Effectiveness Profiles and Dose Dependent Retention of Traditional Disease Modifying Antirheumatic Drugs for Rheumatoid Arthritis. An Observational Study

DANIEL ALETAHA and JOSEF S. SMOLEN

ABSTRACT. ***Objective.*** To determine the fate of traditional disease modifying antirheumatic drugs (DMARD) in the longer term, with special respect to dose related effects on drug retention rates, efficacy, and toxicity.

Methods. Historical analysis of DMARD therapies in 593 patients, comprising a total of 1319 courses of DMARD over a period of 2378 patient-years of therapy. DMARD dosages, treatment durations, and reasons for discontinuation, and measures of C-reactive protein and erythrocyte sedimentation rate were analyzed. Drug retention rates were estimated by Kaplan-Meier analysis.

Results. Methotrexate (MTX), chloroquine, and sulfasalazine (SSZ) emerged as the drugs most commonly applied during the past 15 years, whereas gold salts and D-penicillamine became less frequently used during the past decade. Therapies had to be terminated mostly for adverse events (42%) or inefficacy (37%). Patients taking high dose therapy had significantly longer median retention rates than those taking low doses (SSZ 34 vs 7 mo; MTX 73 vs 39 mo). Toxicity, rather than inefficacy, was the main reason for discontinuation of MTX and SSZ at low doses ($p < 0.001$). Median retention rates lasted < 24 mo for most DMARD, except for high dose MTX (> 36 mo).

Conclusion. MTX, SSZ, and antimalarials have become the most commonly used traditional DMARD for rheumatoid arthritis. Their use is more often limited by toxicity than by inefficacy. If tolerated, they can be retained for long periods of time. (J Rheumatol 2002;29:1631–8)

Key Indexing Terms:
RHEUMATOID ARTHRITIS ANTIRHEUMATIC AGENTS
TREATMENT OUTCOME DRUG TOXICITY SURVIVAL ANALYSIS

The last decade marked a new era in the therapeutic approach to rheumatoid arthritis (RA): the treatment pyramid has been reversed[1], early diagnosis and initiation of disease modifying antirheumatic drug (DMARD) therapy has become mandatory[1-3], and new DMARD, including biologics[4-6], have finally been approved in the USA and Europe. These events make it important to look at the therapeutic state of the art of the past 2 decades to set the stage for future expectations, developments, and success of the new versus the more traditional treatment approaches.

In the treatment of RA, several issues are still under discussion. How effective are the drugs in usual care? How important is drug dose? Are there substantial differences in effectiveness and toxicity between different drugs? Controlled clinical trials, usually double blinded, have shown the efficacy of DMARD[7-11]. Drugs that have proven to be efficacious in such trials are not necessarily effective in usual clinical practice, where neither patient nor physician is blinded and patients may have comorbidities and changing comedication[12]. Moreover, evaluation in controlled clinical trials usually covers only a short period of time, whereas in daily practice longterm outcomes matter[13].

This study aimed to determine the fate of traditional DMARD in the longer term, and, in this context, to identify possible changes in treatment behavior over time right before the introduction of the new agents. Thus, ours is an effectiveness study that deals with the performance of drugs under real life conditions, and on a real life population of RA patients. A main issue was to analyze dose related effects on drug retention rates, efficacy, and toxicity.

MATERIALS AND METHODS

Patient selection. Patients were retrospectively included from 2 rheumatology clinics in Vienna, representative of specialized referral centers as seen in other parts of Europe or the United States. Inclusion was solely limited to patients with RA[14] who were receiving at least one course of DMARD therapy (either terminated or continuing) and had at least one followup examination after initiation of DMARD therapy.

Data were extracted from the files in 1999; files of all patients with RA who were seen in the outpatient clinics after 1993 were available in the archives, since from this time all charts (also those of patients who were lost to followup or have died) were kept for research reasons. Files of patients who had no visit after 1993 were not available for analysis. To determine the potential presence and size of bias we analyzed disease dura-

From the Division of Rheumatology, Department of Internal Medicine III, University of Vienna, Vienna, Austria.

