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Many hands that don't work



ASPECTS OF EARLY RHEUMATOID ARTHRITIS

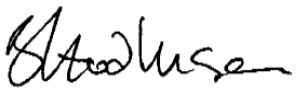
Bridget Dale Hodkinson

A thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand, in fulfillment of the requirements for the degree of

Doctor of Philosophy

Declaration

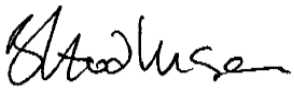
I, Bridget Hodkinson declare that this thesis is my own work. It is being submitted for the degree of Doctor of Philosophy in the University of the Witwatersrand, Johannesburg. It has not been submitted previously for any degree or examination at this or any other university.



Bridget Hodkinson **Date: 29 October 2012**

I certify that the studies contained in this thesis have the approval of the Human Research Ethics Committee of the University of the Witwatersrand, Johannesburg.

Human Research Ethics Committee protocol number: M050338



Bridget Hodkinson **Date: 29 October 2012**

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Chapter Three

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Chapter Five

Hodkinson B, Meyer PW, Musenge E, Ally MM, Wadee AA, Anderson R, Tikly M. The diagnostic utility of the aCCP antibody test is no better than rheumatoid factor in South Africans with early rheumatoid arthritis. Clin Rheumatol 2010; 29:615-8

Chapter Six

Meyer PW, Hodkinson B, Ally M, Musenge E, Wadee AA, Fickl H, Tikly M, Anderson R. HLA-DRB1 shared epitope genotyping using the revised classification and its association with circulating autoantibodies, acute phase reactants, cytokines and clinical indices of disease activity in a cohort of South African rheumatoid arthritis patients. Arthritis Res Ther 2011; 13:R160

Chapter Seven

Meyer PW, Hodkinson B, Ally M, Musenge E, Wadee AA, Fickl H, Tikly M, Anderson R. Circulating cytokine profiles and their relationships with autoantibodies, acute phase reactants, and disease activity in patients with rheumatoid arthritis. Mediators Inflamm; 2010:158514.

Chapter Eight

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List of Presentations

European Congress of Rheumatology

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2010, Rome: Poor Socio-Economic Status predicts Functional Disability in early Rheumatoid Arthritis in South Africa (poster presentation). Hodkinson B, Meyer P, Musenge E, Ally M, Anderson R and Tikly M. Ann Rheum Dis 2010;69(Suppl3):672

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2008, Paris: A prospective study of early Rheumatoid Arthritis in South Africa: response to traditional DMARDs in an impoverished setting (poster presentation). Hodkinson B, Meyer P, Musenge E, Ally M, Anderson R and Tikly M Ann Rheum Dis 2008; 67(Suppl II):199

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2008, Paris: Mutated Citrullinated Vimentin antibodies in early Rheumatoid Arthritis in South Africa (poster presentation). Hodkinson B, Meyer P, Musenge E, Ally M, Anderson R and Tikly M. Ann Rheum Dis 2008;67(Suppl II):599

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2011, Algiers. Low level of formal education yields poorer outcomes in early Rheumatoid Arthritis patients in South Africa (oral presentation). Hodkinson B, Meyer P, Musenge E, Ally M, Anderson R and Tikly M.

2011, Algiers. Response to traditional disease-modifying anti-rheumatic drugs in indigent South Africans with early Rheumatoid Arthritis (oral presentation). Hodkinson B, Meyer P, Musenge E, Ally M, Anderson R and Tikly M.

2007, Nairobi. Auto-antibodies in early RA (oral presentation). Hodkinson B, Meyer P, Musenge E, Ally M, Anderson R and Tikly M.

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South African Rheumatism and Arthritis Association Congress

2011, Johannesburg: Gamma-Interferon is the dominant circulating cytokine in rheumatoid nodulosis (oral presentation). Hodkinson B, Meyer P, Musenge E, Ally M, Anderson R and Tikly M.

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2011, Johannesburg: Matrix Metalloproteinase-3, a marker of disease activity and radiographic damage in early RA (oral presentation). Ally M, Hodkinson B, Meyer P, Musenge E, Anderson R and Tikly M.

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2009, Drakensburg: A Prospective study of response to traditional Disease Modifying Anti-Rheumatic Drugs in indigent South Africans with early Rheumatoid Arthritis. (oral presentation). Hodkinson B, Meyer P, Musenge E, Ally M, Anderson R and Tikly M.

2007, Cape Town: ACCP antibodies in early Rheumatoid Arthritis in South Africa (oral presentation). Hodkinson B, Meyer P, Musenge E, Ally M, Anderson R and Tikly M.

2007, Cape Town: Disease Activity and Health-Related Quality of Life in early Rheumatoid Arthritis (oral presentation). Hodkinson B, Meyer P, Musenge E, Ally M, Anderson R and Tikly M.

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2009, Cape Town: Circulating Cytokine Profiles and their Relationships with Rheumatoid Factor, Antibodies to Citrullinated Peptides / Vimentin, Acute Phase Reactants and HLA-DRB1 Shared Epitope Alleles in patients with Rheumatoid Arthritis (oral presentation). Meyer P, Hodkinson B, Musenge E, Ally M, Tikly M and Anderson R.

Abstract

Objective:

This study prospectively investigated disease activity, functional disability and health-related quality of life (HRQoL) in South Africans with early RA, and sought predictors of clinical response at 12 months to traditional disease modifying anti-rheumatic drugs (DMARD) treatment. In addition, the relationships between disease activity, circulating cytokines, the presence of auto-antibodies, the shared epitope (SE), and rheumatoid nodules (RN) were explored.

Methods:

A cohort of 171 patients with early (≤ 2 years) RA who were DMARD-naïve at inception were prospectively assessed for response to DMARDs over a 12-month period using the simplified disease activity index (SDAI), the Health Assessment Questionnaire-disability index (HAQ-DI) and the Short Form-36 (SF-36). At inception, rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (aCCP) were measured and genomic DNA was analysed using high-resolution PCR typing of the HLA-DRβ1 allele. Circulating cytokines and growth factors were measured using the Bio-Plex® suspension array system.

Results:

The 171 patients (140 females) at baseline had a mean age of 47 years, mean symptom duration of 12 months and had severe disease with a mean SDAI of 39, HAQ of 1.7, and globally low SF-36 scores. In the 134 patients seen at 12 months, despite significant improvements, only 28% achieved low disease activity, and 69% still had substantial functional disability (HAQ-DI >0.5), and 66% had suboptimal mental health (SF-36 mental

composite score <66.6). Baseline predictors of poor outcomes included unemployment, low level of schooling, female sex, high HAQ-DI and pain scores, and a low haemoglobin level. The 6-months SDAI was better than the baseline SDAI in predicting the 12-month SDAI.

The sensitivity and specificity of the aCCP test was 83%, and 85%, and the best specificity seen when both RF and aCCP were positive (95%). SE alleles were found in 92% of patients, and were strongly associated with aCCP, with disease activity and with proinflammatory cytokines. Circulating cytokines in RA reflect a multifaceted increase in immune reactivity with strong correlations between these cytokines, and auto-antibodies, in particular in the subgroup of patients with high disease activity. Subcutaneous RN were seen in 23% of patients, and were associated with more severe joint disease, and significantly higher levels of Th1 and macrophage derived cytokines, with significantly higher vascular endothelial growth factor levels.

Conclusions:

In this, the first prospective study of RA in sub-Saharan Africa, patients had severe RA, with a high disease burden at baseline and a high proportion carrying the SE allele, aCCP and rheumatoid nodules, with a multifaceted increase in circulating pro-inflammatory cytokines and growth factors. A large proportion of early RA patients have ongoing disease activity, substantial functional disability and suboptimal mental health despite 12 months of DMARD therapy. These findings, together with the high number of patients lost to follow-up, underscore the need for better disease control including an aggressive tight control strategy, and biologic therapy, and for patient- centred rehabilitation programmes with close links to psycho-social services.

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Nomenclature

aCCP	anti-cyclic citrullinated peptide antibodies
ACR	American College of Rheumatology
CCL2	chemokine (C-C motif) ligand 2
CHBH	Chris Hani Baragwanath Hospital
CQ	chloroquine
CRP	C-reactive protein
CXR	chest radiograph
DAS-28	28 joint disease activity count
DMARD	disease modifying anti-rheumatic drug
ESR	erythrocyte sedimentation rate
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte macrophage colony-stimulating factor
GREAT	Gauteng Region Early Arthritis
HAQ-DI	Health Assessment Questionnaire – disability index
HDA	high disease activity
Hb	Haemoglobin
HIV/AIDS	Human Immunodeficiency Virus/Aquired Immune Deficiency Syndrome
HLA	human leukocyte antigen
HRQoL	health-related quality of life
IFN-γ	Interferon-Gamma
IL	Interleukin
LDA	low disease activity
MCID	minimum clinically important difference

mcs	mental component score of the SF-36
MDA	moderate disease activity
MDGA	physician global assesment
MTX	methotrexate
NPV	negative predictive value
pcs	physical component score of the SF-36
PGA	patient global assessment
PPV	positive predictive value
RA	Rheumatoid arthritis
RF	Rheumatoid Factor
RN	Rheumatoid nodules
ROC	Receiver operated characteristic
SSZ	sulphasalazine
SDAI	simplified disease activity index
SE	shared epitope
SES	socio-economic status
SF-36	Medical Outcomes Short Form-36
SJC	28-joint swollen joint count
SLE	systemic lupus erythematosus
SSc	systemic sclerosis
TJC	28-joint tender joint count
TNF	tumour necrosis factor
VAS	visual analogue scale
VEGF	Vascular Endothelial Growth Factor

Overview

This thesis is a part of ongoing studies of the presentation and treatment of early Rheumatoid Arthritis (RA) patients in two public hospitals in South Africa: the Chris Hani Baragwanath Hospital, Soweto, and the Steve Biko Hospital. To argue for a patient-centred approach, an approach I hope will develop from this thesis; I begin with the story of Mrs Nomvula V, one of the patients who participated in the study. Her social and health conditions are typical of patients who present themselves for treatment in these state-run facilities.

Chapter 1 provides an outline of the disease, introducing the focus on early diagnosis and therapy, as well as the rationale for and the results of a search for factors that might predict response to therapy. Socio-economic factors are examined in the context of the care and treatment of RA patients. The background to new diagnostic tests, genetic susceptibility markers, circulating cytokines and rheumatoid nodules in RA is discussed. In order to better understand RA within the South African context, and to highlight the gaps in our knowledge, the findings of local studies done thus far are summarized, ending with the aim and research questions to be addressed in this thesis.

Chapter 2 describes the methods used to answer the research questions. This thesis is based on patients enrolled in the GREAT (Gauteng Region Early Arthritis) registry, which is an observational longitudinal cohort of early RA patients. The study design is described, and details of the clinical assessments, radiographic and serological investigations performed are given.

Chapters 3 to 8 present peer reviewed manuscripts, each addressing the research questions outlined at the end of chapter 1. Each of these papers has a signed statement of originality, with a description of the contribution of each author to that paper in the appendices. Permission from each journal to include a copy of the published paper in this thesis has been obtained.

Chapter 9 returns to Mrs Nomvula V, giving details of her disease at enrollment in the GREAT study in December 2007, and after 12 months of therapy in December 2008. Hereafter, a discussion of the results contained within each paper in the broader context of data derived from other studies and the field as a whole, using a framework of 4 themes to link the various aspects of the papers. The themes are:

i. RA severity in Africans
ii. Response to traditional DMARDs and routine clinic care
iii. Being poor matters
iv. Biomarkers of RA

Hereafter, a brief discussion of systems and strategies for the way forward, which summarize the implications at the level of clinical care; training of health care workers and future areas for research and planning. Limitations of the study are then discussed.

Chapter 10 offers final conclusions, followed by a reference section and appendices.



“Life is more than just living, more than the number of days lived… it is the meaning of things, of relationships, and the quality of life and where it is lived that are important”

David Blumsohn “The Pathology of Poverty” 1989 [1]

Mrs Nomvula V's story

Mrs Nomvula V was born in 1953 in Soweto, South Africa, and is one of 7 children. She completed Grade 8 but left to take care of her grandmother in Idutywa, near Butterworth in the Eastern Cape. Her first child, a boy named Luthando, was born there when she was 20 years old (1973) and Neliswa, a girl, was born in 1975. Mrs Nomvula V returned to Soweto after her grandmother's death in 1977 with Luthando, now 4 and Neliswa aged 2. In 1982 a girl, Thobeka, was born.

Mrs Nomvula V now lives in a 1-room outbuilding in Diepkloof, Soweto, and is separated from the father of her lastborn child. The room has electricity, but no bathroom or indoor toilet. She is the caregiver of three children who share the single room. Her youngest daughter Thobeka died of AIDs in 2005, leaving her two children (now aged 4 and 7). Her sister suffered a stroke and died in 2004, and Mrs Nomvula V has taken in her sister's grandchild, Pretty, aged 11, as the child's mother abuses alcohol. Mrs Nomvula V has never been formally employed, but had an income from selling fruit and cigarettes at a street-side stall near her home in Diepkloof. Until the onset of the disease, she was an active person, never one to sit around. Her days began early, heating water to wash, and getting the two older children dressed and ready for school, and then setting off with the youngest child to her stall where the day was filled with socializing with passers-by, customers and neighbours. She made weekly trips into town to buy supplies, leaving the child with neighbours for the day. Sundays were church days, and upon returning home she cleaned the room and washed the family's clothes for the week ahead.

In early 2006, Mrs Nomvula V's fingers and knees became painful and swollen. She visited her local clinic where she was given pain tablets. These did not help her much, and she struggled to manage, particularly in the morning when her hands, knees and ankles "would not get going". Increasingly she struggled to complete tasks, such as dressing herself and the young children and cooking meals for the household. Washing and ironing became impossible. By late 2006 she was relying on Pretty to help with most of these household chores before and after school. Some mornings she could not walk to her vending station because her knees were so painful. It became more difficult to travel to town to restock her supplies by public transport. She struggled most with getting on and off a minibus taxi after her joints had stiffened up, and carrying the produce because her hands and shoulders were painful and weak. Eventually she stopped selling goods and relied on Luthando, who worked as an electrician, for financial support.

