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The Biosimilar CT-P13 Infliximab Is More Immunogenic Than the Original Infliximab In Iraqi Patients with Ankylosing Spondylitis

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ABSTRACT

Introduction: Ankylosing spondylitis is also known as radiographic axial spondyloarthritis, a rare genetic disease affecting people with hereditary factors. In addition, it is one of the autoimmune diseases with systemic chronic inflammatory, progressive, immune-mediated reactions. It may be classified as seronegative spondyloarthropathy, which tests negative for rheumatoid factor and antinuclear antibody. Treatment of ankylosing spondylitis includes lifestyle modification and use of drugs such as the biologic agent infliximab or its biosimilar, CT-P13 infliximab. Despite their therapeutic usefulness, these agents are associated with a number of serious adverse effects such as immunogenicity.

Methods: A retrospective open-label study was conducted from December 2021 to March 2022 at the Rheumatology Unit, Baghdad Teaching Hospital, Medical City, Baghdad. Forty-four patients were taking Infliximab, and another 50 patients were taking CT-P13 (Remsima), both at a dose of 5 mg/kg for 3 months prior to recruitment in current study. Disease activity was assessed by ankylosing spondylitis disease activity (ASDAS-CRP) score, while antibodies and C-reactive protein were tested using ELISA technique. **Results:** Immunogenicity of the biosimilar CT-P13 infliximab was higher than that of the reference infliximab ($P< 0.05$). In addition, a number of patients in both treatment groups developed hypersensitivity reaction to either drug. However, there was no statistically significant correlation between the two variables ($P> 0.05$). **Conclusion:** Immunogenicity of infliximab or its biosimilar (CT - P13) may result in reduced therapeutic effectiveness manifested as increased disease activity. Also, such immunogenicity may be triggered by previous biological treatment and/or the total number of doses.

Keywords: Ankylosing spondylitis, Biologics, Biosimilar, Disease activity, Immunogenicity

INTRODUCTION

Ankylosing spondylitis (AS) is also known as radiographic axial spondyloarthritis, a rare genetic disease affecting people with hereditary factors. In addition, AS is one of the autoimmune diseases with systemic chronic inflammatory, progressive, immune-mediated reactions. It may be classified as seronegative spondyloarthropathy, which tests negative for rheumatoid factor and antinuclear antibody [1]. Ankylosing spondylitis affects the sacroiliac joints and spine and nearby soft tissues such as tendons and ligaments, to a lesser extent peripheral joints and other soft tissues. In addition, this inflammation can eventually progress to fibrosis and calcification, which leads to the loss of flexibility and fusion of the spine, resulting in an appearance similar to "bamboo" and an immobile position in more severe [1, 3, 4]. In addition to HLA-B27 seropositivity, a family history of AS, male gender, age, vitamin D deficiency, mechanical stress, smoking, obesity, and recurrent gastrointestinal infections all increase the likelihood of developing AS in a given individual [1, 2, 5-11]. On the other hand, treatment of AS includes lifestyle modifications [3], administration of NSAIDs and TNF-α inhibitor such as adalimumab, infliximab, certolizumab, and golimumab, etanercept [13]. In addition, the biosimilar of infliximab, CT-P13, and infliximab [12]. The latter is the first biosimilar version of infliximab, known as CT-P13 infliximab, received approval in 2012 from the Ministry of Food and Drug Safety in Korea, in 2013 from the EMA and in 2016 from the US FDA. Moreover, currently it is marketed under the brand name Remsima [12].

TNF-α inhibitors are generally well-tolerated, but risks associated with these medications may appear, which include infusion reactions with infliximab, and injection site reactions to subcutaneously administered drugs (i.e., local erythema and swelling), opportunistic infections, and others. Moreover, the use of these agents may also increase the risk of developing a delayed hypersensitivity reaction (HSR) [13]. Furthermore, there is a strong relationship between immunogenicity of these medications and the loss of clinical effectiveness, because when immune complex is formed the ADAb is connected to therapeutic medication. This immune complex interferes with the function of biologics while also facilitating the clearance of drugs [14, 15]. On the other hand, immunogenicity of a product can be affected by a variety of factors, including product-specific characteristics (e.g. protein structure), treatment-related factors (e.g. usage of concomitant medications, dose, continuous or intermittent delivery) and patient-related factors (e.g. genetic pre-predisposition underlying disease(s)) [16, 17]. Genetic variables and the patient's age are among the factors that influence the immunological response. Among the age-related factors are the age-dependent maturation of the immune system found in children, as well as the possibility of altered immunological response in elderly

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people [18]. Furthermore, it is possible that product-related factors, s uch as significant alteration of the therapeutic protein by glycosylation, pegylation, or the production of fusion proteins, will result in increased or decreased immunogenicity [19]. Additional factors that may cause immunological reactions include interactions between proteins and excipients, as well as contaminants originating from the manufacturing process or during packing [18]

Despite its prescription for treatment of Iraqi patients with AS, little is known regarding safety and efficacy of the biosimilar CT-P13 infliximab. Therefore, the aim of current study was to evaluate the effect of immunogenicity on clinical safety and efficacy of the biosimilar infliximab (CT-P13; Remsima) compared to original infliximab (Remicade) in Iraqi patients with ankylosing spondylitis.

