

Elevated C-Reactive Protein Level Predicts Earlier Treatment with Tumor Necrosis Factor-Alpha Inhibitors in Psoriatic Arthritis

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ABSTRACT: **Background:** Tumor necrosis factor-alpha (TNF α) inhibitors are indicated for patients with psoriatic arthritis (PsA) in whom conventional disease-modifying anti-rheumatic drugs (DMARDs) are insufficient to achieve disease remission. **Objectives:** To determine the value of acute-phase reactant levels at diagnosis of psoriatic arthritis in predicting the need for biologic treatment with TNF α inhibitors. **Methods:** We conducted a longitudinal observational study of an inception cohort of 71 consecutive patients diagnosed with psoriatic arthritis. C-reactive protein (CRP) was assayed for all patients at their first visit. **Results:** All patients were treated with one or more DMARDs, mainly methotrexate (81.6%). Thirty-seven patients (52.11%) had an inadequate response and received at least one TNF inhibitor. CRP level at diagnosis was positively correlated with need for a TNF inhibitor ($P = 0.009$, HR 1.8, 95%CI 1.27–1.85). Patients with CRP > 0.9 mg/dl at diagnosis started biologic treatment significantly earlier than patients with a lower level ($P = 0.003$, HR 2.62, 95%CI 0.393–2.5). **Conclusions:** In patients with psoriatic arthritis, CRP ≥ 0.9 mg/dl at diagnosis significantly predicts an earlier need for a TNF inhibitor to achieve disease control.

IMAJ 2016; 18: 279–282

KEY WORDS: C-reactive protein (CRP), psoriatic arthritis (PsA), tumor necrosis factor-alpha (TNF α) inhibitor, disease-modifying anti-rheumatic drugs (DMARDs)

Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy affecting 6%–42% of patients with psoriasis [1]. Five clinical presentations have been described: symmetric polyarthritis, distal-interphalangeal joint (DIP) (as the predominant pattern) arthritis, oligoarticular asymmetric arthritis, arthritis mutilans, and axial arthritis (ankylosing spondylitis). In 85% of cases the skin disease precedes the arthritis by an average lag time of 10 years; in the remaining cases the joint disease occurs first [1].

Unlike rheumatoid arthritis, the presence of active PsA is not correlated with levels of acute-phase reactants (erythrocyte sedimentation rate and C-reactive protein), and normal values

of acute-phase reactants on laboratory workup do not exclude active joint inflammation. Therefore, these parameters do not serve as reliable markers of baseline disease activity or response to therapy. Nevertheless, an association has been noted between high erythrocyte sedimentation rate (ESR) at presentation and rapid progression of the joint disease and early mortality [2]. The first-line treatment of active chronic peripheral PsA often consists of disease-modifying anti-rheumatic drugs (DMARDs): methotrexate (MTX), sulfasalazine (SSZ) and leflunomide (LFN) [3,4]. In the last decade, randomized placebo-controlled clinical trials of biologic agents found tumor necrosis factor-alpha (TNF α) inhibitors (infliximab, adalimumab, etanercept) to be effective [4-6]. Currently, TNF α inhibitors are recommended for patients with active disease refractory to conventional DMARDs (mainly MTX) [3-6]. Studies have shown that a high C-reactive protein (CRP) level (> 10 mg/L) at baseline is predictive of longer treatment with TNF inhibitor and a good clinical response [7-9]. The better response to biologic therapy was attributed to the probable link of CRP level with systemic inflammation in PsA. However, at present, there are no known parameters for predicting DMARD failure and need for TNF inhibitor treatment.

The aim of this study was to determine whether levels of acute-phase reactants (ESR, CRP) at diagnosis, before initiation of any treatment, can serve as predictors of a future need for a TNF α inhibitor to achieve control of PsA under real-life conditions.

PATIENTS AND METHODS

We performed a longitudinal observational study of 71 consecutive patients with PsA attending the Rheumatology Clinic of Rabin Medical Center, a tertiary university-affiliated hospital in central Israel, during the period 2000–2011. All patients fulfilled the criteria for the Classification of Psoriatic Arthritis (CASPAR) [10] at or within 12 months prior to their first visit to our clinic.

