[26]

Strengths	Limitations
Belinchon (2017)[14]	
• The study included a large number of patients from a registry, representative of the underlying patient population (0.3% declined to participate and 13% were lost to follow-up). • The follow-up time was greater than 7 years, providing long-term safety data.	• The generalizability of the clinical practice for psoriasis in Spain to North American practice settings is unclear. • The doses and administration schedules for the conventional systemic and biologics were not provided. • Baseline characteristics (e.g. PASI score) were not provided by treatment, therefore, it is difficult to assess the comparability of patients among groups. This could potentially be an important source of bias, given that adjusted effect estimates were not calculated.
Davila-Seijo (2017)[15]	
• The study included a large number of patients from a registry, representative of the underlying patient population (0.3% declined to participate and 11.9% were lost to follow-up). • Nearly equal representation of men and women in the cyclosporine and methotrexate groups. • The follow-up time was greater than 7 years, providing long-term safety data.	• The generalizability of the clinical practice for psoriasis in Spain to North American practice settings is unclear. • Doses and administration schedules for cyclosporine and methotrexate were not provided. • Although the paper classifies severity as moderate-severe, the baseline PASI scores for the cyclosporine and methotrexate groups suggests milder forms of disease (i.e. PASI ≤ 10). • The baseline median PASI scores differed between the cyclosporine and methotrexate groups (7.1, IQR 11.2-16.8 vs. 4.1, IQR 7.4-11.3, respectively), indicating that the cyclosporine group had more severe disease. However, in sensitivity analyses that adjusted for baseline PASI, cyclosporine continued to have a higher risk of overall infection compared with methotrexate (RR = 1.58, 95% CI 1.11-2.24).
Arnold (2016)[16]	
• The study provides long-term (11-year) data on length of use of conventional and biologic agents for plaque psoriasis. • Drug therapy may be discontinued for several reasons, including adverse events and lack of efficacy. The study breaks down the outcome of drug survival into discontinuation due to adverse effects versus discontinuation due to lack of efficacy. • The patients receiving biologic agents had higher disease severity at baseline compared with cyclosporine (e.g. baseline PASI in ustekinumab was 18 vs. 12 in cyclosporine). However, baseline PASI was adjusted for in drug survival analyses.	• The generalizability of the tertiary clinical practice for psoriasis in Germany to North American practice settings is unclear. • Few patients received cyclosporine (n=19) and, therefore, the results should be interpreted with caution. • The number and characteristics of patients excluded from analyses were not provided. • It is unclear if follow-up times differed between the treatment groups. Patients were recruited over an 11-year time frame and given the more recent approval of the biologic agents, it is possible that the follow-up with biologics was shorter than the follow-up with conventional systemic therapies. • Although several confounders were adjusted for (i.e. age, gender, psoriatic arthritis, diabetes, cardiovascular disease, depression, number of previous systemic therapies, and baseline PASI), it is unclear how differences in follow-up time was addressed.

Table 7: Strengths and Limitations of Non-Randomized Safety Studies using Downs and Black[26]

Strengths	Limitations
Carpentieri (2016)[17]	
• The study provides long-term (7-year) data on length of use of conventional and biologic agents for plaque psoriasis. • Drug therapy may be discontinued for several reasons, including adverse events and lack of efficacy. The study examined discontinuation due to adverse effects versus discontinuation due to lack of efficacy, disease remission, pregnancy, and loss to follow-up.	• The generalizability of the single practice clinic in Italy to North American practice settings is unclear. • The study population included 100 patients; it is unclear if these patients were representative of the population with plaque psoriasis as losses to follow-up, number of exclusions, and reasons for exclusions were not provided. • The follow-up times for the different treatments groups were not provided, nor were patient characteristics by treatment group (e.g. baseline disease severity, follow-up time). • The study report indicated that 35% switched medication at least once, however it was unclear how this was taken into consideration in the assignment of adverse events. • It is unclear how adverse events were defined and whether the decision to discontinue treatment was based on patient and/or physician decision.
Davila-Seijo (2016)[18]	
• The study included a large number of patients from a registry, representative of the underlying patient population (0.3% declined to participate and about 5% were lost to follow-up). • The follow-up time was greater than 5 years, providing long-term safety data. • Standardized definitions of adverse events were implemented, and training of data collectors and monitoring of data were frequently conducted.	• The generalizability of the clinical practice for psoriasis in Spain to North American practice settings is unclear. • Doses and administration schedules for the conventional systemic and biologics were not provided. • It is unclear if follow-up times differed for the conventional agents versus biologics. • Hazard ratios for serious adverse events were adjusted for age and gender only. • Dose modifications, simultaneous use of conventional agents and biologics, and whether the agent was the first drug to be administered, were not taken into consideration in analyses.
Ahlehoff (2015)[19]	
• The study was a nationwide analysis in Denmark that linked administrative databases to examine the effect of treatments for psoriasis on cardiovascular outcomes and mortality. • The follow-up time was up to 5 years and there were no losses to follow-up. • The potential for different times of inclusion among treatment groups was taken into consideration by including this variable as an adjustment factor in Cox-regression models.	• The generalizability of the clinical practice for psoriasis in Denmark to North American practice settings is unclear. • Data on treatments received for psoriasis in-hospital were not available and, therefore, some patients may have been misclassified by treatment group. • Specifics about dosing, administration schedules, and compliance were not reported.
Reich (2015)[20]	
• The study included patients across Germany from hundreds of dermatology clinics and provided data over a 4-year period. • Important safety outcomes of psoriatic treatments were	• The generalizability of the clinical practice for psoriasis in Germany to North American practice settings is unclear. • Dosing and administration schedules of treatments were not provided.

