

Frequency and Factors Associated with Biologic Monotherapy in Patients with Rheumatoid Arthritis; Experience from an Argentine Center

Abstract

Introduction/objectives: The combination of biologic agents and synthetic disease modifying anti-rheumatic drugs has proven to be effective for the treatment of patients with active Rheumatoid Arthritis; notwithstanding monotherapy was only exceptionally considered. However, with the advent of biologic agents with other modes of action and evidence contributed by tocilizumab studies, this option began to be considered. The aim of this study was to evaluate the prevalence of monotherapy with biologic agents in patients with RA and factors associated with the use of this type of treatment, in the context of everyday practice.

Method: An observational, analytical, cross-sectional study was carried out, including patients over 18 years old who were diagnosed with RA, according to ACR/EULAR 2010 classification criteria, and who were treated with biologics. Demographic, clinical and treatment variables were evaluated.

Results: From a total 450 patients with RA, 171 treated with biologic agents were evaluated. 31.6% received biologic monotherapy, most frequently due to MTX adverse effects. The most commonly used anti-Tumor Necrosis Factor as monotherapy was adalimumab. Monotherapy with biologic agents was seen to be associated with the use of drugs with other mechanisms than TNF blockers, most frequently tocilizumab. Bivariate and multivariate analyses have shown that monotherapy is an independent factor for no NSAID use. Corticosteroid use was lower in patients receiving monotherapy, although it did not reach statistical significance.

Conclusion: The biologic monotherapy frequency was 31.6%. The associated factors were use modes of action other than anti-TNF and a decreased use of NSAIDs.

Abbreviations: RA: Rheumatoid Arthritis; DMARD: Disease Modifying Anti-Rheumatic Drug; MTX: Most Frequently Methotrexate; MOA: Mechanism of Action; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein, RA: Rheumatoid Arthritis; ACPA: Anti-Cyclic Citrullinated Peptide Antibody; NSAIDs: Nonsteroidal Anti-Inflammatory Drugs; SD: Standard Deviation (SD) IQR: Median and Interquartile Range; OR: Odds Ratio

Introduction

Rheumatoid Arthritis (RA) is a chronic autoimmune disease that primarily affects joints, causing inflammation, pain and morning stiffness. Without a proper treatment this leads to severe disability [1]. It predominantly affects women, with an estimated prevalence ranging from 0.2 to 1%, impacting the age group with the greatest work capacity [2,3]. The main target of RA treatment is to achieve disease remission, suppressing inflammation, leading to less structural damage, improving physical function with a positive impact on quality of life and social involvement [4].

According to current EULAR and ACR treatment guidelines, RA treatment should begin with a disease modifying anti-

rheumatic drug (DMARD), most frequently methotrexate (MTX). Those patients with no response or intolerant to these drugs, should switch to a biologic agent or JAK inhibitor (synthetic target-directed DMARD) [5-7]. The following biologic agents are authorized in Argentina: (1) Tumor necrosis factor alpha inhibitors (anti-TNF): adalimumab, certolizumab pegol, etanercept, golimumab and infliximab, (2) selective T-cell co-stimulator modulator: abatacept, (3) CD 20 inhibitor: rituximab, (4) interleukin 6 (IL6) inhibitor: tocilizumab and (5) oral janus kinase inhibitor: tofacitinib [8].

When DMARDs fail, the initial recommendation is the combination of an anti-TNF with a synthetic DMARD due to fact that this combination has shown greater effectiveness in the treatment of patients with active RA; therefore monotherapy is only exceptionally considered [9-11]. However, with the advent of biologics with other mechanism of action (MOA) and evidence contributed by tocilizumab studies, this option began to be considered in those patients who for whichever reason could not receive methotrexate (MTX) [12].

