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Rituximab in the treatment of refractory rheumatoid arthritis in a tertiary academic hospital

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RITUXIMAB IN THE TREATMENT OF REFRACTORY RHEUMATOID ARTHRITIS IN A TERTIARY ACADEMIC HOSPITAL

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Internal Medicine.

Johannesburg, 2019

DECLARATION

I, Tamsin Lovelock, declare that this research report is my own work. It is being submitted for the degree Master of Medicine (in the submissable format with my protocol and an extended literature review) in the branch of Internal Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

……

……day of ……2019

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I also wish to specifically acknowledge my supervisors Dr Claudia Ickinger and Dr Lai-ling Winchow for their excellent guidance, ongoing support and meticulous editing which contributed greatly to the quality of the project. My humble thanks to you both.

PRESENTATIONS ORIGINATING FROM THIS RESEARCH

1. Selected for oral presentation at the Faculty of Health Sciences Research day, University of the Witwatersrand, Johannesburg, 6 September 2018.

2. Selected for poster presentation at the 34th World Congress of Internal Medicine, Cape Town, 18-22 October 2018.

ABSTRACT

Background

Significant disability results from rheumatoid arthritis (RA) when treatment is delayed or inadequate. Rituximab is approved for use in RA in South Africa, but there is a paucity of data on its use in Sub-Saharan African populations.

Objectives

To determine the response to rituximab in refractory RA patients by measuring disease activity and functional status over a 6-month period. To describe predictors of response to rituximab, and to document short term adverse events.

Methods

A single centre retrospective study of adult patients with RA receiving treatment with rituximab at Chris Hani Baragwanath Academic Hospital, between January 2012 and September 2016. Demographics, clinical and laboratory data were collected. The European League Against Rheumatism (EULAR) response criteria and minimal clinically important improvement (MCII) in Health Assessment Questionnaire Disability Index (HAQ-DI) were applied as outcome measures. Baseline characteristics of responders to rituximab therapy were compared with those of non-responders.

Results

Of the 53 patients with RA refractory to at least 3 synthetic disease modifying anti-rheumatic drugs (DMARDs), 75.5% were African and 88.7% were female. At initiation of rituximab the mean age (SD) was 50.8 (10.7) years and disease duration was 12.6 (6.6) years. Over 90% of patients were rheumatoid factor and anti-cyclic citrullinated peptide antibody

positive, 41.5% had extra-articular features and the majority (69.8%) had high disease activity by the simplified disease activity index. The baseline mean (SD) HAQ-DI was 2.3 (0.6). At 3 months, 81.1% of patients achieved a good or moderate EULAR response. Predictors of response to rituximab included higher tender joint counts (p=0.0473) and higher SDAI scores (p=0.0467). A clinically meaningful decrease in HAQ-DI scores was observed in 44 (83%) of patients. Improvements were not sustained at 6 months, although clinical parameters were still better than at initiation. No early adverse events were recorded.

Conclusion

Rituximab therapy was safe and effective in controlling disease activity in addition to improving functional disability in this cohort of predominantly African patients with severe established RA. The findings underscore the need to identify appropriate patients for predictable responses to biologic therapies in prospective longitudinal studies in southern Africa.

TABLE OF CONTENTS

DECLARATION i
ACKNOWLEDGEMENTS ii
PRESENTATIONS ORIGINATING FROM THIS RESEARCH iii
ABSTRACT iv
TABLE OF CONTENTS vi
LIST OF TABLES ix
LIST OF FIGURES x
ABBREVIATIONS xi
CHAPTER 1: PROTOCOL WITH EXTENDED LITERATURE REVIEW 1
Introduction 1
Epidemiology and risk factors 1
Aetio-pathogenesis 2
Auto-antibodies 2
Immune activation 2
Role of T-lymphocytes 2
Role of B-lymphocytes 3
Other mechanisms 5
Clinical manifestations and extra-articular features 6
Diagnosis 7
Assessment of functional disability 8
Assessment of disease activity 8
Assessment of therapeutic response 9
Treatment of rheumatoid arthritis 10
Rituximab in rheumatoid arthritis 11
Mechanism of action 11
Efficacy 12
Predictors of response 13
Pre-treatment screening and administration 14
Dose and treatment intervals 15
Adverse events and safety 16
Economic considerations 18

The role of our study 18
Aim 19
Objectives 19
Methods 20
1. Study setting and design 20
2. Sample population 20
3. Inclusion criteria 20
4. Exclusion criteria 20
5. Measurement of disease activity 20
6. Measurement of functional status 21
7. Refractory rheumatoid arthritis 21
8. Response to rituximab 21
9. Adverse events 21
Data collection 21
Data extracted from clinical records prior to rituximab 21
Data collected at 3 and 6 months after initiation of rituximab 22
Data analysis 22
Ethics 23
Timing 23
Funding 24
Limitations 24
References 25
CHAPTER 2: SUBMISSABLE ARTICLE 31
Abstract 32
Introduction 34
Patients and methods 35
Statistical analysis 37
Results 37
Patient characteristics at initiation of rituximab 37
Clinical and laboratory characteristics at follow-up 39
Patient characteristics according to EULAR response 41
Patient characteristics according to MCII in HAQ-DI 42
Loss of response at 6 months 43

Discussion 44
References 47
CHAPTER 3: APPENDICES 51
Appendix A: 2010 ACR/EULAR classification criteria for rheumatoid arthritis 51
Appendix B: Simplified Disease Activity Score (SDAI) 52
Appendix C: DAS28-ESR (3) Score 53
Appendix D: Health Assessment Questionnaire Disability Index (HAQ-DI) 54
Appendix E: EULAR response criteria 56
Appendix F: Data collection sheet 57
Appendix G: Ethics approval 60
Appendix H: Plagiarism report 61

LIST OF TABLES

Chapter 1:

Table 1: American College of Rheumatology classification criteria for rheumatoid arthritis…….……7

Table 2: EULAR response criteria……...10

Chapter 2:

Table 1. Baseline characteristics of patients receiving rituximab.……..39

Table 2. Clinical and laboratory characteristics at initiation of rituximab (baseline) and at 3 and 6 months after rituximab……...…...……...……40

Table 3. Baseline characteristics of patients according to EULAR response at 3 months after rituximab……..42

Table 4. Baseline characteristics of patients according to MCII in HAQ-DI at 3 months after rituximab…….….43

LIST OF FIGURES

Figure 1: Characteristics of patients at initiation of rituximab (baseline) and at 3 and 6 months after rituximab……..40

Figure 2. Percentage of cohort who achieved MCII and EULAR response at 3 and 6 months……..44

ABBREVIATIONS

Anti-TNF	Anti-tumour necrosis factor
ACPA	Anti-citrullinated peptide antibody
ACR	American College of Rheumatology
BAFF	B-cell activating factor of the TNF family
CHBAH	Chris Hani Baragwanath Academic Hospital
CHQ	Chloroquine
CRP	C-reactive protein
CXCL-12	C-X-C motif chemokine ligand-12
CXCL-13	C-X-C motif chemokine ligand-13
DAMP	Disease associated molecular patterns
DAS	Disease Activity Score
DAS28	Modified Disease Activity Score using 28-joint count
DAS28-ESR (3)	Modified Disease Activity Score using 28-joint count and ESR (3 variable)
DMARD	Disease modifying anti-rheumatic drug
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FLS	Fibroblast-like synoviocyte
HAQ-DI	Modified Health Assessment Questionnaire Disability Index
Hb	Haemoglobin
HDA	High disease activity
HIV	Human immunodeficiency virus
IG	Immunoglobulin
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-1	Interleukin-1
IL-6	Interleukin-6
IL-10	Interleukin-10

IL-17	Interleukin-17
ILD	Interstitial lung disease
INH	Isoniazid
LDA	Low disease activity
LT-β	Lymphotoxin beta
MCID	Minimal clinically important difference
MCII	Minimal clinically important improvement
M-CSF	Macrophage colony stimulating factor
MDA	Moderate disease activity
MMP	Matrix metalloproteinase
MTX	Methotrexate
NODLR	NOD-like receptors
PAMP	Pathogen associated molecular patterns
PGA	Patient global assessment
PhGA	Physician global assessment
PML	Progressive multifocal leukoencephalopathy
PPD	Purified protein derivative
RA	Rheumatoid arthritis
RANKL	Receptor activator of NF-KB ligand
RF	Rheumatoid factor
SARAA	South African Rheumatism and Arthritis Association
SDAI	Simplified Disease Activity Index
SJC	Swollen joint count
SZP	Sulphasalazine
TB	Tuberculosis
TJC	Tender joint count
TLR	Toll-like receptors
TNF-α	Tumour necrosis factor alpha

CHAPTER 1: PROTOCOL WITH EXTENDED LITERATURE REVIEW

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease which results in significant morbidity. The disease primarily involves the joints however, RA is also a disease of systemic inflammation which may manifest in several organ systems as extra-articular features. Untreated or inadequately treated disease results in permanent deformities, disability, diminished quality of life, and premature mortality. [1]

Epidemiology and risk factors

Rheumatoid arthritis has a global distribution and affects up to 1% of the population, with a female to male preponderance of 3:1. [1,2] The disease seems to be more prevalent in urban than in rural areas, implicating environmental risk factors. Cigarette smoking remains the most demonstrable environmental risk factor. [3] Genetic factors are well described and may account for up to half of the risk for developing RA. [1] More than 100 genetic loci have been associated with an increased risk of developing RA. Most of these loci point to immune mediated mechanisms of disease and some have also been associated with other chronic inflammatory diseases. [4] The same amino acid sequences may be shared by various disease-causing alleles. This phenomenon is termed the "shared epitope" and is associated with the presence of the characteristic auto-antibodies of RA. [1,4] Certain genotypes may be associated with more aggressive disease and a less favourable prognosis. Heritability of RA has been estimated at 60%, by using twin studies and family pedigrees and a positive family history of RA may increase the lifetime risk of developing disease by up to 5 times. [4,5]

Aetio-pathogenesis

While the true cause of RA remains elusive, the hallmark of the disease is persistent inflammation. The disease is driven by several cascades which culminate in a final pathway causing synovitis and joint destruction. However, RA is a systemic disease, as evidenced by extra-articular manifestations and the presence of serological changes that may precede clinical joint disease by up to 10 years. [1]

Auto-antibodies

The association of RA with auto-antibodies is well-known, particularly antibodies to immunoglobulin G (IgG), termed rheumatoid factors (RF), and anti-citrullinated peptide antibodies (ACPA), which may predict clinical course and response to treatment. [1,5]

However, the entity of "seronegative RA" accounts for a significant proportion of the disease burden (up to 20%), and both RF and ACPA may be positive in other autoimmune diseases. [6,7] It has been postulated that seronegative RA is a genetically distinct disease. [7]

Immune activation

Mechanisms involved in RA include activation of the innate and adaptive immune system, cytokine networks and intracellular signalling pathways, complement activation and immune complex deposition, and tissue reaction and remodelling. [8] Identifying key components of the inflammatory pathway of RA has been instrumental in developing new and directed therapies. Conversely, many advances in understanding the pathogenesis of RA have arisen from observing the response to different therapies.

