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Research Article

Iraqi Registry Data Proves Safety and Efficacy of Switching to Adalimumab Biosimilar in Treating Rheumatoid Arthritis

Yasameen Abbas Humadi[1*], Nabaa Ihsan[2], Asal Adnan[3], Marwa Moayad[4], Ali AlKazzaz[5], Avin Maroof[6], Ali Abdulrahman[7], Nazar Abdulateef[3], Mohammad AlOsami[3], Faiq Gorial[3], Mohammed Altahhan[2], Zahraa Almansi[2], Ali AlNoori[2]

1 Department of Internal Medicine, Al-Nahrain University, College of Medicine, Baghdad, Iraq
2 Department of Internal Medicine, University of Baghdad, Baghdad, Iraq
3 Rheumatology Consultation Clinic, Medical City, Baghdad, Iraq
4 Rheumatology Consultation Clinic, Al-Yarmouk Hospital, Baghdad, Iraq
5 Department of Internal Medicine, Babylon University, Hilla, Iraq
6 Department of Internal Medicine, School of medicine-University of Kurdistan Hawlêr, Iraq
7 Department of Internal Medicine, University of Mosul, Mosul, Iraq

* Corresponding author's email: jasmine86abbss@nahrainuniv.edu.iq

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ABSTRACT

Background: Adalimumab is approved for Rheumatoid Arthritis (RA). In 2021, A biosimilar (ABP501; Amgevita®) was licensed in Iraq. The current study aimed to ensure the safety and Efficacy of Amgevita-Adalimumab biosimilar- in RA Patients in Iraq.

Subjects and Methods: A Prospective Observational Study Started on 69 RA Records Receiving Amgevita. Data collected from the local registry was then examined for disease activity and adverse reactions for 9 months follow-up.

Results: Thirty patients completed the 9 months of the study: aged (49±14) years; 77.5% females. After 3, 6, and 9 months of follow-up, patients' mean ± (SD) Clinical Disease Activity Index (CDAI) was 27.8 (13.60) which was statistically lower (19.80) (6.96), 17.70 (2.790), and 19 (1.040), $p<0.001$. With a mean change of CDAI: 8 ($p<0.001$), 10.1 ($p<0.001$), and 8.78 ($p<0.001$) after 3, 6, and 9 months. The cumulative percentage of responders was 55.00% and the Cumulative percentage of probability of change of disease activity was 86.00%, No patient achieved remission and no significant Side effects were recorded.

Conclusion: the findings suggest that Amgevita holds promise as an effective and safe option for managing rheumatoid arthritis.

Introduction

Rheumatoid arthritis (RA), An autoimmune condition with a natural chronic history, is characterized by stiffness, especially in the morning, symmetrical polyarthritis, and extra-articular manifestations leading to disability if left untreated, with higher female susceptibility (1).

The discovery of biological agents, particularly tumor necrosis factor (TNFi) inhibitors, resulted in a qualitative advance in RA treatment (2). Adalimumab is a human-derived monoclonal antibody with the

capacity to neutralize TNF-α molecule made up of two light and two heavy chains (kappa and immunoglobulin G1 (IgG1) respectively) with one N-glycosylation site on each of the heavy chains. In The United States, The Food and Drug Administration (FDA) gave its approval for RA management in 2002 (3). Nevertheless, the pricing of biologic therapies continues to be an issue despite their potential health benefits, particularly in countries such as Iraq, where the Iraqi Ministry of Health (MOH) aims to improve health care access (4).

Biosimilars are a novel group of medications designed to be as safe and effective as the original biologics (5). ABP-501- [USA: named accordingly AMJEVITA™ (adalimumab-atto); in European Union regions (EU): AMGEVITA® (adalimumabis the first biosimilar to adalimumab (HUMIRA), that has been authorized (6). Amgevita was recently licensed in Iraq, however, the literature lacks data on its utilization in Iraqi patients diagnosed with RA. Thus, this multi-center study aimed to ensure the efficacy and safety of Amgevita adalimumab biosimilar (bADA) in Iraqi patients with RA**.**

Subjects and Methods

A Prospective multi-center cohort observational study was undertaken among patients with RA for whom Amgevita was prescribed by consultant rheumatologists. Data were collected from Amgevita registry data that were launched in January 2021 till September 2021 across five centers in Iraq. The Rheumatology Unit at the University of Baghdad approved the study protocol in line with the Helsinki Declaration.

