Efficacy and Safety of Infliximab Biosimilar (REMSIMA) in Patients With Ankylosing Spondylitis After Switching From Infliximab Reference Product: 12 Months Comparative Open-label Study

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Research Article

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Abstract

Background: Efficacy, tolerance, and safety of infliximab biosimilar are the same as infliximab reference product (RP) in the management of Ankylosing Spondylitis (AS) patients previously were on infliximab RP. We aimed to evaluate CT-P13 (Remsima) efficacy and safety to its RP.

Methods: Seventy-eight consecutive randomly selected patients were recruited for the study. All were naïve to any other biologics, receiving infliximab RP, and all were in clinical remission. Patients were divided into two subgroups, 40 patients continued on infliximab RP, and 38 patients switched to infliximab biosimilar. Both groups followed up for further 12 months. The disease activity was measured utilizing the Ankylosing Spondylitis disease activity score (ASDAS), using the C-reactive protein, the Bath Ankylosing Spondylitis disease activity index (BASDAI). Remission considered when BASDAI < 4 and ASDAS < 1.3. Functional scores for all patients were assessed using the Bath Ankylosing Spondylitis Functional Index (BASFI).

Results: Both groups showed sustained clinical remission after 12 months of treatment. For the switching group, mean BASDAI, BASFI, and ASDAS were 1.2, 2.4, and 5.2, respectively. For the continuous group, mean BASDAI, BASFI, and ASDAS were 1.2, 2.2, and 5.1, respectively; the difference was statistically insignificant (p values > 0.05). No significant adverse events were noted in the switching group compared to the continuous group.

Conclusion: Infliximab biosimilar CT-P13 (Remsima) was not inferior to infliximab RP and can maintain AS patients in clinical remission.

Introduction

The introduction of the biologic drugs, in particular, the monoclonal antibody and fusion protein against tumor necrosis factor (TNF) and other biologics into the real-life clinical practice have substantially improved the treatment of several autoimmune inflammatory disorders, like; rheumatoid arthritis (RA), AS, psoriatic arthritis, and uveitis [1–4]. However, because of the high cost of the RP biologics [5], there is restricted access to these biologics for patients in several countries [6–8] because some biologics including, the infliximab reference product (RP), have reached patent expiry. Therefore, follow-on biologics (the biosimilars) have been invented to treat different autoimmune diseases. A biosimilar is a biotherapeutic product with high similarity in efficacy, quality, and safety to an already licensed reference product [9]. For biosimilar to get approval, it is necessary to show high similarity to the RP in biological and physicochemical terms. Different clinical studies are essential to establish the equivalence in efficacy and safety of biosimilars [10–12]. Due to the lower cost of biosimilars versus RPs, there is considerable interest in introducing these drugs to the newly diagnosed patients and switching those already on RP to its biosimilar [13,14]. The European Medicines Agency (EMA) has been approved the biosimilar CT-P13 (REMSIMA), which is the infliximab RP generic version for the different indications of infliximab RP like, AS [9]. Clinical evidence for the approval of this biosimilar has been obtained from two studies, one on

patients with AS (PLANETAS) and the second on patients with rheumatoid arthritis (RA) (PLANETRA) [15,16]. Because of the shortage and the expense of biological drugs in our country, so; there is an urgent need for switching from the originator to its biosimilar; therefore, we conducted this study to investigate the efficacy and safety of switching to CT-P13 (Remsima) in AS patients previously treated with infliximab RP (Remicade).

Methods

This prospective observational cohort study was conducted in the biologic therapy center at Basrah teaching hospital from May 2019 till May 2021. A total number of 78 (70 male and 8 female) consecutive unselected naïve to previous biologic treatments patients with AS diagnosed according to the modified New York criteria were enrolled for the study. Data collection was done through interviews with the patients using a special questionnaire developed by the researchers. The questionnaire included age, sex, disease duration, and drug history. All patients were treated intravenously with infliximab RP (5 mg/kg/8 weeks). In May 2020, the patient sample was randomly divided into two subgroups. Forty patients were continued on infliximab RP, and 38 patients were asked to switch from infliximab RP to infliximab biosimilar (Remsima) with the same dose (5 mg /kg/8 weeks). 2010 Microsoft excel was used for randomization to minimize any selection bias. Both subgroups were clinically evaluated and investigated for complete blood cell count, erythrocyte sedimentation rate (ESR), and C reactive protein (CRP) at the switching and follow-up periods. Disease activity was measured using the Bath Ankylosing Spondylitis disease activity index (BASDAI) [17], the Ankylosing Spondylitis disease activity score (ASDAS) [18,19] using the C-reactive protein. These scores were calculated at the switching time and the follow-up period. Remission was defined as BASDAI < 4, and ASDAS < 1.3. The Bath Ankylosing Spondylitis Functional Index (BASFI) 20 was used for measuring functional scores for all patients

Statistical analysis

SPSS software version 25.0 was used to perform statistical analysis for this study. Qualitative data were presented as numbers and percentages, while continuous data were presented as mean $\pm$ standard deviation. Comparison of study groups was carried out using a chi-square test for categorical data and a student t-test for continuous data. A P-value of < 0.05 was considered statistically significant.

