Key Randomized Trials of Single Agents in Early Rheumatoid Arthritis

LEO B.A. van de PUTTE

ABSTRACT. Disease modifying antirheumatic drugs (DMARD) for treatment of rheumatoid arthritis (RA) are well established. As evidence has shown, considerable damage to the joints occurs early in the disease; thus DMARD therapy is being initiated earlier. Clinical trials with DMARD monotherapy in early RA are reviewed with consideration given to efficacy, onset of therapeutic effect, and the toxicity profile of currently available drugs. (J Rheumatol 2002;29 Suppl 66:13–19)

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INTRODUCTION

Disease modifying antirheumatic drugs (DMARD) have been widely used for the treatment of rheumatoid arthritis (RA) for more than 2 decades. Their ability to relieve the signs and symptoms of active RA and evidence of retardation of joint destruction, the hallmark of disease progression, has made them an integral part of the pharmacological management of RA. Historically, the approach to the treatment of patients with RA was sequential addition of drugs with a nonsteroidal antiinflammatory drug (NSAID) as initial treatment and DMARD therapy often withheld until evidence of joint damage was observed. The longterm clinical outcomes of this approach were poor.

As DMARD therapy was considered second-line therapy to be initiated when the pain and inflammation could no longer be managed by NSAID, DMARD were reserved for the later stages of this chronic disease. Therefore clinical investigations with DMARD recruited patients with longstanding RA. However, as knowledge of RA expands, evidence indicates that considerable damage to the joints occurs in the early phase of the disease, at less than 2 years after disease onset, a time when patients may not be receiving DMARD therapy. With the emphasis on slowing or ultimately prevention of disease progression, DMARD are being used earlier in the attempt to minimize joint destruction and maintain the functional ability of the patient.

The clinical efficacy and adverse effects of available DMARD have been well documented. However, the majority of the studies include patients with longstanding disease. While it has been assumed that these agents provide the same benefit when administered in "early" RA, there have been few controlled trials to confirm this assumption. However, in the current environment, where the ongoing trend is to initiate DMARD therapy earlier, it behooves us as clinicians and scientists to reexamine the evidence and confirm their benefit in patients with early RA.

Any assessment of a drug's impact on the outcome of patients with a chronic disease encompasses many considerations — tolerance, safety, efficacy, and cost, for example. When the underlying disease is RA, other factors unique to the rheumatoid process come into play. How quickly and effectively does the drug control inflammation? Gold and D-penicillamine, for example, can take over 3 months to work, during which time joint destruction can continue unabated. Does the patient experience clinical improvement? Perhaps more importantly, does the drug halt or significantly slow the radiographic progression of disease? Given the importance of early pharmacologic intervention and the prolonged course of treatment usually required, safety and adverse events are another pressing concern. How are these potential problems best managed or prevented? The precaution of folate supplementation for patients taking methotrexate (MTX) is a case in point.

There are numerous trials examining the influence of treatment with a single DMARD in men and women with RA. Some have compared a single agent with placebo; others have contrasted different antirheumatic drugs, with or without a placebo control. The majority of the placebo controlled trials were conducted in earlier decades with methodology that would not achieve the standards of today's investigation. Reviewed here are some of the key studies that have provided insight into the benefit of initiating treatment with a single DMARD early in the course of RA.

COMPARISON OF SINGLE AGENTS

Sulfasalazine versus hydroxychloroquine. Sulfasalazine (SSZ) was first compared with hydroxychloroquine (HCQ) by Nuver-Zwart and colleagues[1]. A total of 60 patients with definite or classical RA [according to the American College

From the University Hospital, Nijmegen, The Netherlands.

L.B.A. van de Putte, MD, PhD, Professor of Internal Medicine and Rheumatology.

Address reprint requests to Dr. L.B.A. van de Putte, Department of Rheumatology, University Hospital, Geert Grootplein 8, 6525 GA Nijmegen, The Netherlands.

of Rheumatology (ACR) criteria[2]] inadequately controlled by NSAID were enrolled in this 48 week study. No participant had received DMARD before. Study drugs were given as usual: HCQ, 200 mg BID for the first 6 months, followed by 200 mg daily; SSZ, 500 mg/day initially, followed by increases of 500 mg/day every 4 days, to a maximum dosage of 2 g/day.

