Z Rheumatol 62:155–160 (2003)
DOI 10.1007/s00393-003-0458-2

ORIGINAL CONTRIBUTION

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Termination of disease-modifying antirheumatic drugs in rheumatoid arthritis and in psoriatic arthritis.

A comparative study of 270 cases

Beendigung der Therapie mit langwirkenden Antirheumatika bei RA und Psoriasisarthritis. Ein Vergleich von 270 Fällen

Summary 102 rheumatoid arthritis (RA) and 104 psoriatic arthritis (PsA) patients' records were analysed according to a standardised protocol. Using Cox regression, life-table analysis and log rank test, the effectiveness and toxicity of, and duration of disease modifying antirheumatic drug (DMARD) treatment were compared in RA and PsA.

RA patients were treated with gold sodium thiomalate (GST), methotrexate (MTX) and sulphasalazine (SSZ) for a median duration of 35, 72 and 12 months respectively, whereas PsA patients were treated for 12, 12 and 17 months. The differences for GST and MTX were statistically significant ($p = 0.0043$ and 0.0447).

Drug toxicity was more frequently seen among patients with PsA ($p = 0.0023$).

No difference in efficacy could be proved. Results suggest that there is a significant difference between RA and PsA patients in terms of toxicity of these agents. Therefore, separate treatment strategies are needed, and earlier results with RA may not be directly applicable to PsA.

Received: 5. August 2002
Accepted: 16 October 2002

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Zusammenfassung Es wurden Daten von 102 RA und 104 PsA Patienten analysiert. Alle Patienten wurden mit Basismedikamenten behandelt. Cox Regression Analyse und Kaplan-Meier-Test wurden durchgeführt um die Zeitdauer und die Wirksamkeit der Basistherapie, sowie die Häufigkeit von Nebenwirkungen zwischen RA- und PsA-Patienten zu vergleichen.

RA Patienten erhielten GST, MTX und SSZ für 35, 72 und 12 Monate (Medianwerte), während die entsprechenden Daten für PsA-Patienten 12, 12 und 17 Monate waren. Signifikante Unterschiede ($p = 0.0043$ und $p = 0.0447$) wurden zwischen den beiden Krankengruppen für die Therapiedauer von GST und MTX beobachtet.

Arzneimitteltoxizität wurde bei PsA-Patienten signifikant häufiger dokumentiert ($p = 0.0023$).

Die Ergebnisse weisen darauf hin, dass die Wirksamkeit und die Verträglichkeit der Basismedikamente in den beiden Patientengruppen unterschiedlich sind. Es kann vermutet werden, dass die früheren Erfahrungen bei RA nicht direkterweise bei PsA verwendet werden können und für die Behandlung der psoriatischen Arthritis eine differente Therapieplanung erforderlich ist.

Key words Disease modifying antirheumatic drugs – rheumatoid arthritis – psoriatic arthritis – life table analysis

Schlüsselwörter DMARD – RA – Psoriasisarthritis – Basistherapie

Introduction

Rheumatoid arthritis (RA) and psoriatic arthritis (PsA) are both inflammatory disorders of the joints. Although there are many differences in the aetiology and pathogenesis of the two diseases, the same non-steroidal anti-inflammatory drugs (NSAIDs) and disease modifying antirheumatic drugs (DMARDs) are used in their treatment (14). As soon as it is clear that the arthritis is going to be persistent, DMARDs should be considered. In case DMARDs are to alter the natural history of the chronic disease, an essential prerequisite is the maintenance of the therapeutic effect over a long period.

In contrast to the extensive published experiences with DMARDs in RA (2, 5, 7, 10, 12, 20–22, 24, 26, 28), there have been only a few reports in PsA requiring more than the NSAID treatment (6, 8, 9, 11, 13, 16–19, 23, 25). Intramuscular gold compounds (23), methotrexate (8) and sulphasalazine (6, 9, 11, 17) are accepted treatments for PsA. During long-term treatment of PsA, the clinician faces difficulties which are not present in RA, such as the relative heterogeneity of disease, the high loss of the patients during the follow-up, and the frequent dermatological side effects of the drugs.