In everyday practice, approximately 1/3 of patients with RA

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RN Garcia Salinas^{1*}, MP Girard Bosch¹, MV Martire¹, P Arturi¹, SJ Magri¹, D Giacomone¹ and AS Arturi^{1,2}

¹Rheumatology and autoimmune diseases section, Hospital Italiano de La Plata, Argentina

²School of Medicine, University La Plata, Argentina

*Corresponding author: RN Garcia Salinas, Rheumatology and Autoimmune diseases section, Hospital Italiano de La Plata, Argentina, Email: gsalinasrodrigo@gmail.com

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receive monotherapy with biologic agents due to intolerance or adverse effects associated to MTX. Discontinuation was 75% due to gastrointestinal, hepatic or respiratory adverse events [13,14].

Currently there are various treatment choice criteria for patients with RA based on clinical studies, local or international treatment guidelines and taking into consideration the patient's profile, history of previous infections and comorbidities. There are few head to head clinical studies between two biologic agents in order to establish differences which prioritize the use of one over the other, however there are indirect comparisons and meta-analysis which can help in the decision making process. There is compelling evidence to assert that drugs with modes of action other than anti-TNF, such as tocilizumab (AMBITION, CHARISMA and ACT-RAY) as monotherapy has similar effectiveness as its combination with DMARDs [15-17]. This is so to the extent that current EULAR and ACR guidelines consider this treatment mode, and recommend using tocilizumab [5,6]. There is also evidence supporting the use of tofacitinib as monotherapy (18). Some anti-TNF, such as adalimumab and etanercept, are approved for use without being associated to DMARDs, however studies such as PREMIER or TEMPO have shown that its effectiveness as monotherapy is much lower than when associated to MTX [19,20]. It is noteworthy that in the ADACTA study, which evaluated monotherapy with tocilizumab versus adalimumab in RA patients with inadequate response or intolerance to MTX, tocilizumab was superior regarding clinical parameters such as DAS28 and ACR response, amongst others [21].

Given the controversy found in literature regarding monotherapy with biologic agents, the aim of this study is to estimate the prevalence of biologic monotherapy in patients with RA and associated factors in everyday practice.

Material and Methods

An observational, analytical, cross-sectional study was carried out. Consecutive patients over 18 years of age diagnosed with RA according to ACR/EULAR 2010 criteria [22], treated in the Rheumatology sector of the Hospital Italiano de La Plata from 01/01/2015 until 01/07/2015 were included. From the total RA patients, those receiving treatment with biologics or JAK inhibitors for a period over 3 months were selected.

The following variables were recorded for statistical analysis: age, gender, disease duration, early diagnosis, DAS28, HAQ, Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), Rheumatoid Factor (RF) and anti-Cyclic Citrullinated Peptide antibody (ACPA), current treatment with biologic agents, treatment with DMARDs, use of nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. Monotherapy either with anti-TNF or other MOA was recorded, as well as the reason why DMARDs were not used simultaneously.

The STATA 12 statistical package was used, and data was collected on Microsoft Access. Patient population's general characteristics were described. Continuous variables were informed as mean and standard deviation (SD) or median and interquartile range (IQR) according to its distribution. Frequency distribution analysis of categorical variables was carried out. T-test or Mann Whitney test were used accordingly for bivariate analysis

of continuous variables; and Chi squared test for categorical variables. Odds Ratio (OR) and 95% confidence intervals (95%CI) were calculated, and $p < 0,05$ was considered significant. In order to evaluate the independent association of variables and adjusting for confounding factors a multivariate logistic regression analysis was carried out, considering monotherapy as the dependent variable.

Results

From the 450 patients with RA diagnosis who were evaluated, 171 (38% 95%CI: 33-42) were treated with biologics. 82.5% were women, with a median age of 55 years (IQR 45-63), median disease duration was 7 years (IQR: 4-13), 91.2% were RF positive and 80% ACPA positive. The population treated with biologics presented a median HAQ of 1 (IQR: 0.38-1.4), DAS 28 3.39 (IQR: 2,6-4.5) and 47% were found to have low disease activity defined as DAS28 equal to or less than 3.2. Regarding treatments, the following frequencies were found: 73.7% on anti-TFN, with respectively adalimumab 34.5%, etanercept 18.7%, infliximab 4.7%, certolizumab pegol 12.3%, golimumab 3.5%, while other MOA represented 24%, mostly tocilizumab with 16.4%, followed by abatacept 7.6%. 2.3% of patients were on tofacitinib, 51% of patients received associated NSAIDs and 36.6% corticosteroids. The characteristics of the study population are detailed in Table 1.

