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Efficacy and tolerability of anti-TNF therapy in psoriatic arthritis patients: Results from the South Swedish Arthritis Treatment Group Register

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Background: The use of TNF blocking agents in psoriatic arthritis (PsA) is increasing, and the SSATG register has followed patients with PsA for more than 5 years.

Objective: To present efficacy and tolerability data of TNF-blocking agents on PsA in clinical practice. Also to study potential predictors for drug survival.

Material and Methods: Patients (n=261) with active PsA, starting anti-TNF therapy for the first time in southern Sweden, were included. Basal characteristics, disease activity measures, and termination reason for TNF-blockers were prospectively collected during the period April 1999 to September 2006. Cox proportional hazard models were used to investigate predictors for treatment termination.

Results: Overall, response rates at 3-12 months for VASglobal50 and VASpain50 were about 50%, whereas response rates for EULAR overall and EULAR good were around 75% and 55%, respectively. Concomitant MTX (HR=0.64 (95% CI 0.39-0.95), p=0.03), etanercept (HR=0.49 (0.28-0.86), p=0.01), and high CRP-levels (HR=0.77 (0.61-0.97), p=0.03) at treatment initiation were associated with better overall drug survival. The improved drug survival of concomitant MTX appeared to be related to significantly fewer drop outs because of adverse events (HR= 0.24 (0.11-0.52), p<0.01). The TNF-blockers were well tolerated with a rate of serious adverse events of 5-6% per year. No unexpected serious adverse events were observed.

Conclusion: Concomitant MTX and high CRP-levels are associated with treatment continuation of anti-TNF therapy in patients with PsA regardless of joint distribution. The positive effect of MTX was primarily linked to fewer drop outs because of adverse events.
Introduction:
Psoriatic arthritis (PsA) is a disease associated with psoriasis in the skin or nails accompanied by chronic arthritis, enthesopathy, seronegativity, HLA-B27 association, and dactylitis (1). Until the late nineties the treatment options for this disease were limited to non-steroidal anti-inflammatory drugs (NSAIDs) and regular physiotherapy with marginal benefit of traditional DMARDs (2). The emergence of TNF blocking agents was a breakthrough in the treatment of PsA, due to a large and rapid effect on many aspects of this disease including skin lesions (3-6). Over the past years the usage of these drugs has increased considerably in PsA. However, little is known about the effect and tolerability of TNF blocking treatment in clinical practice in this condition (7). Also the impact of different patterns of joint distribution has not been studied in detail. Previous studies have primarily focused on patients with peripheral arthritis (3-7). The South Swedish Arthritis Treatment Group (SSATG) has followed PsA patients since April 1999.

The objective of this study was to present efficacy and tolerability data on patients treated for psoriatic arthritis in clinical practice. Also we wanted to study the impact of concomitant methotrexate, patterns of joint distribution, and potential other predictors for drug survival with TNF blocking agents in patients with PsA.

Material and Methods:
Patients. Clinical data were collected as described in previous publications (8, 9), and no formal approval from the ethical committee was necessary. Rheumatologists in southern Sweden serving a population of about 1.3 million people supplied information during the period April 1999 through September 2006. Patients were continuously enrolled during the entire study period. Patients, eligible for the study had a diagnosis of PsA according to judgement by experienced physicians specialised in rheumatology, and were selected for anti-TNF therapy based on high disease activity and/or unacceptable steroid use. Furthermore, the indication for TNF blocking therapy was supported by guidelines when they began to emerge (10, 11). No predefined level of disease activity was required and no recommendation of type of anti-TNF agent was issued. Only patients receiving their first treatment course of biologic therapy were enrolled in the present analysis. All anti-TNF therapies were administered as add on therapy, and no other DMARDs were added at treatment initiation. A previous review of the coverage of anti-TNF drug prescription revealed that about 90% of the patients receiving these drugs in southern Sweden were included in the SSATG-database (12).

Etanercept was administered twice a week with a 25 mg subcutaneous dosage. Infliximab was infused at 3 mg/kg at 0, 2, 6, and then every 8th week. Depending on efficacy the dosage of infliximab could be increased in steps of 100 mg to a maximum of 500 mg administered at 4 to 8 week intervals. The average dosage after 6 month was about 5mg/kg every 8th week. Adalimumab was administered as a 40mg subcutaneous dose every other week.

Method. Clinical data were prospectively collected at 0, 3, 6, 12 months, and subsequently every 3-6 months. At inclusion and at each follow-up visit clinical data were registered as described in previous publications (8, 9) (year of disease onset, previous and concomitant DMARD treatment, NSAID usage,
HAQ (health assessment questionnaire), VASpain, VASglobal, Evalglobal, 28 tender and swollen joint count, ESR, and CRP. Baseline characteristics also included overall pattern of joint distribution: spondylitis only, peripheral arthritis only, and combined spondylitis and peripheral arthritis. Arthritis in joints distal to the hip and shoulders were regarded as peripheral arthritis. Spondylitis was solely based on judgment from the treating physician. The registrations of overall joint distribution pattern were incomplete, and retrospective reviews of about 50% of the medical records were performed to complete this information.

Any withdrawal from treatment was registered prospectively and classified by the treating physician as withdrawal caused by adverse events, lack of response/treatment failure, or miscellaneous (9).

To study the impact of concomitant MTX the patients were divided into two groups depending on concomitant MTX use at TNF blocking treatment initiation.

EULAR responses (13) based on 28 joint counts were chosen to assess clinical response because they have recently been validated and found more discriminative than the psoriatic arthritis response criteria (PsARC) in patients with peripheral arthritis (14). Also, improvement in the VASpain and VASglobal of at least 50% (VASpain50 and VASglobal50, respectively) were calculated at given times of follow up, in order to detect response in patients with a component of clinical spondylitis. No criteria for also assessing the spondylitis component of PsA has been validated (15); however relative changes in VASglobal were comparable to ASAS-responses in ankylosing spondylitis as opposed to changes in Physicians global evaluation (16), and relative changes in VASpain has been identified as the most important variable in the ASAS core set (17).

Furthermore, we employed Lund Efficacy Index (LUNDEX) (18) to calculate the fraction of patients, who not only remained on a particular therapy but also fulfilled certain response criteria. LUNDEX is calculated as the fraction of patients adhering to therapy multiplied by the fraction of patients fulfilling a selected response criterion at a given time (18).

