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Immunogenicity of the biosimilar CT-P13 infliximab or the original infliximab in Iraqi patients with Ankylosing spondylitis does not correlate with their demographic characteristics

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Abstract:

Background: Ankylosing spondylitis is a rare disease affecting people with hereditary factors. Its treatment 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.

Objectives: The aim of the current study was to investigate if the immunogenicity of the biosimilar CT-P13 infliximab or the original infliximab, in Iraqi patients with Ankylosing spondylitis, is affected by any of the patients' demographic characteristics.

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, both at a dose of 5mg/kg for 3 months prior to recruitment in current study. Disease activity was assessed by ASDAS-CRP score while antibodies and C-reactive protein were tested by Enzyme-Linked Immunosorbent Assay technique. Statistical analyses were performed using SPSS statistical package for Social Sciences version 20.0. The level of significance was considered at $P<0.05$.

Results: There was non-significant correlation between anti-infliximab antibodies and demographic data of patients ($P>0.05$). Similar data were reported regarding the biosimilar CT-P13 infliximab except for smoking and disease activity which exhibited significant correlation with development of anti-CT-P13 antibodies ($P<0.05$).

Conclusion: Immunogenicity of the biosimilar CT-P13 infliximab, but not that of the original Infliximab, may be influenced by demographic characteristics or disease activity in patients with ankylosing spondylitis.

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

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Introduction:

Ankylosing spondylitis (AS), also known as radiographic axial spondyloarthritis, is a rare genetic disease affecting people with hereditary factors. 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 antibodies [1][2].Ankylosing spondylitis affects the sacroiliac joints, spines and nearby soft tissues such as tendons and ligaments, to a lesser extent peripheral joints and other soft tissues. 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 cases [3]. 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 [4];[5];[1];[6]. Treatment of AS includes life style modifications [3], administration of NSAIDs and TNF- α inhibitors (such as infliximab, etanercept, adalimumab, certolizumab, and golimumab) [7,8], in addition to the biosimilar of infliximab, CT-P13, infliximab [8]. The latter is the first biosimilar version of infliximab, known as CT-P13 infliximab, and had 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. Currently it is marketed under the brand name Remsima [8]. 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.,

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local erythema and swelling), opportunistic infections, and others. The use of these agents may also increase the risk of developing a delayed hypersensitivity reaction (HSR) [7]. On the other hand, the 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)) [9]. Despite its prescription the for treatment of Iraqi patients with AS, little is known regarding the safety and efficacy of the biosimilar CT-P13 infliximab. In another paper (under consideration for publication) we concluded that the biosimilar CT-P13 infliximab has higher immunogenicity than the original infliximab.

The aim of the current study is to investigate if patients' demographic data would affect the immunogenicity of the biosimilar CT-P13 infliximab or the original infliximab in Iraqi patients with ankylosing spondylitis

Patients and Methods:

A retrospective open-label study was conducted from December 2021 to March 2022 at the Rheumatology Unit, Baghdad Teaching Hospital/Medical City, Baghdad, Iraq. The study included 94 patients with ankylosing spondylitis (AS), as defined by New York classification criteria ([10,11]; who were on biological treatment. Of these patients, 44 patients were taking the biological agent Infliximab (Remicade), and the other 50 patients were taking CT-P13 (Remsima), the biosimilar of infliximab. Both groups of patients were on either treatment for at least three months at the time of recruitment to the current study. Patients with AS who had renal impairment, hepatic impairment, pregnant or tend to be pregnant, had other immune diseases and/or using other biological treatments, were excluded from the study. The patients were interviewed to obtain data regarding their medical history and the clinical manifestations of the disease. There are different types of disease activity scores for AS like BASDI and ASDAS [12]. The latter, the Ankylosing Spondylitis Disease Activity Score (ASDAS) is the most reliable and objective one and was developed by the Assessing Ankylosing Spondylitis Group [13]. 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 the patient`s disease progression during the treatment and the C-reactive protein (CRP) test will show up the inflammatory index of disease activity. After that, the five parts of the ASDAS will be measured to give the final score of the index [13] 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. Statistical analyses were performed using the 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. A P value of <0.05 was considered statistically significant.

Results

Demographic Data of participants: The demographic and clinical characteristics of participants are presented in Table 1. The table shows that 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 ($P<0.05$). The occurrence of enthesitis seemed to be significantly higher among patients in the Remsima group than among those in the Remicade group ($P<0.05$).

