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Efficacy of tocilizumab in Takayasu arteritis: Multicenter retrospective study of 46 patients

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ABSTRACT

Objectives: To assess the efficacy of tocilizumab in patients with Takayasu arteritis (TA).
Methods: We conducted a retrospective multicenter study in 46 TA patients treated with tocilizumab. We analyzed factors associated with response to tocilizumab (assessed using NIH score).
Results: Forty-six patients with TA were included, with a median age of 43 years [29–54], and 35 (76%) females. We observed a decrease in the median NIH scale (from 3 [2–3] at baseline to 0 [0–1] and 0 at 3 and 6 months, respectively; $p < 0.0001$). The daily prednisone dose also decreased from 15 mg [8–19] at

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baseline to 4 mg [5–21] and 5 mg [4.5–9] at 3 and 6 months, respectively ($p < 0.0001$) under tocilizumab. The overall tocilizumab failure free survival was 81% [CI 95%; 0.7–0.95], 72% [CI 95%; 0.55–0.95] and 48% [CI 95%; 0.2–0.1] at 12, 24 and 48 months, respectively. The presence of constitutional symptoms (HR 5.6 [CI 95%; 1.08–29], $p = 0.041$), and C-reactive protein level (HR 1.16 [CI 95%; 1.01–1.31], $P = 0.003$) at the time of tocilizumab initiation were significantly associated with tocilizumab event-free survival. The event-free survival was significantly better under tocilizumab therapy in comparison to DMARDs ($p = 0.02$).

Conclusion: This large multicenter study shows that tocilizumab is efficient and may reduce the incidence of relapses in TA.

1. Introduction

Takayasu arteritis (TA) is a chronic inflammatory vasculitis that affect the large vessels, in particular the aorta and its main branches [1]. The main complications are consequence of vascular inflammation, with arterial stenosis, aneurisms and thrombosis. The better treatment strategy in TA remains to be determined. Steroids remain the cornerstone of therapeutic management. However, only 60% of patients achieve a sustained remission with less than prednisone 10 mg/day [2]. The use of steroid-sparing agents like azathioprine, methotrexate, or mycophenolate mofetil have been described mostly in little case-series, and the growing data about the benefit of biological-targeting agents have been recently reported. We recently reported the French multicenter experience showing the benefit of biological-targeted treatments in refractory TA with substantial benefit in comparison to DMARDs for relapse-free and vascular-events free survivals [3].

Increasing evidence supports arguments for a role of IL-6 in the pathogenesis of TA. Data from immuno-histochemical analyses from aortic wall samples in patients with TA showed the presence of IL-6 producing T cells in vascular inflammatory infiltrates [4]. Previous data, mainly case-reports and small series reported rapid and sustained remission with tocilizumab, mostly in refractory TA [5,6]. However, some cases reported vascular progression under tocilizumab [5,7–10]. A recent randomized trial did not show the benefit of tocilizumab for relapse-free survival in comparison to placebo [11].

In this multicenter study, we assessed the long term outcome and the predictive factors of response in 46 TA patients treated with tocilizumab. We also analyzed the efficacy of tocilizumab a) use alone or associated without DMARDs, b) use as first-line therapy or in treatment-experienced patients and c) the event free survival and cumulative incidence of relapses of tocilizumab compared to a control group of TA patients treated by DMARDs therapy.

2. Patients

We conducted a retrospective multicenter study between January 2009 and January 2016. All patients fulfilled TA ACR and/or Ishikawa criteria modified by Sharma et al. The patients' clinical, laboratory and imaging data, treatments were analyzed at baseline, at the initiation of each treatment regimen, at 3, 6, 12, 18 months, 3 years after each line and at the last available visit. Steroids amounts were analyzed at the initiation and the end of each treatment regimen. Disease-specific vascular complications were defined as any ischemic vascular event and/or the need for vascular intervention during the follow-up. The different lines of immunosuppressive agents (conventional DMARDs, biological-targeting treatments and among then the tocilizumab), were analyzed separately for each patient. Five patients in the current case-series have been previously reported [3]. Adverse events were recorded and severe infection was defined as any infection requiring intravenous antibiotic use, hospitalization or infection-related death.

A control group of TA patients treated by DMARDs and which have never been treated with any biological-therapy was extracted from the “French Takayasu network” registry and matched to tocilizumab treated TA according to age, sex and the number of lines of treatment.

3. Disease activity and treatment response definitions

Disease activity was defined according to the NIH criteria as previously defined [12]. Briefly, disease was considered active if NIH score was 2 or more, and inactive otherwise. Steroid dependence was defined as prednisone $\geq$20 mg/day before each new therapeutic.

Treatment response was considered if NIH scale <2, and non-response in other situations [3]. Because of usual decrease of C-reactive protein under tocilizumab, the prednisone decrease and sparing effect was considered in the response definition and combined scale with NIH scale <2 and prednisone <7.5 mg/day was also evaluated at 6 months. Tocilizumab failure was considered in the case of non-response, treatment changes, ischemic vascular event and/or the need for vascular intervention during the tocilizumab treatment time. Relapse was defined as active disease after a remission period and with change of the treatment regimen.

4. Statistical analysis

Data are presented as medians with ranges for continuous variables and frequencies with percentages for qualitative variables. Fisher's exact test was used to compare qualitative variables and the Wilcoxon rank sum test were used to compare continuous variables as appropriate. Treatment and patient’s characteristics at the initiation of each treatment regimen were considered as potential time dependent variables. Event-free and relapse-free survivals under treatments were estimated using Kaplan Meier estimator. Relapse was defined as the fact that disease becomes active after a remission period requiring change of the treatment regimen. Differences between survivals curves were tested using Logrank tests. Hazard Ratios (HR with their 95% CI) of the cause specific hazard of relapse were obtained using Cox proportional hazard model and were tested using Wald tests. Cumulative incidences of relapse were estimated using Gray estimator, with relapse without complicqation considered a competing event of complication. Differences between cumulative incidences were performed using Fine and Gray models and Wald tests. All tests were two-sided and a p. value < 0.05 was considered statistically significant. Statistical analyses were carried out using R (version 3.1.0).

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