EXTENDED REPORTS

Utility of disease modifying antirheumatic drugs in "sawtooth" strategy. A prospective study of early rheumatoid arthritis patients up to 15 years

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Abstract

***Objectives*—To study long term utility of early, continual, and serial use of disease modifying antirheumatic drugs (DMARDs) in early rheumatoid arthritis (RA) in clinical setting.**

***Methods*—A total of 135 patients with early RA were treated according to the "sawtooth" strategy and prospectively followed up to 15 years. DMARD survivals as well as reasons for drug terminations were documented and are reported here.**

***Results*—During 1401 person years of follow up, a DMARD or a combination of two or several DMARDs (COMBOs) was started 606 times. A total of 528 drug periods were terminated because of inefficacy, adverse effects, remission, and other reasons in respective 270 (51.1%), 149 (28.2%), 32 (6.1%), and 77 (14.6%) cases. Severe drug related adverse events were rare. The median duration of DMARD periods of individual DMARDs or COMBOs was 10 months ranging from six to 18 months. Not a single DMARD/COMBO stood out favourably from the others with respect to ineffecacy, toxicity or drug survival.**

***Conclusion*—The use of serial DMARDs/COMBOs was safe even in the long run. Inefficacy rather than toxicity was the leading reason for drug terminations. More powerful drug therapies are needed.**

(*Ann Rheum Dis* 1999;**58**:618–622)

In the 1980s the traditional "pyramidal" approach of treatment with disease modifying antirheumatic drugs (DMARDs) in rheumatoid arthritis (RA) patients was for several reasons[1–3] challenged by more aggressive treatment approach strategies, for example, by the "sawtooth" strategy.[2] While in the pyramidal approach the treatment is started by symptom relieving drugs with subsequent one by one addition of DMARDs starting with the least toxic one, the sawtooth strategy advocates early, continual and serial use of DMARDs, and careful follow up of the patients.[2]

Despite negligible investigational information, the latter strategy was anticipated to offer better long term outcome for the patients. On the other hand, more intensive use of potentially toxic DMARDs obviously raised safety concerns towards the treatment.[4]

The data concerning both efficacy and safety of different treatment strategies can only be obtained in long term observational studies. In this paper we describe the utility of DMARDs in sawtooth strategy in early, prospectively followed up RA patients for up to 15 years from the onset of the disease. Furthermore, we compare several DMARDs with each other with regard to drug survival and reasons for treatment termination.

Methods

The study included a total of 135 early RA patients initially recruited to two separate, prospective patient cohorts[5 6] at Jyväskylä Central Hospital. The first cohort comprised 58 early RA patients from September 1983, and was assembled to study early erosiveness in recent onset RA (Cohort 1). The second cohort of 77 patients was started in the beginning of 1988 as a case-control study to investigate the efficacy and tolerability of sulfsalazine (SSZ) in the treatment of early RA (Cohort 2). All the patients met the American Rheumatism Association (ARA) 1958 criteria[7] for definite or classic RA.

Table 1 Demographic and clinical characteristics (mean, SD) of the 135 early RA patients at the baseline

	Cohort 1	*Cohort 2*
Number	58	77
Age (y)	48.0 (16.0)	52.0 (15.2)
Duration of symptoms (months)	8.1 (6.0)	5.1 (3.7)
Sex, female, number (%)	41 (73%)	49 (65%)
*Seropositive, number (%)	46 (79%)	53 (70%)
ESR	39.8 (25.3)	38.0 (20.2)

*Seropositivity during the follow up. ESR = erythrocyte sedimentaion rate (mm 1st h).