METHODS

A retrospective open-label study was conducted from December 2021 to March 2022 at the Rheumatology Unit, Medical City, Baghdad, Iraq. Current study involved 94 patients with ankylosing spondylitis (AS), as defined by New York classification criteria [19]. They were on biological treatment. Of these patients, 44 patients were taking the biological agent Infliximab (Remicade), and another 50 patients were taking CT-P13 (Remsima), the biosimilar of infliximab. Both groups of patients were at least 3 months on either treatment at the time of recruitment in the current study.

Exclusion criteria: Patients with AS but having renal impairment, hepatic impairment, pregnant or tend to be pregnant, other immune diseases and/or using other biological treatments.

Participating patients were categorized into two groups according to treatment they were receiving: Group1 included forty-four patients who received Remicade (Infliximab) as the only biological drug for at least 12 weeks before recruitment and group 2 that included fifty patients who received the biosimilar CT-P13 (Remsima) as the only biological drug for at least 12 weeks before recruitment.

The participants were subjected to the following: Medical history as well as clinical manifestations of the disease. Also, in order to evaluate the disease activity in patients with AS, there were different types of disease activity scores like BASDI and ASDAS [21] However, the most reliable and objective one was Ankylosing Spondylitis Disease Activity Score (ASDAS), which is developed by the Assessing Ankylosing Spondylitis Group. It is useful to obtain discrimination measurements for patients' self-evaluation and objective inflammatory markers (ESR or CRP). The ASDAS is a new disease activity index in AS that is more practical and has high face validity in clinical practice and research. The four questions of the ASDAS index reflect patient`s disease progression during the treatment and the C-reactive protein (CRP) test that show up the inflammatory index of disease activity. After that, the five parts of the ASDAS were calculated to give the final score of the index [22]. All blood samples were collected from the patients in the biological (infliximab) receiving unit, at Baghdad Teaching Hospital, Medical City/ Baghdad, for measurement of serum C-reactive protein, serum anti-infliximab (Remicade) antibodies and serum anti-CT-P13 (Remsima) antibodies using Enzyme-Linked Immunosorbent Assay technique.

Ethical approval:

The study was approved by the Ethics Board of College of Medicine,University of Baghdad and an informed written consent was taken from each participant in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analyses

Statistics were performed using SPSS statistical package for Social Sciences (version 20.0 for Windows, SPSS, Chicago, IL, USA). Quantitative data were presented as mean ± standard deviation, and range. To test differences between the two treatment groups Student's t-test was used. Median and IQR (Inter Quartile Range) were used to describe Anti-Infliximab antibodies and CRP as their distribution was non-normal (Kolmogorov-Smirnov test). Kruskal-Wallis test was used to study the difference between the two treatment groups. Qualitative data were presented as count and percentage. $P \leq 0.05$ was considered statistically significant.

RESULTS

The results of current study showed that 94 patients with ankylosing spondylitis were recruited in current study where 44 patients were on infliximab (remicade) and 50 patients were on the biosimilar CT-P13 (remsima) both for more than 3 months. Results from current study revealed that 82 (87.23%) of participants were males ($p>0.05$). The mean ages of participants in the remicade and remsima groups was 38.8 ± 9.1 and 40.4 ± 9.8 years respectively ($p>0.05$). Participants in current study had obesity ($p>0.05$). Also, patients in the remicade group received significantly more doses of the biological agent, as well as more doses of NSAIDs, than those in the remsima group ($P<0.05$). However, the incidence of enthesitis seemed to be higher among patients in the remsima group than among those in the remicade group ($P < 0.05$) (Table 1).

