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Original Research Article

Switchs after Initial Treatment with Rituximab in Patients with Rheumatoid Arthritis: Efficacy and Safety. Data from the RBSMR Register at One Year

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Abstract

Objective: The aim of this study was to evaluate the effectiveness and tolerability of biological treatments administered after an initial treatment with Rituximab. ***Methods***: A cross-sectional study was conducted using the baseline data of the Moroccan biotherapy registry for RBSMR. Demographics and disease features were compared using descriptive statistics. The study evaluated the effectiveness of switching to a new biological by measuring DAS28 and ΔDAS28 at baseline, 6 months, and 12 months of follow-up. Adverse effects were also assessed. The study compared the switcher and non-switcher groups, with a significance level set at $p < 0.05$. ***Results*:** A total of 165 patients diagnosed with rheumatoid arthritis were treated with Rituximab as their first biologic. The mean age of patients was 51.79 ± 11.27 years with a majority of females (87.9%). The mean duration of the disease was 13.84 ± 9.07 years. In 21.81% of cases, 36 patients required at least one switch due to ineffectiveness. After 1 year of follow-up, switchers had a greater ΔDAS 28-ESR (-0.31 ± 2.22) compared to non-switchers (-0.17 ± 1.72). At 1-year follow-up, 53.6% of switchers were in remission/LDA compared to 43.8% of non-switchers. Adverse effects to biotherapy were more common in switchers (44.4%) than non-switchers (31%), with infections being the most common adverse effect in both groups (22.2% and 13.2%, respectively). ***Conclusion*:** Switching after Rituximab in RA patients may be as effective and tolerable as switching after TNF inhibitors.

Keywords: Rituximab, Switch, Rheumatoid Arthritis, Moroccan Biotherapy Registry, Therapeutic.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that causes pain, inflammation, and joint destruction, leading to functional impairment and reduced quality of life (Badsha *et al*., 2009; Benbouazza *et al*., 2011; Ibn Yacoub *et al*., 2012).

The management of inflammatory rheumatic diseases has been transformed by the introduction of effective biological treatments (Law & Taylor, 2019). Morocco currently offers seven biological drugs for treating RA, each with a different mechanism of action. These include rituximab, an anti-CD20 monoclonal antibody; infliximab, etanercept, adalimumab, and golimumab, which are TNF-alpha blockers; tocilizumab,

an interleukin-6 receptor inhibitor; and anakinra, an IL1 inhibitor.

In Morocco, the Moroccan Society of Rheumatology (SMR) recommends using rituximab as the first choice among biological treatment when remission or low activity is not achieved with the use of synthetic DMARDs. This is due to two reasons: firstly, tuberculosis (TB) is endemic in the country and rituximab poses fewer problems of reactivation of tuberculosis than other biotherapies. Secondly, rituximab is cheaper compared to other biological DMARDs (Daien *et al*., 2019; Niamane *et al*., 2014; Smolen *et al*., 2020).

If therapy with Rituximab fails or significant adverse effects occur, switching to a TNF inhibitor or another class of biological drug may be considered as the first line of treatment. However, it is important to note that there is currently limited documented hindsight or literature data proving the effectiveness and tolerance of this switch.

Several studies around the world had proved the efficacy and tolerance of the switch from an anti-TNF to another biological drug. Therefore, a transversal multicentric study was conducted to assess drug switching in patients with RA treated initially with Rituximab following the guidelines of the Moroccan Society of Rheumatology and to describe the rates of remission or low activity disease according to DAS28 as well as the tolerance at the end of follow-up, using the Moroccan biotherapy registry database RBSMR.

The aim of our study is to assess the efficacy and tolerance of biological treatments received after a first treatment with Rituximab.

METHODS

Data Source

RBSMR Registry

Data from the RBSMR (Registre des Biothérapies de la Société Marocaine de Rhumatologie) were used. This is a multicentric historical-prospective registry of patients who were treated for RA or SpA with biotherapy (initiation or ongoing biotherapy) in the ten rheumatology departments of the university hospitals of Morocco.

