Time trends in disease activity, response and remission rates in psoriatic arthritis (PsA): results from the NOR-DMARD study 2000-2012

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Time trends in disease activity, response and remission rates in psoriatic arthritis (PsA): results from the NOR-DMARD study 2000-2012

Introduction
Psoriatic arthritis (PsA) is an inflammatory joint disease (1). One often refers to PsA as a variant of peripheral spondyloarthritis (SpA), although PsA may also be considered a disease entity of its own, given that it often seems to present with a poorer outcome compared to other variants of peripheral SpAs (2). PsA equally affects women and men, with disease onset normally within the 4th decade of life (3, 4). PsA is associated with psoriatic skin disease, and the common scenario is the skin disease having its onset approximately 10 years before the arthritis (5). However, the arthritis may be present first, which is seen in about 15 % of the patients (3, 5). Approximately 4-30 % of patients with psoriatic skin disease have arthritis, although estimates show a wide range of variety in different studies (6). There is a correlation between the severity of the skin disease and the arthritis; severe skin disease is a predictor of the development of the joint disease (7). Patients with PsA have been proven to have a reduced quality of life and functional capacity when compared to patients with psoriasis or healthy control groups (8, 9).

PsA was earlier characterized as a mild joint disease, but more recent discoveries have shown that a significant number of the patients develop erosive joint changes only within a few years after disease onset (5). Joint deformities in PsA includes shortening of the digits caused by lysis of the bone or joint, which is referred to as “telescoping of the digits” in the most severe cases. These clinical manifestations can also be detected radiographically, where they are commonly referred to as “pencil in a cup”-changes (5).

The clinical variation of affected joints in PsA may be diverse, with phenotypes including oligoarthritis as well as axial involvement (10). Moll and Wright (1973) suggested five different subtypes (or patterns) for PsA; distal predominant pattern, oligoarticular asymmetrical pattern, polyarticular rheumatoid arthritis (RA)-like pattern, arthritis mutilans and spondylitis (10). The Classification Criteria for Psoriatic Arthritis (CASPAR-criteria), developed by the Group of Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and published in 2006, are currently used for clinical trials and to some extent also as a diagnostic tool for clinicians with PsA patients (11).
There are several clinical factors to help distinguish PsA from RA. A typical clinical feature found in PsA is dactylitis, defined as an inflammation of an entire digit most likely caused by affection of both joints and tendons. In contrast to RA, clinical affection in PsA often shows an asymmetrical pattern, so that all joints of a single digit are more likely to be affected rather than same joints on both sides, which is typically seen in RA patients. Another distinct feature of PsA separating it from RA is the involvement of the distal interphalangeal joint seen in PsA, although this is not the most common presentation (10, 12). Another clinical aspect is the presence of rheumatoid factor, which can be detected in up to 80% of the RA patients but only in about 13% of the PsA patients (5).

**Treatment recommendations**

Despite differences in clinical manifestations, PsA treatment principles are largely adopted from principles and guidelines of RA treatment. The modern treatment of RA includes an early diagnosis and early and aggressive start with methotrexate (MTX) treatment. Treatment with MTX should be initiated as soon as possible after a diagnose has been set, and recommendations over the last couple of years have also suggested treatment should include higher doses (20-30 mg) of MTX as it has been proven to be more effective than lower doses of MTX (7.5-15 mg) (13). Modern RA treatment is also based on setting a treatment target (low-disease activity or remission) (13). A similar “treat-to-target” approach was suggested also to be evaluated and implemented in PsA treatment. In the past few years, “treat to target” recommendations have also been developed and published for PsA (14, 15), focusing on the importance of early and aggressive therapy also in this patient group. However, evidence of long-term outcome is still scarce and the investigation of “treat-to-target” recommendations for PsA and SpAs still remains to be expanded by future research and new randomized trials (14).

