Treatment of early RA in clinical practice: A comparative study of two different DMARD/corticosteroid options

B. Svensson[1], M. Ahlmén[2] and K. Forslind[1], for the BARFOT study group[#]

[1]Section of Rheumatology, Helsingborgs lasarett, Helsingborg, Sweden. [2]Section of Rheumatology, Sahlgrenska University Hospital, Mölndal, Sweden.

Abstract

Objectives

To study the outcome in clinical practice of first DMARD and/or corticosteroid (CS) treatment in patients with recent onset rheumatoid arthritis (RA).

Patients

245 patients with active RA, not previously treated with DMARDs or CS, were randomised to one of two treatment groups, T1 = 7.5 – 15 mg of prednisolone (PRE) daily for one to three months followed, if needed, by methotrexate (MTX) in a weekly dose of 5 - 15 mg in addition to the lowest possible dose of PRE or T2 = sulfasalazine (SAL), supplemented with lowest possible CS dose if needed.

Methods

The EULAR individual response criteria were applied and remission was defined as a final DAS28 < 2.6. Function was assessed by the HAQ and radiographic progression by Larsen scores. A patient who managed to remain on the allocated treatment for two years was described as a "completer".

Results

After 2 years of treatment, 70% of the patients in T1 and 63% in T2 were responders (30% and 33% "good responders", respectively). In T1 29% and in T2 19% were in remission. There was a significant functional improvement in both groups but radiographic progression occurred. The mean decrease in HAQ and increase in the Larsen score were similar in the two groups. One-third of the patients were non-completers, 19% from T1 and 47% from T2. Non-completers had, compared with completers, a significantly lower rate of individual response and remission. Completers and non-completers had similar functional improvement and similar radiological progression.

Conclusions

Individual response and remission was reduced in patients who did not complete their first DMARD/CS treatment option. Treatment failures were significantly more frequent in the sulfasalazine plus optional CS than in the CS plus optional methotrexate treatment group.

Key words

Outcome, early RA, DMARD treatment, corticosteroids, DAS28, EULAR response criteria, remission, HAQ, Larsen score.

Björn Svensson, MD PhD; Monica Ahlmén, MD PhD; and Kristina Forslind, MD.

#The Barfot study group: Monica Ahlmén, Johan Bratt, Kristina Forslind, Ingiäld Hafström, Catharina Keller, Ido Leden, Bengt Lindell, Ingemar Petersson, Christopher Schaufelberger, Björn Svensson, Annika Teleman and Jan Theander.

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Please address correspondence and reprint requests to: Associate Professor Björn Svensson, Blistorpsvägen 105, 290 38 Villands Vånga, Sweden.
E-mail: bjoern.svensson@swipnet.se

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Introduction

Rheumatoid arthritis (RA) is a potentially destructive joint disease of unknown cause. The course may be very varied and reliable predictors of outcome for use in the individual case are still largely lacking (1). It is generally agreed that the early years of the disease are the most critical as regards the development of joint destruction. Therefore, sustained suppression of the inflammatory process should be aimed at as early in the course of the disease as possible (2). Accordingly, there are studies indicating a worse outcome if therapy is delayed (3).

Even if therapy is instituted early, the results of most clinical trials show that a significant proportion of patients either do not tolerate or do not respond to disease modifying anti-rheumatic drugs (DMARDs) (2). Therefore, in order to improve outcome combination therapy with two or more "conventional" DMARDs or with TNFα-inhibitors have been tried. However, even if the number of non-responders may be decreased and intolerance does not seem to increase, treatment failures are still frequent. The termination rate is high with the most commonly used conventional DMARDs, due to toxicity and inefficacy in similar proportions (4). Furthermore, the risk of developing refractory disease increases with the number of DMARDs introduced to a particular patient and is already apparent after only a few treatment failures (5).