The main objective of our study was to examine how long patients remain on the different DMARD therapies in each disease, to note any differences in the reasons of the treatment interruptions, and to observe whether the most frequently applied DMARDs maintain the same effectiveness and toxicity in PsA as in RA.

Patients and methods

In the National Institute of Rheumatology and Physiotherapy a Centre for Psoriatic Arthritis Patients was established in 1985. Medical records of all patients with PsA attending the clinic between 1985 and 1999 were reviewed. Data were obtained on all 104 PsA patients with peripheral arthritis (54 men, and 50 women, mean age at the disease onset: 51.5 years) who were treated with GSM, MTX or SSZ. All of these patients satisfied the Moll and Wright criteria for PsA. Patients were included in this study more than once if they received more than one DMARD treatment. The 104 PsA patients received GST treatment in 40, MTX treatment in 63, and SSZ treatment in 44 cases. Those who were lost during the follow-up were omitted. Patients were not randomly allocated to the therapies; indication for which drug therapy was used, and the causes of withdrawal depended on the physician's judgement.

The RA group consisted of 102 patients, diagnosed according to the American Rheumatism Association 1987 revised criteria. Of the 102 RA patients, there were 7 men, and 95 women, 10 of them were seronegative. Their mean age at the onset of the disease was 55.7 years. The 102 patients received GST treatment in 61, MTX in 43 and SSZ in 19 cases.

We have reviewed the documentation of the patients according to a standardised protocol. Data were collected on the patients' age at the beginning of the disease and the interval between the onset of the disease and the start of the DMARD treatment. Duration of DMARD treatment was determined, as was the cause of withdrawal.

All patients on DMARD were taking concurrent non-steroidal anti-inflammatory drugs and some of them also received systemic corticosteroids. None of them received a combination therapy.

The GST was started with a test dose of 10 mg, and 20 mg, followed by 50 mg intramuscularly for 20 weeks. Then, depending on the clinical response, it was gradually tapered to monthly injections. After 5000 mg cumulative dose, injections were given bimonthly. Oral MTX was started at 7.5 mg once a week. The dosage was increased or lowered as seemed clinically appropriate. The mean dosage of the MTX was 8.35 (5–15) mg. The dose schedule of the SSZ consisted of a starting dose of 500 mg/day, which was increased weekly by 500 mg to a standard dose of 2000 mg/day. In case of mild adverse reactions, the dose was reduced to 1500 or 1000 mg/day, while in cases of lack of efficacy, the dose was increased up to 3000 mg/day.

The statistical analysis was performed using a cumulative survival analysis of termination (Kaplan-Meier test) and a test of comparison between survival curves (log rank test). With the group statistics we used T test for equality of means. Cox regression was used three times: the first time defining the discontinuation for any reason, the second time defining the event as discontinuation because of inefficacy, the third time because of toxicity. All statistical tests were performed using the SPSS statistical software.

Results

Overall 270 treatment courses were evaluated in this study. Table 1 presents the distribution of PsA patients according to the Moll and Wright classification.

The life-table analysis shows a median survival of treatment time of 30 ± 2.0 months in RA and 12.0 ± 2.0 in PsA when all three DMARDs were studied

Table 1 Pattern of arthritis according to the Moll and Wright classification

	MTX	SSZ	GST
Number of patients	63	44	40
Oligoarticular	18	17	7
RA like	24	16	22
DIP predominance	7	4	4
Ankylosing spondylitis with peripheral arthritis	6	6	2
Arthritis mutilans	8	1	5

