The Dynamics of Radiological Changes in Early Rheumatoid Arthritis Patients Treated with Methotrexate or Sulphasalazine

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The aim of the study was to determine the frequency of radiological changes (RC) in the treatment of early rheumatoid arthritis (RA) with methotrexate (MTX) or sulphasalazine (SSZ). Two groups of early (no more than 3 years) RA patients not treated with disease modifying antirheumatics drugs (DMARD) were treated and evaluated for one year. MTX (7.5–15 mg/week) was prescribed for 12 patients and SSZ (2.0 g/day) for 17 patients. In addition to DMARD, all patients were given nonsteroidal antiinflammatory drugs (NSAIDs). The majority of patients used corticosteroids (no more than 10 mg/day). A significant decrease in disease activity was observed in both groups after 6 weeks of treatment. Radiological changes (joint space narrowing and single erosions) in 20 hand joints were found in 69 percent of patients. After one year of treatment new erosions appeared in 4 patients (one patient treated with MTX and 3 treated with SSZ). The index for damaged joints (DS) slightly increased in both groups, however, there was no statistically significant worsening of RC. Admitting that the number of patients was small, we still assert that when patients with rheumatoid arthritis are treated early there is a possibility to stop the progression of RC.

Key words: rheumatoid arthritis, methotrexate, sulphasalazine, radiological changes

INTRODUCTION

There is no generally accepted view on the time of appearance and rate of progression of radiological changes (RC) in rheumatoid arthritis (RA) patients. Some investigators (1, 2) say that RC (joint space narrowing and erosions) appears during the first 3 years of the disease in 67–70% of RA patients, while others (3) indicate that it occurs in 38% of patients. There are also data that RC has slow progression in those patients where disease activity has been reduced by using disease modifying antirheumatic drugs (4, 5). Certain trials have shown that if RA was treated early when there were no erosions, the progression of RC was much slower than in those who began treatment with DMARD when erosions were already present (6).

Data on the effects of disease-modifying drugs on RC are contradictory. Some authors assert that early treatment with methotrexate (MTX) will stop the progression of RC (7) more than sulphasalazine (SSZ) (8), but the effect of cyclosporin A (9) or gold salts (10) on progression are the same as of MTX. Other authors however say that gold salts (11), or D-penicillamine (12) do not stop the progression of RC. Nevertheless, there exists a view that a beneficial effect can be achieved with SSZ (5). Much data exist in the literature indicating that better results in stopping progression of RC are obtained when intensive or combined therapy is applied (13–15).

We investigated RC progression in early RA patients treated with MTX or SSZ for one year.

MATERIALS AND METHODS

Participants of our study included 42 RA patients (disease being present up to 3 years) treated earlier with non steroidal anti-inflammatory drugs (NSAIDs) and intermittently with corticosteroids (CS). The majority (39 patients) began treatment for their disease at the Vilnius University Red Cross Hospital's Department of Rheumatology. RA was diagnosed using American Rheumatology Association criteria.

The first group (20 patients) was treated with MTX (7.5–15.0 mg per week), the second group (22 patients) received SSZ (beginning from 1.0 g per day and later up to 2.0 g per day). All the patients used NSAIDs. Ten patients in the MTX group and 16 patients in the SSZ group were prescribed CS (5–10 mg per day) at the start of treatment. Nine patients of the MTX group and 5 patients of the SSZ group used CS over the whole year without interruption. The dynamics of observation is presented in Table 1.

Table 1. **Dynamics of observation**				
Patient groups	No. of patients at the beginning of observation	No. of patients observed for one year	No. of patients dropped out of the study	No. of patients discontinued due to side effects
Treated with methotrexate	20	12	8	4
Treated with sulfasalazine	22	17	5	4
Total	42	29	13	8

Thirteen patients (8 from the MTX group and 5 from the SSZ group) participated in the study for less than one year. In 8 patients (4 from each group) the treatment was discontinued due to side effects. The remaining 5 patients failed to appear for follow up.

There were 12 patients (6 men, average age 61.1 ± 8.1 years, and 6 females, average age 53.2 ± ± 4.1 years treated with MTX for one year. The average duration of the disease in those patients was 14.0 ± 3.6 months. In the SSZ group 17 patients (4 men, average age 62.5 ± 8.3 years, and 13 females, average age 49.2 ± 4.6 years) were treated with SSZ for one year. The average duration of the disease in this group of patients was 15.3 ± 2.7 months.

In order to be able to evaluate the effectiveness of the treatment, special Case Report Forms were used, which were completed for every patient at the start of treatment, after 6 weeks, and after 1 year. The data recorded included the number of tender joints, the number of swollen joints, Richie index, visual pain scale (10 cm), patient 's global assessment of disease activity, duration of morning stiffness, and grip strength. Laboratory tests included general blood and urine analysis, C-reactive protein, rheumatoid factor, proteinogram, blood clotting indicators, general bilirubin, SGOT, SGPT, alkaline phosphatase, blood urea and creatinine.