The inclusion period was from May 2017 to January 2019, and the follow-up period was 3 years. The study included 404 patients, of which 419 were validated (225 with Rheumatoid Arthritis and 194 with spondyloarthritis). Patients over 18 years old, diagnosed with either Rheumatoid Arthritis or spondyloarthritis, and receiving biotherapy (both initiation and ongoing) were included. Patients with juvenile idiopathic arthritis or those prescribed biotherapy for indications other than rheumatoid arthritis or spondyloarthritis were excluded.

The data were collected by clinicians from all Moroccan university medical centers, at the time of the patient's inclusion, by use of a case report form. Efficacy and tolerance data will be collected at least every six months and whenever patients experience an adverse event or a change in treatment (Hmamouchi *et al*., 2019).

Study Design and Population

A cross-sectional, multicenter, analytical study was performed using the RBSMR registry database, which included 224 patients followed for RA according to the ACR-EULAR 2010 criteria, of whom 165 patients received rituximab as a first biological treatment during the first year of follow-up. Data on sociodemographic characteristics, RA, clinical and paraclinical data were collected. The study involved 165 patients who were divided into two groups: switchers and non-switchers. The switchers group changed biological drug at least once during the one-year follow-up, while the non-switchers group continued to use Rituximab. The effectiveness of the switch was assessed by DAS28-ESR and ΔDAS28-ESR at baseline, six months, and 12 months of follow-up. Safety was assessed by monitoring adverse effects. Reasons for switching and type of new biological drug were recorded. Comparison was made between switchers and non-switchers.

Statistical Analysis

The statistical study was conducted using the database frozen in June 2020. Statistical analysis was performed using SPSS software, version 13.0. Mean ± standard deviation (SD) was used to present normally distributed parameters, while median ± interquartile range (IQR defined as 25–75th percentiles) was used for asymmetric parameters. Qualitative data were presented as frequencies (number and percentage). The study compared switcher and non-switcher patients using the Student's t-test for continuous variables with normal distribution and the Chi-squared test or Fischer's exact test for categorical variables. Statistical significance was determined by p-value less than 0.05.

Ethics Approval and Consent to Participate

The protocol for the original RBSMR study received approval from local institutional review boards and the national ethics committee, namely the Ethics Committee for Biomedical Research at Mohammed V University in Rabat, as well as the Faculty of Medicine and Pharmacy of Rabat. The approval number was 958/09/19 and the date was September 11, 2019. Patients provided written informed consent for publication.

RESULTS

Patient Demographics and Disease Characteristics

A total of 165 patients received Rituximab as their first biological drug. The majority of these patients were female (87.9%). The mean age of the patients was 51.79 ± 11.27 years, and the mean duration of their disease was 13.84 ± 9.07 years. Of the patients, 143

(92.9%) had a positive rheumatoid factor (RF), 156 (94.5%) were receiving corticosteroid therapy, and 156 (97.5%) were receiving methotrexate (MTX). The baseline characteristics of the study population are summarized in Table 1.

Table 1: Baseline characteristics of RA patients from the RBSMR registry who received Rituximab as their first biological:

Parameters	**n = 165**
Gender (Female)[1]	145 (87,9)
Age (years)[2]	51,79 ± 11,27
Educational level	
Illiterate[1]	73 (45,9)
Not illiterate[1]	86 (54,1)
Disease duration (years) [2]	13.84±9.07
Rheumatoid factor[1]	143 (92.9)
ACPA[1]	114 (87.6)
Current corticosteroid treatment[1]	156 (94.5)
MTX treatment[1]	156 (97.5)

ACPA: Anti-citrullinated Peptide Antibody, MTX: Methotrexate
[1]Number and percentage, [2]Mean and standard deviation

Profile of Switches

During the one-year follow-up period, 36 patients (21.81%) underwent at least one switch. 72.2% of the switches were due to ineffectiveness. Actemra was the second biological drug of choice after Rituximab (refer to Table 2). During the one-year follow-up period, 78.2% of patients continued to receive Rituximab. 13.3% of patients switched to a second biological drug and remained on it, while 7.9% switched to a third biological drug. Only one patient (0.6%) switched to a fourth biological drug after switching three times, resulting in a total of 51 switches (see Figure 1).

