

Optimizing biologic therapy in rheumatology: frequency and characteristics from an argentine referral centre

Background: Treatment strategy after achieving sustained remission in rheumatic conditions remains uncertain. **Objetives:** to evaluate biologic therapy treatment doses and intervals in rheumatic patients in daily practice. **Methods:** An observational study including consecutive patients receiving biologic treatment was carried out. Treating physicians determined whether to continue with standard or reduce dose of biologic drugs, considered as a reduction in dose or increased dosing intervals. Sociodemographic, biologic and concomitant treatments, laboratory test and clinimetric data were recorded. Descriptive analysis, variables are described as frequencies, means and medians. In the Rheumatoid Arthritis population, categorical variables were compared using Chi², and variables with a $p \leq 0.2$ were included in multiple logistic regression models, considering dose reduction as the dependent variable. **Results:** 186 patients were included, 73.1% with Rheumatoid Arthritis, 10.8% Psoriatic Arthritis, 3.8% Ankylosing Spondylitis, 1.1% Lupus and 11.3% with other conditions. Of the total population, 24.7% received reduced dose of biologic therapy. Mean DAS28 of Rheumatoid Arthritis patients was 3.85 (SD 1.32), HAQ 1.1 (SD 0.7), and 35.8% had low disease activity (LDA)/remission according to DAS28 criteria. 23.4% of Rheumatoid Arthritis patients received reduced dose, more frequently sustaining LDA/remission according to DAS28 compared to standard dose patients (54.9 vs. 28.6% $p=0.001$). Multivariate analysis showed a significant association with LDA/remission (OR 3.65 (IQR: 1.6-8.3) $p=0.0010$), and with negative Anti Citrullinated Proteins Antibodies [OR 0.1099 (IC: 0.04-0.27) $p<0.0001$]. **Conclusion:** 24.7% of this cohort received reduced dose of biologic treatment as well as 23.4% of Rheumatoid Arthritis patients, being found to be associated with lower disease activity and negative Anti Citrullinated Proteins Antibodies.

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Keywords: rheumatoid arthritis • treatment tapering • immunosuppressive

Introduction

The advent of biologic therapies was one of the most significant breakthroughs in the treatment of rheumatic diseases, thereafter many patients failing to respond to conventional immunosuppressive therapies achieved disease remission [1,2]. Biologic therapies in rheumatology include inhibition of tumor necrosis factor (anti-TNF α), T cell costimulation signal, interleukin 6 receptor, anti-CD20 and Blys/BAFF.

Treatment recommendations guidelines help determine which patients are candidates for biologic therapy; however no consensus exists regarding step-down therapy for patients achieving sustained remission. Reduced dose regimens or increased dosing intervals are frequently observed in daily practice. Some studies have shown that

withdrawing biologic drugs is often associated with a disease flare [3-5]. Nonetheless, biologic tapering strategies in observational studies and treatment recommendation guidelines raise the possibility of reducing the dose to the lowest effective in patients achieving sustained remission [6]. Current ACR/EULAR treatment recommendations for Rheumatoid Arthritis (RA) establish, according to expert opinion, that in a patient with sustained remission, a strategy to reduce biologic dose might be implemented if the patient is not receiving steroids and is receiving concomitant conventional disease modifying antirheumatic drugs (cDMARDs) [7].

As aforementioned, biologic treatment optimization has become a reasonable and meaningful field of study in rheumatology. The

present study describes modifications to biologic therapy regimens in patients with rheumatic diseases from daily practice.

Materials & methods

An observational, cross sectional study was carried out including consecutive patients attending the Italian Hospital of La Plata from January 2014 until March 2015. Key inclusion criteria included patients that received at least one dose of biologic therapy during the study period.

Variables studied:

- Demographic data: gender, age, diagnosis and disease duration
- Data regarding treatment: drugs received treatment duration, dosing (standard or reduced), previous dose reduction attempts, as well as previous biologic treatments (cause of discontinuation and duration). Reduced biologic dose was considered as both a reduction in the biologic dose or an increased dosing interval.
- Laboratory test according to patients' diagnosis: erythrocyte sedimentation rate (ESR), C Reactive Protein (CRP), Rheumatoid Factor (RF), anti-citrullinated protein antibodies (ACPA) and HLA B27.
- Clinimetric data: DAS28, HAQ, BASDAI and BASFI, depending on patients' diagnosis
- Concomitant treatment: nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, hydroxychloroquine, methotrexate (MTX), leflunomide (LFN), sulfasalazine, and azathioprine
- Previous treatments received, duration and cause of suspension: NSAIDs, steroids, hydroxychloroquine, MTX, LFN, sulfasalazine, azathioprine, adalimumab (ADA), etanercept (ETN), infliximab (IFX), rituximab, certolizumab, golimumab, tocilizumab and/or abatacept.
- Imaging techniques: Hand and feet X-Rays for peripheral involvement (for the detection of joint space narrowing and erosions), lumbar and sacroiliac joint X-Rays and Magnetic Resonance Imaging (MRI) for axial involvement (sclerosis, erosions, ankyloses and bone edema).

