Real-life experience of using conventional disease-modifying anti-rheumatic drugs (DMARDs) in psoriatic arthritis (PsA). Retrospective analysis of the efficacy of methotrexate, sulfasalazine, and leflunomide in PsA in comparison to spondyloarthritides other than PsA and literature review of the use of conventional DMARDs in PsA

Euthalia Roussou, Aicha Bouraoui

Abstract

Objective: With the aim of assessing the response to treatment with conventional disease-modifying anti-rheumatic drugs (DMARDs) used in patients with psoriatic arthritis (PsA), data on methotrexate, sulfasalazine (SSZ), and leflunomide were analyzed from baseline and subsequent follow-up (FU) questionnaires completed by patients with either PsA or other spondyloarthritides (SpAs).

Material and Methods: A single-center real-life retrospective analysis was performed by obtaining clinical data via questionnaires administered before and after treatment. The indices used were erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Function Index (BASFI), wellbeing (WB), and treatment effect (TxE). The indices measured at baseline were compared with those measured on one occasion in a FU visit at least 1 year later.

Results: A total of 73 patients, 51 with PsA (mean age 49.8±12.8 years; male-to-female ratio [M:F]=18:33) and 22 with other SpAs (mean age 50.6±16 years; M:F=2:20), were studied. BASDAI, BASFI, and WB displayed consistent improvements during FU assessments in both PsA patients and controls in comparison to baseline values. SSZ exhibited better efficacy as confirmed by TxE in both PsA patients and controls. ESR and CRP displayed no differences in either the PsA or the SpA group between the cases before and after treatment.

Conclusion: Real-life retrospective analysis of three DMARDs used in PsA (and SpAs other than PsA) demonstrated that all three DMARDs that were used brought about improvements in BASDAI, BASFI, TxE, and WB. However, the greatest improvements at FU were seen with SSZ use in both PsA and control cohorts.

Keywords: Psoriatic arthritis, methotrexate, sulfasalazine, leflunomide, spondyloarthritis, literature review

Introduction

Patients with active psoriatic arthritis (PsA) with the potential for a poor prognosis should be started on a disease-modifying anti-rheumatic drug (DMARD). This recommendation is in accordance with the recommendations of the European League Against Rheumatism (EULAR) for the management of PsA published in 2012 (1).

However, there is limited evidence from randomized controlled trials (RCTs) in support of this recommendation (2). Among commonly used DMARDs, data in support of the use of leflunomide (LFN) originate from a very well-designed multicenter RCT, which showed the superiority of LFN versus placebo in patients with PsA (3). Despite its use as a first-line DMARD, data on methotrexate (MTX) have been questioned following a recent report from a multicenter UK RCT (4). Data in support of the use of sulfasalazine (SSZ) at a dosage of 2-3 g/day are derived from six RCTs that took place two decades ago during the period between 1990 to 1996 (5-10).

In this study, we aimed to compare the therapeutic efficacy of these three DMARDs in PsA patients versus patients with other non-PsA spondyloarthritides (SpAs), who were used as controls. From our overall...
patient population, we selected patients who had one or other disease type and had been treated with MTX, SSZ, or LFN for at least 1 year.

Material and Methods

Clinical setting and methodology

Patients with PsA who met the Classification Criteria for Psoriatic Arthritis (CASPAR) (11), following informed consent, were added to a registry of SpAs running in north-east London since 2004, which is named the London Registry of Spondyloarthropathies (LoRoS). This registry contains baseline and follow-up data on patients with SpA. SpA was defined according to the Assessment of Spondyloarthritides International Society (ASAS) criteria for axial (12) and peripheral (13) disease, which were applied retrospectively, as the initial data collection was carried out according to previous criteria for SpAs. Specifically in the case of PsA patients, however, the CASPAR criteria were consistently used.

Patients were on standard treatment instituted by the treating physician according to the National Health Service (NHS) protocol and the National Institute for Health and Care Excellence (NICE) guidelines. The standard dose of SSZ was 2 g/day. The dose of MTX was up to 25 mg/week, depending on the patient’s tolerance. The dose of LFN used was 20 mg/day.

The analysis was undertaken on data provided by the patients at baseline (a point prior to starting any DMARDs and as close as possible to the patients’ initial clinical assessment) and on data provided at a subsequent assessment(s), which took place 1 year from baseline.

Patient selection: Retrospective analysis

The study was retrospective. The analysis of this particular cohort was begun by identifying patients on DMARDs from the longitudinal cohort. By longitudinal, we refer to serial assessments following baseline data. Patients who had provided data following the initiation of DMARD therapy on at least one occasion in the longitudinal database were identified, and these data were compared with those obtained at baseline. In instances where patients had provided data on multiple occasions after the initiation of DMARDs, we used the data from the time visit that was closest in time to 1 year from the baseline assessment, i.e., the first follow-up assessment.

Patient referral

Patients are usually referred to our services by local general practitioners, consultants from other specialties within hospitals, and the local Musculoskeletal Clinical Assessment and Treatment (MCAT) services for back pain. The MCAT services are run by experienced physiotherapists, who mainly treat mechanical back pain. Individuals for whom there is evidence of inflammatory back pain (IBP) or back pain with evidence of peripheral joint disease or inflammatory arthritis are flagged up and referred to secondary care for assessment and treatment.

Baseline assessments

The baseline assessment of all referred patients included a review of their medical history and a clinical examination. The medical history included the family history of psoriasis, inflammatory bowel diseases, and other conditions associated with SpA such as uveitis, dactylitis, and Achilles tendinitis. The clinical examination included an assessment of psoriatic changes in nails or psoriatic rash in the usual parts of the body (elbows, knees, periumbilical area, and scalp). Patients were also asked whether they had any evidence of psoriasis in the genital and perianal areas. Sites of enthesitis were clinically assessed and recorded. The peripheral joints, spine, and sacroiliac joints were routinely examined and the number of arthritic joints, as well as their distribution with regard to symmetry or asymmetry, was noted.

Laboratory tests

The results of routine laboratory tests performed at the initial assessment, such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level, were noted and recorded in the LoRoS. The upper limits of the normal range for our laboratory were defined as ESR=15 mm/hr and CRP=5 mmol/dL.