There are two important sets of treatment recommendations for PsA, the Group of Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommendations (16) and the European League Against Rheumatism (EULAR) recommendations (17). The GRAPPA recommendations were first published in 2009, giving detailed recommendations for every specific feature of PsA including treatment recommendations specifically for the skin disease itself (16). The EULAR recommendations, based on two systematic reviews (SLRs) (17), were first published in 2012 with the intention to present general recommendations for strategic, safe and efficacious treatment of PsA in a clinical setting where multiple pharmacological agents were available, although information and knowledge of their safety and differential efficacy still remained insufficient (17).

The pharmacological treatment of PsA is based on the subgroups of what is referred to as Disease Modifying Antirheumatic Drugs (DMARDs) (18). Both conventional synthetic DMARDs (csDMARDs) and biological DMARDs (bDMARDs) are important pharmacological agents used
in treatment of PsA, although they differ in the way they act and interfere with the immunological components of PsA (18). The conventional synthetic DMARDs (csDMARDs) are recommended in moderate to severe manifestations of peripheral arthritis, with recommendations including MTX, SSZ and leflunomide among others (16), although none of these agents have been proven to be truly disease modifying in PsA. The EULAR recommendations became updated in 2015, and the use of csDMARDs on PsA patients with multiple swollen joints, structural damage with presence of inflammation remains a treatment recommendation. The csDMARDs are generally to be considered given at an early stage of the disease, and MTX is recommended for patients with peripheral arthritis, especially in patients with multiple swollen joints and structural damage in the presence of inflammation (18). MTX is also the preferred agent in those with a relevant skin involvement, as it has been proven efficacious in treating psoriatic skin disease (18) (19). Another csDMARD, leflunomide, is also recommended for treatment of PsA, although its use is limited due to its potential teratogenicity and and other known side-effects (16, 17). SSZ has been proven efficacious in treating PsA (16, 17), possibly also having an effect on axial disease and skin disease (20).

The biological agents, bDMARDs, include the TNFis (tumor necrosis factor inhibitors) such as infliximab and etanercept, and the IL-inhibitors ustekinumab and secukinumab. The introduction of TNFis can be considered a milestone in the treatment of psoriatic skin disease and PsA. Infliximab, etanercept, adalimumab, golimumab and certolizumab are all TNFis approved for use in PsA today, all having shown to be efficacious for both skin and joint involvement, reducing disease activity, inhibiting structural joint damage and preventing radiographic damage (21) (20, 22). The TNFis were the only available bDMARDs for treatment until the IL-inhibitors were introduced. Ustekinumab has been approved for use in PsA patients, and secukinumab is still awaiting consideration for approval (2016) (https://nyemetoder.no/). The targeted synthetic DMARDs (tsDMARDs) include the janus kinase inhibitors (JAK inhibitors) and the phosphodiesterase inhibitors (18). PsA treatment may also include the use of non-steroid anti-inflammatory drugs (NSAIDs), which may be used as a treatment option to help relieve musculoskeletal symptoms and signs, as well as local injections of glucocorticoids (18).

The prescription of TNFi or RA in Norway can be considered liberal, as patients having failed only one sDMARD (MTX if not otherwise contraindicated) are candidates for treatment with a bDMARD, also if only moderate disease activity is present (13). A similar approach has been recommended for PsA, with the 2015 update of the EULAR recommendations for management of PsA suggesting therapy with a bDMARD, usually a TNFi, in PsA patients with peripheral arthritis and inadequate response (treatment target of at least low disease activity not being reached) after undergoing treatment with at least one csDMARD after a certain length of time (usually 3-6 months) (18).
The aim of this study of real-life data from the NOR-DMARD study was to investigate changes in baseline disease activity levels and remission and response rates in PsA patients treated with either MTX in monotherapy or a TNFi in monotherapy or combinational therapy during the period 2000-2012.
Methods

Patients were selected from the NOR-DMARD study, a longitudinal observational study initiated in 2000 as a multicentre study including adult patients (aged >18) with inflammatory joint diseases. The study included patients who started treatment with bDMARDs or sDMARD and were followed by one of the five Norwegian rheumatology departments taking part in the study. Assessments included patient and physician reported outcomes, inflammatory markers, adverse events and details of current medications were performed at baseline 3,6 and 12 months, and then yearly. Either trained nurses or rheumatologists performed the assessments during each session.

