Efficacy and toxicity of old and new disease modifying antirheumatic drugs

Peter Tugwell, Vivian Welch, Maria Suarez-Almazor, Beverley Shea, George Wells

The goal of disease modifying antirheumatic drug (DMARD) treatment is "to induce remission and maintain control of inflammatory joint disease".¹ Disease modification has been recommended by Edmonds² to focus on two components, firstly reduction in the structural damage shown by imaging techniques, and secondly improvement/maintenance of health status in association with decreased inflammatory synovitis. The optimal management of patients with rheumatoid arthritis requires the integration of art and evidence-based science to make a clinical judgement. The evidence-based component needs to incorporate the evidence on four aspects: (a) seriousness of the outcomes; (b) evidence for effectiveness and magnitude of treatment effect; (c) risk of adverse effects; and (d) cost effectiveness of treatment.

Department of
Medicine, Ottawa
Hospital—General
Campus, LM-12, 501
Smyth Road, Ottawa,
Ontario, Canada
K1H 8L6
P Tugwell

Clinical Epidemiology
Unit, Loeb Health
Research Institute, F6
V Welch
B Shea

Epidemiology and
Community Medicine,
University of Ottawa
G Wells

Health Services
Research, Baylor
College of Medicine,
Veteran Affairs
Medical Center
M Suarez-Almazor

Correspondence to:
Dr Tugwell

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Figure 1 Seriousness of outcome in rheumatoid arthritis: What are the "7Ds"?

Figure 2 Hierarchy of evidence.

This should be evidence-based. The most widely accepted approach is to assess the world literature using the Cochrane Collaboration approach to systematic reviews based upon the hierarchy of evidence shown in figure 2. We have completed systematic reviews for many of the "old" DMARDs; and systematic reviews are in progress for the "new" DMARDs such as Leflunomide and the TNF antagonists. Once completed, these are added to the Cochrane Library (box). Abstracts of this can be accessed through the Cochrane web site (www.cochrane.org) and the full reviews obtained either on subscription throughout the web site or alternatively through compact disks that are updated and sent out to subscribers every three months. Table 1 shows the reviews of the "old DMARDs" that have been completed—in trials involving over 5000 patients.

Cochrane Library includes:

- Cochrane Database of Systematic Reviews (CDSR)
- n = 628 reviews and 593 protocols (Disk Issue 4, 1999)
- Database of 2423 Abstracts of Reviews of Effectiveness (DARE)
- Critically appraised, structured abstracts of systematic reviews from around the world
- Cochrane Controlled Trials Register (CCTR)
- Bibliography of 250 798 RCTs
- Results of hand searches

The process of implementing these Cochrane Reviews requires an extensive literature search, extraction of data by two independent

Table 1 Cochrane disease modifying antirheumatic drug reviews

Drug	Placebo controlled trials (n)	Patients (n)	Year updated
Antimalarial drugs	4	592	Nov 1997
Auranofin	9	1177	Feb 2000
Azathioprine	3	81	Feb 1999
Cyclophosphamide	2	70	May 1998
Cyclosporin	3	318	Feb 1998
IM gold	4	425	Aug 1997
Leflunomide	3	1242	In progress
Penicillamine	6	683	Feb 1999
Sulfasalazine	6	468	Nov 1997
Total	40	5056	

reviewers, a quality assessment of the trials, and then a meta-analysis of those trials of adequate quality, to pool the results to obtain an overall estimate of the benefits or side effects, or both. Figure 3 shows this for the outcome of tender joint count in trials of sulfasalazine. Each study has its point estimate shown by a diamond and then the 95% confidence limits are shown by bars. Where these bars cross the midline, the effect is not statistically significant. As can be seen in figure 3, the studies of Williams,⁴ Ebringer,⁵ Hannonen⁶ and Farr⁷ do not each achieve statistical significance, while those of Pullar,⁸ Skosey⁹ and Smolen¹⁰ are statistically significant and clear the midline. Meta-analysis

Figure 3 Example of meta-analysis—sulfasalazine: tender joint count.

Figure 4 Summary of DMARD reviews on tender joint count.

is now the best estimate to be derived that uses the information from all of these studies. In this case, this results in the demonstration of a clear benefit with a standardised mean difference (similar to effect size) of -0.43 with confidence limits that do not cross the midline (-0.61 to -0.24). This represents a difference between sulfasalazine and placebo of about three joints using the 28 joint count method, or a 19% difference relative to baseline.

Figures 4 and 5 show this same approach for the summary estimates impact in reducing joint count for the seven DMARDs reviewed on the Cochrane Database. In addition, meta-analysis of combination treatment will soon be added to the Cochrane Library.¹¹

These type of data described above are difficult for consumers (and some clinicians!) to interpret, so these have been summarised in a format suitable for consumers at a reading level of Grade 7 and placed on the Arthritis Canada web site of the Arthritis Society of Canada (www.arthritis.ca). Figure 6 shows the consumer summary for sulfasalazine that is currently on this web site.