Table 7: Strengths and Limitations of Non-Randomized Safety Studies using Downs and Black[26]

Strengths	Limitations
assessed and categorized into non-severe, serious, and severe, with clear definitions. • The outcomes of malignancies and death were assigned to all previous systemic treatments, regardless of exposure time, and events that occurred within a combined treatment were assigned to all treatments received.	• Patients with at least one missing follow-up visit were excluded from analyses, however the number and characteristics of patients excluded were not reported. • No adjustments were made for baseline characteristics or follow-up times. • There were differences in the proportion of patients with psoriatic arthritis receiving biologics (36.3%) versus conventional treatments (14.1%). • Follow-up time was also longer for biologics (22 months) than convention treatments (14.5 months).
Piaserico (2014)[21]	
• The study evaluated the safety of conventional systemic treatments and biologics for psoriasis specifically in the elderly, which is an under-represented subgroup in clinical trials and observational studies. • Data on long-term safety (5 years) was provided.	• The generalizability of the clinical practice for psoriasis in Italy to North American practice settings is unclear. • The study population was small, with only 36 receiving cyclosporine. • The recruitment of patients was not fully described; the study report indicated that 187 consecutive patients were recruited into a patient registry from various dermatology departments, however it is unclear if patients were treated on an in- or out-patient basis, or if any patients were lost to follow-up. • No adjustments were made for confounders; e.g. baseline disease severity was higher in the cyclosporine group compared with other treatments (baseline PASI 17 cyclosporine vs. 12.7 methotrexate and 14.8 acitretin).
Gisondi (2013)[22]	
• The study was a nationwide Italian study that included a large number of patients on systemic treatments for psoriasis, and specifically a large number of patients on cyclosporine. • Aside from diabetes, outcomes were based on clinical and laboratory measurements (e.g. systolic and diastolic blood pressure, total cholesterol, liver enzymes, and creatinine). • Patients receiving combination therapies were excluded, which increases confidence in the assignment of outcomes to the indicated treatment group. • The analyses were adjusted for age, gender, body mass index, and smoking.	• The generalizability of the clinical practice for psoriasis in Italy to North American practice settings is unclear. • The follow-up time of 16 weeks was relatively short. • Laboratory measurements were not centralized across the 155 centers, which may have introduced variation in outcome assessment. However, internal and external data checks were conducted regularly.

Appendix 4: Main Study Findings and Author's Conclusions

Table 8: Summary of Findings of Systematic Reviews and Meta-Analyses

Main Study Findings	Author's Conclusion
Sbidian (2017)[9]	
1. Primary Outcome: PASI 90 (proportion of patients) *Direct Comparison:* Cyclosporine vs. Methotrexate: 2 studies No. participants: 172 RR (95% CI) = 1.18 (0.47, 2.98) *Network Meta-Analysis (Traditional Systemic Treatments):* Cyclosporine vs. Methotrexate: 1.02 (0.60, 1.73) Cyclosporine vs. Acitretin: 4.07 (0.21, 79.56) Tofacitinib vs. Cyclosporine: RR (95% CI) 2.13 (0.91, 4.97) Apremilast vs. Cyclosporine: 1.92 (0.72, 5.12) *Network Meta-Analysis (Biologics):* Ixekizumab vs. Cyclosporine: RR (95% CI) 8.14 (3.47, 19.10) Secukinumab vs. Cyclosporine: 6.66 (2.89, 15.34) Brodalumab vs. Cyclosporine: 6.38 (2.73, 14.92) Guselkumab vs. Cyclosporine: 5.28 (2.50, 11.12) Certolizumab vs. Cyclosporine: 6.17 (0.74, 51.08) Ustekinumab vs. Cyclosporine: 4.99 (2.16, 11.54) Adalimumab vs. Cyclosporine: 3.73 (1.79, 7.76) Infliximab vs. Cyclosporine: 2.80 (1.51, 5.22) Etanercept vs. Cyclosporine: 2.71 (1.18, 6.18) **2. Primary Outcome: Serious adverse events (proportion of patients)** *Network Meta-Analysis (Conventional Systemic Treatments):* Cyclosporine vs. Methotrexate: 0.98 (0.06, 15.38) Cyclosporine vs. Acitretin: 0.23 (0.00, 33.96) Tofacitinib vs. Cyclosporine: RR (95% CI) 4.35 (0.18, 103.82) Apremilast vs. Cyclosporine: 3.72 (0.16, 88.89) *Network Meta-Analysis (Biologics):* Ixekizumab vs. Cyclosporine: RR (95% CI) = 4.97 (0.21, 117.41) Secukinumab vs. Cyclosporine: 5.26 (0.22, 124.43) Brodalumab vs. Cyclosporine: 4.59 (0.19, 108.16) Guselkumab vs. Cyclosporine: 4.45 (0.18, 107.22) Certolizumab vs. Cyclosporine: 2.18 (0.07, 71.39) Ustekinumab vs. Cyclosporine: 3.95 (0.17, 92.12) Adalimumab vs. Cyclosporine: 4.53 (0.20, 104.39) Infliximab vs. Cyclosporine: 2.47 (0.14, 44.06) Etanercept vs. Cyclosporine: 4.38 (0.19, 101.76) **3. PASI 75 (proportion of patients):** *Direct Comparison:* Cyclosporine vs. Methotrexate: 2 studies; No. participants: 172 RR (95% CI) = 1.37 (0.84, 2.23) *Network Meta-Analysis (Traditional Systemic Treatments):* Cyclosporine vs. Acitretin: RR (95% CI) 1.21 (0.48, 3.03)	"The relative ranking for SAEs strongly suggested that methotrexate was associated with the best safety profile regarding all the SAEs (moderate-certainty evidence), followed by **ciclosporin** (very low-certainty evidence), certolizumab (moderate-certainty evidence), infliximab (very low-certainty evidence), alefacept (low-certainty evidence), then fumaric acid esters (FAEs) (very low-certainty evidence)." (p69) "All of the assessed interventions appeared superior to placebo in terms of reaching Psoriasis Area and Severity Index (PASI) 90. At class level, network meta-analysis showed that the biologics anti- IL17, followed by anti-IL12/23, anti-IL23, and anti-TNF alpha outperformed the small molecules and the conventional systemic agents in terms of reaching PASI 90 measured at the twelfth to the sixteenth week of treatment after randomisation, with small molecules producing a better outcome than conventional systemic agents." (p69) "The number of studies was still low for the following interventions: certolizumab, tildrakizumab, itolizumab, infliximab, ponesimod, acitretin, **ciclosporin**, alefacept, fumaric acid, and methotrexate, meaning we must be cautious of the conclusions drawn for these drugs."(p69) "Our main results (i.e. superiority of efficacy of the biologic treatments anti-IL17, anti-IL12/23, anti-IL23, and anti-TNF alpha compared with small molecules and the conventional systemic agents, with small molecules achieving better results than conventional systemic agents) do not reflect the way patients are managed in "real-life". Currently, biological treatments have been positioned as third-line therapies by regulatory bodies, with mandatory reimbursement criteria that patients must meet before being considered for these treatments (moderate to severe disease after failure, intolerance or contraindication to conventional systemic agents) . . . Such decisions were based on the lack of long-term safety knowledge but also taking into account economic consideration. In this review, we found insufficient evidence to evaluate long-term safety, and we did not address economic considerations; thus, the question of the choice of the first-line treatment for moderate to severe psoriasis is still debated." (p73)