Patients prescribed a TNF α inhibitor for a dermatologic indication (by a dermatologist) were excluded from the study. The following data were recorded from the patients' medical

files and electronic records: demographic features and clinical findings at diagnosis, including co-morbidities, ESR and CRP levels at the first clinic visit (time of diagnosis) and the last study visit, type of DMARDs and TNF α inhibitors prescribed, as applicable, interval from diagnosis to initiation and discontinuation of treatment, as applicable, clinical response (as assessed by the attending rheumatologist), adverse effects of treatment, and cause of death, if applicable. CRP was assayed by the hospital's biochemistry laboratory using the immunoturbidimetric Tina-quant CRP method (Roche Hitachi 911, Roche Diagnostics/Boehringer Mannheim Corp., Indianapolis, IN, USA) (normal range 0.00–0.50 mg/dl); ESR was measured in the hospital's hematologic laboratory using the Sedimatic 100 analyzer (Pharmatop, Bromma, Sweden). The study protocol was approved by the institutional review board.

STATISTICAL ANALYSIS

Data were analyzed with SPSS software, version 20.0. Demographic and disease characteristics were analyzed by frequency and descriptive statistics. Changes in continuous parameters (CRP, ESR) over time were analyzed with paired Student's *t*-test, and the chi-square test was used to compare categorical data between groups. A logistic regression model was used to identify clinical and laboratory variables associated with TNF inhibitor use during the disease course. Kaplan-Meier analysis was used to estimate patients with CRP \leq 0.9 mg/dl compared to those with CRP $>$ 0.9 mg/dl and future need for TNF inhibitor therapy. The significance level was set at $P = 0.05$.

RESULTS

Seventy-one consecutive patients who fulfilled the CASPAR criteria for the diagnosis of PsA [10] were included in our inception cohort; 38 were women (53.5%) and the mean age at diagnosis was 44 ± 10.4 years. Sixty-six patients (93%) were Jewish: 54.5% were of Ashkenazi origin and 45.5% non-Ashkenazi; the remaining 5 patients (7%) were Arabs. The most common articular presentation was symmetric polyarthritis, in 35 patients (49.2%), followed by DIP joint arthritis in 15 (21.1%), oligoarticular arthritis in 10 (14.1%), spondyloarthritis or combined (peripheral and axial) arthritis in 6 each (8.4%), and arthritis mutilans in 5 (7.0%). Mean CRP level at diagnosis, before initiation of any treatment, was 2.84 ± 2.27 mg/dl (range 0.4–10.5 mg/dl), and mean ESR measured 44.8 ± 23.6 mm/hour (range 20–90 mm/hr).

All treatments were prescribed at the discretion of the attending rheumatologist. All patients were treated with at least one conventional DMARD: methotrexate (81.6%), sulfasalazine (61.1%) and leflunomide (88.9%). Thirty-seven patients (52.11%) had an inadequate response to DMARDs and were subsequently treated with at least one TNF inhibitor (with or without continuation of the DMARD): etanercept (67.6%),

adalimumab (21.6%), or infliximab (10.8%); 12 patients (16.9%) received a second TNF inhibitor. The reasons for the switch in TNF inhibitor were inadequate response in 6 patients (50%) and intolerance or adverse effect in 6 (50%). TNF inhibitors were discontinued in 6 of the 37 patients (16.2%) because of intolerance; another 6 patients (16.2%) had an incomplete or no response, as determined by the attending rheumatologist. The most common adverse event associated with TNF α inhibitor use was a hypersensitivity reaction. There were no cases of serious infection, active tuberculosis, or malignancy in the patients treated with TNF α inhibitors.

Twenty-four patients (33.8%) in our cohort had at least one co-morbidity at the time of diagnosis. The most common co-morbidity was hypertension (83%), followed by diabetes mellitus (33.3%) and ischemic heart disease (20.8%). Malignancy occurred in 4 patients (5.6%). Two of our patients (2.8%) died during the study period, one from urosepsis and another from gastric carcinoma.

