Biologics for rheumatoid arthritis: an overview of Cochrane reviews

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ABSTRACT

BACKGROUND: The biologic disease-modifying anti-rheumatic drugs (DMARDs) are very effective in treating rheumatoid arthritis (RA), however there is a lack of head-to-head comparison studies.

OBJECTIVES: To compare the efficacy and safety of abatacept, adalimumab, anakinra, etanercept, infliximab, and rituximab in patients with RA.

METHODS: This 'Overview of Reviews' was done by including all Cochrane Reviews on Biologics for RA available in The Cochrane Library. We included only data on standard dosing regimens for these biologic DMARDs from placebo-controlled trials. The primary efficacy and safety outcomes were ACR50 and withdrawals due to adverse events. We calculated Risk Ratios (RR) for efficacy, Odds Ratio (OR) for safety and combined estimates of events across the placebo groups as the expected Control Event Rate (CER). Indirect comparisons of biologics were performed for efficacy and safety using a hierarchical linear mixed model incorporating the most important study level characteristic (i.e. type of biologic) as a fixed factor and study as a random factor; reducing the between study heterogeneity by adjusting for the interaction between the proportion of patients responding on placebo and the duration of the trial.

MAIN RESULTS: From the six available Cochrane reviews, we obtained data from seven studies on abatacept, eight on adalimumab, five on anakinra, four on etanercept, four on infliximab, and three on rituximab. The indirect comparison estimates showed similar efficacy for the primary efficacy outcome for all biologics with three exceptions. Anakinra was less efficacious than etanercept with a ratio of RRs (95% CI; P value) of 0.44 (0.23 to 0.85; P = 0.014); anakinra was less efficacious than rituximab, 0.45 (0.22 to 0.90; P = 0.023); and likewise adalimumab was more efficacious than anakinra, 2.34 (1.32 to 4.13; P = 0.003). In terms of safety, adalimumab was more likely to lead to withdrawals compared to etanercept, with a ratio of ORs of 1.89 (1.18 to 3.04; P = 0.009); anakinra more likely than etanercept, 2.05 (1.27 to 3.29; P = 0.003); and likewise etanercept less likely than infliximab, 0.37 (0.19 to 0.70; P = 0.002).

AUTHORS' CONCLUSIONS: Based upon indirect comparisons, anakinra seemed less efficacious than etanercept, adalimumab and rituximab and etanercept seemed to cause fewer withdrawals due to adverse events than adalimumab, anakinra and infliximab. Significant heterogeneity in characteristics of trial populations imply that these finding must be interpreted.

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Full review is available (free access) from: http://www.cochranejournalclub.com/biologics-for-rheumatoid-arthritis-clinical/pdf/CD007848.pdf

COMMENTS

The biological disease-modifying antirheumatic drugs (DMARDs) cited in this systematic review on treatments for rheumatoid arthritis have been approved by the Food and Drug Administration (FDA) in the United States and by the Brazilian Health Surveillance Agency (ANVISA) whenever at least one non-biological DMARD (methotrexate, hydroxychloroquine, leflunomide, sulfasalazine or minocycline) has failed or been ineffective in attempts to control the inflammatory activity. Biological DMARDs may or may not be used in association with non-biological DMARDs, except for rituximab, which is indicated after previous use of another biological DMARD has failed or been ineffective and therefore is indicated for cases of greater severity. Anakinra is not available in Brazil (used in < 5% of rheumatoid arthritis cases using biological DMARDs in the United States). All are equally effective when compared with placebo. It would be desirable if there were significant studies that made comparisons between the biological agents ("head-to-head"). Among the studies discussed in this review, the lack of uniformity among them with regard to disease severity, duration, prognostic criteria present and type and length of previous use of non-biological DMARDs were noteworthy.

Regarding the safety of these drugs, all of them, without exception, have potential adverse effects (mainly facilitating the emergence of infections). There are still no consistent conclusions regarding the potential for development of malignancy.

