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Original article

Switching from originator infliximab to biosimilar CT-P13 in real-life: The weight of patient acceptance

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ABSTRACT

Objective: To explore acceptance and retention rate of biosimilar CT-P13 after switching from originator infliximab (OI) in patients with various rheumatic diseases.
Methods: Patients with stable rheumatoid arthritis (RA), ankylosing spondylitis (AS) or psoriatic arthritis (PsA) under OI were proposed to switch to CT-P13 at the same regimen. A prospective cohort of infliximab-naïve patients beginning CT-P13 and a retrospective cohort of patients treated with OI were used as controls. The primary outcome was to evaluate the retention rate of CT-P13. Secondary outcomes were the switch acceptance rate, reasons of failure and safety.
Results: Switch was proposed to 100 patients and accepted by 89 of them (63 AS, 12 PsA and 14 RA). After a median follow-up of 33 weeks, 72% of patients were still treated with CT-P13. This retention rate was significantly lower than the one found in our retrospective and prospective control cohorts: 88% and 90% respectively (P-value = 0.0002). Within patients who asked to be reswitched to OI, 13/25 (52%) presented clinical disease activity, one developed serum sickness and 11 (44%) presented no objective activity. A subanalysis excluding these 11 patients abrogated difference in retention rates between the 3 cohorts (P-value = 0.453). After reswitching to OI, patients without objective disease activity claimed to recover original efficacy.
Conclusions: Retention rate was lower after switching from OI to CT-P13 compared to our control cohorts. However, this difference faded after excluding patients without objective clinical activity, suggesting a reluctance of patients to the switch and a negative perception of the biosimilar.

1. Introduction

Biologic treatments, first of all TNF-inhibitors, have revolutionized the treatment of severe inflammatory rheumatic diseases with a tremendous change in disease outcomes and patient's quality of life [1]. However, the use of biological originator DMARDs (boDMARDs) has huge financial consequences, leading to a three-fold increase in total medical costs, this increase being mainly driven by the cost of these drugs [2]. This is a major limitation for their use in emerging countries and an important concern for health insurances in developed countries [3].

Biosimilar DMARDs (bsDMARDs) offer a unique opportunity to reduce the costs in the treatment of inflammatory diseases. A prediction model of the use of biosimilar infliximab in rheumatoid arthritis (RA) in 4 European countries estimated costs reduction ranging from tens to hundreds million euros [2].

The low number of clinical trials required for the development of this biosimilar limits the information available for clinicians. Moreover, these clinical trials compare biosimilars to originator product at the time of treatment initiation. The marketing of biosimilars in rheumatology is very recent, thus data on switching from originator is still limited. However, biosimilars have been used for longer with good results in other medical specialties, as in haematology with growth factors (epoetin, filgrastim) [4], or in endocrinology with growth hormone [5]. Most clinicians are

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reluctant to change a well-tolerated and effective treatment for a new and unknown product, therefore for a non-medical reason. Finally, although many papers have underlined the differences between biosimilars and generic drugs [6], the confusion between both kinds of drugs remains in minds for patients as well as for clinicians. Considering the poor acceptability of generics, especially in France, this confusion represents a limitation to the use of biosimilars.

We conducted a real-life study in the rheumatology department of the University Hospital of Bordeaux by systematically offering patients treated with originator infliximab (OI) to switch to CT-P13 (Inflectra®). The main goals of our study were:

- to assess the retention rate of CT-P13 in real-life setting after switching from OI;
- to compare this retention rate with the ones observed in a cohort of infliximab-naïve patients starting with CT-P13, and in a retrospective cohort of OI-treated patients.

2. Methods

2.1. Patients

Patients followed in the rheumatology department of Bordeaux University Hospital were proposed to participate in the study if:

- they presented a RA according to the 2010 ACR/EULAR criteria [7], or an ankylosing spondylitis (AS) or a psoriatic arthritis (PsA) according to the 2009 ASAS criteria [8];
- they were treated with infliximab, in monotherapy or in association with conventional synthetic DMARDs (csDMARDs), under stable infliximab treatment regimen for at least 6 months;
- the disease was controlled according to the physician opinion.