D. Aletaha, MD; J.S. Smolen MD.

Address reprint requests to Dr. J.S. Smolen, Division of Rheumatology, Department of Internal Medicine III, University of Vienna, Vienna General Hospital, Waehringer Guertel 18-20, A-1090 Vienna, Austria. E-mail: smj@2me.khl.magwien.gv.at

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tion of therapies and reasons for treatment discontinuation before and after 1993, and found no significant difference (data not shown). Ongoing therapies at the time of data collection were censored for treatment termination to avoid underestimation of duration of therapy.

In both clinics, these patients are seen by physicians in training who already have at least one year of experience in rheumatology and are closely supervised by a senior rheumatologist. The choice of DMARD was made by the treating physician on the basis of the patient's history, clinical examination, and radiographic and laboratory test results after discussion of the options with the patient. Patients were seen regularly for control examinations and followed throughout all their DMARD therapies until the time of data extraction in 1999. The records at each visit comprise reported symptoms, examined signs, laboratory details, medication, diagnosis, and future plan.

In this manner we identified and thoroughly reviewed charts and histories of 593 patients with RA taking DMARD therapy, 477 women (80.4%) and 116 men (19.6%). These patients received 1319 courses of DMARD [women: 1061 (80.4%), men: 258 (19.6%)]. The number of DMARD starts in an individual patient ranged from one to 10 (median 2). Rheumatoid factor at first presentation was positive in 379 patients (63.9%) and negative in 214 (36.1%). The patients' mean age (± SD) at the time of onset of symptoms was 44.7 ± 14.9 years and they were followed a mean of 13.6 ± 9.3 years. Since many patients had received DMARD before they presented at our clinics, the mean disease duration at the time of the true first DMARD is uncertain for these patients; however, 222 patients received their first DMARD at our clinics, and the median lag time from onset of symptoms by history to first DMARD was 9 months (up to 2 years).

In total, 2378 patient-years of DMARD therapy were analyzed and were composed of the following therapies (rounded numbers of patient-years in parentheses): methotrexate (MTX; 751), chloroquine (CQ; 536), sulfasalazine (SSZ; 428), parenteral gold compounds (PG; 218), penicillamine (D-Pen; 164), auranofin (OG; 131), azathioprine (AZA; 56), cyclosporin A (CSA; 27), and combination therapies (67). In the various subgroups, sex, age, and seropositivity profiles were similar (Table 1). With respect to use of nonsteroidal antirheumatic drugs (NSAID) and low dose glucocorticoids, there were no major differences between DMARD groups (roughly 60% and 80%, respectively).

Followup of DMARD therapies. For each DMARD therapy dosage, duration and reason for discontinuation (if applicable) were registered from the patients' charts. Since detailed joint counts had not been assessed prospectively, at the beginning of each therapy surrogate measures of disease activity[4-6,15-21], namely baseline values of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), were compared to values obtained at the end of the respective therapies or, for ongoing therapies, at the time of last evaluation. These variables correlate well with disease activity as well as with radiographic and functional outcomes[4-6,15-21].

Statistical analysis. Data were entered into an Excel 2000 file and analyzed (Kaplan-Meier estimates, paired t test, log-rank test) using the Statistical Package for the Social Sciences (SPSS, version 10.0).

RESULTS

Patterns of DMARD prescription. Eight different DMARD were used alone or as double or triple combination therapies (Table 1)[22-24]. MTX was the most commonly employed drug in terms of application (n = 389; 29.5%) and patient-years (751 years; 31.6%), followed by CQ (n = 285; 21.6%) and SSZ (n = 267; 20.2%). All other regimens together accounted for less than 30%, with combination therapies amounting to 6%. The doses given in Table 1 constitute the median of the maximum stable doses (i.e., sustained for at least 3 months) for patients receiving the respective regimen.

Combination therapies accounted for 6.1% of therapies and were mainly composed of MTX (79% of combinations), CQ (59%), CSA (41%), and SSZ (20%), a consequence of the frequent combination of the latter 3 with MTX.