Table 1: Demographic and clinical data of study groups

Characteristic	Categories	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%)	

Correlation between anti-drug antibody titer and demographic characteristics of participants

Remicade group

Using Pearson's correlation test and Mann-Whitney U test, the results of the current study showed that there was no significant correlation between the demographic data of patients and anti-infliximab antibody titer. (P>0.05, Tables 2 & 3).

Table 2: Correlation between anti-Infliximab antibody titer and demographic/clinical characteristics (Remicade group)

Demographic / clinical characteristics	Correlation (N= 44)	
	R	P value
Age	-0.186	0.292
BMI	0.330	0.056
Duration	-0.192	0.277
Dose	0.181	0.307
Total number of doses	0.312	0.072
ASDAS CRP	0.263	0.133

r: Pearson's correlation coefficient

Table 3: Correlation between anti-Infliximab antibody titer and demographic/clinical characteristics of patients (Remicade group)

Demographic clinical characteristics	/Categories	Median	IQR	P value
Gender	Male	15.50	12.54	0.856
	Female	622.33	1229.74	
Smoking	-ve	14.55	13.25	0.825
	+ve	16.91	15.63	
Previous biological treatments	-ve	14.55	10.41	0.304
	+ve	16.44	99.40	
NSAID	-ve	13.61	66.63	0.359
	+ve	17.38	10.88	
MTX	-ve	15.50	13.25	0.563
	+ve	17.87	37.10	
Enthesitis	-ve	14.55	12.30	0.092
	+ve	21.17	83.56	

Mann-Whitney U test

Remsima group

Table 4 shows a significant correlation between anti-CT-P13 antibody titer and ASDAS-CRP (P<0.05). As for the other demographic characteristics no significant correlation was found (P>0.05). Table 5 shows a significant correlation between immunogenicity of CTP-13 and smoking (P<0.05).

Table 4: Correlation between anti-CT-P13 antibody titer and demographic/clinical characteristics of patients (Remsima group)

Demographic / clinical characteristics	Correlation (N= 50)	
	R	P value
Age	-0.237	0.130
BMI	-0.183	0.245
Duration	-0.055	0.731
Dose	0.042	0.793
Total number of doses	-0.079	0.620
ASDAS CRP	-0.322*	0.037

r: Pearson's correlation coefficient

Table 5: Correlation between anti-CT-P13 antibody titer and demographic and clinical characteristics of patients (Remsima group)

Demographic clinical characteristics	/Categories	Median	IQR	P value
Gender	Male	33.41	68.12	0.092
	Female	29.15	13.18	
Smoking	-ve	29.15	15.01	0.015
	+ve	40.62	117.96	
Previous biology	-ve	33.41	83.09	0.181
	+ve	29.15	12.63	
NSAID	-ve	30.24	16.14	0.820
	+ve	33.41	75.52	
MTX	-ve	33.41	16.57	0.289
	+ve	23.12	77.55	
Enthesitis	-ve	33.41	65.87	0.659
	+ve	29.71	15.72	

Discussion

Demographic data of participants: Altogether, there were 82 males (87.23%) in the two study groups. This finding is in agreement with two previous reports which stated that AS affects males more than females, with the male gender being a risk factor for developing AS [14]). The mean ages of the two groups being in the late years of the fourth decade of life is consistent with previous studies indicating that AS might manifest itself clinically between the ages of 30 and 50 years or even earlier ([15];[6]). Although the mean weight of the cases in the two study groups falls in the "overweight" category, not the obese, weight gain is known to affect the clinical manifestations of AS, including inflammation, disease activity, radiographic damage, physical mobility, health index as well as response to treatment [16] . More than half of the cases in the current study were smokers while a previous study reported 70% of participants were smokers [17]. The effect of smoking on patients with ankylosing spondylitis maybe reflected in 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 pro-inflammatory cytokines [18,19]. The total number of doses of each treatment, received by patients in the respective groups, was significantly different with more doses of Remicade were taken, which may be explained in light of the differences in immunogenicity of the two treatments. In addition, patients in the Remicade seemed to have been administered more NSAIDs than those in the Remsima group, which is in agreement with other studies [20]. 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 [21]. The occurrence of enthesitis was more than double in the Remsima group (46.0%) than the Remicade group (22.7%), while a previous study showed that 27.5% of AS cases had enthesitis [22]. Enthesitis is a serious complication of AS [23]. 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. The high incidence of enthesitis reported in our study might be due to poor response to, and/ or poor compliance with, treatment. The biosimilar CT-P13 might have a poor control on enthesitis.