As Inclusion Criteria, The registry includes eligible individuals with moderate to severe RA who met the criteria set by the American College of Rheumatology (ACR) and who had not reacted or not sufficiently responded to Conventional synthetic Disease Modifying Anti-Rheumatic Drugs (csDMARDs) or other biological treatments were given consideration for biologic Adalimumab (bADA) therapy and who freely agreed to receive bADA as their preferred biologic at the participating institutions. According to the center's standard clinical procedure, all of these patients received bADA 40 mg subcutaneously twice a month. Only patients completing the 9-month study period were included in the final analysis to overcome potential bias.

Patients with overlap diseases and those who did not complete 9 months follow-up period were excluded

All patients were required to sign a written consent form and The Ethical Committee at Baghdad Teaching Hospital approved the study according to the Declaration of Helsinki.

Age, gender, BMI, current smoking status, comorbidities, disease duration, current medications, previous biologics use, disease activity assessed by clinical disease activity index (CDAI), complete blood picture (CBP), renal and liver function tests, and any adverse event reported in the period of follow up were recruited from the registry system.

Statistical analysis was conducted using the 26th version of SPSS for Windows (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as numbers and percentages. The normal distribution of the results was assessed using the Shapiro-Wilk test. In cases of missing data, the last-observation-carried-forward (LOCF) method was employed for data analysis to ensure the robustness of the results.

The paired t-test was utilized to determine the statistical significance of the difference in the Clinical Disease Activity Index (CDAI), a reliable tool for assessing disease activity and guiding response to therapy between the follow-up periods and the baseline. This test allows for the comparison of means within the same group of patients at different time points, thus assessing the effectiveness of Amgevita in reducing disease activity over time.

To assess the cumulative percentage of responders and the transition from severe to moderate disease activity, a Kaplan-Meier survival analysis was employed. This analysis estimates the probability of an event occurring over time, such as a response to treatment or a change in disease activity, providing valuable insights into the long-term outcomes of treatment with Amgevita.

Furthermore, a Cox regression analysis was used to evaluate the impact of demographic and clinical characteristics on the response to Amgevita over time, as well as to predict changes in disease activity. This type of regression analysis is suitable for time-to-event data and allows for the examination of multiple predictors simultaneously, thus identifying factors that may influence treatment outcomes.

A significance level of less than 0.05 for the two-tailed p-value was considered as the cutoff for statistical significance in all analyses, ensuring the reliability of the findings.

Results

A total of 69 patients participated in the study who were recorded retrospectively in the registry system of biological therapy in more than one center in Iraq and followed prospectively for nine months. At the end of this period, only 30 patients had completed the 9 months. Follow-up of 39 patients. The last observation was carried out to analyze the missing data (Figure 1).

Baseline characteristics of the patients Extracted from the Registry

The patient's average age was 49 (plus or minus 14) years. The majority of the patients (77.6%) were female, with a mean BMI of 30.66 (±4.25) kg/m2. Only 4 (7.5%) of the patients were smokers. The average duration of the disease and the time taken to start using the adalimumab biosimilar (Amgevita) was 9.90 (±8.99) years. Other baseline characteristics can be found in Table 1.

Based on the data presented in Figure 2A, the average Clinical Disease Activity Index (CDAI) of the patients was significantly lower after three, six, and nine months compared to the baseline CDAI. Specifically, the mean CDAI(±SD) after three months was 19.8 (±6.96) compared to 27.8(±13.6) at baseline ($p<0.001$); after six months it was 17.7 (SD=2.79) compared to 27.8 (SD=13.6) at baseline ($p<0.001$); and after nine months it was 19 (SD=1.04) compared to 27.8 (SD=13.6) at baseline ($p<0.001$). These results are illustrated in Figure 2A.

Furthermore, the mean change in CDAI from baseline was also calculated. The mean change in CDAI after three months was 8 ($p<0.001$), after six months was 10.1 ($p<0.001$), and after nine months was 8.78 ($p<0.001$). These results are shown in Figure 2B.