She said "I thought life was hard before this arthritis came, but now I really understand…". Feelings of hopelessness began to overwhelm her. She spent more and more of her time lying on her bed in her room, overwhelmed by pain and exhaustion. She stopped attending church and social occasions.

At the clinic, she waited in long queues and was usually given pain tablets and Indomethacin. One of the doctors she saw told her she had gout and old age and should stop drinking alcohol and eating tomatoes, neither of which she did. In late 2007 she met a new doctor at the clinic and asked him if he could help her apply for a disability grant. He performed some blood tests, and referred her to Chris Hani Baragwanath Hospital to complete her application forms. Mrs Nomvula V was seen in casualty, and referred to the Arthritis Clinic. She was assessed as having Rheumatoid Arthritis and enrolled in the Gauteng Region Early Arthritis (GREAT) study.

Chapter 1: Articulating RA: the beginnings of the GREAT study

1.1 Background

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease occurring worldwide, characterized by inflammation of both small and large synovial joints. This inflammation results in bony erosions and eventually destruction of the joint. The disease affects almost 1% of the adult population and carries substantial socio-economic impact to affected individuals and their societies[2]. Studies conducted in Western populations show that Rheumatoid Arthritis is one of the leading causes of physical disability, with more than half of patients deteriorating to severe functional disability after 10 years of disease[3]. In addition, the burden of pain and reduced health-related quality of life is considerable[4], and RA patients have a two-fold higher risk of depression compared to the healthy population[5,6]. Life expectancy is reduced by 3 to 7 years, with the leading cause of death being infection and cardiovascular disease[7]. Survival rates for RA are similar to those for lymphoma, diabetes mellitus, stroke or coronary artery disease[8] . The disease carries substantial economic impact due to both direct costs including medical care, treatment and hospitalization, and indirect costs as a result of productivity loss, with its consequences on the individual, the employer and society[9]. Only 50% of patients are still employed after 15 years of disease[3].

There is a variable course of the disease with remissions and exacerbations, and the outcome is diverse, ranging from mild intermittent non-destructive disease to rapidly progressive disabling arthritis.

1.1.1 Why early RA?

There has been a recent shift in treatment strategies for RA. The first therapeutic approach included bed rest and anti-inflammatory drugs, and disease modifying anti-rheumatic drugs (DMARDS) were reserved for patients with established deformities and ongoing severe disease. In the mid-1980s it was recognized that such an approach was suboptimal, with most patients showing progressive radiological damage[10], long term functional decline, work disability[11], and premature mortality[12].

This led to a revolutionary approach to management of RA, with early and aggressive use of DMARDs to suppress inflammation and achieve a low disease activity state before irreversible joint damage had occurred[13,14]. Initiating early treatment allows better control of disease, with a higher possibility of achieving remission which may be maintained even once DMARD treatment is withdrawn[15]. It is postulated that the biological process in early RA differs to that in established disease, and therapy to rapidly suppress inflammation in its early stages may change the pathway of the disease for years to come[16]. Hence treatment started during this early "window of opportunity" has a greater effect than treatment given at a later stage[17].

Numerous studies have confirmed the benefits of early DMARD therapy, including the prevention of radiographic damage and preservation of functional ability[18,19]. Underscoring this, a meta-analysis showed disease duration to be the primary predictor of response to treatment[20]. The benefits of early DMARDs are still apparent after 10 years of follow-up[21]

where functional status is maintained in patients treated within 6 months of symptom onset as compared to those who started treatment later.

1.1.2 What is early RA?

With the drive to treat RA as early as possible, comes a need to diagnose RA promptly and accurately, but both the terms “early” and “RA” have an indeterminate aspect. The symptom duration defining the disease as ‘early’ differs widely in the literature. Symptom duration of less than 24 months is regarded as a reasonable definition of ‘early’ disease, although recently a symptom duration less than 6 months has been considered early disease[22], and “very early disease” defined as symptom duration less than 12 weeks[23].

Early diagnosis of RA is challenging, because in its initial phases RA may be difficult to distinguish from other types of inflammatory rheumatic conditions, some of which are self-limiting. The diagnosis is clinical, with serological markers lending support. The American College of Rheumatology (ACR) has developed classification criteria[24] to distinguish established RA from other rheumatological conditions in the research setting. These criteria have only a moderate sensitivity and specificity in early inflammatory arthritis[25]. Hence, the ACR criteria have very recently been revised, to address this poor performance in early disease[26].

1.1.3 Response to traditional DMARDs

Traditional DMARDs include methotrexate (MTX), chloroquine (CQ), sulphasalazine(SSZ) as monotherapy or in combination, and these may be combined with low dose corticosteroids.

In recent years, biologic DMARD drugs have been developed for the treatment of RA and other inflammatory conditions. These agents target specific molecules involved in the pathogenesis of RA, and have the potential to induce a rapid and sustained suppression of disease. In early disease, they achieve remission in 40-50 % of patients, thus preserving functional ability and preventing joint destruction[27-29]. Despite their effectiveness, the use of biologics is very limited in developing countries due to the risk of serious infection including tuberculosis associated with their use, and by their high cost. A major challenge is to implement these growing treatment options into everyday clinical practice.

Baseline predictors of response to DMARD therapy could assist in tailoring individualised treatment. A patient with a good prognosis is likely to respond to methotrexate monotherapy, whereas a patient at high risk of rapidly progressive disease should perhaps be started on combination traditional DMARD or biologic DMARD therapy at diagnosis. Such an approach may allow optimum benefit in a resource-constrained setting.

Predictive factors may be categorized as demographic factors, disease specific features and genetic or biologic markers. Key studies, and meta-analyses in particular, which have offered prognostic factors for either response to DMARDs or functional disability in early RA are summarized in Table 1.1. Demographic factors conferring a poor prognosis include female sex, older age at disease onset, cigarette smoking, and having a poor socioeconomic background. Disease-specific poor prognostic factors identified thus far are long symptom duration, high disease activity at baseline including high swollen and tender joint counts and elevated inflammatory markers, high composite disease activity scores and low haemoglobin level. High functional disability at onset bodes a poor prognosis. The

presence of auto-antibodies is associated with worse radiological damage and a higher occurrence of extra-articular disease. Extra-articular disease itself is a marker of poor prognosis. Genetic factors play a role in the severity of RA, and most studies demonstrate that the presence of the HLA-DRB1 shared epitope is a poor prognostic marker[30]. Biological markers including levels of certain synovial and serum cytokines show promise as predictors, but further work in this field is necessary before recommending their use in routine clinical use[31].

1.1.4 The impact of socio-economic status

The association between socio-economic status (SES) and mortality and morbidity has been described for centuries, with poor living conditions impacting negatively on health and on response to treatment. This socio-economic gradient persists into the 21st century despite advances in the understanding of diseases, their pathogenesis and diagnosis, and tremendous improvements in treatments available. Worldwide, poorer communities are more often and more severely affected by acute and chronic, communicable and non-communicable diseases[32,33].

Table 1.1: Predictors of response to DMARD therapy and functional disability in early RA - summary of key studies

	Marker of Poor Prognosis	Response to therapy	Functional Outcome
Demographic Factors	Older age at onset	[34,35]	[36]
	Female Gender	[20,37]	[36]
	Smoking	[37,38]	
	Socio-economic factors	*See Table1.2*	
Disease Specific Factors	Delay in DMARD therapy	[20,21,39]	[40]
	High Baseline functional disability	[20,37,41]	[42-45]
	High Baseline Pain	[46]	[47,48]
	High Baseline Disease activity	[37,49]	[42,45]
	Rheumatoid factor	[49]	[42]
	Anti CCP	[46,50]	
	Radiographic Erosions	[43]	[42,45]
	Depression	[46]	[51]
	Extra-articular disease	[52]	
Genetic / Biologic Factors	HLA-DRB1 Shared Epitope	[30,53]	
	Methotrexate pathway genes	[49,54]	
	Circulating TNF-a	[55]	
	Circulating IL-2	[56]	

Table 1.2: Impact of socio-economic status on rheumatoid arthritis disease expression

Author, Year	Country	Measure of SES	Disease Activity	Functional Disability	Pain	Mental Health	Damage	Other findings
Pincus T 1987[32]	USA	Formal education level	↑	↑	↑	---	---	Most chronic diseases including RA more prevalent
McEntegart A 1997[57]	UK	Carstairs index of social deprivation	No Δ	↑	No Δ	---	---	↑ mortality
Callahan LF 1988[58]	Nashville USA	Formal education level	↑	↑	↑	---	---	
Brekke M 1999[59]	Norway	Affluent vs less affluent suburbs of Oslo	No Δ	↑	---	↑	No Δ	
Jacobi CE 2003[60]	Netherlands	Formal education level	↑	↑	---	↑	---	
Harrison MJ 2005[61]	UK	Townsend score of social deprivation	↑	↑	↑	↑	No Δ	
Solomon A 2005[62]	SA	Public care vs private care	↑	↑	↑	---	↑ deformity score	
Pincus T 2007[63]	USA	Formal education levels	---	↑	---	---	---	↑ mortality
Sokka T 2009[64]	25 countries	High GDP vs low GDP countries	↑	↑	↑	↑	↑	Fewer on biologics
Neovius M 2011[65]	Sweden	Formal education level	---	---	---	---	---	Higher prevalence of RA
Margaretten M 2011[66]	USA	Public hospital vs university tertiary care	↑	↑		↑↑	---	

↑: increased, Δ: change

Amongst RA patients, studies from various countries give strong evidence that a poor socio-economic background predisposes patients to poorer outcomes across all measures. Table 1.2 summarizes studies that demonstrate the negative impact of poor SES on disease activity, functional disability, pain, mental health, radiological damage and mortality. Interestingly, a Swedish study recently reported that the prevalence of RA is influenced by level of education[65]. As Brekke et al conclude, affluence seems to buffer against the burden of RA[59].

There are various ways to measure SES. Some studies have used a social deprivation index based on area of residence[57,61]. Others used the health care institution patients attend as a marker for indigence or affluence[62,66]. Level of formal education has been used by many as a surrogate marker for SES, and is a good marker because of its simplicity, reliability, and the fact that it is uninfluenced by an adult-onset disease[32,60].

1.1.5 Tools to measure RA: disease activity, functional disability and HRQoL

Disease activity can be assessed with a composite score derived from the tender and swollen joint counts, the global assessment of patient and physician, and an acute phase response (either CRP or ESR). Two such scores are the 28 joint disease activity score (DAS-28), and the simplified disease activity index (SDAI)[67,68]. Both scores are validated and show good intercorrelation, with the SDAI having the advantage of being easy to compute in the clinical setting. The SDAI can be regarded as validated in the South African population, because South African patients were included in the database used to show construct and content validity[69].

There are many ways of assessing response to therapy in RA. Traditionally clinical trials and studies have reported relative change in disease activity from baseline, expressed as response criteria like the ACR 20/50/70. In order to fulfill the criteria for an ACR20 response, a patient must have improved by 20% (or 50% or 70% in the case of ACR50 and ACR70 respectively) with respect to tender and swollen joint counts, and in three of the remaining five criteria (pain score, acute phase reactant, physician and patient global assessments and physical disability score)[70]. Recent work shows the importance of absolute disease activity state at endpoint, such as the SDAI, because this state is more strongly associated with functional disability and radiological damage than level of response from baseline[71]. Besides, as Moons et al commented "Prognostic studies should focus on outcomes that are relevant to patients" [72]. In RA, these might include pain and disease activity, physical function, and quality of life at the end-point, rather than the percentage improvement from baseline. For these reasons, this study used absolute disease activity states at 12 months to assess response to therapy.

Disease activity indices alone fail to assess the extensive multi-dimensional issues associated with a chronic illness. The goal of modern RA therapy encompasses such broad objectives as restoration of an individual's functions of daily life and psychological health, and preservation of social and occupational roles. Accordingly, emphasis is now placed on health-related quality of life (HRQoL) assessments in RA. Such measures of HRQoL in RA reflect the inflammatory process in the joints and show good correlation with clinical disease activity[73], and are responsive to treatment[74]. Poor HRQoL scores are predictive of long term disability

and mortality[63]. Measures of HRQoL are a good indicator of the indirect costs of RA[75]. One further and important reason to evaluate HRQoL in RA is that these tools incorporate the patient's perspective and thus give important information about an individual's health status that would otherwise be overlooked[76].

The Health Assessment Questionnaire – Disability Index (HAQ-DI) and the Medical Outcomes Short Form-36 (SF-36) are complementary self administered questionnaires that have been validated to measure HRQoL[77,78]. The HAQ-DI was specifically developed for RA and consists of 24 questions that evaluate physical function in eight domains, and the composite score ranges from 0 (no disability) to 3 (severe disability). The SF-36 is a general measure of overall health and psychological well-being that examines eight domains, four of which constitute the physical component score (pcs). These are physical functioning (ability to perform various activities), role-physical (problems with daily activities due to physical health), body pain and general health. The other four make up the mental component score (mcs) - mental health (anxiety or depression), role-mental (problems with daily activities due to emotional state), vitality and social functioning. Scores in each domain range from 0 to 100, with higher scores reflecting better health. Construct and content validity of the English version of the HAQ-DI and SF-36 questionnaires has been shown in this population in a study of HRQoL in RA and SLE patients[79].

1.2 New diagnostic markers: Anti-cyclic citrullinated peptide antibodies

Rheumatoid Factor (RF) is the principal serological marker for RA, and is present in up to 80 % of established RA patients, but is only present in about 50% of patients with early disease[80].

Furthermore, the RF test has limited specificity (85%) because it is detected in other connective tissue diseases, chronic inflammatory and infectious diseases, as well as in the healthy elderly population[80,81]. Recently anti-cyclic citrullinated peptide antibodies (aCCP) have emerged as sensitive and specific serological markers of RA. Citrullination is a post-translational modification of arginine by deimination, physiologically occurring during apoptosis, inflammation or keratinization. The presence of several citrullinated proteins has been demonstrated in inflamed synovium[82].