The switch was not proposed to patients with inflammatory bowel disease due to the recommendations of the French gastroenterologists society at the time of the study [9]. This cohort was prospectively followed from November 2015 to October 2016.

For comparison, two control cohorts from the same department were used:

- a cohort of infliximab-naïve patients starting anti-TNFα treatment with CT-P13;
- a retrospective cohort of patients treated with OI during the year 2013.

Prospective control cohort of infliximab-naïve patients receiving CT-P13 at initiation consisted of 29 patients among which 24 (83%) with SpA and 5 (17%) with RA. Patient characteristics are shown in Table 1.

Historic control cohort of patients treated with OI in 2013 consisted of 82 patients among which 64 (78%) with SpA and 18 (22%) with RA. Other patient characteristics are presented in Table 1.

2.2. Intervention

Patients were given oral information by the attending physician. The different practitioners reached agreement before the beginning of the study to communicate homogenous information to patients about biosimilars. The information delivered included data supporting biosimilar clinical efficacy and safety. The patients were informed before initiating the biosimilar that upon simple request, switching back to the originator would be possible. After giving oral consent, patients were switched to CT-P13 at the same treatment regimen (dose and time interval) than previous OI. Associated treatments including csDMARDs were not modified at inclusion.

2.3. Follow-up

Usual disease activity scores were recorded at the time of infusion: DAS28-CRP for RA, BASDAI and ASDAS-CRP for AS and PsA. Objective signs of activity were defined for RA patients by a DAS28-CRP ≥ 3.2 and at least one clinical synovitis [10]. For AS patients and PsA, clinical activity was defined by a BASDAI and a physician global assessment (PGA) $\geq 4/10$ as defined in ASAS consensus [11].

2.4. Outcomes

The primary outcome was to evaluate the retention rate of CT-P13 in the switched cohort.

The secondary outcomes were:

- the comparisons of the retention rate of CT-P13 in the switched cohort versus the historic OI cohort and the CT-P13 initiation cohort;
- the acceptance of the switch;
- the reasons for switch failure;
- the predictive factors of switch failure.

2.5. Statistical analysis

Quantitative variables, expressed as mean with standard deviation or median with range, were compared using a bilateral Student comparison test. Qualitative variables, expressed as proportions, were compared using a χ^2-test, or Fisher's exact test if needed. Kaplan–Meier survival curves of retention rate were compared using a log-rank test. Multivariate analysis was conducted using a logistic regression test including all variables associated with the studied outcome with a P-value < 0.15 in the univariate analysis. A P-value less than 0.05 was considered as statistically significant.

3. Role of the funding source

Not applicable.

4. Results

4.1. Population characteristics and switch acceptance

Hundred consecutive patients treated with OI fulfilled the inclusion criteria and were proposed to participate in the study. Among them, 89 (89%) accepted to switch to CT-P13. Patient, disease and treatment characteristics are detailed in Table 1. There was no difference between patients accepting and refusing the switch in terms of age, sex, type of disease, disease duration, number of IFX infusions or concomitant csDMARD use (data not shown).

Among the 89 patients switching from OI to CT-P13, 57% ($n = 51/89$) were men, with mean age 50.5 ± 13.3 years. Seventy-five (84%) patients had spondyloarthritis (SpA), including 63 (84%) with axial involvement and 12 (16%) with PsA. Mean BASDAI and ASDAS-CRP at baseline were 2.03 (± 1.88) and 1.38 (± 0.84) respectively.

Fourteen patients (16%) suffered from RA including 71% ACPA-positive, 86% IgM-RF positive and 79% had erosive disease. At baseline, mean DAS28-CRP was 2.14 (± 0.89) and 79% (11/14) of patients achieved EULAR remission (DAS28-CRP < 2.4).

Among this cohort of 89 patients, 47 (53%) were treated by infliximab as first line biologic whereas 42 (47%) received previously at least another biotherapy. The median dose was 5 mg/kg per

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