Correlation between anti-drug antibody titer and demographic/clinical characteristics of participants: In the current study showed that there was no significant correlation between the anti-infliximab and anti-CT-P13 antibodies and the demographic characteristics of participants except for a significant correlation between anti-CT-P13 and ASDAS-CRP and smoking. Also, there was no significant correlation between age and antibody production, but age remains one of the risk factors for AS. According to previous studies, the influence of age on the development of anti-IFX Abs appeared to be low [24]. There was no significant correlation between patients' gender and ADAbs formation in the two treatment groups. Gender was suggested to be a risk factor for AS development, but not for ADAbs formation [25]. BMI can provide insight into an individual's propensity for developing AS and may even have an impact on their immunogenicity when undergoing biological therapies. In a previous study, among infliximab-treated patients with spondyloarthritis, BMI was reported to have a substantial effect on the development of anti-infliximab antibodies [26]. ASDAS-CRP reflects the disease activity of patients, ASDAS score can be elevated when patients develop ADAbs, which give a sign to focus on the underlying cause for disease worsening. Some studies suggested that when ASDAS increases, it indicates that the ADAbs are detected in the body during the treatment course as an indication of non-response to infliximab [27]. In the current study, both treatment groups had high levels of ASDAS-CRP, but only the CT-P13 group showed a statistically significant correlation between ASDAS-CRP and the development of ADAbs. Some published studies provided information about how the drug dose does impact ADAbs formation as higher doses may influence the immunogenic tolerance when the dose exceeds the desired level. A larger infliximab dose results in more free drugs than would be neutralized by ADAbs [28] [29]. One of the important considerations that affect ADAbs production and may correlate with their development, is how long the patients had the disease. Disease duration reflects the ability of the immune system to react to foreign substances, which may suggest that the immune reaction against the "non-self" therapeutic antibodies is influenced by the status of the immune system, namely an active inflammatory state [30]. The concomitant usage of MTX with TNF-α inhibitors showed a remarkable outcome in controlling clinical signs as MTX can decrease the disease severity and reduce the associated symptoms. A previous study provided evidence that MTX use is significantly associated with a lower incidence of ADAbs development in AS [31] Another study suggested that MTX can inhibit the development of ADAbs in infliximab-treated patients with AS [32], whereas another study failed to demonstrate the

usefulness of MTX in AS patients [33]. There was no difference in immunogenicity between CT-P13 and Remicade in a randomized, double-blind trial for either RA (3mg/kg plus MTX) or AS (5mg/kg monotherapy) [34]. An important risk factor for AS is smoking. The majority of patients in the two treatment groups in the current study were active smokers, which could affect the disease activity in the two groups. Besides, an induction for immunogenicity of the treatments increases by smoking as ADAbs generation in high level is affected by smoking [35]. In the Remicade group, there was no significant correlation between smoking and ADAbs; however, such correlation was significant in the Remsima group. This indicates that patients taking CT-P13 develop ADAbs that are affected by smoking. It had been demonstrated that smoking has an effect on both the humoral and the cell-mediated immune responses [36]. A study on Crohn's disease and rheumatoid arthritis cases indicated that a lifetime of smoking almost doubles the risk of developing ADAb [37]We could not find a significant correlation between ADAbs and usage of NSAIDs, which is in agreement with the findings of a previous study [38]. NSAIDs are used to help to relieve pain and are considered necessary to be included in the treatment of AS [39]. The other important risk factor for the development of ADAbs is the previous use of biologics. In our study, the group on CT-P13 had high ADAbs and the majority were on previous biologics and then switched to Remsima. This indicated a cross immunogenicity between biological treatments. A published study made a similar suggestion regarding the cross-reaction between CT-P13 and Remicade, as the two products share immunodominant epitopes [39]. Another study revealed that all of the antibodies that were generated in patients who were treated with Remicade were shown to cross-react with Remsima. Moreover, it has been demonstrated that ADAbs can still be detected in the blood years after treatment with infliximab has been stopped [40].