Role of T-lymphocytes

Activation of adaptive immunity may be one of the earliest events in the pathogenesis of RA. The important role of T-lymphocytes is emphasised by the presence of high numbers of T-

lymphocytes in synovial tissue in RA and by the clinical response to abatacept which blocks T-lymphocyte co-stimulation, arresting disease in many patients. [5]

The association of RA with Th1 differentiation is well known, but Th17 differentiation also plays a role, [9] and creates a pro-inflammatory T-lymphocyte homeostasis by the production of cytokines including interleukin-1 (IL-1), interleukin- 6 (IL-6), interleukin-17 (IL-17) and tumour necrosis factor alpha (TNF-α). [9,10]

Role of B-lymphocytes

Humoral adaptive immunity and the role of B-lymphocytes is evidenced by the clinical response to B-lymphocyte depletion by biologic agents such as rituximab. B-lymphocytes have multiple roles to play in the pathogenesis of RA including the production of auto-antibodies, antigen presentation and T-lymphocyte activation and cytokine production. [9,11] B-lymphocytes also play a role in osteoclast activation and pathological bone remodelling. [11]

In RA, B-lymphocytes accumulate in the synovium to form aggregates which closely resemble lymphoid germinal centres. This process is termed ectopic lymphoneogenesis and represents a dynamic interaction between circulating B-lymphocytes and the inflamed synovium. Factors which contribute to recruitment, organisation and survival of B-lymphocytes in the synovium include B-cell activating factor of the TNF family (BAFF), CXC chemokine ligand-13 (CXCL-13), CXCL-12 and lymphotoxin-beta (LT-β). [12]

B-lymphocytes interact with T-lymphocytes by processing and presenting antigens to induce T-lymphocyte activation and production of pro-inflammatory cytokines. It has been postulated that T-lymphocyte mediated pathogenetic mechanisms in RA may be B-lymphocyte dependent. Evidence for this comes from suppression of T-lymphocyte activation and cytokine production following B-lymphocyte depletion in mice. [11] B-T

lymphocytes interactions also result in the activation and differentiation of plasma cells to produce auto-antibodies. [11,12] An extensive number of antigens are recognised by the auto-antibody milieu in RA, and many RA-associated auto-antibodies have been characterised but RF and ACPA remain the most widely studied. B-lymphocytes which produce RF are particularly effective at antigen presentation and priming of T-lymphocytes. [12]

The role of B-lymphocytes in bone remodelling in RA has become more apparent. Bony complications of RA include marginal and subchondral erosions, peri-articular osteoporosis and more generalised bone loss. Bony erosions occur in up to 80% of RA patients within the first year. [8] Damage to bone is mediated by osteoclasts, which are up-regulated by several pathways. The cytokines receptor activator of NF-KB ligand (RANKL) and macrophage colony stimulating factor (M-CSF) promote the invasion of bone by osteoclasts. [1,8] Osteoclasts dissolve and destroy mineralised cartilage and subchondral bone. Some "mechanically vulnerable" sites are predisposed to erosions, primarily the second and third metacarpal heads. Minimal repair of erosions occurs in RA, in contrast with other inflammatory arthropathies. [8]

It has been established that increased osteoclast activity occurs secondary to T-lymphocyte activation and pro-inflammatory cytokines, but it has now been recognised that antibodies to citrullinated peptides can induce the differentiation of mononuclear cells to osteoclasts in vitro, directly implicating B-lymphocytes in bone loss. This is in keeping with the finding that ACPA positive RA is associated with more severe bony remodelling when compared to seronegative controls. [11]

It is clear that B-lymphocytes are pathogenic in RA, but evidence is emerging that certain subsets of B-lymphocytes may actually be protective. B-lymphocytes which produce IL-10

may down-regulate autoimmunity by several mechanisms. Depletion of this distinctive subset of cells may be deleterious rather than therapeutic. [12]

Other mechanisms

Macrophages cause inflammation via cytokines, reactive oxygen intermediates, nitrogen intermediates, prostanoids and matrix degrading enzymes, phagocytosis and antigen presentation. Macrophages are activated by toll-like receptors (TLR) and by NOD-like receptors (NODLR). These receptors recognise pathogen associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs) from diverse ligands. [5]

Local tissue response and the synovium itself are, necessarily, important in the pathogenesis of RA. The normal synovium has resident macrophages and fibroblast-like synoviocytes (FLS). In RA, the synovium becomes hyperplastic and FLS behave semi-autonomously. [8] These abnormal cells adopt an aggressive inflammatory and invasive phenotype to form the pannus, the abnormal rheumatoid synovium which invades and destroys the cartilage adjacent to the joint. [8] Fibroblast like synoviocytes in RA also express matrix metalloproteinases (MMP), which are collagenolytic, as well as cytokines which activate osteoclasts. [8,13]

Cartilage destruction is mediated by the binding and invasion of FLS, which secrete MMP 1, 3, 8, 14 and 16 which break down type II collagen network and result in mechanical dysfunction. Cartilage has limited potential for repair even in the absence of disease. In RA chondrocytes undergo apoptosis due to the influence of the cytokines, further inhibiting repair mechanisms. [8] Bone erosion and remodelling has already been discussed.

Clinical manifestations and extra-articular features

Typically, patients with RA present with an insidious onset of swollen and painful joints, which may be accompanied by prolonged early morning stiffness (of more than 30 minutes duration). The small joints of the hands are almost always affected but larger joints may also be involved. Joint involvement is typically symmetrical, and usually affects more than 3 joints. [2] Further investigation reveals elevated inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). [2,14] The early clinical picture is not specific, but it is important to identify disease before the more typical features of advanced disease develop, namely mechanical joint dysfunction and deformity. [1,14]

Extra-articular features of RA occur in up to 40% percent of patients with RA but are usually associated with a longer duration of disease. [2,15] Subcutaneous rheumatoid nodules are the most common and occur in up to a third of patients. [16] Nodules classically occur on extensor surfaces and are usually painless but may ulcerate, especially at pressure points. Extra-cutaneous nodules may occasionally be found on the lungs or heart. Nodulosis is associated with antibody positive RA and is very rare in seronegative RA. [15] Nodulosis is also associated with smoking. [2,15] Episcleritis occurs in around 1% of RA patients and is usually mild and self-limiting. Scleritis is more aggressive, is acutely painful and may be complicated by corneal ulcerations. [15] Vasculitis may be cutaneous or systemic. Cutaneous vasculitic manifestations include splinter haemorrhages, digital and periungual infarcts, leg ulcers and pyoderma gangrenosum. Systemic vasculitis may affect multiple organ systems including the kidneys, lungs, mesentery and peripheral nerves. [15] Rheumatoid interstitial lung disease is characterised by diffuse interstitial pulmonary fibrosis. Pleural effusions may also occur. Cardiac manifestations of RA comprise pericarditis, myocarditis and accelerated atherosclerosis. The presence of rheumatoid nodules on or adjacent to cardiac valves may cause valvular heart disease. [15] A normocytic normochromic anaemia is common, but

thrombocytosis or, less commonly, thrombocytopenia may also occur. [2,15] The importance of extra-articular manifestations of RA is their prognostic value, as they predict more severe disease. [15,16]

Diagnosis

The American College of Rheumatology (ACR) classification criteria for RA were updated in 2010 to reflect the need for earlier diagnosis of RA, as shown in Table 1. [14] Prompt diagnosis is imperative for early initiation of disease modifying anti-rheumatic drugs (DMARDs) to prevent disease progression and disability. Patients fulfilling these criteria are further classified according to the distribution of synovitis, duration of symptoms, serological markers, and acute phase reactants. Radiographs are not required. A score of ≥ 6 points is required to classify definite RA. [14]

Table 1: American College of Rheumatology classification criteria for rheumatoid arthritis

Joint involvement	
1 large joint	0
2 to 10 large joints	1
1 to 3 small joints	2
4 to 10 small joints	3
> 10 joints (at least 1 small joint)	5
Serology (at least 1 test result is needed)	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA (>3 times upper limit of normal)	3
Acute phase reactants (at least 1 test result is needed)	
Normal ESR and normal CRP	0
Abnormal ESR or abnormal CRP	1
Duration of symptoms (reported by patient)	
< 6 weeks	0
≥ 6 weeks	1

Assessment of functional disability

The Health Assessment Questionnaire Disability Index (HAQ-DI) is a patient-reported assessment tool which documents the patient's experience of their arthritis in activities of daily living, work and exercise. [17] The functional status and level of disability is extrapolated from the patient's responses and a score of 0 to 3 is allocated. Higher scores indicate more disability. In early RA, the HAQ-DI score correlates well with disease activity. [18] This correlation lessens with established RA due to the progressive decline in functional status arising from permanent structural damage to joints. [18,19]

The minimal clinically important difference (MCID) describes the concept of the smallest change in an outcome that translates as meaningful improvement (or deterioration) to the patient. The accepted MCID value for HAQ-DI is 0.22 to 0.25 but this applies to both meaningful deterioration and improvement. It has been suggested that the value for minimal clinically important improvement (MCII) may be greater, requiring an improvement in the HAQ-DI score of 0.375. [20]