The disease activity score (DAS) was calculated using the EULAR methodology (16) according to the formula:

$$DAS = 0.555 \sqrt{(28 \text{ tender joints})} + $$

$$+ 0.284 \sqrt{(28 \text{ swollen joints}} + 0.7 \ln (ESR) + 0.0142$$

(patient's global assessment).

X-rays were taken before treatment with MTX or SSZ and at the end of the year's treatment. RC was evaluated using the A. Larsen and J. Thoen methodology (17) by a blind method (the RC-evaluating doctor did not know about the method of treatment and X-ray sequence). According to this methodology, first the number of joints with erosion was recorded and referred to as erosion score (ES) ranging from 0 to 20. Secondly, each joint was graded on a 0–5 point scale focusing on erosions, joint space narrowing, periarticular osteoporosis and soft tissue swelling, and the individual gradings were summed to form a score refferred to as Damage Score (DS) with a range from 0 to 100.

The effectiveness of treatment was evaluated using t tests, correlations.The sensitivity to a change of each measure was computed as effect size (EFS), a standardized measure of change in a group using the methodology of L. E. Kazis et al. (18). According to this methodology, a positive EFS of 0.25 or greater was interpreted as representing improvement in health status, while a negative EFS –0.25 or less indicated disease progression.

RESULTS

Clinical data on patients that used MTX are presented in Table 2. A review of the clinical parameters showed that after the first six weeks of treatment there were reductions in DAS ($p < 0.05$, EFS = 2.0), Ritchie index (EFS = 1.3), average duration of morning stiffness (EFS = 1.4), average intensity of pain (EFS = 1.3), and there was an increase in grip strength: EFS = 2.9 of the right and EFS = 2.5 of the left hand. Statistically significant changes ($p < 0.05$) of Ritchie index, average duration of morning stiffness, average intensity of pain and grip strength occurred after only one year.

Table 2. **Dynamics of clinical parameters for methotrexate-treated patients**

Observation time	DAS	Ritchie index	Average duration of morning stiffness (min)	Average intensity of pain (10 cm scale)	Grip strength (kPa)	
					right hand	left hand
Before treatment	5.4 ± 0.3	11.2 ± 2.5	107.3 ± 39.1	4.7 ± 0.6	29.1 ± 3.7	19.6 ± 3.5
After 6 weeks	4.8 ± 0.1*	8.0 ± 1.8	52.7 ± 15.1	3.9 ± 0.6	34.2 ± 4.8	30.1 ± 4.5
After 1 year	4.0 ± 0.3**	5.4 ± 1.3*	29.1 ± 11.3*	3.1 ± 0.4*	43.6 ± 4.2*	44.2 ± 5.9*

* Compared with index before treatment, $p < 0.05$;
** Compared with index after 6 weeks, $p < 0.05$.

Clinical data on patients that used SSZ are presented in Table 3. A review of the clinical parameters showed that after the first 6 weeks of treatment there were a reductions in DAS ($p < 0.05$, EF = = 2.8), Ritchie index (EFS = 1.7), average intensity of pain ($p < 0.05$, EF = 5.5), average duration of morning stiffness ($p < 0.05$, EF = 3.1) and an increase in grip strength: EFS = 2.9 of the right and EFS = 2.5 of the left hand. Statistically significant changes ($p < 0.05$) of Ritchie index and grip strength appeared after only one year.

While evaluating RC before treatment, a few erosions were established in 9 (31.0%) patients: in 3 (25.0%) of the MTX and in 6 (35.3%) of SSZ group. The average of ES before treatment was 0.4 ± 0.9 in MTX group and 0.7 ± 1.5 in SSZ group. There was a weak correlation of ES with disease activity (correlation coefficient 0.4). Joint space narrowing was established in 20 (69.0%) patients: in 9 (75%) of MTX and 11 (64.7%) of SSZ group (in all those 20 patients erosions were found). The average DS before treatment was 17.6 ± 6.8 in MTX group and 18.5 ± 4.8 in SSZ group.

New erosions after one year of treatment with MTX appeared only in one patient. This patient had no disease relapse during one year. Treatment with MTX was effective evaluating clinical parameters and DAS. A reduction in the activity of the disease (according to DAS dynamics) was not successful in four patients of this group. Nevertheless these patients and their doctors positively evaluated the treatment with MTX. Three patients in this group experienced a relapse of RA which also required hospitalisation. However, treatment was continued with MTX but at a higher dosage. The average DS after 1 year of treatment with MTX increased from 17.6 ± 6.8 to 18.5 ± 4.8. No essential worsening was evident from the evaluation of DS according to EFS.

Table 3. **Dynamics of clinical parameters for sulphasalazine treated patients**

Observation time	DAS	Ritchie index	Average duration of morning stiffness (min)	Average intensity of pain (10 cm scale)	Grip strength (kPa)	
					right hand	left hand
Before treatment	5.2 ± 0.2	9.3 ± 1.8	140.9 ± 26.3	6.1 ± 0.4	25.9 ± 3.8	27.8 ± 3.9
After 6 weeks	4.1 ± 0.3*	6.3 ± 1.4	60.6 ± 16.0*	3.9 ± 0.6*	37.3 ± 3.9	39.6 ± 4.7
After 1 year	3.6 ± 0.2*	4.4 ± 1.1*	30.6 ± 14.2*	2.7 ± 0.5*	45.7 ± 3.7*	45.3 ± 4.0*

* Compared with the index before treatment, $p < 0.05$.

