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Research Article

Evaluation of Therapeutic Response Under Biologic Therapy in Patients with Rheumatoid Arthritis

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Abstract

Biotherapy has revolutionized the therapeutic management of rheumatoid arthritis (RA). The objective of the study was to evaluate and compare the efficacy and tolerance of biological disease modifying antirheumatic drugs (bDMARDs) and conventional disease modifying antirheumatic drugs (cDMARDs) used in RA.

It was a retrospective study covering 13 years at the level of the immunology unit of the UHU Hassiba Ben Bouali Blida and functional rehabilitation service of the CHU Frantz Fanon Blida. We identified 1866 records of patients with RA, 75 receiving biotherapy and 71 receiving conventional treatment. The therapeutic response was evaluated by the DAS 28-ESR (disease activity score based on erythrocyte sedimentation rate) and interpreted according to the EULAR (European league against rheumatism) judgements criteria.

A female predominance of 83%, the average age of RA patients was 49.3 ±13.42 years, the mean starting DAS28-ESR was 5.625± 1.4. 84% of patients initially received MTX (methotrexate) on the front line, the decrease in DAS28-ESR was non- significant, with patients exhibiting intolerance (41%), and (45%) ineffectiveness. The introduction of biotherapy mainly Actemra allowed a decrease of DAS28-ESR of - 1.842±0.3812, a significant decrease according to the criteria of the EULAR. Humira had an adverse efficacy and tolerance profile (including the occurrence of severe adverse effects (AEs)).

In conclusion, biotherapy is more effective than conventional treatments, while in terms of tolerance data are insufficient to make a judgment on it.

Keywords: Rheumatoid arthritis – Biotherapy.

INTRODUCTION

Rheumatoid arthritis is an autoimmune and systemic disease that usually evolves by thrusts interspersed with phases of remission, affecting the joints in the first place, and may present extra-articular manifestations [1,2]. There are different forms, some are asymptomatic, others very aggressive destructive that can lead to disability. Multifactorial etiology and pathophysiology are very complex, the origin of the disease to date is unknown [3].

The treatment of RA has seen a wide advance especially following the appearance of biomedicine. It is based on symptomatic treatments and fund treatments including conventional synthetic treatment and biological treatment (biotherapy). Biotherapy is the result of considerable progress in understanding the pathophysiology of this disease [4]. In this study the monitoring of the therapeutic response to a treatment has two components: efficacy and tolerance. DAS 28 is the most widely used score to assess RA activity and to judge the effectiveness of a treatment [5,6]. In terms of tolerance, it was ensured by a rigorous follow-up of patients each month, to note all adverse reactions occurred during therapy, and all the issues observed in the follow-up reports.

Biomedical medicine is known to have good efficacy offering many strategic opportunities. It is usually indicated after failure of conventional treatment [7]. The prescription and the choice of the bio drug must be adapted under increased vigilance because biotherapy is far from being safe. In this context, we will compare and discuss the efficacy and tolerability of conventional synthetic therapy and biotherapy, in other words; what are the benefits of biotherapy compared to conventional treatments?

MATERIALS AND METHODS:

It is a descriptive and retrospective study covering a period of 13 years (2010-2023) involving 1866 patients (83% woman 17% man, mean age 49,3 ± 13,42 years) diagnosed for RA according to the EULAR 2010 ACR (American college of rheumatology) criteria [8], with a follow-up of 71 patients under cDMARDs and 75 under bDMARDs.

The collection of demographic and immune-biological patient data (2010-2023) took place at immunology unit of UHU

Hassiba Ben Bouali Blida Algeria. For the therapeutic data collection (2013-2023) and patient follow-up during the year 2023 for a period of 6 months, it occurred at the functional rehabilitation service of CHU Frantz Fanon Blida Algeria.

The therapy's effectiveness was assessed through the monitoring of the DAS28-ESR score. To evaluate tolerance, all patients underwent the appropriate pre-therapeutic assessment for each therapy. Additionally, every month, there was a follow-up including a thorough check to detect any issues (e.g., hepatic or lipid disorders), noting any adverse effects on a tracking sheet.