Assessment of disease activity

Disease activity in RA is not accurately represented by any variable alone. Several composite scoring systems exist to monitor disease activity, encompassing both clinical and laboratory findings. Continuous standardised assessment allows prompt and appropriate escalation of therapy to achieve remission, and algorithms to assess response to therapy have also been developed. [18]

The Simplified Disease Activity Index (SDAI) is a validated instrument for measuring disease activity in RA. [18] The SDAI incorporates individual scores for the patient's global assessment (PGA), the physician's global assessment (PhGA), a 28-joint count for tender and

swollen joints and the CRP measurement. The total score is the sum of these individual scores, so the calculation is easy to perform, making SDAI a practical bedside tool. [18] The SDAI score stratifies patients into remission (SDAI ≤ 3.3), low disease activity (SDAI ≤ 11), moderate disease activity (SDAI > 11 and ≤ 26), and high disease activity (SDAI > 26). [18,19]

The modified Disease Activity Score (DAS28) is an index which also incorporates 28-joint counts of swollen and tender joints. The DAS28 was developed from the Disease Activity Score (DAS) which used 44 joints. Reducing the joint count has given DAS28 greater utility even outside the formal research setting, and without sacrificing its validity. The DAS28 correlates well with the original DAS index and with measures of disability and functional status. The PGA, and ESR, or CRP, are also incorporated. The DAS28 calculation returns a value along a continuous scale from 0 to 9.4, dividing disease activity into low (DAS28 ≤ 3.2), moderate (DAS28 > 3.2 but ≤ 5.1), or high (DAS28 > 5.1). [21]

The DAS28-ESR (3) is a modification of DAS28 which incorporates the tender and swollen joint counts and the ESR value but omits the PGA. [21]

Assessment of therapeutic response

Changes in DAS28 values over time may be used to determine the response to therapy. The European League Against Rheumatism (EULAR) developed response criteria which are calculated using the level of disease activity at the time of calculation in conjunction with the change in disease activity over the period of assessment, or since initiating therapy. A patient must therefore show a significant change in disease activity while also achieving disease activity below defined endpoints to be termed a "responder". Response criteria are divided into good, moderate, and no response (see table 2). The EULAR response criteria have been

validated in large clinical trials and correlate well with measures of functional class and radiological progression of joint damage. [21]

Table 2: EULAR response criteria

Improvement in DAS28 →	> 1.2	> 0.6 and ≤ 1.2	≤ 0.6
Present DAS28 ↓			
≤ 3.2	Good response	Moderate response	No response
>3.2 and ≤ 5.1	Moderate response	Moderate response	No response
>5.1	Moderate response	No response	No response

Treatment of rheumatoid arthritis

Specific treatments for RA include synthetic and biologic DMARDs. Commonly used synthetic DMARDs include methotrexate (MTX), leflunomide (LEF), chloroquine (CHQ) and sulphasalazine (SZP). [2,19] Methotrexate is the most commonly used DMARD. [2] Patients who do not respond to MTX monotherapy should be managed with combination therapy, commonly MTX, CHQ and SZP or MTX and LEF [19] Biologic agents are proteins which target specific cell receptors or cytokines. Examples of biologic DMARDs include anti-tumour necrosis factor (anti-TNF) and non-anti-TNF drugs such as abatacept and rituximab, respectively. [19]

The early initiation of DMARD therapy is vital to avert irreversible joint destruction and the associated morbidity. The goal of therapy is to achieve remission within 6 months by reviewing patients frequently and escalating treatment at each visit if low disease activity or remission has not been achieved. [19] Targeting therapy to achieve low disease activity or remission early results in improved patient outcomes with better functional status. The benefits of targeted therapy have been shown by the large-scale trials TICORA, DREAM and ESPOIR. [22,23]

Around two thirds of patients will achieve low disease activity or remission with synthetic DMARD therapy when a protocolised tight control strategy is applied. [24] Biologic therapy is usually reserved for a select group of patients with RA which is refractory to synthetic DMARDs. [19]

In a South African study by Hodgkinson et al in 2015 [24], the factors that predicted a good response to traditional DMARD therapy included lower HAQ-DI scores at baseline and a shorter duration of symptoms. [24]

The South African Rheumatism and Arthritis Association (SARAA) has formulated guidelines for an effective treatment strategy of RA in South Africa. [19] Within these guidelines, therapy with a biologic agent is indicated if there is an inadequate clinical response to at least 3 synthetic DMARDs for a period of at least 6 months, including MTX if not contraindicated. Biologic therapy may also be indicated in those patients with high disease activity (SDAI > 26) or moderate disease activity (SDAI > 11 and ≤ 26) combined with features associated with a poorer prognosis, namely extra-articular features, seropositive disease, presence of erosions on radiographs within two years of onset of RA, and functional disability. [19] According to the current South African guidelines, the choice of biologic DMARD should be guided by the patient's risk factors for adverse events, including tuberculosis. [19]

Rituximab in rheumatoid arthritis

Mechanism of action

Rituximab is a chimeric monoclonal antibody originally developed for use in non-Hodgkin's lymphoma and is directed against B-lymphocytes expressing the CD20 surface marker. Rituximab depletes B-lymphocytes and precursor cells in various stages of maturity, from

early pre-B-cell to memory B-lymphocyte. [25] Terminally differentiated B-lymphocytes not expressing CD20 are spared; stem cells and pro-B-cells are also not affected. B-lymphocytes vulnerable to rituximab are almost completely (though transiently) depleted in peripheral blood. [25] Partial depletion occurs in the bone marrow and synovial tissue. [26] Regeneration of the B-lymphocyte population occurs within 6 to 9 months and is dependent on the bone marrow's regenerative capacity. [25]

Efficacy

A small open study conducted in 1998 was the first trial to demonstrate the efficacy of rituximab mediated B-lymphocyte depletion in RA. [27]

Subsequently, numerous large scale clinical trials have demonstrated the efficacy of rituximab in the treatment of RA. [25] The DANCER trial compared rituximab at two different doses (500mg and 1000mg) to MTX plus placebo in patients with RA refractory to synthetic DMARDs. The trial found that significantly more patients achieved a moderate or good response in the rituximab groups than in the MTX and placebo group. [28] The REFLEX study tested rituximab plus MTX in patients with RA which was refractory to at least one anti-TNF biologic agent and found significantly less radiological disease progression in patients treated with rituximab. [29]

In an attempt to reflect daily practice, a trial by Assous et al [30] enrolled patients who were older, had a longer duration of disease and had received a greater number of synthetic DMARDs. A EULAR response (good or moderate) was achieved in 82% percent of the cohort. Retreatment with rituximab was required in about a third of patients at 6 months. Another daily practice study conducted by McGonagle et al [31] showed a similar EULAR response rate of 88% percent at 3 months after rituximab. The response rate declined to 76% by 6 months.

Rituximab also improves functional disability in RA. A subsequent analysis of the DANCER trial cohort in 2008 showed significant improvements in functional outcomes for patients receiving rituximab at either dose. Functional status was measured by HAQ-DI and other patient reported functional indices. More than 60% of patients exceeded the MCID of 0.22 in both the 500mg and 1000mg dose groups. [32]

Most studies have been conducted in primarily Caucasian populations in developed countries. Little data exists regarding rituximab use in Sub-Saharan African populations. A longitudinal study of 41 patients in Kenya showed that rituximab resulted in improvement of disease activity and functional status in patients with RA refractory to synthetic DMARDs. The SDAI was used to measure disease activity. Patients who had moderate (SDAI > 11 and ≤ 26) or high (SDAI > 26) disease activity after a 6-month trial of synthetic DMARDs were enrolled in the study and received rituximab. Most patients received only one synthetic DMARD, which was MTX in the majority of cases. Most patients in the cohort had been diagnosed with RA 5 to 10 years prior to participating in the study. Patients were followed up at 3 and 6 months after receiving rituximab. A decrease in SDAI was documented in around one third of patients at 3 months and around half the patients at 6 months. Functional disability was assessed with HAQ-DI and 95% of the cohort demonstrated an improvement in HAQ-DI when assessed 6 months after rituximab. [33]

Predictors of response

Predictors of response to rituximab therapy in RA include seropositive disease, prior treatment with fewer DMARDs, elevated CRP level at baseline, complete B-lymphocyte depletion, and genetic factors, but research in this arena has yielded heterogeneous results. [25,34]

A study conducted by Couderc et al [34] found that ACPA positive RA patients displayed a significantly better response to rituximab while those with higher immunoglobulin levels had a poorer response, the effect of RF positivity was less pronounced in this cohort. In contrast, Quartuccio and colleagues reported RF positivity to be a greater predictor of response than ACPA positivity. Furthermore, lower HAQ-DI scores also predicted a good response to rituximab. [35]

Registry data from the British Society for Rheumatology Biologics Register showed RF positivity and higher DAS28 scores to be associated with a better response to rituximab. [36]

Pre-treatment screening and administration

Biologic DMARDs increase the risk of infections. Pre-treatment screening for latent tuberculosis, hepatitis B and human immunodeficiency virus (HIV) infection is recommended prior to initiation of rituximab. A chest radiograph and tuberculin skin test (purified protein derivative (PPD) test) is used for tuberculosis screening. Patients with a positive skin test require isoniazid (INH) prophylaxis for 9 months. Rituximab may be given after one month of chemoprophylaxis has been completed. [19] Chemoprophylaxis should be considered in patients at high risk of contracting tuberculosis (healthcare workers, institutionalised individuals, patients with a previous history of tuberculosis), even if the skin test is negative. [19] The use of biologic agents in patients who are HIV positive or who have active hepatitis B infection is not currently recommended. [19,37]

Administration of pneumococcal, influenza and hepatitis B (if not immune) vaccination is recommended at least 4 weeks prior to commencing rituximab. The use of any live vaccines is not recommended. [19,37]

Immunoglobulin levels should be determined before initiating rituximab. [37] Hypogammaglobulinaemia increases the risk of serious infections following the administration of rituximab. [37,38]

The safety of rituximab in pregnancy has not been established. Rituximab should be avoided in pregnancy unless the benefits of its use significantly outweigh the potential risk of foetal harm. Female patients in their childbearing years require effective contraception during therapy and for up to a year after the last dose of rituximab. [37]

Rituximab is given as slow intravenous infusion and should be administered in a setting where patients can be closely monitored, and resuscitation facilities are available, under the supervision of an experienced healthcare provider. Premedication with an antihistamine (e.g. promethazine) and an antipyretic (e.g. paracetamol) is mandatory prior to each rituximab infusion. Premedication with glucocorticoids may also be used. [37]

Dose and treatment intervals

Rituximab has been studied at two different doses, 500mg and 1000mg. The dosage recommended in the manufacturer package insert is 1000mg per infusion, administered as a series of two infusions, two weeks apart (i.e. on day 1 and day 15). [37] The SERENE study compared patients receiving MTX plus two doses of either 500mg or 1000mg of rituximab to patients receiving MTX and placebo. [39] Clinical and functional outcome (measured by EULAR response and MCID) at 6 months was comparable between the two groups who received rituximab, and significantly superior to the MTX plus placebo group. Almost all the patients randomised to rituximab received a second course of rituximab after the initial course and were reassessed at 12 months. Both groups demonstrated a sustained good clinical and functional outcome. [39] The IMAGE study also compared groups receiving two doses of 500mg or two doses of 1000mg and reported similar clinical efficacy in both groups.