These antibodies have a low to moderate sensitivity for RA (50-70%), similar to RF, but may pre-date the onset of RA[83,84]. Importantly, they are highly specific for RA (over 96%), and are thus particularly useful in diagnosing early RA[85,86]. Moreover, aCCP antibodies offer prognostic information, predicting future radiographic damage[82].

1.3 Genetic susceptibility: the shared epitope

Genetic predisposition may contribute up to 60% of the risk of developing RA[87]. The major susceptibility for RA lies in the HLA-DR genes whose β1 chain contain the shared epitope (SE) conserved amino acid sequence[88]. Alleles expressing this SE are associated with susceptibility to RA, accounting for approximately one-third of the genetic susceptibility to the disease[89]. In addition, most studies show that the SE confers more severe disease with a greater risk of radiographic damage[90,91]. The HLA-DRB1 concept has recently been extended to include the SE sequence at positions 72 to74 together with modulatory amino acids at positions 70 to 72, and reclassified into five allele groups[92]. This classification has allowed “risk stratification” of

genotypes, with alleles S_2 and S_{3P} carrying the highest risk of developing RA, whilst S1 alleles appear to be protective[93,94].

There are several models to explain the role of HLA-DRB1 genes in the loss of self-tolerance that results in autoimmune disease. The HLA molecule binds specific peptides and presents them to CD4+ T lymphocytes via recognition by the T cell receptor. Molecules containing the SE bind a different array of peptides than those not containing it[95]. Recently, it has been shown that the SE confers susceptibility to RA mainy in aCCP positive individuals[96,97]. Hence, the immunopathogenesis of aCCP-positive RA may involve presentation of citrullinated proteins by HLA-DRB1SE subtypes, resulting in activation of autoreactive T cells[98]. In addition, the high affinity of citrullinated peptides for the epitope may "skew" the response towards a Th1 direction[99].

1.4 Circulating Cytokines

Several components of the immune system contribute to rheumatoid inflammation, including T lymphocytes, macrophages, fibroblasts, B lymphocytes, and endothelial cells. Maturation and proliferation of these cells results in synovial inflammation together with cartilage and bone damage, and systemic manifestations of RA. Cytokines, chemokines and growth factors, operating in complex cascades and networks, orchestrate this immune response in RA[100,101].

Recent studies have shown elevated levels of circulating pro-inflammatory cytokines in RA patients[102,103]. Such assays may broaden our understanding of the immunopathogenesis of early and established RA, revealing novel therapeutic targets. In addition, profiling of

circulating cytokines may allow response to therapy to be predicted. Recently, Fabre et al showed that high serum levels of MCP-1 and epidermal growth factor (EGF) at baseline were predictive of a good clinical response to an anti-TNF drug, etanercept at 3 months[104]. Serum TNF and IL-2 levels may predict response to DMARD therapy[55,56].

1.5 Rheumatoid nodules

Rheumatoid nodules (RN) are the most common extra-articular feature of RA, occurring in approximately 20-30% of patients [105]. These subcutaneous nodules occur on extensor surfaces at sites of mechanical irritation. Although benign, RN are of clinical significance to the patient and clinician because they may be painful when exposed to repeated minor trauma, they may be sites for infection, and may be unsightly. Importantly, the presence of nodules are a marker of disease severity, particularly if seen early in the disease, and may herald the development of other extra-articular disease[52,106]. Nodules are a risk factor for premature mortality in RA patients[107,108].

The prevalence of RN differs between ethnic groups, with the highest prevalence described in Caucasians in Europe and North America, and a lower prevalence in Mediterranean countries[109]. In the few studies of RA in Africa a low incidence of RN has been noted in Nigeria (1%)[110], Cameroon (7%)[111], and Uganda (8%)[111]. Studies in black South Africans and Kenyans report a prevalence close to that of patients of European ancestry[112-114]. The reason for this spectrum of prevalence is unclear, but may be linked to genetic or environmental factors such as smoking[115].

The association between genetic susceptibility, specifically the SE and RN is controversial. Two large meta-analyses and other small studies show no significant association between SE and nodulosis [116-118]. Other reports have shown an association between the SE and RN [119,120], and in particular the SE-containing alleles DRB1*0401[121]. The low frequency of HLA DRB1*0401 in African-Americans[122,123] and Africans from Cameroon[111] and Senegal[124] has been suggested as an explanation of the low incidence of RN in these populations.

Histopathologically, the RN is an immune granuloma consisting of a central area of necrosis, surrounded by a "palisade" of macrophages and fibroblasts, and a peripheral vascular area containing T lymphocytes and macrophages [125]. A number of studies have drawn comparisons between the RN and rheumatoid synovium, describing similarities between the tissues with respect to cellular components, immunohistochemical features and cytokine production [126-129], but important differences have been shown with regards to B lymphocyte and fibroblast populations and cell adhesion molecules and cytokine expression [130-132]. In addition to immunohistochemical differences, nodules and synovitis do not run the same clinical course: patients with low disease activity can still develop RN, and increase in nodule size or formation of new nodules is well described with therapy that effectively suppresses joint inflammation, such as methotrexate and anti-TNF drugs [133-135]. This again suggests that the pathogenetic mechanisms of joint inflammation and RN differ.

1.6.1 RA in the developing world

There is increasing awareness of the global burden of all non-communicable diseases, and developing countries carry the brunt of the mortality and morbidity from these conditions[136].

However, much of the work on epidemiology, pathogenesis, disease characteristics and therapy of RA has been conducted in developed countries, with relatively little information on the disease in the developing world which includes South America, South-East Asia and Africa[137]. The few formal epidemiological studies conducted in developing countries, most show a lower prevalence of definite RA than in northern European and American populations[138,139]. This may be due to a true lower occurrence in these regions, or may reflect underestimation of the disease due to methodological variations in these studies[140]. An Indonesian study suggested reduced life expectancy together with a high mortality from RA may explain the low prevalence in this population[141], and this may be true of other developing countries. A recent review of RA in India and Pakistan shows a prevalence of RA in these countries similar to that in Europe and North America, but demonstrates that differences in clinical features do exist[142].

Several studies have compared clinical features of RA in different areas of the world[110,143-147]. The general impression is that disease is more severe amongst Europeans. Despite the difficulty in comparing populations directly, with potential sampling errors together with poor age and disease duration matching of cohorts, these studies highlight not just the diversity of RA expression, but also the importance of cultural and socio-economic influences on disease and its consequences. Conclusions reached about, for example, functional disability and its associations in one part of the world may not be true in another.

Hence research into RA in developing countries is urgently needed to provide better information about prevalence, clinical features, and response to therapy together with the underlying genetic, cultural or socio-economic determinants of outcomes. In resource-

constrained settings, appropriate planning, monitoring and implementing of health care services depends on information from such studies.

"It is not because countries are poor that they cannot afford good health information. It is because they are poor that they cannot afford to be without it."

WHO Health Metrics Network ; 2005

1.6.2 Sub-Saharan Africa and South Africa

There is no evidence that RA existed in Africa before the 20th century, but the prevalence is now increasing [148]. Whether this is a result of an infective agent, a susceptibility gene introduced to the African gene-pool, decreasing incidence of protective infections or the result of an increasingly urban lifestyle remains uncertain. Some of the lowest prevalence rates of RA in the world (0.1-0.28%) have been described in Southern Africa[149-151]. This has been attributed to climate and possibly altitude, where tropical infections including malaria may be protective against autoimmune disease. In addition, a "rural-urban" gradient has been suggested to account for the discrepancies in prevalence between regions, and a more than 3-fold increased prevalence amongst city dwellers suggests that an environmental factor precipitates RA[152]. This phenomenon has also been observed in Nigeria[153].

Another explanation offered for the low prevalence of RA in Africa is the lower prevalence of susceptibility genes. In the relatively few studies assessing HLA-DR genes in Africa, it has been shown that although SE-containing alleles are associated with susceptibility to RA, the

frequency of the SE is lower in the background population and in RA patients compared to European populations. Table 1.3 shows key studies in various populations, highlighting work done in Africa. The allele profile in populations of African origin is distinct from that of Caucasian populations, with a low frequency of certain alleles including HLA DRB1*0401 (S_2 in the new classification) described in African-Americans[153]. The low incidence of RA, mild disease and paucity of extra-articular disease has been attributed to these differences. In the southern African RA population, the frequency of the SE is higher than that reported elsewhere in Africa. Amongst the San population, 52.2% carry the risk alleles[93].

With the impression that the prevalence of RA is increasing, , it becomes clear that there is a need for large epidemiological surveys in sub-Saharan Africa[159].

Rheumatoid arthritis has long been regarded not only as rare, but also as a mild disease on the African continent. Here again there are relatively few studies, and methodological discrepancies between many of these studies make direct comparisons difficult. In addition, most studies have been performed in hospitals, and may not be a reflection of the overall disease in the general population, where the very ill and disabled are unable to attend, or milder cases are not seen. A further consideration is that the demographic features of the background population structure may influence the age and gender of RA patients described -for example, men may be in the cities at work under a migrant labour system, explaining the skewed gender ratios.

Table 1.3: Frequency of HLA DR β1 alleles in key studies in Europe, African Americans and Africa

Investigator and year	Population	RA patients % with HLA DRβ1	Controls % with HLA DRβ1	Relative risk	Comments
Thomson W 1998[154]	United Kingdom	59	44	5-fold	HLA–DRB1p0404 (ie S3p) strongest susceptibility
Hughes 2008[123]	African-Americans	25.2	13.6		Higher level of European admixture associated with a higher likelihood of carrying the SE
Dieye A 1996[124]	Senegal	25.2	13.6	30 for DR10	HLA-DR10 but not HLA-DR4
Singwe-Ngandeu 2010[111]	Cameroon	30	10		
Barnetche 2007[93]	San	52.2	26	3.05	S2 allele
		26	21	1.32	S3p allele
Mody 1989[155]	South Africa	44	10	7.4	
Martell 1989[156]	South Africa (Black patients)	38	13	3.9	
Meyer P[157]	South Africa (Black patients)	46	12	6.1	Particularly HLA-DRB1*0401 and *0404 alleles
Pile 1992[158]	South Africa (Black patients)	78	24		

Table 1.4 summarizes studies of RA in sub-Saharan Africa. Younger age at disease onset together with a higher female preponderance than described in Europe is reported[110]. Milder disease, fewer extra-articular complications and little negative impact on functional ability have been described[160,161] , but recent studies show that severe disease is more common than previously assumed. Mody et al showed 56% of RA patients in the Western Cape have severe disability[112]. Late presentation (a mean 2.7 years delay in referral for treatment) and disability at presentation were the chief determinants of functional disability in Sowetan RA patients in a retrospective study, and after a median follow up period of 3.3 years, a third of patients had severe disability[113]. A cross-sectional study with established RA have shown poor HRQoL and impaired functional ability[79]. Solomon et al demonstrated high disease activity and substantial functional disability, particularly amongst public care patients. A high prevalence of depression amongst urban RA patients was recently reported[162]. Schneider et al highlight the additional burden of poverty carried by women with RA in Soweto, where low income and the lack of services compound pain, social exclusion and loss of independence [163]. The lack of social support and poor infrastructure of health care services are important considerations in developing countries and mean that a chronic disabling illness has a greater impact on patients and their dependants than in an industrialised country. Poor public transport facilities and lack of electricity, outdoor toilets and lack of hot water geysers are a reality for many of these women. Such services and facilities could mitigate the symptoms as well as the lack of independence associated with RA.

The majority of participants in the GREAT study are resident in Soweto, South Africa and its surrounds. Soweto's origins go back to early 1900's when black Africans were accommodated

on the outskirts of Johannesburg under the apartheid regime. The economic development of Soweto was severely curtailed by the apartheid state, which provided very limited infrastructure. Today, Soweto is home to about 1.5 million people, and despite some development, many areas remain impoverished, with an estimated 53% unemployment rate[167]. Most homes are "matchbox" houses, or four-room houses built by the government (Figure 1.2). Informal squatter camps have developed in the poorer districts with almost no infrastructure, with many residents sharing one tap and a portable toilet. Soweto was meant to exist only as a dormitory town for labourers who worked in white homes, factories, and industries and even today almost all of its residents are public transport commuters to other parts of the city. Moreover, in the last two decades, the population of Soweto has been devastated by the HIV/AIDs epidemic, with older women becoming centrally involved in raising grandchildren orphaned by the disease. There are only 50 registered rheumatologists in South Africa, giving a ratio of 1 rheumatologist per million (0.025/25 000) people as compared to developed countries, for example France, where the ratio is 1/25 000. These factors, together with health budget constraints, mean limited therapeutic options are available, and speak to the urgent need for careful planning of future health care services at all levels. This requires research into musculoskeletal diseases, as models used in developed countries may not apply in sub-Saharan Africa.