For the current analyses we selected patients with a clinical diagnosis of psoriatic arthritis (PsA) starting treatment with either MTX in monotherapy (Figure 1) or TNFi-naïve patients starting TNFi in monotherapy in combination with another DMARD (MTX or other) between 2000-2012. Among PsA patients reciving sDMARDS in this period, MTX was the preferred alternative (Figure 1). The analyses are based on assessments made at baseline (V1) and at 3 months (V2).

Assessments

Baseline assessments included in the current study were patient age, sex, disease duration (number of months) treatment history, C-reactive protein (CRP), erythrocyte sedimentation Rate (ESR) and joint counts 32-joint swollen joint (32-SJC) and 32-joint tender joint count (32-TJC)). Also included were assessments made by physician (“Physician Global”) (0-100 mm visual analogue scale (VAS)). Patient reported outcomes (“Patient Global”) (0-100 mm visual analogue scale (VAS)) were also included, and the modified health assessment questionnaire (MHAQ)(23), numbered between 0-3, which is commonly used a measurement of health-related quality of life among patients with rheumatic disease. The composite measure “Disease Activity Level Score “(DAS28) (24) was also included in the assessments. Additionally, we also calculated mean prednisolone doses for both patient groups at baseline and 3 months and MTX doses at baseline for all patients receiving MTX in monotherapy.

Assessing the remission and response rates in both patient groups at 3 months, we used the EULAR good response(24) and the ACR (American College of Rheumatology) response system(25), in addition to the DAS-28 remission(24). We also included the MHAQ-score, 32-
SJC, 32-TJC, ESR, CRP, Patient Global Assessment VAS, Physician Global Assessment VAS, SF-6D and prednisolone dose and change from baseline in these variables.

**Patient selection**
All patients were diagnosed according to ICD-10, according to the clinical judgement made by the treating rheumatologist. By December 2012, a total number of 8485 patients (all diagnoses) were included in the study.

Two groups were analysed: the patient group receiving MTX-monotherapy and the TNFi-naïve patients receiving TNFi-monotherapy or a TNFi in combination with MTX or other DMARD.

**Statistical analysis**
Based on the year of the patients’ baseline visit, we designed a total number of 6 stratified groups with 2-year intervals for all patients receiving MTX-monotherapy from 2001-2012. Groups with 3-year intervals were created for the patient group receiving TNFi therapy between 2000 and 2012. All normally distributed continuous variables are presented with means if normally distributed, or with medians if variables were found to be non-normally distributed. Means were presented with a standard deviation, medians with a 25-75 % percentile. For both baseline and 3-month data in both patient groups we compared first and final time period, and second and final time period using $X^2$-test for categorized variables and two-sample t-test for continuous variables, alternatively the Wilcoxon-Rank-sum test when continuous variables were found to be non-normally distributed. The significant level of p-value was set to 0.05. Response and remission rates were calculated for 3 months, and we also calculated the differences in remission and response between first and last time periods using the two-sample t-test (continuous variables) or $X^2$-test (categorized variables). All statistical analyses were performed with STATA SE-64 (14.0, Statacorp, Lakeway Drive, Texas, USA).
Results

MTX

Patient characteristics
A total number of 729 PsA patients started treatment with MTX in monotherapy from 2001-2012. 357 were female and 372 were men. There were no significant changes to be observed in these baseline characteristics during the study years (Table 1).