[38] This suggests that two doses of 500mg may be equivalent to a 1000mg dose, but more research is needed in this area.

The ideal interval for retreatment with rituximab has not been determined and there are several approaches: retreatment at strict time intervals (e.g. 6-monthly), retreatment on flare, and a treatment-to-target strategy using predefined disease activity endpoints measured by SDAI or DAS28 scores. [25,38] Retreatment has been given as early as 4 months when this strategy is applied. [38] Current South African guidelines do not recommend giving rituximab more frequently than 6-monthly [19]

Monitoring of B-lymphocyte depletion and repopulation has been proposed as a method of predicting clinical relapse and one trial showed that B-lymphocyte repopulation preceded clinical relapse of disease by up to four months. This may prove to be a useful tool in monitoring therapy and determining the ideal time for retreatment. [26]

Adverse events and safety

Rituximab is generally well tolerated and has an established safety database largely derived from its use in the treatment of lymphomas. A pooled case analysis of 3194 RA patients examined the safety profile of rituximab. [40] Infusion reactions are the most common adverse event, occurring in up to a quarter of patients. [40,41] These reactions occur most commonly during the first infusion and are usually mild or moderate in severity, but rarely may be life-threatening with severe bronchospasm, hypoxia, lung infiltrates, angioedema and hypotension. Infusion reactions can be attenuated by the use of premedication with antipyretics and antihistamines. It is also recommended to omit antihypertensive medications for 12 hours preceding rituximab infusion. [37]

Other adverse events have been described, including hypersensitivity reactions, severe skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis, and neutropenia.

Rituximab monotherapy is not myelosuppressive but monitoring of blood counts may be indicated in those patients with pre-existing cytopenias or those receiving other agents which may cause myelosuppression. [37]

Infectious complications are a significant concern with rituximab due to extensive and prolonged B-lymphocyte depletion. The pooled case analysis mentioned above reported that the rate of serious infections with rituximab was comparable to that in patients treated with methotrexate and serious opportunistic infections were rare. Two cases of pulmonary tuberculosis were reported, as well as a single case of progressive multifocal leukoencephalopathy (PML). [40] There were no reported cases of hepatitis B reactivation in this analysis, but this has been described and may result in fulminant hepatitis. Pre-treatment screening for hepatitis B is therefore recommended. [40,37] There was no significant increase in malignancy or cardiovascular disease noted in the analysis. [40]

A case report from Turkey demonstrated the safe use of rituximab in two patients with proven active tuberculosis and concomitant RA. One of the patients had developed reactivation tuberculosis during prior treatment with an anti-TNF agent. Both patients completed a full course (6 months or more) of anti-tuberculous therapy and were subsequently monitored for 3 years; both achieved remission of RA and had no reactivation of their tuberculosis. [42] A systematic review by Cantini examined the use of rituximab in both those countries that have a high burden of tuberculosis as well as those with a low burden and found that the overall risk of reactivation of latent tuberculosis was negligible. This is likely due to the B-lymphocyte mediated action of rituximab which does not affect the immune pathways involved in the control of latent tuberculosis. [43]

Economic considerations

The direct costs involved in treating RA are substantial, and significantly increased by the use of biologic DMARDs, but these costs must be weighed against the indirect costs of poorly controlled and disabling disease. These indirect costs include loss of income and the need for a disability pension, the need for care or assistance at home, and an overall reduction in quality of life. [19] An economic analysis based on the ESPOIR cohort by Chevreul et al [44] compared patients who had received a biologic within the first year of treatment to those who received a biologic later. The analysis was completed over 4 years and determined that the patient group who received a biologic in the first year of treatment had fewer RA associated disabilities, was less likely to require assistance at home, and incurred less medical expenditure not related to direct therapy of RA. Direct costs of treating RA were higher in this group, however this initial cost may become less significant over a longer period of follow-up. [44] Another trial by Betts et al [45] evaluated the costs incurred by patients exposed to multiple synthetic DMARDs prior to treatment with a biologic agent. Patients who had been treated with 3 or more DMARDs had greater all-cause health care costs, highlighting the need for timely escalation of therapy and appropriate initiation of biologic agents. [45]

In South Africa, biologic use in RA is largely restricted to the private sector due to its high cost, discriminating against the majority of the population. Evidence that use of biologic agents like rituximab is both efficacious and cost-effective may help improve access to therapy.

The role of our study

There is increasing evidence that RA in African populations is frequently severe and associated with a high level of functional disability. [46] There is an unmet need to identify

and treat patients who have failed traditional DMARDs and who would benefit from initiation of biologic therapy early in the course of the disease. Furthermore, there is a high burden of tuberculosis in Southern Africa and the risk of primary infection or reactivation of latent tuberculous disease is increased with the use of any immunosuppressants, including methotrexate and glucocorticoids. [19] The risk is markedly increased with the anti-TNF drugs and disseminated and extrapulmonary disease is not uncommon. The risk of tuberculosis may be lower with rituximab making it a safer choice for the treatment of refractory RA patients in areas with a high prevalence of tuberculosis. [41,42] It is therefore of interest to study the profile of RA patients that are refractory to conventional synthetic DMARD therapy and to determine the outcome of rituximab treatment in these patients.

Aim

To describe our experience of rituximab use in patients with RA which is refractory to synthetic DMARDs.

Objectives

To determine the response to rituximab therapy in refractory RA patients by measuring changes in disease activity and functional status from initiation of therapy to 3 and 6 months after therapy.

To describe the baseline predictors of response to rituximab therapy at 3 and 6 months after initiation of rituximab.

To determine the short-term adverse events documented from the initiation of rituximab therapy to 6 months after therapy, including reactivation of tuberculosis.

Methods

1. Study setting and design
A single centre retrospective study of adult patients with RA receiving treatment with rituximab at the Rheumatology Clinic, Chris Hani Baragwanath Academic Hospital (CHBAH), during the period 1 January 2012 to 30 September 2016.

2. Sample population
The study population is estimated to be approximately 70 patients, with the following inclusion and exclusion criteria:

3. Inclusion criteria

- Age 18 years or older
- Fulfil the American College of Rheumatology 2010 classification criteria for RA (Appendix A)
- RA which is refractory to at least 3 synthetic DMARDs (i.e. have not achieved remission or low disease activity)
- No prior treatment with a biologic DMARD
- Completed 6 months of follow-up after initiation of rituximab therapy

4. Exclusion criteria
Incomplete medical records

5. Measurement of disease activity
Disease activity will be assessed by the SDAI score and DAS28-ESR (3)

SDAI: (Appendix B)

- Remission: SDAI $\leq$ 3.3
- Low disease activity (LDA): SDAI $\leq$ 11
- Moderate disease activity (MDA): SDAI >11 and $\leq$ 26
- High disease activity (HDA): SDAI >26

DAS28-ESR (3) (Appendix C)

- Remission: DAS28-ESR (3) < 2.6
- Low disease activity (LDA): DAS28-ESR (3) ≤ 3.2
- Moderate disease activity (MDA): DAS28-ESR (3) > 3.2 and ≤ 5.1
- High disease activity (HDA): DAS28-ESR (3) > 5.1

6. Measurement of functional status
Functional status will be assessed by the HAQ-DI (Appendix D).

Score = 0 (no disability) to 3 (severe disability)

7. Refractory rheumatoid arthritis
For our study, refractory RA will be defined as an inadequate response to 3 or more synthetic DMARDs for 6 months.

8. Response to rituximab
Response to rituximab treatment will be assessed by: EULAR response criteria (Appendix E) and changes in functional status (HAQ-DI score) from baseline (defined as the time of initiation of rituximab) to 3 and 6 months after rituximab therapy was initiated. Minimal clinically important improvement (MCII) in HAQ-DI will be taken as a change of 0.22.

9. Adverse events
Adverse events occurring within 6 months of initiation of rituximab therapy will be documented. Potential early adverse events include infusion reactions and infections.

Data collection

Data will be collected from clinical records from 1 January 2012 to 30 September 2016. A data collection sheet will be used (Appendix F).