Table 8: Summary of Findings of Systematic Reviews and Meta-Analyses

Main Study Findings	Author's Conclusion
Cyclosporine vs. Methotrexate: 1.32 (0.90, 1.93) Tofacitinib vs. Cyclosporine: RR (95% CI) 1.39 (0.77, 2.50) Cyclosporine vs. Apremilast: 0.99 (0.54, 1.80) *Network Meta-Analysis (Biologics):* Ixekizumab vs. Cyclosporine: RR (95% CI) = 3.30 (1.85, 5.88) Secukinumab vs. Cyclosporine: 2.95 (1.66, 5.26) Brodalumab vs. Cyclosporine: 2.72 (1.52, 4.85) Ustekinumab vs. Cyclosporine: 2.47 (1.41, 4.31) Certolizumab vs. Cyclosporine: 2.36 (0.76, 7.29) Guselkumab vs. Cyclosporine: 2.24 (1.30, 3.86) Adalimumab vs. Cyclosporine: 1.87 (1.12, 3.13) Etanercept vs. Cyclosporine: 1.76 (1.02, 3.06) Infliximab vs. Cyclosporine: 1.41 (0.84, 2.38) **4. PGA 0 or 1 (proportion of patients):** *Direct Comparison:* Cyclosporine vs Methotrexate: 1 study No. participants: 88 RR (95% CI) = 0.82 (0.47, 1.46) *Network Meta-Analysis (Traditional Systemic Treatments):* Methotrexate vs. Cyclosporine: RR (95% CI) 1.05 (0.52, 2.13) Cyclosporine vs. Acitretin: N/A Tofacitinib vs. Cyclosporine: 1.43 (0.58, 3.51) Apremilast vs. Cyclosporine: 1.15 (0.46, 2.90) *Network Meta-Analysis (Biologics):* Certolizumab vs. Cyclosporine: RR (95% CI) = 10.17 (1.16, 89.00) Ixekizumab vs. Cyclosporine: 4.57 (1.87, 11.18) Secukinumab vs. Cyclosporine: 4.38 (1.79, 10.75) Brodalumab vs. Cyclosporine: 4.34 (1.76, 10.68) Ustekinumab vs. Cyclosporine: 3.26 (1.37, 7.78) Guselkumab vs. Cyclosporine: 2.99 (1.25, 7.11) Adalimumab vs. Cyclosporine: 2.43 (1.05, 5.58) Infliximab vs. Cyclosporine: 2.09 (0.89, 4.93) Etanercept vs. Cyclosporine: 2.13 (0.90, 5.07) **5. Adverse Events (proportion of patients):** *Direct Comparison:* Cyclosporine vs. Methotrexate 2 studies No. participants: 172 RR (95% CI) = 1.10 (0.90, 1.34) *Network Meta-Analysis (Traditional Systemic Treatments):* Cyclosporine vs. Acitretin: RR (95% CI) N/A Cyclosporine vs. Methotrexate: 1.10 (0.90, 1.34) Tofacitinib vs. Cyclosporine: RR (95% CI) 0.96 (0.76, 1.22) Cyclosporine vs. Apremilast: 0.94 (0.74, 1.19) *Network Meta-Analysis (Biologics):* Ixekizumab vs. Cyclosporine: RR (95% CI) = 1.05 (0.83, 1.32)	