Table (1): Demographic data of participants

Characteristic	Remicade (n=44)	Remsima (n=50)	P-value
Gender			
Male, n (%)	41 (93.2%)	41 (82.0%)	0.130
Female, n (%)	3 (6.8%)	9 (18.0%)	
Age (years)			
Mean ± SD	38.8 ± 9.1	40.4 ± 9.8	0.413
Range	20-60	18-65	
BMI (kg/m²)			
Mean ± SD	28.0 ± 5.5	27.1 ± 5.7	0.924
Range	16.60-39.45	25.34-30.34	
Smoking			
No, n (%)	25 (26.8%)	30 (60.0%)	0.835
Yes, n (%)	19 (43.2%)	20 (40.0%)	
Dose (mg/kg)			
Mean ± SD	5.2 ± 0.4	4.9 ± 0.5	0.059
Range	5-6	3-6	
Total number of dosing			
Mean ± SD	19.7 ± 11.1	8.5 ± 3.8	**0.005**
Range	4-38	4-20	
Duration of the disease (years)			
Mean ± SD	12.1 ± 6.2	11.3 ± 7.5	0.578
Range	2-23	2-28	
Education			
Illiterate, n (%)	1 (2.3%)	0 (0.0%)	0.263
Elementary, n (%)	13 (29.5%)	14 (28.0%)	
High, n (%)	13 (29.5%)	23 (46.0%)	
College, n (%)	17 (38.6%)	13 (26.0%)	
Marital status			
No, n (%)	7 (15.9%)	11 (22.0%)	0.601
Yes, n (%)	37 (84.1%)	39 (78.0%)	
Previous biological treatment			
No, n (%)	29 (65.9%)	30 (60.0%)	0.670
Yes, n (%)	15 (34.1%)	20 (40.0%)	
NSAID			
No, n (%)	18 (40.9%)	32 (64.0%)	**0.038**
Yes, n (%)	26 (59.1%)	18 (36.0%)	
MTX			
No, n (%)	36 (81.8%)	41 (82.0%)	0.595
Yes, n (%)	8 (18.2%)	9 (18.0%)	
Hypersensitivity			
No, n (%)	28 (63.6%)	30 (60.0%)	0.832
Yes, n (%)	16 (36.4%)	20 (40.0%)	
Enthesitis			
No, n (%)	34 (77.3%)	27 (54.0%)	**0.030**
Yes, n (%)	10 (22.7%)	23 (46.0%)	
Extra-articular			
No, n (%)	19 (43.2%)	17 (34.0%)	0.400
Yes, n (%)	25 (56.8%)	33 (66.0%)	

Immunogenicity of treatments

The results of current study showed that patients in remsima group developed a statistically significant higher antibody titer than those in the remicade group (P<0.05) (Table 2).

Table (2): Distribution of antibodies against the two treatments used in current study

	Treatment								**P value**
	Remicade (n=34)				**Remsima (n=42)**				
	Med.	IQR	Min.	Max.	Med.	IQR	Min.	Max.	
Anti-bodies titer ng/ml	15.5	14.9	4.6	1237.2	31.8	30.1	11.3	760.8	**0.001***

Hypersensitivity of patients to the treatments

The result of current study showed that there was no significant difference in the number of patients who were, or were not, hypersensitive to either treatment (P >0.05) (Table 3).

Table (3): Hypersensitivity of patients to treatments

		Treatment				**P-value**
		Remicade (n=44)		**Remsima (n=50)**		
		No.	%	No.	%	
Hypersensitivity	**NO**	28	63.6%	30	60.0%	0.832
	YES	16	36.4%	20	40.0%	

Correlation between immunogenicity and hypersensitivity of study treatments

Results from current study showed that there was no significant correlation between immunogenicity of either treatment and the experience of hypersensitivity by patients in the respective groups (Table 4).

Table (4): Correlation between immunogenicity of, and patients' hypersensitivity to, the study treatments

Immunogenicity	**Hypersensitivity**				**P value**
	NO		**YES**		
	Median	IQR	Median	IQR	
Remicade group	14.08	8.52	29.71	174.98	0.241
Remsima group	29.15	21.34	40.62	103.26	0.127

DISCUSSION

Demographic data of participants

In terms of gender distribution, current study revealed that 82 (87.23%) of participants were males. Moreover, the dominance of male gender was also demonstrated within the two groups of study as the percentages of male participants in the remicade and remsima groups were 93.2% and 82.0%, respectively. This finding is in agreement with previous two reports stated that AS affects males more than females as well as that male gender is a risk factor for developing AS [23].

Results from current study showed that the mean age of participants in the Remicade and Remsima groups was 38.8 ± 9.1 and 40.4 ± 9.8 years respectively. These findings are consistent with previous data stated that AS might manifest itself clinically between an age of 30 and 50 years and even earlier [5, 7, 24].

Participants in current study had obesity as the mean BMI of participants in the Remicade and Remsima groups was 28.0 ± 5.5 and 27.1 ± 5.7 Kg/m^2 respectively. Indeed, weight gain affects the clinical manifestations of AS, such as inflammation, disease activity, radiographic damage, physical mobility, and health index as well as response to treatment [7, 25].

The effect of smoking on patients with ankylosing spondylitis maybe reflected on patients' quality of life and disease activity, because smoking will increase the possibility of direct toxic effects of nicotine, which will inhibit the effect of proinflammatory cytokines [26].