CRP AND TNF α INHIBITOR TREATMENT

Statistical analysis demonstrated a positive correlation between the serum level of CRP at diagnosis and the need for TNF α inhibitor treatment during the disease course. A higher serum CRP level at diagnosis significantly predicted the use of a TNF α inhibitor: $P = 0.009$, hazard ratio (HR) 1.8, 95% confidence interval (95%CI) 1.27–1.85. Eighty percent of the patients who eventually needed a TNF inhibitor had a serum CRP level of 0.9 mg/dl or higher at diagnosis. Division of the cohort by this cutoff showed that patients with a serum CRP level of \geq 0.9 mg/dl at diagnosis of PsA were treated with a TNF α inhibitor significantly earlier than patients with a lower CRP level ($P = 0.003$, HR 2.62, 95%CI 0.393–2.5). Figure 1 shows the Kaplan-Meier

Figure 1. Kaplan-Meier estimate of the use of a TNF α inhibitor to treat patients with psoriatic arthritis and high (\geq 0.9 mg/dl, solid line) or low ($<$ 0.9 mg/dl, dotted line) highly sensitive C-reactive protein level at diagnosis ($P < 0.006$)

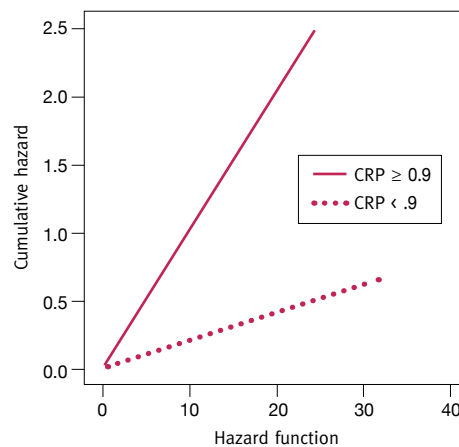
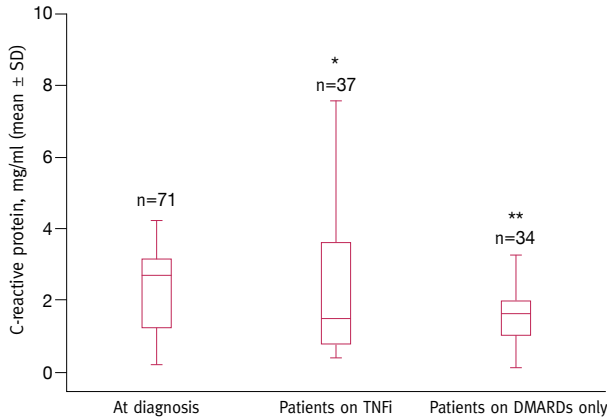


Figure 2. Mean C-reactive protein (CRP) between patients at baseline, patients treated with conventional DMARDs, and patients treated with a TNF inhibitor at the last study encounter



*Comparison of CRP levels at the last study encounter between patients treated with conventional DMARDs and patients treated with a TNFi ($P = 0.001$)

**Comparison of CRP levels of the cohort at diagnosis and of patients who continued to be treated with the conventional DMARDs at the last study encounter ($P = 0.013$)

analysis. There was no association between ESR at diagnosis and future requirement for a TNF α inhibitor ($P = 0.527$). Figure 2 shows the mean CRP in different time points: at diagnosis of PsA before initiation of any treatment in patients treated with DMARDs only and in patients treated with a TNF inhibitor

DISEASE DURATION AND THE USE OF TNF α INHIBITORS

We sought to determine whether the duration of PsA affected the decision to start a TNF α inhibitor in our cohort. For that purpose, we divided our patients into two groups according to disease duration since the diagnosis of PsA: early PsA defined as disease duration of < 2 years (20 patients, mean disease duration 1.2 ± 0.5 years) and established PsA defined as disease duration of ≥ 2 years (51 patients, mean disease duration 13.4 ± 1.51 years). Although we found no difference in the rate of administration of TNF α inhibitor between the early and the established PsA groups (8 patients, 40%, vs. 29 patients, 56.8%, respectively, $P = 0.29$), the CRP level at diagnosis of the patients with early PsA who had been treated with a TNF α inhibitor was significantly higher than in those not treated with a TNF α inhibitor (2.83 ± 1.23 mg/dl vs. 1.67 ± 0.97 mg/L, respectively, $P = 0.03$), whereas in the group of established PsA the difference in CRP at diagnosis was not statistically significant between those who were and were not treated with a TNF α inhibitor (2.01 ± 1.67 mg/dl vs. 1.34 ± 1.1 mg/dl, $P = 0.1$).

