Experience with rituximab in patients with rheumatoid arthritis in Nairobi, Kenya

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Abstract

Background: Rheumatoid Arthritis (RA) is a disease associated with significant morbidity and mortality. Newer therapies include B-cell targeted therapies such as rituximab.
Objectives: To study the outcome in RA patients receiving rituximab following resistance to Disease Modifying Anti-Rheumatic Agents (DMARDS) and to determine the change in disease activity and functional status.
Methods: A longitudinal prospective study was carried out on RA patients in Nairobi, Kenya. Patients resistant to DMARDS and on rituximab therapy were identified. Their disease activity was assessed using the Simplified Disease Activity Index (SDAI) and the functional status determined using Health Assessment Questionnaire-Disability Index (HAQ DI). The scores were recorded at the beginning of the study then at 3 and 6 months after the initiation of rituximab therapy.
Results: Forty-one patients (36 females and 5 males) receiving rituximab were recruited in this study. At baseline, 18 had moderate and 23 with high disease activity. After 6 months, 7% were in remission, 11% with low, 17 moderate and 6 with high disease activity. There was significant improvement in the SDAI scores witnessed in 13(31.7%) patients in first 3 months and in 22(53.7%) patients after 6 months. There was a significant improvement in the functional and disability score in 95% of the patients after 6 months. There was no significant correlation between the SDAI and the different variables as age, disease duration, type of DMARD and steroids used.
Conclusion: Rituximab use resulted in improvement of disease activity, functional status and disability index in patients with RA in Nairobi.

Keywords: Rituximab, Rheumatoid arthritis, SDAI, HAQI, Nairobi, Kenya

Introduction

Rheumatoid arthritis is a chronic systemic inflammatory disorder characterized by deforming symmetrical polyarthritis often leading to joint destruction, deformity and loss of function[1]. While the exact cause of RA is unknown, multiple different factors interact in genetically susceptible hosts to initiate polyarticular synovitis. The immune mechanisms responsible for the pathogenesis of RA include T and B cells activation, and various inflammatory cytokines[2,3]. Treatment modalities include Non-Steroidal Anti-Inflammatory Agents (NSAIDs), agents targeting the immune system include steroids, Disease Modifying Anti-Rheumatic Agents (DMARDS), anti-TNF agents and B cell targeted therapies such as rituximab[4]. While NSAIDs, steroids and DMARDs (non-biological) have been the mainstay of treatment since 1970s, newer therapies such as anti-Tumor Necrosis Factor (TNF) agents and B-cell targeted therapies have been more recently introduced [4].

For early, moderately active RA, drugs used include NSAIDs, steroids and single agents or combinations of non-biologic DMARDs, such as hydroxychloroquine (HCQ), sulfasalazine (SAZ), methotrexate (MTX), and leflunomide (LFN). In patients who do not respond adequately to initial DMARD therapy, particularly those with a poor prognosis, treatment with TNF-alpha inhibitors may be considered as an alternative to non-biologic DMARD combination[5]. For patients with persistently active RA (disease of ≥6 months' duration that has continued despite the use of DMARDs, treatment include the use of biologic DMARDs in combination with non-biologic DMARDs. They usually target specific cytokines or their receptors, such as TNF-α. They may also act as B cell depleting agents and T cell costimulatory blockers [6].

Rituximab is a non-biological DMARD agent acting on the B cells. It is recommended by the Food and Drug Administration (FDA) in treatment of RA in patients resistant to anti-TNF therapy. It received approval for use in RA in February 2006[7]. In one famous trial known as the REFLEX trial, they randomly assigned 520 patients with

active RA despite treatment with both MTX and an anti-TNF agent to receive two IV infusions of rituximab one week apart. Mean disease activity, as measured by the disease activity score for 28 joints (DAS28), decreased significantly from baseline over the first four weeks and did not rise after four weeks during the subsequent 20 weeks. In the group receiving MTX and placebo the mean DAS28 rose steadily during the subsequent 20 weeks. Studies have shown it is also effective as first line biological therapy rather than a second line therapy for DMARD resistant RA alone or in combination with other DMARDs such as methotrexate[8].