Conclusion

Immunogenicity of the original Infliximab may not correlate with any of the demographic characteristics or disease activity in patients with AS. However, immunogenicity of the biosimilar CT-P13 infliximab correlates with disease activity and smoking in patients with AS. Prior treatment with, and number of doses of, either treatment received by patients may play a role in such immunogenicity.

Ethical Clearance was obtained from the Scientific Research Ethics Committees at the Department of Pharmacology and the Department of Medicine at the College of Medicine/ University of Baghdad.

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مناعة البديل الحيوي للإنفلكسيماب والإنفلكسيماب الأصلي في المرضى العراقيين المصابين بالتهاب الفقار اللاصق: العلاقة مع الخصائص الديموغرافية والسريرية للمرضى

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الخلاصة:

الخلفية: يعرف إلتهاب الفقار اللاصق أيضا بإسم إلتهاب الفقار الفقاري المحوري الشعاعي؛ وهو مرض وراثي نادر يصيب الأشخاص الذين يعانون من عوامل وراثية؛ بالإضافة إلى ذلك فهو أحد أمراض المناعة الذاتية مع تفاعلات التهابية مزمنة تقدمية. يشمل علاج إلتهاب الفقار اللاصق تعديل نمط الحياة واستخدام الأدوية مثل العامل البيولوجي إنفليكسيماب أو البديل الحيوي CT-P. على الرغم من فائدتهما العلاجية ترتبط هذه العلاجات بعدد من الآثارالضارة الخطيرة مثل المناعة ضد العلاج من قبل الجهاز المناعي للجسم، حيث يمكن ان يتأثر بالعديد من العوامل المتعلقة بالمرضى وقد يؤدي إلى فشل العلاج.

الهدف: التحقق مما إذا كانت مناعة البديل الحيوي للإنفلكسيماب والإنفلكسيماب الأصلي في المرضى العراقيين المصابين بالتهاب الفقار اللاصق تتأثر بأي من الخصائص الديموغرافية للمرضى.

المرضى وطرق العمل : أجريت دراسة بأثر رجعي مفتوحة التسمية من كانون الأول (ديسمبر) 2021 إلى آذار (مارس) 2022 في وحدة أمراض الروماتيزم، مستشفى بغداد التعليمي / مدينة الطب، بغداد. كان أربعة وأربعون مريضًا يتناولون عقار الإنفلكسيماب وخمسون مريضا يتناولون المتشابه الحيوي للإنفلكسيماب؛ بجرعه 5 ملم\كغم لمدة ثلاثة أشهر على الأقل قبل بدء الدراسة. بينما تم إختبار الأجسام المضادة والبروتين التفاعلي بتقنية الفحص المناعي المرتبط بالإنزيم. تم تقييم نشاط المرض من خلال قياس درجة ASDAS-CRP . أجريت التحليلات الإحصائية باستخدام الحزمة الإحصائية للعلوم الإجتماعية spss الإصدار (20.0) مع مجموعة من الإختبارات الإحصائية وإختبارات الإرتباط. تم النظر في مستوى الأهمية عند ($p<0.05$).

النتائج: لم يكن هناك إرتباط إحصائي بين الأجسام المضادة للإنفلكسيماب والمتغيرات الديموغرافية للمرضى. أيضا كانت نتائج مماثلة للمتشابه الإحيائي للإنفلكسيماب. باستثناء التدخين ونشاط المرض الذي أظهر إرتباطا كبيرا بتطوير الاجسام المضادة ضد المتشابه الاحيائي. CT-P13

الإستنتاج: قد لا تتأثر المناعة في العلاج الأصلي الإنفلكسيماب بالخصائص الديموغرافية أو نشاط المرض في المرضى الذين يعانون من إلتهاب الفقار اللاصق ومع ذلك قد تتأثر مناعة المتشابه الإحيائي بنشاط المرض وكذلك التدخين عند المرضى الذين يعانون من إلتهاب الفقار اللاصق. قد يلعب العلاج المسبق الذي يأخذه المريض وعدد جرعاته دورا في هذه المناعة. CT-P13

الكلمات المفتاحية: إلتهاب الفقار اللاصق, العوامل البيولوجية, المتشابه الإحيائي, نشاط المرض, المناعة