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CONTROL OF RHEUMATOID ARTHRITIS AT  
RHEUMATOLOGY OUTPATIENT DEPARTMENT OF  
UNIVERSITAS HOSPITAL, BLOEMFONTEIN

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**Masters of Medicine in Internal Medicine**

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**University of the Free State**

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**Clarification of layout for examiners:**

In accordance with the regulations for dissertation of a MMed research project, as prescribed by the University of the Free State, this mini-dissertation is written in the format of a publishable article. The layout of the article is as prescribed by the South African Medical Journal (SAMJ) for publication of a research article.

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## **Declaration of own work**

I, Richard Michael Neno Carter, declare that the work:

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is that of my own work and that I have received no assistance outside of what is permitted by the regulations of the University of the Free State.

### **I further certify that:**

- 1: The work was performed for the purpose of the research component of the MMed (Internal Medicine) at the University of the Free State and has not been submitted for any other qualification.
- 2: I have formally cited or otherwise fully acknowledged the quotations, ideas, and wording used here from other sources whether published or unpublished, in written or electronic form.
- 3: I have engaged in no falsification or misrepresentation of data or experience in this submission.

Signed:



Name: Richard Carter

Student number: 2005078486

Place: Bloemfontein

Date: 04/11/2017

## **Abstract**

### **Background:**

Rheumatoid arthritis is a highly prevalent disease with a significant negative impact on morbidity and life expectancy. There is a paucity of literature relating to the current state of disease control in South Africa, and none so in the Free State province.

### **Objectives:**

1. To evaluate the degree of control of rheumatoid arthritis at the Rheumatology outpatient department of Universitas Central Hospital.
2. To determine the relative impact of various factors contributing to the prevention of disease control.

### **Methods:**

A cross sectional study was undertaken over a period of 8 months from December 2016 to August 2017 at the Rheumatology outpatient department of Universitas Central Hospital in Bloemfontein. Data were collected by means of information sheets completed by treating physicians. The information obtained was related to the current disease state, possible reasons for poor control, and relevant demographic data.

### **Results:**

Information was collected from 169 participants and data analysis was performed on 161 of these patients. The results revealed that 34 (21.12%) patients were controlled. Of the 127 patients not controlling, 61 (37.89%) reported dispensing issues related to poor drug availability, and 72 (56.69%) were on insufficient treatment for their disease state. In 69.29% of these patients, however, concomitant dispensing issues were reported. Other factors such as transport/access problems, administrative issues, adverse events, and poor compliance/insight played minor roles. In terms of monthly dispensing: 95.65% of patients reported to have received all of their Disease Modifying Anti-Rheumatic Drugs (DMARDs) during the first month (the vast majority of which were dispensed from Universitas Hospital). This reduced to 73.91% during the second month (mostly from district units) and only 55.26% reported receiving all of their DMARDs from their down referral units.

### **Conclusions:**

The disease control in this institution is suboptimal when comparing to local and international standards. The main contributors to poor control seem to be problems related to dispensing of medication as well as inadequate escalation of therapy by doctors. The bulk of concern with the dispensing of medication lies with the poor availability of DMARDs in peripheral unit pharmacies. These are remediable factors which should be attended to.

## Article

### Background

Rheumatoid arthritis (RA) is a common condition with a global prevalence of around 1% (1). African based studies report a prevalence of roughly 0.7%, which seems to be on the rise in the setting of rapid urbanization (2). The disease is associated with decreased life expectancy, impaired quality of life, and places a significant financial burden on patients as well as society at large (3). Numerous developments have recently come to the forefront in the management of RA. Most notably the importance of early aggressive management according to a “treat-to-target” approach (4) and the introduction of biologic Disease Modifying Anti-Rheumatic Drugs (bDMARDs). These are expensive agents, but have shown to have a remarkable effect on disease control with regards to retarding clinical and radiological progression, delaying joint destruction, and improving quality of life; with an effect superior to that of conventional synthetic DMARD (csDMARD) therapy (5).

