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Original article

Incidence of paradoxical reactions in patients treated with tocilizumab for rheumatoid arthritis: Data from the French registry REGATE

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ABSTRACT

Objectives: Assess the frequency of paradoxical reactions encountered in daily practice under tocilizumab, using the REGATE (Registry-RoActemra) registry. The secondary objectives were to determine the type of paradoxical reaction and the consequences of these reactions.
Methods: The REGATE registry is an independent prospective registry, promoted by the French Society of Rheumatology, consisting of patients treated with tocilizumab for rheumatoid arthritis. The paradoxical reaction was retained if it was a paradoxical precipitation of a condition for which tocilizumab was indicated, if tocilizumab was being used for an alternative indication, and if it appeared after at least one tocilizumab infusion.
Results: Among the 1491 patients included with at least one follow-up visit (3429 patient-years), a paradoxical reaction occurred in 9 patients (0.60% of patients; 2.62/1000 patient-years). These were 7 de novo pathologies (3 vasculitis, 3 uveitis, 1 lupus) and 2 exacerbations of pre-existing conditions (1 vasculitis, 1 lupus). Permanent discontinuation of tocilizumab was chosen for 5 patients.
Conclusions: In the REGATE registry, the occurrence of paradoxical reactions in patients treated with tocilizumab was rare.
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1. Introduction

Tocilizumab is a humanized monoclonal antibody specific to the alpha subunit of the receptor for interleukin-6 (IL-6) available since 2007. It is indicated for the treatment of moderately-to-severely active rheumatoid arthritis (RA) [1,2], but also in the treatment of progressive polyarticular juvenile idiopathic arthritis [3].

A paradoxical drug reaction constitutes an outcome that is opposite from the outcome that would be expected from the drug's known actions [4]. There are three types:

- a paradoxical response in a condition for which the drug is being explicitly prescribed;
- a paradoxical precipitation of a condition for which the drug is indicated, when the drug is being used for an alternative indication;

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- effects, which are paradoxical in relation to an aspect of the pharmacology of the drug but unrelated to the usual indication.

In our study, we decided to focus on the paradoxical precipitation of conditions for which tocilizumab is indicated, when tocilizumab is being used for an alternative indication [5,6]. These paradoxical reactions have been widely explored in patients under TNF alpha inhibitors [7]. Paradoxical reactions under tocilizumab are very rare, except for a few case reports [8–20]. To our knowledge, there is no data assessing the occurrence of paradoxical reactions under tocilizumab therapy from a large cohort.

The main objective was to assess the frequency of paradoxical reactions encountered in daily practice under tocilizumab therapy, using the REGATE (Registry-RoActemra) registry. The secondary objectives were to determine the type of paradoxical reaction and the consequences of these effects (severity, permanent discontinuation).

2. Methods

2.1. REGATE registry

The REGATE registry is a French prospective multicenter observational registry, promoted by the French Society of Rheumatology, to assess the efficacy and safety of tocilizumab in patients with active RA. The data on safety and efficacy is reported on an electronic CRF by clinical researchers at the initiation of treatment, at 3 months, 6 months and every 6 months or during a relapse of the disease during the follow-up period. Financial support is provided by the laboratory Roche Chugai, which was not involved in the design, protocol, data collection or statistical analysis of the registry. Additional data on the methodology of the registry has been described [21]. The study was conducted in full concordance with the principles of the Declaration of Helsinki and with the laws and regulations of France. This study was therefore approved by the French authorities (« Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé » and « Commission nationale de l'informatique et des libertés », and registered as N° 910346).

2.2. Identification of cases

The paradoxical reaction was retained if it was a paradoxical precipitation of a condition for which tocilizumab is indicated, if tocilizumab was being used for an alternative indication, and if it appeared after at least one tocilizumab infusion. Apart from rheumatoid arthritis and polyarticular juvenile idiopathic arthritis, for which tocilizumab has a marketing authorization [1–3], the conditions for which articles from the literature show an efficiency of tocilizumab are uveitis [22], lupus [23,24], Crohn's disease [25], vasculitis [26,27], Still's disease [28]. If patients had one of these conditions de novo while under tocilizumab therapy for another indication, it was considered to be a paradoxical reaction. The aggravation of a pre-existing condition was also considered as a paradoxical reaction [6]. When there was a doubt about the confirmation of a pathology, which appeared under tocilizumab therapy, we contacted the clinician of the center in charge of the patient's care. We excluded:

- pathologies that appeared under tocilizumab therapy and for which tocilizumab has not showed an efficacy for this indication (psoriasis. . .);
- patients in whom the potential paradoxical reaction appeared under another biotherapy;
- pathologies that could be considered as a natural progression of rheumatoid arthritis (scleritis for instance).

2.3. Data collection

For each patient for whom we diagnosed a paradoxical reaction induced by tocilizumab therapy, we analyzed the data that had been collected on the electronic CRF. If additional data was needed, we contacted the clinician of the center in charge of the patient's care.

Data collected at baseline on the REGATE registry were the patient's medical history, demographic characteristics, clinical and biological features, dosage and frequency of administration of tocilizumab, associated treatments. Among the paradoxical reactions, we specified those considered serious by the clinician, that is to say those which, regardless of the drug dose [29]:

- resulted in death or endangered the patient's life.
- caused a major or lasting disability.
- required hospitalization or prolongation of hospitalization.
- were medically significant or required an intervention to prevent the occurrence of one or more of the changes listed above.

2.4. Statistical analysis

A descriptive analysis was carried out. Categorical variables were described by their number and their percentage. Quantitative variables were described by their mean and standard deviation or median and interquartile range. The incidence of paradoxical reactions was calculated and presented in a number of events/1000 patient-years. Univariate analysis was performed to analyze the secondary objectives. The 2 groups (presence of a paradoxical event and lack of paradoxical event) were compared. Categorical variables were compared by Chi^2 test or Fisher exact test according to the application conditions. Quantitative variables were compared using a *T*-test or Mann–Whitney test according to the application conditions. A *P*-value < 0.05 was considered statistically significant. Statistical analyses were performed with SAS 9.4 software (SAS Institute, Cary, NC, USA).

3. Results

3.1. Characteristics of patients who presented a paradoxical reaction

At the time of analysis, 1491 patients with at least one follow-up visit included in the REGATE registry were analyzed. Median follow-up was 2.4 years (Q1 = 1.5/Q3 = 3.1) (3429 patient-years). Of the 1491 patients, 5120 adverse reactions were reported. We rejected the adverse effects that did not meet the predefined criteria of paradoxical reactions (Fig. 1). In the end, 9 paradoxical reactions occurred in 9 patients (0.60% of patients, 2.62/1000 patient-years).

The mean disease duration of RA was 18.3 (± 10.8) years. There were 6 women and 3 men. Among these 9 patients with a paradoxical effect, two were smokers, one had chronic obstructive pulmonary disease, one had type 1 diabetes and one had liver failure. No patient had hepatitis B, hepatitis C, HIV, a history of neoplasia or an immune deficiency.

All the patients received tocilizumab infusions every 28 days, with a dose of 8 mg/kg. Only one patient had a dose of 7.02 mg/kg/28 days, for an unknown reason (Table 1).

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