Table 8: Summary of Findings of Systematic Reviews and Meta-Analyses

Main Study Findings	Author's Conclusion
Secukinumab vs. Cyclosporine: 0.99 (0.78, 1.24) Brodalumab vs. Cyclosporine: 0.96 (0.76, 1.21) Ustekinumab vs. Cyclosporine: 0.92 (0.74, 1.16) Certolizumab vs. Cyclosporine: 0.86 (0.63, 1.17) Guselkumab vs. Cyclosporine: 0.88 (0.69, 1.12) Adalimumab vs. Cyclosporine: 0.91 (0.72, 1.13) Etanercept vs. Cyclosporine: 0.96 (0.77, 1.21) Infliximab vs. Cyclosporine: 0.98 (0.78, 1.24) **6. Quality of Life:** No data on cyclosporine **7. Proportion of patients with at least one relapse in the maintenance phase (52 to 104 weeks):** No data	
Zweegers (2016)[10]	
1. Primary Outcome: PASI 75 (proportion of patients) In the single cyclosporine study included in the review of 36 patients: 46% reached PASI 75 at week 12. "At short-term, PASI 75 was 35–68% for adalimumab, 12–66% for etanercept, 38–53% for infliximab, 63–80% for ustekinumab, 27% for acitretin, 47% for fumarates, 46% for cyclosporine and 40–49% for methotrexate." (p457) **2. Other secondary outcomes:** No data on cyclosporine	"In conclusion, biologic and conventional systemic agents are effective in daily practice. Combination therapies of biologics with conventional systemic treatments and dose adjustments of biologics were frequently applied strategies . . . There was a high heterogeneity in study design, treatment regimen and patient population between included studies." (p457)
Schmitt (2014)[11]	
1. Primary Outcome: PASI 75 (proportion of patients) Meta-analysis of the same two studies as in the review by Sbidian 2017, however effect estimate is the absolute risk difference (RD) rather than a relative risk. *Direct Comparison:* Cyclosporine vs. Methotrexate: 2 studies RD (95% CI) = 0.15 (-0.01, 0.30) *Indirect Comparison (based on placebo-controlled trials):* Cyclosporine vs. Methotrexate: RD (95% CI) 0.15 (-0.35, 0.66) **2. Other secondary outcomes** **PASI 50 and PASI 90:** No data for cyclosporine **3. Adverse events and withdrawals:** No quantitative data presented "Patients receiving CSA [cyclosporine] were less likely to experience an adverse event than patients receiving etretinate, and were less likely to be withdrawn from study compared with those taking MTX [methotrexate]." (p291)	"Head-to-head trials indicate the superiority of adalimumab and infliximab over MTX [methotrexate], the superiority of ustekinumab over etanercept, the nonsignificant superiority of CSA [**cyclosporine**] over MTX, and the dose-dependent efficacy of etanercept and ustekinumab." (p297) "Infliximab, adalimumab and ustekinumab are more efficacious than CSA [**cyclosporine**] and MTX." (p297) – *note: this is based on placebo comparisons, no head-to-head comparisons were available* Guidelines recommend biologics as a second-line treatment option for patients with moderate-to-severe psoriasis who have failed to respond to conventional treatments, have become intolerant to conventional systemic therapy, and/or cannot receive conventional systemic therapy because of an increased risk of developing drug-related toxicity. The lower direct costs of conventional treatments such as MTX, CSA [**cyclosporine**] or fumaric acid esters justify the initial treatment with these agents, although they are less efficacious during the induction period than the biologics infliximab, ustekinumab and adalimumab." (p299)

CI = confidence interval; No. = number; PASI = Psoriasis Area and Severity Index; PGA = Physician Global Assessment; RR = relative risk

Table 9: Summary of Findings of Randomized Controlled Trials

Main Study Findings	Author's Conclusion
Choi (2017)[12]	
1. PASI Score Cyclosporine vs. Methotrexate: "Between the two groups, the scores of [PASI] showed no statistically significant differences at 2, 4, 8, 12 and 16 weeks of treatment [P = 0.36]." (p1740) **2. Modified PASI 75 (head area assessment was excluded) and Time required to achieve Modified PASI 75** Cyclosporine vs. Methotrexate: ". . . there were no differences in the proportion of patients who reached mPASI 75 and the time required to achieve mPASI 75 (P = 0.60 and P = 0.79, respectively)." (p1740) **3. Laboratory abnormalities** Cyclosporine vs. Methotrexate: "After 16 weeks of treatment, there were no significant differences in the number of reported laboratory abnormalities (P = 0.18)." (p1740)	"Based on the present and previous studies, the effectiveness and tolerability of ciclosporin and methotrexate seem comparable." (p1740)
Ikonomidis (2017)[13]	
PASI Score at baseline and 4 months: median (IQR) Cyclosporine: Baseline 12.8 (6-18) and 4-month 2.5 (1-4) Etanercept: Baseline 13.8 (6.3-20) and 4-month 2.4 (2-6) Ustekinumab: Baseline 13.3 (8.7-20.4) and 4-month 1.6 (1-3.2)	"PASI was similarly improved in all treatment arms at 4-month treatment [P=0.8]." (p7) *Note: The primary objective of this study was to examine the role of IL-12 inhibition on vascular and myocardial function. The PASI outcome was reported secondarily.*