Table 2 DMARD periods grouped with respect to reason for discontinuation

Reason for discontinuation	*Number*	*%*	*Duration of period, months, median (min, max)*
Inefficacy	270	51.1	10 (1, 148)
Adverse effects	149	28.2	4 (1, 115)
Other reasons	77	14.6	14 (1, 87)
Remission	32	6.1	35.5 (3, 75)
		100.0	
Continues	78		30 (1, 164)

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Accepted for publication
21 May 1999

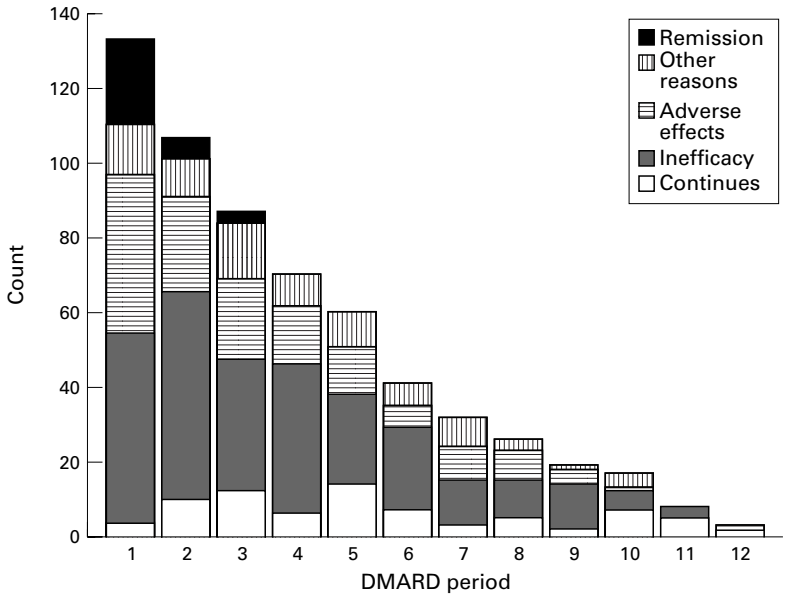

Figure 1 The reasons for discontinuations of the DMARD periods in rank order 1–12. (DMARD=disease modifying antirheumatic drug).

Table 1 shows the demographic and clinical characteristics of the patients at the baseline. The data of the only patient lost to follow up (one year after the diagnosis) are excluded from table 1.

For the Cohort 1 patients were given intramuscular aurothiomalate (GST) at the time of diagnosis, while SSZ or placebo was initially administered to the Cohort 2 patients. Subsequently all the patients were enrolled in a prospective follow up study to evaluate the utility of continual and serial use of DMARDs or their combinations (COMBOs), later nominated as sawtooth strategy by Fries.[2] According to the written protocol, in case of inefficacy or toxicity, GST was started as the second DMARD in Cohort 2 patients but otherwise the rank order choice of DMARDs depended on the discretion of the treating clinician. With a few exceptions the cohort patients were met only by the investigators, although all rheumatologists in the clinic shared common treatment principles. If clinical remission[8] or significant clinical improvement was not achieved within six months, or if the patient clinically, functionally or radiograhpically deteriorated, it was mandatory to change the used DMARD to another one or to combine it with (an)other DMARD(s).

The patients were clinically assessed every three months for the first two years, and at least yearly thereafter, in case of active disease more frequently, until the latest visit before January 1999, or until death (25 cases). The use of DMARDs was documented at each visit. The interval from the initiation to the discontinuation of a DMARD or a COMBO was defined as a DMARD period. All DMARD periods were included in the analysis regardless if a patient had more than one DMARD period on a particular DMARD.

The median maintenance daily doses were 300 mg for hydroxychloroquine (HCQ), 2000 mg for SSZ, 450 mg for d-penicillamine (DPA), 150 mg for azathioprine (AZA), 200 mg for cyclosporin-A (CYA), 6 mg for auranofin (AURA), 300 mg for podofyllotoxine derivatives (CPH82), 4 mg for chlorambucil (KB), and 150 mg for cyclophosphamide (CYP). The respective median doses for GST and methotrexate (MTX) were 50 mg monthly and 10 mg weekly. With the exception of 1000 mg daily dose for SSZ the same median doses were used in COMBOs as well.