Data extracted from clinical records prior to rituximab

- Demographics: age, sex, ethnicity

- Date of onset of symptoms of RA and date of diagnosis
- Smoking history
- Clinical features: tender joint count (TJC) and swollen joint count (SJC), patient global assessment (PGA) and physician global assessment (PhGA)
- Presence of extra-articular features: nodulosis, scleritis, vasculitis, interstitial lung disease
- SDAI, DAS28-ESR (3) and HAQ-DI scores
- Laboratory investigations, including: CRP, ESR, haemoglobin (Hb), albumin, immunoglobulins (IGs), RF and ACPA
- Results of screening for latent TB infection (chest radiograph and PPD skin test)
- Treatment history, including previous DMARD therapy and use of corticosteroids
- Rituximab dose received
- Adverse events at initiation of Rituximab therapy

Data collected at 3 and 6 months after initiation of rituximab

- SDAI and HAQ-DI scores
- Laboratory investigations: CRP, ESR and IGs
- Maintenance treatment regimen: DMARDs and use of corticosteroids
- Adverse events during the 6 months following rituximab therapy

Data analysis

Data will be entered into a database using Microsoft Excel and analysed by a statistical software package. Appropriate descriptive analyses will be performed on demographic, clinical, and laboratory characteristics. Continuous data will be expressed as means (+/- standard deviation) or medians (interquartile range). Categorical data will be expressed as

percentages. Comparisons between groups will be made using the Chi-squared test or Fisher's exact test for qualitative data, and the two-tailed unpaired Student's t-test for quantitative data.

Ethics

Approval for the project will be sought from the Human Research Ethics Committee of the University of the Witwatersrand. Written approval to conduct the project at CHBAH will be obtained from the Medical Advisory Committee, the hospital superintendent as well as the head of the department of Internal Medicine.

Study numbers will be used to protect the identity of participants and no personal identifying characteristics (name, hospital or identity number, or date of birth) will be included on the data sheet. Data sheets and electronic data captured from patient records will be stored securely.

The research will be conducted in accordance with the principles contained in the Declaration of Helsinki.

Timing

	Aug/ Sep '16	Oct/ Nov '16	Dec/ Jan '16/' 17	Feb/ Mar '17	Apr/ May '17	Jun /Jul '17	Aug/ Sep '17	Oct/ Nov '17	Dec/ Jan '17/' 18	Feb/ Mar '18	Apr/ May ‘18	Jun/ Jul ‘18
Writing protocol												
Protocol assessment												

Ethics application												
Data collection												
Data analysis												
Write up												

Funding

The project will be self-funded.

Limitations

Single centred study with a relatively small sample population.

Retrospective study reliant on information obtained from clinical records, which may be incomplete.

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CHAPTER 2: SUBMISSABLE ARTICLE

Title: Rituximab in the treatment of refractory rheumatoid arthritis in a tertiary academic hospital

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Short title: Rituximab in refractory rheumatoid arthritis

Conflict of interest: None

Keywords: Rheumatoid arthritis, rituximab, sub-Saharan Africa

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Abstract

Background

Significant disability results from Rheumatoid arthritis (RA) when treatment is delayed or inadequate. Rituximab is approved for use in RA in South Africa, but there is a paucity of data on its use in Sub-Saharan African populations.

Objectives

To determine the response to rituximab in refractory RA patients by measuring disease activity and functional status over a 6-month period. To describe predictors of response to rituximab, and to document short term adverse events.

Methods

A single centre retrospective study of adult patients with RA receiving treatment with rituximab at Chris Hani Baragwanath Academic Hospital, between January 2012 and September 2016. Demographics, clinical and laboratory data were collected. The European League Against Rheumatism (EULAR) response criteria and minimal clinically important improvement (MCII) in HAQ-DI were applied as outcome measures. Baseline characteristics of responders to rituximab therapy were compared with those of non-responders.

Results

Of the 53 patients with RA refractory to at least 3 synthetic disease modifying anti-rheumatic drugs (DMARDs), 75.5% were African and 88.7% were female. At initiation of rituximab the mean age (SD) was 50.8 (10.7) years and disease duration was 12.6 (6.6) years. Over 90% of patients were rheumatoid factor and anti-cyclic citrullinated peptide antibody positive, 41.5% had extra-articular features and the majority (69.8%) had high disease activity by the simplified disease activity index. The baseline mean (SD) HAQ-DI was 2.3

(0.6). At 3 months, 81.1% of patients achieved a good or moderate EULAR response. Predictors of response to rituximab included higher tender joint counts (p=0.0473) and higher SDAI scores (p=0.0467). A clinically meaningful decrease in HAQ-DI scores was observed in 44 (83%) of patients. Improvements were not sustained at 6 months, although clinical parameters were still better than at initiation. No early adverse events were recorded.

Conclusion

Rituximab therapy was safe and effective in controlling disease activity in addition to improving functional disability in this cohort of predominantly African patients with severe established RA. The findings underscore the need to identify appropriate patients for predictable responses to biologic therapies in prospective longitudinal studies in southern Africa.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease which results in significant morbidity. Inadequately treated disease results in permanent deformities, disability, diminished quality of life, and premature mortality. [1,2] The economic burden of RA is substantial, due to the cost of managing the disease and because up to 40% of patients experience disability which affects their work. [3]

Universal aims in current RA management include early diagnosis and prompt initiation of disease modifying anti-rheumatic drugs (DMARDs) using a tight control strategy to rapidly achieve low disease activity (LDA) or remission, as outlined in the new European League Against Rheumatism (EULAR) recommendations for management of RA. Eliminating or reducing functional disability is an essential outcome measure in the treatment of RA. [4,5]

In black South African patients with RA, severe disease is not uncommon and functional outcomes are often poor, particularly in the public sector. [6] Socioeconomic factors and a lack of resources contribute to these findings.

Despite comprehensive guidelines for the treatment of RA, [5,7] the management of cases which are refractory to synthetic DMARDs may be more challenging in the developing world.

A significant development in the treatment of RA has been the use of biologic DMARDs, to control RA in those patients who have failed therapy with synthetic DMARDs. [7] Rituximab is a chimeric monoclonal antibody directed against B-lymphocytes expressing the CD20 surface marker. Rituximab has proven efficacy in the treatment of RA and it reduces functional disability [8]. Several authors have sought to delineate the clinical characteristics which might predict an improved response to rituximab in RA. [9,10] Some predictors of response to rituximab therapy in RA include seropositive disease, prior treatment with fewer

DMARDs, elevated C-reactive protein (CRP) level at baseline, complete B-lymphocyte depletion, and genetic factors, but research in this arena has yielded heterogeneous results. [8,9]

Few of these studies have been conducted in resource constrained settings or included African patients with RA. [11] The cost impact of biological agents is frequently prohibitive and selection of the most appropriate patients to receive rituximab may be an important facet of cost-effective use.

Rituximab causes prolonged B-cell and immunoglobulin depletion and may increase the risk for infections such as tuberculosis, though it confers a lower risk than anti-tumour necrosis factor drugs. [7,12] This aspect is particularly noteworthy in a cohort drawn from a population with a high burden of tuberculosis, such as in southern Africa.

We therefore undertook to measure the response to rituximab therapy in a cohort of predominantly African patients with RA refractory to synthetic DMARDs, and to delineate the factors which predict this response. The short-term safety of rituximab was also assessed. The study was approved by the Human Research Ethics Committee (Medical), University of the Witwatersrand (approval no. M161029).

Patients and methods

A single centre retrospective study of adult patients with RA with an inadequate response to synthetic DMARDs treated with rituximab at the Rheumatology clinic, Chris Hani Baragwanath Academic Hospital (CHBAH), from January 2012 to September 2016.

Patients were included if they met the 2010 ACR criteria, [4] were ≥ 18 years of age, and had demonstrated an inadequate therapeutic response (remission/LDA) to at least 3 synthetic

DMARDs, including methotrexate (MTX). Other DMARDs received included chloroquine (CHQ), sulphasalazine (SZP) and leflunomide (LEF). Patients included had also completed at least 6 months of documented follow-up at the hospital after receiving rituximab.

Screening for latent tuberculosis with a chest radiograph and purified protein derivative (PPD) skin test was also performed prior to receiving rituximab. All patients with a positive skin test received isoniazid prophylaxis for 9 months. Screening for hepatitis B and C and human immunedeficiency virus (HIV) was performed on all patients prior to administering rituximab.

Patient records at initiation of rituximab, and at clinic visits 3 and 6 months were examined. Demographics, smoking history and data on extra-articular manifestations were collected from records prior to initiation of rituximab. Disease duration was defined as the time from the onset of symptoms of RA to the time of receiving rituximab. Baseline was defined as the time of initiation of rituximab.

Clinical parameters for each visit were collected, including: tender and swollen joint counts (TJC and SJC), patient and physician global assessment scores (PGA and PhGA), and Health Assessment Questionnaire Disability Index (HAQ-DI) scores. Laboratory parameters, including rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA) positivity at baseline, and erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values at each visit were also collected. Immunoglobulin levels were collected, if available.

Disease activity was measured using the calculated Simplified Disease Activity Index (SDAI) and DAS28-ESR (3) scores. Functional status was measured by the HAQ-DI score. [13] The minimal clinically important improvement (MCII) in HAQ-DI was taken as 0.22. [14]

Patients received 2 infusions of rituximab (either 500mg or 1000mg) on day 1 and day 15.

The EULAR response criteria [15] were used to stratify patients into groups of 'responders' (good or moderate response) and 'non-responders'. The degree of response was determined 3 months following initiation of rituximab. Patients were also stratified according to improvement in functional disability and whether the MCII in HAQ-DI was achieved or not.

Statistical analysis

Statistical analysis was performed using GraphPad InStat 3 software. Continuous variables were expressed as the mean +/- standard deviation and categorical variables were expressed as percentages. Univariate analysis was applied to determine the relationship between patient characteristics and EULAR response at 3 months. Categorical variables were analysed with Fisher's exact test or a chi-squared test. The Student's t-test or Mann-Whitney test was applied for quantitative variables. Paired values were compared with the Wilcoxon signed-rank test. A p-value of ≤ 0.05 was taken as significant.

Results

Patient characteristics at initiation of rituximab

Of the 68 RA patients who received rituximab, 15 were excluded as they did not meet the inclusion criteria. The baseline patient characteristics are shown in Table 1. A total of 53 patients were included in the cohort, the majority were African (75.5%) females (88.7%). Most of the cohort had established disease with a mean (SD) disease duration of 12.6 (6.6) years. The mean lag time from a confirmed diagnosis of RA to receiving rituximab was 8.5 years.

Over 90% of the cohort were RF or ACPA positive. Extra-articular features of RA were present in 41.5% of patients, most commonly nodulosis (26.4%).

