Can we discontinue synthetic disease-modifying anti-rheumatic drugs in rheumatoid arthritis?

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ABSTRACT

Objective. *When rheumatoid arthritis (RA) patients have achieved sustained good clinical responses can their disease-modifying anti-rheumatic drugs (DMARDs) be reduced or discontinued? This review addresses this question by summarising the clinical evidence about DMARD withdrawal. It includes an assessment of predictive factors for sustained DMARD-free remissions.*

Methods. *We evaluated the evidence for discontinuing DMARDs in stable RA in both randomised controlled trials (RCTs) and observational studies.*

Results. *Six RCTs evaluated DMARD monotherapy withdrawal in 501 RA patients with good clinical responses. Flares occurred in 43/248 (17%) patients who continued DMARD monotherapy and in 117/253 (46%) patients who discontinued DMARDs. Individuals in whom DMARDs were withdrawn were three times more likely to have flares. Restarting DMARDs post-flare was usually successful. Four RCTs evaluated step-down DMARD combinations in comparison to DMARD monotherapy. Patients achieved good clinical responses with combination DMARDs, which were maintained after treatment was tapered to DMARD monotherapy. Four observational studies of tapering or stopping DMARDs in patients with sustained low disease activity states provided supportive evidence for discontinuing DMARDs in some patients. Flares during drug-free remissions were predicted by rheumatoid factor and anti-citrullinated protein antibody status.*

Conclusion. *Drug-free remission is achievable in some RA patients. Discontinuation of DMARDs after patients achieve sustained remissions results in flares in many patients, which can usually be reversed by restarting DMARDs. Step-down DMARD combinations are effective and achieve sustained responses. Further research is required to establish predictors of drug-free remission; these will identify individuals most likely to benefit or experience disease flares after discontinuing DMARDs.*

Introduction

Current rheumatoid arthritis (RA) management emphasises the benefits of early disease-modifying anti-rheumatic drugs (DMARDs), particularly methotrexate, in active disease. Increasing evidence also supports DMARD combinations, which may include glucocorticoids (1, 2). The benefits from using DMARDs extensively must be balanced against patients' wishes to minimise drug use, potential toxicities, and costs of long-term DMARDs. Discontinuing DMARDs when patients achieve sustained low disease activity ameliorates these concerns. It is particularly relevant for DMARD combinations. Some international guidelines recommend reducing DMARDs when patients enter prolonged remissions (3, 4).

The main evidence for discontinuing DMARDs comes from randomised controlled trials (RCTs) in patients with stable RA taking long-term DMARD monotherapy. These RCTs evaluate the impact of stopping treatment on disease activity. Additional evidence comes from RCTs and observational studies in which intensive combination DMARD prescribing follows a step-down approach with combination DMARDs reduced to monotherapy alongside observational studies of stopping DMARDs when patients achieve sustained remission. We summarise these various strands of evidence to provide an overview of the risks and benefits of discontinuing DMARDs.

DMARD retention rates

Strategies for discontinuing DMARDs in good responders must be consid-

ered from the perspective of general retention rates when using DMARDs (5-7). Almost half of patients initiating DMARDs discontinue treatment by 2-3 years. Retention rates differ across DMARDs (Fig. 1). One meta-analysis of 110 studies showed RA patients stay longer on methotrexate than other DMARDs (8). Yazici *et al*. quantified the low risk of discontinuing methotrexate; in 1007 person-years of observation the probability of continuing methotrexate for five years was 79% (9). Low retention rates are commoner in patients receiving combination DMARDs and in those with high disease activity (10).

These low retention rates of patients starting DMARDs mean it is crucial to consider carefully the benefits and risks of discontinuing DMARDs in patients in whom therapy is controlling RA and is not causing adverse effects.