Baseline disease activity
Baseline disease activity in the group receiving MTX in monotherapy was significantly decreasing, observing a reduction in disease activity score DAS28 from mean (SD) of 4.71 (1.2) in 2001-2002 to 3.73 (1.11) in 2011-2012. Table 1 also shows the reduction in inflammatory markers with median (25-75 % percentile) CRP from 11(5-24) in 2001-2002 observational group to 6(3-11) in the 2011-2012 group, as well as a significant lowering of ESR values when comparing the 2001-2002 group with the 2011-2012 group. A significant decrease in baseline disease activity measurements 32-SJC and 32-TJC was also seen. Subjective markers patient global assessment VAS, physician global assessment VAS and SF-6D showed significant decrease over the study time, as for MHAQ-score with a significant decrease from median (25-75% percentile) 0.7 (0.4-1) in the 2001-2002 group to 0.4 (0.1-0.8) in the 2011-2012 observational group. Comparable results were seen comparing 2003-2004/2011-2012.

Disease duration
There was a significant decrease in the disease duration in the MTX group. Median (25-75 %) disease duration for the 2001-2002 group was 15.9 (4-60) months and 1.1 (0.03-13.3) months for the 2011-2012 group (Table 1).

MTX doses
The MTX doses for the group receiving MTX in monotherapy increased significantly between 2001-2012, from mean (SD) of 9.4 (3.10) in 2001-2002 group to 15.96 (3.49) in the 2011-2012 group (Table 1).

Prednisolone doses
No significant change was observed in prednisolone dosage when comparing first and last observational group receiving MTX in monotherapy (Table 1).
**Remission and response rates (3 months)**

A significant increase in EULAR remission rate was observed for the MTX monotherapy group. ACR20, ACR50, ACR70 and EULAR good response all presented with an overall tendency of increasing from 2001-2002 to 2011-2012 observational groups, although not significant (Figure 2).

**TNFi**

**Patient characteristics**

From 2000-2012, a total number of 569 PsA patients started their treatment with TNFi in monotherapy or TNFi with other DMARD. A total number of 268 patients were female, and an increase in the percentage of female was observed over the study years, from 32.0 % in the 2000-2003 group to 50.7 % in the 2010-2012 observational group.

**Baseline disease activity**

Baseline disease activity measurements showed an overall significant reduction. Both DAS28 (mean, SD) and DAS28-CRP showed a decrease, from 4.8(1.4) in 2000-2003 observational group to 3.7(1.3) for the 2010-2012 observational group for DAS28 and from 4.78(1.31) to 3.67(1.10) for DAS28-CRP (Table 2). Similar results, also significant, were found when comparing second and last observational groups for TNFi. Swollen joints, 32-SJC, and 32-TJC also showed a significant reduction comparing the 2001-2003 and 2010-2012 observational groups. CRP and ESR were both significantly reduced, so were subjective markers Physician Global Assessment VAS and Patient Global Assessment VAS. A decrease, however not significant, was also observed in MHAQ-score (Table 2).

**Disease duration**

A significant reduction in disease duration (median (25-75%)) was seen from 10.72 (5-20) months in the 2000-2003 observational group to 4.02 (0.92-10.86) months in the 2010-2012 observational group (Table 2).

**Conventional DMARDs**

A significant decrease in number of conventional dMARDs used prior to starting a TNFi was observed between 2000-2003 and 2010-2012 observational group (Table 2).
**Prednisolone doses**
There was no significant change to be observed in prednisolone dosage when comparing first and last TNFi observational group.

**Remission and response**
There was an increase in remission rate (EULAR remission), although not significant (Figure 3). EULAR good response showed a trending towards a lower response, but this change in response was not significant. There was found to be a significant decrease for ACR20 response criteria (Figure 3).