Risk of adverse events

Table 1 shows the drop outs owing to toxicity from the different studies of sulfasalazine. It is important to appreciate that most controlled trials are not large enough, nor last long enough, to provide the information on rare serious events and rigorous post-marketing surveillance is needed for this.

The efficacy and toxicity then need to be integrated in the context of the benefit/risk ratio so these can be put into context in the situation of deciding whether the trade off between the treatment and the risks are worthwhile. Figure 7 shows the methods of doing this developed by David Felson and colleagues.¹²

Cost effectiveness of treatment

Once you have decided that the benefit outweighs the risks then this needs to be integrated with the economic aspect, which can be done through cost effectiveness evaluations. These are discussed by Claire Bombardier (C Bombardier, Advances in Targeted Therapies, 2000, Miami).

The OMERACT conferences are considering a number of important issues relevant to the efficacy and toxicity of DMARDs; the last one was OMERACT 5 in Toulouse, 4–7 May 2000. One OMERACT Task Force focuses upon Minimal Clinically Important Differences. Different studies use different definitions of responsiveness and can be categorised using the classification of Beaton and Bombardier.¹³ This emphasises three issues regarding the reporting of data from clinical trials.

1 The difference between presenting mean differences across groups of patients versus improvement in individual patients. In the past, end of study results have frequently been presented in the form of mean or median changes across groups such as mean changes in tender joint score, mean change in sedimentation rate, mean change in Sharp and Larsen score and radiographs. There is increasing

Figure 5 Summary of DMARD reviews on swollen joint count.

acceptance that there needs to be estimates of change in the patients such as the DAS score and the ACR 20/50/70.

2 Method of comparisons: some trials look at differences between patients while other studies look at differences within the patient over the course of the trial (the second is probably preferable).

3 Type of change or difference: some estimates have used a statistical basis for deciding on important differences, but there is increasing interest in moving beyond this to observing demonstrated changes in those estimated to have had an important difference or change as judged by the patient.

The current status of studies that fits within each of the above categories has been summarised for rheumatoid arthritis and is in press with the *Journal of Rheumatology*, along with recommendations for a research agenda to establish consensus on these.

A second OMERACT Task Force is looking at methods for better assessing structural damage in both radiographs and magnetic resonance imaging, which are important aspects of assessing the efficacy of old and new DMARDs. Currently, the focus is on establishing a Minimal Clinically Important Difference for the Sharp and Larsen Scales.

Another OMERACT Task Force is working on Safety Issues. These include standardisation of an adverse drug reaction questionnaire so that results from trials are standardised and can be compared. Likewise, a patient self assessment questionnaire has been developed from the Stanford Toxicity Index with modifications to incorporate other elements of interest to clinicians and approval agencies. These elements include patient rating of the importance of the side effects, assessment of the economic costs of the investigations of the side effects and the assessment of patient satisfaction with their experience with the drug, taking into account both benefit and adverse effects. There are also plans being developed to ensure that the large pharmaco-vigilance and post-marketing surveillance databases around the world are linked so that data can be accumulated as fast as possible to detect rare serious side effects should they occur.

A fourth OMERACT Task Force on Health Economics is developing a core dataset for Cost Effectiveness studies so that cost effectiveness of different DMARDs can be compared.

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Sulfasalazine for rheumatoid arthritis

Background:

- Sulfasalazine is a disease modifying antirheumatic drug (DMARD), so named because it can slow the progress of rheumatoid arthritis (RA)
- As with other DMARDs, it may take a few months before it helps

Purpose:

- To determine if sulfasalazine is helpful for the treatment of RA

Research methods:

- This is a summary of a systematic review of six randomised trials and 468 patients conducted by the Cochrane Musculoskeletal Group, which is part of the Cochrane Collaboration

Findings:

- Sulfasalazine at 2–3 g per day for six months reduced pain for 66% of people and reduced overall pain for 51% of people when compared with a placebo (a sugar pill)

Side effects:

- Of patients receiving sulfasalazine, 10% developed stomach upset and digestion side effects, 7% developed skin rashes, 2% developed abnormal white blood cell counts, and 4% developed liver problems

Conclusions:

- Sulfasalazine improves symptoms of RA for 51–66% of people taking it, compared with those in a placebo group
- Up to 22% of patients stopped treatment because of side effects

Authors: ME Suarez-Almazor, E Belseck, B Shea, G Wells, and P Tugwell.

Figure 6 Sample consumer summary from The Arthritis Society web site (www.arthritis.ca).

Figure 7 Method of comparing efficacy and toxicity developed by Felson DT *et al.*¹²

pared not only on efficacy and toxicity but also on the costs of treatment, side effects and utilisation of medical care. This again is highly relevant to comparing old and new DMARDs, with each other as well as with other treatments being reviewed for inclusion in formularies.

These are exciting times with many new advances in DMARD treatment. The new studies being conducted provide an important opportunity to validate potential improvements in the methods for demonstrating efficacy and safety of these agents.

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