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SAFETY OF BIOLOGICS FOR THE TREATMENT OF AUTOIMMUNE DISEASES: A CROSS-SECTIONAL STUDY FROM SAUDI ARABIA

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ABSTRACT

Purpose: This cross-sectional study explored the safety of biological therapies, association between patient characteristics, adverse events (AEs) and biological therapy among treated patients and assess patient-perceived treatment effectiveness of the biologics in autoimmune diseases (AD) patients in Riyadh, Saudi Arabia. ***Methods:*** AD patients (ulcerative colitis [UC] and Crohn's disease [CD], rheumatoid arthritis [RA], and psoriasis [PsO]) who received adalimumab, infliximab, rituximab, or etanercept were analyzed. ***Results:*** Of the 115 biologically-treated AD patients (CD=80; RA=18; UC=16; PsO=1), 88.7% received infliximab. Over 95% of the patients experienced at least one AE, with higher prevalence in infliximab cohort than other cohorts. Most common AEs were weight gain (20%–57.1%), hair loss (20%–42.8%), and stomach pain (14.3%–22.6%). Infections occurred in 16.5% of patients; acute nose, throat, and sinus infections and urinary tract infections were the most common infections. There was a lack of association between the variables, biological therapy, and AEs among the treated AD patients. Majority of the treated-patients (89%) reported improvement after treatment with biological therapy; 92% expressed their willingness to continue with the prescribed biological therapy. ***Conclusions:*** This study provides valuable data on the safety and patient perceived treatment effectiveness of biologics used for the treatment of various AD.

KEYWORDS: adverse events · autoimmune disease · biologics · infections · treatment effectiveness.

ABBREVIATIONS

AD, autoimmune diseases

AE, adverse events

CD, Crohn's disease

IBD, inflammatory bowel disease

ILD, interstitial lung disease

KFMC, King Fahad Medical City

KSUMC, King Saud University Medical City

PsO, psoriasis

RA, rheumatoid arthritis

SD, standard deviation

UC, ulcerative colitis

UTI, urinary tract infection

INTRODUCTION

Autoimmune diseases (AD) are a heterogenous group of disease characterized by dysregulation of various aspects of normal immunity and inflammation.[1] Inflammatory bowel disease (IBD) including both ulcerative colitis (UC) and Crohn's disease (CD), psoriasis (PsO), and rheumatoid arthritis (RA) are among the most common AD. It negatively impacts patient's daily lives and impair their quality of life physical and mental status and often requires life-long treatment.[2,3] Although few studies have reported increase in the prevalence of various AD in Saudi population.[4-9] the true prevalence remains highly elusive. The etiology of AD is multifactorial is reported to result from a complex interplay of genetic environmental, and aberrant immune regulation.[10]

The chronic nature of these diseases places a significant on patients, caregivers, employers, and healthcare system.[11-13] The treatment plan to manage various AD is dependent on multiple factors such as patient characteristics, treatment history, comorbid conditions, and toxicity profiles of therapy options. The advent of biologic drugs has led to a paradigm shift in the effective management of AD. The targeted capabilities of the biologics offer an edge over the other regimens and is one of the major reasons for their increased use in the treatment of AD.[14] A growing number of biological therapies including adalimumab, etanercept, infliximab, rituximab, and certolizumab pegol are available for the treatment of various AD.[14]

Although treatment with biologics are quite effective, they are often associated with meaningfully high rates of adverse events (AEs).[13,15,16] Treatment–related AEs have the potential to impact clinical care by causing treatment delays or dose reductions in therapy. The safety concerns associated with biologic therapies across various geographies has been well documented.[13,15,16] However, there are no studies which have assessed the safety data among AD patients treated with these agents in Saudi Arabia. Therefore, this cross-sectional study was designed with the following objectives.

a) To compare the safety of the approved biological therapies (adalimumab, infliximab, rituximab, and etanercept) in the treatment of various AD (UC, CD, PsO, and RA) in Riyadh, Saudi Arabia.
b) Measure the association between patient characteristics, AEs and biological therapy among treated AD patients.
c) Assess patient-perceived treatment effectiveness (improvement and continuation) after biological therapy.

