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Original article

Efficacy and safety of tocilizumab in elderly patients with rheumatoid arthritis

Yves-Marie Pers[a,*], Roxane Schaub[b], Elodie Constant[c], Joseph Lambert[d], Marie Godfrin-Valnet[e], Clémentine Fortunet[f], Waafa Bourichi[a], Béatrice Pallot Prades[c], Daniel Wendling[e], Philippe Gaudin[d], Christian Jorgensen[a], Jean-Francis Maillefert[f], Hubert Marotte[c]

[a] Clinical immunology and osteoarticular diseases Therapeutic Unit, Lapeyronie University Hospital, Montpellier, France
[b] Clinical Research and Epidemiology Department, La Colombière University Hospital, Montpellier, France
[c] Rheumatology Unit, Saint-Étienne University Hospital, Saint-Étienne, France
[d] Rheumatology Unit, Grenoble University Hospital, Grenoble, France
[e] Rheumatology, Besançon University Teaching Hospital, Besançon, France
[f] Rheumatology, Dijon University Hospital, Dijon, France

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ABSTRACT

Objective: To assess the safety and efficacy of tocilizumab (TCZ) in elderly (≥ 65 years) rheumatoid arthritis (RA) patients treated in daily practice.
Methods: We conducted a retrospective study of TCZ use in RA patients in five French university hospitals between 2009 and 2012. We considered two age groups, under 65 years (< 65) and over 65 years (≥ 65). TCZ efficacy was evaluated at 24 weeks by the European League Against Rheumatism (EULAR) response and remission score. We also evaluated drug maintenance and safety, relative to adverse events discontinuation. A multivariate cumulative logit model for ordinal categories was performed to assess the relationship between age class and EULAR response (none, moderate and good) adjusted on possible confounders. TCZ retention (drug survival) over time was estimated with the Kaplan–Meier method. Treatment retention curves were compared according to age group with the log-rank test.
Results: Among 222 RA patients treated with TCZ, 61 (27.5%) were ≥ 65 years at the initiation of treatment. After 6 months, this elderly patient group less often reached remission (27.8% versus 45.6%; $P = 0.02$) or good EULAR response (40.7% versus 61.0%; $P < 0.01$) compared to the younger patient group (< 65). Multivariate analysis adjusted on baseline C-reactive protein and disease duration confirmed that elderly patients were more likely to have a lower EULAR response (none vs moderate-good or none-moderate vs good) (OR: 3.63; 95% CI [1.86–7.06], $P < 0.001$) compared to younger patients. Drug maintenance for TCZ and adverse events discontinuation rates were similar between the two age groups.
Conclusion: In daily practice, TCZ seems to be well tolerated in RA patients but is less efficient in elderly patients. A broader field of analysis to include an international register will be required to confirm these results.

1. Introduction

Rheumatoid arthritis (RA) is the most common chronic inflammatory arthritis in adults and may lead to joint damage and deformity. The population of elderly individuals with RA is expanding, due mainly to increasing life expectancy. The fate of elderly RA patients seems heterogeneous [1]. Some studies reported a better prognosis than younger patients, whereas others found a similar or more unfavourable outcome. Management of RA is more difficult in elderly individuals due to the impact of comorbidities. Also, treatments, such as steroids, methotrexate and biologics are often less well tolerated [2]. Recently, Widdifield et al. described increased morbidity related to serious infections in elderly RA patients, and identified some predictive factors, such as higher comorbidity, markers of disease severity and previous infection [3]. These results emphasize that many RA drugs may

* Corresponding author. Clinical immunology and osteoarticular diseases Therapeutic Unit, CHRU Lapeyronie, 371, avenue du Doyen-Gaston*Giraud; 34295 Montpellier, France. Tel.: +33 4 67 33 72 31; fax: +33 4 67 33 72 27.
E-mail address: ympers2000@yahoo.fr (Y.-M. Pers).

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increase the risk of infection. Together, these factors complicate disease treatment and necessitate careful patient management [2]. However, therapeutic goals for elderly RA patients are no different from those of younger individuals: control clinical symptoms, prevent radiological damage, avoid functional disability and reduce mortality [2].

Data from clinical trials suggest that disease modifying antirheumatic drugs (DMARDs) and tumor necrosis factor (TNF) antagonists are efficacious and are well tolerated in elderly patients with RA [4–7]. However, clinical trials, often initiated by the pharmaceutical industry, have included only a small percentage of over 65 years old patients, and those with comorbidities were excluded [8]. In addition, they failed to take into account efficacy and safety of treatment in elderly patients in daily practice. Registry data and cohort analyses developed since the advents of biological therapies are better suited to address this issue. Thus, data obtained from cohorts are important to evaluate prognosis as a result of new treatments, such as tocilizumab (TCZ), in patients over 65 years old in daily practice [9] However, careful monitoring of cohort data would be required to take into account any limitations due to missing data or methodological bias. TCZ is the first therapeutic agent targeting IL-6 to be effective in the treatment of RA. However, postmarketing surveillance in Japan suggested a higher risk of infections in RA patients over 65 years of age due to TCZ [10]. TCZ has been available and approved in France since 2009 for the treatment of moderate-to-severe active RA in patients who have had an inadequate response to one or more DMARDs and/or TNF antagonists [11]. Our study aimed to compare efficacy and safety of TCZ in RA patients over 65 compared to RA patients under 65 followed in daily practice.