IQR = interquartile range; PASI = Psoriasis Area and Severity Index

Table 10: Summary of Findings of Non-Randomized Safety Studies

Main Study Findings	Author's Conclusion
Belinchon (2017)[14]	
1. Adverse events leading to discontinuation of therapy "Of 4218 systemic treatments, 3054 were discontinued, primarily due to ineffectiveness or loss of effectiveness in 914 (22%), remission in 832 (20%) and 447 (11%) due to an AE [adverse event]." (p1702) *Incidence Rate (95% CI) – traditional systemic treatments* Cyclosporine: 49.18/100 person-year (41.91, 57.72) Methotrexate: 15.15/100 person-year (13.18, 17.42) Acitretin: 14.5/100 person-year (11.76, 17.87) *Incidence Rate (95% CI) – biologics* Infliximab: 26.52/100 person-year (20.98, 33.51) Adalimumab: 10.83/100 person-year (9.2, 12.75) Etanercept: 10.58/100 person-year (8.91, 12.56) Ustekinumab: 2.6/100 person-year (1.83, 3.69) **2. Serious adverse events leading to discontinuation of therapy** *Incidence Rate (95% CI) – traditional systemic treatments* Cyclosporine: 4.59/100 person-year (2.72, 7.75) Methotrexate: 1.31/100 person-year (0.81, 2.10) Acitretin: 0.82/100 person-year (0.34, 1.98) *Incidence Rate (95% CI) – biologics* Infliximab: 7.95/100 person-year (5.19, 12.20) Adalimumab: 2.93/100 person-year (2.14, 4.01) Etanercept: 1.22/100 person-year (0.74, 2.02) Ustekinumab: 0.50/100 person-year (0.23, 1.12) **3. Specific adverse events leading to discontinuation** With regard to individual AEs [adverse events], the most common cause of discontinuation for all systemic agents was infections . . . with infliximab as the first biologic associated, and ustekinumab in the last place . . . whereas between classics, **cyclosporine** was the primary one, and acitretin the last one, without cases." (p1706) "Gastrointestinal tract disorders . . . 21 on **cyclosporine** (6.89/100 PY, 95% CI: 4.49–10.56), 42 on methotrexate (3.23/100 PY, 95% CI: 2.39–4.37), 6 on infliximab (2.27/100 PY, 95% CI: 1.02–5.06) and 15 on etanercept (1.22/100 PY, 95% CI: 0.74–2.02)." (p1703) "**Cyclosporine** was the second drug for the most AEs [adverse events] related to skin disorders (3.28/100 PY: 1.76–6.09). . ." (p1703)	". . . it should be noted that the elevated rate of cyclosporine suspensions was associated with vascular disorders, especially related to hypertension." (p1706) "Biologics presented a lower IR [incidence rat] of total AEs [adverse events] related to discontinuation than did classics drugs, but not with respect to serious AEs." (p1707) "In classic systemic therapies, cyclosporine had the highest number of suspensions associated with AE [adverse event], and infliximab had the highest for biologics. Ustekinumab was the drug with the lowest incidence of stopping associated with AE. Infection and gastrointestinal tract disorders were the most common AEs responsible for all systemic treatments, with infliximab associated with infections and cyclosporine associated with vascular and gastrointestinal tract disorders." (p1707)