Table 1: Study population general characteristics.

	n: 171
Age (years)	53.7 (SD: 13.9)
Female (%)	82,5
Disease duration (years)	7 (IQR: 2-38)
RF (positive)	91,2%
ACPA (positive)	80%
DAS 28 (mean)	3.39 (IQR: 2,6-4.5)
HAQ	1 (IQR: 0.38-1.4)
DMARD use (%)	68.4
Anti-TNF (%)	76
Other MOA (%)	24

Biologic monotherapy was used by 31.6% of the patients, (95%CI: 24.8 -39.18). The remaining 68.4% of patients receiving concomitant DMARDs, 70% used MTX in doses equal to or higher than 15 mg/week and 15% leflunomide. The main cause for not using DMARDs was intolerance 78% (13% good response and 9% lack of adherence); transaminase increase and gastrointestinal intolerance were the most frequently reported (45% and 36% respectively).

In bivariate analysis comparison of patients treated with combined therapy in contrast with those receiving monotherapy, no difference was observed regarding age, gender, disease duration, RF or ACPA positivity, DAS 28 (continuous variable), DAS 28 equal to or less than 3.2, HAQ and early diagnosis. However, in relation to corticosteroid use, there was a numeric difference, though not statistically significant, in favor of patients

undergoing monotherapy. A lower NSAID use percentage was observed, 33.3% versus almost 60% in patients receiving combined treatment (p=0.001), as well as a statistically significant

difference (p=0.0001) for monotherapy with other MOA, including tocilizumab, abatacept and tofacitinib (Table 2).

Table 2: Variables associated with monotherapy (bivariate analysis).

Variable	Monotherapy YES	Monotherapy NO	p
Age	54.3 (13)	53.4 (14.3)	0.71
Disease duration	115.6 (102)	114.7 (94)	0.79
Female	0.796	0.838	0.5
RF	0.926	0.906	0.6
ACPA	0.83	0.778	0.4
DAS28	3.4 (1.3)	3.7 (1.4)	0.07
HAQ	1.02 (0.57)	0.99 (0.67)	0.6
CRP (positive)	0.76	0.71	0.5
NSAIDs	0.333	0.598	0.001
Corticosteroids	0.278	0.402	0.1
DAS28 ≤ 3.2	0.574	0.419	0.06
Early onset	0.925	0.895	0.5
other MOA	0.561	0.439	0.0001

With regards to monotherapy modes of action, in the anti-TNF group 23.8% (95%CI: 16.8-32.1) was used as monotherapy, most frequently adalimumab (63.3%, 95%CI: 42.3-77.6). Amongst biologics with other MOA, 56% (95%CI: 39.7-71.5) were used as monotherapy, most frequently tocilizumab (61.5%, IC95: 40.5-88.2). We could observe that, in general anti-TNF was used in both modalities without any statistically significant differences except for etanercept where a statistical difference was found

between both treatment forms. Regarding other MOA in spite of a numeric difference regarding use frequency, which was higher for monotherapy, only tocilizumab presented statistically significant values (Figure 1).

In multivariate logistic regression analysis monotherapy was an independent factor associated to less NSAIDs use. A positive and independent association was found between monotherapy and use of other MOA (Table 3).