RESULTS

The majority of patients (56.25%) initially presented with a DAS28-ESR score > 5.1 before any therapy. (Figure 1)

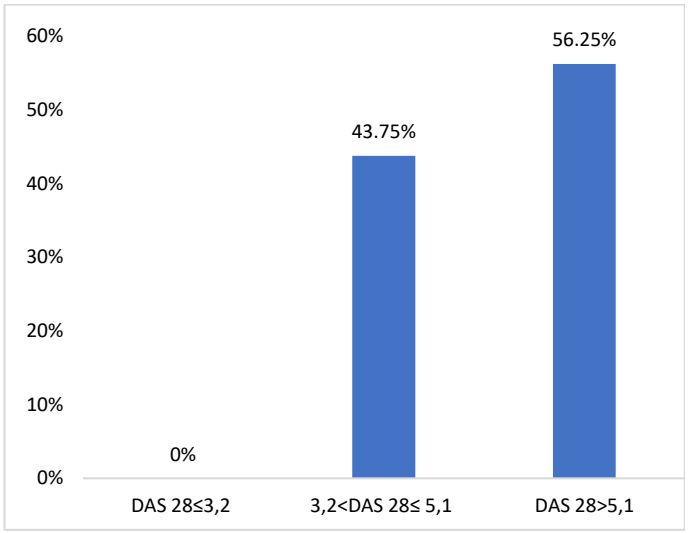

Figure 1: Distribution of PR patients by disease activity assessed by DAS28-ESR.

Efficacy

The Delta DAS28-ESR before and after the initiation of cDMARDs, mainly MTX (84% at a dosage of 7.5 to 15 mg/week), was <0.6. (Figure 2, Table 1)

45% of the patients experienced therapeutic failure with the cDMARDs. (Figure 2 and 3)

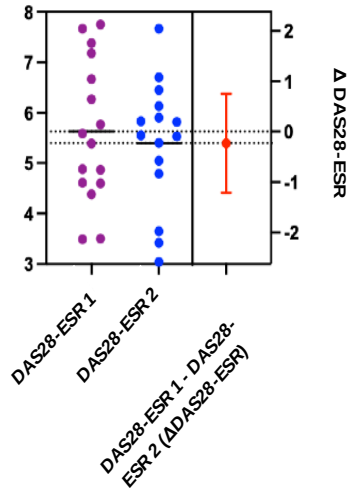

Figure 2: DAS28-ESR before and after cDMARDs.

Table 1: Difference between means of DAS28-ESR 1 and 2 .

Mean DAS28-ESR 1 (Before)	5,625
Mean DAS28-ESR 2 (After)	5,39
Δ (DAS28 1 – DAS28 2)	-0,2297 ± 0,4803