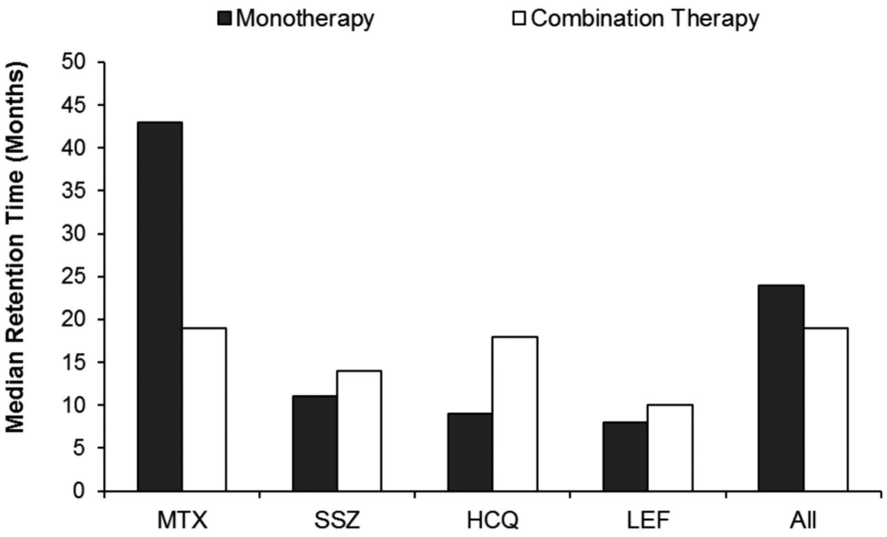

Fig. 1. Retention times on different DMARDs
MTX: methotrexate; SSZ: sulfasalazine; HCQ: hydroxychloroquine; LEF: leflunomide; "All" DMARDs comprise methotrexate, sulfasalazine, hydroxychloroquine, chloroquine, leflunomide, gold, D-penicillamine, azathioprine; Figure adapted using data from the report by Aggarwal *et al*. (5).

Table I. Relative risk of a disease flare in individuals continuing DMARDs compared to those in whom DMARDs were withdrawn.

Study	Year	DMARDs	Patients	Relative risk
Ahern *et al*. (11)	1984	Penicillamine	38	0.13 (0.04, 0.50)
De Silva and Hazleman (12)	1981	Azathioprine	32	0.11 (0.02, 0.73)
Gotzsche *et al*. (13)	1996	Mixed	112	0.25 (0.13, 0.49)
Kremer *et al*. (14)	1987	Methotrexate	10	0.27 (0.07, 1.11)
ten Wolde *et al*. (15)	1996	Mixed	285	0.57 (0.39, 0.84)
Van der Leeden *et al*. (16)	1986	Gold	24	1.18 (0.08, 16.8)
Overall			501	0.31 (0.16, 0.57)

Data from a systematic review and meta-analysis of DMARD withdrawal by O'Mahony *et al*. (17). Pooled relative risks calculated using a random effects model.

Clinical trials examining DMARD withdrawal

Six RCTs published before 2000 evaluated DMARD withdrawal in RA patients in remission or achieving good clinical responses (11-16). The trials, which lasted up to 24 months, enrolled 501 patients. They examined withdrawing a range of DMARD monotherapies including methotrexate, gold, penicillamine and azathioprine. DMARDs were tapered in one RCT (11) and stopped in five RCTs (12-16). The impact of DMARD withdrawal was subsequently evaluated in a meta-analysis by O'Mahony *et al*. (17). It showed that remaining on DMARDs substantially reduced flares (Table I). There were 43/248 (17%) flares in patients staying on DMARDs and 117/253 (46%) flares in patients discontinuing DMARDs. The relative risk of a flare in patients remaining on DMARDs compared to patients in whom DMARDs were stopped was 0.31 (95% confidence interval 0.16 to 0.57; $p<0.001$). Individuals in whom DMARDs were withdrawn were three times more likely to suffer flares than individuals in whom DMARDs were continued.

The largest trial by ten Wolde *et al*. (15) lasted one year and enrolled 285 RA patients with good long-term therapeutic responses. Half the patients continued DMARDs; the others received placebos. The end-point was recurrent synovitis due to flares. By 52 weeks flares had occurred in 38% and 22% of patients receiving placebos and DMARDs, respectively. The trends were similar across all DMARDs (Figure 2), though the study was not powered to compare specific drugs. One limitation in this trial is that it involved very few patients receiving methotrexate. There is evidence that methotrexate achieves better long-term benefits (18) and therefore the benefits of remaining on DMARDs may be underestimated from the perspective of current prescribing practice.