Sulfasalazine (SAL) and methotrexate (MTX) are today the most commonly used DMARDs (2) and recent studies have shown a similar efficacy of these drugs (6). The aims of this open, randomised study of patients with recent onset RA were to compare the individual response and remission after two year's treatment with two different options frequently used in clinical practice in Sweden, including SAL, MTX and corticosteroids (CS) and to study the number and nature of treatment failures. The patients are recruited from a long-term observational study on patients with early RA.

The BARFOT study

"BARFOT" (acronym for "Better Anti Rheumatic FarmacOTherapy") is a multi-centre programme for care and long-term follow up of patients with early RA in southern Sweden. The patients belong to five rheumatological units covering both urban and rural districts. As of autumn 2002, about 1800 patients have been included. Participating rheumatology units are second referrals with well developed contact nets with the primary health care units in the referral area. All available patients with a diagnosis of RA according to the 1987 revised ACR criteria (7) are included provided they are seen within one year of the first definite symptom or sign of synovitis suggestive of RA. A minority of the patients included at the earliest had a somewhat longer disease duration, in no case exceeding two years. The patients are followed up at predetermined intervals using a structured protocol with validated measures of disease activity, joint destruction, function and overall health.

The present study

Patients and treatment

During a three-year period (August 1992 until September 1995), 411 patients were included in the BARFOT programme. By the treating physician's judgment 359 of these were considered to be in need of DMARDs and/or CS. The patients had not previously been treated with such drugs. They were considered for participation in an open trial aiming at assessing the outcome after two years of two alternative first treatment options. 245 of those who were considered suitable for the study agreed to take part in the trial. The 114 patients not participating were for various medical or non-medical reasons regarded as not suitable or were unwilling to participate.

Each of the 245 patients was allocated to one of the two treatments, treatment group 1 or 2 (T1 or T2). Randomisation was performed by cluster. Thus, in some centres (departments) the eligible patients were given only T2 and in the other centres only T1 was given. In so doing neither the participating physician nor the patient could influence the treatment given (T1 or T2).

At the initiation of this study, SAL and

MTX were the DMARDs of choice in Sweden. Methotrexate was at that time still regarded as a drug associated with a significant risk of serious toxicity. Therefore, to assess the intensity of the inflammatory process and if possible avoid MTX in low active cases, low dose prednisolone was given initially and MTX was started only if this treatment failed and the maximal weekly dose was decided to be 15 mg. Thus, T1 medication comprised 7.5 – 15 mg of prednisolone (PRE) daily for one to three months, with subsequent reduction to the lowest possible dose. Optionally, PRE could be supplemented by methotrexate (MTX) in a weekly dose of 5 - 15 mg. T2 medication comprised sulfasalazine (SAL) 2-3 g daily. In addition, PRE up to 10 mg daily could be added if needed, with the intention of a gradual dose reduction.

A completer was defined as a patient who, during the two-year observation period, did not surrender the allocated treatment schedule because of inefficacy or intolerance. Non-completers were in most cases offered either some other DMARD and/or CS and were followed for two years in the same way as completers. Change of therapy was based on the treating physician's clinical judgement without access to the current DAS28 value. NSAIDs and analgesics were given as required. The patients were given physiotherapy and/or occupational therapy when needed.

Ethics: The study was judged by the ethics committee as being well within the accepted norms of clinical practice.

Clinical investigations

Depending on the routines of the participating centres, rheumatoid factor (RF) was measured either by a latex test, the sheep red cell agglutination test or an ELISA test.

Disease activity was assessed by the "Disease Activity Score (DAS)" (8), a validated composite index of inflammation integrating in a continuous variable the ESR, the number of swollen and the number of tender joints,and the patient's assessment of overall disease activity ("patient global health") on a 0-100 mm horizontal visual analogue scale (VAS). For patients assessed early in the study, their original DAS-values were transformed to DAS28 using a formula described by van Gestel *at al.* (9).

Disability was assessed by the validated Swedish version (10) of the Health Assessment Questionnaire (HAQ) (11).

Larsen scores were calculated (12) based on readings of posterior-anterior radiographs of the hands and forefeet. The radiographs were examined blindly and independently by two trained rheumatologists.

