Disease-modifying anti-rheumatic drugs in rheumatoid arthritis and ankylosing spondylitis

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Received and accepted on July 29, 2009.

Clin Exp Rheumatol 2009; 27 (Suppl. 55): S159-S163.

Key words: DMARD, rheumatoid arthritis, ankylosing spondylitis, comparison.

ABSTRACT

Disease modifying antirheumatic drugs (DMARDs) are widely used and well accepted for the treatment of patients with rheumatoid arthritis (RA). Many studies have been performed with monotherapy and combinations of DMARDs showing their efficacy and safety. In ankylosing spondylitis (AS) DMARDs, sulfasalazine especially, are recommended only for the peripheral involvement and not for the axial symptoms. For this disease there is a lack of clinical trials and most of the trials did not show efficacy on the axial symptoms of the disease. In this paper, the differences and similarities of DMARDs in the treatment of RA and AS patients will be discussed.

Introduction

The term "Disease Modifying Anti-Rheumatic Drug" (DMARD) comprises a group of drugs, which act more than symptomatically in the treatment of inflammatory joint diseases, especially rheumatoid arthritis (RA). A substance is regarded as disease modifying, if it has proved to stop or at least delay the joint destruction in RA on radiographs of hands or feet. Using this definition also corticosteroids and biologics have to be regarded as DMARDs, since they demonstrated to have a marked effect on joint destruction. However, this comparative review focuses only on the "classical" DMARDs sulfasalazine (SSZ), methotrexate (MTX) and leflunomide (LEF) as these play the major roles in therapeutic considerations, in both RA and spondyloarthritis (SpA). Meanwhile, also in RA alone, gold salts, cyclosporine and antimalarials share restricted use due to different reasons (limited efficacy or side effects).

The body of evidence for DMARDs in inflammatory joint disease relies mainly on historical studies for placebo controlled studies, which for ethical reasons will hardly be conducted in the future. Since DMARDs are the "basic therapy" in addition to placebo or verum in all newer studies with biologic agents, some evidence of their efficacy can also be drawn. Since almost all of them use methotrexate as the "conventional" comparative drug, we are faced with a huge amount of data on this and rather few on the other substances. Also studies comparing different therapeutic strategies in daily-practice allow for drawing some evidence for the classical DMARDs.

Regarding efficacy in contrast to the dominant role of conventional DMARDs in the treatment of rheumatoid arthritis, DMARDs have no proven efficacy for the axial manifestations of ankylosing spondylitis (AS). For the peripheral manifestations there is only limited evidence of efficacy. This is in contrast to daily clinical practice, where up to 40% of patients with AS are treated with DMARDs (1-3). However, for AS there is also a lack of appropriate clinical trials (CT), for some DMARDs no clinical trials are available at all. For peripheral involvement in SpA and RA there are some similarities regarding the mode of action and duration of a clinically appreciable effect of DMARDs and preferentially sulfasalazine as the only tested DMARD in contolled trials (CTs) is recommended to use in peripheral SpA.

Sulfasalazine

A systematic review of the Cochrane collaboration regarding the use of Sulfasalazine in RA comprises all studies until 1997 (4). Six trials, including 468 patients were included and a statistically significant benefit was observed for sulfasalazine when compared to placebo for tender and swollen joint scores, pain and ESR. The standardized weighted mean difference between treatment and placebo was -0.49 for

Competing interests: none declared.

tender and swollen joint scores, and -0.42 for pain. The difference for ESR was -17.6 mm. Withdrawals due to adverse reactions were significantly higher in the sulfasalazine group (OR=3.0). Patients receiving placebo were four times more likely to discontinue treatment because of lack of efficacy than patients receiving sulfasalazine. The authors concluded that sulfasalazine appears to have a clinically and statistically significant benefit on the disease activity of patients with RA. Its effects on overall health status and radiological progression are not clear at this time, but would appear to be modest".