**Discussion**

Our analyses of use of MTX and TNFi in patients with PsA 2000-2012 show an overall significant reduction in baseline disease activity for both patient groups. Disease duration was also significantly reduced during observational time for both patient groups. A significant increase in remission rate was observed in patient group receiving MTX in monotherapy. An increase in response rates was also observed, however not significant. A significant increase in remission rate was not seen in TNFi therapy group. Response rates were trending towards lower rates for TNFi patient group during observational time. MTX doses given in monotherapy were found to increase significantly over the observational time.

Results showed an overall significant decrease in disease duration in both MTX monotherapy and TNFi combinational therapy group. In the TNFi group this is very likely at least in part due to an “accumulation” of eligible patients prior to TNFi becoming available. We do however think that the significant decrease observed in disease duration in the MTX group is reflecting an increasing focus on importance of an early start of therapy soon after diagnose has been set, and this might be true for TNFi aswell.

Baseline disease activity was significantly higher in the first observational groups (2001-2002 and 2000-2003 groups), possibly due to an accumulation effect where patients included at baseline were traditionally not to be considered eligible for treatment unless high disease activity. However, our analyses show a tendency of reduction in baseline disease activity measurements parallel to the reduction in number of months of disease duration over the observational time, as patients in late observational groups became included and started
therapy at an even earlier stage of the disease, therefore presenting with a shorter disease duration. This may suggest an increasing focus on an earlier initiation of treatment despite patient moderate (but not high) disease activity, supporting the idea that this kind of approach in therapy should be considered crucial. As for patients receiving TNFi therapy, TNFi has gradually become a preferred alternative for patients after failing MTX treatment, and is now to be considered as one of the important therapeutic agents in PsA treatment, with 2015 EULAR recommendation updates suggesting use of bDMARD (usually TNFi) when patient with at least moderate disease activity (by disease activity composite measure) has failed at least one csDMARD (usually MTX)(18).

In our MTX patient group, analyses of changes in baseline disease activity were made both for first and second observational group compared with the last observational group included, and the baseline disease activity was found to be significantly reduced when comparing both first and second observational groups with the last group. This supports the idea that a significant reduction in disease activity could be observed not only because of a higher disease activity with those included at study start, but also a general tendency towards including patients to treatment in an earlier stage despite not high but moderate disease activity.

MTX doses were significantly increasing for patients receiving MTX over the course of the study. The increase in dosage reflects modern treatment principles with a more aggressive MTX treatment with a significantly higher dose of MTX given in therapy. Comparing with MTX treatment in RA patients, Aga et al(13) found a similar increase in MTX doses for RA patients receiving both MTX in monotherapy and MTX in combinational therapy with a TNFi between 2000-2010. This change reflected the updated recommendations for RA, that includes early, aggressive treatment with MTX, as high weekly doses (20-30 mg) of MTX had been proven more efficient than lower weekly doses (7.5-15 mg) (13). Our study suggests that a similar clinical approach has been adopted also in PsA treatment.

**Remission and response rates**

There was an increase in EULAR remission rates after 3 months for patient group receiving MTX (Figure 1), however not for the patient group receiving TNFi (Figure 2). As previously stated, disease duration and disease activity measurements were decreasing during observational time due to a trend towards earlier initiation of treatment after diagnose has been set. In the last years of observational time, patients had an overall low disease activity, allowing patients to achieve remission more easily. There was an increase in response rates for MTX group, however not significant. Response rates were decreasing for TNFi patient group
during study time, which might be due to the fact that patients being included had a lower disease activity from which response is harder to achieve compared to patients groups with high disease activity.

There are some limitations to our study. The first observational group contains patients whom might have been eligible for a TNFi over many years while they were not available. We have therefore also compared results between the second and last groups and found similar results. Also, our analyses simply compare to groups without assessing gradual change so whether changes are linear or non-linear has not been assessed. It can however be argued that whether the changes is truly linear is of little relevance and we do overall observe numerically a gradual change over the study period.