Main Study Findings	Author's Conclusion
"**Cyclosporine** had the highest amount of AEs [adverse events] related to vascular (hypertension) and nervous system disorders [8.52% (95% CI: 5.8–12.52) and 6.23% (95% CI: 3.97–9.77), respectively]." (p1703)	
Davila-Seijo (2017)[15]	
1. Overall infection Cyclosporine vs. Methotrexate: RR (95% CI): 1.58 (1.17, 2.15) **2. Serious infection** Cyclosporine vs. Methotrexate: RR (95% CI): 3.12 (1.11, 8.77) **3. Recurrent infection** Cyclosporine vs. Methotrexate: RR (95% CI): 0.63 (0.3, 1.31)	"The raw rate of recurrent infections in the same patient appeared to be higher among patients treated with biologics compared with those treated with methotrexate, and it was lower among patients who were treated with **cyclosporine** or acitretin." (p317) "**Cyclosporine** was the only drug that showed a significant increased risk of serious infections compared with methotrexate." (p319) "Finally, our study showed no significant change over time in the incidence rate of infections between patients taking methotrexate and patients taking other drugs or drug combinations." (p319)
Arnold (2016)[16]	
1. Drug survival (interval between first dose and last dose) "According to theoretically predicted survival curves, the crude probability of survival was highest for UST [ustekinumab], followed by ADA [adalimumab], ETA [etanercept], INF [infliximab], FAE [fumaric acid esters], MTX [methotrexate], ACI [acitretin], and finally CyA [cyclosporine] . . ." (p1091) *Months (95% CI) – traditional systemic treatments* Methotrexate: 22.3 (17.6, 27.1) Acitretin: 22.6 (14.9, 30.3) Cyclosporine: 8.4 (5.8, 11.0) *Months (95% CI) - biologics* Adalimumab: 56.0 (47.6, 64.5) Etanercept: 44.3 (28.6, 60.0) Infliximab: 29.5 (16.9, 42.1) Ustekinumab: 52.9 (46.6, 59.2) **2. Percent patients who stopped treatment due to adverse events:** Cyclosporine: 57.9% Methotrexate: 39.7% Acitretin: 38.1% Infliximab: 35.0% Adalimumab: 12.4% Etanercept: 10.9% Ustekinumab: 5.1%	"Taking all series and medications together, 468 reasons for discontinuation were identified. Most frequently, these included adverse events (30.2% of 696 courses), followed by lack of efficacy for psoriatic skin lesions (21.3 %) and lack of efficacy with regard to PsA [psoriatic arthritis] (6.9%)." (p1095) Traditional systemic agents were most commonly stopped due to adverse events . . . ADA [adalimumab], ETA [etanercept], and UST [ustekinumab] were most frequently discontinued because of inefficacy for the skin, . . . more rarely due to adverse events . . . Regarding INF [infliximab], the discontinuation rate due to adverse events was higher than that of other biologics . . . with failure to sufficiently improve skin lesions being the second most common reason." (p1095) "These patients are more likely to have severe, refractory psoriasis than patients from other institutions, which may have biased the results in favor of new treatment options, in particular, novel biologics." (p1097)
Carpentieri (2016)[17]	
1. Adverse events leading to discontinuation of therapy (proportion of patients)	"Compared with the other traditional treatments prescribed (methotrexate, acitretin and phototherapy), cyclosporine was

Main Study Findings	Author's Conclusion
Cyclosporine: 24% Acitretin: 25% Methotrexate: 9%	associated with fewer treatment interruptions due to lack of efficacy and to greater proportions of patients achieving disease remission and discontinuing treatment for this reason." (p403) "Promising results are emerging from trials with biologics, but the current lack of head-to-head comparisons between conventional and biological drugs does not enable any conclusion about the superiority of targeted therapies over conventional immunosuppressive agents." (p404) ". . . traditional therapies, though widely used and supported by decades of use in clinical practice, are far from optimal in patients with psoriasis. Further studies are needed to define the position and to compare head-to-head the various options available, including biologics." (p404)
Davila-Seijo (2016)[18]	
1. Drug discontinuation due to adverse events (proportion of total discontinuations by treatment) *Traditional Systematic Treatments:* Cyclosporine: 17.6% - no difference compared to methotrexate Methotrexate: 17.3% Acitretin: 14.2% *Biologics:* Infliximab: 23.6% Adalimumab: 12.6% Etanercept: 12.1% Ustekinumab: 7.7% **2. Drug survival probability at first year based on discontinuation due to adverse events** *Traditional Systematic Treatments (Probability, 95% CI):* Acitretin: 88.7 (84.0, 92.1) Methotrexate: 87.8 (84.6, 90.4) Cyclosporine: 78.5 (72.1, 83.6) - significant difference compared to methotrexate *Biologics (Probability, 95% CI):* Ustekinumab: 98.8 (97.1, 99.5) Adalimumab: 93.8 (91.3, 95.6) Etanercept: 92.6 (89.7, 94.7) Infliximab: 88.7 (82.1, 92.9) **3. Serious adverse events** *Traditional Systematic Treatments (HR, 95% CI compared with methotrexate):* Cyclosporine: 3.7 (1.6, 8.8) Acitretin: 1.4 (0.6, 3.0) *Biologics (HR, 95% CI compared with methotrexate):* Infliximab: 3.6 (1.6, 8.2) Adalimumab: 1.8 (1.0, 3.4)	"Major reasons for treatment discontinuation were lack of efficacy (36%), followed by remission (27%). AEs [adverse events] accounted for 15% of withdrawals." (p1948) "We did not take into account dose modifications (intensification or deintensification) during the study, simultaneous use of biologics and classic drugs (these patients were considered as exposed to the biologic), or whether the drug was the first drug to be used or not. These modifications might affect survival." (p1948)