Causes for termination of DMARD. The leading causes for termination of therapies were insufficient efficacy (333 courses, 37%) and subjective symptoms of side effects (n = 268, 29%) followed by laboratory abnormalities (n = 72, 8%) and objective signs of adverse events by virtue of clinical examinations (n = 43, 5%), while remissions were the reasons for discontinuation in only 3%. (Today, remission would not be regarded as reason for discontinuation, since stopping DMARD in patients with inactive disease is associated with a significant risk of flares[25]). Thus, withdrawals due to adverse events totaled 42%. Inefficacy and/or clinical side effects led to treatment discontinuation in almost 4 of 5 patients.

Duration of DMARD therapy. Kaplan-Meier estimates were used to analyze cumulative drug retention rates (Figure 1A).

Table 1. Distribution, dose, and survival time of DMARD therapies.

DMARD	N (%)	Median Dose*	Patient-years (rounded)	Female, %	RF+, %	Mean Patient Age, yrs	Mean Disease Duration, yrs	Median Retention Time, mo (quartiles)	Years of Application
Methotrexate	389 (30)	10.0 mg/week	751	79.7	70.6	59.5	8.6	40 (12,113)	1985–99
Chloroquine	285 (22)	250 mg/day	536	82.1	60.0	61.3	6.1	20 (7,50)	1972–99
Sulfasalazine	267 (20)	2000 mg/day	428	80.2	63.2	57.7	7.7	23 (5,63)	1984–99
Parenteral gold	109 (8)	50 mg/mo	218	84.4	68.3	56.9	6.2	20 (4,60)	1970–98
Penicillamine	68 (5)	300 mg/day	164	81.5	67.2	61.8	10.2	21 (6,56)	1977–96
Oral gold	65 (5)	6 mg/day	131	73.5	65.6	57.0	4.8	17 (4,51)	1984–98
Cyclosporin A	31 (2)	200 mg/day	27	83.9	66.7	56.7	12.3	13 (3,23)	1990–99
Azathioprine	25 (2)	100 mg/day	56	92.0	81.0	59.7	14.9	38 (4,77)	1989–99
Combinations	80 (6)	—	67	73.8	77.9	57.3	10.2	—	1990–99
Total	1319	—	2378	80.4	66.9	59.1	8.0	21 (6,65)	1970–99

* The 25/75 percentiles were MTX 7.5/10.0 mg/week; chloroquine 250/250 mg/day; SSZ 1500/2500 mg/day; PG 50/50 mg/mo; D-Pen 250/400 mg/day; OG 6/6 mg/day; CSA 150/250 mg/day; AZA 75/150 mo.

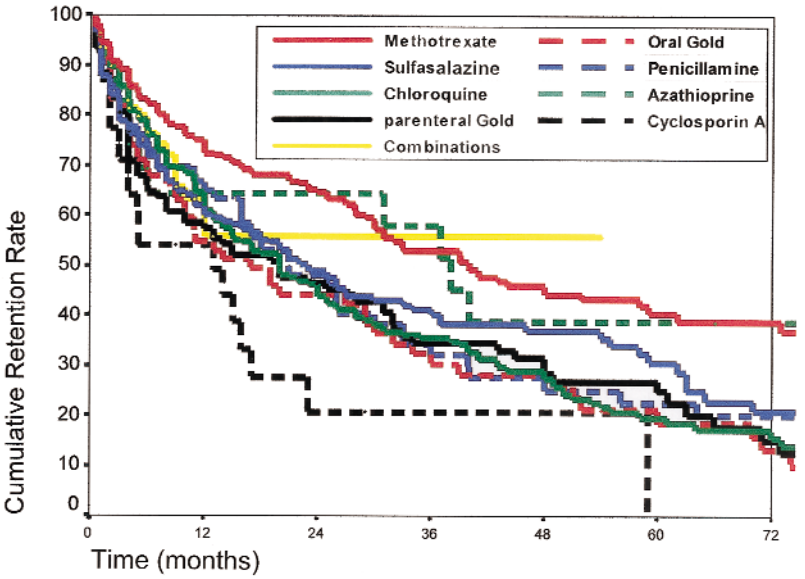

Figure 1A. DMARD retention rates. Overall retention rates: Kaplan-Meier analysis of the total discontinuation proportion of individual DMARD. Log-rank statistics indicate MTX was retained longer ($p < 0.001$) than other DMARD (except AZA and Combination), CSA was retained for less time ($p < 0.05$) than other DMARD (except parenteral gold and oral gold).