Table 2: Profile and causes of switches

	Switch 1 (n=36)	**Switch 2 (n=14)**	**Switch 3 (n=1)**
BDMARS[1]			
ENBREL[1]	8 (22.2)	3 (21.4)	1 (100)
HUMIRA[2]	3 (8.3)	2 (14.3)	0
REMICADE[1]	4 (11.1)	0	0
REMSIMA[1]	2 (5.6)	1 (7.1)	0
ACTEMRA[1]	19 (52.8)	8 (57.1)	0
Reasons for discontinuation			
Intolerance[1]	2 (5.6)	1 (7.1)	0
ineffectiveness[1]	26 (72.2)	7 (50)	0
Other raison[1]	8 (22.2)	6 (42.9)	1 (100)

[1]Number and percentage

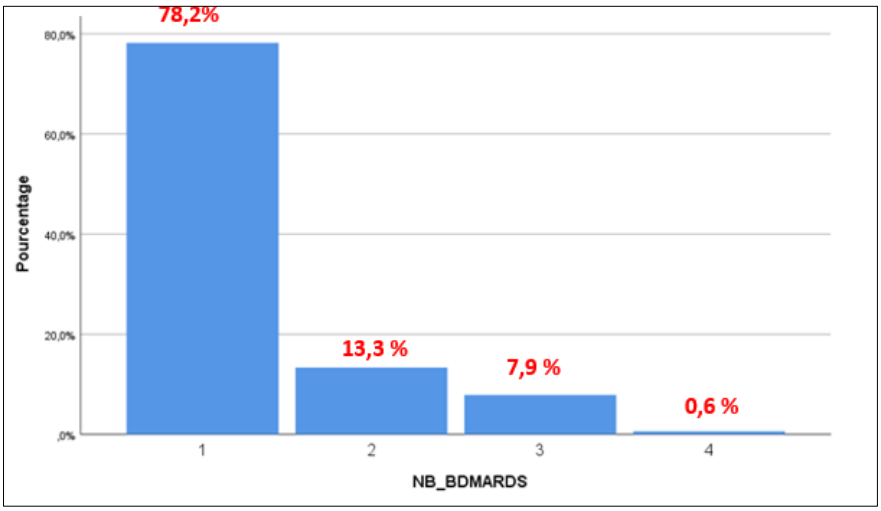

Figure 1: Distribution of patients according to the number of bDMARDS received

Effectiveness

At inclusion, the Disease Activity Score 28-Erythrocyte Sedimentation Rate (DAS28-ESR) and Visual Analogue Scale (VAS) scores for patients were significantly lower in the group who switched compared to the non-switcher group (3.52 ±1.84 *vs* 4.27 ±1.38 and 3.4 ±2.4 *vs* 5.2 ±2.2 respectively). (See Table 3). After 1 year of follow-up, there is no significant difference between the switcher and non-switcher groups in terms of disease activity parameters, except for the VAS patient score, which is slightly higher at 1.5 in the switcher group compared to the non-switcher group (Table 4). At baseline, six months, and 12 months of follow-up, the switcher group exhibited a higher prevalence of remission or low disease activity (LDA) compared to the non-switcher group. However, this difference is only statistically significant at inclusion (Table 5).

