Table C.7. Characteristics of the included studies in KQ 1d FeNO response to administration of Leukotriene receptor antagonists (LTRA)

| Author, Year (ref) | Study Country, Study Design, Study Settings, Risk of Bias | FeNO and Comparisons | Patient Characteristics (Age, Gender, Race, BMI/Weight, Tobacco Use, Asthma Phenotype, Atopy, etc) | Ways of Administration (Frequency, Use of Alcohol/Mouthwash, Beta-Agonists Prior to Test) | Medication (Frequency, Dose, Duration, etc.) | Asthma Outcomes | Test Findings (Mean, SD) | Conclusions |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Bisgaard, 1999 124 | Denmark, RCT with cross-over, outpatient setting, unclear risk of bias. | FeNO, N= 26 | Mean age 12 years (6-15). | Measured by online Aerocrine NO system, at 110 ml/sec, two times per visit, steroid use prior to test was 42.3% | 2 weeks of 5 mg montelukast once daily or placebo, then cross over for 2 weeks additional of 200 mg budesonide. | FeNO was significantly reduced with montelukast and budesonide Compared with placebo. This effect was independent of concurrent steroid treatment.  | Montelukast mean difference from placebo7.3 ppb (1.4 to 13.1).Budesonide mean difference from placebo15.7 ppb (9.5 to 22.0). | FeNO was significantly reduced by 20% after 2-wk treatment with montelukast and budesonide. This effect was independent of concurrent steroid treatment.  |
| Spirometry, N= 24 |  | Spirometry exhibited a tendency to improve after montelukast and after budesonide as compared with the placebo treatment period, but this was not statistically significant | FEV1 Montelukast mean difference from placebo0.132 L (-0.022 to 0.286)FEV1 Budesonide mean difference from placebo0.116 L (-0.045 to 0.277). |
| Bratton, 1999 125 | United States, longitudinal nonrandomized, outpatient setting, high risk of bias. | FeNO, N=24 | Mean age 9.3 years (SD: 1.6), 67 % males. | using a chemiluminescentanalyzer (Model 280 NOA, Sievers Instruments,Inc., Boulder CO). | Montelukast sodium (5 mg chewable tablet) administeredonce daily at bedtime, and after a 2-week posttreatmentwashout period. | Change of FeNO after montelukast sodium treatment | Mean difference from baseline 24 ppb(P < 0.01) | In 12 children with chronic asthma, FeNO concentrations decreased after 4 week treatment with montelukast sodium, which again rose after treatment was withdrawn. |
| Spirometery, N=24 |  | Change of FEV1 (% predicted) after montelukast sodium treatment. | FEV1 at baseline 81 % pred (SD: 4) After Montelukast 85 % pred (SD: 4). |
| Montuschi, 2007 126 | Italy, RCT, outpatient setting, low risk of bias. | FeNO, N= 26 | Montelukast group (N= 14)Mean age 10.8 years (SD: 0.5), 78.5% male Placebo group (N= 12)Mean age 10.5 years (SD: 0.6), 83% male | Measured by online NIOX system (Aerocrine; Stockholm, Sweden), at 50 ml/sec.  | 1 month of montelukast 5mg/day or placebo then 2 weeks treatment withdrawal. | Montelukast showed a significant reduce in FeNO, however, it was increased 2 weeks after withdrawal. No changes were seen in placebo group. | Montelukast groupWeek 1: 45.5 ppbWeek 5: 37.9 ppbWeek 7: 52.2 ppbPlacebo groupWeek 1: 37.5 ppbWeek 5: 46.3 ppbWeek 7: 40.6 ppb | Montelukast reduced FeNO concentrations in children with asthma, and withdrawal can result in increased FeNO values and worsening of Spirometry. |