Each month, patients were evaluated for duration of morning stiffness, grip strength, patient pain assessment, patient general health assessment, number of painful joints, number of swollen joints, and Ritchie Articular Index. Patients were also followed with laboratory tests [including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and rheumatoid factor], ophthalmologic evaluation, and hand/foot radiographs (radiographs were obtained at baseline, midpoint, and end of the study).

SSZ produced earlier benefit than HCQ; significant clinical improvement occurred at 4 weeks versus 12 weeks, respectively. However, the 2 groups did not differ much with respect to disease activity at 48 weeks.

Primary reasons for discontinuing treatment were adverse reactions in the SSZ group and lack of efficacy in the HCQ group. However, all adverse reactions appeared within the first 3 months of treatment and were completely reversible.

Van der Heijde and colleagues[3] compared the effects of SSZ and HCQ on radiographic progression of joint damage in the 60 DMARD naive patients of the above study. Radiographs of the hands and feet were obtained at baseline, 24 weeks, and 48 weeks. Joint space and number of erosions were assessed in a modified way according to Sharp, and scores were summed to give the total score. Of the 30 patients randomized to each drug, 28 HCQ and 22 SSZ patients remained available for evaluation throughout the entire duration of the study.

Radiographic scores were comparable in both groups at the start of treatment. With time, however, the total number of erosions increased more for the HCQ than the SSZ group, becoming significant after 48 weeks. At this point, 32% of patients in the SSZ and 12% of patients in the HCQ group had no erosions, and 27% of patients in the SSZ and 61% of patients in the HCQ group had over 10 erosions. The total score showed a difference in progression between the SSZ and HCQ groups, with the SSZ group faring significantly better. This difference was already evident at 24 weeks, remained significant at 48 weeks, and persisted at 3 years. The earlier onset of action for SSZ versus HCQ was probably responsible for this difference.

Leflunomide versus SSZ. Smolen and colleagues[4] conducted a placebo controlled, double blind randomized trial of leflunomide and SSZ in 358 patients with active RA. Forty-one percent of study participants had a duration of RA of less than 2 years, and in the different patient groups 40% to 53% had not previously received DMARD. Patients were allowed to continue taking NSAID and oral corticosteroids during the study. Treatment dosage for leflunomide was 100 mg/day for 3 days, followed by 20 mg/day, and for SSZ was 500 mg/day, increasing to 2 g/day.

Efficacy was assessed by standard clinical laboratory and radiographic criteria (Larsen score). Primary outcome measures were swollen and tender joint counts and the patient/physician assessment of overall disease activity. Investigators also assessed the proportion of patients showing a clinical response as defined by the ACR 20% response criteria.

Clinical efficacy outcomes are summarized in Table 1. Mean values of most variables were significantly better in the leflunomide than in the placebo group at weeks 4, 12, and 24. At week 4, clinical variables were significantly better in the leflunomide than in the SSZ group. The percentages of patients responding to treatment by the ACR 20% response criteria were significantly better in the active drug than in the placebo group, but did not differ significantly between leflunomide (55%) and SSZ (56%). The mean time to ACR 20% response was 7.3 weeks with leflunomide, 10.1 weeks with placebo, and 8.3 weeks with SSZ. In this study, leflunomide was well tolerated, and had a similar safety profile to SSZ.

Larsen scores showed significantly less radiographic progression in the active treatment groups than in the placebo group. Changes in eroded joint count were better in the active drug than the placebo group, but were similar between SSZ and leflunomide.

Leflunomide versus MTX. Short and longterm efficacy of leflunomide was compared with that of MTX in a multicenter, double blind trial of 999 patients[5]. Study participants, 40% of whom had RA for less than 2 years and 66% of whom had received at least one DMARD, were randomized to either leflunomide 100 mg/day for 3 days followed by 20 mg/day, or MTX 10–15 mg/wk. MTX was given without folate supplement. Patients were allowed to continue taking NSAID and oral corticosteroids.

The 4 primary efficacy endpoints were tender and swollen joint count and global physician and patient assessments. Time to first response and percentage of responders during the first and second years of treatment were also compared. Radiographs were assessed at baseline and after one year with the Larsen score (increasing score representing worsening of disease). The number of eroded joints was also counted.