South African guidelines for the management of RA have been published in 2013. Drafted by the South African Rheumatism and Arthritis Association (SARAA), these guidelines were written in accordance with international standards of treatment. The guidelines advocate early use of csDMARDs and rapid escalation of therapy, with the goal of reaching a state of “Low Disease Activity” (LDA) or preferably a state of “remission”. These csDMARDs include: Methotrexate, Sulphasalazine, Chloroquine (or Hydroxychloroquine), and Leflunomide (6). Methotrexate remains the anchor of treatment with these agents, with other drugs being added either sequentially or initiated simultaneously (7). If the disease is not controlled to target (LDA or remission) by 6 months (despite adequate escalation in treatment), patients should, according to these guidelines, be considered for initiation on a biologic agent (6). Although there is significant cost involved with procurement of medication, the financial implications of poor control seem to be far costlier. Inadequate disease control results in recurrent flares associated with repeated admissions, increased need for surgical intervention, and a rise in work absenteeism and early retirement (3,8).

There seems to be a paucity of data relating to the current degree of disease control in South Africa. A study done by Hodkinson et al. in 2015 comparing various disease activity scores, revealed that more than 60% of patients were in a state of LDA or remission with minimal variation between the scoring tools (9). International data regarding disease control varies markedly depending on the regimen of therapy and the duration of disease, amongst other factors (10,13).

Interviews with various patients and health care workers suggested that a likely bulk of the concern would lie with poor accessibility to medication as a result of deficiencies in drug availability at down referral pharmacies. The system of dispensing of anti-rheumatic medication to patients from Universitas Hospital works as follows:

- Medication is designated specific restriction codes (2 – 5 for hospital level medication).
- Universitas Hospital pharmacy issues the first month’s medication.
- The district hospital/unit pharmacy then dispenses medication for the second month and sends parcels containing hospital level medication to down referral clinic pharmacies.
- Issuing of the remaining repeat prescriptions (months 3 - 6) will be the responsibility of the down referral clinics.

It is evident that there are many steps involved in the distribution of the medication and that there are various areas vulnerable to being flawed. The current state of disease control in this institution is not known. There may be numerous factors contributing to the prevention of ideal disease control which need to be investigated to ensure continuous improvement of care.

## **Objectives**

1. To evaluate the degree of disease control of RA at the Rheumatology outpatient department of Universitas Central Hospital.
2. To determine the relative impact of various factors contributing to the prevention of disease control.

## **Methods**

### **Study design**

This was a cross-sectional study which took place at Universitas Central Hospital's Rheumatology outpatient department during the arthritis clinics on Mondays and Thursdays where all patients with RA are seen. The department sees the majority of patients with RA in Bloemfontein's public sector, as well as a large portion from the rest of the Free State and a number of patients from the Northern Cape. The department serves as the only Rheumatology department in the Free State and Northern Cape provinces.

### **Participants**

Participants deemed eligible for inclusion were patients with RA fulfilling the American College of Rheumatology/European League against Rheumatism (ACR/EULAR) criteria of 2010 (as per South African RA guidelines (6)) who have been treated for at least 6 months, thus ensuring sufficient time for adequate escalation of therapy by the time of enrolment. Exclusion criteria were as follows: patients not fulfilling said criteria for RA, uncertainty regarding the diagnosis, patients who have been treated for a period of less than six months, and patients on biologic agents. Patients were selected consecutively until a predetermined minimum of 150 participants were included.

### **Data collection**

Prior to each clinic, patient files were screened for participants eligible for enrolment. These patients were then handed information documents with a detailed description of the intended study and proceedings to follow. After discussing all aspects of the study with each patient, written informed consent was obtained. Information sheets were then completed by the treating physician or the researcher himself. A copy was kept in each source file to prevent re-screening of the same patient.

The following information was obtained from the information sheets:

- basic demographic data (age, gender, and race),
- the Clinical Disease Activity Index (CDAI) score,
- the pharmacies which the patient was attending each month (viz. 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> – 6<sup>th</sup> months),
  - possible reasons for poor disease control, completed by means of ticking relevant boxes (additional space was provided for elaboration on unforeseen factors),
- what DMARDs the patient was on at the time, and
  - other possible contributors to poor disease control.