All adverse events were prospectively collected by the treating physicians and classified according to the World Health Organisation adverse event terminology using forms from the Swedish Medical Products Agency. Also patients were independently urged to report adverse events by special forms systematically distributed to the patients prior to each follow-up. Seriousness was graded as mild, moderate, or serious (WHO definitions). In this study, we only report serious adverse events (SAE).

**Statistical analysis.** Baseline clinical characteristics were analysed by Mann-Whitney U-test for comparison of groups for continuous variables. Chi-square test was used for categorical variables. Drug survival data were estimated according to Kaplan Meier and further analysed with log-rank statistics for comparing different treatments. Cox proportional hazard models were used to investigate the effect of possible risk factors for treatment termination (age, gender, disease duration, concomitant NSAID, pattern of joint distribution, CRP-level, VASglobal, number of previous DMARDs, anti-TNF therapy, and concomitant MTX). Potential risk factors were selected a priori based on previous reports (9,19) and objectives of the study. A covariate correlation
<0.25 was required. The model assumptions for using Cox regression analysis were tested and found valid. Treatment responses were analyzed using Chi-square test and Wilcoxon's paired rank test was used for studying changes in CRP-level. Adverse events were compared using Rate Ratios (RR) with 95% confidence interval. Level of significance was chosen to be p<0.05.

Results

Baseline data. During the observational period a total of 261 patients were enrolled in the study. A review of 100 patients showed that 94% of the patients fulfilled the European Spondylarthropathy Study Group (ESSG) classification criteria for PsA (20). Demographic data and clinical characteristics of patients studied are presented in table 1. At baseline patients receiving regular NSAID were significantly more common in the MTX group, however, no other significant differences were found between patients with or without concomitant MTX. The median age was about 47 years; about half of the patients were female, and the disease duration at inclusion was around 8 to 9 years. 161 of the patients (62%) received concomitant MTX at treatment initiation, and the median dosage was 15.0 mg/week (IQR 10.0-20.0). Also, the pattern of joint distribution was similar in the two groups with around 6% of the patients having spondylitis only, 55-60% had peripheral arthritis only, and approximately 35-40% of the patients had both spondylitis and peripheral arthritis. For patients with peripheral arthritis the disease activity as measured by DAS28 was scored, and no differences were noted between the groups. During the treatment course 16 patients stopped MTX treatment. None of the patients started new MTX therapies after inclusion. A subgroup of 63 patients had 68 tender and 66 swollen joint counts at inclusion. Of these, 52% had polyarticular disease (5 or more joints) whereas 41% had mono or oligoarticular disease (4 or fewer joints). None of the subjects had distal interphalangeal (DIP) joint involvement only. In 47 of the patients joint counts and other variables were missing at baseline. These patients were included in the survival analysis, but had to be omitted from the responder analysis. The 47 patients did not differ from the rest of the patients with regard to age, gender, CRP-level, HAQ and concurrent methotrexate use. However, they had significantly longer disease duration (12.2 years vs. 7.8 years, p<0.01).

Drug survival estimated by Kaplan Meier plots are shown in figure 1. Overall, patients receiving concomitant MTX showed a trend for increased survival on drug (figure 1A) (p=0.10). When studying withdrawal from a treatment due to adverse events (figure 1B) or treatment failure (figure 1C) patients without MTX showed significantly lower drug survival due to adverse events (p<0.01), whereas no differences were found in withdrawal due to treatment failure (p=0.36). There were no significant differences between the treatments owing to withdrawal for the reason “miscellaneous” (data not shown). Regression analysis was applied to identify predictors for treatment termination and to evaluate whether potential baseline differences influenced drug survival. The multivariate Cox proportional hazard regression analysis is
presented in figure 1. When adjusting for the different covariates, concomitant MTX was significantly associated with reduced treatment termination of TNF blockers in patients with PsA (p=0.03). Among MTX treated patients the dosage-level or cessation of MTX therapy did not show any linkage to drug survival. Also, CRP-level at treatment initiation was significantly influencing survival on drug (p=0.03). The higher the CRP-level the better chance of drug survival. The Hazard Ratio (HR = 0.77) in the figure refers to risk reduction per Standard Deviation (29.7 mg/l) increment in CRP-level. Finally, patients treated with etanercept showed about half the risk of stopping therapy when compared to infliximab (p=0.01). No differences were found between infliximab and adalimumab (p=0.12) as well as adalimumab and etanercept (p=0.96).

Gender (p=0.48), age (p=0.34), concomitant NSAID usage (p=0.33), pattern of joint distribution (p=0.10), previous number of DMARDs (p=0.44), VASglobal (p=0.51) and disease duration (p=0.09) prior to treatment initiation did not predict the level of drug survival.

In a subgroup multivariate regression analysis on termination reason was performed to elucidate to what extent MTX, high CRP-level, and etanercept was associated with the reason of termination. Accordingly, the protective association of concomitant MTX appeared due to significantly fewer drop outs (p<0.01) because of adverse events (HR= 0.24 (0.11; 0.52)). In contrast concomitant MTX was not related to dropout because of treatment failure (HR = 1.39 (0.61; 3.18)). Likewise, etanercept treated patients showed significantly lower risk of termination because of adverse events (HR = 0.30 (0.11; 0.80), p=0.02) when compared to infliximab treated patients, while no differences were found in withdrawal due to failure (HR = 0.55 (0.25; 1.20). No other covariates showed significant hazard ratios when the Cox proportional hazard analysis was performed for patients stopping therapy due to adverse events or treatment failure only (data not shown).

No significant statistical interaction was found between concurrent MTX treatment and type of anti-TNF agent with regard to level of survival on drug.

Response data The per protocol proportion of patients fulfilling VASglobal50, VASpain50, EULAR good response, and EULAR overall (moderate plus good) responses based on the 214 patients with joint counts at baseline are shown in Table 2. Not all patients were followed up at each time point due to dropout and the premises of an observational setting. EULAR responses were not calculated for patients with clinical spondylitis only. Accordingly the actual numbers of evaluated patients are also displayed in table 2. Because of insufficient response recordings at late time points only response data at 3, 6 and 12 months of follow up are given. Overall, response rates for VASglobal50 and VASpain50 were about 50%, whereas response rates for EULAR good and EULAR overall were around 55% and 75%, respectively. Treatment responses for patients receiving concurrent MTX did not differ from those not receiving MTX. Pattern of joint distribution and type of anti-TNF therapy did not show differences in the level of treatment response (data not shown). The median CRP-level decreased significantly over 12 month to 3.5 mg/dl (IQR 1.0-10.2; p<0.01) in the MTX group and to 8.0 mg/dl (IQR 2.0-11.8; p<0.01) in the group of patients without MTX. No difference were noted between patients with or without MTX at 12 months (p=0.13).
LUNDEX adjusted responses were also calculated for the treatment groups and presented in table 2. The LUNDEX corrected response fractions all decreased during the follow up period as a consequence of drop out during the observational period. Generally, patients treated with concomitant MTX had a trend for higher LUNDEX values.