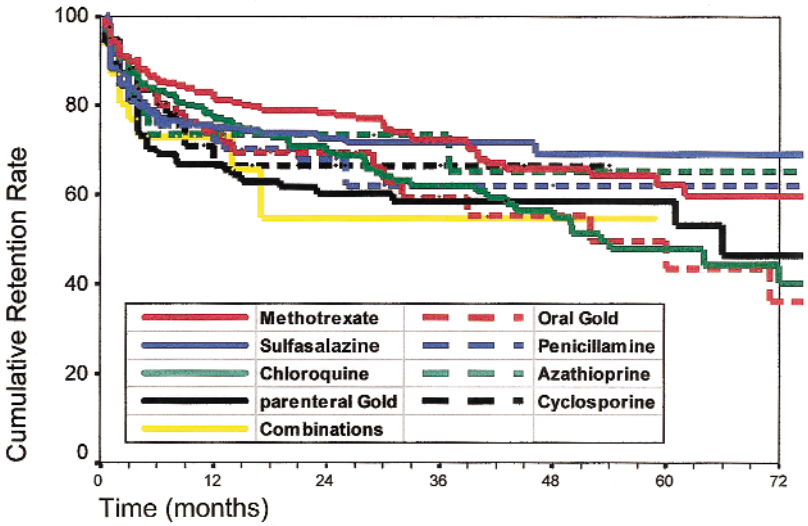

Figure 1B. DMARD retention rates by safety: only discontinuation due to toxicity was analyzed, assuming permanent efficacy otherwise. Log-rank statistics indicate MTX was retained longer ($p < 0.05$) than chloroquine, parenteral gold, and cyclosporin A; SSZ was retained longer ($p < 0.05$) than parenteral gold.

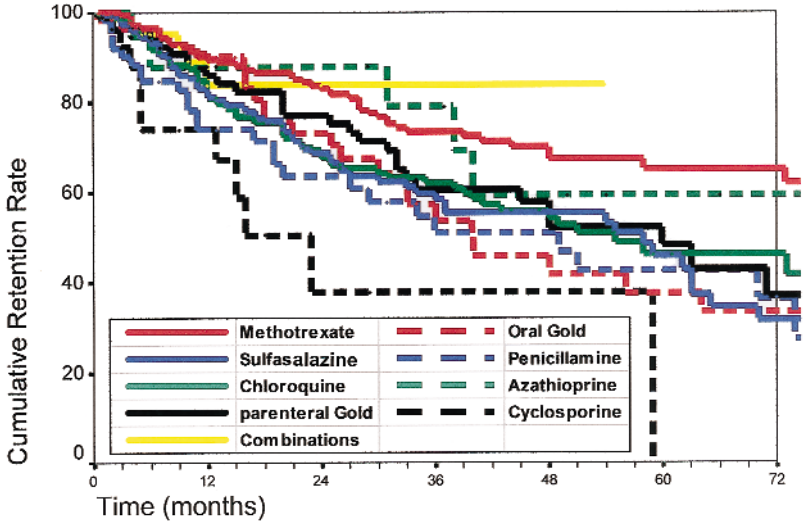

Figure 1C. DMARD retention rates by efficacy: only discontinuation due to inefficacy was analyzed, assuming permanent lack of significant toxicity otherwise. Log-rank statistics reveal MTX was retained longer than SSZ, chloroquine, oral gold, cyclosporin A ($p < 0.001$) and parenteral gold and penicillamine ($p < 0.05$); cyclosporin A was retained for less time than MTX ($p < 0.001$) and SSZ, chloroquine, oral gold, penicillamine, and AZA ($p < 0.05$).

MTX had a higher ($p < 0.001$) retention rate (median drug survival time 40 mo) than all other drugs (except AZA and combination therapies). This retention rate was somewhat lower than those described for MTX in other studies[26-30]. By contrast, the DMARD with the worst retention rate was CSA (13 mo median drug survival time; significantly shorter than all other DMARD except gold compounds).