Three trials involving 479 participants and comparing methotrexate with sulfasalazine found similar response rates.(5-7). Even though comprising many early cases the last study did not restrict patients to early stages of their disease as the two first did (≤1 year disease duration). However, these used a rather low target dose of weekly methotrexate (7.5 mg). An indirect hint for a superior effectiveness of methotrexate compared to sulfasalazine is given in a meta-analysis of 71 trials and 88 observational studies (end search date, August 1997): at 5 years more patients continued methotrexate therapy (36%) than sulfasalazine therapy (22%), whereby discontinuation rates because of adverse events did not differ substantially (8). In a very comprehensive systematic review comparing the effectiveness and harms of DMARDs in RA no statistically significant differences in frequency of serious adverse events between sulfasalazine, methotrexate, and leflunomide were found (9).

For the treatment of AS, sulfasalazine is the best investigated DMARD. A cochrane review article from 2005 analysed eleven studies in AS (10). The pooled analysis showed that the difference between the intervention groups was significant only in erythrocyte sedimentation rate and morning stiffness, favouring sulfasalazine over placebo, but not for the other variables. Only one trial investigating patients with a relative short disease duration (less than 6 years) showed a benefit in primary outcome parameters, including back pain, spinal mobility and patient's well being (11).

However, several trials showed a higher efficacy of sulfasalazine compared to placebo in the presence of peripheral arthritis (12, 13). A very recent trial in patients with undifferentiated axial SpA or early AS showed also some efficacy for spinal symptoms (14). There was no effect of sulfasalazine on peripheral enthesitis in one observational study (15). One randomised controlled trial (RCT) was retrieved showing that sulfasalazine reduces the occurrence of recurrent acute anterior Uveitis in patients with AS (16). However, taking all results together, sulfasalazine is not recommended for the treatment the of axial manifestations of AS but for peripheral arthritis AS patients (17).

Methotrexate

Although in comparative studies there is no striking difference between the conventional DMARDs, methotrexate has become the first-line drug for treatment of active or established RA. This still might reflect a higher potency (as rheumatologists tend to believe, despite missing results in meta-analyses) but may also be due to the simplicity, safety, feasibility, low costs and convenience of this therapy. MTX is the "basic-therapy" in so far all studies with biologic agents, used also in the placebo (better MTX alone) arms of these studies. Treatment response is considerable and mostly not worse than with biologics alone, this "ancient" drug has gained acceptance of its effectiveness in RA like no other single drug so far (perhaps with the exception of corticosteroids).

Randomised controlled and placebo-controlled clinical trials in RA have been meta-analysed in a Cochrane review from 1998 (18). Five trials comprised 300 patients with long standing RA who had previously failed other DMARDs. A statistically significant benefit was observed for MTX when compared to placebo. Participants on MTX were three times more likely to discontinue treatment because of adverse reactions (OR 3.47) and four times less likely to withdraw due to lack of response (OR 0.22). Twenty-two percent of people on MTX withdrew due to adverse effects compared to seven percent in the placebo group.

Since these studies evaluated only a short-term (12 to 18 weeks) duration of MTX-therapy, additional long-term evaluation in open-label prospective treatment cohorts are of additional interest. In a prospective multicenter study over a five-year period in 123 patients with RA, methotrexate was associated with significant improvement in all clinical disease variables (pain, tender and swollen joints, functional status, and ESR) compared to the assessment at study entry (19). Another prospective study of 26 patients demonstrated that the benefit continued over 36 months of MTX therapy, and in twelve patients remaining in the study at 84 months there still was persistent reduction in the number of painful and swollen joints as well as on improvement in physician's and patient's global assessment. A significant reduction in prednisolone dosage was also achieved in those 14 patients taking prednisone at study entry (20).

Not all studies have found consistent long-term radiographic benefits with MTX but in early disease the influence of MTX on joint destruction could be proved (21). In a series of 24 patients with new onset RA (11 patients with and 13 without radiographic erosions), the use of MTX as the first DMARD halted disease progression in approximately 50% of patients, particularly among those without erosions at baseline (22).

Some evidence that MTX is also beneficial qoad vitam in RA patients comes from a cohort study comprising 1240 patients treated in the 1980s and 1990s (prior to the era of biologics) (23). After adjusting for possible confounding factors (age, gender, disease duration, obesity, disability, blood pressure, diabetes etc.) the hazard ratio for mortality of all causes among MTX treated patients was 0.4 (95% CI 0.2-0.8). The reduction in cardiovascular risk was statistically significant, while that of non-cardiovascular mortality was not. Use of other traditional DMARDs did not appear to have a similar survival advantage.