METHODS

Study Design

This was a descriptive, cross-sectional survey that collected data using a validated questionnaire from AD patients treated with biologics at King Saud University Medical City (KSUMC) and King Fahad Medical City (KFMC), Riyadh, Saudi Arabia. Both are tertiary care hospitals in Saudi Arabia. The study protocol was approved by the Institutional Review Boards of KSUMC and KFMC.

Participants

Adults (18 years and older) with a diagnosis of IBD (UC or CD), PsO, or RA and at least one prescription for any of the approved biological agents (adalimumab, etanercept, infliximab, and rituximab), were eligible for inclusion. Patients were further required to be residents of Saudi Arabia. The first recorded prescription for any of the above biological agents was defined as the index event. Patients who were non-residents of Saudi Arabia, pregnant or lactating females, and those on corticosteroid therapy, were excluded. The study period spanned from September 2017 to January 2018.

Outcomes

Data on all adverse events (AEs) that occurred after initiation of biologic therapy were captured. Patient-perceived treatment effectiveness of the prescribed biological therapy was

assessed by patient response to the following questions: "Do you feel better after using biological therapy?" and "Do you want to continue using the prescribed biological therapy?" Patients were asked to respond either "yes" or "no". Patients demographics and clinical characteristics were recorded during the baseline period.

Statistical Analysis

All study variables were summarized descriptively for all the treatment cohorts. Categorical variables were summarized as counts and percentages. Continuous variables were reported as means and standard deviations (SD). Statistical comparisons were conducted to analyze the association between the AEs and the biological therapy administered using Fisher's exact test. A p-value <0.05 was set as the threshold for statistical significance. All data were analyzed using SPSS version 21.0 (IBM Corp. Armonk, NY, USA).

RESULTS

Study Population and Baseline Characteristics

The final sample size consisted of 115 patients diagnosed with AD (CD=80; RA=18; UC=16; PsO=1) who received treatment with biological therapies. Overall, patients averaged 34.8 (SD=13.6) years of age and had more males than females (53.9% vs. 46.1%). Majority of the patients (96.5%) had a diagnosis established for over one year.

Of the included patients, 88.7% received infliximab, 6.1% received rituximab, 4.3% received adalimumab, and 0.9% received etanercept. Majority of patients (77.4%) were in receipt of biological therapy for more than one year. Approximately 82% of patients received medication for AD. Overall, 17% received influenza vaccine after biological therapy (Table I).

Adverse Events

Table II summarizes the occurrence of AEs among AD patients treated with biological therapy. Majority of the treated patients (over 95%) reported at least one AE, with higher prevalence of AEs in infliximab cohort compared to other cohorts. Weight gain was the most common AE, with prevalence ranging from 20% in adalimumab cohort to 57.1% in the rituximab cohort. Hair loss (41.7%) others (40%), and stomach pain (20.9%) were the other AEs experienced by the overall cohort. By the class of the AEs, chest pain (18.3%), arrhythmia (14.8%), and swelling of ankles or feet (13.9%) were the most common cardiovascular AEs. Motor deficit (17.4%), vision impairment (16.5%), speech impairment

(14.8%) and cognitive impairment (10.4%) were the most common neurological AEs. Bruising (12.2%) and pain (10.4%) were the most frequent injection site reactions. Difficulty in breathing (16.5%) was the most commonly reported respiratory AE. Other most common AEs experienced by the overall cohort were stomach pain (20.9%) and anemia (13%).

Fig. 1 summarizes the prevalence of infection among AD patients treated with biological therapy. Overall, 16.5% patients developed any infection, with infliximab cohort reporting higher rates than the other cohorts.

Table III describes the association between the demographic and clinical characteristics, and AEs after biological therapy. There were no significant differences observed between the variables, biological therapy, and AEs among the treated AD patients.

Patient-perceived Treatment Effectiveness

Majority of the patients (89%) reported improvement after treatment with biological therapy and 92% expressed their willingness to continue with the prescribed biological therapy (Fig. 2).

