Seminars in Arthritis and Rheumatism 45 (2016) 386–390

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Predictive factors for induction of remission in patients with active rheumatoid arthritis treated with tocilizumab in clinical practice

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ARTICLE INFO

Keywords:
Rheumatoid arthritis
Tocilizumab
Remission
Predictors of response

ABSTRACT

Objective: To identify predictors of early response to tocilizumab (TCZ) in patients with active rheumatoid arthritis (RA) seen in daily routine clinical practice.
Methods: A multicenter ambispective observational study of 126 RA patients treated with TCZ as a first- or second-line biological therapy. The variables associated to achieve the therapeutic goal (remission defined as a DAS28-ESR < 2.6) at 3 and 6 months were identified using regression analysis.
Results: TCZ was administered as the first biologic in 26% of patients. Overall, 34% of patients received TCZ as monotherapy. EULAR response and remission were obtained in 82% and 31% of patients at 3 months and in 86% and 40% at 6 months.

In the multivariate analysis, the predictive factors increasing the likelihood of clinical remission at 3 months were baseline ESR > 30 mm/h (OR = 19.07, 95% CI: 2.720–133.716), baseline CRP > 10 mg/L (OR = 4.95; 95% CI: 1.464–13.826), and the presence of extra-articular manifestations of the disease (OR = 15.45, 95% CI: 2.334–102.319). The factors that decreased it were higher concentrations of hemoglobin (OR = 0.53, 95% CI: 0.319–0.910), higher baseline DAS28-ESR (OR = 0.30, 95% CI: 0.145–0.635) and the number of previous DMARDs (OR = 0.41, 95% CI: 0.221–0.779), and biological therapies used (OR = 0.33, 95% CI: 0.155–0.734).

The only factor that remained statistically significant at 6 months was higher baseline DAS28-ESR (OR = 0.55, 95% CI: 0.347–0.877). No relationship was found with the neutrophil count or with the RF or ACPA positivity.
Conclusion: In routine clinical practice, strong acute phase response, the presence of extra-articular manifestations, and the number of previous DMARDs and biological therapies used may help to identify patients who will have a rapid response to TCZ. However, it is likely that no parameter will predict response if taken separately.

Introduction

Treatment goals for rheumatoid arthritis (RA) have shifted toward achieving remission [1]. Many biological therapies for RA have become available during the past decade (including TNF blockers, abatacept, rituximab, or tocilizumab), making clinical remission an achievable goal. However, responsiveness to biological agents is variable among individuals, and there are poor responders to certain biologic treatments. Given the destructive nature of RA, the risk of adverse events, and the considerable costs

Abbreviations: ACR, American College of Rheumatology; ACPA, anti-citrullinated peptide antibodies; CI, confidence interval; CRP, C-reactive protein; DAS, disease activity score; DMARD, disease modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; EULAR, European League against Rheumatism; HAQ, Health Assessment Questionnaire; IL-6, interleukin-6; OR, odds ratio; RA, rheumatoid arthritis; TNF, tumor necrosis factor; TCZ, tocilizumab; WBC, white blood cell.

J.N. oversaw the analysis, conceptualized the project, and drafted the article. J.N., B.M., C.D.T., M.V.H., D.R., and H.C. provided the data and revised the article. R.S., J.M. L.L., A.R.S., and J.M.N. revised the article.

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http://dx.doi.org/10.1016/j.semarthrit.2015.07.001
0049-0172/

of biologic therapy, there is a need to identify predictors of response to biologics, which should allow for more personalized therapy.

Tocilizumab (TCZ) is a humanized interleukin-6 (IL-6) receptor monoclonal antibody that competitively inhibits the binding of IL-6 to its receptor [2]. It was approved in Europe in 2009 for the treatment of moderate to severe RA in patients with inadequate response to one or more disease modifying anti-rheumatic drugs (DMARDs) and/or TNF antagonists [3]. However, although it has been on the market for a long time, information about the predictive factors of early response to TCZ, which would be of use in routine clinical practice, remains limited. For this reason, this study aimed to identify the predictive factors for induction of remission in a real-life cohort of 126 patients with active RA treated with TCZ as the first biological therapy or after failure of at least one biological agent.

Methods

The sample included all patients with active RA (all of whom met the American College of Rheumatology (ACR) classification criteria for RA) [4] who were routinely treated from January 2009 to November 2012 with TCZ at the rheumatology departments of four referral tertiary care hospitals from Barcelona (Spain) and followed for at least 6 months after beginning TCZ treatment. A retrospective analysis of prospectively collected data was performed.

In accordance with the guidelines of our institutional ethics committee, formal approval for this study was not required. The local ethics committee agreed that the findings in this report were based on normal clinical practice and were therefore suitable for dissemination. Informed consent was not obtained from the patients, but their clinical records and information were anonymized prior to analysis. This study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference for Harmonization.