Outcome measurements used are not designed for PsA patients in particular, and a reduced joint-count (32-joint count) was used instead of the recommended 68-joint count, which gives a somewhat inaccurate measurement of PsA disease activity. PsA patients affected with axial disease, dactylitis or enthesitis could potentially have a low score in 32-joint count, what may create a “false” observation of low disease activity in these patients. DAS-28 disease activity score, used in our analysis, does not include recommended full joint counts for PsA although it has have been proved useful in several clinical trial settings (24, 26, 27). In the work of designing and validate composite measurements of disease specifically designed for PsA, a Composite Psoriatic Disease Activity Index (CPDAI) has been presented by GRAPPA(28) and the Disease Activity Index for Psoriatic Arthritis (DAPSA)(29) has been tested in clinical trials. Smolen et. al (30) reviewed and evaluated DAPSA index in 2015, and found it useful in clinical practice, clinical trials and observational studies as it had been proven to have a high level of validity in other studies(30).

**Conclusion**

Our study observed changes in disease activity and baseline disease activity throughout study time in both groups, likely reflecting the trend towards a more early, aggressive PsA treatment over the study years. An increase in MTX doses give may explain the trend towards a lower disease activity, although the focus on an early initiation of therapy should also be considered an important factor here. Our results support the role of methotrexate as an important first DMARD in PsA treatment.
References