Table I: Baseline Characteristics of AD Patients Treated with Biological Therapy.

	all patients (n=115)
age (years), mean (sd)	34.8 (13.6)
male, %	53.9%
type of ad, %	
cd	69.5%
ra	15.7%
uc	13.9%
pso	1.7%
duration of ad diagnosis	
<1 year	3.5%
>1 year	96.5%
ad medication	81.7%
biological therapy	
infliximab	88.7%
rituximab	6.1%
adalimumab	4.3%
etanercept	0.9%
length of biological therapy	
<1 year	22.6%
>1 year	77.4%

Abbreviations: AD, autoimmune disease; CD, Crohn's disease; PsO, psoriasis; RA, rheumatoid arthritis; SD, standard deviation; UC, ulcerative colitis.

Table II: Occurrence of AEs After Treatment with Biological Therapy.

	All Patients (N=115)	Infliximab (N=102)	Rituximab (N=7)	Adalimumab (N=5)	Etanercept (N=1)
Metabolic, %					
Weight gain	52.2%	53.9%	57.1%	20.0%	0.0%
Anemia	13.0%	14.7%	0.0%	0.0%	0.0%
Cancer	3.5%	2.0%	14.3%	0.0%	100.0%
Diabetes mellitus	1.7%	0.9%	7.1%	0.0%	0.0%
Cardiovascular, %					
Chest pain	18.3%	19.6%	14.3%	0.0%	0.0%
Arrhythmia	14.8%	15.7%	14.3%	0.0%	0.0%
Swelling of ankles or feet	13.9%	13.7%	28.6%	0.0%	0.0%
Respiratory, %					
Difficulty in breathing	16.5%	16.7%	14.3%	0.0%	100.0%
Severe ILD	0.9%	1.0%	0.0%	0.0%	0.0%
Neurological, %					
Motor deficit	17.4%	17.6%	28.6%	0.0%	0.0%
Vision impairment	16.5%	17.6%	14.3%	0.0%	0.0%
Cognitive impairment	10.4%	10.8%	14.3%	0.0%	0.0%
Speech impairment	14.8%	5.9%	14.3%	0.0%	0.0%
Injective site reaction, %					
Bruising	12.2%	12.7%	0.0%	0.0%	100.0%
Pain	10.4%	8.8%	14.3%	20.0%	100.0%
Erythema	7.0%	7.8%	0.0%	0.0%	0.0%
Other AEs, %					
Hair loss	41.7%	42.2%	42.9%	20.0%	100.0%
Others	40.0%	40.2%	14.3%	80.0%	0.0%
Stomach pain	20.9%	22.5%	14.3%	0.0%	0.0%
Mouth blisters	7.8%	6.9%	28.6%	0.0%	0.0%

Table III: Association Between Patient Characteristics, Biological Therapy And Aes In Treated Ad Patients.

	Infliximab (N=102)	Rituximab (N=7)	Adalimumab (N=5)	Etanercept (N=1)	p-value
Variable, %					
Weight gain	53.9%	57.1%	20.0%	0.0%	0.29
Neurological	52.0%	71.4%	0.0%	0.0%	0.34
Cardiovascular	49.0%	57.1%	0.0%	0.0%	0.77
Hair loss	42.2%	42.9%	20.0%	100.0%	0.61
Injection allergies	29.4%	14.3%	20.0%	100.0%	0.45
Stomach pain	22.5%	14.3%	0.0%	0.0%	0.78

Influenza vaccine	18.6%	0.0%	20.0%	0.0%	0.66
Respiratory	17.6%	14.3%	0.0%	100.0%	0.27
Infection	17.6%	14.3%	0.0%	0.0%	0.69
Anemia	14.7%	0.0%	0.0%	0.0%	0.36
Mouth blisters	6.9%	28.6%	0.0%	0.0%	0.21
Tumor	2.0%	14.3%	0.0%	100.0%	0.06
Diabetes mellitus	1.0%	14.3%	0.0%	0.0%	1.0