Safety. The TNF blocking agents were generally well-tolerated during the observational period, with a similar incidence of severe adverse events around 5-6% per year in patients treated with or without concomitant MTX (Table 3). Two malignancies were reported: one chronic lymphatic leukaemia (CLL), and one fatal non-Hodgkin lymphoma. Three life threatening adverse events were recorded, all in patients without concomitant MTX: Septicaemia with E. coli bacteria, and two anaphylactic infusion reactions. All severe infusion reactions occurred during infliximab treatment. No rare or unexpected adverse events were reported during the treatment period.

Discussion
This study identifies high CRP-levels at baseline and concomitant MTX treatment as positive predictors for anti-TNF drug survival in PsA independent of joint distribution pattern. The positive effect of concomitant MTX was primarily associated with decreased risk of treatment cessation because of any adverse events. Also patients receiving etanercept had prolonged drug survival compared to patients receiving infliximab, mainly because of fewer drop outs because of adverse events.

On the other hand, when studying serious adverse events only, no differences were found between patients treated with or without concomitant MTX, and the TNF blocking agents were generally well-tolerated during the observational period. Also, in accordance with previous studies (4-6) concomitant MTX did not seem to improve response to anti-TNF therapy. However, when calculating the true responder fractions as measured by LUNDEX (19), the group treated with concurrent MTX had a trend for higher treatment responses.

The pattern of joint distribution in this cohort of established PsA closely matches findings from previous reports. Thus the report by Moll and Wright (21) and the study by Helliwell and coworkers (22) consistent with our findings describe frequencies of isolated spondylitis in 5% and 6% of patients with PsA, respectively. In addition, Helliwell and coworkers (22) report combined spondylitis and peripheral arthritis in another 30% of patients as compared to about 36% in our material. The patients included in this observational cohort therefore seem representative for the broad spectrum of chronic PsA without selection of certain joint distribution phenotypes.

The response rates observed in this study were slightly lower than those found in randomized controlled clinical trials. Thus about 75% and 55% of the patients showed EULAR overall response and EULAR good responses, respectively. In clinical studies (4-6) with PsA treated with either etanercept or infliximab EULAR overall and EULAR good responses were about 90% and 60%, respectively.
As mentioned above, overall drug survival was associated with concomitant MTX, especially because of reduced withdrawal due to adverse events. This is in accordance with findings in patients with rheumatoid arthritis (RA) (9, 19). One reason underlying this difference could be that MTX effectively inhibits the formation of immunopathogenic antibodies against anti-TNF products, thus decreasing the risk for adverse events (23-25). Another explanation could be that patients not receiving MTX also have uncharacterised co-morbidities predisposing to lower drug survival. For instance they may be more disposed to gastro-intestinal intolerance, which could explain the lower NSAID use at baseline. Thus at the present stage the connection between concomitant MTX and improved drug survival in PsA remains an association without established cause-effect relationship.

The finding that high CRP-level at inclusion seems to protect against treatment termination has also been observed in anti-TNF treated RA patients (9). This is probably because patients with a high level of systemic inflammation have a larger potential for improvement during therapy (9). Interestingly, this is also in line with the recent study by Gratacos et al reporting a positive association with baseline CRP-level and ACR50 response (7).

The result that etanercept when compared to infliximab is associated with increased drug survival should be interpreted with caution. Confounding by indication and varying access of different TNF blocking drugs during the inclusion time from 1999 through September 2006 (9) makes the findings suggestive only at present.

The levels of SAE seemed generally lower in this population of PsA (5-6% per year) compared to patients with rheumatoid arthritis (8-13% per year) treated in the same area and monitored according to the same protocol (8). One explanation might be that RA patients were on average about 10 years older than the PsA patients (8). The SAE rates are also somewhat lower than rates reported from RCTs (8-18% per year) on anti-TNF treated PsA (5, 6). However, our data on adverse events mainly rely on a systematic voluntary adverse event reporting system, which may underestimate the true level of adverse events (26). At the same time, it should be noted that routine database reporting of adverse events has been proven up to twenty times superior compared to unstructured spontaneous adverse event reporting (27).

Finally, another important observation is that no unexpected types of SAE were reported.

Limitations of this open non-randomized study include risk of bias, both when collecting data and during the selection of patients for treatments. Thus, further studies on TNF blocking drugs used in PsA are needed to validate the results of this study, especially before making any interpretations of causality between the positive effect on drug survival of MTX and etanercept.

In conclusion, concomitant MTX and high CRP-levels at inclusion was associated with longterm drug survival of anti-TNF agents in patients with PsA regardless of joint distribution. The predictive value of MTX was primarily linked to fewer drop outs because of adverse events. Treatment responses were not affected by concomitant MTX and were generally lower compared to randomized controlled trials. In this observational cohort, TNF blocking agents
were generally well tolerated with few serious adverse events and no unexpected ones.

Competing interests:
LEK has received a fee for speaking by Wyeth, the manufacturer of etanercept; PG has received fees for speaking by Wyeth, Abbott, and Schering-Plough, the manufacturers of etanercept, adalimumab and infliximab, respectively. The sum of all fees adds up to < 10,000 USD per person.

References


Table 1: Demographic and clinical characteristics at baseline. Values are the median and interquartile range except where stated otherwise.