Rituximab is a chimeric monoclonal antibody against the CD20 surface marker on B cells. It causes B cell depletion through several mechanisms: Fc receptor gamma-mediated antibody-dependent cytotoxicity complement-mediated cell lysis growth arrest B cell apoptosis[9]. Eliminating B cells decreases production of TNF-α by macrophages, decreases T cell activation and decreases T cell dependent synovial inflammation[10]. A course of rituximab consists of two 500 or1000 mg IV infusions in combination with methotrexate: an initial dose is administered, followed 2 weeks later by a second dose[11,12]. Pre-medication with glucocorticoids, and/or antihistamines and antipyretics should be given to lessen infusion reactions[13]. Adverse events in RA include fatal infusion reactions, tumor lysis syndrome, acute respiratory failure, cardiac events, and severe mucocutaneous reactions[13]. The majority of experienced infusion reactions occurs during the first infusion, and includes flu-like illness, fever, chills, nausea, urticaria, bronchospasm, hypotension, angio-oedema, headache and hypoxia[13]. Infusion reactions are most severe with the 1st infusion and lessen with repeated infusions.

The aim of this work was to study the outcome in RA patients receiving rituximab following resistance to DMARDS and to determine the change in disease activity and functional status.

Materials and Methods

Study design: This was a longitudinal prospective outcome study on RA patients failing standard DMARD therapy receiving rituximab. Patients were eligible to the study if they had presented at least 6 months prior with moderate to severe RA despite ongoing treatment with optimal doses of standard DMARDS (MTX, SAZ, LFN, HCQ or combination DMARD therapy). Patients must have failed prior treatment, manifesting as a lack or loss of response to treatment with at least 1 DMARD. Patients who were on concomitant glucocorticoid therapy and/or NSAID were included in the evaluation.

The disease activity was assessed using the Simplified Disease Activity Index (SDAI)[14] and the level of physical functioning and disability was determined using Health Assessment Questionnaire- Disability Index (HAQ DI)[15]. Patients who had moderate to high disease activity at six months of follow up were considered to have failed therapy. The study was approved by the local university ethical committee and the study performed in accordance with the ethical standards of the 1964 Helsinki declaration. All patients gave their informed consent prior to their inclusion in the study.

Study treatment: Rituximab was administered by intravenous infusion at 1000mg on days 0 and 15. To mitigate acute drug reaction, methyl prednisone at 100mg was given as premedication, together with 2 tablets of paracetamol and 25mg of promethazine; at days 0 and 15.

Trial end points: The primary study end point was the proportion of patients attaining clinical remission as per the SDAI scoring at months 3 and 6. Secondary and exploratory analyses examined group differences in SDAI improvements among various treatment and demographic categories of patients.

Statistical analysis: All data was collected on the study proforma. Data entry and statistical analysis was done using the Statistical Package for Social Sciences (SPSS) version 17. Comparison of means was done using Student's t test for Mann Whitney U test. Wilcoxon's matched-pairs signed rank test used to measure the significance of the change from baseline of the SDAI scores.

Results

Patients' characteristics: Of the 41 patients studied, 36(87.8%) were females and 5(12.2%) were males. The sample comprised of 27 married respondents, 11 were single, 2 were divorced and 1 widowed. Majority (73.2%) of the respondents resided in urban areas and the rest peri-urban. Most (92.7%) of the respondents had attained tertiary level education, 4.9% had attained secondary level of education while 2.4% had no education at all. Thirty respondents were employed and 4 housewives and self employed each while 3 were retired.

The majority (46.3%) of the patients had first RA diagnosis made 5-10 years prior to enrollment. The lowest

percentage (2.4%) of respondents had their first RA diagnosis for less than 1 year. 85.4% of the respondents were on concurrent NSAID therapy. Majority of the patients (78%) had failed MTX or MTX containing combination DMARD regimens. Table 1 summarizes the treatment modalities and the duration of treatment among the studied patients.