Table 1.4: Severity of RA in sub-Saharan Africa- a summary of key studies and their major findings

Year	Study design	City, country	No of pt	Disease duration (yrs)	Positive RF (%)	F:M ratio	Age of onset (yrs)	Radiographic erosions (%)	% with nodules	Disability (Functional Class 3 or 4)	Treated with DMARD (%)	Comments
1988-2002[160]	R	Kinshasa DRC	82	6	63	3.5:1	45.3	No erosions	0.01 (1/82)	_	_	Uncommon, mild
1989[112]	C	Cape Town, SA	52	8.2	87	3.7:1	44.6	+++	25	29/52	65	Severe disease
1991[110]	C	Ibadan Nigeria	23	2.7	48	1.5:1	33	30	8.4	5/23		Young age of onset
1994[145]	C	Harare, Zimbabwe	84	5.8	77.8	3.9:1	49	+	25	mean HAQ 2.8	89	No urban/rural differences
1998[161]	R	Congo-Brazzaville	36	9.5	70	28:0	43.5	100	0.04 (1/28)	0.3 (8/28)	_	Nodules rare
2003[113]	R	Soweto, SA	182	7	87	6.9:1	40.7	_	19	49	93	Late presentation, severe disease
2003[164]	R	Lagos, Nigeria	200	5.3	38.5	2.4:1	46.9	29.2	30	_	100	Common, severe
2005[79]	C	Soweto, SA	100	9	90	_	40.5	++	_	mean HAQ 1.2	_	Impaired HRQoL
2009[165]	C	Kenyatta Kenya	60	9.5	79	6.5:1	41.4	_	13	_	47	Active disease
2009[166]	C	Dakar, Senegal	100	4.5	78	7.3:1	40.3	56	0.03	_	_	Delayed diagnosis, severe disease
2010[111]	C	Yaoundé, Cameroon	56	3	43	19:1	53.5	44	7	_	91	Active disease

RF: Rheumatoid factor; **F:M**: female to male ration; **C**: cross sectional; **R**: retrospective

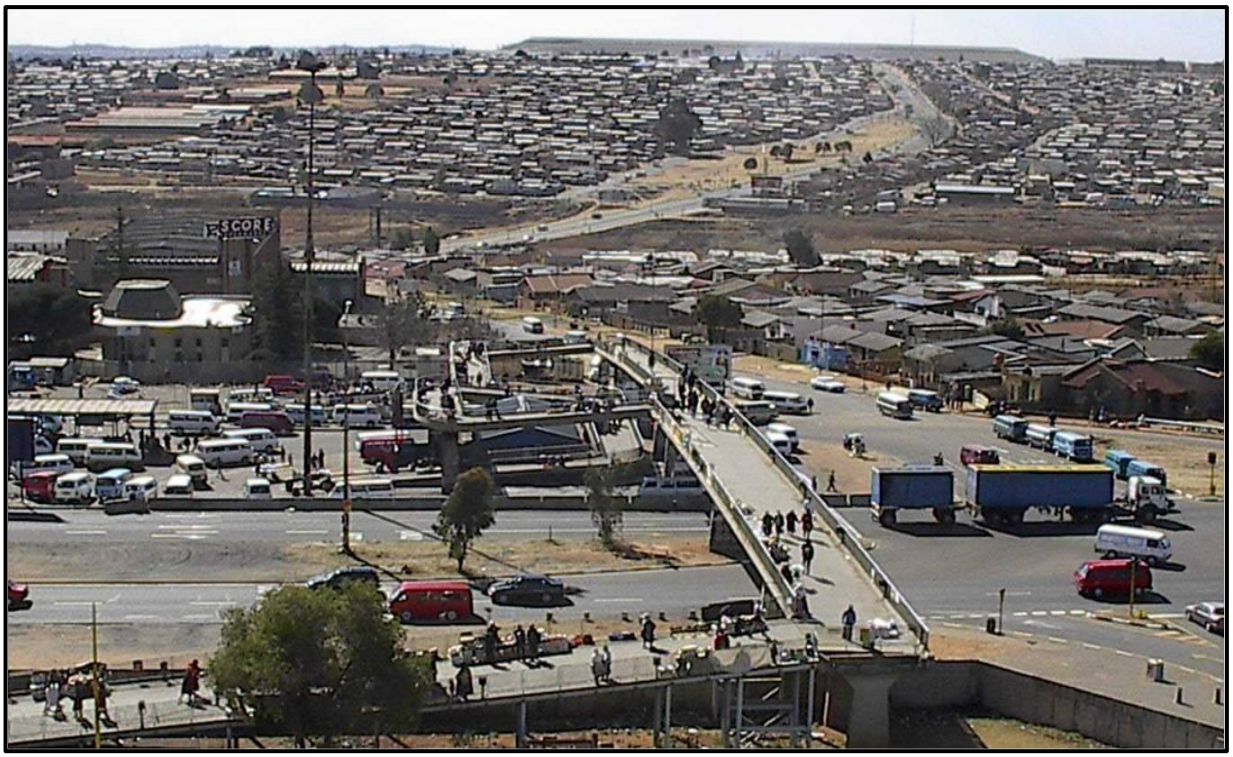


Figure 1: a photograph of Soweto, South Africa taken from Chris Hani Baragwanath Hospital, where the majority of women and men in this study live.

1.7 The gaps in our knowledge

South Africa has a unique combination of excellent clinicians and up to date scientific laboratory services, with a large indigent population dependent on state hospital services. In this resource constrained setting, information on early RA, its severity and response to available inexpensive therapy, together with the factors which influence outcome in terms of disease activity, functional disability and HRQoL are vital for planning of future health services at all levels. In addition, newly diagnosed South African patients need information on how the disease is likely to affect major aspects of their lives.

To date, there are no published prospective longitudinal studies on response to therapy in early RA patients in sub-Saharan Africa, and few in the developing world. Similarly, there are very few studies focusing on functional disability and HRQoL emerging from the developing world. Most studies of aCCP antibodies have been carried out in patients of European ancestry, and the clinical utility of aCCP antibodies in diagnosing RA has not yet been defined in a sub-Saharan African population. Better understanding of the circulating cytokines in serum of patients with early disease might offer clues to the immunopathogenesis of RA, may provide novel biomarkers for assessing therapy, and may offer novel targets for future biologic therapy. There are currently no studies centred on rheumatoid nodules and their associations in Southern Africa, and little work exploring the cytokine profile of such patients.

1.8 Objective and Research Questions

We set out to study early RA in modern urbanized predominantly black South Africans, and to explore the various facets of the disease. The investigation centres on the individual patient with RA, and each of 6 research question focuses on the disease and its consequences at levels which may include genetic, immunological, physical, functional and psycho-social facet of an individual's life.

Research question 1: (addressed in Chapter 3)

What are the baseline clinical characteristics of early RA in this population, and which demographic, clinical and laboratory features predict response to therapy?

Research question 2: (addressed in Chapter 4)

What is the burden in terms of functional ability and quality of life, with particular emphasis on mental health, at baseline and after 12 months of treatment?

Research question 3: (addressed in Chapter 5)

What is the clinical utility of the aCCP test in this population?

Research question 4: (addressed in Chapter 6)

Are various shared epitope subtypes associated with autoantibodies, and with clinical and circulating biomarkers of disease activity?

Research questions 5: (addressed in Chapter 7)

What are the circulating cytokine profiles of early RA patients?

Do circulating cytokine profiles correlate with acute phase reactants, autoantibodies, and disease activity?

Research question 6: (addressed in Chapter 8)

What is the occurrence of rheumatoid nodules in this population of early RA patients, and are they associated with disease activity, radiographic damage, autoantibody status, the presence of the shared epitope, and circulating cytokines?

The findings will be discussed according to 4 major themes. Key points from each chapter as applicable to each theme are shown in Table 1.5. This matrix serves as the framework that will structure the discussion in Chapter 9.

Table 1.5 Key points from each chapter applicable to major themes of the thesis

	Background (Chapter 1)	***Predictors of response (Chapter 3)***	***Functional Disability and HRQoL (Chapter 4)***	***Rheumatoid factor and aCCP (Chapter 5)***	***Shared epitope (Chapter 6)***	***Circulating Cytokines (Chapter 7)***	***Rheumatoid Nodules (Chapter 8)***
RA severity in Africans	·Reports of less severe disease in Africa ·Recent studies challenge this veiw	· high disease activity with substantial radiological damage	·Moderate to severe baseline functional disability at ·poor sf-36 scores particularly emotional, body pain & physical role domains	·high proportion of RA patient were positive for aCCP and RF ·No correlation between baseline features and autoantibodies	·high frequency of SE allele (92%) ·SE associated with higher disease activity	·Globally increased cytokines, chemokines and growth factors	·23% of patients had nodules ·associated with more severe RA
Response to traditional DMARDs	·in developed countries, about a third % of patients achieve a low disease activity	·28% acheived low disease activity at 12 months	·69% still had substantial functional disability ·66% had suboptimal mental health			·some cytokines were biomarkers of high disease activity, and may predict response to therapy	
Being poor matters	·Poverty worsens the burden of RA	·the group overall had a low level of education ·those with fewer years of schooling fared worse	·unemployment and low level of schooling were associated with worse outcomes in disability and mental health				
Biomarkers of RA	·elevated levels of circulating pro-inflammatory cytokines ·the shared epitope (SE) confers susceptibility to RA in aCCP +ve patients			·strong correlations between auto-antibodies and cytokines ·aCCP antibodies strongly associated SE	·SE associated with aCCP antibodies and with circulating cytokines and disease severity	·Circulating cytokines in RA reflect a multifaceted increase in immune reactivity	·Patients with nodules have an exaggerated Th1 and macrophage cytokine profile, with significantly higher VEGF levels ·neither SE nor aCCP associated with nodules

Chapter 2: Patients and Methods

2.1 Patients

The Gauteng Region Early Arthritis (GREAT) registry is an ongoing multi-dimensional project at two tertiary hospitals in Gauteng, South Africa, Chris Hani Baragwanath Hospital, Soweto and Steve Biko Academic Hospital, Pretoria. These state-funded hospitals service a predominantly black African indigent urban and peri-urban population. Patients fulfilled the following inclusion criteria:

1. met the 1987 revised ACR classification criteria for RA[24]
2. ≥18 years of age
3. ≤ 2 years duration of symptoms
4. naive to DMARD therapy at baseline
5. stable dose of oral corticosteroids ≤ 10 mg (if on any) for at least two weeks prior to enrollment

2.1.1 Recruitment of patients

All patients included in the GREAT registry were referrals from primary care practitioners, either primary care clinics or general practitioners. Patients were screened on arrival at the Arthritis Clinic, and were fast-tracked with an appointment for full assessment as soon as possible if they appeared to meet the study inclusion criteria.

2.1.2 Medical therapy

Standard of care was provided with DMARDs and patients were assessed at routine follow-up visits at 2 to 4-monthly intervals. Oral MTX, CQ or SSZ were prescribed as either monotherapy or combination therapy, with or without low dose oral prednisone (≤ 7.5mg/day). Therapy was adjusted by the attending physician, based on the clinical response and adverse effects. No patients received anti-TNF or other biologic therapy. All patients met with the rheumatology nurse educator for information about the disease and therapy at first visit. Poor adherence to therapy was defined as failing to take DMARD therapy as prescribed for 1 month or longer during the 12 months period.

2.2 Study design and assessments

Al l patients gave written informed consent to participate in the study. Data for the study was collected at baseline, 6 months and 12 months, independent of routine clinic visits, as per Table 2.1. Demographic and clinical details were recorded according to a standardized case report form. Demographic details captured at inception included age, symptom duration, current employment status, highest level of education and a smoking history.

2.2.1 Clinical Assessments

At each study visit the 28-joint swollen (SJC) and tender (TJC) counts, and physician global assessment (a Visual Analogue Scale (VAS) of 0 to 100mm). Patients completed a pain and patient global assessment score (a VAS of 0 to 100mm), the HAQ [77], and the SF-36

questionnaire with the help of the study coordinator if needed (Figure 2.1). The presence of subcutaneous nodules was documented.

Table 2.1: Assessments performed at GREAT study visits

		Baseline	**6 month visit**	**12 month visit**
Clinical Assessments	28-Joint Swollen and Tender Count	✓	✓	✓
	Patient Global Assessment	✓	✓	✓
	Pain score	✓	✓	✓
	Physician Global Assessment	✓	✓	✓
	HAQ, SF-36 Questionnaire	✓	✓	✓
Laboratory Investigations	ESR, CRP, haemoglobin and platelet count	✓	✓	✓
Radiographic assessment	Hand and Feet Radiographs	✓		✓
	Chest Radiograph	✓		
Serological tests	Circulating Cytokines	✓	✓	✓
	Autoantibodies	✓		
	Genetic Analysis	✓		

HAQ: Health assesment Questionairre**, SF-36:** medical short Form 36 questionairre

Table 2.2: Disease activity formulas and definitions of disease states

	Formula	Remission	Low Disease Activity	Moderate Disease Activity	High Disease Activity
SDAI	TJC + SJC +PGA(cm) + MDGA(cm) + CRP(mg/dl)	≤3.3	≤11	>11 ≤26	>26
DAS 28-ESR	0.56√(TJC) + 0.28√(SJC) + 0.7ln(ESR) + 0.014(PGA (mm))		<3.2	≥3.2 <5.1	≥5.1
DAS 28-CRP	0.56√(TJC) + 0.28√(SJC)+ 0.17ln(CRPμg/l)+1) + 0.014(PGA(mm))				

SDAI: Simplified Disease Activity Index; **DAS-28:** 28 Joint Disease Activity Count; **TJC**: Tender Joint Count; **SJC**: Swollen Joint Count; **PGA**: patient global assessment; **MDGA**: physician global assessment **ln:** natural logarithm

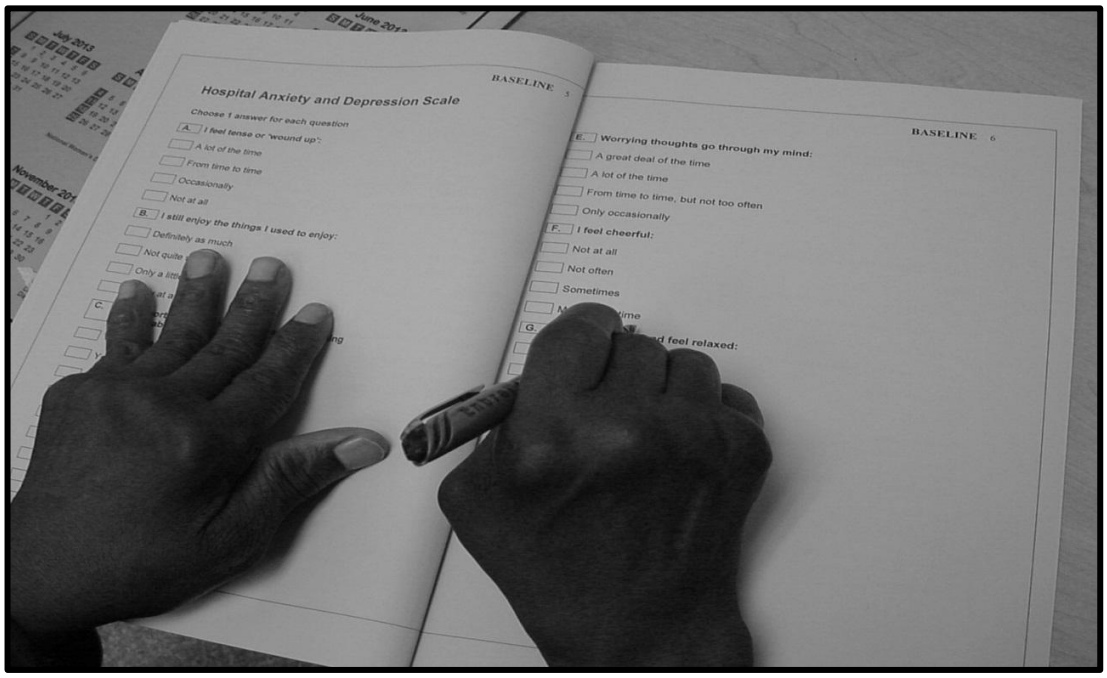


Figure 2.1: An RA patient with a symptom duration of 24 months completing a self-administered questionnaire at the baseline visit. Notice the difficulty with which this patient holds a pen, the "Z" thumb and the ulnar deviation and subluxation at the metocarpophalangeal joints of her left hand- deformities associated with established disease.