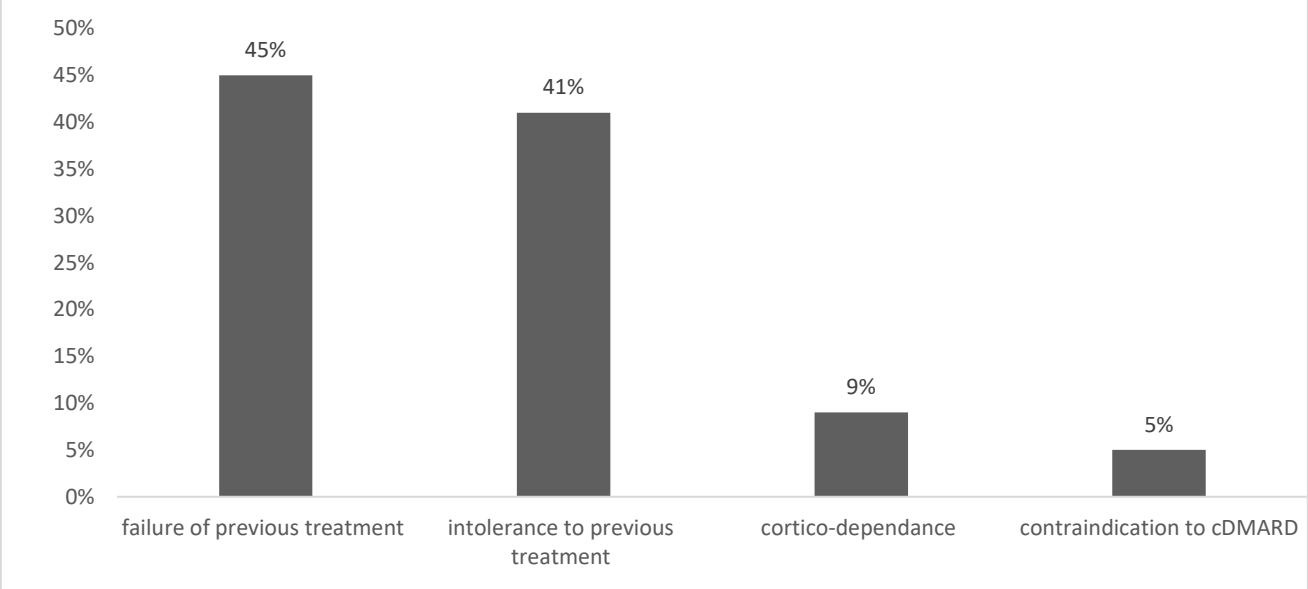

Figure 3: Indications for Biotherapy.

Following the initiation of bDMARDs (Table 2), there is an observed decrease in the mean DAS28-ESR with a Δ DAS28-ESR before and after biologic therapy >1.2 (p=0.0001, significant correlation <0.05). There was also a slight increase observed in the DAS28-ESR during 2022. (Figure 4).

44% of patients achieved remission with the bDMARDs, while 26% of patients still exhibited high disease activity. (Figure 5) .Among the patients who achieved remission (44%), the majority were under the Actemra molecule (84%), whereas none were under Humira.

Table 2: Distribution of patients according to the administered biologic therapy and its dosage.

Molecules	%	Dosages and routes of administration
Actemra (Tocilizumab)	65,3	4mg - 8mg /kg IV (once / month)
Enbrel (Etanercept)	12,7	50ml SC (once / week)
Humira (Adalimumab)	4,5	40ml SC (once / 15 days)
Rituximab	1,5	1000mg IV (once / 15 days)

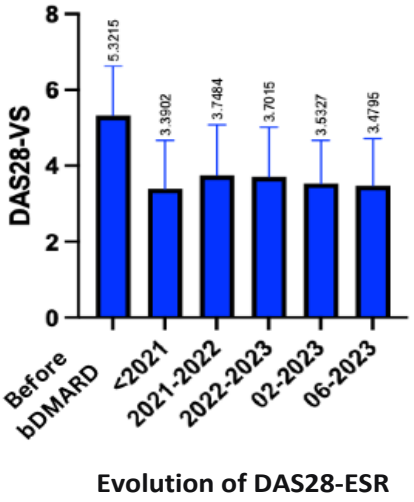

Figure 4: Evolution of DAS28-ESR before and after biotherapy.