Next, the influences of drug toxicity and efficacy on maintenance of therapy were analyzed separately. In the first scenario, the probability of discontinuation due to adverse events was estimated by Kaplan-Meier analysis (Figure 1B), and for all therapies permanent efficacy was assumed. The lowest discontinuation rates were observed for MTX and SSZ ($p < 0.05$, log-rank test statistics: MTX compared to CQ, PG, or CSA; SSZ compared to PG). These data suggest that MTX and SSZ are among the safest of the traditional DMARD.

In the second scenario, discontinuation rates due to inefficacy were estimated, and for all therapies no other reason for discontinuation was assumed (Figure 1C): In this respect, MTX had significantly ($p < 0.05$ to < 0.001) higher retention rates compared to SSZ, CQ, OG, PG, CSA and D-Pen, suggesting that the possibility to treat RA longer with MTX than with any other drug is also driven by higher efficacy of this drug. Only combination therapies and AZA did not differ significantly from MTX. CSA had the lowest retention rate of all therapies (significantly shorter than most other drugs) (Figure 1C). Thus, taking data of both efficacy and safety into account, the relation between efficacy and toxicity was best for MTX, followed by SSZ and CQ (data not shown).

Influence of DMARD dose. The influence of DMARD dose on treatment duration or retention rates was analyzed (Table 2). There was a tendency to increase doses of MTX and SSZ during the last decade (data not shown). We found 59% of patients taking low dose MTX (≤ 10.0 mg/week, n = 285) discontinued the drug, whereas only 36% of patients taking high dose MTX (≥ 12.5 mg/week, n = 89) terminated therapy ($p < 0.001$). Indeed, higher doses of MTX were continued significantly longer than lower doses (Figure 2A, Table 2): after 5 years, 57% of patients were still taking high dose MTX (median retention time 73 mo) compared to only 37% of patients taking low dose MTX (median retention 39 mo) ($p < 0.05$). Patients taking high dose SSZ (≥ 2000 mg/day, n = 184) retained therapy significantly better than those taking low doses (SSZ < 2000 mg/day, n = 62) — 59% discontinuations compared to 81% ($p < 0.05$). The 5 year retention rate for SSZ was 34% for high doses and 25% for low doses, the median retention rates 34 and 7 months, respectively ($p < 0.05$). However, low dose MTX also had significantly longer retention rates than both SSZ regimens or CQ (data not shown).

To determine the reason for longer retention of higher doses, additional analyses were performed. As shown in Figure 2B, treatment discontinuation rates due to adverse events with MTX and SSZ were significantly lower at high doses than at low doses. In other words, it appears that patients who did not tolerate low doses of MTX or SSZ were withdrawn from treatment before higher doses were reached. This is particularly evident for SSZ therapies, where 35% of patients were withdrawn from low dose therapy due to adverse events during the first 3 months. This is confirmed by the analysis of efficacy: when treatment termination due to inefficacy was analyzed, low and high doses of the 2 DMARD had similar retention rates (Figure 2C), although patients taking MTX fared significantly better than those taking SSZ ($p < 0.05$).

Change of acute phase responses. Generally, disease activity is assessed by composite scores[31-34]. However, detailed joint counts and patient derived variables were not routinely prospectively assessed in the clinics in the past and were not available for this analysis. In contrast, laboratory variables (CRP and/or ESR) were available for most patients. Since, all limitations in mind, CRP and ESR constitute surrogate markers of RA disease activity[4-6,15-21], they were used here to estimate efficacy of DMARD therapy by comparing values at the beginning to values at the end of each therapy (or end of observation for ongoing therapies). CRP values (upper normal limit 0.5 mg/dl) showed a reduction of 31% from a median of 1.6 mg/dl before to 1.1 mg/dl at the end of therapies; median ESR values changed by 28%, from 36 to 26 mm/h. For both variables improvement was significant (Wilcoxon test, $p < 0.001$). This reduction of the acute phase response suggests an overall efficacy of these DMARD therapies, since in clinical trials CRP and ESR usually do not change significantly with placebo[4-6].