All patients had refractory RA prior to the initiation of rituximab (64.2% had received 4 DMARDs and the remainder had received 3 DMARDs). Three quarters of the patients were on oral corticosteroid therapy at the time of initiating rituximab, at doses ranging from 2.5mg to 7.5mg per day. Only 4 patients (7.5%) had a history of previous tuberculosis but 13 (24.5%) had positive PPD skin tests, all 13 patients received INH prophylaxis. All patients tested negative for hepatitis B and C and HIV.

Table 2 represents the baseline clinical and laboratory characteristics. The majority (69.8%) of patients had high disease activity (SDAI>26), the remainder had moderate disease activity (SDAI>11 and ≤26). Patients also had severe functional disability with a mean (SD) HAQ-DI score of 2.3 (0.6).

Most patients (86.8%) received rituximab 500mg, two doses two weeks apart. The remainder received 2 doses of 1000mg. The majority (83.0%) of patients were given MTX as maintenance therapy following rituximab. No adverse events were documented for any patient in the 6 months following rituximab infusion.

Table 1. Baseline characteristics of patients receiving rituximab	
	RA patients (n=53)
Age, in years:	50.8 (10.7)
Women, n (%)	47 (88.7)
African, n (%)	40 (75.5)
Smokers, n (%)	11 (20.8)
Disease duration, in years	12.6 (6.6)
RF positive, n (%)	48 (90.6)
ACPA positive, n (%)	49 (92.5)
Extra-articular features, n (%)	22 (41.5)
Nodulosis, n (%)	14 (26.4)
Vasculitis, n (%)	2 (3.8)
Interstitial lung disease, n (%)	2 (3.8)
Scleritis, n (%)	4 (7.6)
Received 3 DMARDs, n (%)	19 (35.9)
Received 4 or more DMARDs, n (%)	34 (64.2)
Received corticosteroids, n (%)	39 (73.6)
Previous PTB, n (%)	4 (7.5)
PPD positive, n (%)	13 (24.5)
Received INH, n (%)	13 (24.5)
Rituximab 500mg, n (%)	46 (86.8)
Rituximab 1000mg, n (%)	7 (13.2)
All values are mean (SD) unless otherwise stated **RA = rheumatoid arthritis; RF = rheumatoid factor; ACPA = anti-citrullinated peptide antibody; DMARD = disease modifying anti-rheumatic drug; PTB = pulmonary tuberculosis; PPD = purified protein derivative (tuberculin skin test), INH = isoniazid.**	

Clinical and laboratory characteristics at follow-up

The clinical and laboratory characteristics of patients at baseline and at 3- and 6-month follow-up visits are shown in Table 2 and depicted in Figure 1.

At 3 months after rituximab all clinical parameters (TJC, SJC, PGA, PhGA) had declined significantly (p=<0.005). A 25.2% and 51.4% reduction was noted for ESR and CRP, respectively. Remission or LDA was achieved by 45.3% of patients and 81.1% achieved a good or moderate response by EULAR response criteria. Marked improvement was also evident on functional assessment with a decline in mean (SD) HAQ-DI from 2.3 (0.6) at baseline to 1.3 (0.4) at 3 months (p=<0.005).

These improvements were however not sustained at 6 months after rituximab. Clinical measures of disease activity and inflammatory markers increased, though not as high as prior

to initiation of rituximab. Improvement in HAQ-DI scores was the most durable, with a mean (SD) HAQ-DI of 1.6 (0.9) at 6 months.

Table 2. Clinical and laboratory characteristics at initiation of rituximab (baseline) and at 3 and 6 months after rituximab

	Baseline	3 months	6 months
TJC	9.0 (5.4)	2.8 (3.1)	4.8 (4.5)
SJC	9.0 (4.9)	3.3 (3.6)	4.0 (3.7)
PGA	6.9 (2.3)	3.6 (2.4)	4.4 (2.6)
PhGA	7.4 (2.0)	3.4 (2.5)	4.3 (2.6)
ESR in mm/hour	42.1 (29.0)	27.3 (21.8)	29.4 (23.8)
CRP in mg/litre	24.5 (19.5)	11.9 (11.6)	14.4 (13.7)
SDAI	34.4 (12.9)	14.2 (9.5)	18.9 (12.1)
DAS28-ESR (3)	5.4 (0.9)	3.7 (1.1)	4.2 (1.1)
HAQ-DI	2.3 (0.6)	1.3 (0.4)	1.6 (0.9)

All values are mean (SD) unless otherwise stated
Wilcoxon signed-rank test for trend $p < 0.005$
TJC = tender joint count; SJC = swollen joint count; PGA = Patient Global Assessment; PhGA = Physician Global Assessment; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; SDAI = Simplified Disease Activity Index; DAS28-ESR(3) = Disease Activity Score in 28 joints using ESR (3 variable); HAQ-DI = Health Assessment Questionnaire Disability Index score

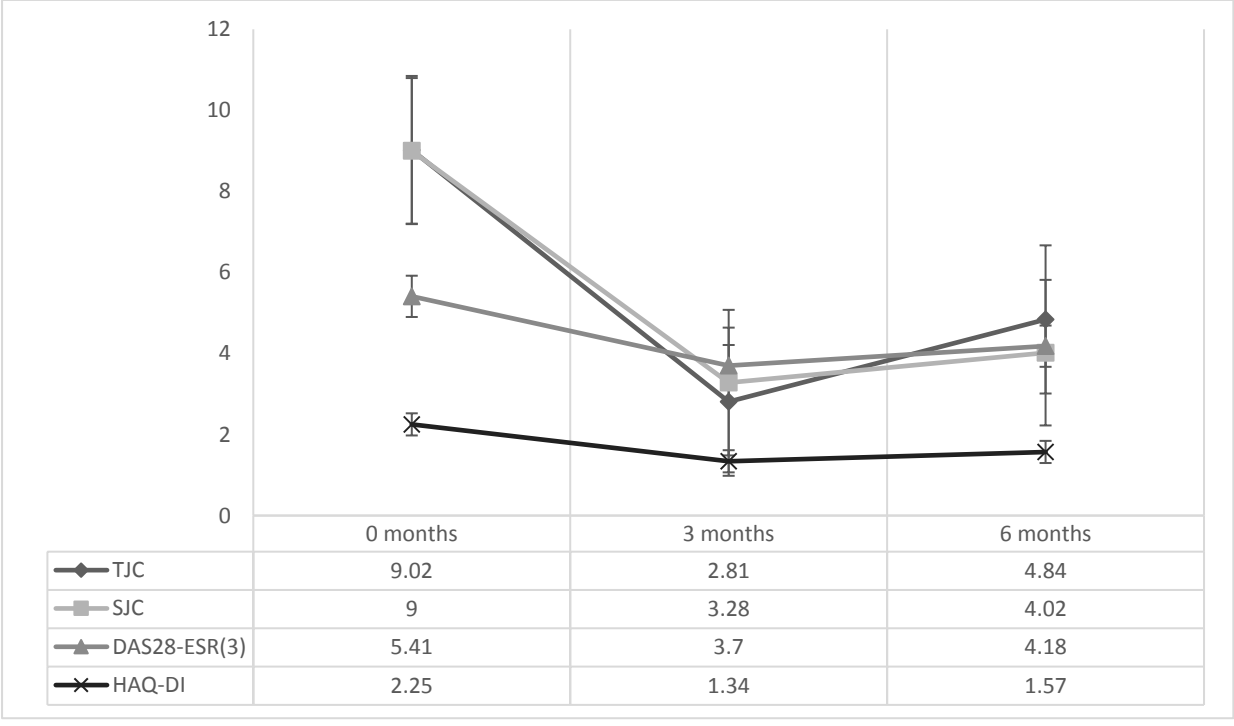


Figure 1. Clinical characteristics at initiation of rituximab (baseline) and at 3 and 6 months after rituximab

TJC = tender joint count; SJC = swollen joint count; DAS28-ESR (3) = Disease Activity Score in 28 joints using ESR (3 variable); HAQ-DI = Health Assessment Questionnaire Disability Index score

Patient characteristics according to EULAR response

Table 3. shows the characteristics of patients at the time of receiving rituximab according to EULAR response at 3 months. Non-responders were older (mean age 57.0 years) and had a longer disease duration (mean 15.9 years) than responders (mean age 49.4 years and disease duration 11.9 years), however these variables were not statistically significant. Responders had higher SDAI scores overall, with a mean (SD) SDAI of 35.3 (12.3) versus 28.3 (14.2) in non-responders (p=0.0467). This seemed to be primarily driven by higher TJC and PhGA scores in responders compared to non-responders (p=0.0473 and 0.0491, respectively). Gender status, a history of smoking, nodulosis, auto-antibody positivity, inflammatory markers and HAQ-DI scores did not differ significantly between the 2 groups. Although no patients in the non-responder group received a rituximab dose of 1000mg, this was not found to be significant as so few patients in the cohort received this higher dose.