Disease control was assessed by means of the CDAI score. This is an internationally accepted composite scoring system utilising four parameters to determine overall disease activity (viz. a swollen joint count, a tender joint count, the patient's global assessment of the disease state, and the doctor's global assessment of the disease state) (6). As opposed to other validated scoring systems, the CDAI score was used in this study as it is the current standard of assessment in this institution. Furthermore, the accuracy is highly comparable to that of other validated disease activity scores (9). The degree of disease control was grouped into categories based on their CDAI score:

- $\leq 2.8$  = remission,
- 2.9 - 10 = low disease activity,
- 11 - 22 = moderate disease activity, and
- $> 22$  = high disease activity.

A score falling within the categories of LDA or remission was considered to be "controlled".

The minimal acceptable treatment for a patient with uncontrolled disease was considered to be that of at least 3 csDMARDs at optimally high doses, defined in this study as: Methotrexate of at least 20 mg weekly, Sulphasalazine of at least 1 g twice daily, Chloroquine of at least 200 mg daily, and Leflunomide of at least 20 mg daily. Patients who were not controlling despite fulfilling the minimal treatment requirements were considered to be on insufficient treatment for their disease state. In a situation where an adverse event caused by a DMARD was the only factor preventing further escalation of therapy, the treatment would still be considered sufficient. In cases where the disease was not controlled despite absence of any possible explanation for poor control, it was considered to be disease refractory to csDMARDs.

Steroid use was not evaluated in the study population as these agents should ideally be considered only for use in acute control of RA as "bridging therapy" (6). Patients assessed in this study would have been on treatment for at least 6 months, allowing sufficient time for escalation of DMARD therapy and weaning of steroids. Steroid availability has always been freely available from peripheral units.

The data collected were transferred onto an excel spreadsheet for analysis. Various factors were identified as possible contributors to poor control and were grouped as follows: insufficient treatment for disease state, dispensing problems, adverse effects of medication, poor compliance/insight, administrative problems, problems involving access/transport, and other unexpected issues.

### **Statistical analysis**

Data were analyzed by the Department of Biostatistics of the University of the Free State using the Systemic Analysis System (SAS) Version 9.3. Results were summarized using frequencies and percentages (categorical variables) and percentiles (numerical variables with skew distributions).

### **Ethical considerations**

Ethical approval was given by the Health Sciences Research Ethics Committee of the University of the Free State (ref. no. HSREC #108/2016) prior to data collection. Provincial approval was then granted by the Free State Department of Health (ref. no. FS\_2016RP3\_140). Written informed consent was obtained from all participants enrolled.

## Results

Data were collected from 169 participants over a period of 8 months. Of the 169 participants, 8 patients were excluded from data analysis: 6 of these were on the basis of insufficiently completed information sheets and 2 were due to current or planned pregnancy (the authors considered this to be a confounding factor in that pregnancy has an effect on disease control and that pregnant patients cannot use certain DMARDs due to teratogenic effects). Data analysis was performed on the remaining 161 participants (see Fig. 1).