Individual response and remission

A patient was judged as a responder ("moderate" or "good") by the EULAR response criteria for RA (9) provided the DAS28 had reached a certain level of change from the study start in relation to the value attained. A decrease in DAS28 by more than 1.2 in combination with an end-point DAS28 of 3.2 or less defined a good responder. A moderate responder must either have decreased by more than 1.2 while having attained any DAS28 over 3.2 or have decreased by less than 1.2 but by more than 0.6 in combination with an end-point DAS28 not exceeding 5.1.

A patient was considered as being in remission if he/she had a DAS28 less than 2.6 after two years treatment (13).

Statistical methods

Statistics was performed using the SPSS software, 11.0. The Mann-Whitney and Kruskal-Wallis tests were used for between group comparisons, the Wilcoxon signed-ranks test for paired samples and the Chi-square test for differences between proportions. The differences in mean change in the Larsen and HAQ scores between groups were analysed by the independent samples T-test. Differences between treatment groups after two years were analysed according to intention to treat. Life tables have been constructed for comparison of the discontinuing rates of the treatment groups

Results

245 patients entered the study; 131 patients into treatment group 1 (T1) and 114 into treatment group 2 (T2). 221 patients (113 T1 and 108 T2 patients) remained for analysis since 18 patients in T1 and 6 in T2 were excluded for various reasons (Fig. 1).

96% of the patients had radiographs of the hands and feet taken at baseline. However, radiographs eligible for calculating Larsen scores were available in only 74% of the cases at baseline and in 70% at 2 years. To exclude selection bias, demographic and baseline data were compared between patients with and without baseline Larsen scores. As shown in Table I, no differences in these respects were detected.

Nineteen patients had a disease duration of more than 12 months, between 13 and 18 months in thirteen patients and between 19 and 24 in six patients. At follow-up after two years these patients had, compared with the group of patients with a disease duration of 12 months or less, similar values for the

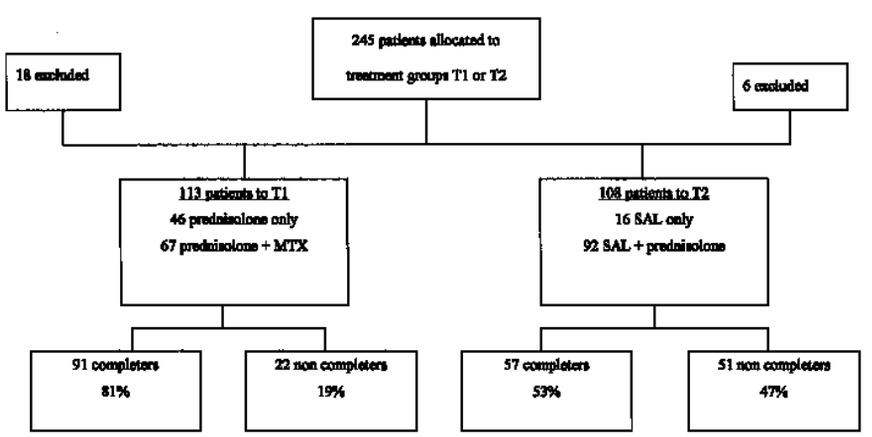

Fig 1. Flow chart showing the treatments given and the proportion of patients remaining on initial treatment after two years (completers).

Table I. Baseline characteristics in patients with and without radiographs eligible for calculating Larsen scores at two years.

	Baseline Larsen (N=163)	No baseline Larsen (N=58)	P-value
Age (median, min/max)	53 18/84	57 22/83	0.330
Disease duration (months) (median, min/max)	6 1/24	7 1/23	0.414
% women	61	69	0.265
% with rheumatoid factor	53	63	0.222
DAS28 (median, min/max)	4.9 2.4/8.3	5.0 3.0/10	0.373
HAQ (median, min/max)	0.9 0/2.3	0.9 0/2.7	0.117

frequency of remission (p = 0.180) and individual response (p = 0.095), and the median HAQ (p = 0.424) and median Larsen scores (p = 0.299).