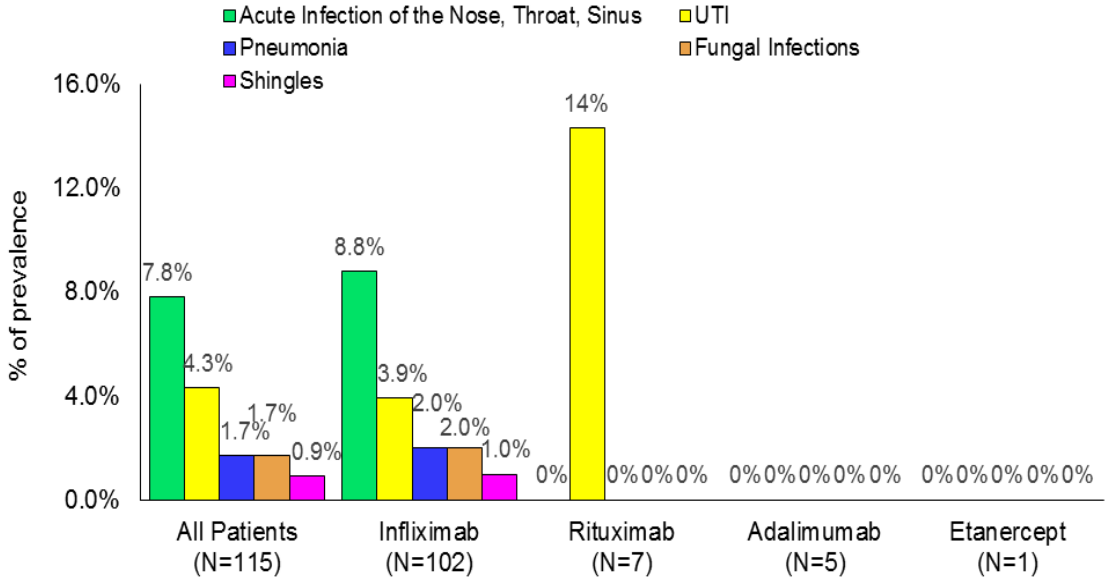

Fig. I: Prevalence of Infection in AD patients After Treatment with Biological Therapy.

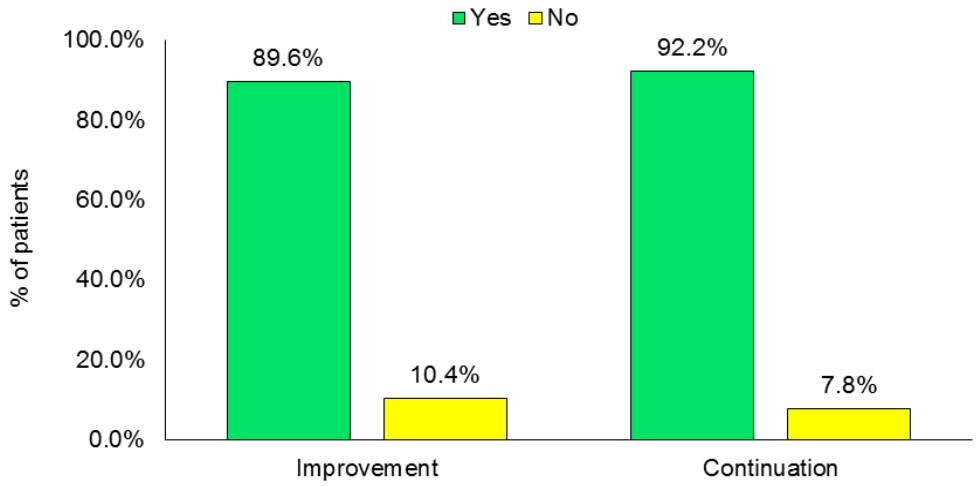

Fig. II: Patients Perception of Improvement and Willingness to Continue Treatment with the Biological Therapy.

DISCUSSION

To the best of our knowledge, this is the first study that compared the safety profile of AD patients treated with biologic medications in Saudi Arabia. Results of this study demonstrated that the majority of patients experienced at least one AE. Weight gain, other AEs, and hair loss were the most frequently diagnosed AEs in this study population, with no significant difference between the treatment cohorts. The rate of occurrence of various infections was low. There was a lack of association between patient characteristics, biological therapy, and AEs among the treated AD patients. Furthermore, majority of the patients reported improvement in their disease status and expressed their willingness to continue treatment with the prescribed biological therapy.