2.2.2 Disease activity

Disease activity was assessed with a composite disease activity score. For chapters 3, 4 and 8, the SDAI was calculated, and in the case of chapter 5, the 28 joint disease activity score (DAS28-ESR) was used. Papers 6 and 7 used the DAS-28- CRP. Both the SDAI and theDAS-28 (whether utilizing CRP or ESR to calculate) are validated disease activity indices, and have excellent correlation[68]. The decision to use the SDAI was based on its simplicity, hence it is increasingly used in clinical practice, including by the South African Rheumatism and Arthritis Association. Formulas for the disease activity scores and definitions of disease activity states are shown in Table 2.2.

2.2.3 Functional Disability and HRQoL

"Minimal" functional disability was defined as a HAQ-DI of ≤0.5, and "substantial" functional disability, a HAQ-DI >0.5. For mental health outcomes, an arbitrary cutoff point of 66.6 on the SF-36 mcs was used, and "good" mental health was defined as a score ≥ 66.6, versus "suboptimal" mental health (score <66.6). To assess change in scores from baseline, the minimum clinically important difference (MCID) was calculated. This is the smallest improvement in a score that patients perceive as beneficial, and may not be the same as a statistically significant difference. Based on previously published work in Western populations, the MCID of -0.25 and 5 for the HAQ-DI and SF-36 scores respectively were used[168,169].

2.2.4 Radiographic assessment

Plain radiographs of the hands and feet and chest radiography (CXR) were performed at baseline. Radiographs were scored by two rheumatologists (B Hodkinson and M Ally) using the modified Larsen method. The maximum obtainable score was 200 [170]. Patients were classified as having "erosive" disease if one or more marginal erosion was observed.

2.2.5 Local laboratory investigations

At each study visit an erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), haemoglobin (Hb) level and platelet count were done and analysed by the National Health Laboratory Service at Chris Hani Baragwanath Hospital or Steve Biko Academic Hospital. Anaemia was defined as Hb < 12g/dl in females and < 13g/dl in males [171].

2.2.6 Serological tests

Venous blood (30ml) was collected in endotoxin-free, silicone-coated glass tubes containing a gel separator. The blood samples were allowed to stand at room temperature to coagulate (<1 hour) followed by centrifugation (3000 rpm for 10 minutes ie 1190g) after which the serum was removed, aliquoted, and stored at minus 20◦C until performance of the various assays described below.

2.2.6.1 Auto-antibodies

Rheumatoid factor was assayed by nephelometry (Siemens Healthcare Diagnostics,BN Prospec Nephelometer, Newark, USA) and aCCP antibodies were measured by a second

generation immunofluorometric procedure using the Immunocap 250 system (Phadia AB, Uppsala, Sweden). Values of 15 IU/ml and 10 U/ml respectively were considered positive.

2.2.6.2 Serum cytokines, chemokines and growth factors

The Bio-Plex® suspension array system (Bio-Rad Laboratories Inc, Hercules, CA, USA) which utilizes Luminex® xMAP™ multiplex technology was used to detect and quantify multiple different analytes in a single sample. The following analytes were measured simultaneously: IL-1β, IL-1Ra, IL-2, IL-4, IL-6, IL-7, IL-8, IL-10, IL-12, IL-17A, IFN-γ, TNF, G-CSF, GM-CSF, CCL2, CCL4, and VEGF. The system uses an array of beads in liquid suspension, each containing different ratios of two spectrally distinct fluorophores, thereby assigning a unique spectral identity. The beads were then conjugated with a monoclonal antibody specific for a target protein. These antibody-coupled, colour-coded beads were then incubated with the serum sample (¼ dilutions), washed, followed by addition of a biotinylated detection antibody, washed again, and finally incubated with streptavidin-phycoerythrin. A wide range of standards (0.38 – 91756.00 pg/ml) were used to enable quantitation of the individual cytokines using a Bio-Plex array reader with a dual laser detector and real time digital signal processing. Because of the small number of controls, the upper limits of normal for these analytes were calculated as the mean +1SD for 10 healthy control subjects.

2.2.6.3 Typing of HLA-DRB1 alleles

Venous blood (5ml) was collected in EDTA acid sample tubes and stored at minus 20◦C. Once thawed, genomic DNA was extracted using the Maxwell 16 Blood DNA Purification Kit (Promega, Madison, WI, USA). HLA-DRB1 alleles were determined by using a DNA-based

high-resolution typing method, the LABType HD Class II DRB1 Typing Test (One Lambda Inc, Canoga Park, CA, USA), with reverse sequence-specific oligonucleotide probes and Luminex technology. The target DNA (HLA-DRB1 gene) was amplified by PCR using group-specific primers biotinylated for detection with streptavidin R-phycoerythrin conjugate. The PCR product was then denatured and hybridised to complementary DNA probes conjugated to fluorophores. Bound DNA was detected on the Luminex system and assigned the represented HLA-DRB1 alleles according to the RAA amino acid sequence at positions 72-74 as SE (S) and non-SE (X), and the S group was further subdivided according to amino acid groups at positions 70 and 71 as described by du Montcel et al[92].

Laboratory analysis of auto-antibodies, cytokines and genotyping was done by Dr P Meyer at the National Health Laboratory Service in Pretoria.

2.3 Details of each sub-study

This thesis is based on the first 171 patients enrolled in the GREAT registry between mid-2005 and 2009. Figure 2.2 shows the patient flow for the longitudinal study and summarizes the subgroups of patients included in each of the papers in this thesis. The patients included in the subgroup for Paper 3 were only black African patients. The selection of patients for the remaining subgroups was based on patients with complete data sets at the time of preparing each paper.

Chapter 3 and 4 (Longitudinal study)

These papers are based on a prospective observational study of 171 patients over 12 months. Two deaths occurred and 35 patients that were lost to follow-up, and hence data was available for only 134 patients at the 12-month visit.

Chapter 5 (Cross-sectional study)

Most studies of aCCP antibodies have been carried out on patients of European ancestry, and our interest was in exploring auto-antibodies in black African patients, hence only black patients (n=120) were included in this cross-sectional analysis. The control group consisted of 30 healthy subjects (adults with no clinical disease), 35 systemic lupus erythematosus (SLE) patients and 28 systemic sclerosis (SSc) patients. These black African control patients were attending the Connective Tissue Disease Clinic at Chris Hani Baragwanath Hospital.

Chapter 6 (Cross-sectional study)

In this cross-sectional study 143 patients with complete data sets were assessed.

Chapter 7 (Cross-sectional study)

140 patients were included in this cross-sectional study. A control group of 10 healthy subjects was used to generate normal reference ranges for the cytokine levels.

Chapter 8 (Cross-sectional study)

This cross-sectional study was based on 149 patients with a complete set of clinical, radiographic, cytokine levels and genetic analysis.

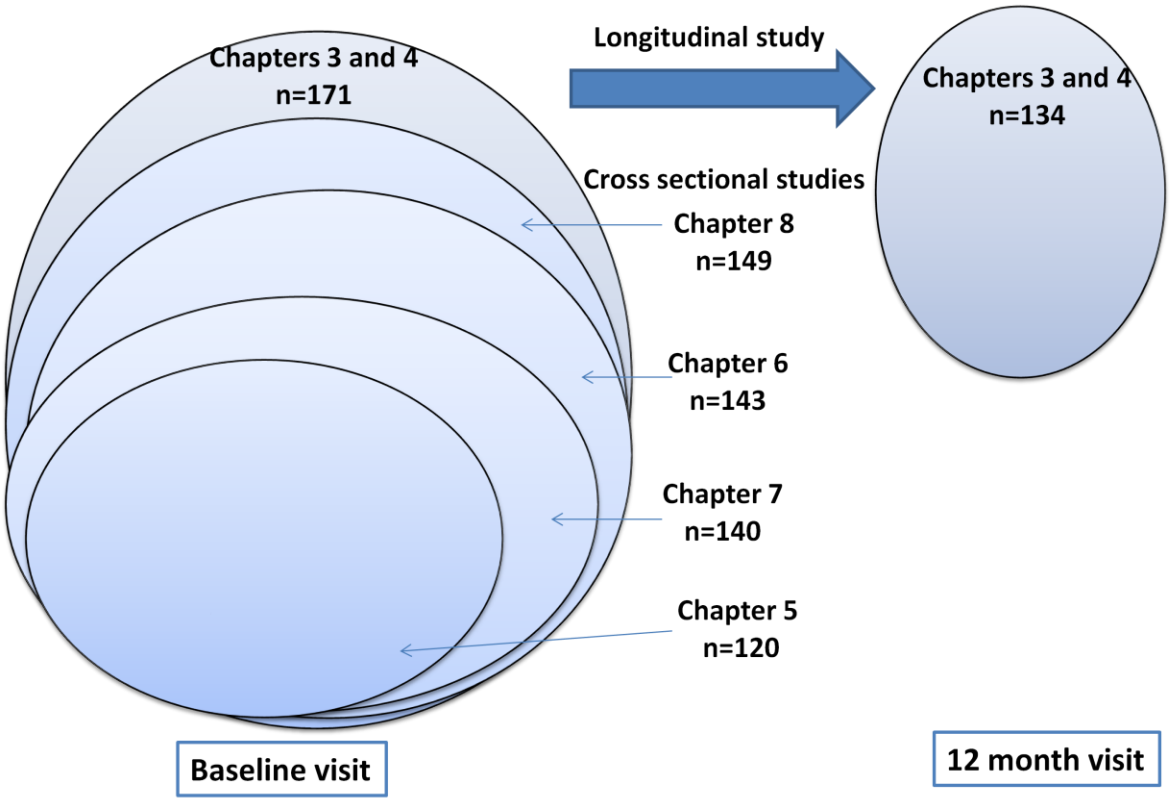


Figure 2.2 Patients included in the longitudinal and cross sectional substudies

2.4 Statistical analysis

Descriptive and inferential statistical methods were performed with the assistance of an expert biostatistician, Eustasius Musenge from the University of the Witwatersrand Epidemiology Data Centre. All statistical analysis was performed using Stata 10 software (StataCorp, USA) or Statistica 10 (Statsoft, USA). A p value <0.05 was considered significant.

For continuous variables, the Students t test, and where appropriate, the Wilcoxon rank sum test was applied. Spearman's correlation coefficient test was used to assess correlations. In the case of categorical variables, Pearson's Chi-Square test, or where indicated, the 2-tailed

Fishers' Exact test was used. The sensitivity, specificity and predictive powers, as well as Cohen's kappa coefficient for agreement were calculated for RF and aCCP tests. Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive powers of the 6 and 12 month SDAI.

Multivariate analyses were performed using backward stepwise logistic regression, and any demographic and baseline variables with a p-value ≤ 0.15 in the univariate analysis were included in the models.

2.5 Strategies to maintain the cohort

Patients who failed to attend their scheduled study visit were contacted by telephone in order to reschedule their appointments. These visits were deemed acceptable if within a month of the original date.

2.6 Ethics approval

The study was approved by the University of the Witwatersrand Committee for Research on Human Subjects (No R14/49), and the FacultY of Health Sciences Research Ethics Committees of the University of Pretoria (No 145/2005) (see Appendix E).

Chapter 3:

Response to traditional disease-modifying anti-rheumatic drugs in indigent South Africans with early rheumatoid arthritis

Summary: This publication describes disease activity at baseline and following 12 months of treatment, and explores predictors of response by comparing clinical characteristics of patients who achieve low disease activity at 12 months to those who have moderate or high disease activity.

Statement of originality of document: please see Appendix C

Chapter 4:

Functional Disability and Health-Related Quality Of Life in South Africans with Early Rheumatoid Arthritis

Summary: This publication presents functional disability and quality of life in RA patients, evaluating improvements over 12 months of therapy and searching for demographic and clinical factors predicting physical disability and suboptimal mental health

Statement of originality of document: please see Appendix C

Chapter 5:

The diagnostic utility of the aCCP antibody test is no better than rheumatoid factor in South Africans with early rheumatoid arthritis

Summary: This publication investigates anti-cyclic citrullinated peptide antibodies and compares their clinical utility to that of Rheumatoid Factor in this cohort. The prevalence of these autoantibodies is compared to that of healthy controls and patients with connective tissue diseases.

Statement of originality of document: please see Appendix C

Chapter 6:

HLA-DRB1 shared epitope genotyping using the revised classification and its association with circulating autoantibodies, acute phase reactants,cytokines and clinical indices of disease activity in a cohort of South African rheumatoid arthritis patients

Summary: This publication explores genetic predisposition to RA in this cohort. The HLA-DRB1 shared epitope alleles and their relationship with disease activity, circulating cytokines and autoantibodies are reported.

Statement of originality of document: please see Appendix C

Corrigendum note:

Table 1 page 2 of this chapter:

C-reactive protein concentration units are incorrect: they should be mg/l not µg/l

Chapter 7:

Circulating Cytokine Profiles and Their Relationships with Autoantibodies, Acute Phase Reactants, and Disease Activity in Patients with Rheumatoid Arthritis

Summary: This manuscript investigates circulating cytokines, their correlations and relationship with disease activity and autoantibodies.