The total number of doses of each treatment, received by patients in the respective groups, were significantly different with more doses of Remicade were taken (P<0.05). In addition, patients in the Remicade seemed to be administered more NSAIDs than their colleagues in the Remsima group (P<0.05. This finding is

in agreement with that reported by Shimabuco *et al.* [27]. The usage of NSAIDs may be helpful for reducing symptoms associated with AS. Also, because AS runs a long-term course, many patients might take these drugs frequently and without prescription when pain appears suddenly [28].

Demographic data gathered in current study showed that the number of patients who had enthesitis was more in the Remsima group (23; 46.0%) than in the Remicade group (10; 22.7%). A previous study showed that 11 patients with AS out of 40 had enthesitis [29]. Enthesitis represents a serious complication associated with the disease and to control the manifestation, treatment should be properly assessed to manage the enthesitis as long as patients did not receive enough doses that may affect the management.

Immunogenicity of treatments

In current study, the results showed a significant difference in antibody titer between the two treatment groups ($P< 0.05$).

In this study, patients on Remicade were taking this treatment since the launch of their treatment of AS. However, some of those receiving Remsima had been switched to CT-P13 from Remicade for certain reasons. Moreover, transient detection of anti-drug antibodies (ADAbs) was reported in patients with inflammatory bowel disease who treated with infliximab [30]. Another study which explained the difference in immunogenicity between the two treatments group presented the results as numbers of patients detected with ADAbs. After 30 weeks of treatments, 32 (27%) patients on CT-P13 developed ADAbs while 25 (22.5%) patients on Remicade did [31]. Moreover, in another study which explained the immunogenicity of Remicade and Remsima, presented their data as the numbers of patients observed with ADAbs rather than as antibody titer. In that study, immunogenicity was studied over 54 weeks and the study reported that for the CT-P13 group, 20 (22.2%) patients had ADAbs while for the Remicade group 22 (26.2%) patients had ADAbs. The study extended then to another 48 weeks but the results were different in the number of patients who had ADAbs in the group who switch from Remicade to Remsima as 23 (27.4%) patients had ADAbs compared to 21 (23.3%) patients from the group who continued with Remsima [32].

These findings may be attributed to the fact that both biosimilar and reference medicine are based on having the same pharmacological characteristics including form, strength, content, and method of administration as well as to the complicated make-up of these molecules and the inherent unpredictability of the manufacturing process. The term immunogenicity refers to formation of antibodies in the body against the drug, this could interfere with drug action by increasing clearance. In addition, immunogenicity is one of the most significant concerns linked with the usage of TNF inhibitors. The development of neutralizing ADAbs, which render the therapeutic agent ineffective, is one of the primary factors contributing to failure of treatment with TNF inhibitors. The production of ADAb is coupled to other safety concerns and frequently causes infusion responses in individuals who are receiving treatment with infliximab. In another word, when the treatment is first being administered, immunogenicity should be of serious interest [33].

It is clinically crucial to identify individuals who are at risk of developing ADAbs in order to detect ADAbs in a timely manner and hence prevent therapeutic failure as well as immunogenicity-related side effects. An increase in our knowledge of risk variables will make it easier to select treatment techniques that will prevent the production of ADAbs [34].

From the results of current study, antibodies were more in patients receiving Remsima. It might be due to a number of factors that affect the immune system. For example, most of the patients on Remsima had a previous biological treatment that might be considered a trigger for immunogenicity. In addition, the total number of doses plays a crucial role in antibodies formation, as the patient receives more doses, the body became tolerant and have no reactions against the drug and this might have happened with the second group of patients who received Remicade [35].

Hypersensitivity to treatments

Results from current study showed that 16 (36.4%) patients from the Remicade group and 20 (40%) patients from the Remsima group did have hypersensitivity to the treatment they received. However, the results were not significantly different ($P> 0.05$).

Correlation between the immunogenicity of, and patients' hypersensitivity to, the treatments

Current study revealed non-significant correlation between immunogenicity and hypersensitivity to infusion of drugs ($P>0.05$). Patients using biological drugs frequently experience infusion responses, some of which are mild while others can be life-threatening. The size of the immune complexes generated may determine whether the immunological reaction is an IgG (immune complex) or IgE (allergic hypersensitivity reaction) [13].

CONCLUSION

Immunogenicity of infliximab or its biosimilar (CT-P13) may result in reduced therapeutic effectiveness manifested as increased disease activity. In addition, such immunogenicity may be triggered by previous biological

treatment, the total number of doses, smoking and/or higher disease activity. However, immunogenicity did not correlate with the occurrence of infusion-related hypersensitivity to either treatment.

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