A follow-up study (19) assessed DMARD resumption after flares occurring post-treatment discontinuation. It enrolled 51 patients from the ten Wolde *et al*. trial (15). Patients who had flared showed significant improvements in disease activity measures within three months of restarting DMARDs. Initially they had worse disease activity than before treatment was discontinued. However, by 12 months 35% of patients had inactive disease and 43% had mild disease activity. Only 8% of patients were unable to benefit from resumption of their long-term treatment due to inefficacy.

These studies have a number of limitations: they are small, they include DMARDs that are now rarely used, they have defined flares in a variety of ways and they are of variable quality. Although flares could be controlled by restarting DMARDs, the overall benefit of this strategy was uncertain.

Clinical trials examining step-down DMARDs

Three RCTs evaluated tapering combination DMARDs to monotherapy in strategies based on step-down intensive combination DMARD therapy in early RA. The first step-down RCT was the COBRA early RA trial (20). Its intensive treatment comprised high-dose reducing prednisolone for 28 weeks, low-dose methotrexate for 40 weeks with sulfasalazine as maintenance therapy. Controls received sulfasalazine monotherapy. Both disease activity and erosive progression were better controlled by combination DMARDs. Subsequent follow-up in routine practice settings over 4-5 years showed that the benefits of intensive initial treatment on radiological progression were maintained after tapering (21).

The FIN-RACo trial also assessed step-down treatment (22). It evaluated combination therapy with sulphasalazine, methotrexate, hydroxychloroquine and prednisolone. Treatment was tapered in patients achieving remission during the first year; prednisolone and methotrexate were discontinued. Controls received monotherapy with sulfasalazine followed by methotrexate for patients with adverse effects or non-responders. More patients had good clinical responses and achieved remission with intensive treatment. The radiological benefits were maintained long-term with a subsequent 11-year follow-up report showing less radiologic damage in patients receiving initial combination DMARDs compared to those receiving monotherapy. Mean Larsen score changes over 11 years in the combination and monotherapy groups were 17 (95% CI 12 to 26) and 27 (95% CI 22 to 33), respectively (p=0.037) (2).

Marchesoni *et al*. (23) evaluated maintenance therapy with cyclosporine and methotrexate after 6 months combination treatment with both drugs in 57 early, non-erosive RA patients. Stepping down to single agent maintenance therapy was successful only with methotrexate.

The BeSt study compared four different treatment strategies in 508 patients with recent-onset RA. These comprised DMARD monotherapy, step-up DMARD combinations, step-down DMARD combinations (based on the COBRA regimen) and methotrexate combined with infliximab (1). When patients achieved remission DMARDs were tapered and stopped. Five-year follow-up data evaluated the frequency and impact of DMARD tapering (24). During this period, 23% of patients had drug-free remissions. Subsequently, 46% restarted treatment for increasing disease activity and 51% had drug-free remissions. The frequencies of drug-free remissions were similar across initial treatment groups (Fig. 3). The evidence suggests sustained drug-free remission is uncommon and tapering DMARDs in patients in remission has questionable benefits.

Step-down DMARDs have been evaluated only in a single RCT in established RA. Clegg *et al*. (25) examined if hydroxychloroquine monotherapy extended the benefits of combination therapy with hydroxychloroquine and methotrexate. Patients received open-label combinations of hydroxychloroquine and methotrexate for 24 weeks followed by a double blind period evaluating either methotrexate or hydroxychloroquine as maintenance therapy for 36 weeks. Combination therapy responders were randomised into 3 groups: hydroxychloroquine with methotrexate for flares (40 patients); hydroxychloroquine monotherapy (41 patients); placebo with methotrexate as needed for flares (40 patients). After methotrexate withdrawal, hydroxychloroquine maintenance delayed flare onset (p=0.023). Whilst supporting initial combination therapy, followed by hydroxychloroquine maintenance treatment, this trial did not evaluate methotrexate maintenance therapy, which might be more effective and