GST gold sodium thiomalate, *MTX* methotrexate, *SSZ* sulphasalazine

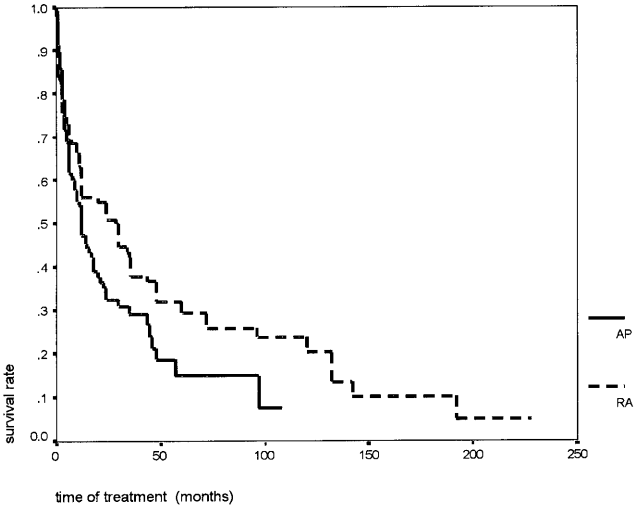

Fig. 1 Cumulative survival curves of the DMARD treatments of our RA and PsA patients. Comparison of 270 cases (*RA* rheumatoid arthritis; *PsA* psoriatic arthritis; *DMARD* disease modifying antirheumatic drugs; p = 0.01)

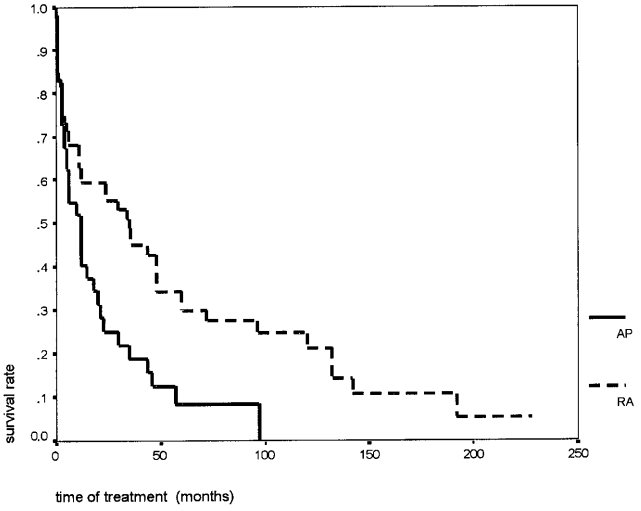

Fig. 2 Cumulative survival curves of GST treatments in 61 RA and 40 PsA patients (*RA* rheumatoid arthritis; *PsA* psoriatic arthritis; *GST* gold sodium thiomalate; p = 0.0043)

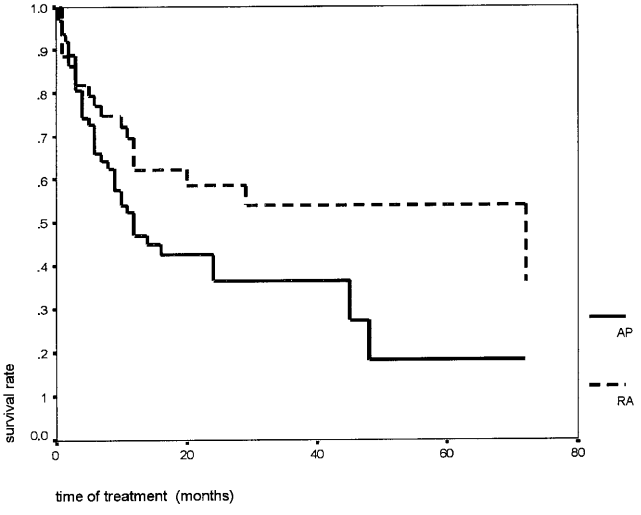

Fig. 3 Cumulative survival curves of MTX treatments in 43 RA and 63 PsA patients (*RA* rheumatoid arthritis; *PsA* psoriatic arthritis; *MTX* metothrexate; p = 0.0447)

together. The log rank test showed a significant difference (p = 0.01) between the two curves (Fig. 1). Examining the different DMARDs independently, the median GST treatment time in RA was 35 ± 7.9 months, while in PsA it was 12.0 ± 2.5 months. The curves of GST treatment differed statistically (Fig. 2) (p = 0.0043). The median MTX treatment time in RA was 72 ± 1.8 months, while in PsA it was 12.0 ± 3.1 months (Fig. 3) (p = 0.0447). No statistically significant difference was found in the SSZ treatment times: in RA 12 ± 1.8 and in PsA 17 ± 2.5 months (p = 0.3651): (Fig. 4). How long a patient remained on DMARD therapy, depended only on the diagnosis calculated by Cox regression (p = 0.0034).