Statement of originality of document: please see Appendix C

Corrigendum note:

Table 2 page 3 of this chapter:

Heading is incorrect: should read Moderate Disease Activity (MDA) not LDA

Chapter 8:

Circulating Cytokine profile of early Rheumatoid Arthritis patients with Rheumatoid Nodules

Summary: This study, submitted for publication, investigates clinical features and serum cytokine levels in patients with rheumatoid nodules by comparing these patients to patients without nodules.

Statement of originality of document: please see Appendix C



Mrs Nomvula V: December 2007

The hands of Mrs Nomvula V, at enrolllment in the study. There is evidence of active disease with swollen second and third metacarpophalangeal joints, proximal interphalangeal joints and wrists. She had very active disease, with 18 swollen and 18 tender joints and an SDAI of 52.7, a pain score of 100mm and a global assessment of 75mm. She had poor grip strength, and struggled with clothes washing, particularly wringing out of clothes, and carrying groceries, and walking and climbing steps was difficult because of knee pain. At inception, her HAQ-DI score was 2.6. The SF 36 questionnaire was low in the physical domains, and very low in the mental domains with vitality, role-emotional and social functioning the poorest areas.

Her blood tests revealed a normochromic anaemia, and she was RF and aCCP positive. Her hand and feet X-rays had erosions, and the Larsen score was 36. She was started on MTX, CQ and low dose prednisone. Over the next year, the MTX was increased, and she received intra-articular steroid injections of her knees, elbows and her wrists. After 8 months of therapy she was referred to the social worker, who arranged childcare grants for the grandchildren. Mrs Nomvula V has also applied for a state disability grant, but at the 12-month visit was still waiting to hear of the outcome of her application.



Mrs Nomvula V: December 2008

Mrs Nomvula V's hands at the 12-month visit. No synovitis or deformity is obvious in her hands, but she had swollen knees and elbows. She had 4 swollen and 9 tender joints and an SDAI of 22.5 (moderate disease activity), a pain score of 75mm, and a global assessment of 75mm. Her physical function had improved, but still she had substantial functional impairment with a HAQ-DI of 1.75. She continued to struggle with walking, carrying groceries but she was once again able to cook, wash and dress herself because her hand function had recovered. The SF-36 physical scores had improved somewhat, as had the mental domains of social function and vitality, but role-emotional remained low. At the 12-month visit, Mrs Nomvula V told me that she was generally better than she had been a year ago, but cited pain as her biggest burden. She was able to go to church most Sundays, but she was always careful "not to overdo it" because she knew "the pain would punish her later". She felt her future was uncertain, and this was her biggest worry with the grandchildren to care for.

Chapter 9: Discussion

This thesis describes aspects of early RA in a cohort of patients treated at either the Steve Biko Memorial Hospital in Pretoria or the Chris Hani Baragwanath Hospital in Soweto, South Africa. Against a background of few studies of early RA from developing countries, and from sub-Saharan Africa in particular, data on this chronic, disabling disease and its features and consequences in this population are urgently needed. The prospective longitudinal observational study fills some of the gaps in our knowledge by describing the changes in disease activity, physical function and health related quality of life in patients treated with traditional DMARD therapy and followed up with routine clinic care over 12 months. The cross sectional studies add to the understanding of circulating cytokines, auto-antibodies, susceptibility genes and a common extra-articular feature of the disease, and the relationships between these variables. These aspects of the disease have not been widely studied in South Africa or elsewhere.

The findings will be discussed according to 4 major themes. Table 1.5 given at the end of Chapter 1 presents a matrix that highlights key points from each chapter as applicable to each theme, and these will be elaborated in the following discussion.

i. RA severity in Africans
ii. Response to traditional DMARDs and routine clinic care
iii. Being poor matters
iv. Biomarkers of RA

This is followed by a discussion of systems and strategies that could improve outcomes in South African RA patients.

9.1 RA severity in Africans

Patients in this cohort had very active disease at presentation, characterized by high swollen and tender joint counts, high global assessment scores, which in combination resulted in high composite disease activity scores. A large proportion of patients were anaemic. In spite of a relatively short symptom duration with a mean of about 12 months, over half of patients had radiographic erosions. Not surprising, therefore, that the overall cohort had moderate to severe functional disability, as measured by the HAQ-DI, with global impairment of HRQoL as measured by the SF-36. In particular, patients scored poorly in the physical domains of role physical, body pain, and physical function, and in mental health domains of role emotional, vitality, and social functioning.

Biochemical and genetic tests showed features of severe, active RA. A high proportion of patients were both aCCP and RF positive (83 and 82% respectively) which is higher than reported elsewhere where the aCCP test and RF have moderate sensitivity in the range of 50-70%[84,85].

The vast majority of patients (92%) in the GREAT cohort carried one or both SE alleles. In the relatively few studies assessing HLA-DR genes in RA patients in Africa, a low frequency of SE-containing alleles compared to European populations has been described (see Table 1.3). The low incidence of RA, mild disease and paucity of extra-articular disease has been attributed to these differences. In the southern African RA population, the frequency of the SE is higher

than that reported elsewhere in Africa, where frequencies around 40% [155-157], and as high as 78% [158] have been described. The present study, in keeping with these reports, reveal s a frequency that is similar to or higher than that described amongst European RA patients[154].

A global increase in circulating cytokines and growth factors amongst patients was demonstrated, with particularly strong intercorrelations of cytokines amongst patients with very active disease.

Nearly a quarter of patients had subcutaneous rheumatoid nodules (RN). Early RN were associated with high disease activity and radiological damage, suggesting more severe RA in this subgroup, and this is consistent with findings elsewhere[52].

The data from the present study argues against the idea that RA in Africa is generally a mild disease, with minimal functional disability and few extra-articular complications. Our findings may be different to those of previous African studies for a number of reasons.

Firstly, there is likely to have been a referral bias. In our health care setting, only the most symptomatic patients are referred to specialized RA clinic. Very early or mild disease with few swollen joints as described in cohorts in Europe and North America were not observed. Hence our patients represent those at the extreme end of the severe disease spectrum and results are place specific and may not apply to other parts of the country.

Secondly, the relatively late referral of patients to specialist centres may have contributed to the severity characteristics of the cohort. “Early” disease in developed countries is now accepted as symptom duration of less than 12 weeks[172]. In our GREAT cohort, although we set out to enroll patients with early disease and used symptom duration as less than 24 months, the mean symptom duration was 11.6 months, with only 29% of patients referred

within 6 months, and 11% within 12 weeks of symptom duration. Strategies to reduce the referral and the diagnostic delay need to be explored. Additionally, there may have been inaccuracies in reporting the date of symptom onset, so in fact many patients had much more established disease than our data shows.

Finally, the impact of urbanization and its associated environmental triggers of RA, including cigarette smoking and infectious agents, may be a further explanation for the severe disease in this urban population. In addition, climatic factors, in particular the protective effect of tropical infections described in Nigeria, are not relevant to temperate South Africa[173].

At baseline, the group overall had nearly every disease-specific poor prognostic feature identified in RA and summarized in Table 1.1. These, together with the poor SES of many of our patients, hold an important clinical message: these patients require aggressive treatment to avoid poor outcomes.

9.2 Response to traditional DMARDs and routine clinic care

9.2.1 Disease activity

Despite improvements in disease activity of the group overall, less than a third (28%) of patients had low disease activity after 12 months of therapy, and remission was achieved in only 10% (Figures 9.1 and 9.2). These results are not dissimilar to findings elsewhere in early RA patients treated for 12 months with traditional DMARDs. In the ERAN study in the UK, and in a mixed US and Mexican cohort and a Swedish cohort, 29%, 32% and 34% of patients, respectively, achieved a low disease activity state [174-176].

Poor prognostic factors identified in the present study included older age, high baseline disease activity and functional disability, low haemoglobin level and high platelet counts, together with a low level of formal education. These factors are consistent with predictors of outcome identified elsewhere, and are somewhat "intuitive' to physicians treating RA patients and may be of some use to the clinician treating early RA patients. However, the correlation co-efficient of the multivariate model in this study shows that these factors accounted for only 14% of the variability in response. Complicated prediction scores have been devised from large databases with weighting of variables to stratify patients into benign, moderate or severe disease categories[49,177], but these models may be of limited use in clinical practice. Perhaps one of the most important clinical messages arising out of the present study is that disease activity at 6 months was strongly predictive of disease activity at 12 months. This concept that early response to therapy is the most useful predictor of response has been shown elsewhere. In a large set of early RA patients, disease activity at 3 months from the start of treatment correlated strongly with disease activity at 1 year[178]. Another large study of early RA patients showed that there was a low chance of achieving low disease activity (or minimal functional disability) during the second or third years of DMARD therapy if low disease activity had not been achieved during the first year[174]. Similar findings were reported in a smaller study in the Netherlands[46]. Hence, a passive "wait and see" approach, so often applied in clinical practice, and followed in the present study, in patients who have not achieved a suppressed level of disease within 3 to 6 months of therapy is unlikely to result in low disease activity.



Figure 9.1: A third of patients achieved low disease activity on traditional DMARD therapy. This patient has no synovitis, an SDAI of 3.3 and has normal hand function after 12 months of therapy. She continues to work as a pre-school teacher.

9.2.2 Disability and HRQoL

In early RA the principal determinant of physical disability is disease activity, specifically synovitis and pain, with improvement in HAQ-DI scores as treatment is commenced [179]. This is in contrast to established disease, where permanent joint damage, as measured by radiological scores and deformity, leads to progressive disability that is less likely to reverse[48,180]. In the present study, despite improvements in functional disability in the group overall, a third of patients failed to achieve a clinically significant improvement in physical ability. At the end of 12 months of therapy, two thirds of patients still had substantial physical disability. This impacted on activities of daily living: a third of patients remained

unable to climb a flight of stairs, could not shop for groceries independently, and accomplished less than they would have liked because of their physical health. There are relatively few reported inception cohorts of early RA that have focused on functional disability and HRQoL, and the majority of these studies use Steinbrocker's functional grading as a measure of disability making direct comparisons with this study difficult. Most patients improve, with one large study showing the percentage of patients having no functional impairment increasing from 33% to 40% over 5 years, with significant disability seen in only 9% at baseline and 16% at 5 years[181]. In the present study, poorer outcome was seen amongst females, patients with poor baseline physical function and high pain scores. Studies elsewhere show similar risks for disability in early RA[47,182,183].

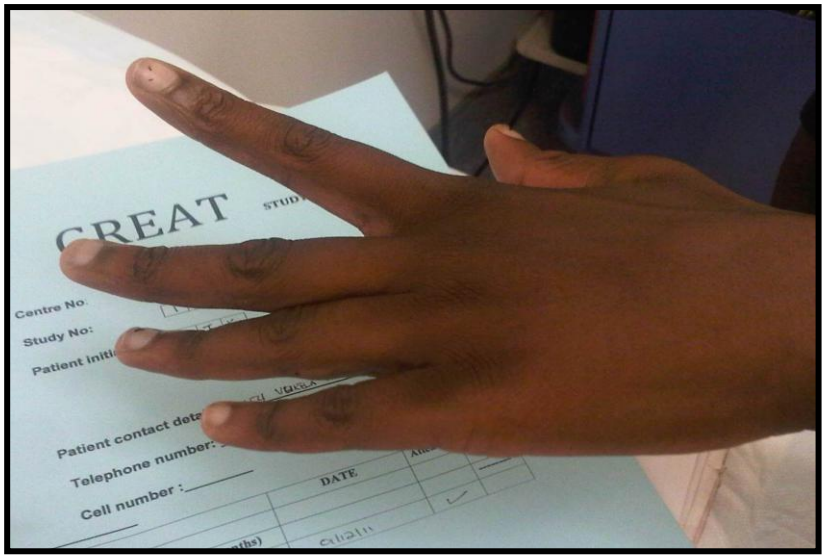


Figure 9.2: Despite significant improvement in disease activity in the group overall, a substantial number of patients remained in a moderate or high disease activity state at the 12-month visit.. This young patient enrollled in the GREAT study clearly has severe disease which has responded poorly to traditional DMARD therapy, and uncontrolled wrist synovitis has led to partial extensor tendon rupture of fingers 3, 4 and 5.

In terms of mental health scores, improvements were even poorer (only 43% achieved a clinically meaningful change). The majority (66%) of patients had suboptimal mental health despite 12 months of RA treatment, with particularly blunted participation in social activities, poor emotional well-being and low energy levels. A large meta-analysis has shown depression to be 2 to 3 times more common amongst established RA patients than the healthy population[184]. As many as 40% of established RA patients met criteria for depression in recent studies in Japan and the USA[51,185]. In early disease, however, the low scores in the mental health scales, particularly in vitality, social functioning, and role emotional observed at baseline returned to normal after 12 months of either MTX or anti-TNF therapy[186].

In the present study, patients most at risk of suboptimal mental health were those who were unemployed, had a low level of formal education, high baseline pain and functional disability at baseline. Other studies have shown similar complex relationships between depression and pain, physical disability and SES factors [51,187,188]. Katz et al refined the broad concept of functional impairment, and show that the loss of valued activities were the most likely to result in depressive symptoms. These might include simple daily tasks like cooking, visiting with family or neighbours, shopping or gardening[189]. The nature of the relationships between poor mental health and active disabling disease are difficult to determine, because pain and physical impairment can lead to depression, but equally depression is likely to hinder physical activity, adherence to therapy and increase pain perception. Disentangling such processes is difficult, and it may be that the explanations co-exist. In a recent study, patients with

depression were less likely to achieve remission, and reciprocally, patients who achieved remission were less likely to remain depressed[190].