Results

From the total sample of 78 (70 male and 8 female) ankylosing spondylitis patients, there were 40 patients in the infliximab RP continued group and 38 patients in the switching group. The mean age, BMI, and disease duration were 33.37 ± 8.15 years, 24.27 ± 5.3 , and 11.50 ± 2.6 years for the infliximab RP continued group respectively and were 34.89 ± 6.20 years, 23.90 ± 3.6 , and 10.95 ± 2.7 years for the switching group, respectively. Involvement of axial disease, peripheral disease, and enthesitis were 40(100%), 6(15.0%), and 5(12.5%) patients in the infliximab RP continued group respectively and were 38(100%), 6(15.8%), and 5(13.15%) for the switching group respectively, as shown in Table 1. At

switching time, ESR, CRP, VAS, ASDAS, BASDAI, and BASDAI were 16.20 ± 4.34 , 3.68 ± 0.92 , 3.35 ± 0.75 , 1.47 ± 0.39 , 2.70 ± 0.44 , and 3.04 ± 0.52 in the infliximab RP continued group respectively and were 15.89 ± 4.36 , 3.79 ± 0.93 , 3.26 ± 0.91 , 1.52 ± 0.41 , 2.67 ± 0.27 and 2.94 ± 0.48 for the switching group respectively, the difference was statistically not significant ($p > 0.05$ for all) as shown in Table 2. At the end of the study, ESR, CRP, VAS, ASDAS, BASDAI, and BASDAI were 15.04 ± 2.37 , 3.10 ± 0.88 , 3.10 ± 0.78 , 1.52 ± 0.40 , 2.80 ± 0.37 , and 3.05 ± 0.24 in the infliximab RP continued group respectively and were 15.15 ± 1.45 , 2.89 ± 0.89 , 3.21 ± 0.69 , 1.59 ± 0.57 , 2.76 ± 0.45 and 2.89 ± 0.92 for the switching group respectively, the difference was statistically not significant ($p > 0.05$ for all) as shown in Table 3. Allergic reaction, upper respiratory tract infection, headache, skin infection, and UTI were reported in (5%- 2.5%) and (5.26%- 0%) in the infliximab RP continued group and switching group, respectively, as shown in Table 4.

Discussion

Biologic agents targeting cytokines, T or B cells have been used to treat different autoimmune rheumatic diseases (ARDs), which have revolutionized the management of these disorders [21]. Biological drugs targeting components of the immune system have been used for the treatment of rheumatoid arthritis (RA), AS, inflammatory bowel diseases (IBD), psoriasis, psoriatic arthritis (PsA), systemic lupus erythematosus (SLE), and vasculitis [22]. Due to their lower cost compared to the high cost of the RP, there is considerable interest in introducing biosimilars in rheumatologists' armamentarium [23]. CTP-13, under the commercial name Inflectra/Remsima, was approved by the EMA in 2013 [24]. The European League Against Rheumatism (EULAR) guidelines also recommended the switching from RP to its biosimilar [25]. The bioequivalence of the biosimilar was considered by the local health authorities following the results of two studies investigating the efficacy and safety of biosimilar in patients with RA and patients with AS the PLANETRA and the PLANETAS studies, respectively [15,16]. These two studies showed similar safety, efficacy, and tolerance of CT-P13 compared to RP in naïve patients after 30 weeks of treatment. In extension studies of PLANETRA and PLANETAS [26,27], patients who received RP were switched to CT-P13 at week 52 and compared to the group receiving CT-P13 from the beginning. After an additional 12 months of follow-up, they found no difference in terms of safety, efficacy, and tolerance. These two studies were approved by the FDA and EMA for the use of CT-P13 and extrapolation to all RP indications. In this study, 40 patients with AS receiving infliximab RP who were in clinical remission were continued receiving RP, and 38 patients were switched to the biosimilar (Remsima). After 12 months of follow-up, no differences in clinical efficacy and safety were found between both groups, and both groups remained in clinical remission. Our findings are consistent with the PLANETAS study [15] and comparable to a study done by Evripidis Kaltsonoudis et al. [28]. They found no significant statistical difference between the switching and the continuing groups. In this study, adverse effects were comparable between both groups, and the result of our study supports the proposal of switching from RP to biosimilar without any detrimental impact on biosimilar safety and efficacy [29]. However, treatment-related adverse events were reported in 71.4% of the patients upon switching from infliximab originator to CT-P13 compared with 48.9% of those who maintained CT-P13 for the second-year extension of the PLANETAS study [15].