The question of optimal dosage and the route of administration of methotrexate in RA has been addressed in a recent systematic review by Visser and van der Heijde (24). Start doses of 25 mg/wk or

Table I.

Therapeutic agent	Evidence on efficacy		Strength of recommendation (A-D)	
	RA	AS	RA	AS
Sulfasalazine	Ia	Ia ±	A	A
Methotrexate	Ia	Ib -	A	A
Leflunomide	Ib	Ib -	A	A

Evidence was categorized as following: **Ia**: meta-analysis of randomised controlled trials; **Ib**: randomised controlled trial; **RA**: rheumatoid arthritis; **AS**: ankylosing spondylitis,
Strength of recommendation: **A**: category I evidence; **B**: category II evidence; **C**: Category III evidence or extrapolated from category I or II evidence; **D**: Category IV evidence or extrapolated from category II or III evidence; Adopted from Zochling J *et al*. (17).

fast escalation with 5 mg/month to 25-30 mg/wk were associated with higher clinical efficacy in comparison with doses of 5-15 mg/wk and slow escalation. However, the higher the dose the more (gastrointestinal) adverse events have been noticed.

A switch to intramuscular route of administration starting with 15 mg MTX/wk and escalating up to 45 mg/wk did not result in increased efficacy after failure of 15-20 mg/wk orally (25). In contrast, after 16 weeks significantly more patients who started on subcutaneous MTX achieved an American College of Rheumatology (ACR) $_{20}$ response than those who started on oral (85% *vs*. 77% respectively, OR=1.7 [1.01-2.9]). A trend for more ACR_{20} and ACR_{70} responses was also seen after 24 weeks. However, patients on subcutaneous MTX more often discontinued therapy due to toxicity, without differences in the type of adverse events (AEs) (including gastrointestinal toxicity) (26).

The authors of the review concluded that "starting on MTX 15 mg/wk orally, escalating with 5mg/month to 25-30 mg/wk, or the highest tolerable dose, with a subsequent switch to subcutaneous in case of an insufficient response, seems to be the optimal evidence-based dosing and routing recommendation for MTX in RA" (24).

Given the good efficacy of methotrexate for the treatment of RA the lack of good studies in AS is surprising (27). A systemic review of the use of methotrexate in AS showed no evidence for an effect on inflammatory back pain and inconclusive evidence for an effect on peripheral arthritis (28). Similarly, a more recent 16-week open label trial of methotrexate, using a relatively high dosis of 20 mg subcutaneously per week, did not show any effect on axial and only some non-significant improvement in peripheral symptoms (29). Therefore, methotrexate is neither recommended for the axial nor for the peripheral manifestations of AS. However, in some patients with predominant peripheral arthritis, a treatment trial might be justified.

Leflunomide

Studies leading to the licensing of the pyrimidine antagonist leflunomide for treatment of RA (in Europe 1999) provide good evidence for its efficacy (30-32). "Leflunomide improves all clinical outcomes and delays radiographic progression at 6 and 12 months of RA treatment compared to placebo" (33). Compared to methotrexate, leflunomide was not different in the efficacy and tolerability and compared to sulfasalazine, leflunomide was more efficacious at 24 months (30). The maximum dosis of MTX employed in these studies was up to 15 mg/wk.

Progression of radiographic changes was also significantly slower with leflunomide than with placebo and not significantly different from that of SSZ or MTX (33).

Even though each substance tends to have its own profile of side-effects, in the cited meta-analysis leflunomide, methotrexate and sulfasalazine showed no statistically significant differences in frequency of serious adverse events (9).

Leflunomide was tested in AS in two trials with negative results (34, 35). Again, a possible effect was seen in a subgroup of patients with additional peripheral arthritis (34). All in all, there is no evidence that any of the other DMARDs often used for the treatment of RA do play a role in treatment of *AS* patients.

Other substances

Thalidomide has also been tested for the treatment of AS patients in open uncontrolled trials with some success, but is regarded as too toxic for widespread use (36-38).