In this paper the reasons for discontinuations of DMARD periods are cathegorised as (1) inefficacy: (a) insufficient suppression of clinical disease activity and (b) loss of the beneficial effect after primary response as assessed by the attending physician, (2) remission (8), (3) toxicity: (a) cytopenias, (b) proteinuria, (c) clinically meaningful increase in serum creatinine concentration, (d) clinically meaningful increase in blood pressure, (e) increase in serum transaminase activities, (f) gastrointestinal adverse effects, (g) dermal and mucocutaneous adverse effects, (h) adverse effects in the respiratory tract, (i) accelerated growth of rheumatoid nodules, and (j) miscellaneous symptoms without objective findings, and (4) other reasons: (a) pregnancy, (b) comorbidities, (c) drug costs, (d) other, often unexplained unwillingness of the patient to continue on the chosen DMARD.

Table 3 Proportions of ongoing treatments and terminations grouped according to causes of terminations of individual DMARDs and COMBOs

		Discontinued				
		Inefficacy	*Adverse effects*	*Other reasons*	*Remission*	
DMARD/COMBO	*(n (%) out of 606 starts)*	*(n (%) within a DMARD/COMBO)*				*Ongoing*
GST	131 (21.6)	52 (39.7)	45 (34.4)	14 (10.7)	9 (6.9)	11 (8.4)
HCQ	50 (8.3)	22 (44.0)	11 (22.0)	8 (16.0)	4 (8.0)	5 (10.0)
SSZ	110 (18.2)	49 (44.5)	28 (25.5)	10 (9.1)	15 (13.6)	8 (7.3)
DPA	28(4.6)	14 (50.0)	8 (28.6)	3 (10.7)		3 (10.7)
AZA	38 (6.3)	19 (50.0)	8 (21.1)	8 (21.1)	1 (2.6)	2 (5.3)
CYA	10 (1.7)	6 (60.0)	2 (20.0)	2 (20.0)		
MTX	52 (8.6)	20 (38.5)	13 (25.0)	6 (11.5)		13 (25.0)
AURA	39 (6.4)	24 (61.5)	9 (23.1)	1 (2.6)	2 (5.1)	3 (7.7)
CPH82	19 (3.1)	12 (63.2)	2 (10.5)	4 (21.1)		1 (5.3)
CYP	2 (0.3)		1 (50.0)	1 (50.0)		
KB	1 (0.2)	1 (100.0)				
TENIDAP	1 (0.2)	1 (100.0)				
COMBO without MTX	53 (8.7)	31 (58.5)	6 (11.3)	8 (15.1)	1 (1.9)	7 (13.2)
COMBO with MTX	72 (11.9)	19 (26.4)	16 (22.2)	12 (16.7)		25 (34.7)

For abbreviations, see text.