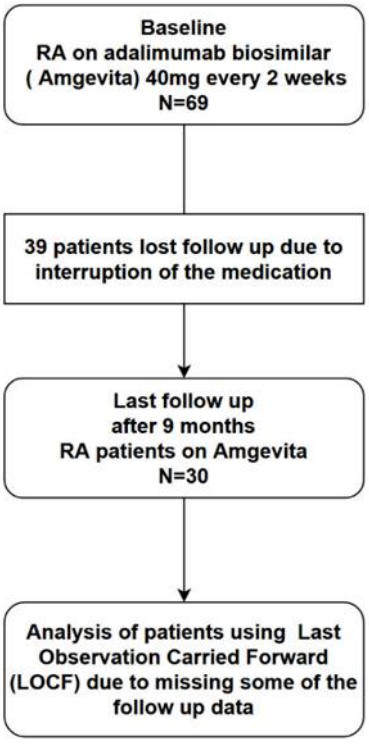

Figure1: Study flow chart

Table 1: Baseline characteristics of the 69 patients

Variables	Value
Age, mean (±SD), years	49 (±14)
Female, N (%)	52 (77.6)
BMI, mean (±SD), kg/m2	30.66 (±4.25)
Smokers, N (%)	4 (7.5)
Disease duration, mean (±SD), years	9.90 (±8.99)
Time to start Amgevita from the onset of the disease	9.90 (8.99)
Positive RF, N (%)	15 (93.8)
Positive ACPA. N (%)	10 (76.9)
Steroid users, N (%)	21 (31.3)
Previous use of other bDMARDs, N (%)	31 (70.5)
csDMARDs users, N (%)	53 (93%)

SD, standard deviation, N, number; BMI, Body Mass Index; RF, Rheumatoid factor; ACPA, Anti-citrullinated-peptide-antibody; bDMARDs, biological disease-modifying antirheumatic drugs, csDMARDs, conventional disease-modifying antirheumatic drugs

Outcome measurement

The cumulative percentage of responses and the transition from severely to moderately active disease

According to the EULAR CDAI response criteria, the cumulative percentage of response among active RA disease patients who were treated with adalimumab biosimilar (Amgevita) was 55%, where a minor response was considered if there was at least a >50% change in CDAI from baseline. Over 9 months, the cumulative percentage of probability of change from high to moderate disease activity was 86%, but none of the patients had changed to a mild or remission state during that time (Figure 3A and B).

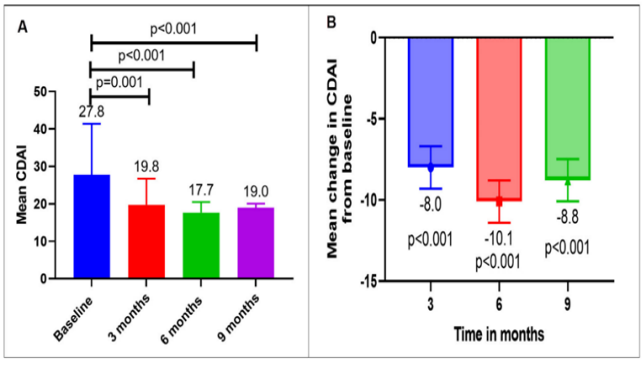

Figure 2: A. Mean CDAI in RA on adalimumab biosimilar (Amgevita) over 9 months. B. Mean change in CDAI over 9 months. CDAI, clinical disease activity index.