Next, therapies were subdivided according to types of DMARD and reasons for treatment discontinuation. For individual drugs, the reduction of CRP levels between last and baseline values was significant (Wilcoxon test, $p <$

Table 2. DMARD dose and DMARD retention.

	Methotrexate			Sulfasalazine		
	High Dose (≥ 12.5 mg/wk)	Low Dose (≤ 10 mg/wk)	p (high vs low)	High Dose (≥ 2000 mg/day)	Low Dose (≤ 1500 mg/day)	p (high vs low)
Overall discontinuation, %	36	59	< 0.001	59	81	< 0.05
5 year retention rate, %	57	37	< 0.05	34	25	< 0.05
Median retention, mo	73	39	< 0.05	34	7	< 0.05

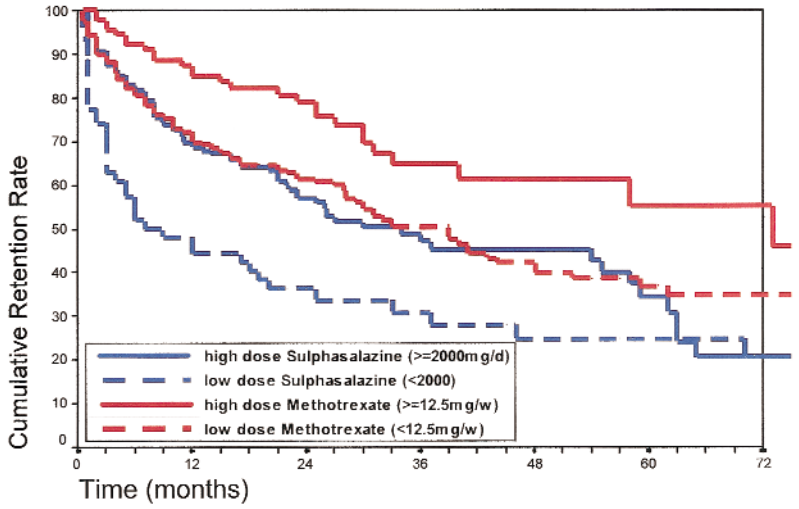

Figure 2A. Retention rates of high versus low dose regimens. Kaplan-Meier analysis of the total discontinuation proportion of individual regimens. Log-rank statistics indicate high dose MTX was retained longer than SSZ regimens ($p < 0.001$) and low dose MTX ($p < 0.05$); low dose SSZ was retained for less time than MTX regimens ($p < 0.001$) and high dose SSZ ($p < 0.05$).

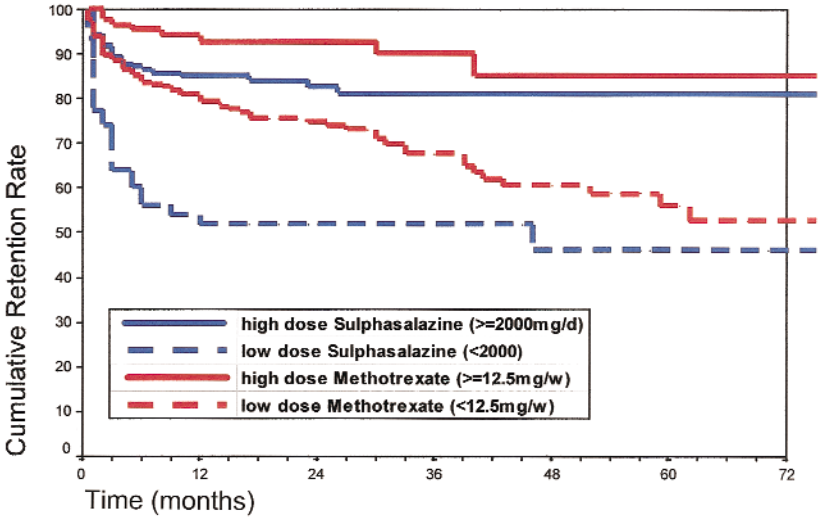

Figure 2B. Retention rates of high versus low dose regimens by safety: only discontinuation due to toxicity was analyzed, assuming permanent efficacy otherwise. Log-rank statistics show high dose MTX was retained longer ($p < 0.001$) than low dose MTX or low dose SSZ; high dose SSZ was retained longer ($p < 0.001$) than low dose SSZ; low dose MTX was retained longer ($p < 0.001$) than low dose SSZ; high dose SSZ was retained longer ($p < 0.05$) than low dose MTX.