HLA B27 status

For all patients with evidence of inflammatory arthritis, an assessment of human leukocyte antigen B27 (HLA B27) status was requested at the clinician’s discretion. This was more likely to be requested in younger patients with negative findings from other tests who nevertheless had a strong history suggestive of IBP, as recommended by Calin et al. (14), Rudwaleit et al. (15), and the ASAS criteria for IBP (16).

Radiological investigations

Radiological investigations included radiographs of the spine (cervical, thoracic, and lumbar spine), hips, and pelvis, in addition to radiographs of the hands, wrists, feet, and ankles if there was evidence of peripheral disease. If sacroiliitis was not evident from plain radiographs of the hips and pelvis, dedicated radiographic evaluation of the sacroiliac joints was performed, followed by magnetic resonance imaging of the sacroiliac joints if this was considered appropriate (17).

Questionnaire

Patients with confirmed SpA completed a semi-structured questionnaire. This questionnaire, which was originally developed in 2001, has been validated and used in this group of patients since 2004. The data presented here were collected between 2004 and 2013. The questionnaire was in English. A description of the questionnaire and its validation has been presented previously (18).

Controls

From the same LoRoS, an analysis was performed on longitudinal data referring to patients with SpAs other than PsA who were on DMARDs.

Assessment of disease activity

A total of three indices were used for the assessment of disease activity (in addition to the standard laboratory tests of ESR and CRP).

For both PsA patients and controls, these were:

a) the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (19) and b) the effect of the disease on wellbeing over the previous week (WB). For PsA patients only, c) the Psoriatic Arthritis Quality of Life (PsAQoL) index was additionally used (20), whereas for controls the Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL) was used (21).

BASDAI: In brief, BASDAI is an index designed to be used in ankylosing spondylitis (AS) but which has also been shown to have a high ability to assess PsA when compared with other indices such as the health assessment questionnaire (HAQ) index (22, 23).

Wellbeing over the previous week (WB): Wellbeing was assessed on a 10 cm visual analog scale (VAS), on which patients were asked to grade the impact of the disease on their wellbeing over the previous week by drawing a vertical line at a point reflecting their choice on the scale. A vertical line at 0 indicated that the disease had no effect on the patient’s wellbeing and 10 indicated that the disease had the worst possible effect on the patient’s wellbeing.

PsAQoL: PsAQoL is an index specifically designed for patients with PsA (20). In brief, PsAQoL contains 20 items, which comprise statements that the patient is asked to describe as either true or false. For every true statement, a mark of 1 is given. The higher the total score (up to a maximum of 20), the higher is the impact of PsA on the individual patient’s quality of life.

ASQoL: This is an 18-item dichotomous scale that assesses the impact of interventions in AS,
on which the higher the value is the worse the impact of the disease is, which is indicative of an adverse effect on quality of life.

**Functional ability**

The Bath Ankylosing Spondylitis Function Index (BASFI) is well established as a means of assessing a patient’s functional ability (24).

**Assessment of the effect of treatment (TxE)**

The effect of treatment was assessed using a 10 cm VAS, on which patients were asked to grade the perceived effect that the treatment had on their disease by drawing a vertical line on a scale from 0 to 10, where the maximum beneficial effect was indicated by a line at 10, whereas no effect was indicated by a line at 0.

**Baseline assessment of demographic and clinical characteristics of the PsA and SpA/control groups**

Baseline demographic characteristics, including age, gender, and ethnicity, were recorded for both PsA and control groups, as were the following clinical characteristics: disease duration, phenotypic predominance, type of arthritis, dactylitis, enthesitis, HLA status, ESR, CRP, BASDAI, BASFI, WB, TxE, PsAQoL (for the PsA group), and ASQoL (for the SpA/control group).

**Assessing differences between different DMARD treatments in PsA patients and controls**

Assessing differences between baseline and following treatment with DMARDs

For both PsA and control groups, patients’ data obtained via the baseline questionnaire were compared with follow-up data (representing the post-treatment effect of DMARDs).

**Assessing differences between the three commonly used DMARDs (MTX, SSZ, and LFN) in PsA**

The use of the three commonly used DMARDs (i.e., MTX, SSZ, and LFN) in PsA was evaluated. The initial analysis took place with the aim of assessing differences between three groups of PsA patients, who were treated with just one of the DMARDs. Within each group, we compared the clinical characteristics at baseline with those at follow-up. We then compared the same data across groups to evaluate the effect of each of the DMARDs.

Patients on other DMARDs such as ciclosporin (CsA) or on combination treatment (MTX plus SSZ or MTX plus LFN) were not included in the analysis.

**Assessing differences between the two most commonly used DMARDs (MTX and SSZ) in SpAs other than PsA (controls)**

The DMARD effects of MTX and SSZ on SpAs excluding PsA (controls) were analyzed and compared with the effect of each drug on PsA. There were no patients on LFN in this treatment group because LFN is not licensed for use in SpAs other than PsA.

**Assessing differences in the TxE of MTX and SSZ across the PsA and control groups**

The efficacy of MTX and SSZ as indicated by TxE was analyzed and compared across the PsA and control groups.

**Statistical analysis**

Statistical Package for the Social Sciences (SPSS) software version 21.0 (IBM Corp.; Armonk, NY, USA) was used for statistical analysis. Statistical analysis was conducted using a non-parametric Chi² test to determine differences between the treatment and control groups.

**Ethical approval**

The data analyzed in this study were part of a larger longitudinal study that aimed to assess differences in the disease progression of SpAs between ethnic groups. The project was approved by the Ethics Committee (REC: 07/H0701/74).

**Results**

From a total of 263 patients with any SpA who had follow-up data (longitudinal data) available in the LoRoS, there were a total of 73 patients on MTX, SSZ, and LFN. Among these, 51 patients (male-to-female ratio [M:F]=18:33) had PsA (22 on MTX, 16 on SSZ, and 13 on LFN) and 22 had an SpA other than PsA and served as the control group (10 were on MTX and 12 were on SSZ).

**Treatments**

MTX: A total of 32 patients were on MTX. Among these, 22 patients had PsA (mean age of 50.8 years, standard deviation [SD] of ±15.5 years, range of 18–80 years) and 10 patients had an SpA other than PsA (mean age of 43.9 years, SD of ±15.5 years). Although the patients with PsA on MTX were generally older than the control, the difference was not statistically significant (p=0.25).