<table>
<thead>
<tr>
<th></th>
<th>MTX (n=161)</th>
<th>No MTX (n=100)</th>
<th>Level of significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age; years</td>
<td>48.2 (38.6-53.9)</td>
<td>46.0 (36.4-56.5)</td>
<td>p=0.99</td>
</tr>
<tr>
<td>Male; % (number)</td>
<td>52.2% (84)</td>
<td>45.0% (45)</td>
<td>p=0.07</td>
</tr>
<tr>
<td>Disease duration; years</td>
<td>7.9 (3.7-15.0)</td>
<td>9.4 (4.2-17.8)</td>
<td>p=0.29</td>
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<td>Spondylitis only (number) [133; 81]*</td>
<td>6.0% (8)</td>
<td>6.2% (5)</td>
<td>P=0.96</td>
</tr>
<tr>
<td>Peripheral arthritis only (number) [133; 81]*</td>
<td>56.4% (75)</td>
<td>58.0% (47)</td>
<td>P=0.81</td>
</tr>
<tr>
<td>Combined Peripheral arthritis and spondylitis (number) [133; 81]*</td>
<td>37.6% (50)</td>
<td>35.8% (29)</td>
<td>P=0.79</td>
</tr>
<tr>
<td>Number of previous DMARDs</td>
<td>2 (1.0-2.0)</td>
<td>2 (1.0-2.0)</td>
<td>p=0.20</td>
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<td>HAQ [160;91]*</td>
<td>1.00 (0.63-1.38)</td>
<td>1.00(0.50-1.50)</td>
<td>p=0.67</td>
</tr>
<tr>
<td>CRP; mg/l [160;88]*</td>
<td>9.1 (3.3-26.5)</td>
<td>11.0 (3.0-30.5)</td>
<td>p=0.72</td>
</tr>
<tr>
<td>ESR; mm/hr [160;90]*</td>
<td>18.0 (10.0-30.0)</td>
<td>17.5 (8.0-34.0)</td>
<td>p=0.67</td>
</tr>
<tr>
<td>DAS28 score [125; 76]**</td>
<td>4.93 (3.87-5.71)</td>
<td>4.82 (3.83-5.46)</td>
<td>p=0.57</td>
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<tr>
<td>Regular NSAID usage (number)</td>
<td>60.9% (98)</td>
<td>48.0% (48)</td>
<td>p=0.04</td>
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<td>Irregular NSAID usage (number)</td>
<td>13.0% (21)</td>
<td>9.0% (9)</td>
<td>P=0.32</td>
</tr>
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<td>Adalimumab; % (number)</td>
<td>10.6% (17)</td>
<td>11.0% (11)</td>
<td>P=0.99</td>
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<tr>
<td>Etanercept; % (number)</td>
<td>43.5% (70)</td>
<td>49.0 % (49)</td>
<td>P=0.38</td>
</tr>
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<td>Infliximab; % (number)</td>
<td>46.0% (74)</td>
<td>40.0% (40)</td>
<td>P=0.35</td>
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</table>

*In some patients joint counts and other baseline characteristics were lacking, the numbers within square brackets [MTX; no MTX] are the actual number of patients observed for the particular variable.

**Only calculated for subgroup of patients with joint counts and peripheral arthritis.

Figure 1: Drug survival for psoriatic arthritis patients treated with anti-TNF therapies is shown as the fraction (between 1 and 0) of patients remaining on therapy during the observation period. Withdrawal due to any reason (1A), adverse events (1B), or failure to treatment (1C) is presented separately. The number of patients under observation at each time point is listed below the figures.

Figure 2 shows hazard ratios, 95% confidence intervals, and level of significance on a logarithmic scale from the multivariate Cox-regression analysis for the predictors of treatment termination studied. Low hazard ratios indicate good drug survival. The hazard ratio for CRP is given per SD (29.7 mg/l) increment of CRP concentration. Only the hazard ratio for concomitant MTX, CRP-level, and type of anti-TNF treatment are shown, the other covariates were not significant and only described in the text.
Table 2. Per protocol response rates and LUNDEX adjusted response rates at follow up times grouped according to concomitant methotrexate treatment. Values are shown as percentages of patients fulfilling the particular response criteria at follow up times 3, 6, and 12 months respectively. The per protocol number of patients evaluated for either VAS or EULAR response at each time point is listed in the table.

<table>
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<th>Follow-up month</th>
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<td>12</td>
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<td>Number at observation for VAS responses</td>
<td>n=108</td>
<td>n=87</td>
<td>n=79</td>
<td>n=71</td>
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<td>n=31</td>
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<td>VASglobal 50% improvement</td>
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<td>53</td>
<td>41</td>
<td>48</td>
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<td>45</td>
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<tr>
<td>VASpain 50% improvement</td>
<td>49</td>
<td>57</td>
<td>42</td>
<td>44</td>
<td>52</td>
<td>39</td>
</tr>
<tr>
<td>Number at observation for EULAR responses</td>
<td>n=104</td>
<td>n=82</td>
<td>n=74</td>
<td>n=67</td>
<td>n=54</td>
<td>n=27</td>
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<tr>
<td>EULAR overall</td>
<td>78</td>
<td>76</td>
<td>69</td>
<td>75</td>
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<td>EULAR good</td>
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<td>LUNDEX adjusted treatment responses</td>
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<td>LUNDEX\textsubscript{VASglobal50}</td>
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Table 3. Serious adverse events during the observational period graded according to WHO terminology. Exposure time, total rates and subtypes of adverse events are shown in the table.

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<tr>
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<th>MTX</th>
<th>No MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total treatment time (years)</td>
<td>319.5</td>
<td>209</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All SAE (number)</td>
<td>5.32 (17)</td>
<td>5.74 (12)</td>
</tr>
<tr>
<td>Infections *</td>
<td>1.56 (5)</td>
<td>0.96 (2)</td>
</tr>
<tr>
<td>Circulatory ** events</td>
<td>0.94 (3)</td>
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<tr>
<td>Musculoskeletal***</td>
<td>0.94 (3)</td>
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<td>Malignancies</td>
<td>0.31 (1)#</td>
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<tr>
<td>Infusion reactions</td>
<td>0.63 (2)</td>
<td>1.44 (3)</td>
</tr>
<tr>
<td>Other****</td>
<td>0.94 (3)</td>
<td>1.44 (3)</td>
</tr>
</tbody>
</table>

# Fatal non-Hodgkin lymphoma (diffuse large B-cell lymphoma)
## Chronic lymphatic leukaemia (CLL), with probable subclinical debut prior to anti-TNF treatment
* Mainly respiratory tract infections with no reported events of tuberculosis.
** One transient ischemic attack, two acute coronary syndromes, and two tachyarrhythmias.
*** Three peripheral fractures and one cervical spinal stenosis requiring surgery.
**** Severe vertigo, Irritable bowel disease after hospitalisation and endoscopic biopsy, benign stenosis of the esophagus, concrement in the urinary tract, non-infectious pleuritis, severe dysplasia of cervix uteri.
Efficacy and tolerability of anti-TNF therapy in psoriatic arthritis patients: Results from the South Swedish Arthritis Treatment Group Register

Lars Erik Kristensen, Anders Gülfe, Tore Saxne, and Pierre Geborek
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**Background:** The use of TNF blocking agents in psoriatic arthritis (PsA) is increasing, and the SSATG register has followed patients with PsA for more than 5 years.