2. Methods

2.1. Study population

Our retrospective cohort included all patients who initiated TCZ therapy for RA between December 2009 and December 2012 in the rheumatology departments of 5 University hospitals in France (Besançon, Dijon, Grenoble, Montpellier and Saint-Étienne). All patients fulfilled the 1987 ACR criteria for RA [12]. The clinical and biological data were collected retrospectively from medical records. TCZ was given every 4 weeks at a usual dose of 8 mg/kg and could be adapted according to the French or European recommendation authorities [13,14]. In the study, dose modulation of prednisone and DMARD were possible, according to the referring physician. The study was approved by the local ethical committee (Comité de Protection des Personnes Sud Méditerranée IV, Montpellier, France) in accordance with the Helsinki Declaration, and oral informed consent was obtained from each patient.

2.2. Efficacy assessment

Response to TCZ treatment (good, moderate or no response) was evaluated using EULAR criteria [15] at 6 months (primary endpoint). RA disease activity was assessed by the DAS28 score, taking into account erythrocyte sedimentation rate (ESR) [16]. We also evaluated the efficacy of TCZ on the number of patients in remission, defined as DAS28-ESR < 2.6. We decided to evaluate the response at 6 months, as recently recommended [17]. This minimum period of evaluation allowed for a timely decision on the therapeutic efficacy and suitability of TCZ in this study.

2.3. Safety assessment

The clinical and biological tolerance of TCZ was assessed in all patients. Adverse events (AE) and causes of discontinuation for intolerance were collected. Biological parameters (neutropenia) were monitored closely. TCZ drug retention rate (drug survival) was also analysed using time until drug discontinuation, whatever the cause (primary failure, secondary failure or AE).

2.4. Statistical analyses

Comparisons of patient's qualitative characteristics, treatment failure (primary or secondary) and intolerance rates according to patient's age (in two classes: ≥ 65 and < 65 years at treatment initiation) were performed by Chi^2 test or Fisher's exact test. Comparisons of quantitative variables between age classes were performed using Student's *t*-test or Wilcoxon–Mann–Whitney test. Changes in white blood cells and neutrophils count between baseline and 3 and 6 months were analyzed using the Wilcoxon signed-rank test for repeated measures. Multivariate cumulative logit model for ordinal categories was performed to assess the relationship between age in two classes and EULAR therapeutic response (no response, moderate, good response). Odds ratios (OR) obtained with this model correspond to the odds of being in a lower (versus higher) response category, i.e. the odds of "no response versus moderate or good response" and the odds of "no or moderate versus good response". Potential confounding factors considered were disease duration, baseline CRP and ESR values, cardiovascular history, tobacco, sex, erosive RA, previous use of biologics and concomitant treatment with DMARDs at baseline. Variables associated with therapeutic response in the univariate analysis with a *P* value < 0.2 were included in the model. Proportional odds assumption and linearity of the relationship between continuous covariates and therapeutic response have been verified. If relevant, interaction between covariates was investigated. The model was built by a stepwise procedure (input threshold = 0.20, output = 0.05). As a result of missing data for the primary endpoint, sensitivity analyses were performed to assess the robustness of the model, considering missing data as no response to treatment (worst case scenario), good response (best case scenario) or with last observation carried forward (LOCF) analysis. The probability of treatment retention over time (drug survival) was estimated using the Kaplan–Meier method. The comparison of treatment retention curves depending on the age group was performed using the log-rank test. All statistical tests were two-sided and with 0.05 significance level. Statistical analyses were performed using SAS software version 9 (SAS Institute, Cary, NC).

3. Results

3.1. Baseline characteristics

A total of 222 RA patients were included in the cohort database. Of these, 61 (27.5%) were ≥ 65 years of age (elderly) and 161 (72.5%) were < 65 years. Baseline characteristics of RA patients are summarized in Table 1. We found no difference between age groups regarding gender, previous history of cancer, rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA) positivity, prior biologics use, percentage of biologic-naive patients, percentage of patients treated with association of methotrexate (MTX), MTX dose, TCZ dose, and baseline DAS28-ESR.

However, elderly patients had a longer disease duration (median 18.5 years, interquartile range (IQR) 7–20, versus 12.0 years, IQR 11.5–28.5; $P < 0.001$), were less active smokers (6.3% versus 30.6%; $P < 0.001$), had more cardiovascular disease (34.4% versus 18%; $P = 0.009$), had previously been treated more often by various DMARDs (median 4 versus 3; $P < 0.001$) and RA was more often erosive (91.7% versus 74.2%; $P = 0.005$). Elderly RA patients were receiving as many corticosteroids as younger patients