Appendix
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<tbody>
<tr>
<td>All patients (n=)</td>
<td>94</td>
<td>125</td>
<td>116</td>
<td>167</td>
<td>126</td>
<td>101</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age, years (mean, (SD))</td>
<td>49.1 (13.0)</td>
<td>50.3 (13.2)</td>
<td>49.3 (12.4)</td>
<td>49.5 (12.5)</td>
<td>48.9 (12.5)</td>
<td>49.9 (13.6)</td>
<td>0.66</td>
<td>0.77</td>
</tr>
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<td>Female sex (n (%))</td>
<td>53 (56.4)</td>
<td>53 (42.7)</td>
<td>52 (44.8)</td>
<td>86 (52.4)</td>
<td>63 (50.0)</td>
<td>50 (49.5)</td>
<td>0.68</td>
<td>0.86</td>
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<tr>
<td>Disease duration, months (median (25-75 % percentile))</td>
<td>15.9 (4.0-60)</td>
<td>5.19 (0.6-56.0)</td>
<td>3.7 (0.1-18.6)</td>
<td>2.1 (0.0-39.3)</td>
<td>1.0 (0.0-16.6)</td>
<td>1.1 (0.03-13.3)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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<td>MTX dose (mg) (mean, (SD))</td>
<td>9.4 (3.10)</td>
<td>10.77 (3.28)</td>
<td>11.67 (3.48)</td>
<td>13.33 (3.58)</td>
<td>14.98 (6.76)</td>
<td>15.96 (3.49)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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<tr>
<td>Prednisolone dose (mean, (SD))</td>
<td>6.33 (5.53)</td>
<td>5.0 (6.1)</td>
<td>2.84 (6.1)</td>
<td>3.08 (4.67)</td>
<td>3.56 (5.44)</td>
<td>5.09 (5.47)</td>
<td>0.32</td>
<td>0.5530</td>
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<td>DAS28 (mean (SD))</td>
<td>4.71 (1.2)</td>
<td>4.5 (1.6)</td>
<td>4.3 (1.1065)</td>
<td>3.99 (1.2)</td>
<td>4.1 (1.23)</td>
<td>3.73 (1.11)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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<td>DAS28 –CRP (mean, (SD))</td>
<td>4.51 (0.99)</td>
<td>4.25 (1.00)</td>
<td>4.2 (1.0)</td>
<td>3.83 (0.99)</td>
<td>3.92 (1.06)</td>
<td>3.67 (1.00)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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<td>Swollen joints (Y/N, n (%))</td>
<td>85 (91.4)</td>
<td>117 (95.1)</td>
<td>105 (95.5)</td>
<td>133 (80.6)</td>
<td>107 (86.3)</td>
<td>83 (83.0)</td>
<td>0.083</td>
<td>0.001</td>
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<td>32-SJC (median (25-75 % percentile))</td>
<td>5 (2-8)</td>
<td>4 (2-8)</td>
<td>4 (2-6)</td>
<td>2 (1-5)</td>
<td>4 (1-6)</td>
<td>3 (1-5)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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<td>32-TJC (median (25-75%))</td>
<td>7 (4-11)</td>
<td>6 (3-11)</td>
<td>6 (3-10)</td>
<td>4 (2-8)</td>
<td>6 (3-10)</td>
<td>4 (2-9)</td>
<td>&lt;0.0001</td>
<td>0.0004</td>
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<td>CRP mg/L (median (25-75 %))</td>
<td>11 (5-24)</td>
<td>12 (5-28)</td>
<td>10 (4-25)</td>
<td>6 (3-16)</td>
<td>5 (3-15)</td>
<td>6 (3-11)</td>
<td>&lt;0.0001</td>
<td>0.0095</td>
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<td>SR (median (25%-75 %))</td>
<td>21 (10-41)</td>
<td>16.5 (10-35)</td>
<td>15 (8-26)</td>
<td>16 (7.5-28.5)</td>
<td>17 (8-31)</td>
<td>14 (9-26)</td>
<td>0.019</td>
<td>0.7858</td>
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<td>MHAQ-score (0-3) (median (25-75 percentile))</td>
<td>0.7 (0.4-1)</td>
<td>0.6 (0.3-9)</td>
<td>0.6 (0.3-9)</td>
<td>0.5 (0.2-0.8)</td>
<td>0.5 (0.3-0.8)</td>
<td>0.4 (0.1-0.8)</td>
<td>0.0004</td>
<td>0.0003</td>
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<td>Physician Global Assessment VAS (mean (SD))</td>
<td>39.9 (14.5)</td>
<td>32.9 (14.4)</td>
<td>33.9 (16.0)</td>
<td>29.5 (16.7)</td>
<td>31.0 (13.3)</td>
<td>29.4 (14.5)</td>
<td>&lt;0.0001</td>
<td>0.0145</td>
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<td>Patient Global assessment VAS (mean (SD))</td>
<td>54.8 (20.6)</td>
<td>50.0 (19.6)</td>
<td>49.5 (21.7)</td>
<td>46.9 (22.9)</td>
<td>49.2 (23.6)</td>
<td>42.5 (22.9)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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<td>SF-6D (mean(SD))</td>
<td>0.59 (0.12)</td>
<td>0.6 (0.13)</td>
<td>0.6 (0.12)</td>
<td>0.62 (0.12)</td>
<td>0.62 (0.12)</td>
<td>0.61 (0.12)</td>
<td>&lt;0.0001</td>
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* p-value when comparing 2001-2002 observational group with 2011-2012 group
** p-value when comparing 2003-2004 observational group with 2011-2012 group
Table 2: Time trends in baseline characteristics at initiation of TNFi therapy

