



Podcast transcript

Biologics for rheumatoid arthritis: an overview of Cochrane reviews (Methodological Considerations)

Cochrane Overviews are intended primarily to summarize multiple Cochrane Reviews addressing the effects of two or more interventions for a single condition or health problem. For the overview of “Biologics for rheumatoid arthritis”: the condition was rheumatoid arthritis which causes considerable discomfort, limits quality of life, and can lead to severe joint destruction. The interventions were the ‘biologic disease-modifying anti-rheumatic drugs’ (referred to as Biologic DMARDs) which can suppress the immune system, reduce the inflammation in the joints and inhibit joint destruction. The objective of the review was to compare the benefits and harms of six different biologics (abatacept, adalimumab, anakinra, etanercept, infliximab, and rituximab) in patients with rheumatoid arthritis. The primary benefit of interest was a commonly used composite score known as the American College of Rheumatology 50% responder criteria, or simply the ACR50, and the primary harm was withdrawal due to adverse events.

An Overview differs from other kinds of Cochrane Review in that a Cochrane Review gets its data from the original studies. The Overview uses Cochrane Reviews as its source. This raises the question of whether the Cochrane Reviews were sufficient for obtaining the needed data. The authors of the Overview found that the data for the primary benefit, ACR50, and harm, withdrawal due to adverse events, were available, but that they needed some more information about the original studies than was available in the reviews. Furthermore, although most of the existing Cochrane Reviews were up to date, the authors of the overview needed updates for two of them and these updates were provided by the review authors.

In order to be eligible, the comparison for an included Cochrane review had to be the ‘Biologic DMARD on trial’, possibly used in conjunction with other drugs, versus a placebo version of the Biologic DMARD, used in conjunction with the same other drugs. The quality of the eligible Cochrane Reviews was assessed using a tool called AMSTAR, and the quality of the evidence was evaluated using the GRADE system.

The overview describes the effects of the biologic drugs, using both risk difference and number needed to treat, or NNT, as absolute measures, and relative risks for benefit and odds ratio for harm as relative measures. The weighted placebo response rate across all trials was used to obtain a control event rate for calculating the NNTs, because the estimates for each biologic compared to placebo were based on a single statistical model, such that the biologic specific control event rates could not be used.

No trial compared one Biologic DMARD with another. Direct head-to-head comparisons within randomized trials are the ideal for comparing interventions. However, in the absence of such studies, indirect comparisons can be considered. For example, suppose that some trials have compared the effects of 'Drug A versus Placebo' in treating a disease, and others have compared the effects of 'Drug B versus Placebo', but no trials have compared 'Drug A versus Drug B'. We would then need to learn about the relative effects of 'Drug A versus Drug B' by contrasting trials of 'A versus Placebo' with trials of 'B versus Placebo', using the 'Placebo' as what is called the linking treatment. This is the situation for the Cochrane overview of "Biologics for rheumatoid arthritis".

To tackle this, the authors re-analysed and combined the data from the Cochrane Reviews based on a generalized linear mixed model using the SAS software. This provided indirect treatment effect estimates comparing each of the Biologic DMARDs to one another. In addition, each comparison of a biologic to placebo was adjusted by taking into account the comparisons of the other biologics with placebo. Whether an indirect treatment comparison provides a valid estimate of the relative effects depends on: the comparability of the linking treatment; the comparability of patients; and the methodological comparability of the included trials.

This Overview required the expertise of clinicians, methodologists and statisticians. The clinicians identified and interpreted the major outcomes and definitions from the myriad of outcomes found across the reviews; the methodologists tracked the similarity of the participants, interventions, outcomes and comparisons; and the statisticians implemented and conducted the indirect comparisons providing added value to the Overview.