SSZ: A total of 28 patients were on SSZ. Among these, 16 patients were treated for PsA (mean age of 47.6 years, SD of ±10.4 years, range of 30–63 years) and 12 were treated for SpAs other than PsA (mean age of 57.4 years, SD of ±16.5 years). There were no notable differences in disease activity and functional ability between patients in the SSZ group and those in the other two treatment groups (MTX and LFN).

LFN: A total of 13 patients were on LFN (all of whom had PsA), with a mean age of 51 years (SD of ±12.7 years) and a range of 33–73 years.

**Indications for DMARDs in the control group**

The indications for the use of DMARDs in the control group were as follows:

- In the MTX group (n=10), eight patients were treated for uveitis, two of whom had AS and peripheral disease in addition to uveitis, and two patients for undifferentiated SpA. All patients except one were Caucasians. Four of the 10 patients had a family history of SpA.
- In the SSZ group (n=12), there were two patients with AS and peripheral arthritis, six patients with ulcerative colitis, two patients with Crohn’s disease, and two patients with reactive arthritis.
- There were no patients on LFN in this group with SpAs other than PsA to act as a control group for the PsA patients on LFN, as there is no approval for the use of this drug in this group of patients.

**Total Groups of PsA Patients and Controls**

Baseline assessment of demographic and clinical characteristics of PsA patients and controls on treatment

**Baseline clinical assessments and differences between PsA patients and controls**

With regard to demographic characteristics, there were significantly more women in the control group than in the PsA group (M:F=2:20 versus 18:33; p=0.02) (Table 1).

Clinical assessment showed that there were more patients with enthesitis (13 versus 9; p=0.003) and having both axial and peripheral disease (7 versus 2; p=0.006) in the control group in comparison to the PsA group (Table 1).

Regarding the clinical assessment characteristics, the PsA group had worse BASDAI and BASFI scores at baseline in comparison to the controls (7.3±1.6 versus 6.2±2.05; p=0.03 and 7.1±1.5 versus 5.1±2.4; p=0.001, respectively) (Table 1).

**Post-DMARD TxE in PsA patients and controls**

On examining the effects of DMARDs in the control and PsA groups, the BASFI score and TxE after treatment with DMARDs were worse in the PsA group in comparison to the controls (6.3±2.1 versus 4.9±2.8; p=0.04 and 3.8±2.9 versus 5.9±2.4; p=0.002, respectively).

The baseline demographics, clinical characteristics, and statistically significant differences in
the characteristics of patients in each group (PsA patients versus controls) are summarized in Table 1.

Assessing differences between treatments in PsA patients and controls

Assessing differences between baseline and the situation following treatment with DMARDs

PsA: Differences between baseline and follow-up between the three different DMARDs used

The demographic and clinical characteristics, including BASDAI, BASFI, WB, TxE, and PsAQoL, of the PsA group on each of the DMARDs used (MTX, SSZ, and LFN) and statistically significant differences between treatments are shown in Table 2.

Figure 1 is a graphical representation of the mean values of each of the indices (BASDAI, BASFI, TxE, and WB) as recorded at baseline and following treatment with MTX, SSZ, and LFN in the PsA group. No statistically significant difference was identified.

Controls: Differences between baseline and follow-up between the two different DMARDs used

Figure 2 is a graphical representation of the mean values of each of the indices (BASDAI, BASFI, TxE, and WB) as recorded at baseline and following treatment with MTX and SSZ in the control group. No statistically significant difference was identified.

Assessing differences between the three commonly used DMARDs (MTX, SSZ, and LFN) in PsA

Baseline: Comparison between patients on each of the three DMARDs at baseline in the PsA group

Among the PsA patients, there were more female patients in the SSZ subgroup (p<0.05). There was no other difference between the three PsA subgroups at baseline with regard to age, ethnic origin, disease onset and duration, CRP, or ESR (Table 2).

Clinical assessments in PsA

Patients on LFN had a worse BASFI score at baseline in comparison to patients subsequently treated with MTX and SSZ (p=0.08).

Table 1. Demographic and clinical characteristics of the total group of patients with PsA and the total group of patients with SpAs other than PsA (controls) on conventional DMARDs