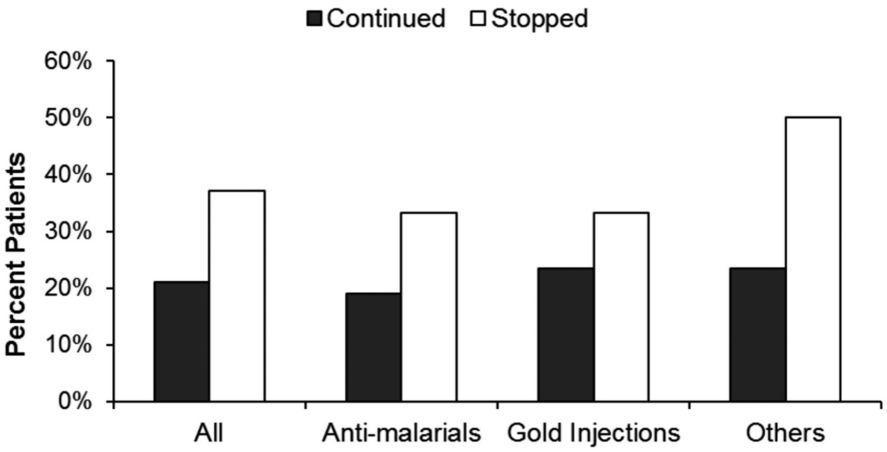

Fig. 2. Cumulative frequency of flares in a trial of DMARD withdrawal. Figure adapted using data from the report by ten Wolde *et al*. (15).

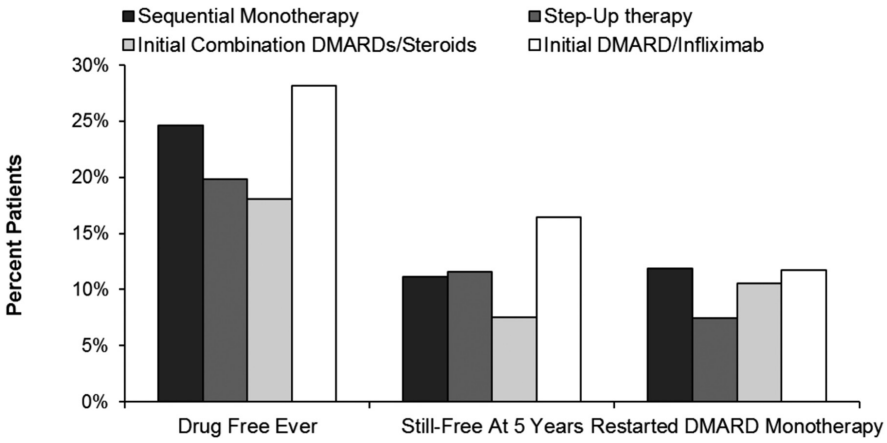

Fig. 3. Drug-free remission rates during five years of follow-up of the BeST early RA study. Figure adapted using data from the report by Klarenbeek *et al*. (24).

when treatment has been stabilised results in low levels of adverse effects.
Overall these RCTs in early and established RA show that step-down combination therapy is effective and has sustained benefits. To reduce subsequent flares at least one anchor DMARD should be retained. The optimal maintenance DMARD regimen was not defined in these RCTs.

Observational studies examining DMARD withdrawal

Frequency reduction

Two very small historical case series examined reducing the frequency of DMARD administration. Reducing methotrexate from weekly to fortnightly in 15 patients in remission showed 13 patients remained in remission and only two flared (26). Reducing penicillamine over 6 months from every day to taking it for one week in four was studied in 14 patients in partial remission on stable treatment (27). Twelve patients had unchanged clinical status over two years and only two flared.

Dose reduction

The 12-month iRAMT trial evaluated reducing methotrexate to a target dose of 5mg/week in patients receiving infliximab (28) in 210 patients. Methotrexate was tapered in the 159 patients with clinical improvements after 22 weeks of infliximab; 92 (58%) subsequently tapered methotrexate without flares. Although it is possible to taper methotrexate when patients have responded to biologics, the overall benefit is uncertain.