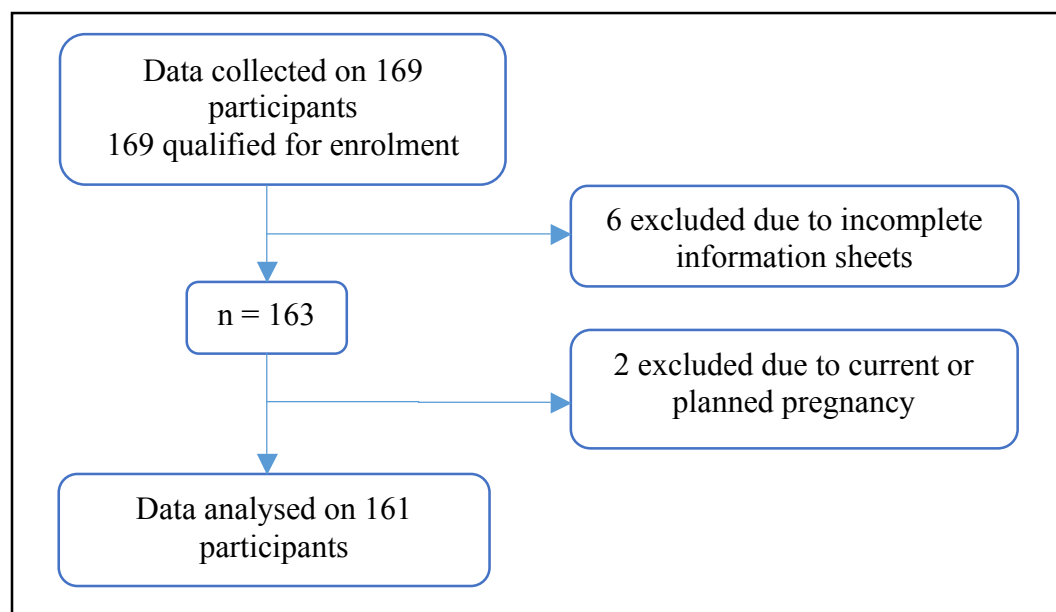


Fig. 1. Enrolment of participants.

### Demographic data:

The median age of the participants was 58 with the eldest being 83 and the youngest 19. Of the 161 participants; 138 (85.71%) were female and 23 (14.29%) were male. In terms of ethnicity: 131 (81.37%) were African, 21 (13.04%) were Caucasian, 7 (4.35%) were of Mixed race (Coloured), and 2 (1.24%) were Indian.

### Degree of disease control:

Of the 161 patients analysed, 34 (21.12%) were controlled. The frequencies of the degree disease control are represented in table 1.

**Table 1. Degree of disease control. N=161 (%).**

Low disease activity	29 (18.01%)
Remission	5 (3.11%)
Moderate disease activity	56 (34.78%)
High disease activity	71 (44.10%)

### Contributors to poor control:

Table 1 reveals the frequencies of the various factors which may contribute to poor disease control in (1) the total study population, (2) patients with sub-optimally controlled disease, and (3) patients in whom the disease was deemed to be controlled. In 21 (13.04%) participants no discernible reason for poor control was found and were deemed to have disease that is refractory to csDMARDs.

Of the 34 patients that were deemed to be controlling, 24 (70.59%) had no documented factors that may have impacted on control and only 10 (29.41%) were controlled despite having possible factors that may have led to poor control.

**Table 1. Possible causes for poor disease control.**

<b>Reported reasons for poor control for all patients</b>	<b>Total N = 161 (%)</b>	<b>Uncontrolled patients N = 127 (%)</b>	<b>Controlled patients N = 34 (%)</b>
Insufficient treatment for disease state	72 (44.72)	72 (56.69)	N/A
Dispensing issues	71 (44.10)	61 (48.03)	10 (29.41)
Insufficient treatment without dispensing concerns	39 (24.22)	39 (30.71)	N/A
Side effects	9 (5.59)	8 (6.30)	1 (2.94)
Administrative	7 (4.35)	7 (5.51)	0 (0)
Transport/access to treatment	1 (0.62)	1 (0.79)	0 (0)
Compliance/Insight	4 (2.48)	3 (2.36)	1 (2.94)
Other	0 (0)	0 (0)	0 (0)
<b>Refractory disease</b>	<b>21 (13.04)</b>	<b>21 (16.54)</b>	<b>N/A</b>

Regarding pharmacies involved in dispensing: during the first month's issuing of treatment, 154 (95.65%) participants reported receiving their treatment from Universitas Hospital and 159 (98.76%) reported receiving all of their medication. In the second month, all 5 districts of the Free State province and around 40 different institutions were involved in the dispensing process during which 119 (73.91%) reported receiving all of their DMARDs. During the 3<sup>rd</sup> – 6<sup>th</sup> months of dispensing (from down referral institutions), again all 5 districts and about 50 institutions were involved with only 89 (55.28%) reported receiving all of their DMARDs (See Fig. 2).