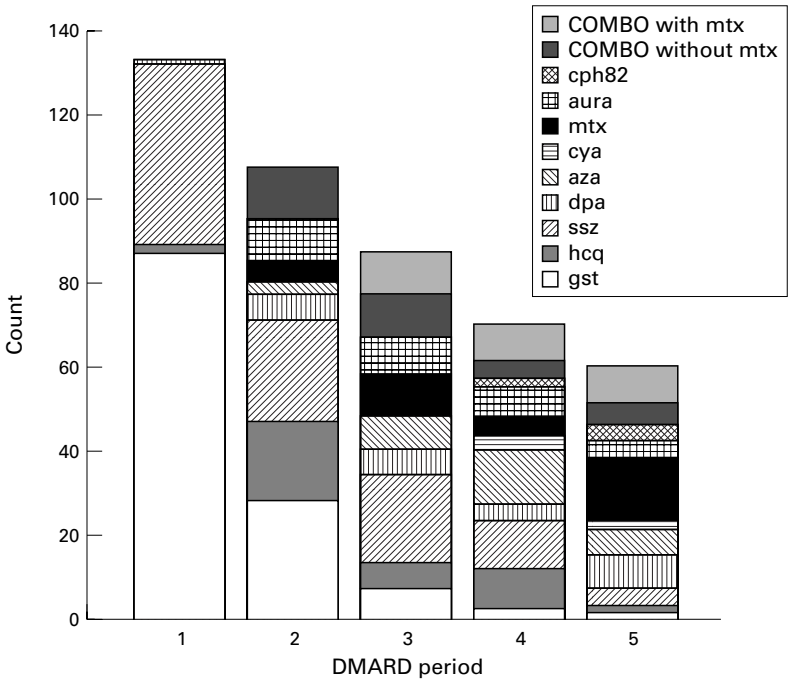

Figure 2 Distribution of DMARDs or COMBOs in the DMARD rank order periods 1–5. (DMARD=disease modifying antirheumatic drug, COMBO=combination of DMARDs, gst=aurothiomalate, hcq=hydroxychloroquine, ssz=sulfasalazine, dpa=D-penicillamine, aza=azathioprine, cya=cyclosporin-A, mtx=methotrexate, aura=auranofin, chp82=podofyllotoxin derivatives).

Results

During a total of 1401 person years of follow up, the 135 patients were challenged 606 times with a single DMARD or a COMBO. The median (range) number of DMARD periods was six (1–16) and three (0–12, one patient never needed DMARDs because of a self remitting arthritis) in the Cohorts 1 and 2, respectively.

A total of 528 (87.1%) out of the 606 DMARD periods have been discontinued. As shown in table 2, respectively 270 (51.1%), 149 (28.2%), and 77 (14.6%) DMARD periods were terminated because of inefficacy, adverse reactions and other reasons, while only in 32 (6.1%) cases a DMARD period was stopped because of clinical remission. While the DMARD periods discontinuated because of adverse effects and inefficacy took a respective medians of 4 and 10 months, a DMARD period leading to clinical remission had continued for a median of 35.5 months before cessation (table 2).

Figure 1 shows the reasons for discontinuations of the DMARD periods in rank order 1–12. A DMARD could be stopped because of clinical remission only during the three first rank order DMARD periods, while inefficacy remained the leading reason for discontinuations throughout the follow up (fig 1).

Figure 2 shows the distribution of DMARDs or COMBOs in the rank order DMARD periods 1–5.

GST and SSZ were the most commonly used DMARDs followed by COMBOs (with or without MTX), MTX, HCQ, AURA, and AZA (table 3). Table 3 also indicates that remissions, with rare exceptions, occurred during the treatment periods with SSZ, GST or HCQ, while the COMBOs with MTX, MTX, and GST periods least often were discontinuated because of inefficacy. DMARD period terminations because of adverse effects and other reasons were comparable between the most commonly used DMARDs (table 3).

The DMARD periods terminated because of adverse effects are summarised with regard to type of adverse event and the DMARD used in figure 3. Expectedly, adverse effects manifested as skin and/or mucosal and gastrointestinal findings, and miscellaneous symptoms without objective findings comprised 74% of all adverse reactions leading to discontinuation of DMARD use (table 3).

Serious adverse reactions were rare. One elderly man developed reversible agranulocytosis during a SSZ period and another man suffered from GST induced pneumonitis. Less severe cytopenias caused discontinuation of additional seven DMARD periods. Furthermore, none of the deaths during the follow up were related to the DMARD use.

The median survival of all the 606 DMARD periods (including the 528 discontinued and at present ongoing 78 periods) was 10 months ranging from six to 18 months for individual DMARDs, as shown in figure 4.