Table 4. **Dynamics of radiological changes in patients treated with methotrexate or sulphasalasine for one year**

Patient groups	No. of patients with erosions		Average erosion score (ES)		Average damage score (DS)	
	before treatment	after treatment	before treatment	after treatment	before treatment	after treatment
Treated with methotrexate	3 (25.0%)	4 (33.3 %)	0.4 ± 0.9	0.5 ± 0.9	17.6 ± 6.8	18.5 ± 4.8
Treated with sulphasalazine	6 (35.3%)	8 (47.1 %)	0.7 ± 1.5	0.9 ± 1.5	18.5 ± 6.4	18.8 ± 6.2
Total	9 (31.0 %)	12 (41.4 %)	0.6 ± 1.1	0.7 ± 1.0	18.1 ± 6.1	18.7 ± 5.2

New erosions after one year of treatment with SSX appeared in three patients: in two patients erosions were established for the first time, in one patient the number of erosions increased. In the remaining five patients in whom erosions were found before the treatment, the number of erosions after one year of treatment did not change. The average DS after one year of treatment with SSZ increased from 18.5 ± 6.4 to 18.8 ± 6.2 (EFS = –0.05). According to DAS dynamics, essential disease activity did not appear in six patients from this group. However, both the patients and their doctors had a favorourable evaluation of this treatment. No relapses were experienced in the SSZ group which required hospitalisation.

DISCUSSION

Our data suggest that in RA patients never treated with disease-modifying antirheumatic drugs, erosions and joint space narrowing appear in the majority (69.0%) of cases during the first 2–3 years of the disease. The appearance of RC has a weak correlation with disease activity. Our data support the findings of other investigators who suggest that erosions and joint space narrowing appear during the first 2 to 3 years of the disease in 67–70% of patients (1, 2).

After 6 weeks of treatment with disease modifying antirheumatic drugs it was possible for us to reduce the level of disease activity. However, neither in the MTX or SSZ group were we able to stop or reduce the progression of erosions and DS. Of course, these data can only suggest a tendency, because the effect did not support a worsening of ES and DS.

Our data did support the hypothesis that erosions more frequently progress in those patients who already had erosions before the treatment with disease-modifying antirheumatic drugs. In our patient groups we found erosions in only 9 patients and we saw the progression of erosions in only one patient.

Cautiously evaluating our data which were based on a comparatively small number of patients, we would like to state that if treatment with MTX or SSZ starts early and a favorable result occurs in reducing the disease activity, then there is a grounded possibility of stopping the progression of RC. This is also suggested by other investigators (4–7).

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RADIOLOGINIŲ PAKITIMŲ DINAMIKA, GYDANT METOTREKSATU ARBA SULFASALAZINU LIGONIUS SERGANČIUS ANKSTYVU REUMATOIDINIU ARTRITU

S a n t r a u k a

Iki šiol nėra vieningos nuomonės, kada prasideda radiologiniai pokyčiai ligoniams, susirgusiems reumatoidiniu artritu, koks šių pokyčių progresavimo greitis ir kokia gydymo įtaka šiam progresavimui.

Mūsų darbo tikslas buvo nustatyti radiologinio progresavimo dažnį vienerius metus gydant ankstyvąjį reumatoidinį artritą metotreksatu arba sulfasalazinu. Dvi grupės pacientų, sergančiųjų ankstyvu (iki 3 metų) reumatoidiniu artritu, anksčiau negydytų ligą modifikuojančiais vaistais, buvo gydomos ir kliniškai stebimos vienerius metus. Metotreksatą (7,5–15 mg/sav.) vartojo 12 pacientų, sulfasalaziną (2,0 g per parą) – 17 pacientų. Kartu dauguma pacientų vartojo kortikosteroidus ir visi – nesteroidinius vaistus nuo uždegimo. Po pirmųjų 6 savaičių abiejose grupėse statistiškai patikimai sumažėjo ligos aktyvumas. Radiologiniai pokyčiai (sąnarių tarpų susiaurėjimas ir pavienės erozijos) plaštakose (20-yje sąnarių) prieš gydymą buvo nustatyti 69,0% pacientų. Po vienerių gydymo metų naujos erozijos atsirado 4 pacientams: 1 pacientui, gydytam metotreksatu, ir 3 – gydytiems sulfasalazinu. Radiologinis sąnarių pakenkimo indeksas (DS) šiek tiek padidėjo abiejose grupėse, tačiau esminio, statistiškai patikimo radiologinių pakitimų pablogėjimo nenustatėme.

Atsargiai vertindami gautus duomenis dėl nedidelio ligonių skaičiaus galime teigti, kad reumatoidinį artritą anksti pradėjus gydyti metotreksatu arba sulfasalazinu, išvengiama ryškaus radiologinių pokyčių progresavimo.

Raktažodžiai: reumatoidinis artritas, metotreksatas, sulfasalazinas, radiologiniai pokyčiai