<table>
<thead>
<tr>
<th>Psoriatic arthritis (n=51) mean numbers (±SD)</th>
<th>Controls (n=22) mean numbers (±SD)</th>
<th>Statistical significance p&lt;0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (total group) 49.8 (±12.8)</td>
<td>50.6 (±16)</td>
<td>0.82</td>
</tr>
<tr>
<td>Gender (M:F) 18:33</td>
<td>2:20</td>
<td>0.02</td>
</tr>
<tr>
<td>Caucasian/Asian/ African/mixed 31/14/2/4</td>
<td>17/4/1/0</td>
<td>0.13/0.45/0.82</td>
</tr>
<tr>
<td>Disease duration (years) 9.9 (±9.1)</td>
<td>16 (±15.7)</td>
<td>0.09</td>
</tr>
<tr>
<td>Predominant axial disease 4</td>
<td>5</td>
<td>0.06</td>
</tr>
<tr>
<td>Cervical spine 11</td>
<td>3</td>
<td>0.42</td>
</tr>
<tr>
<td>Thoracic spine 5</td>
<td>5</td>
<td>0.12</td>
</tr>
<tr>
<td>Lumbar spine 9</td>
<td>3</td>
<td>0.66</td>
</tr>
<tr>
<td>Arthritis 23</td>
<td>15</td>
<td>0.07</td>
</tr>
<tr>
<td>Symmetrical 4</td>
<td>3</td>
<td>0.4</td>
</tr>
<tr>
<td>Asymmetrical 15</td>
<td>2</td>
<td>0.06</td>
</tr>
<tr>
<td>Oligoarticular 4</td>
<td>3</td>
<td>0.4</td>
</tr>
<tr>
<td>Both axial and peripheral disease 2</td>
<td>7</td>
<td>0.0006 SS</td>
</tr>
<tr>
<td>Enthesitis 9</td>
<td>13</td>
<td>0.0003 SS</td>
</tr>
<tr>
<td>Dactylitis 2</td>
<td>0</td>
<td>0.41</td>
</tr>
<tr>
<td>HLA B27 Positive 2</td>
<td>5</td>
<td>0.008 SS</td>
</tr>
<tr>
<td>Negative 22</td>
<td>15</td>
<td>0.05</td>
</tr>
<tr>
<td>Not done 27</td>
<td>2</td>
<td>0.0005</td>
</tr>
<tr>
<td>ESR at baseline (mm/hr) 20.3 (±19.9)</td>
<td>19.4 (±14.8)</td>
<td>0.82</td>
</tr>
<tr>
<td>CRP at baseline (mg/dL) 6.7 (4±133)</td>
<td>16.4 (±21.9)</td>
<td>0.05</td>
</tr>
<tr>
<td>BASDAI at baseline 7.3 (±1.6)</td>
<td>6.2 (±2.05)</td>
<td>0.032 SS</td>
</tr>
<tr>
<td>BASDAI after DMARDs 6.5 (±2.2)</td>
<td>6.1 (±1.9)</td>
<td>0.43</td>
</tr>
<tr>
<td>BASFI at baseline 7.1 (±1.5)</td>
<td>5.1 (±2.4)</td>
<td>0.001 SS</td>
</tr>
<tr>
<td>BASFI after DMARDs 6.3 (±2.1)</td>
<td>4.9 (±2.8)</td>
<td>0.045 SS</td>
</tr>
<tr>
<td>Wellbeing at baseline 5.1 (±2.1)</td>
<td>6 (±2.5)</td>
<td>0.14</td>
</tr>
<tr>
<td>Wellbeing after DMARDs 5.9 (±2.6)</td>
<td>5.9 (±2.4)</td>
<td>0.99</td>
</tr>
<tr>
<td>TxE at baseline 3.6 (±2.4)</td>
<td>3.9 (±2.5)</td>
<td>0.63</td>
</tr>
<tr>
<td>TxE after DMARDs 3.8 (±2.9)</td>
<td>5.9 (±2.4)</td>
<td>0.002 SS</td>
</tr>
<tr>
<td>PsAQoL (follow-up) 12.5 (±5.1)</td>
<td>Not done</td>
<td>N/A</td>
</tr>
<tr>
<td>ASQoL (follow-up) Not done</td>
<td>12.05 (±4.15)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

SS: statistically significant.
ESR: erythrocyte sedimentation rate (mm/hr); CRP: C-reactive protein (mg/dL); BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Function Index; TxE: treatment effect; PsAQoL: psoriatic arthritis quality of life; ASQoL: ankylosing spondylitis quality of life

Roussou and Bouraoui. DMARDs in PsA Eur J Rheumatol 2017; 4: 1-10
Table 2. Differences from comparisons of conventional DMARDs in the PsA group

<table>
<thead>
<tr>
<th>Demographic Characteristics and parameters</th>
<th>MTX group (n=22)</th>
<th>LFN group (n=13)</th>
<th>SSZ group (n=16)</th>
<th>MTX vs LFN</th>
<th>SSZ vs LFN</th>
<th>SSZ vs MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [mean (sd)]</td>
<td>50.8±15.51</td>
<td>51.0±12.7</td>
<td>47.6±10.41</td>
<td>0.9</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Gender [M:F]</td>
<td>9:13</td>
<td>7:6</td>
<td>2:14</td>
<td>0.1</td>
<td>0.01</td>
<td>0.05</td>
</tr>
<tr>
<td>Caucasian [nr (%)]</td>
<td>16 (72.7%)</td>
<td>7 (53.8%)</td>
<td>8 (50%)</td>
<td>0.07</td>
<td>0.8</td>
<td>0.1</td>
</tr>
<tr>
<td>Asian [nr (%)]</td>
<td>5 (22.7%)</td>
<td>5 (38.4%)</td>
<td>4 (25%)</td>
<td>0.5</td>
<td>0.4</td>
<td>0.8</td>
</tr>
<tr>
<td>African/Afro-Caribbean [nr (%)]</td>
<td>1 (4.5%)</td>
<td>1 (7.6%)</td>
<td>2 (12.5%)</td>
<td>0.8</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Mixed [nr (%)]</td>
<td>0</td>
<td>0</td>
<td>2 (12.5%)</td>
<td>NS</td>
<td>0.1</td>
<td>0.08</td>
</tr>
<tr>
<td>Disease duration [mean (sd)]</td>
<td>8.7±7.7</td>
<td>11.2±8.3</td>
<td>10.7±11.3</td>
<td>0.3</td>
<td>0.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Mean age of disease onset [mean (sd)]</td>
<td>38.8±19.4</td>
<td>31.7±17.2</td>
<td>35±6.72</td>
<td>0.2</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Mean age at diagnosis [mean (sd)]</td>
<td>44.7±16.6</td>
<td>38.7±11.8</td>
<td>40.5±9.43</td>
<td>0.3</td>
<td>0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>ESR baseline [mean (sd)]</td>
<td>17.8±15.6</td>
<td>21.1±22.8</td>
<td>16.3±10.3</td>
<td>0.6</td>
<td>0.4</td>
<td>0.7</td>
</tr>
<tr>
<td>ESR on follow up [mean (sd)]</td>
<td>17.9±16.4</td>
<td>23.1±24.7</td>
<td>20.1±18.5</td>
<td>0.4</td>
<td>0.7</td>
<td>0.6</td>
</tr>
<tr>
<td>CRP baseline [mean (sd)]</td>
<td>7.1±5.8</td>
<td>8.4±6.6</td>
<td>5.3±2.3</td>
<td>0.5</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>CRP follow up [mean (sd)]</td>
<td>9.6±7.6</td>
<td>7.1±6.6</td>
<td>6.95±4.44</td>
<td>0.3</td>
<td>0.9</td>
<td>0.2</td>
</tr>
<tr>
<td>BASDAI baseline [mean (sd)]</td>
<td>6.1±1.7</td>
<td>7.3±1.5</td>
<td>6.5±1.5</td>
<td>0.04</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>BASDAI after DMARDs [mean (sd)]</td>
<td>5.6±1.99</td>
<td>7.03±2.5</td>
<td>6.6±2.2</td>
<td>0.07</td>
<td>0.6</td>
<td>0.1</td>
</tr>
<tr>
<td>BASFI baseline [mean (sd)]</td>
<td>5.5±2.24</td>
<td>7.08±2.5</td>
<td>5.7±2</td>
<td>0.08</td>
<td>0.1</td>
<td>0.7</td>
</tr>
<tr>
<td>BASFI after DMARDs [mean (sd)]</td>
<td>5.4±2.07</td>
<td>7.1±2.4</td>
<td>6.6±2.1</td>
<td>0.03 (SS)</td>
<td>0.5</td>
<td>0.09</td>
</tr>
<tr>
<td>Effect of Tx baseline [mean (sd)]</td>
<td>4.2±2.5</td>
<td>4.9±2.2</td>
<td>4.2±2.6</td>
<td>0.4</td>
<td>0.5</td>
<td>0.9</td>
</tr>
<tr>
<td>TxE effect after DMARDs [mean (sd)]</td>
<td>3.7±3</td>
<td>2.9±3.1</td>
<td>4.9±2.6</td>
<td>0.4</td>
<td>0.07</td>
<td>0.2</td>
</tr>
<tr>
<td>WBpw baseline [mean (sd)]</td>
<td>5.6±1.99</td>
<td>6.4±2.9</td>
<td>6.4±1.2</td>
<td>0.3</td>
<td>0.9</td>
<td>0.1</td>
</tr>
<tr>
<td>WBpw after DMARDs [mean (sd)]</td>
<td>5.9±2.6</td>
<td>5.9±3.1</td>
<td>6.2±2.2</td>
<td>0.9</td>
<td>0.8</td>
<td>0.7</td>
</tr>
<tr>
<td>PsAQoL** [mean (sd)]</td>
<td>14.5±5.5</td>
<td>13.3±6.1</td>
<td>10.2±3.9</td>
<td>0.7</td>
<td>0.1</td>
<td>0.025 (SS)</td>
</tr>
</tbody>
</table>