Adverse events spurred 19% of withdrawals in the leflunomide group and 15% in the MTX group during the first year of treatment (incidence of adverse events declined by about half during the second year of the study). Lack of efficacy was the second most common reason for stopping treatment, and accounted for 7% of leflunomide and 3% of MTX withdrawals.

Both leflunomide and MTX produced significant

Table 1. Leflunomide versus placebo and sulfasalazine: mean outcome measures (% change). Adapted from Smolen JS, *et al*[4], with permission.

Variable	Leflunomide	Placebo	Sulfasalazine	p†
Tender joint count	52	26	48	0.0001
Swollen joint count	44	21	40	0.0001
Physician assessment	32	9	29	0.001
Patient assessment	30	11	31	0.001
ESR (mm/h)	13	2	33	0.001
Rheumatoid factor (U/ml)	40	5	42	0.0001
CRP (mg/l)	51	5	32	0.0001
Morning stiffness (min)	65	7	38	0.03
Pain (VAS, mm)	43	15	36	0.0001
Health Assessment Questionnaire	45	4	29	0.0001

VAS: visual analog scale. † Leflunomide vs placebo.

improvement in all primary study endpoints. The difference between baseline and endpoint measurements was greater for MTX than leflunomide during the first year of the study, but this difference tended to fade with time. By the second year of treatment, the improvements in tender joint count and patient global assessment were similar between the 2 drugs (Table 2). Both drugs also produced significant improvement in secondary clinical efficacy endpoints, but the quantitative difference in response between MTX and leflunomide was minimal and was gone by 2 years. Similarly, the percentage of ACR 20% responders did not differ significantly between the leflunomide and MTX groups by 2 years.

Both treatment groups demonstrated a small, comparable increase from baseline in overall Larsen score. Among patients treated for 2 years, there was no further increase of joint damage in the leflunomide group and a slight improvement in the MTX group. Overall, there was a small but significant treatment difference in the change in radiographic scores of the 2 groups after 2 years.

Table 2. Mean changes in primary clinical efficacy endpoints after 2 years of treatment with leflunomide or methotrexate. Adapted from Emery P, *et al* [5], with permission.

	Leflunomide	Methotrexate	p
Tender joint count			
Baseline	16.9	17.2	
Change at 1 yr	–10.2	–11.0	
Change at 2 yrs	–10.5	–10.9	NS
Swollen joint count			
Baseline	16.0	16.1	
Change at 1 yr	–8.6	–10.0	
Change at 2 yrs	–9.1	–10.3	0.017
Physician global assessment			
Baseline	3.5	3.6	
Change at 1 yr	–1.3	–1.5	
Change at 2 yrs	–1.1	–1.4	0.015
Patient global assessment			
Baseline	3.5	3.6	
Change at 1 yr	–1.2	–1.4	
Change at 2 yrs	–1.2	–1.3	NS

Both drugs worked quickly: 62% of the leflunomide and 54% of the MTX group responded within the first 12 weeks of treatment. This increased with time: at one year, 82.8% of the leflunomide and 86.8% of the MTX group met the ACR 20% response criteria at least once during treatment. At 2 years, 90% of patients responded at some point for both drug groups.

HCQ versus penicillamine versus MTX. In a randomized controlled trial, van Jaarsveld and colleagues[6] compared 3 therapeutic strategies with DMARD monotherapy in patients with a diagnosis of RA and duration of symptoms of less than one year. DMARD were selected to investigate a specific treatment strategy: (1) mild DMARD with long lag time [HCQ (400 mg daily) replaced by auranofin (6–9 mg/day) if needed]; (2) potent DMARD with long lag time [IM gold (50 mg weekly) replaced by D-penicillamine (500–750 mg/day) if needed]; (3) potent DMARD with short lag time [oral MTX (7.5–15 mg weekly) replaced by SSZ (2–3 g/day) if needed].

Patients entering the study were randomly assigned to one of the 3 therapeutic strategies, and the initial DMARD (HCQ, intramuscular gold, or MTX) was continued unless adverse events or ineffectiveness deemed it necessary to discontinue, in which case the second DMARD of that particular strategy was administered.

Following one year of treatment, responses were assessed in each patient. When improvement of at least 50% from the baseline assessment was observed in at least 3 of 4 variables (pain, joint score, morning stiffness, ESR), the DMARD was continued. If the patient did not meet the above criteria, the initial DMARD was discontinued and therapy initiated with the alternative DMARD of that specific therapeutic strategy.