Thirty-five patients were treated with CS only. At follow-up, this group of patients had a rate of remission and of individual response, median HAQ and Larsen scores similar to the group of patients ever treated with DMARDs with or without additional CS (p = 0.184, p = 0.368, p = 0.218 and p = 0.473, respectively).

Demographic and baseline clinical data (Table II)

At baseline, the patients had a median age of 54 years and median disease duration of six months. Sixty-three percent of the patients were women and 56% had RF. Ninety-two percent of the patients had a DAS28 above 3.2 indicating a high or moderate disease activity. The median HAQ score was 0.9 and the median Larsen score 4.0.

There were some differences in baseline characteristics between groups. Thus, the median Larsen score and the frequency of RF-positivity were significantly higher in T1 than in T2, and non-completers had compared with completers significantly higher baseline median DAS28 and HAQ.

Treatments (Fig.1, Table III).

Treatment group 1: In accordance with the protocol, prednisolone was started in all 113 T1 patients and in 67 cases (59%) MTX was added, in 40 within 3 months from the start.

91 of the 113 (81%) patients completed two years therapy while 22 (19%) abandoned the treatment option (non-completers) and were given some other DMARD, which in 10 cases was SAL. The reasons were drug intolerance in 13 cases, insufficient treatment effect in 8 and another reason in one case.

Treatment group 2: All 108 patients were started on SAL. In addition, 85% of the patients were also treated with prednisolone.

In this group 57 of the 108 (53%) patients were completers while 51 (47%) were non-completers. Forty-seven of these received some other DMARD, in 33 cases MTX. The reasons for premature termination were drug intolerance in 36 cases and insufficient treatment effect in 15.

Survival analysis

As shown in a life table (Fig. 2) there was a highly significant difference in survival times between the two treatments. Terminal events were defined as withdrawals due to adverse reactions or inefficacy (Table III).

Bringing the T1 and T2 groups into one, non-completers were found to be exposed to more months with DMARDs than completers (median 21 vs. 18 months, p = 0.016) while there was a non-significant difference as to accumulated prednisolone intake (3600 vs. 3370 mg, p = 0.425).

Outcome (Table IV)

After two years of treatment, the mean (SD) DAS28 had decreased from 5.10 (1.25) to 3.66 (1.37) (p < 0.0005). The percentage of patients with a DAS28 of 3.2 or more decreased from 92% to 54% and the proportion of patients with very high disease activity decreased from 44% at baseline to only 13% at the end of the study.

The proportion of patients in remission increased from 0.9% at baseline to 21%. Patients in remission had significantly lower baseline DAS28 (p < 0.0005) while baseline age, HAQ and Larsen scores were not significantly different from those in patients without remission (p = 0.583, 0.672 and 0.058 respectively).

After two years of treatment, a similar proportion of patients, 70% in T1 and 63% in T2, were classified as responders (30% and 33% "good responders", respectively). In T1 29% and in T2 19% were in remission (difference not significant). There was a significant

Table II. Baseline characteristics of participating patients by treatment groups and completer status.

	Count[o]	Treatment group 1 N = 113	Treatment group 2 N = 108	Δ P-value	Completers N = 148	Non-completers N = 73	Δ P-value
Age#	221	54 47/63	52 43/67	0.945	56 47/67	51 41/62	0.080
Disease duration (months)#	221	6 4/10	7 4/10	0.484	6 4/10	7 4/10	0.338
% women	221	59	67	0.257	59	71	0.072
% with rheumatoid factor	218	71	39	0.0005	60	47	0.062
DAS28 (0-10)#	216	5 4.2/5.9	4.9 4.5/5.8	0.937	4.9 4.2/5.7	5,4 4.6/6.0	0.006
HAQ (0-3)#	210	0.9 0.5/1.38	0.9 0.4/1.4	0.971	0,80 0.4/1.3	1.1 0.6/1.5	0.003
Baseline Larsen score (0-200)#	163	5 1.5/10	3 0/7.5	0.023	4.5 6/10	3 0/7	0.065

[o]Number of patients with valid values; #Median and 25th/75th percentiles given.