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>All patients (n=)</td>
<td>50</td>
<td>107</td>
<td>179</td>
<td>233</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age, years (mean, (SD))</td>
<td>45.6 (35.6 - 56.7)</td>
<td>46.6 (38.2 - 55.8)</td>
<td>47.4 (38.5 - 57.0)</td>
<td>46.7 (38.2 - 54.2)</td>
<td>0.5456</td>
<td>0.971</td>
</tr>
<tr>
<td>Female sex (n (%))</td>
<td>16 (32.0)</td>
<td>46 (43.0)</td>
<td>90 (50.3)</td>
<td>116 (50.7)</td>
<td>0.017</td>
<td>0.19</td>
</tr>
<tr>
<td>Disease duration, months (median, 25-75 %)</td>
<td>10.72 (5-20)</td>
<td>7.32 (3.63 - 15.2)</td>
<td>4.5 (1.17 - 10.72)</td>
<td>4.02 (0.92)</td>
<td>&lt;0.0001</td>
<td>0.0002</td>
</tr>
<tr>
<td>Concomitant DMARD (frequency, (percentage))</td>
<td>37 (74.00)</td>
<td>68 (63.55)</td>
<td>105 (58.66)</td>
<td>143 (61.37)</td>
<td>0.092</td>
<td>0.701</td>
</tr>
<tr>
<td>Number of conventional dMARDs</td>
<td>2 (1-3)</td>
<td>2 (1-3)</td>
<td>1 (1-2)</td>
<td>1 (0-1)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prednisolone dose (mg/day) (median, (25-75%))</td>
<td>3.75 (0-5)</td>
<td>2.5 (0-5)</td>
<td>0 (0-5)</td>
<td>0 (0-5)</td>
<td>0.33</td>
<td>0.5240</td>
</tr>
<tr>
<td>DAS28 (mean (SD))</td>
<td>4.8 (1.4)</td>
<td>4.7 (1.2)</td>
<td>4.0 (1.3)</td>
<td>3.7 (1.3)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DAS28-CRP (mean, (SD))</td>
<td>4.78 (1.31)</td>
<td>4.55 (1.10)</td>
<td>3.9 (1.15)</td>
<td>3.67 (1.10)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MHAQ-score (0-3) (median (25-75%))</td>
<td>0.75 (0.36-1.13)</td>
<td>0.75 (0.5 – 1)</td>
<td>0.63 (0.25 – 1)</td>
<td>0.63 (0.25 – 1)</td>
<td>0.1961</td>
<td>0.0222</td>
</tr>
<tr>
<td>Swollen joints (Y/N, n (%))</td>
<td>44 (89.8)</td>
<td>88 (88.9)</td>
<td>135 (78.0)</td>
<td>142 (61.5)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>32-SJC (median (25-75 %))</td>
<td>6 (3-8)</td>
<td>5 (2-8)</td>
<td>3 (1-5)</td>
<td>1 (0-4)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>32-TJC (median (25-75 %))</td>
<td>7 (3-11)</td>
<td>8 (4-13)</td>
<td>5 (2-11)</td>
<td>4 (1-8)</td>
<td>0.0148</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CRP (mg/L) (median (25-75 %))</td>
<td>20 (10-48)</td>
<td>9 (5-30)</td>
<td>7 (4-19)</td>
<td>5 (3-12)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SR (median (25-75 %))</td>
<td>21 (10-42)</td>
<td>18 (10-30)</td>
<td>15 (8-26)</td>
<td>13 (6-24)</td>
<td>0.001</td>
<td>0.0039</td>
</tr>
<tr>
<td>Physician Global Assessment VAS (mean (SD))</td>
<td>49.45 (21.03)</td>
<td>40.77 (18.05)</td>
<td>34.59 (16.15)</td>
<td>32.07 (16.00)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Patient Global Assessment VAS (mean (SD))</td>
<td>59.34 (23.69)</td>
<td>54.56 (20.43)</td>
<td>53.48 (23.11)</td>
<td>51.92 (23.36)</td>
<td>0.044</td>
<td>0.3259</td>
</tr>
</tbody>
</table>

*p-value when comparing 2000-2003 group with 2010-2012 group.

**p-value when comparing 2004-2006 group with 2010-2012 group.
Figure 1: Patients receiving sDMARDs between 2000-2012:

Figure 2: Time trends in response and remission rates after 3 months for PsA patients receiving MTX in monotherapy between 2001-2012:

First vs. last period: p=0.470  p=0.194  p=0.067  p= 0.324  p=<0.0001
Figure 3: Time trends in response and remission rates for patients receiving TNFi in combinational therapy between 2000-2012

First vs. Last group: p=0.009    p=0.075    p=0.739    p=0.172    p=0.305