The primary endpoints of the study were pain, functional disability, joint score, ESR, and radiological damage. Assessments were performed at baseline and repeated every

3 months, with the exception of radiological damage assessment, which was assessed annually.

All strategies reduced disease activity. A greater percentage of patients improved clinically with strategy 2 and 3 than with strategy 1. Joint score improvement was 79% (strategy 2) and 82% (strategy 3), significantly better than strategy 1 (66%). Radiological damage (modified Sharp method) was significantly lower in strategies 2 and 3. At the end of 2 years, the mean scores were 11 and 10, respectively, for strategies 2 and 3, compared to 14 for strategy 1 ($p < 0.05$). Toxicity was increased in strategy 2 compared with the other strategies.

Although the study was not designed to compare single drugs, the results at the end of year 1 reflect the effectiveness of the initial DMARD: 86% of the patients were still with their initial DMARD after one year. At the end of year 2, the initial DMARD was only being used by 47% of the patients.

The conclusion of the study was that strategy 3, MTX or SSZ, produced the best results when balancing effectiveness and toxicity. HCQ or auranofin were slightly less effective, and intramuscular gold or D-penicillamine were associated with increased toxicity.

SSZ versus placebo. Hannonen and colleagues[7] conducted a 48 week, double blind, prospective, placebo controlled study in 80 patients with early RA (duration of symptoms less than 12 months). None of the study participants had ever received DMARD. All but one (in the placebo group) were treated simultaneously with NSAID. Three patients in the placebo group and 5 in the SSZ group took low dose corticosteroids during the study.

SSZ treatment began at a dosage of 500 mg/day, increasing by 500 mg each week to 2000 mg/day. Patients taking placebo received identical tablets and dosage increases. Study participants were evaluated at baseline and at weeks 4, 8, 12, 24, and 48 for joint tenderness and swelling, patient and physician global assessment of disease activity, grip strength, duration of morning stiffness, and patient pain assessment. Other evaluations included laboratory tests (ESR, CRP, rheumatoid factor), scintigraphy of the hands and feet (12 and 24 weeks), and radiographs of the hands, wrists, and feet (baseline and 48 weeks).

At baseline, clinical markers of disease activity were similar between the SSZ and placebo groups. The only significant difference was the number of swollen joints, which averaged 6.8 in the SSZ group and 5.3 in the placebo group.

At 48 weeks, 18 of the SSZ and 11 of the placebo patients were still taking the study drug. Thus, the dropout rate was high. All side effects prompting discontinuation of treatment appeared within the first month. SSZ and placebo did not differ significantly with respect to adverse effects. Lack of efficacy prompted a switch to gold in 14 patients taking SSZ and 28 taking placebo (this difference was statistically significant).

By study end, 18 patients (9 in each group) were in remission. All clinical variables, except for early morning stiffness and physician global assessment, improved significantly — by as early as 4 weeks — in the SSZ versus placebo group. Joint scintigraphic activity scores decreased significantly more in the SSZ group than the placebo group, an effect noted during the first 24 weeks of treatment.

Baseline films had revealed no erosion or joint space narrowing in 21 (55.3%) of the SSZ group and 26 (65%) of the placebo group. Films taken at 48 weeks showed absence of disease progression in 12 (33.3%) of the SSZ and 8 (21.6%) of the placebo group. Although the SSZ group fared better than the placebo group, the differences in erosive indices were not statistically significant.

The investigators concluded that SSZ is better than placebo at controlling inflammation and clinical disease activity in persons with RA. While SSZ retards the rate at which joint erosions develop, it does not prevent disease progression. It also acts quickly; in this study, some benefits were observed at 4 weeks. Side effects also appear early, and do not generally appear to warrant discontinuation of therapy. The high numbers of remissions in this study suggest that patients included had relatively mild disease.