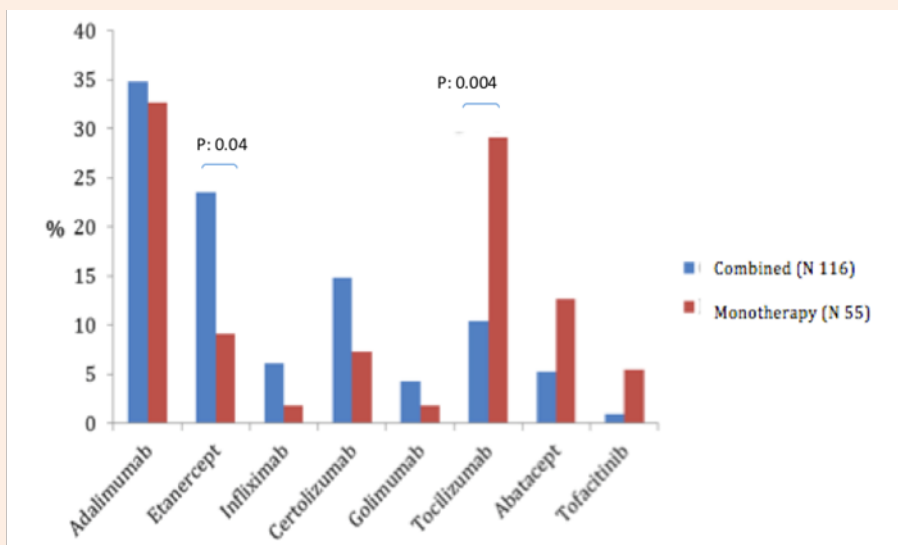


Figure 1: Frequency of each biologic agent in both treatment modalities.

Table 3: Multivariate analysis (dependent variable: monotherapy Yes/No).

	OR	95%CI		P Value
ACPA (positive)	0.9686	0.3588	2.6148	0.9498
NSAIDs use	0.2292	0.0972	0.5400	0.0008
Early onset	0.5994	0.1551	2.3171	0.4582
Corticosteroid use	0.7814	0.3210	1.9021	0.5868
RF (positive)	0.8460	0.1897	3.7718	0.8264
HAQ median	0.8820	0.3319	2.3436	0.8011
CRP (positive)	0.5159	0.2162	1.2312	0.1359
DAS28 ≤ 3.2	1.5182	0.6444	3.5767	0.3396
Other MOA use	6.8263	2.8105	16.5802	0.0000
Female	0.8771	0.3254	2.3640	0.7955

Discussion

Treatment with biologic agents has proven, throughout the past years, to achieve RA symptom control, inflammation suppression, induce remission and inhibit radiologic progression [23].

The objective of this study was to evaluate the use of biologics as monotherapy in our center and its associated factors. In our experience we could observe that the frequency of monotherapy was 31.6%, somewhat higher than that observed in a multicentric Argentine study where the frequency was 21.4% [24]. Global records inform that the use of monotherapy varies between 12 and 39% [25,26].

In our experience, the main reason for MTX discontinuation whilst received in association with biologics, was intolerance, secondly a persistently good response to such combination. Regarding adverse events, hepatic disorders were the most frequent, coinciding with what was previously reported in the aforementioned multicentric study, informing 32% hepatotoxicity and around 22% gastrointestinal intolerance [24]. Even though this is the most frequently reported cause we must not stop considering the lack of adherence to MTX, where it is widely known that patients frequently discontinue MTX without informing the treating physician [27]. Different studies have shown that this lack of adherence can vary from 25 up to 40% [28]. In a study carried out by the Argentine RA study group by means of the Compliance Questionnaire on Rheumatology (CQR) and the Simplified Medication Adherence Questionnaire (SMAQ), DMARD adherence was shown to be 50%, the main causes were due to patients' decision and missed doses [29]. There are studies carried out in closed populations in Canadian centers where in spite of medical prescription, 58% of patients would not retrieve their medication from the pharmacy [30].