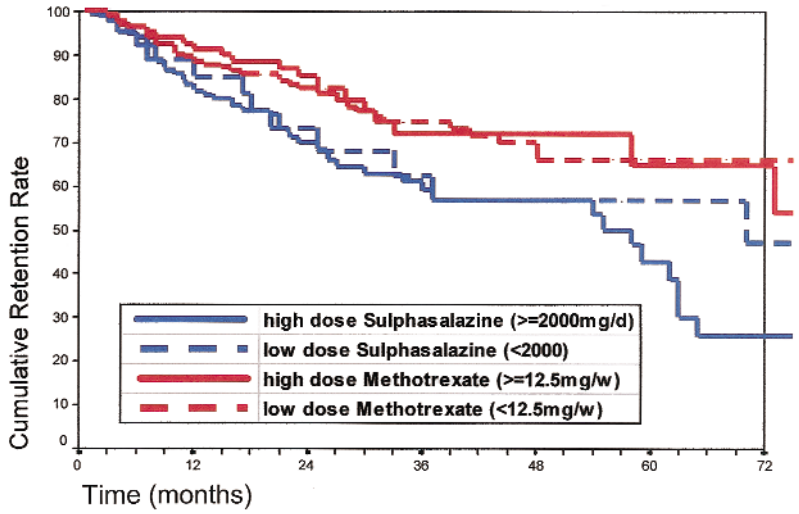

Figure 2C. Retention rates of high versus low dose regimens by efficacy: only discontinuation due to inefficacy was analyzed, assuming permanent lack of significant toxicity otherwise. Log rank statistics reveal p was nonsignificant between the 2 MTX or the 2 SSZ regimens; $p < 0.05$ between MTX and SSZ regimens.

0.001) for MTX, SSZ, CQ, and PG, with the highest decrease of CRP with MTX (Mann-Whitney U test, $p < 0.05$ vs SSZ or CQ) (data not shown). Not surprisingly, when groups were formed according to the state of therapy, the highest degree of improvement ($p < 0.001$ for CRP and ESR) was seen in patients with ongoing therapies, compared to therapies terminated for adverse events or inefficacy (Mann-Whitney U test, $p < 0.05$) (detailed data not shown).

DISCUSSION

Data on efficacy and toxicity are important to facilitate decision making in the care of patients with RA. The selection of the individually appropriate drug and dose can reduce risks of adverse events and increase clinical effectiveness, treatment duration, outcome, and quality of life. Our data confirm the dilemma of treating RA: despite their principal efficacy[7-13], only relatively few patients could tolerate DMARD beyond a short period of time even at the end of the 1990s[35]. MTX seems to be the single exception to the rule[27]; however, a significant proportion of patients with RA taking MTX still have to terminate therapy within a few years.

One finding of this study is that toxicity is more frequently the reason for discontinuation of DMARD than inefficacy. This observation does not necessarily suggest that the respective therapies would have been efficacious if not terminated due to adverse events, but it reveals that toxicity constitutes a major problem with the traditional DMARD. Among the adverse events, the subjective adverse events were preponderant, in particular gastrointestinal toxicity that prevented continuation of therapy. Obviously, this constitutes an area for further improvement of counteractive or preventive means, and folate substitution[36] and antiemetic compounds may have a prolonging effect on continuation rates.

Toxicity and inefficacy are the 2 major factors determining duration of drug therapy. Inefficacy was judged solely by the physician at the time of visits at the outpatient clinic. Although "loss of efficacy" was not judged, it is unlikely that patients would continue to take a drug for many months or years if it had no efficacy. Thus it was possible to consider inefficacy or loss of efficacy in terms of of discontinuation rates. Contrarywise, although the vast majority of the patients did not achieve remission, all patients who did not discontinue DMARD because of toxicity or lack of efficacy must be assumed to have achieved a state of disease that satisfied them as well as the rheumatologist. Indeed, the overall efficacy of DMARD is supported by the observations on the improvement of the acute phase response: CRP reduction amounted to > 30% over all DMARD.