METHOTREXATE

MTX has been widely prescribed for patients with RA for 2 decades now. Weinblatt[8] reviewed findings that support the value of MTX for retarding RA induced articular damage. Highlights from his review are as follows:

- Various open studies, involving from 14 to 78 patients, treated at dosages ranging from 7.5 to 22.5 mg/wk for 3 months to 10 years, noted favorable responses to MTX in a significant percentage (27% to 58%) of patients[9-12]. One exception was a trial in which patients took up to 50 mg/week MTX; while some patients improved in as little as 4 weeks, 35% of patients had to discontinue treatment because of side effects[13].
- Randomized, placebo controlled trials then were done to examine the short term efficacy of MTX[14-17]. All study participants had been unresponsive to or intolerant of other second-line therapies.

Weinblatt and colleagues[15], in a 24 week, placebo controlled, randomized crossover study of 35 patients, reported significant improvement in clinical variables at 12 weeks in the MTX group. This group also had a decrease in mean number of painful joints — from 37 at baseline to 11 at 12 weeks. The number of swollen joints decreased from 34 at baseline, to 20 at 12 weeks. Patients began responding to MTX as early as 3 weeks after starting treatment. In the second half of the study, disease activity increased in patients who had received MTX but were now randomized to placebo. Andersen and colleagues[17] noted similar results in their randomized, placebo controlled, crossover study.

The results of all of these studies confirmed the short

term efficacy of MTX in patients who are unresponsive to other second-line treatments, including gold and D-penicillamine. These studies also showed that after MTX is discontinued, RA flares, frequently within 4 to 6 weeks.

• MTX was compared with azathioprine, oral gold, and cyclosporin A. In comparisons with azathioprine, both drugs caused improvement, but MTX worked faster and its effects were more marked and sustained[18-20]. Similarly, MTX produced significantly greater improvement than auranofin in all measures of disease activity[21]. In a comparison with cyclosporin A, MTX treatment led to greater improvement in physician and patient global assessments, Health Assessment Questionnaire scores, and tender joint count[22].

• In several longterm prospective studies, MTX's beneficial effects on clinical measures of disease activity were prolonged (up to 7 yrs)[23,24]. Some patients taking MTX were able to discontinue or significantly reduce their dosage of corticosteroids.

• Several radiographic studies report that MTX retards articular damage, as assessed by erosion score and joint space narrowing[25,26].

DMARD COMPARED

In looking at the results of the studies reviewed here, it seems clear that DMARD monotherapy modifies the disease by controlling clinical disease activity and retarding radiographic progression of disease. There are clear advantages of DMARD monotherapy over placebo, but the distinctions between the various DMARD are somewhat less clear cut.

In making a choice for a particular DMARD, the length of time to benefit is one of its most important characteristics, given the direct relationship between rampant inflammation and articular damage. MTX, SSZ, and leflunomide are the fastest acting DMARD, while HCQ, D-penicillamine, injectable gold salts, and oral gold take longer to achieve a therapeutic effect (Figure 1).

The balance between DMARD efficacy and toxicity is another critical factor when trying to select which DMARD to give the patient. This topic was the subject of a large metaanalysis[27].

Efficacy/toxicity tradeoffs. The metaanalysis completed by Felson and colleagues[27] included 79 trials and 6518 patients treated with all DMARD in use at the time — antimalarial drugs, MTX, auranofin, injectable gold, D-penicillamine, SSZ, azathioprine — as well as placebo. The mean duration of treatment was 33.7 weeks.

The investigators tested 3 measures of efficacy, each plotted against 3 different toxicity measures. Efficacy measures included composite efficacy, tender joint count alone, and a measure of the number of patients who stopped treatment because of inefficacy. Toxicity measures were the proportion of patients who dropped out because of toxicity, an assessment of toxicity severity in these same dropout patients, and the proportion of patients who experienced severe toxicity. Their findings were summarized as follows:

• Plots of efficacy versus toxicity suggested that MTX and antimalarial drugs had the highest efficacy related to toxicity. MTX scores placed it among the most efficacious of the drugs and, of these, MTX had the least toxicity. Antimalarial drugs showed only moderate efficacy, but had the lowest toxicity. SSZ scored close to MTX but was slightly more toxic[27] (Figure 2).