Table 3. Baseline characteristics of patients according to EULAR response at 3 months after rituximab

	EULAR responders (n=43)	EULAR non-responders (n=10)	*p*
Age, in years	49.4 (11.0)	57.0 (6.7)	0.0562
Women, n (%)	37 (86.1)	10 (100)	0.5807
Smokers, n (%)	10 (23.3)	1 (10.0)	0.6671
Disease duration, in years	11.90 (6.6)	15.9 (6.0)	0.0781
Nodulosis, n (%)	10 (23.3)	4 (40.0)	0.4258
TJC	9.6 (5.2)	6.6 (5.5)	0.0473
SJC	9.4 (4.7)	7.2 (5.9)	0.1264
PGA	7.1 (2.2)	6.3 (2.7)	0.3328
PhGA	7.6 (1.9)	6.3 (2.1)	0.0491
SDAI	35.8 (12.3)	28.3 (14.2)	0.0467
DAS28-ESR (3)	5.5 (0.9)	5.0 (0.7)	0.0801
HAQ-DI	2.2 (0.7)	2.5 (0.4)	0.2875
ESR, in mm/hour	42.7 (29.0)	39.5 (30.0)	0.7564
CRP, in mg/litre	25.3 (20.7)	21.0 (13.4)	0.7587
RF positive, n (%)	40 (93.0)	8 (80.0)	0.2345
ACPA positive, n (%)	40 (93.0)	9 (90.0)	1.0000
Rituximab 1000mg, n (%)	7 (16.3)	0 (0.0)	0.3235

All values are mean (SD) unless otherwise stated
EULAR = European League Against Rheumatism; TJC = tender joint count; SJC = swollen joint count; PGA = Patient Global Assessment; PhGA = Physician Global Assessment; SDAI = Simplified Disease Activity Index; DAS28-ESR = Disease Activity Score in 28 joints using ESR; DAS28-CRP(3) = Disease Activity Score in 28 joints using ESR (3 variable); HAQ-DI = Health Assessment Questionnaire Disability Index score; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; RF = rheumatoid factor; ACPA = anti-cyclic citrullinated peptide antibody

Patient characteristics according to MCII in HAQ-DI

The characteristics of patients stratified by MCII in HAQ-DI at 3 months are shown in Table 4. Overall, only 9 patients did not achieve a MCII and in most patients the improvement in HAQ-DI significantly exceeded the predefined MCII of 0.22. Similar to the EULAR responders, the patients who achieved a MCII had higher SDAI scores at initiation of rituximab, but this was driven more by higher PGA and PhGA than by TJC. Notably, the MCII in HAQ-DI was also achieved by a significant proportion (70.0%) of our non-responder group by EULAR criteria.

Table 4. Baseline characteristics of patients according to MCII in HAQ-DI at 3 months after rituximab

	Achieved MCII (n=44)	Did not achieve MCII (n=9)	*p*
Age, in years	51.1 (10.5)	49.8 (12.0)	0.8829
Women, no. (%)	39 (73.6)	8 (88.9)	1.000
Smokers, no. (%)	10 (22.7)	1 (11.1)	0.6652
Disease duration, in years	12.9 (6.9)	11.5 (4.9)	0.6272
RF positive, n (%)	39 (73.6)	9 (100)	0.5743
ACPA positive, n (%)	41 (93.2)	8 (88.9)	0.5364
TJC	8.8 (5.3)	6.2 (4.4)	0.1642
SJC	8.8 (4.8)	7.2 (4.5)	0.3722
PGA	7.3 (1.9)	5.3 (3.2)	0.0426
PhGA	7.7 (1.7)	5.8 (2.5)	0.0305
SDAI	36.0 (12.5)	26.8 (12.5)	0.0838
DAS28-ESR (3)	5.4 (0.9)	5.2 (0.9)	0.4896
HAQ-DI	2.3 (0.5)	1.9 (1.1)	0.3651
ESR, in mm/hour	39.9 (22.8)	53.0 (31.8)	0.2758
CRP, in mg/litre	25.1 (20.5)	21.3 (14.0)	0.8126

All values mean (SD) unless otherwise stated
MCII HAQ-DI = Minimal Clinically Important Improvement in HAQ-DI; HAQ-DI = Health Assessment Questionnaire Disability Index score; TJC = tender joint count; SJC = swollen joint count; PGA = Patient Global Assessment; PhGA = Physician Global Assessment; SDAI = Simplified Disease Activity Index; DAS28-ESR = Disease Activity Score in 28 joints using ESR; DAS28-CRP(3) = Disease Activity Score in 28 joints using ESR (3 variable); ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; RF = rheumatoid factor; ACPA = anti-cyclic citrullinated peptide antibody

Loss of response at 6 months

The good or moderate EULAR response to rituximab had declined to 67.9% of the cohort by 6 months (Fig 2) and mean values for all clinical parameters had deteriorated (as noted in table 2). Improvements in HAQ-DI scores seemed more robust than improvements in disease activity. At 6 months a "functional" response was maintained in 75.5% of the cohort, who still fulfilled the criteria for MCII in HAQ-DI when compared to HAQ-DI at initiation of rituximab (Fig 2).

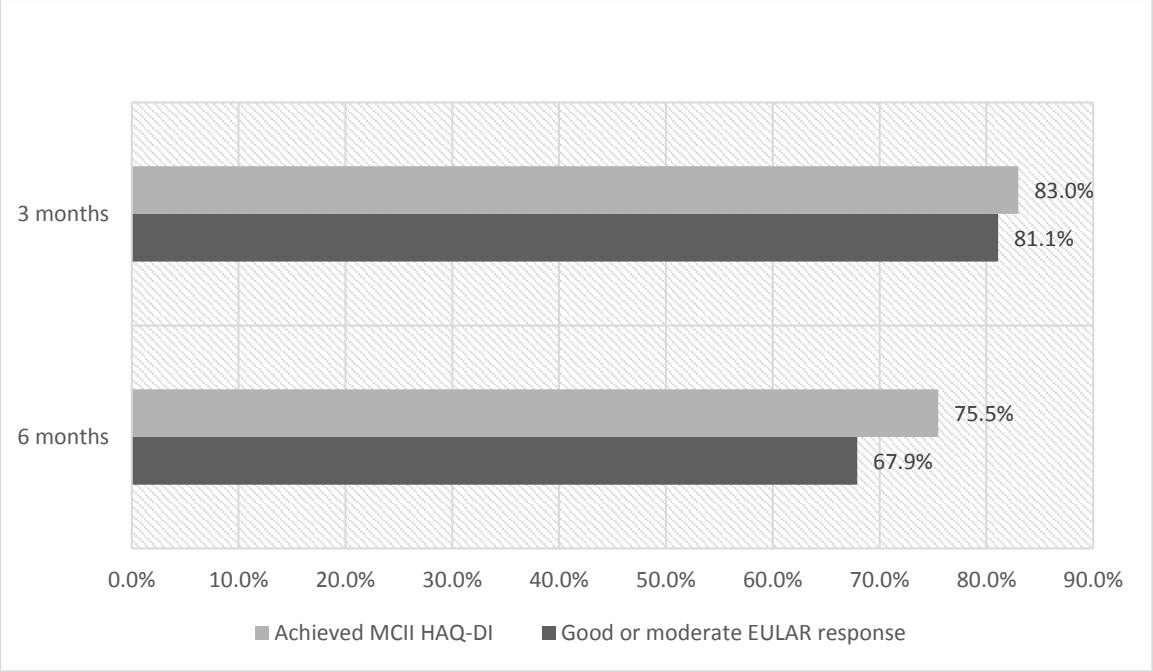


Figure 2. Percentage of cohort who achieved MCII and EULAR response at 3 and 6 months

MCII HAQ-DI = Minimal Clinically Important Improvement in HAQ-DI; EULAR = European League Against Rheumatism

Discussion

The findings in this study support the effectiveness of rituximab in a cohort of predominantly African patients with RA.

All our patients had refractory RA, and most of our patients were older with established RA of long duration. A large proportion of patients (41.5%) had extra-articular features of RA. Despite all these factors, therapy with rituximab significantly improved clinical disease activity and functional status in our patients. The substantial EULAR response rate of 81% in this cohort is similar to that observed in other studies (85%) [8,16,17]. The importance of treating RA early, and individualising treatment to achieve LDA or remission as soon as possible, is well known. [5,7] In a local study of indigent patients, around two thirds of RA patients will respond adequately to synthetic DMARDs if a tight control strategy is used. [18] Those patients who fail to respond adequately stand to benefit from treatment with rituximab.

We propose that the use of rituximab in a population of younger patients with a shorter duration of disease, even within the first 6 to 12 months of diagnosis, may yield an even better response to rituximab than was demonstrated by our study. The use of biologic DMARDs in patients with an inadequate response to synthetic DMARDs for 6 months is in line with the current South African Rheumatism and Arthritis Association (SARAA) guidelines. [7] The documented disease duration and long delay between being diagnosed with RA and receiving rituximab in our cohort shows that the challenge lies in the implementation of this guideline.

The most significant predictor of response to rituximab in our cohort was higher disease activity, measured by SDAI, at initiation of rituximab. This was primarily driven by higher TJC and PhGA scores. Responders tended to be younger and to have a shorter duration of disease. As our cohort was almost exclusively either RF or ACPA positive, the contribution of auto-antibodies to response could not be assessed. The role of immunoglobulin levels and their depletion could also not be assessed. These are both factors which have been found to predict response to rituximab in previous studies. [10,19,20]

Rituximab resulted in significant and sustained improvements in functional status, despite our patients having advanced disease, likely with established joint damage. Improvements in HAQ-DI scores remained significant at 6 months after rituximab, despite worsening disease activity, with the MCII being maintained in over 70% of patients at 6 months. This durable improvement in functional status may represent the most meaningful outcome of this study. Interestingly, functional disability was improved even in our non-responder group, where 70.0% achieved a MCII in HAQ-DI at 3 months.

The clinical improvements observed at 3 months following rituximab therapy in our cohort were not sustained indefinitely, with worsening disease activity by 6 months. This suggests that the optimal treatment interval for rituximab lies somewhere between 4 and 6 months and may differ for each patient. Additional data collected at 4 and 5 months after initiation of rituximab may have been valuable to determine exactly when disease activity began to increase. This highlights the importance of close follow-up and frequent reassessment of these patients to determine when retreatment is required. This strategy of treating-to-target, on the basis of predefined disease activity endpoints, may be more appropriate than offering retreatment at strict intervals. [21]

The majority of our patients received 2 infusions of 500mg of rituximab. A higher dose of 2 infusions of 1000mg was not found to be superior, but the utility of our data is limited as so few patients in our cohort received the higher dose. The equivalence of a lower (500mg) dose is, however, consistent with data from several large-scale trials, including the SERENE, DANCER, and IMAGE trials. [8,21,22] Proven efficacy at lower doses could inform practitioners on the cost-effective use of rituximab in resource-limited settings, though more research may be needed in this area.

Rituximab was found to be safe in our cohort. No short-term adverse events were documented and there were no cases of tuberculosis, despite a significant proportion of patients with a positive PPD skin test. Notably, all patients with a latent tuberculosis received INH prophylaxis. The documented safety of rituximab in a population at high risk for tuberculosis is an important finding, even though the cohort was small.