Table III. Reasons for premature termination from first treatment option and alternative DMARDs given.

	Treatment group 1 22 withdrawals	Treatment group 2 51 withdrawals
Adverse reactions	13	36
Inefficacy	8	15
Other reason	1	
Changed to other DMARD	22 (SAL in 10 cases)	47 (MTX in 33 cases)

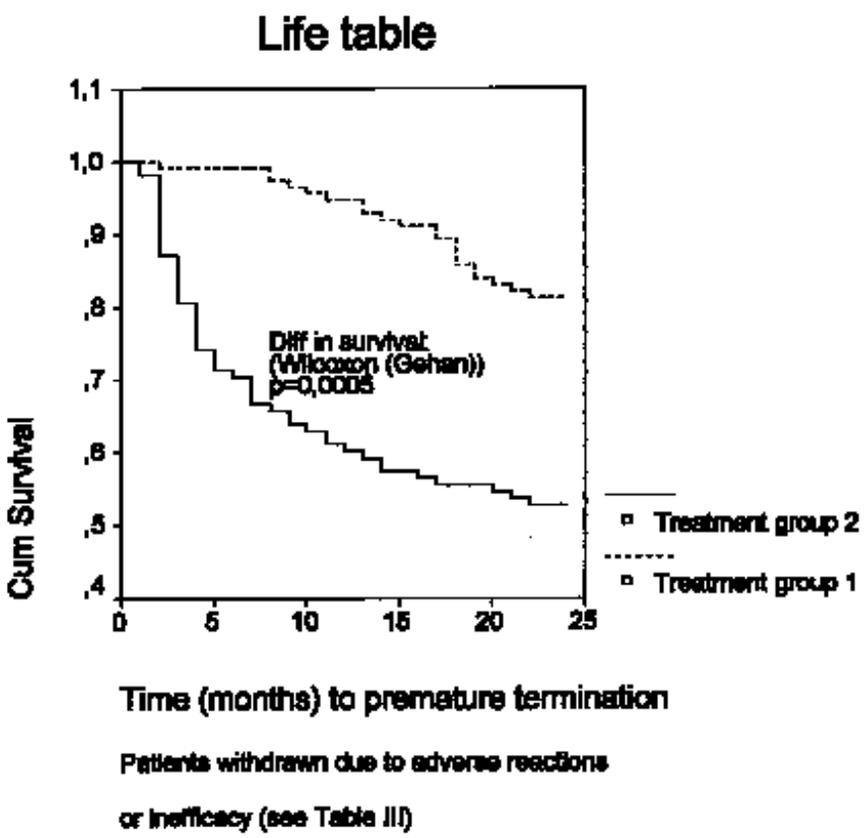

Fig 2. The figure shows a comparison of survival curves for the two different treatments. Terminal events were defined as withdrawals due to adverse reactions or inefficacy (Table III).

overall functional improvement ($p < 0.0005$) and radiographic progression ($p < 0.0005$). The mean change in HAQ and Larsen scores was similar in the two groups.

73 of the 221 patients (33%) did not continue their initial treatment option throughout the first two years, 19% from T1 and 47% from T2 ($p < 0.0005$) (Fig. 1). After two years non-completers had, compared with completers, a significantly lower rate of individual response (17% vs. 39% "good response", $p = 0.006$) and remission (14% vs. 28%, $p = 0.030$). Completers and non-completers showed similar functional improvement while non-completers tended to have a larger mean increase in the Larsen scores than completers (mean change 7.9 vs. 3.9, $p = 0.075$).

Discussion

The present study, performed in clinical practice, compared the effect of prednisolone plus optional MTX with SAL plus optional prednisolone. At treatment start the patients were considered by their physicians to have active disease, which was supported by a DAS28 above 3.2 in 92% of the patients. The overall results after two years of treatment as regards individual response and remission were similar to those of many recent clinical trials of DMARD mono- or combination therapy (e.g. 14-16).