Due to inefficacy, 27 RA and 22 PsA patients interrupted DMARD treatment. This difference was not significant. Analysing all interruptions due to toxicity, significantly more toxic events occurred in the PsA group (69), than among the RA patients (36), (p = 0.0023). Likewise, significantly more interruptions were found during the GST and MTX treatment in the PsA group (p = 0.007 and 0.018) by the log rank test, while there was no statistical difference between the two SSZ treated groups. Details of the side effects leading to cessation of therapy are shown in Table 2. The leading toxicity of the GST treatment was dermatological disorder in both diseases, but due to rash, dermatitis and psoriasis flare-up significantly more interruptions were made in the PsA group (p = 0.02). Four PsA patients stopped the GST treatment due to psoriasis flare.

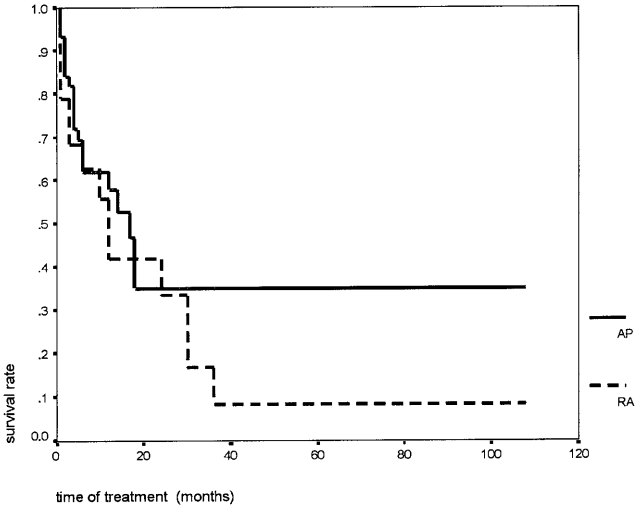

Fig. 4 Cumulative survival curves of SSZ treatments in 19 RA and 44 PsA patients (*RA* rheumatoid arthritis; *PsA* psoriatic arthritis; *SSZ* sulphasalazine; p = 0.3651)

The MTX treatment was more frequently interrupted in the PsA group than in the RA group (p = 0.018). The most common cause of withdrawal from the MTX therapy was elevation of transaminases in PsA patients (p = 0.018), and infection in RA patients (p = 0.939).

Interruption of the therapy due to complete remission occurred in 5 RA and in 2 PsA patients treated with GST. Four PsA patients treated with SSZ were able to stop treatment due to complete remission; 1 RA and 1 PsA patient was withdrawn from the MTX therapy due to clinical remission. There was no difference regarding the number of interruptions due to lack of compliance between the groups.

Discussion

While many investigators studied the underlying mechanism of inflammation and the mode of action of DMARDs in RA (3), little is known about their mechanism in PsA. The different causative factors and pathogenesis of the two diseases may require different modes of action, and may result in different efficacy, side effects rate, and remission rates.

Relatively few clinical trials on treatment are available for this condition (15, 19, 27). Often management is extrapolated from trials in RA, but there is evidence in the literature suggesting that this may not be appropriate (4).

The results of Wolfe's 14 year long study indicate that half of all RA patients receiving gold, hydroxychloroquine or penicillamine will discontinue such therapy within two years after the start of it (29). These observations suggest that most DMARD therapy is, at practical level, an insufficient treatment for RA.