Table 3: Comparison of activity parameters between switcher and non-switcher groups at baseline

Characteristics	Switchers (n=36)	N-Switchers (n=129)	*p*
DAS 28 ESR[1]	3.52 ±1.84	4.27 ±1.38	0.03
DAS 28 CRP[1]	3.24 ±1.52	3.81 ±1.32	0.03
ESR (mm/h)[2]	20 [9.5 ;47.75]	34 [18 ;47]	0.06
CRP (mg/l) [2]	9.97 [4 ;23.55]	14.8 [5.7 ;29.4]	0.13
Painful joint[2]	3 [1 ;10.5]	6 [2 ;12]	0.17
Swollen joint[2]	1 [0 ;5]	4 [0 ;7]	0.14
VAS patient (0-100)[1]	3.4 ±2.4	5.2 ±2.2	0.0001

DAS28: Disease Activity Score, ESR: Sedimentation rate, CRP: Protein-C- Reactive
[1]Mean and standard deviation, [2] Median and Interquartile range

Table 4: Variations in disease activity parameters in the two groups switcher and non-switchers between V0 and V12

Characteristics	Switchers (n=36)	N-Switchers (n=129)	*p*
ΔDAS 28 ESR[1]	-0.31 ±2.22	-0.17 ±1.72	0.71
ΔDAS 28 CRP[1]	-0.44 ±2.04	-0.79 ±1.53	0.28
ΔESR[1]	-9 ±24.53	-5.27 ±21.23	0.44
ΔCRP[1]	-5.65 ±21.66	-10.37 ±26.42	0.33
Δ Painful joint[1]	-1.61 ±11.76	-2.96 ±9.73	0.51
Δ Swollen joint[1]	-1.41 ±7.57	-2.49 ±5.97	0.40
Δ VAS patient [1]	1.5 ±3.27	-0.48 ±2.99	0.001

DAS28: Disease Activity Score, ESR: Sedimentation rate, CRP: Protein-C- Reactive, N-switcher: Non switcher
[1]Mean and standard deviation

Table 5: Evaluation of remission and LDA in the two groups switcher and non-switcher between V0 and V12

	V0			V6			V12		
	Switcher (n=36)	N-switcher (n=129)	*p*	Switcher (n=36)	N-switcher (n=129)	*p*	Switcher (n=36)	N-switcher (n=129)	*p*
Remission/LDA[1]	18 (52.9)	27 (22)	0.0001	21 (77.8)	58 (63.7)	0.173	15 (53.6)	39 (43.8)	0.367

N-switcher: Non switcher, LDA: Low disease activity
[1]Number and percentage

Safety

A summary of safety is shown in Table 6. The incidence and type of adverse effects (AEs) observed in the two groups evaluated in this study were broadly similar. Forty-four percent of switchers experienced AEs compared to 31% of non-switchers, without statistical significance. Infections predominated in both groups (22.2% and 13.2% respectively), infusion reactions in the non-switching group (13.2%), and neoplasia was absent in both groups.

Table 6: Assessment of the tolerance of switches in patients who received Rituximab as the first biological

	Switchers (n=36)	N-Switchers (n=129)	*p*
Side effects [1]	16 (44.4)	40 (31)	0.132
Infection[1]	8 (22.2)	17 (13.2)	0.181
Cancer[1]	0	0	

	Switchers (n=36)	**N-Switchers (n=129)**	***p***
Lymphoma[1]	0	0	
paradoxical effects[1]	1 (2.8)	3 (2.3)	1
sarcoidosis[1]	0	0	
vasculitis[1]	0	0	
induced lupus[1]	0	1 (0.8)	1
infusion reactions[1]	2 (5.6)	17 (13.2)	0.253
immediate intolerance[1]	2 (5.6)	14 (10.9)	0.527
leukopenia[1]	1 (2.8)	3 (2.3)	1

[1]Number and percentage

DISCUSSION

While switching from TNF inhibitor agents as the first biological drug in RA is widely used around the world, in Morocco, rituximab is the first biological drug used in RA, and no data are available to rheumatologists to rationally determine the subsequent efficacy and tolerability of switching in patients who previously failed to respond to rituximab.