**Objective:** To present efficacy and tolerability data of TNF-blocking agents on PsA in clinical practice. Also to study potential predictors for drug survival.

**Material and Methods:** Patients (n=261) with active PsA, starting anti-TNF therapy for the first time in southern Sweden, were included. Basal characteristics, disease activity measures, and termination reason for TNF-blockers were prospectively collected during the period April 1999 to September 2006. Cox proportional hazard models were used to investigate predictors for treatment termination.

**Results** Overall, response rates at 3-12 months for VASglobal50 and VASpain50 were about 50%, whereas response rates for EULAR overall and EULAR good were around 75% and 55%, respectively. Concomitant MTX (HR=0.64 (95% CI 0.39-0.95), p=0.03), etanercept (HR=0.49 (0.28-0.86), p=0.01), and high CRP-levels (HR=0.77 (0.61-0.97), p=0.03) at treatment initiation were associated with better overall drug survival. The improved drug survival of concomitant MTX appeared to be related to significantly fewer drop outs because of adverse events (HR= 0.24 (0.11-0.52), p<0.01). The TNF-blockers were well tolerated with a rate of serious adverse events of 5-6% per year. No unexpected serious adverse events were observed.

**Conclusion:** Concomitant MTX and high CRP-levels are associated with treatment continuation of anti-TNF therapy in patients with PsA regardless of joint distribution. The positive effect of MTX was primarily linked to fewer drop outs because of adverse events.
Introduction:
Psoriatic arthritis (PsA) is a disease associated with psoriasis in the skin or nails accompanied by chronic arthritis, enthesopathy, seronegativity, HLA-B27 association, and dactylitis (1). Until the late nineties the treatment options for this disease were limited to non-steroidal anti-inflammatory drugs (NSAIDs) and regular physiotherapy with marginal benefit of traditional DMARDs (2). The emergence of TNF blocking agents was a breakthrough in the treatment of PsA, due to a large and rapid effect on many aspects of this disease including skin lesions (3-6). Over the past years the usage of these drugs has increased considerably in PsA. However, little is known about the effect and tolerability of TNF blocking treatment in clinical practice in this condition (7). Also the impact of different patterns of joint distribution has not been studied in detail. Previous studies have primarily focused on patients with peripheral arthritis (3-7). The South Swedish Arthritis Treatment Group (SSATG) has followed PsA patients since April 1999.

The objective of this study was to present efficacy and tolerability data on patients treated for psoriatic arthritis in clinical practice. Also we wanted to study the impact of concomitant methotrexate, patterns of joint distribution, and potential other predictors for drug survival with TNF blocking agents in patients with PsA.

Material and Methods:
Patients. Clinical data were collected as described in previous publications (8, 9), and no formal approval from the ethical committee was necessary. Rheumatologists in southern Sweden serving a population of about 1.3 million people supplied information during the period April 1999 through September 2006. Patients were continuously enrolled during the entire study period. Patients, eligible for the study had a diagnosis of PsA according to judgement by experienced physicians specialised in rheumatology, and were selected for anti-TNF therapy based on high disease activity and/or unacceptable steroid use. Furthermore, the indication for TNF blocking therapy was supported by guidelines when they began to emerge (10, 11). No predefined level of disease activity was required and no recommendation of type of anti-TNF agent was issued. Only patients receiving their first treatment course of biologic therapy were enrolled in the present analysis. All anti-TNF therapies were administrered as add on therapy, and no other DMARDs were added at treatment initiation. A previous review of the coverage of anti-TNF drug prescription revealed that about 90% of the patients receiving these drugs in southern Sweden were included in the SSATG-database (12).

Etanercept was administrered twice a week with a 25 mg subcutaneous dosage. Infliximab was infused at 3 mg/kg at 0, 2, 6, and then every 8th week. Depending on efficacy the dosage of infliximab could be increased in steps of 100 mg to a maximum of 500 mg administered at 4 to 8 week intervals. The average dosage after 6 month was about 5mg/kg every 8th week. Adalimumab was administered as a 40mg subcutaneous dose every other week.

Method. Clinical data were prospectively collected at 0, 3, 6, 12 months, and subsequently every 3-6 months. At inclusion and at each follow-up visit clinical data were registered as described in previous publications (8, 9) (year of disease onset, previous and concomitant DMARD treatment, NSAID usage,
Baseline characteristics also included overall pattern of joint distribution: spondylitis only, peripheral arthritis only, and combined spondylitis and peripheral arthritis. Arthritis in joints distal to the hip and shoulders were regarded as peripheral arthritis. Spondylitis was solely based on judgment from the treating physician. The registrations of overall joint distribution pattern were incomplete, and retrospective reviews of about 50% of the medical records were performed to complete this information.

Any withdrawal from treatment was registered prospectively and classified by the treating physician as withdrawal caused by adverse events, lack of response/treatment failure, or miscellaneous (9). To study the impact of concomitant MTX the patients were divided into two groups depending on concomitant MTX use at TNF blocking treatment initiation.

EULAR responses (13) based on 28 joint counts were chosen to assess clinical response because they have recently been validated and found more discriminative than the psoriatic arthritis response criteria (PsARC) in patients with peripheral arthritis (14). Also, improvement in the VASpain and VASglobal of at least 50% (VASpain50 and VASglobal50, respectively) were calculated at given times of follow up, in order to detect response in patients with a component of clinical spondylitis. No criteria for also assessing the spondylitis component of PsA has been validated (15); however relative changes in VASglobal were comparable to ASAS-responses in ankylosing spondylitis as opposed to changes in Physicians global evaluation (16), and relative changes in VASpain has been identified as the most important variable in the ASAS core set (17).