| Spirometry, N= 26 | Spirometry (Pony FX; Cosmed; Rome, Italy), and the best of three consecutive maneuvers were chosen. | Montelukast had no effect on Spirometry test results in asthmatic children, however, test results were lower than baseline after the 2 week treatment withdrawal. Placebo treatment and its withdrawal had no effect on Spirometry tests. | Montelukast groupFEV1 % pred Week 1: 93.1 (SD: 3.1)Week 5: 92.9 (SD: 3.0)Week 7: 90.7 (SD: 2.8)FEV1/FVCWeek 1: 96.7 (SD: 2.2)Week 5: 95.9 (SD: 3.0)Week 7: 94.7 (SD: 3.0)Placebo groupFEV1 % pred Week 1: 94.3 (SD: 2.4)Week 5: 95.7 (SD: 2.9)Week 7: 90.6 (SD: 3.1).FEV1/FVCWeek 1: 99.2 (SD: 2.4)Week 5: 99.8 (SD: 2.8)Week 7: 96.4 (SD: 2.8). |
| Ohkura, 2009 127 | Japan, longitudinal nonrandomized, outpatient setting, low risk of bias. | FeNO, N= 20 | Mean age 68.1 years (SD: 12), 75% male.  | Measured by online chemiluminescence at a flow rate of 0.05 L/sec. Steroid prior to test was 100%. | 1 month of Pranlukast 450 mg/day added to ICS+LABA (salmeterol 100 μg/day), then 1 month of washout period (only ICS+LABA (salmeterol 100 μg/day).  | FeNO decreased significantly after adding pranlukast. FeNO after wash-out period was also lower than baseline. | Baseline 26.6 ppb (SD: 1.1).Pranlukast + ICS+ LABA 18.3 ppb (SD: 1.9).ICS+LABA 21.1 ppb (SD: 1.1). | Pranlukast added to ICS and inhaled LABA reduced FeNO. |
| Spirometry, N= 20 |  |  | FEV1 increased significantly after pranlukast was added and decreased significantly after wash-out period. | Baseline 2.08 L (SD: 0.12).Pranlukast + ICS+ LABA 2.14 L (SD: 0.56).ICS+LABA 2.08 L (SD: 0.58). |
| Sandrini, 2003 128 | Canada, RCT with crossover, outpatient setting, unclear risk of bias. | FeNO, N=20 | mean age 34.8 years (SD: 12.6),25% males,5% smoker.12 received placebo and 8 received Montelukast.  | Performed according to ATS recommendations, using an expiratory flow rate of 0.046 L/s.[20](http://www.sciencedirect.com/science/article/pii/S0012369216486769#bib20)The exhaled breath condensate was collected using a commercial apparatus (Cryocond; Boehringer Ingelheim; Burlington, ON, Canada) that cools and freezes the exhaled air to −30°C while patients breathe at tidal volume, wearing nose clips, for 5 min. Frozen samples were stored at −70°C. H2O2 was measured as described previously. | Two 2-week treatment periods with Montelukast (10 mg daily) or matching placebo, with each treatment being followed by 1 week of washout. The tablets were taken in the evening, and visit 2 was considered to be the initial day of the first treatment arm. | Montelukast resulted in a significant reduction of FeNO from day 1 of treatment to day 14, however, FeNO remained lower in comparison to baseline during the washout period. The maximal effect was observed on day 7. Montelukast median difference from baseline at day 7 was −11.3 ppb (25th to 75th percentile, −16.8 to −4.6), and the median difference for placebo was 1.5 (25th to 75th percentile, −1 to 9.9).  | FeNO in Montelukast group (N= 8): 52.5 (38 to 102).Placebo group (N=12): 44 (28 to 95). | Montelukast reduced FeNO in adults with mild asthma in an RCT, reduction was noted as early as day 1 with a maximum effect on day 7. |
| Spirometry, N=20 | Spirometry was performed after ENO measurement and breath condensate collection using ATS standards. |  | FEV1 % in Montelukast(N= 8) :88% (range 83 to 95)Placebo group (N=12):91% (range 83 to 98) |

ATS standards: American Thorcic Society standards; FeNO: fraction exhaled nitric oxide; FEV1: forced expiratory volume in the first second; FEV1% pred: forced expiratory volume in the first second percentage predicted; FVC: forced vital capacity; ICS: inhaled corticosteroid; LABA: long acting beta agonist; RCT: randomized clinical trial; SD: standard deviation.