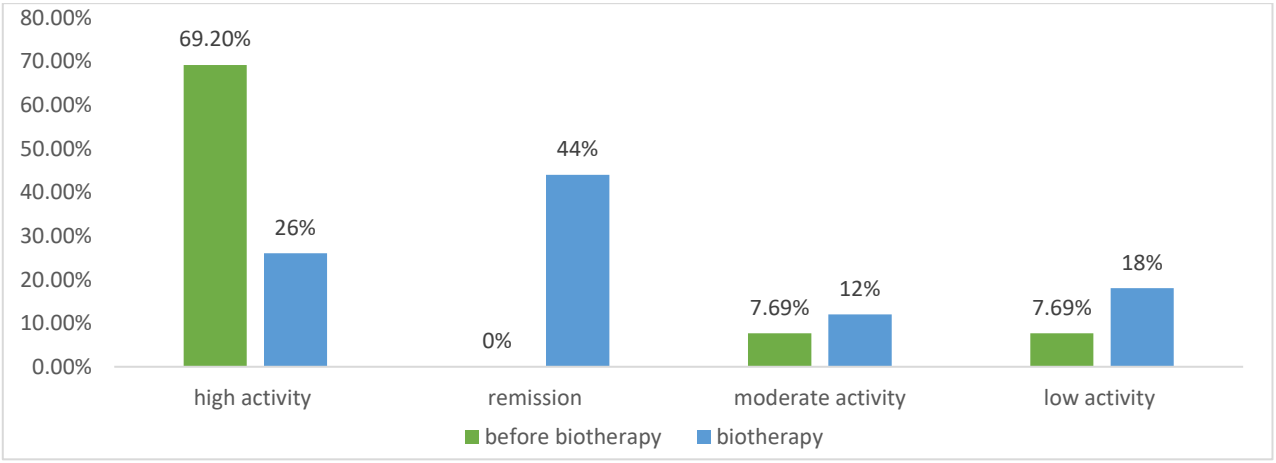

Figure 5: Disease activity before and after biotherapy.

During the follow-up in 2023 with three biologics (Enbrel, Humira, Actemra), an increase in DAS28-ESR was observed under the Humira molecule, with a Δ DAS28-ESR = 0.9683 ± 0.3689. (Figure 6)

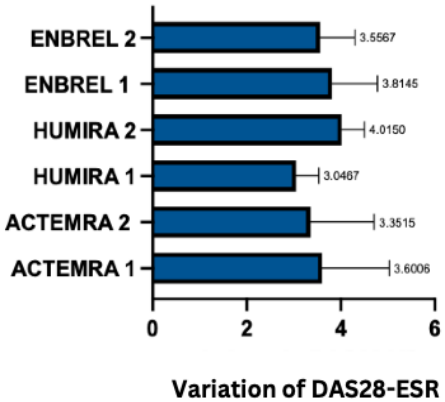

Figure 6 : Evolution of DAS28-ESR under Actemra , Humira and Enbrel.

Safety

41% of patients receiving conventional cDMARDs treatment experienced adverse effects, primarily intolerances (n=12). (Figure 3, Table 3)

Table 3: Distribution of RA patients according to the observed adverse events following the intake of cDMARDs.

Adverse effects	N
Dry cough	1
Asthenia	1
Intolerance (hematologic toxicity, gastro-intestinal issues etc.)	12

Several adverse events were noted, but the majority were correctable or disappeared after cessation of treatment, mainly involving hematological disorders (n=18) and lipid disturbances (n=8).(table 4)

However, a few notable adverse effects were observed ;

1- Chest tightness (n=1), a local allergic reaction following infusion that disappeared after 24 hours (n=1), and a vein phlebitis (n=1) under Enbrel.

2- Peripheral erythema of 10 cm with swelling (n=1), muscular weakness (n=2), epicardial ischemia, and hypertensive peak (n=2) under Humira.

3- Sub-occlusive syndrome (n=1) and jaundice (n=1), also a relatively high risk of infection (3) under Actemra.

Table 4: Distribution of patients based on the various observed adverse events during biologic therapy.

Adverse effects	N
Lipid disorders	8
Hepatic disorders	5
Hematologic disorders	18
Cutaneous disorders	4
Digestive disorders	5
Cardiovascular disorders	3
Muscular disorders	2
Infections	6
Headaches	4
Astenia	8
Others (inflammatory lymph node, eye burns, chest tightness etc.)	5

DISCUSSION:

According to the literature, the majority of our patients exhibited strong disease activity, as the average DAS28-ESR in our population was 5.625 [9]. The indication for biologic therapy, following the ineffectiveness of conventional treatment (with a non-significant decrease in DAS28-ESR of 0.2297, <0.6), and methotrexate intolerance in 41% of patients aligns with the latest updates (2019) and recommendations from EULAR[9].