Furthermore, we employed Lund Efficacy Index (LUNDEX) (18) to calculate the fraction of patients, who not only remained on a particular therapy but also fulfilled certain response criteria. LUNDEX is calculated as the fraction of patients adhering to therapy multiplied by the fraction of patients fulfilling a selected response criterion at a given time (18).

All adverse events were prospectively collected by the treating physicians and classified according to the World Health Organisation adverse event terminology using forms from the Swedish Medical Products Agency. Also patients were independently urged to report adverse events by special forms systematically distributed to the patients prior to each follow-up. Seriousness was graded as mild, moderate, or serious (WHO definitions). In this study, we only report serious adverse events (SAE).

**Statistical analysis.** Baseline clinical characteristics were analysed by Mann-Whitney U-test for comparison of groups for continuous variables. Chi-square test was used for categorical variables. Drug survival data were estimated according to Kaplan Meier and further analysed with log-rank statistics for comparing different treatments. Cox proportional hazard models were used to investigate the effect of possible risk factors for treatment termination (age, gender, disease duration, concomitant NSAID, pattern of joint distribution, CRP-level, VASglobal, number of previous DMARDs, anti-TNF therapy, and concomitant MTX). Potential risk factors were selected a priori based on previous reports (9,19) and objectives of the study. A covariate correlation
<0.25 was required. The model assumptions for using Cox regression analysis were tested and found valid. Treatment responses were analyzed using Chi-square test and Wilcoxon’s paired rank test was used for studying changes in CRP-level. Adverse events were compared using Rate Ratios (RR) with 95% confidence interval. Level of significance was chosen to be p<0.05.

Results

Baseline data. During the observational period a total of 261 patients were enrolled in the study. A review of 100 patients showed that 94% of the patients fulfilled the European Spondylarthropathy Study Group (ESSG) classification criteria for PsA (20). Demographic data and clinical characteristics of patients studied are presented in table 1.

At baseline patients receiving regular NSAID were significantly more common in the MTX group, however, no other significant differences were found between patients with or without concomitant MTX. The median age was about 47 years; about half of the patients were female, and the disease duration at inclusion was around 8 to 9 years. 161 of the patients (62%) received concomitant MTX at treatment initiation, and the median dosage was 15.0 mg/week (IQR 10.0-20.0). Also, the pattern of joint distribution was similar in the two groups with around 6% of the patients having spondylitis only, 55-60% had peripheral arthritis only, and approximately 35-40% of the patients had both spondylitis and peripheral arthritis. For patients with peripheral arthritis the disease activity as measured by DAS28 was scored, and no differences were noted between the groups. During the treatment course 16 patients stopped MTX treatment. None of the patients started new MTX therapies after inclusion.

A subgroup of 63 patients had 68 tender and 66 swollen joint counts at inclusion. Of these, 52% had polyarticular disease (5 or more joints) whereas 41% had mono or oligoarticular disease (4 or fewer joints). None of the subjects had distal interphalangeal (DIP) joint involvement only.

In 47 of the patients joint counts and other variables were missing at baseline. These patients were included in the survival analysis, but had to be omitted from the responder analysis. The 47 patients did not differ from the rest of the patients with regard to age, gender, CRP-level, HAQ and concurrent methotrexate use. However, they had significantly longer disease duration (12.2 years vs. 7.8 years, p<0.01).

Drug survival estimated by Kaplan Meier plots are shown in figure 1. Overall, patients receiving concomitant MTX showed a trend for increased survival on drug (figure 1A) (p=0.10). When studying withdrawal from a treatment due to adverse events (figure 1B) or treatment failure (figure 1C) patients without MTX showed significantly lower drug survival due to adverse events (p<0.01), whereas no differences were found in withdrawal due to treatment failure (p=0.36). There were no significant differences between the treatments owing to withdrawal for the reason “miscellaneous” (data not shown).

Regression analysis was applied to identify predictors for treatment termination and to evaluate whether potential baseline differences influenced drug survival. The multivariate Cox proportional hazard regression analysis is...
presented in figure 1. When adjusting for the different covariates, concomitant MTX was significantly associated with reduced treatment termination of TNF blockers in patients with PsA (p=0.03). Among MTX treated patients the dosage-level or cessation of MTX therapy did not show any linkage to drug survival. Also, CRP-level at treatment initiation was significantly influencing survival on drug (p=0.03). The higher the CRP-level the better chance of drug survival. The Hazard Ratio (HR = 0.77) in the figure refers to risk reduction per Standard Deviation (29.7 mg/l) increment in CRP-level. Finally, patients treated with etanercept showed about half the risk of stopping therapy when compared to infliximab (p=0.01). No differences were found between infliximab and adalimumab (p=0.12) as well as adalimumab and etanercept (p=0.96).

Gender (p=0.48), age (p=0.34), concomitant NSAID usage (p=0.33), pattern of joint distribution (p=0.10), previous number of DMARDs (p=0.44), VASglobal (p=0.51) and disease duration (p=0.09) prior to treatment initiation did not predict the level of drug survival. In a subgroup multivariate regression analysis on termination reason was performed to elucidate to what extent MTX, high CRP-level, and etanercept was associated with the reason of termination. Accordingly, the protective association of concomitant MTX appeared due to significantly fewer drop outs (p<0.01) because of adverse events (HR= 0.24 (0.11; 0.52)). In contrast concomitant MTX was not related to dropout because of treatment failure (HR = 1.39 (0.61; 3.18)). Likewise, etanercept treated patients showed significantly lower risk of termination because of adverse events (HR = 0.30 (0.11; 0.80), p=0.02) when compared to infliximab treated patients, while no differences were found in withdrawal due to failure (HR = 0.55 (0.25; 1.20). No other covariates showed significant hazard ratios when the Cox proportional hazard analysis was performed for patients stopping therapy due to adverse events or treatment failure only (data not shown).

No significant statistical interaction was found between concurrent MTX treatment and type of anti-TNF agent with regard to level of survival on drug.