SS: statistically significant.

Demographic and clinical characteristics, including indices of disease activity (ESR, CRP, and BASDAI) and function (BASFI), the effect of the disease on wellbeing over the previous week (WB), treatment effect (TxE), and psoriatic arthritis quality of life (PsAQoL), of the PsA group on each of the DMARDs used (MTX, SSZ, and LFN) and differences determined from comparisons between the three different DMARDs used in PsA.

Post-DMARD use

Comparison between PsA patients across the three treatment subgroups (MTX, SSZ, and LFN)

Regarding the BASDAI, TxE, and WB scores, no statistically significant difference was noted between the three different subgroups of PsA patients (Table 2). Differences were, however, noted in the BASFI and PsAQoL scores (Table 2).

BASFI

The elevated BASFI index in the LFN group during baseline assessment remained high after treatment in comparison to the other two treatment groups (MTX and SSZ). This difference was statistically significant between the MTX and LFN groups (p=0.03) after treatment with DMARDs (Table 2).

PsAQoL

The PsAQoL index was noted to be lower in patients on SSZ (10.2±3.9 for SSZ in comparison to LFN 13.3±6.1 and MTX 14±5.5)), with a statistically significant difference between the SSZ and MTX groups (p=0.02).

Trends toward statistical significance

Although the effect of the disease on wellbeing was similar between the three groups, the BASDAI score was lower in the MTX group both at baseline and after treatment (6.1±1.7 and 5.6±1.9, respectively) and higher in the LFN group (7.3±1.5 and 7.03±2.5, respectively). The difference, although it was significant at baseline (p=0.04), was not significant after treatment (p=0.07).

TxE

Treatment with LFN gave rise to a trend toward worse TxE values, with a mean value of 2.94±3.1 at the follow-up assessment with regard worse TxE values, with a mean value of 4.96±2.6 in comparison to 3.78±3 in the MTX group and 2.9±3.1 in the LFN group (p=0.07 between SSZ and LFN) (Table 2 and Figure 1).

Differences between the two DMARD subgroups (MTX and SSZ) in the control group (SpAs other than PsA)

Differences in demographic characteristics between the control subgroups

Although there were significantly more women in the control group than in the PsA group, as was previously noted (M:F=2:20 versus 18:33; p=0.02) (Table 1), the difference was not statistically significant between women on MTX (M:F=1:19) and those on SSZ (M:F=1:11) (p=0.8) in the control group.

Differences in clinical characteristics between the control subgroups at baseline

The clinical characteristics, including indices of disease activity (ESR, CRP, and BASDAI) and function (BASFI), WB, TxE, and ASQoL, of the control group subgroups are shown in Table 3.

Differences in clinical characteristics between the control subgroups post-DMARD use at follow-up

The values of the indices (BASDAI, BASFI, TxE, and WB) used to assess the response to treatment with MTX/SSZ are shown in Figure 2. An improvement is indicated by lower values of BASDAI, BASFI, and WB and higher values of TxE.

Assessing differences in TxE for MTX and SSZ treatment between the PsA and control groups

Comparisons between PsA and control groups on MTX and SSZ

Demographic characteristics

Patients with PsA on MTX were older, with a mean age of 43.9±15.5 years. The difference, however, was not statistically significant between women on MTX (M:F=1:9) and those on SSZ (M:F=1:11) (p=0.8) in the control group.

Clinical assessments of controls

The disease duration was longer in the control group than in the PsA group, as was previously noted (M:F=1:20 versus 18:33; p=0.02) (Table 1), the difference was not statistically significant between women on MTX (M:F=1:19) and those on SSZ (M:F=1:11) (p=0.8) in the control group.
Differences in TxE for MTX and SSZ treatment between the PsA and control groups

The differences between the MTX and SSZ groups in disease activity, function, WB, and TxE for PsA patients versus controls are shown in Figure 3.

Discussion

We present in this paper the results of an analysis of an observational retrospective pragmatic study on the three conventional DMARDs methotrexate (MTX) and sulfasalazine (SSZ), and leflunomide (LFN) in the PsA group.

The effectiveness of traditional DMARDs (MTX and SSZ) in treating patients with PsA was compared with their effectiveness in treating other non-PsA spondyloarthropathies. Patients with other SpAs included those with AS, peripheral disease, ulcerative colitis, and uveitis and specifically excluded those with PsA or psoriasis.