These results are consistent with several studies. For instance, a 2021 study on 67 patients with RA found intolerance in 40.3% of patients, with an initial DAS28-ESR of 4.06±1.4 [10]. Meanwhile, a retrospective study in 2017, involving 100 patients with initially low disease activity (In contrast to our population), revealed that 60% achieved remission, while 40% experienced intolerances [11].

Inefficiency in patients with high disease activity and intolerances often stems from the general mechanism of action of the conventional treatment [12]. This is why, in the therapeutic strategy, when there is resistance to conventional treatments , a switch to biotherapy is implemented [7].

Following the initiation of biologic therapy, primarily tocilizumab (Actemra), there was a reduction in DAS28-ESR >1.2, demonstrating significantly superior efficacy compared to conventional treatment, despite the high disease activity at the outset. This was evidenced in a 2012 study involving 168 patients on conventional treatment and 86 on biologic therapy. After the initiation of conventional treatment, the DAS28-ESR was 4.5, whereas under biologic therapy, it was 3.8 [13].

In another study conducted at the University of Oxford in 2014, involving a total of 204 patients with an initial DAS28-ESR of 5.14, 86.1% of the patients achieved remission with biologic therapy (Tocilizumab). [14]. Additionally, a study conducted in Romania in 2014, involving 4499 patients with an average baseline DAS28-ESR of 6.97, the majority of whom exhibited an inadequate response to methotrexate, revealed that following the initiation of Anti-TNF, the average DAS28-ESR decreased to 2.58 [15].

The superior efficacy of biologic therapy compared to conventional treatment is entirely logical, as biologic therapy operates through a targeted mechanism of action based on the pathophysiology of the disease [4,16].

On the other hand, Humira (Adalimumab), introduced in the management of our population in 2022, proved to be the least effective and least tolerated molecule. In line with several studies, including a 2022 study on 2259 patients with RA it demonstrated the inferior efficacy of Adalimumab biosimilar compared to other biologic therapies (including tocilizumab). This study explained that the sole advantage of Adalimumab biosimilar was its lower cost and the availability of the biosimilar[17].

Furthermore, a study conducted in 2014 with 706 patients revealed that 63% were on methotrexate with an average DAS28-ESR of 5.22 before initiating biologic therapy. Among them, 32% discontinued Adalimumab due to ineffectiveness, and 19.7% due to adverse effects [18]. Another study in 2023, involving 183 patients, observed an increase in disease activity in 15.3% of patients treated with the biosimilar [19]. In a double-blind study in 2013 with 325 patients, 163 were treated with tocilizumab and 162 with Adalimumab. The reduction in DAS28 under tocilizumab was -3.3, while with Adalimumab, it was -1.8 [20].

Meanwhile, a 2023 study in the United Kingdom involving 590 patients with rheumatoid arthritis demonstrates the promising effectiveness of the Adalimumab biosimilar. Only 9.4% of patients experienced treatment failure or adverse events, accompanied by a reduction in DAS from 5.22 to 2.9 [21].

The ineffectiveness of the Humira biosimilar in our population can be attributed to the development of autoantibodies, rendering the population resistant. A study showed that, after a few weeks of treatment with the Humira biosimilar, between 40% and 60% of patients developed anti-adalimumab antibodies [22].

Regarding tolerance, unlike methotrexate, which exhibits severe and potentially serious intolerances with digestive, hepatic, and hematological toxicities leading to therapy discontinuation and requiring additional care, biologic therapy

presents several manageable moderate disturbances. This is evidenced by a 2013 study involving 325 patients, showing elevated cholesterol levels, disturbances in liver transaminase levels, and a decrease in platelet count as correctable issues associated with biologic therapy [20].