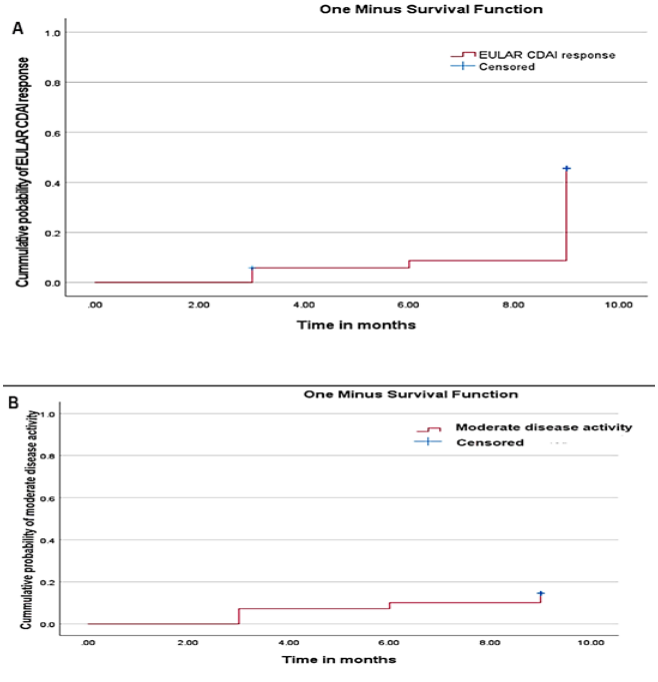

Figure 3: A: Cumulative percentage of EULAR CDAI response criteria in RA patients. B: Cumulative probability of change from severe to moderate disease activity."

Multivariate modeling

We conducted a multivariate Cox regression analysis to determine the factors that may predict response to adalimumab biosimilar (Amgevita) over time or the possibility of transitioning from severe to moderate disease activity. However, we found that baseline demographic and clinical characteristics had no statistically significant impact on the outcome of interest, as shown in Tables 2 and 3.

Table 2: Cox regression analysis to assess predictors of response over time

Variables	HR	P value
Age	0.57	0.99
Female compared to male	0.16	0.54
Smokers compared to non-smokers	0.30	2.04
Disease duration	0.88	1.01
Time to start Amgevita	0.98	0.46
Steroid users compared to non	0.75	0.87
csDMARDs users compared to non	0.86	1.23
Previous bDMARDs users compared to non	0.43	1.75
Presence of comorbidity compared to absence	0.84	0.85

HR, Hazard ratio; csDMARDs, conventional disease-modifying antirheumatic drugs bDMARDs, biological disease-modifying antirheumatic drugs

Table 3: Cox regression analysis to predict moderate disease activity over time

Variables	HR	P value
Age	0.99	0.89
Gender	1.06	0.88
Smokers compared to non-smokers	1.11	0.89
Disease duration	0.99	0.52
Time to start Amgevita	0.99	0.63
Steroid users compared to non	1.00	1.00
csDMARDs users compared to non	1.30	0.73
Previous bDMARDs users compared to non	0.85	0.64
Presence of comorbidity compared to absence	1.00	1.00

HR, Hazard ratio; csDMARDs, conventional disease-modifying antirheumatic drugs bDMARDs, biological disease-modifying antirheumatic drugs

Safety measures

The clinical and hematological effects of adalimumab biosimilar (Amgevita) therapy were monitored and no significant adverse effects or changes were observed (refer to Table 4 for biochemical investigations).

Discussion

Despite the growing evidence supporting the clinical use of biosimilars in the field of autoimmune diseases, many physicians do speculate that this evidence is driven by the big pharmaceutical companies. Hence, they often request more real-world data that can reflect the true characteristics of a given drug; highlighting the need for more experience-based observations (7–10)). To our knowledge, this is the first study attempting to display the results of real registry data of rheumatoid arthritis patients treated by the biosimilar "Amgevita". The study comprised 69 rheumatoid arthritis patients recruited through the local registry system and observed for 9 months. Only 30 patients completed the entire 9-month study period. The results demonstrate that after 9 months, the participants' disease activity (as evaluated by CDAI) was significantly better when compared to the baseline CDAI (figure 2), with the mean CDAI dropping from 27.8 to 19, with a cumulative response of 55%. Figure (3) which reflects clear efficacy of the drug.

Table 4: Laboratory findings during Amgevita therapy over 9 months of treatment

Variables	Baseline	Last, follow up	p
WBC, mean ±SD, 109/L	8.47± 2.71	7.51± 1.93	0.196
HB, mean ±SD, g/dl	12.54± 1.72	12.9± 1.12	0.339
ALT, mean ±SD, U/L	17.976±6.380	18.235±7.704	0.893
AST, mean ±SD, U/L	17.567±8.465	16.472 ± 8.500	0.597
Blood urea, mean ±SD, mg/dl	29.612±11.719	31.206±9.388	0.561
Creatinine, median (IQR), mg/dl	0.7 (0.57 - 0.7)	0.7(0.6 to 0.8)	0.317

These results were comparable with other studies demonstrating clear efficacy of adalimumab biosimilar Amgevita in RA management, such as Cohen et al.'s study, which directly compares the bio-originator Humira with its biosimilar Amgevita (11).