This study found no difference amongst both treatment modalities in relation to clinical parameters, seeming that there is a tendency to use tocilizumab as monotherapy, as various clinical studies have shown its effectiveness. Recently different metaanalysis have been considering various other outcomes. Buckley et al. have shown that monotherapy with tocilizumab

reached similar ACR 20/50/70 responses in comparison to tocilizumab and MTX (OR: 1.08 and 95%CI: 0.4-2.84) [31]. The Bayesian analysis based on 10 clinical studies carried out by Migliore et al., showed that tocilizumab had a 100% probability to be the best treatment as monotherapy in order to achieve ACR 20, in comparison to MTX, adalimumab and etanercept; similarly, a 99.8% and 98.7% probability to achieve ACR 50 and 70 respectively [32].

It is important to take into consideration that the effectiveness of tocilizumab and biologics with other MOA different to anti-TNFs has an immunologic support, given that TNF inhibitors in combination with MTX have a synergic therapeutic effect in RA targeting monocytes, dendritic cells and lymphocytes, whose action mechanism is mainly directed to monocytes and dendritic cells, in association to MTX, a lymphocyte inhibitor, have a synergic therapeutic effect in rheumatoid arthritis. Tocilizumab has the a broadest effect in comparison to other TNF inhibitors, and its effect is primarily directed to T and B lymphocytes, as well as dendritic cells and monocytes, therefore it is not surprising to find that various studies have shown that monotherapy with tocilizumab is as effective as tocilizumab combined with MTX [33]. This data, in addition to that cast by clinical studies such as ADAPTA, support EULAR recommendations for RA, where tocilizumab and abatacept, not only occupy the first line of biologic treatment along with anti-TNF as combined treatment, but tocilizumab is preferred in case of treatment with biologics as monotherapy [5].

Due to the aforementioned, anti-TNF should be more frequently used in combination; however, in our practice we found that all of them are used as monotherapy (23%), more frequently adalimumab. We consider that this might be due to the previously mentioned MTX adherence issues, as extensive evidence shows that the effectiveness of anti-TNF increases as a combined therapy, and its association to MTX decreases the formation of anti-drug antibodies [34]. Notwithstanding, we know that adalimumab, etanercept and certolizumab are approved for use as monotherapy, in spite of not being so by international guidelines [35]. Even though, this data is supported by multiple pivotal anti-

TNF clinical studies, some metaanalysis have shown that overall anti-TNF have an 87% and 90% probability of achieving ACR 20 and 50 respectively, with an 2.4 OR with regards to monotherapy [36].

In spite of a non statistically significant numeric difference in the use of abatacept as monotherapy, recent studies have shown that it might not be effective in said modality. The AVERT study evaluated a population with early RA, the arm receiving abatacept monotherapy did not show any difference in primary outcomes (DAS28 remission) versus the placebo+MTX arm (42.5%-45.2% OR: 0.92 95%CI: 1.57) [37].

There are few patients in our study treated with tofacitinib, but currently there is evidence that this new molecule is effective as monotherapy. ORAL solo and ORAL start studies have shown great results, both in patients with established RA or MTX-naive, with a comparable effectiveness as monotherapy or associated to MTX [18,38]. In the ORAL start study, tofacitinib proved to be better than MTX in the inhibition of radiologic progression [38].

Regarding a decreased use of NSAIDs we consider that there might be two possible explanations which were not taken into consideration in this study, firstly the greater use of tocilizumab as monotherapy and its potent anti-inflammatory action may decrease its use as we also evidenced less corticosteroid use in this population; or due to the fact that as hepatotoxicity is the main reason for monotherapy, that this might be a confounding factor with regards to less NSAID use.

We highlight that the main weakness of this study was its observational, analytical, cross sectional design, and as such, studies with a greater number of patients are necessary in order to be able to establish the impact of this therapeutic modality.

We can conclude that in our experience there is a tendency to use modes of action other than anti-TNF when monotherapy is required, preferring tocilizumab. However, there is a low but not-negligible frequency of anti-TNF use in this modality and DMARD adherence must be considered to have a fundamental role, which must be studied further.

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