In the life-table analyses of PsA patients Gomez-Vaquero et al. demonstrated a median survival time of 6 months for gold, and SSZ, and 16 months for MTX (15). In this study the median drug treatment's survival time was 30.0 months in RA and 12.0 months in PsA, which is certainly not sufficient for a long-term, disease modifying effect in either chronic disease.

Our data suggest that PsA patients are taking DMARD therapy for a considerably shorter time than RA patients. According to our results this significant difference arises from the different toxicity profile of DMARDs in the two diseases. No differences were seen among the frequency of interruptions due to inefficacy or lack of compliance.

Table 2 Causes of therapy discontinuation [1]

	RA				PsA			
	GST	MTX	SSZ	Total	GST	MTX	SSZ	Total
Treatment present	15	23	5	34.9%	3	21	10	23.1%
Remission	5	1	0	4.8%	2	1	4	4.7%
Withdrawal due to inefficacy	16	3	8	21.9%	7	4	11	14.9%
Withdrawal due to other reasons	3	5	3	8.9%	3	7	5	10.2%
Withdrawal due to toxicity total	**22**	**11**	**3**	**29.2%*****	**25**	**30**	**14**	**46.9%** ***
Rash, dermatitis	9*	0	1	8.13%	14*	0	3	11.56
Increased transaminases	5	2**	0	5.69%*	0	13**	4	11.56*
Infection	0	4	0	3.25%	0	6	0	4.08%
Haematological disorders	3	0	0	2.4%	5	5	0	6.8%
Gastrointestinal discomfort	1	2	2	4.06%	0	3	6	6.12%
Hematuria/proteinuria	3	0	0	2.4%	6	0	0	4.08%
Malignancy	0	0	0	0%	0	1	0	0.6%
Others	1	3	0	3.25%	0	2	1	2.04%

RA rheumatoid arthritis; *PsA* psoriatic arthritis; *GST* gold sodium thiomalate, *MTX* methotrexate, *SSZ* sulphasalazine; [1] Values are given as actual number of patients, as otherwise indicated; p *< 0.05; **< 0.01; ***< 0.001 (determined by t test)

In all treatment groups, interruption due to toxicity was more common among PsA patients. The higher frequency of dermatological disorders in GST treated patients can be attributed to a pronounced skin sensitivity related to the underlying disorder. Significant differences were found in the rate of interruptions due to elevated liver enzymes during the MTX treatment. It is known that 6–64% of psoriatic patients not taking MTX have mildly abnormal liver histology presumably attributed to the underlying disease or other unrelated risk factors, such as obesity and excessive alcohol intake (1). This fact may be implicated in the genesis of common liver enzyme elevation.

We recognise several limitations of this study. Duration of treatment is determined by the balance between the severity of disease and risk/benefit ratio of the drug – therefore, life-table analysis is an indirect method for comparing the efficacy and toxicity of different drugs. The life-table analysis undertook only one datapoint to measure effectiveness, namely how long the patients remain on the drug. It is important to recognise that while therapy discontinuation means that it is either ineffective or causes adverse effects, continuing it does not necessarily mean that it is beneficial.

The great number of GST treated RA and PsA patients is unusual in European studies. This is a result of the fact that the Psoriatic Arthritic Clinic was established more than fifteen years ago, when MTX and SSZ were not available in Hungary. Since then MTX has become more frequently used in both patient groups, and the average weekly dosage is currently much higher. Subgroup analyses in PsA were not possible because of the relatively small number of patients in each group.

This study provides a comprehensive overview of the causes to terminate DMARDs in PsA and RA. We have found that DMARD treatment times in RA are superior to PsA. The significant difference found in the life-table analysis suggests that the toxicity of the examined DMARDs is different. This is especially true for the GST treatment. The much more frequent interruption of DMARD treatment due to adverse effects in PsA patients supports the hypothesis that, owing to the considerable differences in the pathogenesis of these two diseases, the traditionally used treatment strategies in RA are not directly applicable to PsA patients.

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