For PsA, all the indices used to assess the effects of DMARDs showed that all the conventionally used DMARDs have some beneficial effect. However, for the non-PsA SpAs the effect of these medications was significantly better on two of the indices used (BASFI and TxE, as reported by the patients).

In the PsA group, of the three DMARDs studied, SSZ was shown to lead to significantly better TxE values. MTX and LFN both gave rise to better outcome measures of disease activity in patients following treatment in comparison to baseline, although these were not found to be statistically significant. Similarly, quality of life as assessed by the PsAQoL index was better in the SSZ group in comparison to the MTX and LFN groups in the sense that an effect was observed, but this was not found to be statistically significant.

The lack of statistical significance may be related to the small number of patients included in the three retrospectively assessed treatment arms. With this limitation in mind, observable trends were, nevertheless, noted and exact values derived from the statistical analysis were described.

Methotrexate has previously been shown to be less effective than SSZ in the treatment of PsA, which is in contrast to current NICE guidelines, which suggest that MTX should be a cornerstone of treatment. Kingsley et al. (4) recently published a nationwide UK study, which demonstrated that MTX was ineffective in treating PsA. This study has been criticized on account of its short duration. It has been argued that insufficient time was allowed from the final dose increment to assessment of the effect of treatment. In another recent study that assessed an approach based on tight control of PsA in the early stages of the disease, 26% of the tight-control group remained on MTX monotherapy at week 48 of treatment, assuming that the remaining patients experienced either toxicity, inefficacy, or lack of tolerance that required additional treatment or a change in treatment (25).

Our analysis of the retrospective data collated in this study agrees in principle with that of Kingsley et al. (4), and the efficacy of MTX in treating PsA and its position as a cornerstone treatment are indeed questionable.

The benefit of this study is that the data that were analyzed represent real-life data. The patients were not selected or randomized to any defined arm. The data were obtained pragmatically by the administration of a questionnaire.
Table 3. Comparison between DMARDs in control group

<table>
<thead>
<tr>
<th>Demographic characteristic</th>
<th>MTX group (n=10)</th>
<th>SSZ group (n=12)</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>43.9 (±15.5)</td>
<td>57.4 (±16.5)</td>
<td>0.0624</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>1:9</td>
<td>1:11</td>
<td>0.88</td>
</tr>
<tr>
<td>Caucasian/Asian/African†</td>
<td>9/1/0</td>
<td>8/3/1</td>
<td>0.19 (0.36/0.35 [ns])</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>12.2 (±10.1)</td>
<td>19.8 (±21.3)</td>
<td>0.2</td>
</tr>
<tr>
<td>Mean age at diagnosis (years)</td>
<td>37.3 (±18.4)</td>
<td>45.2 (±17.1)</td>
<td>0.3</td>
</tr>
<tr>
<td>Predominant axial disease*</td>
<td>3</td>
<td>2</td>
<td>0.45</td>
</tr>
<tr>
<td>Cervical/thoracic/lumbar (spine)</td>
<td>2/3/2</td>
<td>1/2/1</td>
<td>0.42/0.45/0.42</td>
</tr>
<tr>
<td>Arthritis</td>
<td>7</td>
<td>8</td>
<td>0.86</td>
</tr>
<tr>
<td>Symmetrical</td>
<td>2</td>
<td>1</td>
<td>0.42</td>
</tr>
<tr>
<td>Asymmetrical</td>
<td>1</td>
<td>1</td>
<td>0.88</td>
</tr>
<tr>
<td>Oligoarticular</td>
<td>2</td>
<td>1</td>
<td>0.42</td>
</tr>
<tr>
<td>Both axial and peripheral disease</td>
<td>3</td>
<td>4</td>
<td>0.453</td>
</tr>
<tr>
<td>Enthesitis</td>
<td>4</td>
<td>9</td>
<td>0.096</td>
</tr>
<tr>
<td>Dactylitis</td>
<td>0</td>
<td>0</td>
<td>N/A</td>
</tr>
<tr>
<td>BASDAI at baseline</td>
<td>6.6 (±2.1)</td>
<td>5.9 (±2.04)</td>
<td>0.4</td>
</tr>
<tr>
<td>BASDAI after DMARDs</td>
<td>6.7 (±1.9)</td>
<td>5.6 (±1.9)</td>
<td>0.19</td>
</tr>
<tr>
<td>BASFI at baseline</td>
<td>5.2 (±2.8)</td>
<td>5.03 (±2.8)</td>
<td>0.8</td>
</tr>
<tr>
<td>BASFI after DMARDs</td>
<td>5.3 (±2.7)</td>
<td>4.5 (±3)</td>
<td>0.51</td>
</tr>
<tr>
<td>ESR</td>
<td>17.1 (±14.5)</td>
<td>21.8 (±13.3)</td>
<td>0.44</td>
</tr>
<tr>
<td>CRP</td>
<td>22.5 (±33.9)</td>
<td>10.1 (±10.06)</td>
<td>0.28</td>
</tr>
<tr>
<td>HLA B27 status (positive/negative/not done)</td>
<td>2/5/3</td>
<td>3/10/3</td>
<td>0.09</td>
</tr>
<tr>
<td>TxE at baseline</td>
<td>3.3 (±2.8)</td>
<td>4.6 (±2.4)</td>
<td>0.26</td>
</tr>
<tr>
<td>TxE after DMARDs</td>
<td>3.36 (±2.8)</td>
<td>4.6 (±2.4)</td>
<td>0.28</td>
</tr>
<tr>
<td>WB at baseline</td>
<td>6.4 (±2.8)</td>
<td>5.6 (±2.2)</td>
<td>0.47</td>
</tr>
<tr>
<td>WB after DMARDs</td>
<td>6.4 (±2.8)</td>
<td>5.5 (±2.1)</td>
<td>0.41</td>
</tr>
<tr>
<td>ASQoL</td>
<td>13 (±3.3)</td>
<td>11.5 (±1.5)</td>
<td>0.299</td>
</tr>
</tbody>
</table>

Demographic and clinical characteristics, including indices of disease activity (ESR, CRP and BASDAI) and function (BASFI), the effect of the disease on wellbeing over the previous week (WB), treatment effect (TxE), and ankylosing spondylitis quality of life (ASQoL), of the group with SpAs other than PsA (controls) on each of the DMARDs used. Differences determined from comparisons between the different DMARDs used in the control group with SpAs other than PsA.