9.3 Being poor matters

Most patients in the present study were of a low SES background, with high unemployment rates and low levels of formal education (Figure 9.3 and 9.4). These factors no doubt contributed to the fairly low response rate to therapy in the group overall, and were shown to be predictors of poor outcome. Patients who achieved low disease activity at 12 months were significantly younger and had completed more schooling than patients who remained in a moderate or high disease activity state. That older age was a poor prognostic factor may be a reflection of the pre-1994 apartheid system in which most black Africans were deprived of quality education. Similarly, with respect to both functional disability and mental health at 12 months, low levels of formal education, and unemployment were poor prognostic factors. These links between poor SES and poor outcomes have been shown elsewhere. Margaretten et al refer to a "vulnerable population" of RA patients where background poverty and high functional disability give rise to a high risk for mental ill-health[66].

In the absence of a validated index in South Africa, level of education and unemployment were used as markers of SES in the present study. Perhaps a more complex tool to better define the SES of a patient would show that poverty influences outcome even more strongly than we have demonstrated. Such a tool needs validation in the South African population, and needs to be updated regularly. For example, Norris et al showed that television

ownership in 1990 was a useful marker of good SES in Soweto, South Africa, but clearly in 2012 most households, even indigent ones, have a television.

Reasons for the impact of SES on clinical status are complex, and may include delays in initiating DMARDs with late presentation to health care services because of low awareness of symptoms and treatments available for arthritis. Another explanation might be limited access to health care. Lack of or underutilization of available resources, in particular allied health care, by less educated patients, may further contribute to poorer outcomes[60]. Lifestyle factors associated with poverty, including poor diet and exercise, stress exposure and weaker social support may worsen outcomes[58,191]. Indigent patients living in areas with poor infrastructure, including inadequate public transport necessitating walking long distances, carrying of water and use of outside toilets experience their physical disabilities in a much more profound way than wealthier patients who own a car, have domestic help and indoor bathrooms with hot water geysers.

In addition, patients with poor SES are less likely to participate in leisure activities, and tend to "close down" their social networks when a chronic disease befalls them [192]. It seems that patients with better education take a more active role in problem solving [193]. Successful behavioural coping strategies might include analyzing problems from various perspectives, seeking different solutions and viewing problems as challenges – and this may mediate illness perception and the overall impact of a chronic illness such as RA [194].



Figure 9.3: The Soweto home of one of the study patients showing sparse socio-economic circumstances where basic services and facilities are largely unavailable to many RA patients. Electricity, indoor toilets and hot water geysers are basic services that could mitigate the symptoms of RA.



Figure 9.4: This study, like studies elsewhere, showed that RA patients with poor socio-economic backgrounds such as this informal settlement in a district of Soweto are at risk for poor outcomes. Poor infrastructure, including inadequate public transport necessitating walking long distances, carrying of water and use of outside toilets means that RA patients experience their physical disabilities in a much more profound way than more affluent patients.

9.4 Biomarkers of RA

Until recently, RF has been the principal serological marker for RA, with the recent discovery of aCCP which have excellent diagnostic and prognostic properties, and may be particularly useful in early RA. In the present study of black South Africans, the overall diagnostic performance of aCCP antibodies and RF was similar, with good sensitivity of both the aCCP test and RF (78% and 79% respectively), comparable to that reported in other populations[85]. The combination of both RF and aCCP positivity had the highest specificity, indicating that, ideally, both tests be done for diagnostic certainty when assessing a patient with inflammatory polyarthritis. However, this study supports a resource-saving strategy stepwise approach: testing for RF first, and performing an aCCP test only where the RF test is negative and there is a strong clinical suspicion of inflammatory arthritis. In this cross-sectional study, aCCP was not associated with any clinical or radiographic severity features, however long-term follow up will allow investigation of the prognostic utility of aCCP test in this population.

The sub-study of genetic susceptibility to RA in this population revealed, as mentioned above, a very high occurrence of HLA-DRB1 SE alleles in RA patients. This prevalence is in keeping with other studies performed in South Africa, and is much higher than described amongst patients elsewhere in Africa. In terms of the new classification of SE risk alleles, our RA patients had an over-expression of the “high risk” alleles S2 and S3P, whilst the S1 allele is undertransmitted, a pattern similar to that seen amongst RA patients in the San population of southern Africa[93]. It has been previously shown that the genetic predisposition to RA conferred by the SE occurs exclusively in aCCP positive patients[96,195], and the interaction

between citrullinated proteins and SE alleles may in fact initiate the immune response in RA[98]. In keeping with these concepts linking genetic predisposition, auto-antibodies and activation of the immune system, the present study revealed an association between the SE, in particular the S2 and S3P alleles, with aCCP antibodies and with a Th1, Th2 and macrophage cytokine response together with increased IL1-Ra levels.

Globally increased levels of circulating cytokines, chemokines and growth factors in early RA patients were observed , in keeping with other studies[102,196], and underscoring the central role of Th1 lymphocytes, macrophages and fibroblasts in the immunopathogenesis of RA. However, there were only weak to moderate correlations between auto-antibody and circulating cytokine levels, and no relationship between disease activity and circulating cytokines. The approach of stratifying patients according to baseline disease activity may be useful in the search for predictive biomarkers, because patients with highly active disease at baseline may have different pathogenetic events to those who start with low disease activity[178]. Of interest then, is analysis of cytokines in the subgroup of patients with high disease activity in the present study. In this subgroup, cytokines were highly intercorrelated and VEGF, a marker of angiogenesis, correlated well with other circulting cytokines, with radiological damage and with autoantibodies. VEGF has emerged as a major marker of disease activity and radiographic progression in both established and early RA[197-199]. These findings may suggest that endothelial dysfunction and angiogenesis play an important role in the immunopathogenesis of RA[198,200], perhaps in severe disease subtypes in particular, and may provide another molecular target for therapy of RA. Although offering important information about the possible pathogenesis of RA, this study has demonstrated that neither

the SE nor circulating cytokines offer prognostic information over and above the traditional biomodel. Further work is needed to assess the utility of baseline circulating cytokines as predictors of medium and long-term outcomes. The relationship between these baseline biomarkers, perhaps VEGF in particular, and disease activity, radiological damage and new extra-articular complications of disease in this cohort needs to be extended to 2, 5 and 10 year visits. This work is already underway.

Rheumatoid nodules have been described in under 10% of patients with early RA, and here they confer a poor prognosis, predicting the development of other extra-articular complications and radiological damage [52,106]. In the present study, 23% of patients had RN. Given that patients included in the study had early disease, and since RN have been described as rare in patients of African origin in a study of West African RA patients[110], this high prevalence was unexpected. These patients had higher disease activity and radiographic damage scores than patients without RN, but there were no significant differences in terms of smoking history, frequency of aCCP antibodies, RF or SE alleles.

Histopathologically, RN are immune granulomas consisting a central area of necrosis, surrounded by a "palisade" of macrophages and fibroblasts, and a peripheral vascular area containing T lymphocytes and macrophages [125]. A recent immunohistochemical study concluded that the RN is a Th1 granuloma based on the presence of Th1-derived cytokine transcripts in RNs[128].

In the subgroup study of rheumatoid nodules (RN), our results suggest the Th1-mediated response is exaggerated in patients with RN. Circulating cytokines of Th1 and macrophage

origin were significantly higher in these patients, independent of disease activity. Furthermore, levels of pro-angiogenic factors VEGF and IL-8 were significantly higher in RN patients, suggesting angiogenesis is an important feature of the RN, and may support earlier reports of vasculitis in the immunopathogenesis of RN [125,201]. These findings may offer clues to the immunopathogenesis of RN and possibly other extra-articular complications of RA.

Chapter 10: Conclusions

10.1 Limitations of the study

This study has a number of limitations that require comment. Firstly, the sample size was relatively small. Furthermore, in the longitudinal study, there was a significant amount of incomplete data. Over the 12 months of the study, 20% of patients were lost to follow-up. These patients represent an important group because they had more severe disease at baseline. As mentioned above, the study cohort most likely reflects a selection bias of patients referred to a tertiary hospital; hence results cannot be generalized to RA patients elsewhere in sub-Saharan Africa.

The follow-up period of 12 months was relatively short, and only baseline radiographic scores were assessed. The majority of patients in this cohort have already completed their 5-year visit, and data from this is under analysis. There is much information to be gained on the medium and long term outcomes of these patients and their relationship to baseline parameters.

We relied on the SF-36 mental component score to assess depression and anxiety, and would have obtained better information from a specifically validated depression score.

The assessment and adjustment of therapy at the routine clinic visits was performed by clinicians with variable expertise. We did not assess intra- and inter-observer variability in joint counts or global assessment scores, and clinicians were not blinded to the therapy of

their patients. Although this may have contributed to the low response rates, a fairly accurate reflection of “real life” care in most state-sector hospitals in South Africa has been obtained, and this is one of the strengths of this study.

Hand and feet radiographs were scored at the baseline visit by two rheumatologists who assessed the x-ray simultaneously and reached a consensus score. Furthermore, the x-rays were performed at 2 different centres and no standard radiology protocol was followed. This is not ideal, and may be satisfactory for this cross-sectional study, but may cause inaccuracies in further longitudinal studies.

10.2 Systems and strategies for the future

I have chosen the phrase “***many hands that don’t work***” as a subtitle for this thesis. This is a reference to the RA patients who have ongoing disease activity and substantial functional disability despite therapy; and also alludes to the high unemployment rate amongst indigent South Africans. In addition, there are many hands at work in caring for rheumatoid arthritis patients, but this study has revealed that despite significant improvements, they are somewhat ineffective in relieving the patients' symptoms and the ongoing effect of those symptoms in their lives, and in the lives of their dependents. The web of interconnecting relationships that manage the care of patients is manifold and, in South Africa, beset with challenges. To delve too deeply into the shortcomings of the current clinical care of patients would be a departure from the objectives and the important findings of this thesis. In the interests of progress, and to inspire further research, what follows is a practical exposition of possibilities.

10.2.1 Control of disease activity

The diagnostic delay is an area for improvement, because the evidence is that a delay in starting treatment cannot be made up in the long term[20]. Investigation of where the delay lies- in late patient presentation to health care system, or in sluggish referral from primary health to tertiary centres, or a combination- will direct intervention. There is a need to increase public awareness of the symptoms of arthritis, and the benefits of therapies now available, particularly if started early, so that patients with joint symptoms visit their clinics or family doctor timeously. This may involve media campaigns and public awareness days- an extension of work started under the international "Bone and Joint Decade" initiative[202]. Primary health care workers- general practitioners, clinic sisters and doctors- need training in order to diagnose early inflammatory arthritis. This requires concerted efforts in continuing medical education programmes, with discussion of the findings of this study with respect to autoantibody testing, and with sharing of the new ACR diagnostic criteria to assist in early diagnosis[26]. Referral pathways can be set up at such meetings so that health care workers have links to each other to facilitate queries and feedback. Early arthritis clinics at tertiary hospitals which rapidly screen walk-in referrals with a quick joint examination, and thereafter "stream" patients for an urgent versus a semi-urgent assessment visit have been developed in Leiden, Netherlands and have been useful to referring physicians, patients and rheumatologists.

The complex relationships between disease activity, pain, functional disability and mental health are demonstrated by this study. Interventions to improve both physical and mental

health in RA may be most successful if each of these areas is addressed. Poor control of disease activity itself, present in over two thirds of patients, speaks to the need for new strategies and new drugs. Both physical disability and mental health scores, including emotional well-being, improve with effective management of RA using either DMARDs or biologic drug therapy[186]. Recently it has been shown that traditional DMARDs can be used more effectively with minimal added expense if a "tight" control strategy is employed. Such a strategy involves formal assessment of disease activity at regular visits (more frequent than performed in the present cohort), and "treating to target" with modification of therapy according to a treatment algorithm if low disease activity (or ideally, remission) is not achieved. The TICORA study (in Glasgow, UK) showed patients managed with a tight control strategy were much more likely to achieve remission than those offered routine care (65% vs 16%, $p<0.0001$)[203]. In addition, patients had better outcomes in terms of physical function, health-related quality of life and radiological progression. Similar excellent results have been shown elsewhere: the BeST study in the Netherlands, and FIN-RACo trial in Finland, and in the Netherlands[204-206]. Such a strategy has not yet been explored in southern Africa.

Patients who do not show an adequate response to therapy within 3 to 6 months require new strategies. This might include combination DMARDs, addition of another DMARD such as leflunomide as monotherapy or in combination with MTX. There is also clearly a need for biologic therapy in patients who have ongoing active disease, although access to these drugs remains a challenge in our setting. Clinicians need to lobby on behalf of their patients, both to the pharmaceutical industry to reduce the cost of these drugs to within reach of resource-constrained settings such as ours, and to the state sector to provide funding for these drugs,

taking into account the long term cost-effectiveness of disease control which has been shown elsewhere[207].

10.2.2 Mobility

There is clearly a need for more aggressive rehabilitation by allied health professionals for RA patients. Physiotherapy programmes need to be accessible (perhaps run at local clinic level), and practical, exploring new ways to keep patients on an exercise programme. A recent study in the Netherlands showed that “motivational interviewing” is a useful strategy to enhance motivation and thus improve participation in exercise and joint strengthening programmes [208]. Such an approach could be explored in our context. Occupational therapy has a central role to play in the ergonomic assessment of a patient’s home and workplace, splinting and adaptative equipment guidance and education for patients and family members (Figure 10.1). The Chris Hani Baragwanath Hospital hand occupational therapist, Carin Dreijer du Plessis, successfully showed that intensive week-long inpatient training sessions, with home visits, in our RA patients, were very effective, with improvements in both functional disability and mental health scores[209]. We need larger scale initiatives to come out of this work.



Figure 10.1: A Futura wrist splint worn by a GREAT study participant. Such a splint reduces pain and improves task performance. Occupational therapists offer RA patients instruction on joint protection and energy conservation, education and counselling, assistive devices and splints, resulting in improved functional performance and social participation. Rehabilitation teams may have been underutilised in this study, and outcomes may be improved by early referral and intensive inpatient sessions.