Limitations of this study include a small sample size, short duration of follow-up and its retrospective nature. Our cohort was homogeneous, largely made up of older patients with advanced, seropositive disease. We also lacked a control population.

In summary, our study documents the efficacy and safety of rituximab in African patients with established RA and highlights the need for further research, particularly into the use of rituximab in our population with early RA. Direct comparison of treatment-to-target and fixed interval retreatment with rituximab would also be valuable. The role of B-cell depletion and immunoglobulin levels as therapeutic monitoring in rituximab as well as the use of rituximab in concomitant HIV infection merit further exploration.

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CHAPTER 3: APPENDICES

Appendix A: 2010 ACR/EULAR classification criteria for rheumatoid arthritis

A. Joint involvement	
1 large joint	0 points
2-10 large joints	1 point
1-3 small joints (with or without large joint involvement)	2 points
4-10 small joints (with or without large joint involvement)	3 points
>10 joints (with at least 1 small joint)	5 points
B. Serology (at least 1 test result is needed)	
Negative RF and negative ACPA	0 points
Low-positive RF or low-positive ACPA	2 points
High-positive RF or high-positive ACPA (>3 times ULN)	3 points
C. Acute phase reactants (at least 1 test result is needed)	
Normal CRP and normal ESR	0 points
Abnormal CRP or abnormal ESR	1 point
D. Duration of symptoms (patient reported)	
Less than 6 weeks	0 points
6 weeks or more	1 point

A score of ≥6 is required for the classification of definite RA

Appendix B: Simplified Disease Activity Score (SDAI)

		Left		**Right**	
		Swollen	Tender	Swollen	Tender
Shoulder					
Elbow					
Wrist					
MCP	1				
	2				
	3				
	4				
	5				
PIP	1				
	2				
	3				
	4				
	5				
Knee					
Subtotal					
Total		Swollen		Tender	

Patient global assessment- ask the patient:
On a scale of 0 to 10, where 0 is very good and 10 is extremely bad, how is your arthritis?
Physician global assessment
Holistic assessment of patient's clinical and functional status, on a scale of 0 to 10.
Investigations
Requires CRP measurement in mmol/L

Swollen Joint Count (0-28)	
Tender Joint Count (0-28)	
CRP in mmol/L	
Patient global assessment (0-10)	
Physician global assessment (0-10)	
SDAI = sum of all values	

Appendix C: DAS28-ESR (3) Score

DAS28-ESR (3) = [0.56 x √(TJC28) + 0.28 x √(SJC28) + 0.70 x ln(ESR)] x 1.08 + 0.16

TJC: tender joint count (28 joints)

SJC: swollen joint count (28 joints)

ESR: erythrocyte sedimentation rate in mm/h

Appendix D: Health Assessment Questionnaire Disability Index (HAQ-DI)

Please tick the one response that best describes your usual abilities over the past week.

	Without any difficulty	With some difficulty	With much difficulty	Unable to do
1. Dressing and grooming- are you able to:	0	1	2	3
Dress yourself, including tying shoelaces and doing buttons?	0	1	2	3
Shampoo your hair?	0	1	2	3
2. Rising- are you able to:	0	1	2	3
Stand up from an armless straight chair?	0	1	2	3
Get in and out of bed?	0	1	2	3
3. Eating- are you able to:	0	1	2	3
Cut your meat?	0	1	2	3
Lift a full glass or cup to your mouth?	0	1	2	3
Open a new carton of milk or soap powder?	0	1	2	3
4. Walking- are you able to?	0	1	2	3
Walk outdoors on flat ground?	0	1	2	3
Climb up 5 steps?	0	1	2	3

Please tick any aids or devices that you usually use for any of these activities:

Cane	
Walking frame	
Crutches	
Wheelchair	
Devices for dressing (button hook, zipper pull, shoe horn)	
Special utensils	
Special chairs	
Other (please specify):	

Please tick any categories for which you usually need help from another person:

Dressing and grooming	
Eating	
Rising	
Walking	

Please tick the one response that best describes your usual abilities over the past week:

	Without any difficulty	With some difficulty	With much difficulty	Unable to do
5. Hygiene- are you able to:	0	1	2	3
Wash and dry your entire body?	0	1	2	3
Take a bath?	0	1	2	3
Get on and off the toilet?	0	1	2	3
6. Reach- are you able to:	0	1	2	3
Reach up and get down a 2kg object from just above your head?	0	1	2	3
Bend down to pick up clothing from the floor?	0	1	2	3
7. Grip- are you able to:	0	1	2	3
Open car doors?	0	1	2	3
Open jars, which have been previously opened?	0	1	2	3
Turn taps on and off?	0	1	2	3
8. Activities- are you able to:	0	1	2	3
Run errands and shop?	0	1	2	3
Get in and out of a car?	0	1	2	3
Do chores such as vacuuming, housework or light gardening?	0	1	2	3

Please tick any aids or devices that you usually use for any of these activities:

Raised toilet seat	
Bath seat	
Bath rail	
Long handled appliances for reach	
Jar opener (for jars previously opened)	
Other (please specify):	

Please tick any categories for which you usually need help from another person:

Hygiene	
Gripping and opening things	
Reach	
Errands and housework	

Appendix E: EULAR response criteria

Improvement in DAS28 →	> 1.2	> 0.6 and ≤ 1.2	≤ 0.6
Present DAS28 ↓			
≤ 3.2	Good response	Moderate response	No response
>3.2 and ≤ 5.1	Moderate response	Moderate response	No response
>5.1	Moderate response	No response	No response

Appendix F: Data collection sheet

Study number:
Date of data collection:

Part 1: information at initiation of rituximab

Demographics				
Age				
Gender	Male		Female	
Ethnicity	African	Caucasian	Asian	Mixed ancestry
Smoker	Ever		Never	

Onset of disease	
Date of onset of RA symptoms	
Date of diagnosis with RA	

Clinical features at baseline					
Tender joint count					
Swollen joint count					
Extra-articular features	Yes		No		
Specify:	Nodulosis	Vasculitis	ILD	Scleritis	Other

Scores at baseline	
SDAI (total)	
Patient global assessment	
Physician global assessment	
HAQ-DI	

Investigations at baseline					
CRP(mg/L)		Albumin(g/dL)		IgG(mg/dL)	
ESR(mm/h)		RF(IU/ml)		IgM(mg/dL)	
Hb(g/dL)		ACPA(U/ml)		IgA(mg/dL)	

TB screening at baseline				
Previous TB	Yes		No	
Chest radiograph	Normal	Evidence active TB	Evidence previous TB	Not done
Skin test (PPD)	Negative	Positive (>5mm)	Not done	
INH prophylaxis	Yes		No	

Treatment history				
Total number of DMARDs				
DMARDs used	MTX	SZP	CHQ	Leflunomide
On corticosteroids at baseline	Yes		No	
Corticosteroid dose (average)				

Initiation of Rituximab		
Date of first dose		
Dose received	500mg	1000mg
Adverse events at initiation	Yes	No
Details		

Part 2: information at 3-month follow-up

Scores at 3 months	
SDAI (total)	
Tender joint count	
Swollen joint count	
Patient global assessment	
Physician global asssessment	
HAQ-DI	

Investigations at 3 months	
CRP	
ESR	

Maintenance therapy		
DMARD	MTX	Leflunomide
Corticosteroids	Yes	No
Corticosteroid dose (average)		

Adverse events		
Adverse event in preceding 3 months	Yes	No
Details		

Part 3: information at 6-month follow-up

Scores at 6 months	
SDAI (total)	
Tender joint count	
Swollen joint count	
Patient global assessment	
Physician global asssessment	
HAQ-DI	

Investigations at 6 months	
CRP	
ESR	
IgG	
IgM	
IgA	

Maintenance therapy		
DMARD	MTX	Leflunomide
Corticosteroids	Yes	No
Corticosteroid dose (average)		

Adverse events		
Adverse event in preceding 6 months	Yes	No
Details		

Abbreviations
RA: rheumatoid arthritis
ILD: interstitial lung disease
SDAI: Simplified Disease Activity Index
HAQ-DI: Health Assessment Questionnaire Disability Index
CRP: C-reactive protein
ESR: erythrocyte sedimentation rate
Hb: haemoglobin
RF: rheumatoid factor
ACPA: anti-citrullinated peptide antibodies
IgG: immunoglobulin G
IgM: immunoglobulin M
IgA: immunoglobulin A
TB: tuberculosis
PPD: purified protein derivative
INH: isoniazid
DMARD: disease modifying anti-rheumatic drug
MTX: methotrexate
SZP: sulphasalazine
CHQ: chloroquine

Appendix G: Ethics approval

R14/49 Dr Tamsin Lovelock

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M161029

NAME: (Principal Investigator)	Dr Tamsin Lovelock
DEPARTMENT:	Internal Medicine Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Rituximab in the Treatment of Refractory Rheumatoid Arthritis in a Tertiary Academic Hospital
DATE CONSIDERED:	28/10/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Claudia Ickinger and Dr Lai-Ling Winchow
APPROVED BY:	Professor P. Cleaton-Jones,Chairperson, HREC (Medical)
DATE OF APPROVAL:	03/03/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004,10th floor, Senate House/2nd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated,from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review in October and will therefore be due in the month of October each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix H: Plagiarism report



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ORIGINALITY REPORT

10%	6%	13%	1%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	acrabstracts.org Internet Source	4%
2	"2016 ACR/ARHP Annual Meeting Abstract Supplement", Arthritis & Rheumatology, 2016 Publication	2%
3	"2017 ACR/ARHP Annual Meeting Abstract Supplement", Arthritis & Rheumatology, 2017 Publication	1%
4	"2015 ACR/ARHP Annual Meeting Abstract Supplement", Arthritis & Rheumatology, 2015. Publication	1%
5	"Abstract Supplement 2018 ACR/ARHP Annual Meeting", Arthritis & Rheumatology, 2018 Publication	1%
6	"2013 Annual Meeting Abstract Supplement", Arthritis & Rheumatism, 2013. Publication	1%