Response data The per protocol proportion of patients fulfilling VASglobal50, VASpain50, EULAR good response, and EULAR overall (moderate plus good) responses based on the 214 patients with joint counts at baseline are shown in Table 2. Not all patients were followed up at each time point due to dropout and the premises of an observational setting. EULAR responses were not calculated for patients with clinical spondylitis only. Accordingly the actual numbers of evaluated patients are also displayed in table 2. Because of insufficient response recordings at late time points only response data at 3, 6 and 12 months of follow up are given. Overall, response rates for VASglobal50 and VASpain50 were about 50%, whereas response rates for EULAR good and EULAR overall were around 55% and 75%, respectively. Treatment responses for patients receiving concurrent MTX did not differ from those not receiving MTX. Pattern of joint distribution and type of anti-TNF therapy did not show differences in the level of treatment response (data not shown). The median CRP-level decreased significantly over 12 month to 3.5 mg/dl (IQR 1.0-10.2; p<0.01) in the MTX group and to 8.0 mg/dl (IQR 2.0-11.8; p<0.01) in the group of patients without MTX. No difference were noted between patients with or without MTX at 12 months (p=0.13).
LUNDEX adjusted responses were also calculated for the treatment groups and presented in table 2. The LUNDEX corrected response fractions all decreased during the follow up period as a consequence of drop out during the observational period. Generally, patients treated with concomitant MTX had a trend for higher LUNDEX values.

**Safety.** The TNF blocking agents were generally well-tolerated during the observational period, with a similar incidence of severe adverse events around 5-6% per year in patients treated with or without concomitant MTX (Table 3). Two malignancies were reported: one chronic lymphatic leukaemia (CLL), and one fatal non-Hodgkin lymphoma. Three life threatening adverse events were recorded, all in patients without concomitant MTX: Septicaemia with E. coli bacteria, and two anaphylactic infusion reactions. All severe infusion reactions occurred during infliximab treatment. No rare or unexpected adverse events were reported during the treatment period.

**Discussion**
This study identifies high CRP-levels at baseline and concomitant MTX treatment as positive predictors for anti-TNF drug survival in PsA independent of joint distribution pattern. The positive effect of concomitant MTX was primarily associated with decreased risk of treatment cessation because of any adverse events. Also patients receiving etanercept had prolonged drug survival compared to patients receiving infliximab, mainly because of fewer drop outs because of adverse events. On the other hand, when studying serious adverse events only, no differences were found between patients treated with or without concomitant MTX, and the TNF blocking agents were generally well-tolerated during the observational period. Also, in accordance with previous studies (4-6) concomitant MTX did not seem to improve response to anti-TNF therapy. However, when calculating the true responder fractions as measured by LUNDEX (19), the group treated with concurrent MTX had a trend for higher treatment responses.

The pattern of joint distribution in this cohort of established PsA closely matches findings from previous reports. Thus the report by Moll and Wright (21) and the study by Helliwell and coworkers (22) consistent with our findings describe frequencies of isolated spondylitis in 5% and 6% of patients with PsA, respectively. In addition, Helliwell and coworkers (22) report combined spondylitis and peripheral arthritis in another 30% of patients as compared to about 36% in our material. The patients included in this observational cohort therefore seem representative for the broad spectrum of chronic PsA without selection of certain joint distribution phenotypes.

The response rates observed in this study were slightly lower than those found in randomized controlled clinical trials. Thus about 75% and 55% of the patients showed EULAR overall response and EULAR good responses, respectively. In clinical studies (4-6) with PsA treated with either etanercept or infliximab EULAR overall and EULAR good responses were about 90% and 60%, respectively.
As mentioned above, overall drug survival was associated with concomitant MTX, especially because of reduced withdrawal due to adverse events. This is in accordance with findings in patients with rheumatoid arthritis (RA) (9, 19). One reason underlying this difference could be that MTX effectively inhibits the formation of immunopathogenic antibodies against anti-TNF products, thus decreasing the risk for adverse events (23-25). Another explanation could be that patients not receiving MTX also have uncharacterised co-morbidities predisposing to lower drug survival. For instance they may be more disposed to gastro-intestinal intolerance, which could explain the lower NSAID use at baseline. Thus at the present stage the connection between concomitant MTX and improved drug survival in PsA remains an association without established cause-effect relationship.

The finding that high CRP-level at inclusion seems to protect against treatment termination has also been observed in anti-TNF treated RA patients (9). This is probably because patients with a high level of systemic inflammation have a larger potential for improvement during therapy (9). Interestingly, this is also in line with the recent study by Gratacos et al reporting a positive association with baseline CRP-level and ACR50 response (7).

The result that etanercept when compared to infliximab is associated with increased drug survival should be interpreted with caution. Confounding by indication and varying access of different TNF blocking drugs during the inclusion time from 1999 through September 2006 (9) makes the findings suggestive only at present.

The levels of SAE seemed generally lower in this population of PsA (5-6% per year) compared to patients with rheumatoid arthritis (8-13% per year) treated in the same area and monitored according to the same protocol (8). One explanation might be that RA patients were on average about 10 years older than the PsA patients (8). The SAE rates are also somewhat lower than rates reported from RCTs (8-18% per year) on anti-TNF treated PsA (5, 6). However, our data on adverse events mainly rely on a systematic voluntary adverse event reporting system, which may underestimate the true level of adverse events (26). At the same time, it should be noted that routine database reporting of adverse events has been proven up to twenty times superior compared to unstructured spontaneous adverse event reporting (27). Finally, another important observation is that no unexpected types of SAE were reported.

Limitations of this open non-randomized study include risk of bias, both when collecting data and during the selection of patients for treatments. Thus, further studies on TNF blocking drugs used in PsA are needed to validate the results of this study, especially before making any interpretations of causality between the positive effect on drug survival of MTX and etanercept.

In conclusion, concomitant MTX and high CRP-levels at inclusion was associated with longterm drug survival of anti-TNF agents in patients with PsA regardless of joint distribution. The predictive value of MTX was primarily linked to fewer drop outs because of adverse events. Treatment responses were not affected by concomitant MTX and were generally lower compared to randomized controlled trials. In this observational cohort, TNF blocking agents
were generally well tolerated with few serious adverse events and no unexpected ones.

**Competing interests:**
LEK has received a fee for speaking by Wyeth, the manufacturer of etanercept; PG has received fees for speaking by Wyeth, Abbott, and Schering-Plough, the manufacturers of etanercept, adalimumab and infliximab, respectively. The sum of all fees adds up to < 10,000 USD per person.

**References**


Table 1: Demographic and clinical characteristics at baseline. Values are the median and interquartile range except where stated otherwise.