During the study period, 142 patients were identified; among them, 126 received treatment for at least 6 months and comprise the basis of our analysis. We excluded 16 patients for whom complete information was not available (missing efficacy data, $N = 6$) or treatment was discontinued before completing 6 months due to serious adverse events ($N = 10$, including 2 cases of infusion reaction, 1 case of TCZ-induced psoriasiform rash, and 7 cases of serious infections).

TCZ was given every 4 weeks at a usual dose of 8 mg/kg and could be adapted according to EULAR and local recommendations [5,6]. Increased or decreased doses of prednisone and DMARD were possible at the discretion of the referring physician.

Inpatient and outpatient charts were comprehensively reviewed following a specifically designed protocol. Baseline data collected at the time of TCZ prescription included the following: age, gender, disease duration, evidence of erosions (as established by hand and feet radiographs), the presence of extra-articular manifestations, details of past and present anti-rheumatic therapies (DMARDs, steroids, and number of biological agents previously used), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and blood parameters [hemoglobin, white blood cell (WBC), neutrophil, and platelet counts]. In addition, there was an assessment of disease activity, which included the patient global assessment, the swollen and tender joint count in 28 joints, the DAS28-ESR score, the Clinical Disease Activity Index (CDAI), and the health assessment questionnaire (HAQ). The assessments of disease activity were recorded again after 1, 3, and 6 months of treatment. The baseline serological status for rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA) was also collected. ACPA antibodies were measured using commercially available second-generation ELISA kits: EliA™ ACPA Assay on the ImmunoCAP250 instrument (Phadia, Germany) in three hospitals, and the Immunoscan RA™ (Euro-Diagnostica, Malmö, Sweden) in one hospital.

The primary outcome measure of the study was the rate of remission, which was defined as a DAS28-ESR < 2.6 at 3 and 6 months. Secondary efficacy endpoints included the percentage of patients with low disease activity defined as a DAS28-ESR ≤ 3.2, the percentage of CDAI remission (≤ 2.8) and CDAI low disease activity (≤ 10), the percentage of patients fulfilling the ACR 20/50/70 responses, the progression of functional disability [the change from baseline on the Health Assessment Questionnaire (HAQ) disability index], and the European League against Rheumatism (EULAR) response criteria. Good response was defined as a significant decrease in DAS28-ESR score (> 1.2) and a low level of disease activity (≤ 3.2). Non-response was defined as a decrease of ≤ 0.6 or a decrease of 0.6–1.2 with a score of > 5.1 on the DAS28. Any scores between these limits were regarded as indicative of moderate responses.

Parameters associated with early response to tocilizumab

We investigated putative predictive factors (clinical or laboratory) of remission at 3 and 6 months of treatment with TCZ. Several parameters that could be related to a better or a worse response were analyzed: age, gender, disease duration, the presence of extra-articular manifestations, presence of erosions, baseline DAS28-ESR, RF, or ACPA positivity, baseline ESR and CRP levels, baseline blood parameters levels (hemoglobin, WBC, neutrophils, and platelets), change in neutrophil count between baseline and 1 month, number of previous DMARDs, and number of previous biological therapies used. A priori threshold of a decrease of $> 25\%$ in neutrophil count between initiation of TCZ and 1 month was determined by analysis of the literature [7].

Statistical analysis

Continuous data were described as mean $\pm$ standard deviation (SD) or median (minimum and maximum), while categorical variables were presented as number of cases with percentages.

The comparison between groups was performed using the Wilcoxon or Student's test depending on the distribution for quantitative variables and using the chi-square test for qualitative variables. When the conditions of validity of the chi-square test were not met, it was replaced by the Fisher's exact test.

Multivariate analysis (logistic regression) was performed to highlight the respective influence of each covariate on the endpoint studied (i.e., remission defined as a DAS28 < 2.6 at 3 and 6 months). Variables significantly associated with the endpoint in the univariate analysis ($P < 0.05$) and a stepwise selection process was used to select the final model. When the hypothesis of an interaction between covariates was relevant, it was investigated. Adjusted ORs and 95% CIs were calculated. The significance level was set at 5% for all tests used. Statistical analysis was performed using SAS software version 9 (SAS Institute, Cary, NC).

Results

Baseline characteristics

Patient and treatment characteristics at baseline are shown in Table 1. All patients had a history of failed treatment with at least one DMARD (mean $\pm$ SD: 2.53 $\pm$1.4; range: 1–7). Of the 126 patients, 43 (34%) received TCZ monotherapy and 83 (66%) received TCZ plus DMARD, 55 received methotrexate (MTX), 26