Main Study Findings	Author's Conclusion
Ustekinumab: 1.2 (0.6, 2.7) Etanercept: 1.1 (0.6, 2.0)	
Ahlehoff (2015)[19]	
1. Composite cardiovascular endpoint (cardiovascular death, myocardial infarction, and stroke) *Incidence rate per 1000 patient-years (95% CI):* Biologics: 4.16 (2.30, 7.51) Cyclosporine: 6.08 (1.96, 18.85) Methotrexate: 6.28 (4.78, 8.27) Retinoids: 18.95 (12.99, 27.63) **2. All-cause mortality** *Incidence rate per 1000 patient-years (95% CI):* Biologics: 4.14 (2.94, 7.48) Cyclosporine: 8.08 (3.03, 9.46) Methotrexate: 7.34 (5.70, 9.46) Retinoids: 21.45 (15.08, 30.50)	"In this nationwide cohort of patients with severe psoriasis treated with systemic anti-inflammatory therapies and followed for up to 5 years, methotrexate was associated with lower risk of the composite of cardiovascular death, myocardial infarction and stroke compared to patients treated with other therapies. In addition, methotrexate and biological drugs were associated with reduced all-cause mortality, and tumour necrosis factor inhibitors were associated with reduced cardiovascular risk, whereas the interleukin-12/23 inhibitor was not. By contrast, treatment with **cyclosporine** and retinoids was not associated with reduction in cardiovascular events, as compared to other treatments, including topical treatments, phototherapy and/or climate therapy." (p1130-1131)
Reich (2015)[20]	
1. Infections (severe and serious): No significant differences (data presented in figures) **2. Cardiovascular events (severe)**: No significant differences (data presented in figures) **3. Malignancies:** No significant differences (data presented in figures) **4. Malignancies and major cardiac events (MACE):** No significant differences (data presented in figures)	"In conclusion, this analysis from The German Psoriasis Registry PsoBest confirms pharmacovigilance data from other registries, indicating a satisfying safety of the systemic and biological drugs used in Germany for moderate to-severe psoriasis." (p881)
Piaserico (2014)[21]	
1. Rate of adverse events (per patient-year) *Traditional systemic treatments:* Cyclosporine: 1.4 (significantly higher than methotrexate) Acitretin: 0.32 MTX: 0.12 *Biologics:* Adalimumab: 0.35 Ustekinumab: 0.26 Infliximab: 0.19 Etanercept: 0.11 **2. Rate of infections (per patient-year)** *Traditional systemic treatments:* Cyclosporine: 0 Acitretin: 0	"In our population **cyclosporine** was associated with the highest risk of adverse events (1.4/patient-year), mainly hypertension (0.76/patient-year) and renal insufficiency (0.35/patient-year). To our knowledge, no studies have systematically evaluated the safety profile of **cyclosporine** in the elderly. Given the baseline age-related renal impairment, the high prevalence of cardiovascular comorbidities and the high risk of drug interactions, this treatment should be used with extreme caution in elderly patients." (p296) "One of the most common concerns when treating an elderly patient with psoriasis is the use of immunosuppressive agents in an already immunosuppressed individual . . . In the studied population, infections appeared to be the most frequent adverse event associated with anti-psoriatic treatments . . . Rates of infections/patient-year tended to be higher for adalimumab compared with other drugs . . . however, the small number of patients did not allow complete statistical evaluation,

Main Study Findings	Author's Conclusion
MTX: 0.01 *Biologics:* Adalimumab: 0.12 Infliximab: 0.05 Etanercept: 0.05 Ustekinumab: 0	and therefore definite conclusions cannot be drawn." (p296)
Gisondi (2013)[22]	
1. Hypercholesterolemia (cyclosporine vs. all other treatments combined) OR (95% CI) = 1.34 (1.00, 1.78) **2. Hypertriglyceridemia (cyclosporine vs. all other treatments combined)** OR (95% CI) = 0.91 (0.67, 1.21) **3. AST increase ≥2 times (cyclosporine vs. all other treatments combined)** OR (95% CI) = 0.40 (0.23, 0.70) **4. ALT increase ≥2 times (cyclosporine vs. all other treatments combined)** OR (95% CI) = 0.77 (0.54, 1.08) **5. Hypercreatininemia (cyclosporine vs. all other treatments combined)** OR (95% CI) = 1.63 (0.43, 6.19) **6. Diabetes mellitus (cyclosporine vs. all other treatments combined)** OR (95% CI) = 2.88 (1.00, 8.31) **7. Arterial hypertension (cyclosporine vs. all other treatments combined)** OR (95% CI) = 3.31 (2.07, 5.28)	"Total cholesterol and triglyceride levels increased after 8 and 16 weeks of continuous treatment with acitretin or **cyclosporine** . . ." (pe34) "An increase in mean serum creatinine levels and increased SBP [systolic blood pressure] and DBP [diastolic blood pressure] values were only observed in patients receiving **cyclosporine…** We observed a significant increase in mean blood pressure measurements as early as week 8" (pe35-e36) "Moreover, **cyclosporine** was associated with a significant risk of developing diabetes, which is not surprising because the calcineurin inhibitors tacrolimus and **cyclosporine** are associated with a higher risk of new-onset diabetes in transplant recipients." (pe36) "Based on our observations, acitretin and **cyclosporine** should be used with caution in psoriatic patients with cardio-metabolic comorbidities due to their potential to increase serum lipids and, for **cyclosporine** only, associated diabetogenic and pro-hypertensive effects." (pe38)

CI = confidence interval; HR = hazard ratio; OR = odds ratio; RR = relative risk

Appendix 5: Additional References of Potential Interest

Guidelines & Consensus:

1. Soleymani T, Vassantachart JM, Wu JJ. Comparison of guidelines for the use of cyclosporine for psoriasis: a critical appraisal and comprehensive review. J Drugs Dermatol. 2016;15(3):293-301.

   This paper reviews recommendations for the use of cyclosporine for psoriasis from four guidelines: the American Academy of Dermatology (AAD), the European S3, the National Institute for Health and Care Excellance (NICE), and the Canadian Dermatology Association. Recommendations for monitoring parameters prior to initiation of therapy, contraindications, starting doses for plaque psoriasis, intermittent versus long-term therapy, monitoring during treatment, and management of side effects are provided.

2. Mrowietz U, de Jong EM, Kragballe K, Langley R, Nast A, Puig L, et al. A consensus report on appropriate treatment optimization and transitioning in the management of moderate-to-severe plaque psoriasis. J Eur Acad Dermatol Venereol. 2014;28(4):438-453.