However, the response in the current study is lower compared to the overall change in disease activity because, despite the mean disease activity dropped from high to moderate, none of the participants reached remission or low disease activity by the end of the study period. While in Cohen et al's study, the percentage of active patients who achieved remission was increased over time for both groups (Amgevita and Humira) from weeks 2 to 18 (range: 6.3%–31.1%, Amgevita; 2.8%–27.1%, Humira). At the end of the 24th week, 30.5% (Amgevita) and 35.5% (Humira) of patients had reached remission.

While none of the patients in the current study reached a complete response, this could be attributable to the patients' prior therapies where the majority of the participants in the current study had prior bDMARDs use (70.1%) (Table 1). While in Cohen et al.'s study, the majority were biologic naïve patients (73.1% in the Amgevita arm and 71.8% in the Humira arm), otherwise, both studies carry similar case characteristics.

Another observation by the PREMIER study is that people with RA may achieve a complete response after around 2 years of usage (12), and another Indian registry study showed that 58% of the treated patients at 12 months were in remission or low disease activity (13). So, extended follow-up may give the chance for a few cases to reach remission.

The fact that a large number of people (39 patients) stopped using the drug may also have an impact on the remission criteria, people who felt better after a few months might have escaped further doses.

A similar study on 149 RA patients in India (the ASPIRE registry data) has shown very similar results where, after 6 months, about 58% and 15% of patients were moderate and good EULAR responders.

Although not mentioned directly in the study, no patients reached remission as well from observation of the results (14).
In an attempt to investigate a potential response predictor, some variables were studied as shown in Tables (2 and 3) including age, gender, smoking status, disease duration, drug starting time, steroid use, csDMARDs, previous use of biologics, and comorbidities, but none showed a significant impact on response. This has been observed in other studies, where the clinical predictors of response were incoherent between studies and between groups of patients with high and moderate disease activity, whereas the more expensive biochemical or immunological predictors were not (15,16).

Concerning Amgevita's safety, the side effects seen were quite modest, with no substantial clinical or laboratory issues of concern (table 4). These findings are consistent with earlier trials that showed that both adalimumab and biosimilars are well tolerated (17).
The ASPIRE trial, on the other hand, found a 2% infection rate and 5% tuberculosis activation. However, in addition to RA, their records included individuals with ankylosing spondylitis (AS), psoriatic arthritis (PSA), and juvenile Idiopathic arthritis (JIA) (9).
Limitations of this study are the lost data from the 39 patients who didn't complete the 9 months of follow-up because of the interruption of the medication supply besides the effect of COVID-19 on the patients and their fear of taking the medication. and the lack of direct comparison with the bio-originator "Humira" due to unavailability at the time of collection.

Conclusion

The current study's findings provide valuable insights into Amgevita's potential effectiveness and safety in treating rheumatoid arthritis (RA). However, a larger sample size is necessary for a more comprehensive assessment. Future studies should focus on including more participants by extending the duration of drug registration in related centers. This would enable a better evaluation of Amgevita's efficacy and safety in managing RA within the Iraqi population

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Conflict of Interest
Authors declare no conflict of interest.
Data availability
Data are available upon reasonable request.

ORCID

Marwa Moayad 0000-0001-5686-6311
Ali AlKazzaz 0000-0002-7852-1581
Avin Maroof 0000-0002-6554-5314
Ali Abdulrahman 0000-0003-4561-8528
Nazar Abdulateef 0000-0003-0659-8130
Mohammad AlOsami 0000-0001-8521-5876
Faiq Gorial 0000-0002-2760-5566
Mohammed Altahhan 0000-0002-8507-8303
Zahraa AlMansi 0000-0002-2784-4815
Ali AlNoori 0000-0002-0551-7725

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