ESR: erythrocyte sedimentation rate (mm/hr); CRP: C-reactive protein (mg/dL); BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Function Index; TxE: treatment effect; PsAQoL: psoriatic arthritis quality of life; ASQoL: ankylosing spondylitis quality of life

*There were no mixed-race patients in the control group
†Predominant axial disease: indicative of Ankylosing Spondylitis

at baseline and longitudinally during clinical assessments. Despite the small number of patients in each DMARD treatment arm, the longitudinal data are of value. They enabled a comparison not only of patients’ perceptions of the disease before and after treatment but also between patients with PsA and those with other SpAs treated in two different arms with the same treatment namely MTX and SSZ.

Patients underwent diagnosis by rheumatologists, and the choice of treatment was in each case in accordance with the relevant national guidelines.

Various other observations can be derived from this study. Firstly, regarding the age of patients included in the three groups, although there was no statistically significant difference between the mean ages of patients in the three groups, MTX was given to patients over a broader age range (from 18 to 80 years) by when compared to the other two DMARDs. The age ranges for SSZ and LFN were 30-63 years and 33-73 years, respectively. This suggests that clinicians (at least in our hospitals) are perhaps more confident in the use of MTX in both younger and older patient age groups. This is in addition to the consideration of MTX use as a first-line option according to clinical guidelines.

A limitation of this study is that the exact dose of MTX was not recorded. Therefore, we are unable to assess in retrospect whether patients on MTX were offered the maximum treatment dosages or were undertreated.

Another limitation is that the indices used may be questionable because they represent perceptions and are not specific for PsA, as the registry was initially developed for patients with IBP and the archetypal model used was that of AS. Consequently, BASDAI and BASFI (indices of AS) were used. When it subsequently became apparent that a significant number of patients with characteristics of IBP who were included in the registry had psoriasis, the registry was expanded to include PsA patients, and, furthermore, generic indices were used (such as HAQ and Short Form 36), which, however, were not included in the initial assessment in 2004. This prevented these indices from being included in this analysis. ESR and CRP data (although these were routinely obtained for all our patients) were not able to be accurately obtained at the time of the relevant follow-up assessments owing to technical issues (a change from paper to electronic results), and, because the use of these indices is questionable in SpAs and PsA, they were not used in the follow-up analysis.

The small number of patients included in each arm of the treatment groups in both PsA patients and controls prevented us from being able to perform a statistical analysis. Our data did not show any statistically significant difference in the effect of treatment between MTX and LFN in the PsA group. Nevertheless, despite the small numbers, there was a statistically significant difference in some parameters, such as the PsAQoL score, between MTX and SSZ (p=0.02) in the PsA group, as patients on SSZ displayed a better quality of life as assessed by the PsAQoL score.

The fact that the baseline data for LFN were worse may be explained by the protocols that were followed, as LFN is not a first-line treatment in the NHS. Perhaps the patients on LFN
Roussou and Bouraoui. DMARDs in PsA Eur J Rheumatol 2017; 4: 1-10

were those that had worse disease and were therefore started on the relevant treatment.

Strength of conclusions permitted by study design
This type of retrospective analysis does not permit conclusions to have the same strength as may be facilitated by RCTs. It does, however, represent real-life data, and RCTs are developed to be applied in real life. Ideally, RCT data and real-life data should coincide in the level of clinical significance they provide. Failure to do so may represent poor design of the RCT.

A review of RCTs of the DMARDs used in PsA is presented below.

DMARDs for PsA

Review
Most data support the use of SSZ for PsA with peripheral joint disease. The effect, however, seems to be modest. There are six RCTs, which included a total of 782 patients (5–10), that compared SSZ monotherapy (n=385) versus placebo (n=397) or symptomatic treatment using analgesics, small doses of prednisolone (≤5 mg/day), or non-steroidal anti-inflammatory drugs (NSAIDs). Their findings support the use of SSZ for PsA in both its peripheral and axial manifestations and also showed improvements in skin psoriasis (26-28).

Clegg et al. (8) conducted a multicenter study in 221 patients who were given either SSZ (2 g/day) or placebo for 36 weeks. The primary evaluation criterion was achievement of the Outcome Measures in Rheumatology response (improvement of 30% or greater in two of the following four items: tender joint count, swollen joint count, overall patient assessment, and overall physician assessment). The proportion of patients who met the response criteria was significantly greater in the SSZ group in comparison to the placebo group (57.8% versus 44.2%; p<0.05). SSZ was ineffective in axial disease in this study.

In a multicenter randomized placebo-controlled study of patients (n=351) with SpA, of whom 136 had PsA treated with either SSZ (3 g/day) or placebo for 24 weeks, the SSZ group showed significant improvements in overall patient VAS and VAS on pain (10).

MTX
Methotrexate has been the subject of great debate, in particular from the results of a recent multicenter RCT in the UK. This trial ran for 6 months to assess the use of MTX in PsA (4). Patients with active PsA involving at least one peripheral joint were randomized to receive either MTX at a target dose of 15 mg/week or matched placebo. MTX was given initially at 7.5 mg/week and increased at 4 weeks to 10 mg/week and, at 8 weeks, to the target dose of 15 mg/week. According to the study protocol, in patients with persistent active disease the dosage could be increased at the discretion of the supervising rheumatologist to 20 mg/week at 4 months and 25 mg/week at 5 months. Consequently, because the study ran for 6 months those patients who needed 20 mg/week remained in the study for 8 weeks, whereas those who needed 25 mg/week remained in the study for a further 4 weeks prior to undergoing the final 6-month assessment.

Regression analysis showed a statistically significant benefit in the MTX group, but only as indicated by the patients’ and assessors’ global assessment. Assessments of tender/swollen joints, ESR, CRP, and pain were not statistically different between the MTX and the placebo group. Enthesitis, dactylitis, and superimposed axial disease were not included in the disease characteristics, and the fact that the study included an assessment of monoarticular disease, which is difficult to control, raised concerns.