<table>
<thead>
<tr>
<th></th>
<th>MTX (n=161)</th>
<th>No MTX (n=100)</th>
<th>Level of significance</th>
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<tr>
<td>Age; years</td>
<td>48.2 (36.6-53.9)</td>
<td>46.0 (36.4-56.5)</td>
<td>p=0.99</td>
</tr>
<tr>
<td>Male; % (number)</td>
<td>52.2% (84)</td>
<td>45.0% (45)</td>
<td>p=0.07</td>
</tr>
<tr>
<td>Disease duration; years</td>
<td>7.9 (3.7-15.0)</td>
<td>9.4 (4.2-17.8)</td>
<td>p=0.29</td>
</tr>
<tr>
<td>Spondylitis only (number) [133; 81]*</td>
<td>6.0% (8)</td>
<td>6.2% (5)</td>
<td>p=0.96</td>
</tr>
<tr>
<td>Peripheral arthritis only (number) [133; 81]*</td>
<td>56.4% (75)</td>
<td>58.0% (47)</td>
<td>p=0.81</td>
</tr>
<tr>
<td>Combined Peripheral arthritis and spondylitis (number) [133; 81]*</td>
<td>37.6% (50)</td>
<td>35.85% (29)</td>
<td>p=0.79</td>
</tr>
<tr>
<td>Number of previous DMARDs</td>
<td>2 (1.0-2.0)</td>
<td>2 (1.0-2.0)</td>
<td>p=0.20</td>
</tr>
<tr>
<td>HAQ [160;91]*</td>
<td>1.00 (0.63-1.38)</td>
<td>1.00(0.50-1.50)</td>
<td>p=0.67</td>
</tr>
<tr>
<td>CRP; mg/l [160;88]*</td>
<td>9.1 (3.3-26.5)</td>
<td>11.0 (3.0-30.5)</td>
<td>p=0.72</td>
</tr>
<tr>
<td>ESR; mm/hr [160;90]*</td>
<td>18.0 (10.0-30.0)</td>
<td>17.5 (8.0-34.0)</td>
<td>p=0.67</td>
</tr>
<tr>
<td>DAS28 score [125; 76]**</td>
<td>4.93 (3.97-5.71)</td>
<td>4.82 (3.83-5.46)</td>
<td>p=0.57</td>
</tr>
<tr>
<td>Regular NSAID usage (number)</td>
<td>60.9% (98)</td>
<td>48.0% (48)</td>
<td>p=0.04</td>
</tr>
<tr>
<td>Irregular NSAID usage (number)</td>
<td>13.0% (21)</td>
<td>9.0% (9)</td>
<td>p=0.32</td>
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<tr>
<td>Adalimumab; % (number)</td>
<td>10.6% (17)</td>
<td>11.0% (11)</td>
<td>p=0.99</td>
</tr>
<tr>
<td>Etanercept; % (number)</td>
<td>43.5% (70)</td>
<td>49.0 % (49)</td>
<td>p=0.38</td>
</tr>
<tr>
<td>Infliximab; % (number)</td>
<td>46.0% (74)</td>
<td>40.0% (40)</td>
<td>p=0.35</td>
</tr>
</tbody>
</table>

*In some patients joint counts and other baseline characteristics were lacking, the numbers within square brackets [MTX; no MTX] are the actual number of patients observed for the particular variable.

**Only calculated for subgroup of patients with joint counts and peripheral arthritis.

Figure 1: Drug survival for psoriatic arthritis patients treated with anti-TNF therapies is shown as the fraction (between 1 and 0) of patients remaining on therapy during the observation period. Withdrawal due to any reason (1A), adverse events (1B), or failure to treatment (1C) is presented separately. The number of patients under observation at each time point is listed below the figures.

Figure 2 shows hazard ratios, 95% confidence intervals, and level of significance on a logarithmic scale from the multivariate Cox-regression analysis for the predictors of treatment termination studied. Low hazard ratios indicate good drug survival. The hazard ratio for CRP is given per SD (29.7 mg/l) increment of CRP concentration. Only the hazard ratio for concomitant MTX, CRP-level, and type of anti-TNF treatment are shown, the other covariates were not significant and only described in the text.
Table 2. Per protocol response rates and LUNDEX adjusted response rates at follow up times grouped according to concomitant methotrexate treatment. Values are shown as percentages of patients fulfilling the particular response criteria at follow up times 3, 6, and 12 months respectively. The per protocol number of patients evaluated for either VAS or EULAR response at each time point is listed in the table.

<table>
<thead>
<tr>
<th>Follow-up month</th>
<th>MTX</th>
<th>No MTX</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Number at observation for VAS responses</td>
<td>n=108</td>
<td>n=87</td>
</tr>
<tr>
<td>VASglobal 50% improvement</td>
<td>48</td>
<td>53</td>
</tr>
<tr>
<td>VASpain 50% improvement</td>
<td>49</td>
<td>57</td>
</tr>
<tr>
<td>Number at observation for EULAR responses</td>
<td>n=104</td>
<td>n=82</td>
</tr>
<tr>
<td>EULAR overall</td>
<td>78</td>
<td>76</td>
</tr>
<tr>
<td>EULAR good</td>
<td>51</td>
<td>60</td>
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LUNDEX adjusted treatment responses

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<tr>
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<th>MTX</th>
<th>No MTX</th>
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<tbody>
<tr>
<td>VASglobal50</td>
<td>46</td>
<td>47</td>
</tr>
<tr>
<td>VASpain50</td>
<td>47</td>
<td>51</td>
</tr>
<tr>
<td>EULARoverall</td>
<td>74</td>
<td>68</td>
</tr>
<tr>
<td>EULARgood</td>
<td>48</td>
<td>53</td>
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</table>
Table 3. Serious adverse events during the observational period graded according to WHO terminology. Exposure time, total rates and subtypes of adverse events are shown in the table.

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<td>0.94 (3)</td>
<td>1.44 (3)</td>
</tr>
</tbody>
</table>

# Fatal non-Hodgkin lymphoma (diffuse large B-cell lymphoma)
## Chronic lymphatic leukaemia (CLL), with probable subclinical debut prior to anti-TNF treatment
* Mainly respiratory tract infections with no reported events of tuberculosis.
** One transient ischemic attack, two acute coronary syndromes, and two tachyarrhythmias.
*** Three peripheral fractures and one cervical spinal stenosis requiring surgery.
**** Severe vertigo, Irritable bowl disease after hospitalisation and endoscopic biopsy, benign stenosis of the esophagus, concrement in the urinary tract, non-infectious pleuritis, severe dysplasia of cervix uteri.