The mean CRP levels of patients at baseline, patients treated with conventional DMARDs, and patients treated with a TNF inhibitor at the last study encounter were significantly different [Figure 2]. The mean \pm SD CRP of patients treated with conventional DMARDs and patients treated with a TNF inhibitor at

the last study encounter were 1.81 ± 1.01 (n=34) vs. 1.33 ± 0.75 (n=37), $P = 0.001$, respectively. The mean \pm SD CRP of patients at baseline and patients treated with conventional DMARDs were 2.84 ± 2.27 (n=71) vs. 1.81 ± 1.01 (n=34), $P = 0.013$, respectively.

DISCUSSION

This study investigated the value of acute-phase reactant levels at diagnosis of PsA in predicting the need for treatment with TNF α inhibitor to achieve disease remission. The recently published guidelines of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) [4] and the European League Against Rheumatism (EULAR) [5] recommend the use of TNF α inhibitors in patients with active arthritis who exhibit an inadequate response to at least one conventional DMARD, in patients with active enthesitis and/or dactylitis and an inadequate response to a non-steroidal anti-inflammatory drug (NSAID) and/or local steroid injection, and in patients with active axial disease and an inadequate response to a NSAID [4-6]. The main TNF α inhibitors, adalimumab, etanercept, infliximab and golimumab, were found to be effective in all clinical domains of PsA, including the joints, skin, ligaments and tendons, digits and spine, and to significantly improve function and quality of life [3,8-11]. They were also shown to inhibit structural damage in several randomized controlled trials and in cohort studies [12-16]. However, there are as yet no known clinical or laboratory parameters to identify patients at high risk of an inadequate response to a NSAID and/or DMARD, who would then require biological therapy with a TNF inhibitor.

The results of the present study suggest that a CRP level ≥ 0.9 mg/dl at the time of PsA diagnosis is predictive of an inadequate response to treatment with conventional DMARDs and a high probability of the need for treatment with a TNF α inhibitor. On Kaplan-Meier analysis, a serum CRP level ≥ 0.9 mg/dl at the time of diagnosis was associated with an earlier need for TNF α inhibitor treatment ($P < 0.006$, HR 2.62) [Figure 1]. Our findings are in line with earlier studies showing that elevated levels of acute-phase reactants are associated with more aggressive disease in patients with PsA, and that a high ESR at presentation is correlated with both disease progression and early mortality [2]. In the Adalimumab Effectiveness in PsA Trial (ADEPT), an elevated baseline CRP level was the only risk factor that was independently and strongly associated with radiographic progression of PsA (CRP ≥ 1.0 mg/dl, odds ratio 3.28, 95%CI 1.66-6.51, $P < 0.001$) [17]. Analysis of Danish and Swedish registries of patients with PsA demonstrated a link between a high CRP level prior to onset of TNF α inhibitor treatment and better patient response and survival [7,8].

The present long-term, single-center, observational study of a “real life” inception cohort shows for the first time that elevated CRP level at diagnosis is significantly predictive of earlier need for treatment with a TNF α inhibitor drug to control disease

activity in PsA. Although our study is limited by its retrospective observational design, all our patients were evaluated for CRP level at the first clinic visit, at the time of diagnosis of PsA and prior to administration of a DMARD, and all were prescribed DMARD and/or TNF α inhibitor therapy to achieve disease control based on the clinical judgment of the attending rheumatologist. Therefore, we can draw reliable conclusions regarding the predictive ability of CRP level at diagnosis, before the onset of any treatment, to identify patients at high risk for failure of conventional therapy who are potential candidates for early initiation of TNF α inhibitor treatment. The decision of switch treatment with conventional DMARDs to a TNF α inhibitor was based on the attending rheumatologist's clinical assessment, thus it reflects a real-life situation.

Another limitation of the study is the lack of information about the patients' weight. Since obesity is a prevalent cause of elevated CRP, the average weight of patients with elevated CRP could not be compared with that of patients with normal CRP.

Our study findings have important clinical implications, suggesting that patients whose serum CRP level at disease onset is ≥ 0.9 mg/dl have a greater probability of their disease not completely responding to conventional DMARDs and will require treatment with biologics such as TNF inhibitors.

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