This is the first multicenter study to evaluate switching from rituximab as a first-line biologic in RA patients. 165 patients received rituximab as a first-line biologic. During one year of follow-up, 36 (21.81%) patients received at least one switch due to ineffectiveness in 72.2% of cases. 53.6% of patients who switched were more likely to achieve LDA or remission than those who did not switch, although this was not statistically significant. We also found similar switch-related safety in the two groups.

Several other observational studies have been conducted to analyze switching from a TNF inhibitor to a first-line biologic. A study conducted in Brazil in 2018, including 85 patients with RA who received a TNF inhibitor as their first biologic drug over a period of 8 years, found similar results, suggesting that half of the patients have switched due to therapeutic ineffectiveness. Also, half of them achieved remission or LDA, without any precision on the safety of the switch (de Lucena Valim, Gonçalves Chaer, Guimarães da Silveira, da Silva e Lima, & Batista de Souza, 2018). Furthermore, the American CORONA registry published in 2015, which included 1002 cases of patients taking TNF inhibitors for more than one year, found that 265 patients switched to Rituximab and 737 to another TNF inhibitor agent. In the rituximab group, 34% achieved remission or LDA versus 33% in the other group, with no significant difference in safety (Harrold *et al*., 2015). Data from a global study, SWITCH-RA, published in 2015, which included 728 patients treated with a TNF inhibitor agent as a first biologic, showed that after discontinuation of a first TNF inhibitor, 405 patients switched to rituximab and 323 patients switched to an alternative TNF inhibitor, achieving significantly better clinical responses over 6 months in both groups. The safety profiles of the two treatment groups were similar, with a predominance of urinary tract infections (Emery *et al*., 2015).

This study had several limitations. First, the use of data from a national registry means that some data were missing. Second, the type of insurance and the health economic cost of biologicals influenced the choice of biologicals. Also, in an endemic TB country like Morocco, the risk of TB reactivation required rituximab to be the first-choice biological drug. Finally, as this is an ongoing study, the final results will be more accurate and will help to determine the efficacy and safety of this switch in RA patients who have not responded to Rituximab. In this situation, the results and conclusions should be interpreted with caution.

This study also has some strengths. It is the first multicenter research of its type and size to investigate the efficacy and safety aspects of switching after rituximab as the first biologic drug, with data from real-life follow-up over 1 year of RA patients in the Moroccan RBSMR registry, which is the first multicenter biotherapy registry in North Africa.

CONCLUSION

This study suggests that switching from rituximab in RA patients may be as effective and safe as switching from a TNF inhibitor, based on the Moroccan Biological Therapies in Rheumatic Diseases Registry. Future analyses are needed to confirm these results and to better identify which patients are likely to respond to a particular agent based on their response to prior medications.

Declarations

Ethics Approval and Consent to Participate:

The protocol for the original RBSMR study was reviewed and approved by local institutional review boards and the national ethic committee: Ethics committee for biomedical research Mohammed V university- RABAT. Faculty of medicine and pharmacy of RABAT. Approval number: 958/09/19 and date: September 11, 2019

Consent to Publish: Written informed consent for publication was obtained from the patients.

Availability of Data and Materials: The datasets are available from the RBSMR registry of the Moroccan Society of Rheumatology.

Disclaimer:

We confirm that the manuscript has no actual or potential conflict of interest with any party, including but not limited to any financial, personal or other relationship with other people or organization. We confirm that the paper has not been published previously, is not under consideration for publication elsewhere, and is not being simultaneously submitted elsewhere.

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Author Contributions:

We declare that we participated at the study as following: A.Souissi performed the statistical analysis and interpretation, reviewed the literature and drafted the manuscript. S.Rostom participated in article writing and reviewed critically the manuscript. I.Hmamouchi and R.Abouqal reviewed and interpreted the statistical analysis. B.Amine, I.El binoune and R.Bahiri reviewed critically the manuscript. All authors have reviewed and approved the final manuscript.

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