   This paper provides recommendations for optimizing treatment and switching therapies in patients with moderate-to-severe plaque psoriasis, based on consensus of dermatologists from 33 countries and systematic literature reviews.

Other Efficacy Outcomes:

3. Nast A, Sporbeck B, Rosumeck S, Pathirana D, Jacobs A, Werner RN, et al. Which antipsoriatic drug has the fastest onset of action? Systematic review on the rapidity of the onset of action. J Invest Dermatol. 2013;133(8):1963-1970.

   This study reviews the evidence for the onset of action of conventional systemic treatments and biologics for moderate-severe plaque psoriasis. Onset of action was defined as the weighted average time that 25% of patients achieved a PASI 75 response. Results: infliximab – 3.5 weeks; ustekinumab – 4.6 weeks high dose and 5.1 weeks low dose; adalimumab – 4.6 weeks, etanercept – 6.6 weeks high dose and 9.5 weeks low dose; alefacept – 15.4 weeks high dose; cyclosporine – 6.0 weeks; limited data for methotrexate – 3.2 weeks high dose and 9.9 weeks low dose; no data for retinoids.

4. Jacobs A, Rosumeck S, Nast A. Systematic review on the maintenance of response during systemic antipsoriatic therapy. Br J Dermatol. 2015;173(4):910-921.

   This study reviews the evidence for the maintenance of response of conventional systemic treatments and biologics in patients with psoriasis (type of psoriasis not specified). The patient population had achieved PASI 75 response or PGA of at least almost clear during an induction period of up to 6 months. Of the conventional systemic treatments, studies were available only for cyclosporine compared with placebo. For biologics, data were available for adalimumab, etanercept, and infliximab, No head-to-head comparisons with cyclosporine and other agents were presented. The authors conclude that limited evidence is available for choice of treatment during the maintenance period and a clear ranking of treatments is not possible.

Other Safety Outcomes:

5. Yiu ZZ, Warren RB, Mrowietz U, Griffiths CE. Safety of conventional systemic therapies for psoriasis on reproductive potential and outcomes. J Dermatolog Treat. 2015;26(4):329-334.

   This is a narrative review of the safety of conventional systemic treatments for psoriasis in patients of reproductive potential. Evidence was obtained from large-scale registries, adverse-event reporting databases, clinical trials, and case reports. Safety outcomes included congenital malformations, lactation, male fertility, and mutagenicity.

6. Richard MA, Barnetche T, Horreau C, et al. Psoriasis, cardiovascular events, cancer risk and alcohol use: evidence-based recommendations based on systematic review and expert opinion. J Eur Acad Dermatol Venereol. 2013;27 Suppl 3:2-11.9.

   This study conducted a systematic review and sought consensus from 39 dermatologists about comorbidities and their management in patients with psoriasis (type of psoriasis not specified). A total of 12 recommendations were formulated. Patients with psoriasis have a moderate increased risk of cardiovascular disease. Aside from methotrexate which may be cardioprotective, there was lack of evidence that conventional systemic treatments have any effect on cardiovascular risk. Patients with psoriasis have an increased risk of solid cancer and non-melanoma skin cancer. According to one of the recommendations: the increased risk of skin carcinoma may be associated with PUVA and cyclosporine use (Grade B).

List of Non-Randomized Studies of Effectiveness, not included in the review by Zweegers 2016[10]

7. Arnold T, Schaarschmidt ML, Herr R, Fischer JE, Goerdt S, Peitsch WK. Drug survival rates and reasons for drug discontinuation in psoriasis. Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG. 2016;14(11):1089-1099.

8. Bae SH, Yun SJ, Lee JB, Kim SJ, Won YH, Lee SC. Algorithm to select optimal systemic anti-psoriatic drugs in relation with patients' Psoriasis Area and Severity Index score for plaque psoriasis. J Dermatol. 2016;43(6):643-649.

9. Carpentieri A, Pacello L, De Marco IM, Loiacono A, Picconi O, Loconsole F. Retrospective analysis of the effectiveness and costs of traditional treatments for moderate-to-severe psoriasis: A single-center, Italian study. J Dermatolog Treat. 2016;27(5):399-405.

10. Davila-Seijo P, Dauden E, Carretero G, et al. Survival of classic and biological systemic drugs in psoriasis: results of the BIOBADADERM registry and critical analysis. J Eur Acad Dermatol Venereol. 2016;30(11):1942-1950.

11. Takeshita J, Wang S, Shin DB, et al. Comparative effectiveness of less commonly used systemic monotherapies and common combination therapies for moderate to severe psoriasis in the clinical setting. J Am Acad Dermatol. 2014;71(6):1167-1175.

12. El-Eishi NH, Kadry D, Hegazy RA, Rashed L. Estimation of tissue osteopontin levels before and after different traditional therapeutic modalities in psoriatic patients. J Eur Acad Dermatol Venereol. 2013;27(3):351-355.

13. Akasaka E, Mabuchi T, Manabe Y, et al. Long-term efficacy of psoriasis vulgaris treatments: analysis of treatment with topical corticosteroid and/or vitamin D3 analog, oral cyclosporin, etretinate and phototherapy over a 35-year period, 1975-2010. J Dermatol. 2013;40(4):238-243.