Currently, treatment of rheumatoid arthritis with biological agents should be indicated based on the individual characteristics of each rheumatoid arthritis patient (aggressiveness of the disease, prognostic factors, sequelae, comorbidities etc.); on the cost-effectiveness of the treatment; and, especially, on the consensus that has been reached with the patient, after extensive discussion about the possible benefits, side effects and risks from the treatment.[1,2]

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Regular treatment with formoterol and an inhaled corticosteroid versus regular treatment with salmeterol and an inhaled corticosteroid for chronic asthma: serious adverse events

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ABSTRACT

BACKGROUND: An increase in serious adverse events with both regular formoterol and regular salmeterol in chronic asthma has been demonstrated in comparison with placebo in previous Cochrane reviews. This increase was significant in trials that did not randomise participants to an inhaled corticosteroid, but less certain in the smaller numbers of participants in trials that included an inhaled corticosteroid in the randomised treatment regimen.

OBJECTIVES: We set out to compare the risks of mortality and non-fatal serious adverse events in trials which have randomised patients with chronic asthma to regular formoterol versus regular salmeterol, when each are used with an inhaled corticosteroid as part of the randomised treatment

SEARCH STRATEGY: Trials were identified using the Cochrane Airways Group Specialised Register of trials. Manufacturers' web sites of clinical trial registers were checked for unpublished trial data and Food and Drug Administration (FDA) submissions in relation to formoterol and salmeterol were also checked. The date of the most recent search was July 2009.

SELECTION CRITERIA: Controlled clinical trials with a parallel design, recruiting patients of any age and severity of asthma were included if they randomised patients to treatment with regular formoterol versus regular salmeterol (each with a randomised inhaled corticosteroid), and were of at least 12 weeks duration.

DATA COLLECTION AND ANALYSIS: Two authors independently selected trials for inclusion in the review and extracted outcome data. Unpublished data on mortality and serious adverse events were sought from the sponsors and authors.

MAIN RESULTS: Eight studies met the eligibility criteria of the review recruiting 6,163 adults and adolescents. There were seven studies (involving 5,935 adults and adolescents) comparing formoterol and budesonide to salmeterol and fluticasone. All but one study administered the products as a combined inhaler, and most used formoterol 50 mcg and budesonide 400 mcg twice daily versus salmeterol 50 mcg and fluticasone 250 mcg twice daily. There were two deaths overall (one on each combination) and neither were thought to be related to asthma. There was no significant difference between treatment groups for non-fatal serious adverse events, either all-cause (Peto OR 1.14; 95% CI 0.82 to 1.59, I2 = 26%) or asthma-related (Peto OR 0.69; 95% CI 0.37 to 1.26, I2 = 33%). Over 23 weeks the rates for all-cause serious adverse events were 2.6% on formoterol and budesonide and 2.3% on salmeterol and fluticasone, and for asthma-related serious adverse events, 0.6% and 0.8% respectively. There was one study (228 adults) comparing formoterol and beclomethasone to salmeterol and fluticasone, but there were no deaths or hospital admissions. No studies were found in children.

AUTHORS' CONCLUSIONS: The seven identified studies in adults did not show any significant difference in safety between formoterol and budesonide in comparison with salmeterol and fluticasone. Asthma-related serious adverse events were rare, and there were no reported asthma-related deaths. There was a single small study comparing formoterol and beclomethasone to salmeterol and fluticasone in adults, but no serious adverse events occurred in this study. No studies were found in children. Overall there is insufficient evidence to decide whether regular formoterol and budesonide or beclomethasone have equivalent or different safety profiles from salmeterol and fluticasone.

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This section was edited under the responsibility of the Brazilian Cochrane Center
The full review is available (free access) from: http://www.cochranejournalclub.com/formoterol-vs-salmetrol-adverse-events-clinical/pdf/CD007694_full.pdf

COMMENTS

Inhalatory medications (inhalatory medications and bronchodilators) are the basis for treatment of the stable phase of asthma and for chronic obstructive pulmonary disease (COPD). The pathogenesis of asthma results from an inflammatory process in the airways that leads to contraction of the smooth musculature and triggers the symptoms of coughing, expectoration and dyspnea. Therefore, the treatment for stable asthma is based on the use of inhalatory corticoids for all patients with persistent conditions (mild, moderate or severe). For some patients, this is used in association with long-duration bronchodilators (LABAs) because of the clinical and functional state (spirometry). Inhalatory corticoids include beclomethasone, budesonide, fluticasone and ciclesonide, while formoterol and salmeterol are LABAs. Through previous systematic