Complete withdrawal

The potential of "drug-free" remission as a treatment goal has been reviewed by Goekoop-Ruiterman and Huizinga (29). They noted that in observational studies sustained drug-free remission occurred in 15% of patients in a Dutch Early Arthritis Cohort and 9% of patients in a British cohort (30). The chance of achieving such drug-free remission had not changed over the last two decades. Although stopping DMARDs appears achievable in a small proportion of patients, its constant frequency in different cohorts of patients over time suggests it is the 'natural history' of an RA subset. It most likely represents spontaneous remission without any direct relationship to treatment.
One small 15-year observational study of DMARD withdrawal by Tiippana-Kinnunen *et al*. (31) evaluated DMARD continuity in 70 patients treated since diagnosis with DMARDs following the 'sawtooth' strategy. These patients formed three distinct groups: "continuous DMARDs" (50 patients) receiving continual DMARDs; "discontinued and restarted DMARDs" (9 patients) and "permanently discontinued DMARDs"' (11 patients). In the latter two groups DMARDs were discontinued due to remission lasting at least 12 months or a prolonged symptom-free phase with minor disease activity. Fifteen-year remission rates in these three groups comprised 6%, 0% and 64% respectively. Although DMARDs could be discontinued due to clinical remission or low disease activity states in 29% at 15 years, half of these individuals experienced flares and the overall benefit of stopping treatment is uncertain.

Predicting flare after DMARD withdrawal

Several studies have examined which factors identify individuals attaining sustained drug-free remission on DMARD withdrawal. Van der Woude et al evaluated predictive factors for DMARD-free sustained remission in 454 patients from a Dutch early arthritis clinic and 895 patients from the Early RA Study (ERAS) [30]. Multivariate analyses identified three independent predictors of drug-free remission in both cohorts. These comprised symptom duration, IgM-rheumatoid factor (RF) positivity and presence of the *HLA-DRB1* shared epitope alleles. Of these factors, IgM-RF was by far the strongest predictor with an associated hazard ratio for achieving sustained DMARD-free remission of 0.28 (95% CI 0.16–0.49) in ERAS and 0.19 (95% CI 0.11–0.35) in the Dutch Early Arthritis Clinic; these results show that patients who were IgM-RF positive were far less likely to develop remission that IgM-RF negative patients
Five-year follow-up data from the BeST study also showed that serology predicts drug-free remission (24). Anti-citrullinated protein antibodies (ACPA) positivity was the strongest independent predictor for a flare during drug-free remission (OR 7.5; 95% CI 2.9–19.4). Other predictors of flares included higher mean DAS scores until remission (OR 4.7; 95% CI 1.5–15.2), a lower baseline HAQ (OR 0.41; 95% CI 0.19–0.88) and the use of sulfasalazine as the last DMARD (OR 3.5; 95% CI 1.5–15.2).

Recommendations in international guidelines

After reviewing the available evidence, expert groups have different perspectives about discontinuing DMARDs. There appears to be no overall consensus. UK guidelines from the National Institute for Health and Clinical Excellence (NICE) recommend that if RA is stable, DMARD doses should be cautiously reduced, returning promptly to disease controlling doses if there are any indications of a flare (3). EULAR guidelines are more guarded about DMARD tapering (4). They recommend that in sustained long-term remission cautious titration of synthetic DMARD dose may be considered. By contrast American College of Rheumatology guidelines do not comment on DMARD withdrawal (32).

Conclusions

There is strong evidence from RCTs that treating active RA with step-down DMARD combinations is effective and, in early RA, achieves sustained responses. There is also good evidence that drug-free remission is achievable in a small minority of cases. Many if not most patients who achieve sustained remissions on DMARDs sometimes flare, and the risks of flaring are increased when DMARDs are discontinued, though restarting DMARDs usually reverses these flares. The best current predictors of flares on discontinuing DMARDs are IgM-RF and ACPA-positivity. Further work is required to identify additional predictors of sustained remission on DMARD withdrawal; combining these within

a predictive framework would allow the identification of individuals most likely to benefit from DMARD cessation. Currently, the risks and benefits of stopping DMARD monotherapy in good responders remain uncertain and the evidence for stopping or continuing DMARDs is currently incomplete.

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