Methotrexate has been recommended as a first-choice DMARD on the basis of its broad therapeutic dose range (7.5-30 mg/week), different administration forms (oral, intramuscular [IM], or subcutaneous), and the availability of data on both PsA and psoriasis but also other rheumatic diseases (26). For example, evidence from rheumatoid arthritis (RA) suggests that a dose of 25 mg/week is more efficacious and more appropriate than lower dosages. Four randomized controlled double-blind studies and seven open-label studies have been identified that relate to the use of MTX in PsA.

Data supporting the use of MTX in PsA were first presented in 1964 for 21 patients (27). This was a crossover study in which patients were given MTX at 25 mg intravenously, followed by three escalating dosages of 1-3 mg/kg intravenously at intervals of 10 days. Significant improvements were noted in swollen joint count, range of motion, skin lesions, and ESR. However, one patient died from marrow aplasia and reports of several other side effects suggested an unacceptable safety profile (28).

In a study by Wilkens et al. (29), 16 patients received MTX at a weekly dosage of 7.5–15 mg orally in three divided dosages at intervals of 12 hours and 21 patients received placebo. After 12 weeks of treatment, the MTX group showed a significant improvement in psoriatic skin lesions as assessed by the physician; however, the tender and swollen joint counts were not significantly different in the two groups. A pilot 6-month RCT in PsA patients (n=35) compared MTX (10 mg IM) for 6 months versus NSAIDs for 3 months followed by MTX for the remaining 3 months. Patients who were matched by articular pattern showed statistically significant improvements in tender/swollen joints, ESR, CRP, and patient and physician global assessment (30).

Open-label or retrospective studies have taken place that show efficacy in peripheral arthritis in PsA and psoriasis. Abu-Shakra et al. (31) showed that MTX could not prevent radiographic pro-

Figure 3. BASDAI and BASFI indices, treatment effect (TxE), and wellbeing assessed over the previous week (WB) of PsA patients and controls on MTX and SSZ after at least 1 year of treatment with the two DMARDs.
effect on efficacy in RA (43). The same regime reduces abnormalities in liver function with no increased risk of increases in transaminases have also been found to be associated with other hepatotoxic drugs such as statins. Male gender and increased age with obesity, diabetes, alcohol intake, non-alcoholic steatohepatitis, or concurrent therapy with other hepatotoxic drugs such as statins. In some cases a liver biopsy may be recommended (41). Male gender and increased age have also been found to be associated with an increased risk of increases in transaminases (42), whereas supplementation with folic acid reduces abnormalities in liver function with no effect on efficacy in RA (43). The same regime of folic acid is recommended for PsA. Liver toxicity observed with MTX is summarized in a review by Soriano and McHugh (44).

A study comparing MTX and CsA by Spadaaro et al. (45) found that the two drugs were equally effective in bringing about clinical improvements in parameters such as the number of painful/tender joints, Ritchie index, grip strength, Psoriasis Area and Severity Index (PASI), and patient and physician global assessments. Liver toxicity was observed in the MTX group but not in the CsA group.

Kragballe et al. (35) demonstrated in their retrospective analysis that the response of PsA to MTX was mainly due to the short duration of arthritis and was not related to the severity of disease. Ranza et al. (36) from their data confirm that MTX is of value in most patients with psoriatic polyarthritis (60%), but in their experience MTX provides maximum efficacy if 6 months of therapy is allowed.

Ricci et al. (37) in their observational retrospective analysis demonstrated that in a setting of clinical practice MTX had good performance over 3 years in patients with peripheral PsA. Almost 60% of them were still taking this drug at the end of the study period, and toxicity was more than acceptable. In their opinion, MTX might be considered the non-biological DMARD of choice for the treatment of this condition. However, it should be used earlier and at higher doses. A similar report was made by Chadran et al. (38). They reported that the dose of MTX used (10 mg/week versus 16 mg/week) did not alter its ability to achieve a 40% reduction in joint count; however, starting treatment earlier in the disease course can slow the radiographic progression of disease. Chadran et al. (31) presented a reappraisal of data and reviewed older reports published by the same department and presented by Abu-Shakra.

Transaminases should be carefully monitored in patients with PsA receiving MTX owing to the potential of increased hepatic toxicity (39, 40). The risk is increased in association with obesity, diabetes, alcohol intake, non-alcoholic steatohepatitis, or concurrent therapy with other hepatotoxic drugs such as statins. In some cases a liver biopsy may be recommended (41). Male gender and increased age have also been found to be associated with an increased risk of increases in transaminases (42), whereas supplementation with folic acid reduces abnormalities in liver function with no effect on efficacy in RA (43). The same regime of folic acid is recommended for PsA. Liver transaminase levels should be carefully monitored with MTX. A similar report was made by Schellenberg et al. in their observational retrospective analysis that the response of PsA to MTX was mainly due to the short duration of arthritis and was not related to the severity of disease. Ranza et al. (36) from their data confirm that MTX is of value in most patients with psoriatic polyarthritis (60%), but in their experience MTX provides maximum efficacy if 6 months of therapy is allowed.

In an open trial of patients with previous exposure to DMARDS, 8 of the 12 patients who were enrolled exhibited at least a partial response (46). Liang et al. (47) showed that in a preliminary study of 10 patients with psoriasis vulgaris and PsA treatment with LFN led to an improvement in PsA but not in psoriasis vulgaris.

Ethics Committee Approval: The ethics committee approval was received for this study from the ethics committee of South East Coast Surrey (07/H0701/74).

Informed Consent: Written informed consent was obtained from who participated in this study. Peer-review: Externally peer-reviewed.


Acknowledgements: The authors would like to thank Jonathan Dinmore and Andreas Georgiou.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

References

classification criteria for peripheral spondyloarthritides and spondyloarthritis in general. Ann Rheum Dis 2011; 70: 25-31. [CrossRef]


17. Roussou E, Reik G. Difficulties for the detection of positive signs of sacroiliitis in spondyloarthritides by magnetic resonance imaging (MRI) in everyday clinical practice. Clin Exp Rheumatol 2011; 29: 594-5. [CrossRef]


29. Zachariae H, Zachariae E, Methotrexate in psoriatic arthritis; double blind study on 21 patients with diabetes type 2 are at high risk of developing liver fibrosis during MTX treatment. J Hepatol 2007; 46: 1111-18. [CrossRef]