No significant differences between the treatment groups as regards individual response, remission, function or radiological progression were detected by the intention to treat analysis after two years of treatment. This is probably mostly due to the fact that several patients withdrawing from treatment group 2 (T2) and some from treatment group 1 (T1) were changed over to MTX and SAL, respectively, making the two treatment groups very similar.

The dose of MTX, varying between 7.5 and 15 mg weekly, may today be regarded as rather low. However, this need not necessarily be the case, as is illustrated by a recent controlled study (17) on MTX using a fixed dose of only 10 mg/week (no folic acid supplementation) in 50 patients with active rheumatoid arthritis and a disease duration of less than two years. After 24 weeks all clinical variables reflecting disease activity including acute phase reactants were highly significantly improved.

Moreover, there were baseline differences between the two groups, further making the detection of differences in outcome difficult. Thus, T1 had a higher baseline median Larsen score and a higher frequency of rheumatoid factor positivity than T2, indicating more severe disease in T1. The reason for this disparity is difficult to understand. Age, sex distribution and disease duration were similar in the two groups. Furthermore, there were no group differences as far as regards smoking habits and physical work load, and the patients were recruited from similar geographic areas with comparable ethnicity and environmental factors (data not shown).

During the follow-up for two years as many as 47% of the patients in the SAL plus optional prednisolone treatment group (T2) withdrew and had to change to another DMARD. This is in agreement with a recent meta-analysis of termination rates in clinical trials and observational studies of the most commonly used DMARDs (4), which

Table IV. Outcome after treatment for two years.

	Treatment group 1 N=113	Treatment group 2 N=108	Difference between groups P-value	Completers N=148	Non-completers N=73	Difference between groups P-value
Good/moderate/no response[#]	30/40/30%	33/30/37%	0.319	39/29/32%	17/47/36%	0,006
Remission	29%	19%	0.095	28%	14%	0,030
Mean (SD) change in HAQ	-0.35 (0.61)	-0.38 (0.55)	0.752	0,35(0,57)	-0,38 (0,62)	0,727
Mean (SD) change in Larsen score[o]	6.2 (12.2)	4.1 (10.9)	0.298	3,9 (10,9)	7,9 (12,8)	0,075

[#]According to EULAR individual response criteria; [o]130 patients had x-rays both at baseline and after 2 years.

shows that less than 50% of patients given sulfasalazine remain on treatment after two years. Although many factors influence the choice of DMARDs, the high number of sulfasalazine withdrawals should be taken into consideration when selecting the initial DMARD treatment for the individual patient.

Importantly, only 19% of the patients allocated to the prednisolone plus optional MTX group (T1) withdrew. The above-mentioned meta-analysis found that about 60% of patients given MTX remained on treatment after two years. In the present study, starting with low dose corticosteroids and then adding MTX when needed was rewarded by an even higher completer rate of 81%. This treatment option thus seems attractive provided the side effects of corticosteroids can be adequately avoided and even more attractive should it be confirmed that corticosteroids do have a joint protective effect, as has been recently suggested (18, 19).

As mentioned, a number of patients do not tolerate or do not respond to their first treatment option and have to change DMARDs more or less often (4). Some of these treatment failures develop refractory disease (5) and should be identified early. It is, however, not easy to foresee patients who will become non-responders. In the present study the group of non-completers had higher baseline disease activity and more disability than completers, which may be an indication of more severe disease and risk of treatment failure. However, other markers of less favourable prognosis at baseline like radiological changes and RF positivity were similar in these two groups.

To conclude, this study in clinical practice of first DMARD/CS treatment of patients with recent onset RA has demonstrated similar rates of response and remission as in many recent drug trials. Response and remission was reduced in patients who did not complete their first DMARD/CS treatment and treatment failures were significantly more frequent in the SAL plus optional CS than in the CS plus optional MTX treatment group.

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