Serious AEs, albeit rarely observed under biologic therapy in our study, may lead to the temporary or permanent discontinuation of such therapy. In a study previously mentioned, which involved 4499 RA patients, 473 patients experienced AEs under biologic therapy, primarily infections, skin rashes, and respiratory disorders [15]. These various AEs are attributed to the immunosuppressive mechanism of action of biologic therapies, rendering the immune system susceptible to various conditions, not to mention individual variability.

The AEs observed in our population, primarily under the biosimilar molecule of Humira, align with several studies. For instance, a 2019 study in France with 17 patients using adalimumab reported one patient experiencing injection site erythema [23]. Another study at Stanford in 2019, involving 474 patients using Humira biosimilar, noted musculoskeletal disorders (n=67), cardiovascular disorders (n=23), and hypertensive episodes (n=12) [24]. Similarly, a study in Germany in 2022 with 22 patients using adalimumab biosimilar reported severe pain at the injection site (n=4) and nausea and vomiting with treatment ineffectiveness (n=1) [25].

Under the Enbrel molecule, a 2011 study with 67 patients reported one patient experiencing phlebitis. Another study in Taiwan in 2013, involving 22 patients using etanercept, noted one patient experiencing chest tightness [26].

The biosimilars of Humira available in Algeria are AMGEVITA and SOLYMBIC [27]. AMGEVITA, produced using Chinese Hamster Ovary cells with marketing authorization granted in August 2017, has been reported to cause swelling and pain at the injection site in more than one in ten patients, and it may lead to serious adverse events such as Stevens-Johnson syndrome and neurological disorders [28]. SOLYMBIC, according to its 2019 Summary of Product Characteristics (RCP), is associated with numerous adverse events in more than one in ten patients, including headaches, muscle pain, and respiratory/cardiac disorders [29].

The occurrence of certain adverse events, as seen with the Humira biosimilar or severe allergic reactions, may be linked to the manufacturing process. Despite precautions taken, every step in the manufacturing process introduces variability, and there is a significant likelihood of variations due to manufacturing defects, contaminations, impurities, or formulation errors. The differences between batches of cells used (E. Coli, Chinese Hamster Ovary cells) for production can also impact the quality of the final product and lead to adverse events. Also, the main issue with biologic therapies remains immunogenicity, leading to the production of anti-drug antibodies [22].

The manufacturing process of biosimilars is not identical to that of the reference molecule, and small molecular differences are almost inevitable. Additionally, the manufacturing process of all biologic therapies can introduce changes that may enhance or diminish their effects. Such modifications can impact the clinical profile and the degree of similarity to the reference molecule [22,30].

The European Medicines Agency (EMA) and the Food and Drug Administration (FDA) emphasize the importance of post-market surveillance (pharmacovigilance) of biosimilar biopharmaceuticals to verify their safety profile [22]. For instance, pharmacovigilance played a crucial role in detecting red blood cell aplasia following an adjustment in the manufacturing process of recombinant erythropoietin (EPO), specifically EPREX [22].

CONCLUSION:

Biologic therapy has indeed demonstrated its superior efficacy compared to conventional treatment. However, when it comes to tolerance, the picture is not always clear-cut. Conventional treatment often comes with severe intolerances, whereas with biologic therapy, in the majority of cases, the disturbances are moderate and correctable. Yet, it is noteworthy that, albeit less frequently, biologic therapy may lead to even more serious adverse events than those observed with conventional treatment.

Our study confirms the significance of early and, more importantly, tailored management based on disease activity. Early diagnosis alone is not sufficient; the selection of the right treatment and its availability, through collaboration between hospital pharmacists, prescribing physicians, and patients, enables achieving remission rapidly, avoiding therapeutic failures, and preventing economic losses.

Algeria should allocate resources for post-marketing studies, particularly in terms of pharmacovigilance, on various biosimilars. This would help gain a better understanding of the causes of intolerances and assess the interchangeability among biosimilars. Also, the new therapeutic prospects involving miRNA are intriguing and warrant further in-depth exploration.

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