Biologic therapy remains the mainstay of treatment in the management of AD.[17,18] Nevertheless, they are not without risk as considerable proportion of patients experience an AE during the course of treatment.[18] While various studies have demonstrated the occurrence of an array of AEs.[19-23], there is a paucity of data reported from Saudi Arabia. Understanding the patterns of treatment-related AEs may provide useful insights while selecting optimal biologic therapy for the treatment of AD.

This survey based, cross-sectional study was conducted in two tertiary care hospitals in Riyadh, Saudi Arabia. Data on AEs were collected from AD patients (UC, CD, RA, or PsO) treated with any of the approved biological therapy (adalimumab, etanercept, infliximab, and rituximab). The current study found that more than 95% of AD patients experienced at least one AE. Weight gain (20%–57.1%), hair loss (20%–42.8%), and stomach pain (14.3%–22.6%), were the most frequent AEs recorded in the overall population. Infections occurred in 16.5% of the study population. Acute infection of nose, throat and sinus (7.8%), and urinary tract infection (UTI) (4.3%) were the most common infections that occurred in the study population. With regards to the profile of the AEs, there was a tendency of greater prevalence of weight gain and hair loss in rituximab and infliximab users and a tendency of greater incidence of infections (acute infection of nose, throat and sinus, UTI, and pneumonia) in the group treated with infliximab. Our estimates on the prevalence of AEs and infection exhibit some similarities and differences with those reported in the literature. However, it is difficult to directly compare the findings due to the differences in methodology, patient population, and time frame of the study. Moreover, there are no studies from Saudi Arabia that have

reported safety data in AD patients, thereby, restricting us to draw a temporal trend of the occurrence of AEs and infections in this population.

Patients perception of treatment effectiveness is critical as their decision often influence treatment plans.[24-25] In this study, majority of patients (90%) treated with biological therapy reported improvement in their disease status, and most of them (92%) expressed their willingness to continue with the prescribed biological therapy. Although the estimates reported in this study are notably high, it overall endorses the findings of the previous studies.[25-28] The differences in the estimates may be primarily attributed to methodological distinctions, sample differences, or temporal differences in the study periods.

This study has several limitations which merit consideration. The cross-sectional observational nature of the study prohibits causality inferences. Non-biologics and those treated with a combination of biologics, were not evaluated. There is a potential for selection bias as patients were recruited from tertiary care hospitals. The low sample size is another major limitation, which means that some cohorts were too small for reliable statistical comparisons. The questionnaire used in this survey was not rigorously validated. The subjective nature of survey conducted implicates reporting bias. Moreover, the data from this survey was self-reported by respondents; thus, there is a potential of recall bias. The data on treatment effectiveness was purely based on the patients' perception of their disease status, which may not be a true reflection of their actual disease condition. Finally, the survey was administered to AD patients who were treated at tertiary care centers. Thus, the results of this study may not be generalizable to non-academic centers that do not have the same level of staff support.

Nevertheless, the self-reported nature of this study with respect to the evaluation of patient perception represents a distinct strength of this study. Furthermore, despite the low patient numbers with AD, this study provides evidence on the safety of biological therapy in the treatment of AD.

In summary, AD patients treated with biological therapy experienced one or more AEs, while the rate of infection was low in the treated population. Weight gain, other AEs, and hair loss were the most common AEs reported in this study. There was a lack of association observed between variables, biological therapy, and AEs among the treated AD patients. With regards to patient-perceived treatment effectiveness, majority of the patients reported improvement in

their disease status and expressed their willingness to continue with the prescribed biological therapy. These results provide important cues on the safety of biological therapy and its effectiveness and underlines the need to monitor the safety profiles on an ongoing basis among AD patients in Saudi population. Future studies in a larger cohort of patients are warranted to provide further insights into the therapeutic benefits of biological therapy for the treatment of AD.

Conflict of Interest

The authors declare no conflict of interest.

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