Table 1: Disease duration and treatments received before commencement of rituximab

Treatment	Disease duration (years) No. (%)			Total
	1 - 5	5 - 10	> 10	
MTX	7 (17.1)	19(46.3)	6 (14.6)	32 (78)
HCQ	8 (19.5)	0 (0)	0 (0)	8 (19.5)
SAZ	0 (0)	0 (0)	0 (0)	0 (0)
Steroids	10(24.4)	11(26.8)	1 (2.4)	22 (53.7)
NSAIDS			35 (85.4)	35 (85.4)
Other			38 (92.7)	38 (92.7)

MTX: Methotrexate, HCQ: Hydroxychloroquine, Sulphasalazine (SAZ), NSAIDS: Non-steroidal anti-inflammatory drugs.

Disease activity in the studied patients: The mean SDAI decreased significantly ($p < 0.001$) at 3 and 6 months. There was a significant difference in the SDAI score between 0 and 3 months, 3 and 6 months and between 0 and 6 months, ($p<0.001$). The SDAI score of the patients are presented in Table 2.

Table 2: The Simplified Disease Activity Index (SDAI) at baseline and after 3 and 6 months

SDAI score	Minimum	Maximum	Mean	±SD
At baseline	2.2	77.8	29.2	±16.7
At 3 months	1.9	49.3	21.4	±12.7
At 6 months	1.3	34.7	14.4	±9.3

SDAI: Simplified Disease Activity Index

There were 6 patients remaining with high disease activity at the end of 6 months, as shown in Table 3**.**

There was no difference in the median of SDAI score across the various categories of time of first RA diagnosis. This implied that improvement in disease activity did not depend on the time of first RA diagnosis. There was consistent decline in SDAI scores irrespective of the time of first RA diagnosis (Table 4).

Table 3: Comparison of the number of rheumatoid arthritis patients according to the Simplified Disease Activity Index (SDAI) at baseline and after 3 and 6 months

	RA patients Baseline	Study duration (months) After 3	After 6
SDAI score	Remission	0	2	7
	Low Activity	0	6	11
	Moderate Activity	18	19	17
	High Activity	23	14	6

RA: Rheumatoid arthritis, SDAI: Simplified Disease Activity Index

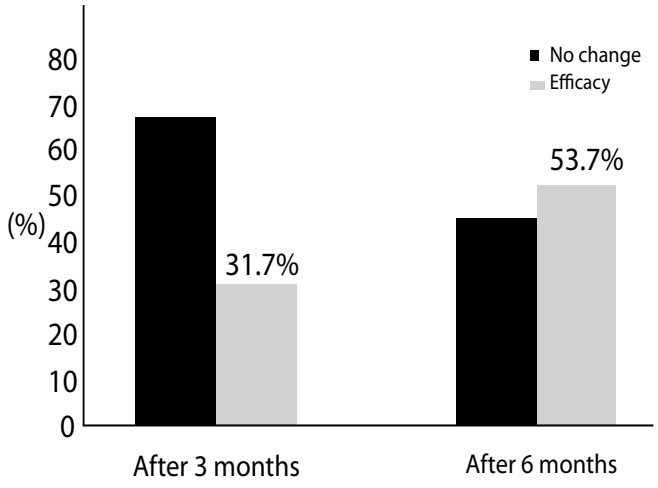
Table 4: Comparison of the SDAI score in RA patients according to the first diagnosis of the disease at baseline and after 3 and 6 months

First RA diagnosis Median	SDAI score At baseline	After 3 months	After 6 months	P value
< 1 year	12.4	11.7	10.3	-
1 - 5 years	27.9	17.5	13.9	<0.001
5 -10 years	24.1	18.2	11.0	<0.001
> 10 years	27.1	21.7	17.3	<0.001

RA: Rheumatoid arthritis, SDAI: Simplified Disease Activity Index

There was significant improvement in the SDAI scores witnessed in 13(31.7%) patients in the first 3 months and in 22(53.7%) patients after 6 months (Figure 1).