Further, about 6% of 647 patients in the DANBIO registry [30] stopped treatment within three months after switching from RP to CT-P13 because of the lack of efficacy and adverse events. Our patient sample, in particular, those who switched to the biosimilar, responded very well to the study, and we reported no back switch for any patient of the study population; this was in line with the high retention rate for the biosimilars in other studies [29,31]. However, the retention rate at a median time of 33 weeks after switching to CT-P13 was 72% in the NOR-SWITCH study done by Jørgensen K et al. [31] which is lower than the retention rate of our study. This may be related to the shared-decision strategy adopted by the researchers; this is comparable to data suggesting that shared-decision strategy results in a better therapeutic response with fewer nocebo effects in contrast to non-medical switching [32,33]. Real-life experiences on the switch from an originator drug to its biosimilar and even back switch for economic and other non-medical reasons are essential for the rheumatologists and the patient [29]. In this study, we did not switch back any of our study population, in contrast to a study done by M. Scherlinger et al most patients (82%) who were switched back to RP have good efficacy, suggesting that multiple switches did not promote immunogenicity [29].

Conclusion

Findings from this study showed that switching from infliximab originator to CT-P13 (Remsima) was not inferior to continued treatment with infliximab RP and can maintain AS patients in clinical remission.

Declarations

Ethical Approval and Consent to participate

Written informed consent was obtained from all participants prior to their involvement. The study was conducted according to the principles of the Declaration of Helsinki.

The research committee of Barah health directorate approved the study protocol before starting the study on 7/Jan./2019.

Consent for publication

Not Applicable

Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Conflict of interest

None

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Authors appreciate the role of the patients

Authors contributions

AM has made a significant contribution to the conception acquisition of data and analysis of the manuscript. In addition, AH has created the design and interpretation of data. AK participated in the design analysis and the interpretation of data.

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Tables

Table 1: Demographic and clinical data of infliximab continued group versus switching group of AS

Characteristics	Infliximab RP continued group	Switching group	P value
Total no (%)	40(100%)	38(100%)	
male	37(92.5%)	33(86.8%)	>0.05
female	3(7.5%)	5(13.2%)	
Age	33.37±8.15	34.89±6.20	>0.05
BMI	24.27±5.3	23.90±3.6	>0.05
Disease duration	11.50±2.6	10.95±2.7	>0.05
Axial disease	40(100%)	38(100%)	
Peripheral disease	6(15.0%)	6(15.8%)	>0.05
Enthesitis	5(12.5%)	5(13.15%)	>0.05

BMI: Body mass index

Table 2: Inflammatory parameters and disease activity scores in continuous versus switching groups of AS at the switching time

Parameter	Infliximab RP continued group	Switching group	P value
ESR	16.20±4.34	15.89±4.36	>0.05
CRP	3.68 ± 0.92	3.79± 0.93	>0.05
VAS	3.35±0.75	3.26±0.91	>0.05
ASDAS	1.47±0.39	1.52±0.41	>0.05
PASDAI	2.70±0.44	2.67±0.27	>0.05
PASFI	3.04±0.52	2.94±0.48	>0.05

ESR: Erythrocyte sedimentation rate, CRP: C reactive protein, VAS: Visual analogue scale, ASDAS: Ankylosing Spondylitis disease activity score, PASDAI: Ankylosing Spondylitis disease activity index, PASFI: Bath Ankylosing Spondylitis Functional Index.

Table 3: Inflammatory parameters and disease activity scores in continuous versus switching groups of AS at the end of the study

Parameter	Infliximab RP continued group	Switching group	P value
ESR	15.04±2.37	15.15±1.45	>0.05
CRP	3.10±0.88	2.89±0.89	>0.05
VAS	3.10±0.78	3.21±0.69	>0.05
ASDAS	1.52±0.40	1.59±0.57	>0.05
PASDAI	2.80±0.37	2.76±0.45	>0.05
PASFI	3.05±0.24	2.89±0.92	>0.05

ESR: Erythrocyte sedimentation rate, CRP: C reactive protein, VAS: Visual analogue scale, ASDAS: Ankylosing Spondylitis disease activity score, PASDAI: Ankylosing Spondylitis disease activity index, PASFI: Bath Ankylosing Spondylitis Functional Index.

Table 4: Adverse events in continuous versus switching groups of AS.

Adverse effect	Infliximab RP continued group	Switching group	P value
Allergic reaction	2(5%)	2(5.26%)	>0.05
Upper respiratory tract infections	1(2.5%)	1(2.6%)	
Headache	1(2.5%)	1(2.6%)	
Skin infection	1(2.5%)	1(2.6%)	
UTI	1(2.5%)	0(0%)	
Fever	1(2.5%)	2(5.3%)	

UTI: Urinary tract infection