Pamidronate, a bisphosphonate, has been tested in rheumatic diseases because of its possible anti-inflammatory and inhibiting effect on osteoclasts. In a six-month randomised controlled trial of 60 mg pamidronate given intravenously once a month was superior to a small placebo-like dosage of 10 mg pamidronate with a significant improvement of function and pain (39). Such an effect only became evident after 3 months of treatment. A positive effect was not observed in other open trials treating AS patients with the same dosage over 3 months (40, 41). Therefore, further studies are needed before this therapy can be recommended.

Combination therapy

Principal problems in evaluating combination therapy in RA are well addressed in the review by Smolen; Aletaha and Keystone on this topic (42). As many others, the authors underline the importance of early treatment and tight control of the disease what is more obvious and consented than the question whether, and if, which type of combination might be meaningful.

With "combination therapy" the use of 2 or more traditional DMARDs is meant and not the concomitant treatment of DMARDs with NSAIDs, corticosteroids or biologic agents, even though for the latter two the evidence of additional efficacy can be regarded as good. As stated above, the role of antimalarials and cyclosporine in RA is commonly restricted to early or special cases and since these drugs have not been proven to be efficacious in SpA, they are discussed here as potential candidate for a combination therapy.

In patients with early rheumatoid arthritis (5, 6), ACR response rates, radiographic changes, and functional

capacity were similar with combination therapy of methotrexate and sulfasalazine *vs*. each substance alone. The MASCOT study in longer lasting RA (up to 10 years) from 2007 (7) revealed a statistically significant superiority in effectiveness of the combination of sulfasalazine with MTX over either drug alone. In the first study from 1997 this was the case only for those patients with a suboptimal response to sulfasalazine (5).

A study by Kremer *et al*. demonstrated significant efficacy of adding leflunomide in inadequate MTX-responders (43), but since there was no treatment group comparing the combination with switching to leflunomide alone, it cannot be excluded that the effect was only due to the added drug. A recent analysis of an prospective observational database regarding the retention rates of the traditional DMARDs methotrexate, sulfasalazine and leflunomide alone and in combination with each other indicated that in situations where one of these drugs is ineffective add-on combination therapy has no advantage over switching to an another DMARD (44).

A not very clear of view is derived from prospective trials on different therapeutic strategies. In the FIN-RACo trial early RA patients treated with a combination of DMARDs (methotrexate, sulfasalazine, hydroxychloroquine with prednisolone) reached more frequently clinical remission and had less radiographic progression at 2 years than patients treated with a single DMARD plus prednisolone (45). Similar results were found in the COBRA trial in which the step-down approach of a combination therapy of MTX, SSZ and prednisolone was superior to a monotherapy with sulfasalazine (46). Also in the BeSt-Study initial combination therapy including either prednisone (group 3) or infliximab (group 4) resulted in earlier functional improvement and less radiological progression compared to the initial sequential monotherapy (group 1) and step-up combination therapy (group 2) (47).

These results seem to favour initial combination rather than monotherapy. However, in the FinRACo trial the monotherapy to start with was sulfasalazine and not methotrexate (which might have led to better results in the monotherapy group), in the COBRA trial the effect might be attributed to incomparable potency of the strategies (MTX+Prednisolone+SSZ versus SSZ alone) and one could argue that starting with combination therapy just accelerates the "sieving" of responders compared to sequential approaches.

Since patients treated with initial combination therapy still had significantly better outcomes after 5 (BeST) and 11 (FIN-RACo) years as compared with the initial monotherapy groups (with escalation to other therapies including biologics when not in remission), this argues more in favour of a "hit hard and early" strategy for RA than for a superiority of a certain combination strategy (48, 49).

In contrast to RA, there are no studies in SpA on combination therapies of DMARDs, probably because of their inefficacy in monotherapy.

Summary

Taken together, as far as only traditional DMARDs are considered (and not corticosteroids and biologics), the differences in their use and usefulness between RA and spondyloarthrithidies overweight the similarities by far. Even when some questions remain still unresolved in RA (*i.e*. comparative listing of DMARDs according to their efficacy, use of combination therapy) there is good evidence of principal efficacy of these drugs in this disease. It is also clear that early treatment and tight control is essential for the prognosis and outcome of RA-patients. In AS, however, the body of evidence is much lower. DMARDs are not efficacious for the axial manifestations of the disease and if at all of limited use for peripheral joint involvement.

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