Figure 1: Percentage of RA patients with significant SDAI change after rituximab therapy for 3 and 6 months



The correlations of the studied parameters with the disease activity (SDAI) are presented in Table 5.

Table 5: Correlation between demographic/treatment variables and disease activity in rheumatoid arthritis patients

Variable in RA patients	SDAI	
	r	p
Age	0.13	0.36
Disease duration	0.11	0.45
DMARD used	0.24	0.13
Steroid use	0.003	0.99

RA: Rheumatoid arthritis, SDAI: Simplified disease activity index, DMARD: Disease modifying anti-rheumatic drug

Functional status: The level of physical disability and functioning improved consistently from baseline to the 6th month in the RA patients receiving rituximab as shown in the Table 6.

Table 6: Level of physical disability and functioning from baseline to 6 months

HAQ-DI	Minimum	Maximum	Mean	±SD
At baseline	0	3.8	1.19	±0.8
After 3 months	0	2.9	0.94	±0.57
After 6 months	0	1.9	0.67	±0.27

The HAQ-DI score at baseline was the highest and decreases with time tending towards a normal curve at the third month (p=0.03). The improvement in functioning and disability was witnessed in the majority (95.1%) patients.

Discussion

It has been confirmed that a single course of rituximab, given as 2 infusions 2 weeks apart, is highly effective over 24 weeks in the treatment of active RA in patients showing incomplete response to standard DMARD therapy[11]. Rituximab has a novel mode of action that results in the depletion of B cells, and it is therefore distinct from other biologic therapies for RA that target T cells and their related cytokines.

This evaluation of patients receiving rituximab following treatment failure of conventional DMARDS, reviewed 41 patients from Nairobi, Kenya. This study demonstrated significant clinical improvement of patients receiving rituximab both at 3 months and at 6 months. This is consistent with findings from other studies; notably the DANCER trial[16] which showed significant DAS28 changes from baseline at week 24 in patients receiving both 500mg and 1000mg doses as compared to placebo.

Out of the 41 patients, 6 (15%) had low disease activity at 3 months of follow up with 2 being on remission. At 6 months; 11 (27%) patients had low disease activity with 7 (17%) patients achieving remission. This study compares favorably with results from the study of Nasonov *et al*[16] in a prospective cohort biologic register report that noted clinical remission in 12.3% at 6 months with 11.7% having low disease activity.

Disease duration for more than 1 year was significantly associated with changes in SDAI upon rituximab infusion. This was an interesting finding as patients who had less than one year of disease duration did not show significant change in SDAI scores. This could be a selection bias as such patients would have had severe baseline disease activity with poor prognostic indicators resulting in poor outcomes even with rituximab infusion. Pretreatment prognostication is not routinely done in our clinic setting; this would have given us an insight into this cohort. A larger study cohort is required to draw conclusions.

Our study did not establish any significant correlation of clinical response with other variables such as duration of disease, age and type of DMARD therapy used. The DANCER trial similarly did not establish significant effect on ACR20 response in patients who were on concomitant glucocorticoid therapy. However in this study, glucocorticoid therapy was associated with reduced incidence and severity of acute infusion reaction. Our study did not however look at the safety outcomes.

There was an improvement in the mean function and disability as measured by HAQ score. Percinkova *et al* [17] demonstrated subjective improvement in functional status with significant decrease in night pain and morning stiffness and decreased number of painful and swollen joints in a similar study of patients with severe, active RA refractory to multiple DMARDS after rituximab therapy.

Our study though had a number of limitations. Our analysis did not scrutinize safety data partly due to short duration of follow-up and missing data on the same. Analysis of long term treatment outcome and safety data is ongoing and shall be reported in future. Many studies have shown that in real life patients move in and out of

remission; thus an analysis of sustained remission (at least 3 months of persistency) would be better.

In conclusion, rituximab infusion resulted in significant improvement of disease activity in patients failing standard DMARD therapy in Nairobi with enhancement in the functional status and disability index.

Conflict of interest: None.

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