Our data show best retention rates for MTX in clinical practice, which is consistent with previous findings[26-30]. However, the median survival time of MTX therapies was lower than in those reports. This finding may be partly associated with the fact that folate replacement was given in < 10% of patients, since it was not regularly used until the most recent years; however, the availability of other therapeutic options also might have contributed to frequent changes of DMARD, possibly even before sufficient efficacy could be obtained. As well, we are considering rather low doses of MTX in our trial, partly because the observation period dates back to the 1980s, when new therapies were employed more cautiously. AZA and combination therapies had comparable retention rates to MTX; however, the smaller number of applications limit the interpretation of this finding. This is also the case for CSA, which showed the worst retention in this series.

Treatment duration not only reflects DMARD effectiveness and toxicity, but is also influenced by individual factors such as the number of previous DMARD or the remaining therapeutic options. It is possible that DMARD courses are maintained longer if there are no therapeutic options left. In contrast, the DMARD dose might not be increased to maximum — and therapy discontinued earlier — if there are many other options available.

Many measures of clinical improvement are available in RA, singly or combined into scores[31-34]. Here, the acute phase response was used to assess improvement[4-6,15-21,34]. With all the limitations of applying such surrogate markers to assess clinical improvement, the data suggest and confirm significant beneficial effects of DMARD, as judged by the 30% reduction of CRP, a result not achieved by placebo[4-6]. However, mean levels of CRP (and ESR) usually did not reach normal values, confirming that the term "remission inducing drugs" is not applicable to the drugs that are currently available, that the efficacy of DMARD is limited[30], and that new and better drugs are needed. This is in accord with the small number of patients with RA (3%) who appear to have achieved clinical remission.

Among the most important observations in this study is the finding that drug retention rates were significantly higher in patients treated with high doses of MTX (≥ 12.5 mg/week) or SSZ (≥ 2 g/day) compared to lower doses. The Kaplan-Meier plots suggest that the differences found for MTX and SSZ, as well as for high versus low doses of these drugs, are determined within the first 6 months of therapy, while later the slope of the curves is similar. Interestingly, when these data were subjected to subanalysis, it was higher toxicity in the low dose groups rather than inefficacy that led to discontinuation in the vast majority of patients treated with lower doses of MTX and SSZ. This indicates significant efficacy of even low dose MTX and SSZ, which is further supported by similar degrees of CRP/ESR reduction on low compared to higher doses of these drugs (data not shown). However, if low dose therapies are tolerated but not effective, dose increases will be the consequence, and the respective therapies will contribute to the high dose rather

than to the low dose group. Also, in a large number of patients MTX and SSZ are not tolerated even at relatively low doses, and patients are not able to escalate the dose needed for better efficacy appropriately. Thus, these data allow us to conclude only that low dose regimens may be effective in some patients, since those who need higher doses to reach similar efficacy may not be able to tolerate the increased dose.

Another major finding from our analysis is that once higher doses have been established safely, the risk of discontinuation from adverse events is very low with both MTX and SSZ, their long retention rates being indirect evidence of efficacy as well. This observation is in accord with previous findings on the efficacy/toxicity ratio of these agents[37].

The patient population investigated here, comprising cohorts from 2 different hospitals, is representative of RA patients with no selection of either severe or mild cases, since patients were self-referred and were also referred from general practitioners or rheumatologists. Further, it is unlikely that severe or fatal adverse events were overlooked due to the mode of selection in this study, since all files were kept after 1993. The issue of left censorship can therefore be put aside, due to the long period with no loss of patient data.

We found DMARD distribution and retention rates were similar to former reports; however, we observed dose dependent effects on DMARD survivals and found that toxicity is the major limiting factor of antirheumatic therapy. The introduction of new agents[4-6] brings new hope, but it remains to be seen if effectiveness, drug retention rates, and potential to achieve remissions will be better than with the traditional agents. Studies like the present one will have to be performed for the new agents over the coming years to determine if they are as efficacious as the results of clinical trials suggest.

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