Statistical Analysis: Continuous variables are described as means and medians, with

their corresponding standard deviation (SD) and interquartile range (IQR). Frequency distribution analysis of categorical variables was performed. For bivariate analysis of continuous variables, T Test or Mann Whitney Test was used as appropriate, and for categorical, Chi2 Test. Odds Ratio (OR) was calculated and Confidence Interval was kept at 95% (CI 95%). Variables with a p value ≤ 0.2 were included in multivariate analysis, adjusting for confounders and using dose reduction as the dependent variable. A p value < 0.05 was considered significant.

Data was recorded on Microsoft Access, and STATA 12 software was used for statistical analysis.

Results

186 patients were included in the analysis; 73.1% had RA, 10.8% Psoriatic Arthritis (PsA), 3.8% Ankylosing Spondylitis (AS), 1.1% Lupus, and 11.3% other rheumatic conditions. Median disease duration was 77 months (IQR 46-456), mean age 48.9 years (SD 17.4) and 76.9% were female. Reduced biologic dose was received by 24.7% of the patients (95% CI 13.9-30.8), being the most frequent biologic agents used in this modality ADA (38.2%), ETN (21%) and tocilizumab (12.4%).

Mean DAS28 of RA patients was 3.85 (SD 1.32), median HAQ 1.1 (SD 0.79) and 35.8% had low disease activity (LDA) or remission according to DAS28 criteria. Only 18.2% of the patients were on biologic monotherapy, while 81.8% received concomitant treatment with MTX (61.3%), steroids (38%), LFN (18.2%), hydroxychloroquine (7.3%) or sulfasalazine (0.7%). 23.4% (95% CI: 16.7-31.6) of RA patients received reduced dose of biologics, and were more frequently on LDA or remission according to DAS28 compared to those with standard dose (54.9 vs. 28.6% $p=0.001$). Both bivariate and multivariate analysis showed that RA patients on reduced dose were significantly associated with disease activity [LDA/remission OR 3.65 (IQR: 1.6-8.3), $p=0.001$], and with negative ACPA [OR 0.1099 (IC: 0.04-0.27), $p<0.0001$] (Table 1).

Discussion

The optimization of biologic therapy has become a matter of discussion in the daily practice of rheumatology given their proved long-term efficacy, achievement of sustained remission, as well as their economic burden to the health care system.

Table 1. Multivariate analysis: association between reduced biologic dose and disease characteristics.

Variable	OR	95%	CI	P value
ACPA (Positive/Negative)	0.0353	0.0091	0.1365	0.0000
LDA-Remission according to DAS28 (Yes/No)	5.1654	1.4575	18.3060	0.0110
Concomitants steroid treatment (Yes/No)	1.5603	0.4145	5.8730	0.5106
RA duration (<2 years/≥2 years)	0.8706	0.2948	2.5707	0.8019
RF (Positive/Negative)	2.5688	0.3006	21.9520	0.3888
HAQ (Severe/Low)	0.8328	0.2166	3.2021	0.7900
Concomitant MTX treatment (Yes/No)	0.3342	0.0843	1.3257	0.1190
Erosions on x-rays (Yes/No)	3.0239	0.3659	24.9875	0.3044
Joint space narrowing on x-rays (Yes/No)	1.5204	0.1931	11.9703	0.6907
Female sex (Yes/No)	1.2155	0.2315	6.3830	0.8176
CRP (positive/negative)	0.4726	0.1101	2.0277	0.3132
Actual concomitant treatment (Yes/No)	1.0705	0.2123	5.3963	0.9343
Previous treatment (Yes/No)	1.5777	0.1861	13.3740	0.6759

ACPA: Anti-Citrullinated Protein Antibodies; LDA: Low Disease Activity; DAS: Disease Activity Score; RA: Rheumatoid Arthritis; RF: Rheumatoid Factor; HAQ: Health Assessment Questionnaire; CRP: C Reactive Protein

The present study described and analyzed patients' characteristics after a biologic therapy regimen modification, when achieving sustained remission. Biologic dose modification was not based on treatment recommendations but on physicians' criteria. The sample size was exclusively comprised by patients from daily practice. Regardless of diagnosis, 24.7% of our patients received a reduced biologic dose regimen.