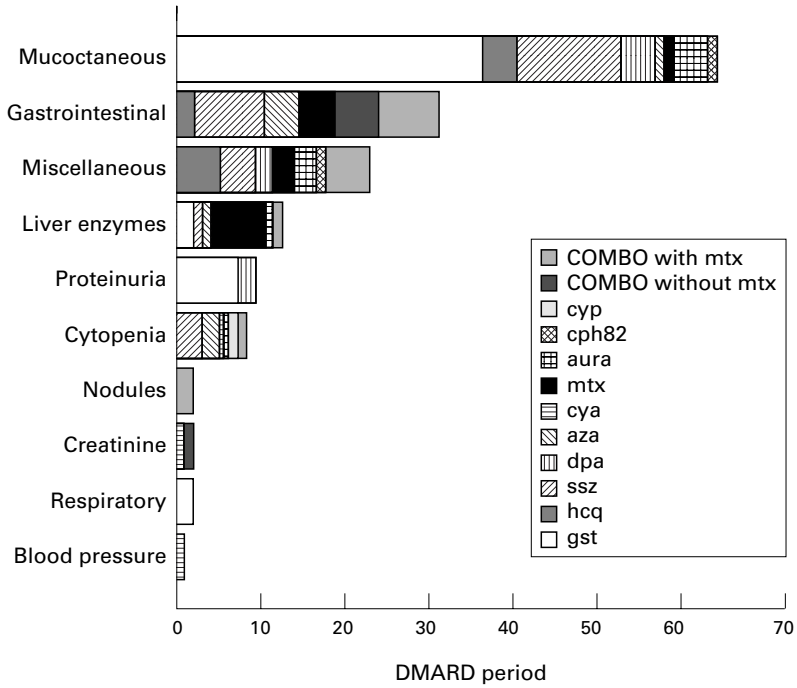

Figure 3 The DMARD periods terminated because of adverse effects with regard to type of adverse event and the DMARD. cyp=cyclophosphamide. Other abbreviations as in figure 2.

Discussion

To our knowledge this is the first detailed description of the use of DMARDs according to the sawtooth principle in patients with RA who have been followed up prospectively from the diagnosis in clinical setting. The main finding of this study was that serial and continual use of DMARDs is safe also in the long run and that inefficacy is the leading reason for cessation of the use of DMARDs in the majority of cases.

The finding is in contrast with the reports from the 1980s indicating that toxicity was the most common reason for discontinuation of