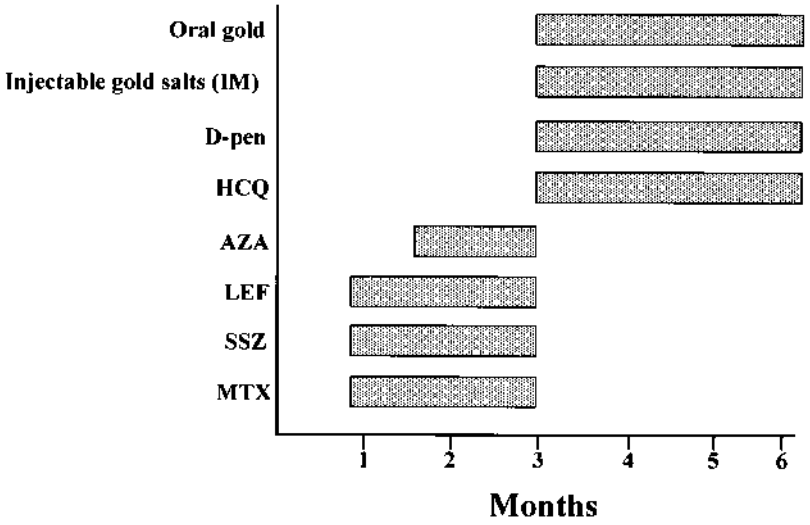

Figure 1. The time to benefit varies among DMARD and influences overall efficacy. Methotrexate (MTX), sulfasalazine (SSZ), and leflunomide (LEF) work most rapidly, within 1 to 3 months, while hydroxychloroquine (HCQ), D-penicillamine (D-Pen), and gold preparations take the longest amount of time. Azathioprine (AZA) is somewhat intermediate.

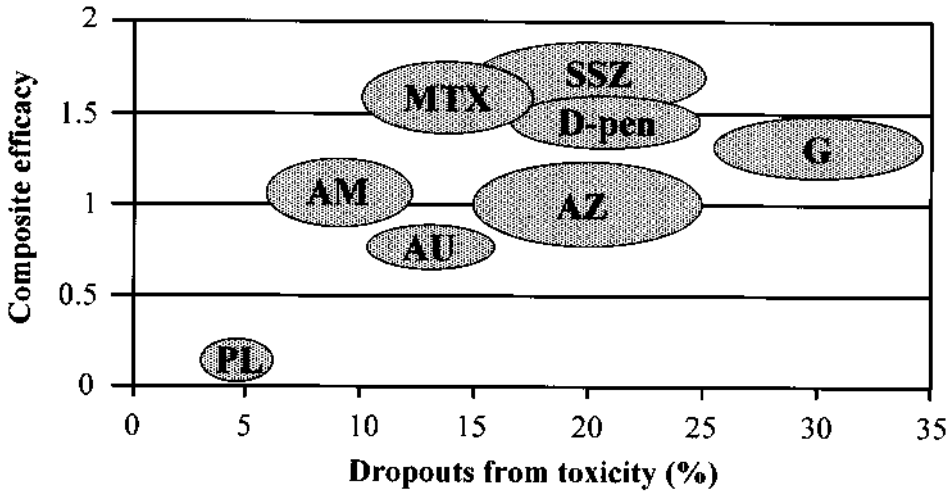

Figure 2. The balance between efficacy and toxicity favors the selection of methotrexate (MTX) and antimalarial agents (AM) for patients with RA. Azathioprine (AZ) is intermediate in terms of both efficacy and toxicity. Sulfasalazine (SSZ) is relatively potent, with modest toxicity. D-penicillamine (D-Pen) is slightly less effective than SSZ, with similar toxicity. Injectable gold (G) is the most toxic DMARD, and auranofin (AU) is the weakest. (PL, placebo). From Felson, *et al*[27], with permission.

SUMMARY

To summarize the findings from these key studies, evidence supports the use of single DMARD therapy in early RA. The benefit of DMARD in early RA, i.e., clinical improvement and the retarding of radiographic progression, is comparable to those observed with these agents in patients with RA of longer duration. For best outcome, it is important to select a DMARD, such as SSZ or MTX, that works quickly. Delay is expensive to the patient, as uncontrolled inflammation leads to irreversible joint damage.

The other side of the equation to consider is DMARD toxicity. One advantage of SSZ in this regard is that side effects appear within the first month of treatment, and generally subside by 6 months. Antimalarial agents are very safe, but less effective than SSZ or MTX. Gold compounds remain very toxic; as such, they remain outside the mainstream of current RA care. As more DMARD become available, clinicians will have an expanding armamentarium from which to optimize patient treatment.

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