Particularly in RA, the suspension of biologic treatment is still controversial. Notwithstanding, scheme modifications, with either dose reduction or dosing interval increase, are implemented empirically in daily rheumatology practice. Our results reflect that 23.4% of RA patients receive reduce dose of biologics, especially after achieving LDA or remission with the standard dose.

Remission in RA was assessed according to DAS28 criteria, which might be refuted. Although it does not reflect the strictest definition of remission and patients under DAS28 remission might still have a significant swollen joint count, it is widely used in daily practice [8,9]. It is important to consider predictors of reduced dose maintenance as well as risk factors of a disease relapse. In this way, the set of criteria used to outline remission comprise a broad field of study. SDAI, CDAI or the Boolean remission criteria indicate a profound state of remission [10], however their ability to predict a disease flare after a dose reduction or treatment suspension is controversial [5]. The HONOR study, using DAS28 as a composite index, demonstrated that after the suspension of ADA, patients with a DAS28 less than 1.98 remained more frequently in LDA than those with values between 1.98 and 2.6 [11].

Regarding biologic suspension, while some studies have shown a disease relapse after stopping the drug [3,4], the BeSt study demonstrated that the suspension was possible in more than 50% of the patients who were initially randomized to IFX plus MTX [12]. However, biologic therapy is not considered as first line therapy in our country, on the contrary, it is indicated in patients failing to respond to cDMARDs. Tanaka et al, proved that it is possible to induce remission with IFX in early RA patients unresponsive to cDMARDs. Nevertheless, the use of LDA as an alternative treatment target to remission may weaken the results [13]. As for biologic suspension, the HIT HARD study showed that in early RA patients, those initially treated with ADA for 24 weeks and later suspended it, had less radiographic progression. Unfortunately, this sustained effect was not observed for the primary objective of DAS28 reduction [14]. The OPTIMA study also proved that those patients initially treated with remission induction anti-TNF therapy with ADA plus MTX achieved the target of LDA according to DAS28 more frequently compared to those receiving MTX monotherapy [15].

Data from the BeSt study and from the Leiden early arthritis cohort suggest that drug free remission is most frequently observed in patients ACPA negative [16-18]. Likewise, ACPA negative patients from our study had a higher probability of receiving reduced biologic dose. In light of the well-known physiopathogenic role of ACPA in RA and its relationship with disease severity [19,20], their presence could indicate an underlying risk that impedes therapy reduction or suspension.

Biologic dose reduction might be a challenge itself since most biologics are available in only one pharmacological presentation. In this scenario, treating physicians frequently chose to increase the dosing interval, which might result controversial given that in terms of pharmacokinetics these two options are not equivalent. STRASS was a non-inferiority study comparing increase ETN dosing interval versus stable ETN dose in RA patients under remission. The authors concluded that these two strategies were not comparable; with the increase dosing group representing the highest risk of a disease flare [21]. On the other hand, the PRESERVE study including long standing RA patients with moderate disease activity according to DAS28 and with failure to respond to MTX, resolved that reduced or conventional ETN doses plus MTX were more effective in maintaining LDA than suspending ETN and continuing with MTX monotherapy [22].

The re-gaining of remission in patients re-starting a biologic agent deserves a special mention. Van Vollenhoven *et al.*, recently demonstrated that after discontinuing or diminishing the biologic dose, 91% of the patients achieved LDA when the biologic agent was restarted at standard dose [23]. Similar results were observed in the HONOR study, where most exacerbated

patients achieved a clinical response following ADA restart [11].

The weakness of our study includes the fact that is not longitudinal, so there is no data on when the biologic was tapered and some of them tend to have clinically significant activity a few weeks to months after tapering/stopping it.

Taking the economic burden of biologics to the health care system into consideration, the confirmation of an efficacious reduced dose for maintenance therapy is important from an economic point of view. However, more data with long term results, including radiographic progression, and a larger sample size is required [23].

To our knowledge, this is the first argentine study analyzing biologic dose reduction. Regarding RA patients, reduced biologic dose therapy was associated with disease activity (remission and LDA according to DAS28) and negative ACPA. Further studies will be of utter importance in order to support the effectiveness of biologic dose reduction in patients with autoimmune rheumatic diseases.

All sources of support, including pharmaceutical and industry support that require acknowledgment

No support to declare.

Disclosure of funding received for this work

None.

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