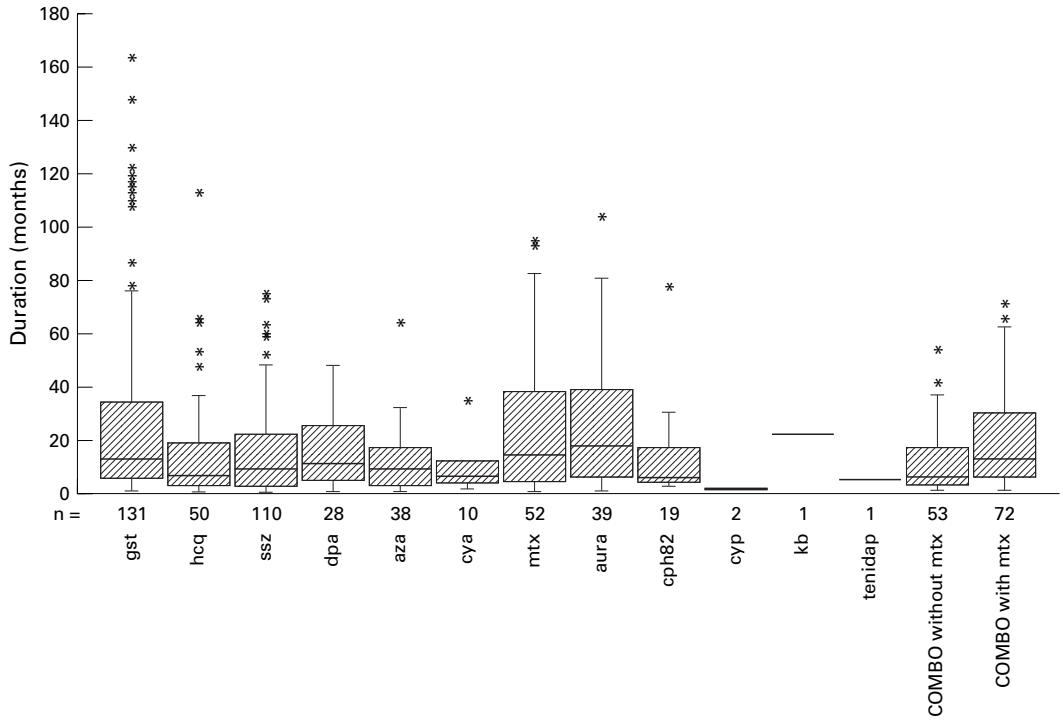

Figure 4 Box-whisker plot of survivals of DMARD periods of individual DMARDs/COMBOs. kb=chlorambucile. Other abbreviations as in figure 3.

DMARDs in long term clinical use. Situnayake *et al*[9] reported that adverse effects led to withdrawal of GST, DPA, and SSZ in respective 57%, 41.2%, and 27% of cases during five years. In another retrospective study regarding several DMARDs by Thompson *et al*,[10] adverse effects accounted for 60% of all discontinuations. Furthermore, in two large patient materials from the US, adverse reactions were more common reason for termination of the use of DMARDs than inefficacy.[11 12]

In accordance with this study, in two other European patient cohorts from Spain[13] and the Netherlands[14] inefficacy more commonly than toxicity led to termination of the use of DMARDs. Furthermore, in a recently published, but early 1980s initiated study from Wales, Jessop and coworkers reported that from the DMARD naive RA patients with a median disease duration of two years a total of respective 53%, 34%, 31%, and 30% initially treated with DPA, GST, AURA, and HCQ continued on the drug or were in remission at five years.[15] Obviously, toxicity of DMARDs has not changed, but the shift from toxicity to inefficacy as the leading reason for discontinuation of the use of DMARDs most probably mirrors the altered attitude towards the treatment with DMARDs. During the period of few available DMARDs and prevailing prejudices against DMARDs regarded as toxic drugs some clinical RA activity was accepted if the patient tolerated the drug, while we have been taught to treat the patients to have "no signs of the disease".[16]

Although the number of the patients in the study was rather small, the results obtained further support our earlier findings that with careful monitoring continual and serial use of DMARDs is safe.[17]

The median duration of DMARD periods of individual DMARDs or COMBOs ranged from six to 18 months only. In contrast with earlier reports,[11 12 18] MTX did not stand out favourably from the other DMARDs, but rather seemed to be comparable. The result is in line with that obtained in a Dutch early RA patient cohort.[19] In accordance with other DMARDs, the major reason for MTX discontinuations in our series was inefficacy. Whether the diverging results depend on different patient choice (early compared with advanced RA), different dose of the drug (median 10 mg weekly compared with not reported), type of the study (prospective compared with retrospective), differences in the rank order of prescribed DMARDs, differences in the use of folic acid as a co-medication (our patients have used folic acid routinely from 1995), or possible different attitudes and expectations of the treating physicians remain to be shown. Our aim, according to the sawtooth strategy, was to treat the patients to clinical remission; in 70% of cases ineffective MTX was replaced by a COMBO including MTX.

Longlasting remission in RA is exceptional.[20] In our series remission (n=32) was obtained only during the three first DMARD periods. Consequently, most of the remissions were achieved with GST, HCQ, and SSZ. In 18 cases remission sustained for years. Our figure is in accordance with other early RA cohorts indicating that DMARD treatment can be terminated in 4-6% of early RA cases because of remission.[14 21] Some of these patients may have had a self remitting disease course, as 5–12% of patients have achieved remission also with placebo treatment.[22 23] On the other hand, remissions seen during the first DMARD periods may reflect a therapeutic window

during the early stages of disease. Furthermore, the results undisputably indicate that our present drugs to treat progressive RA are insufficient and more powerful treatments are badly needed. The place of COMBOs of presently available DMARDs in early RA remains to be shown, although preliminary results from the Netherlands and Finland seem promising.[24 25]

Funding: this study was supported by grants from Central Finland Health Care District and Kuopio University Hospital (EVO-funding), Finland.

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