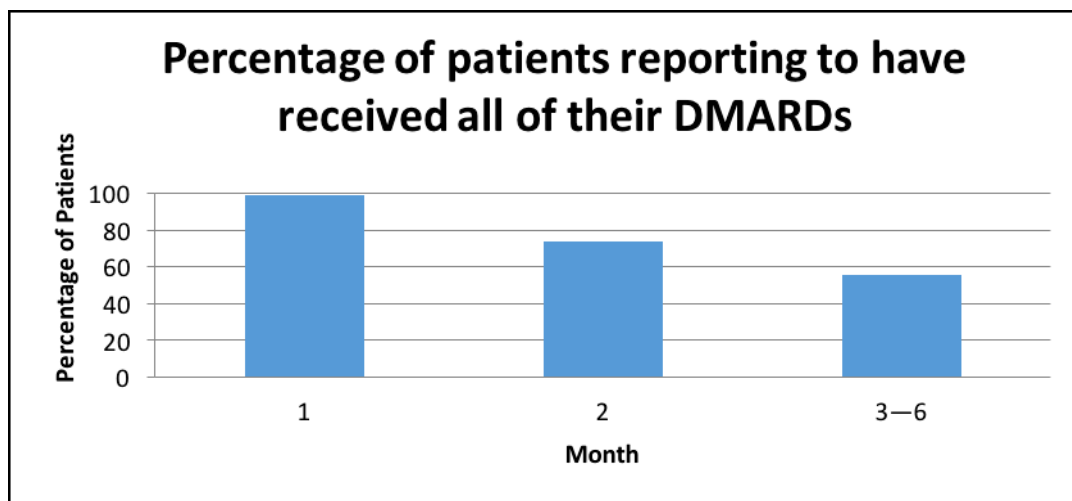


Fig. 2. Percentage of patients reporting to have received all of their DMARDs.

## Discussion

The disease control of RA in this setting is suboptimal compared to available local and international data (10–13). Provincial studies reporting control are however limited and more research is required on provincial and national levels. The largest contributors to poor control seem to be inadequate escalation of treatment and problems with the dispensing system, resulting in a lack of availability of medication (predominantly from peripheral unit pharmacies).

A large portion of patients seem to be on inadequate treatment for their disease state. It should however be noted that common practice dictates that a practitioner would not escalate therapy until confirming that a patient is receiving all prescribed medication and adherence is ensured. In the group that was not controlled, 33 (45.83%) of the 72 patients deemed to be on inadequate medication for their disease state had concomitant dispensing issues. Therefore, only in 39 (30.71%) of these cases can it be assumed that inadequate escalation of therapy may be directly involved in poor control. It however remains to be a large portion of patients and this needs to be addressed. A likely explanation for the inadequate escalation of therapy may be attributed to the fact that currently in the public sector, there is only one rheumatologist serving the entire Free State and Northern Cape provinces. Due to the vast quantity of patients attending this clinic, many patients will be seen by registrars and interns who may not be as prone to aggressive escalation in therapy as may be required to ensure tight control.

It is therefore evident that the largest correlation can be made between the lack of treatment availability and poor disease control (directly or indirectly by preventing escalation of therapy), and most notably so from the down referral clinics. The importance of access to DMARD therapy for the control of RA is further evidenced by the fact that 24 (70.59%) of the 34 patients who were controlled reported to have received all of their medication. Although determining the reasons behind the poor drug availability did not form part of the aim of this study, it is likely to be multifactorial. After interviews with pharmacists it appears that the following may be contributing: problems with budget allocation in district as well as down referral pharmacies, staff shortages in pharmacies (most notably in district units), and issues with medication delivery. It has also been noted that many patients often attend pharmacies which lie outside of the down referral protocol for their area. As level 2-5 medications are sent to relevant down referral pharmacies on a “per patient” basis, patients

not following the correct down referral channels will often not receive their medication. In situations where medication is not available at clinics, a patient would often be advised to return to their district hospital to receive their treatment. Two problems arise here: firstly, these institutions often also do not have certain medication in stock, and secondly, access to transport is often problematic for many patients.

In this population, the vast majority of patients reported good adherence. Furthermore, poor insight seems to have played a negligible role in disease control. A mere hand full of patients reported problems relating to transport or administrative issues and only 5.95% reported adverse effects affecting their treatment regimen.

The reported compliance seems to be far better than that suggested by current literature (14). This may be as a result of recall bias or due to inaccurate reporting from patients as a result of the Hawthorne effect. Although a formal pill count would have been the ideal means of determining compliance, this was not feasible within the time constraints of this study.

According to our data, at least 13.04% of patients have disease refractory csDMARDs. The frequency is however, expected to be far higher. It is likely that a large portion of patients who are deemed to be poorly controlled for various reasons would in reality have refractory disease. This can however only be determined after excluding other possible causes for poor control; which cannot be achieved in the majority of these patients. In practice, identifying these patients is of importance as they may require escalation of therapy to bDMARDs as per local guidelines (6). Biologic agents are known to be highly efficacious in disease control. Due to the significant cost of these agents however, patients would not qualify until any reversible cause for poor control is addressed. A concerning finding is that of the 127 patients who are not controlling, 55.9% (44.10% of the total population) were in the high disease activity group. These patients are at high risk for debilitating disease and attaining tighter control on an urgent basis should be a priority.

The majority of the factors contributing to poor disease control are remediable and measures should be taken to attempt to correct of these factors as far as possible. Doctors should be trained in the importance of aggressive escalation of therapy. The addition of more rheumatologists or practitioners experienced in rheumatology into the system is likely to assist with ensuring appropriate management. In terms of the lack of availability of medication in the periphery; doctors and patients require a better understanding of the down referral system and staffing issues need to be addressed. After conducting this study, the dispensing protocol has been reviewed with the plan of instituting a Central Chronic Medicine Dispensing and Distribution unit (CCMDD) which is expected to improve availability of medication to patients. Once these factors have been corrected as far as possible, follow up studies would be in order to determine the effect of good practice on disease control.

### **Study limitations**

As with all validated disease activity scores, the CDAI score is subject to a degree of subjectivity. All efforts however were employed to ensure accurate scores by means of training sessions and involvement of senior doctors with the assessments.

In an ideal situation, data would have been collected by one physician and more specifically by a rheumatologist. Unfortunately, in this setting it was not technically possible. The information sheet however was clear and the majority of the information could be obtained

from source notes. Information sheets with inadequate or unclear information crucial to the aim of the study likely were excluded.

Certain information obtained from patients was dependent on the patient's memory and was therefore subject to recall bias. This mostly involved the recollection of medication which the patient was not receiving from pharmacies. The majority of patients did not have their previous prescriptions available at the time of the interview. Patients were however assisted by means of memory aids in the form of descriptions and pictures of drugs when needed. The objective of this study in this regard however was to determine to what degree poor DMARD availability was affecting disease control and not to establish what specific DMARDs were involved.

A number of information sheets were not clear as to which pharmacies were involved in dispensing, most notably regarding the step-down units. Therefore, when reporting these results only estimations were used. Once again however, this was additional information and did not form part of the primary or secondary aims of this study. Further research would be required to attain accurate information in this regard.

## **Conclusion**

Rheumatoid arthritis has a large impact on morbidity and life expectancy of patients and places a significant economic strain on the country. The current control in this setting is suboptimal when comparing to current local and international data. Many factors contribute to poor disease control, the largest concern lies with a lack of drug availability from pharmacies (particularly from peripheral units) and insufficient escalation of therapy by practitioners. Many of these issues are remediable and measures should be taken to resolve these concerns as far possible. Once these factors have been attended to, a follow up study would be in order to determine the effect of good practice on disease control.

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**Author contributions.** Dr Carter developed the research concept, drafted the protocol, assisted with data collection, and wrote the manuscript. Prof Joubert assisted with the study design and performed statistical analysis. Dr Jansen van Rensburg assisted with supervision and review of the manuscript.

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**Conflicts of interest.** None.

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