10.2.3 Mental Health

Closer links with psycho-social services with screening for and treatment of depression at baseline and at follow-up visits are called for. Recent work showed a simple 2-question screening test for depression to be useful and practical[210]. These two questions are “Have you felt down, depressed or hopeless over the last 2 weeks?” or “Have you little interest or pleasure in doing things over the last 2 weeks?” . We need to explore this test or adapt it for our patients. Strategies to treat depression might include individual and group therapy sessions, as well as antidepressants. Self-management techniques including cognitive

behavioral therapy and relaxation techniques have been shown to improve pain, self-care and participation in social events[211,212]. A recent study by psychiatrists in Connecticut, US asked RA patients to report their daily pain, mood and activities for 75 consecutive days[213]. This study confirmed the relationship between depression or anxiety and heightened joint pain. There were coping strategies, including relaxation, distraction and support-seeking, observed amongst patients with low pain scores and positive moods that could be of use to other RA patients. There are likely to be lessons to learn from RA patients in South Africa who cope with pain that we have not considered formally exploring. Antidepressants in depressed patients with musculoskeletal disease have been shown to improve not only mental health status, but physical disability and pain scores[214]. The effectiveness of these and other strategies in South Africa are areas for further research.

10.3.4 Maintaining relationships

The solutions to poor adherence to chronic medication are complex, because the ability of a patient to follow her treatment plan is compromised by any one or more of a number of "barriers" [215]. These might include economic and social factors; problems with access to the health care system; patient-related factors, and the therapy itself. Amongst our patients, reasons for not returning for treatment may be related to poor SES, where the cost of transport to and from hospital, and the consequences of a day of unpaid leave for patients with jobs, was a deterrent. A service to supply monthly medication to the nearest clinic or to the patient's home would greatly assist patients, and very likely improve treatment adherence. Some patients, particularly those doing badly on treatment, may have sought

alternative treatment at other hospitals or with traditional healers. Others did not “buy into” the importance of early aggressive DMARD therapy. Our message failed to take root.

Intuitively, it seems that communication with patients about their disease and treatment offered could be helpful. All patients enrolled in this cohort had a brief education session about the disease and the medication prescribed. In addition, all RA patients attending the Arthritis Clinic attend a midday group multidisciplinary meeting where the rheumatology nurse educator, an occupational therapist, physiotherapist, social worker and podiatrist speak briefly about RA and then answer individual questions. This session was cited by patients as being very useful[163]. These existing sessions need to be maintained and developed. Perhaps abstract information about the disease and the interventions available to retard disease progression may be of use to well educated patients in Europe and North America, although interestingly research has not proven such sessions to improve adherence[216]. A new approach is called for in southern Africa, centered on our patients, with their unique references, belief systems and individual domestic situations. Patients need to be invited to participate in interactive sessions which are facilitated by a rheumatology nurse practitioner. Such sessions would offer non-medical explanations of the disease and treatment options, and give patients a good understanding of how to take the prescribed therapy and an idea of possible side-effects that might be experienced. The session could conclude with a discussion of expectations, and realistic goal setting. Education sessions are more effective when combined with a patient-focused educational booklet that patients can take home and read with their families[217]. Such material needs to be developed in South Africa and translated into local languages. In addition, family and, where applicable,

employer support can play a large role in improving adherence. Patients could be encouraged to enlist the understanding and help of family, employers and colleagues. Awareness of chronic illnesses, and musculoskeletal problems, amongst the community could be widened via television and radio programmes, and this would benefit patients.

An untapped resource is RA patients themselves. An opportunity for a newly diagnosed RA patient to meet and interact with patients who have lived with the disease and its therapies for many years could offer inspiration and sharing of coping strategies. Soweto has a few arthritis support groups, but more patients could benefit from a wider-reaching programme which specifically includes newly diagnosed RA patients.

The challenge is also to arthritis clinics, at secondary or tertiary level, to improve the service offered. Smoother clinic running with short waiting times, and an opportunity for relaxation and refreshment for patients whilst waiting for a consultation would be ideal (Figure 10.2). A "call-in" service for disease flares could be beneficial. Patient-centred assessments, incorporating the patients' agenda and interests, could shift the physician-patient relationship from passive and somewhat unproductive to a more interactive and empowering partnership, resulting in better patient retention and adherence, and indeed better disease outcomes. Measuring outcomes that are important to patients, rather than just capturing outcomes that clinicians are interested in, is a growing field in modern rheumatology, and deserves attention in our context. A simple question like "Which areas would you most like to see improvements in the next 6 months?" from the rheumatology nurse, the occupational therapist or physician could yield important answers, and encourage patients to prioritize their difficulties[218]. Another enquiry that captures the loss of valued

activities might be “Can you do the things that you want to do? If not, list these activities” which could complement the HAQ-DI and allow health care workers and patients to focus on solutions together[189].

10.2.6 RA specialists at every level of the care team

A significant advance in modern rheumatology is the recognition of the importance of the rheumatology nurse practitioner. The responsibilities of such a professional include drug monitoring, education, counseling of patients and co-ordinating the multidisciplinary team caring for an RA patient. It has been shown that rheumatology nurse practitioners are of great benefit to patients and central to the operation of the multidisciplinary team [219,220]. Training programmes have been developed in Europe and North America, and there is clearly a need to train specialist nurses in the field of rheumatology in South Africa.

Ongoing training and support of all health care workers is needed, because patients bear the brunt of poor care from overstretched and “burnt-out” nurses, administrative personnel and doctors. Patients need to feel that they are seen and heard as individuals, and this is impossible to achieve if staff are not nurtured and acknowledged. Empowered health care can empower patients.

“Shared care” has been very successful in Europe. In such a programme, patients are diagnosed with RA and started on therapy, and once they achieve remission or low disease activity, are referred back to primary care doctors for treatment and monitoring, with 6 to 12 monthly reviews by a rheumatologist at a tertiary centre. This approach is convenient and

less costly for patients, and makes better use of health care facilities. In SA we have failed to set up such partnerships, and better primary health care facilities, training and support of their staff and dispensaries might allow such programmes to begin.



Figure 10.2: Queuing for care. The long waiting times in our clinic, with rows of patients waiting much of the day to be seen by a doctor, could be used more effectively. A more patient-centred clinic, with meaningful interaction and support group meetings could take place in this time. This may improve adherence to therapy and to follow-up visits, and would empower patients and very likely improve outcomes.

10.2.7 Better use of resources

South Africa, in comparison to other sub-Saharan African countries, has plentiful resources. There are more effective ways to use these existing resources, applicable to both health care planners and to individual patients themselves. This is an area where South Africans often fall short, preferring to feel that they are indigent and trapped rather than looking for solutions, not necessarily financial ones, to improve their situation. As members of the health care team, we need to focus on using existing resources more effectively, endeavoring to share this attitude with our patients.

"It is what we make out of what we have, not what we are given, that separates one person from another."

Nelson Mandela, 1995 [221]

10.2.8 Public services

There are other unmet needs that are highlighted by this study, falling within the realms of social services and government departments. These include job retention in patients who have jobs, and better public transport systems so that indigent patients with disabilities have fewer challenges not just with hospital attendance, but also to maintain their occupational and social lives. There is an urgent need to develop stronger partnerships not just within the medical team, but in the domains of transport, and the pharmaceutical industry to allow

patient-centred health care services. There is a social message, common to all chronic disorders that highlightS the fundamental importance of formal education at primary and secondary school level. Lack of formal education has grim consequences on many facets of an individual and her community. In SA, our broken education system urgently needs attention for the sake of tomorrow's adults.

In health, there is freedom. Health is the first of all liberties.

Henri-Frederic Amiel, 1860 [222]

In our young democracy, freedom will only be truly realized when we can offer good health care to all the peoples of South Africa.

10.3 The way forward

Unmet needs and areas for future action and research are highlighted by the present study. In particular, new treatment approaches, including intense patient education and biologic therapy, might allow better outcomes to be achieved. Earlier referrals of inflammatory arthritis to specialist centres need to be encouraged.

Long-term follow up of this cohort might allow the prognostic utility of the aCCP test and the SE in this population to be established. Further work is needed to assess the role of baseline circulating cytokines as predictors of medium and long-term outcomes.

An investigation of the changes in circulating cytokine profiles of patients with RN and other extra-articular complications over time and with therapy, accompanied by immunohistochemical studies, will be of interest.

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Appendices

A. Health Assessment Questionnaire

We are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments at the end of this form.

Please tick the one response, which 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:				
Dress yourself, including tying shoelaces and doing buttons?	_____	_____	_____	_____
Shampoo your hair?	_____	_____	_____	_____
2. **RISING** Are you able to:				
Stand up from an armless straight chair?	_____	_____	_____	_____
Get in and out of bed?	_____	_____	_____	_____
3. **EATING** Are you able to:				
Cut your meat?	_____	_____	_____	_____
Lift a full cup or glass to your mouth?	_____	_____	_____	_____
Open a new carton of milk or soap powder?	_____	_____	_____	_____
4. **WALKING** Are you able to:				
Walk outdoors on flat ground?	_____	_____	_____	_____
Climb up five steps?	_____	_____	_____	_____

Please tick the one response, which 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:				
Wash and dry your entire body?	_____	_____	_____	_____
Take a bath?	_____	_____	_____	_____

Get on and off the toilet? _____ _____ _____ _____

6. REACH Are you able to:

Reach and get down a 2kg object (e.g. bag of potatoes)

from just above your head? _____ _____ _____ _____

Bend down to pick up clothing from the floor? _____ _____ _____ _____

7. GRIP Are you able to:

Open car doors? _____ _____ _____ _____

Open jars, which have been previously opened? _____ _____ _____ _____

Turn taps on and off? _____ _____ _____ _____

8. **ACTIVITIES** Are you able to:

Run errands and shop? _____ _____ _____ _____

Get in and out of a car? _____ _____ _____ _____

Do chores such as vacuuming, housework or light gardening? _____ _____ _____ _____

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

_____ Raised toilet seat _____ Bath rail

_____ Bath seat _____ Long handled appliances for reach

_____ Jar opened (for jars previously opened)

Other (Specify): _____

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

_____ Dressing and Grooming _____ Eating _____ Rising _____

B. SF-36 Questionnaire

INSTRUCTIONS: THIS QUESTIONNAIRE ASKS FOR YOUR VIEWS ABOUT YOUR HEALTH. THIS INFORMATION WILL HELP KEEP TRACK OF HOW YOU FEEL AND HOW WELL YOU ARE able TO DO YOUR USUAL ACTIVITIES. PLEASE BE SURE TO ANSWER EACH QUESTION BY CIRCLING ONE OF THE RESPONSES PROVIDED. IF YOU ARE UNSURE ABOUT HOW TO ANSWER A QUESTION, GIVE THE BEST ANSWER YOU CAN.

1. IN GENERAL, WOULD YOU SAY YOUR HEALTH IS:

EXCELLENT 1 VERY GOOD 2 GOOD 3 FAIR 4 POOR 5

2. COMPARED TO ONE YEAR AGO, HOW WOULD YOU RATE YOUR HEALTH IN GENERAL NOW?

MUCH BETTER NOW THAN ONE YEAR AGO 1

SOMEWHAT BETTER NOW THAN ONE YEAR AGO 2

ABOUT THE SAME AS A YEAR AGO 3

SOMEWHAT WORSE NOW THAN ONE YEAR AGO 4

MUCH WORSE NOW THAN ONE YEAR AGO 5

3. THE FOLLOWING ITEMS ARE ABOUT ACTIVITIES YOU MIGHT DO DURING A TYPICAL DAY. DOES YOUR HEALTH NOW LIMIT YOU IN THESE ACTIVITIES? IF SO, HOW MUCH?

ACTIVITIES	YES, LIMITED A LOT	YES, LIMITED A LITTLE	NO, NOT LIMITED AT ALL
A. *VIGOROUS ACTIVITIES,* SUCH AS RUNNING, LIFTING HEAVY OBJECTS, PARTICIPATING IN STRENUOUS SPORTS	1	2	3
B. *MODERATE ACTIVITIES,* SUCH AS MOVING A TABLE, PUSHING A VACUUM CLEANER, BOWLING OR PLAYING GOLF	1	2	3

C. Lifting or carrying groceries	1	2	3
D. Climbing several flights of stairs	1	2	3
E. Climbing one flight of stairs	1	2	3
F. Bending, kneeling or stooping	1	2	3
G. Walking more than a mile	1	2	3
H. Walking several blocks	1	2	3
I. Walking one block	1	2	3
J. Bathing or dressing yourself	1	2	3

4. During the *past 4 weeks,* have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	No
A. Cut down the amount of time you spent on work or other activities	1	2
B. Accomplished less than you would like	1	2
C. Were limited in the kind of work or other activities	1	2
D. Had difficulty performing the work or other activities (e.g., it took extra effort)	1	2

5. During the *past 4 weeks,* have you had any of the following problems with your work or other regular daily activities *as a result of emotional problems* (such as feeling depressed or anxious)?

	Yes	No
A. Cut down the *amount of time* you spent on work or other activities	1	2
B. *Accomplished less* than you would like	1	2
C. Didn't do work or other activities as *carefully* as usual	1	2

6. During the *past 4 weeks,* to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

NOT AT ALL 1 SLIGHTLY 2 MODERATELY 3 QUITE A BIT 4 EXTREMELY 5

7. HOW MUCH *BODILY* PAIN HAVE YOU HAD DURING THE *PAST 4 WEEKS*?

NONE 1 VERY MILD 2 MILD 3 MODERATE 4 SEVERE 5 VERY SEVERE 6

8. DURING THE *PAST 4 WEEKS,* HOW MUCH DID *PAIN* INTERFERE WITH YOUR NORMAL WORK (INCLUDING BOTH WORK OUTSIDE THE HOME AND HOUSEWORK)?

NOT AT ALL 1 A LITTLE BIT 2 MODERATELY 3 QUITE A BIT 4 EXTREMELY 5

9. THE FOLLOWING QUESTIONS ASK HOW YOU FEEL AND HOW THINGS HAVE BEEN WITH YOU DURING THE PAST 4 WEEKS. FOR EACH QUESTION, PLEASE GIVE THE ONE ANSWER THAT COMES CLOSEST TO THE WAY YOU HAVE BEEN FEELING.

HOW MUCH OF THE TIME DURING THE PAST 4 WEEKS

	ALL OF THE TIME	MOST OF THE TIME	A GOOD BIT OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
A. DID YOU FEEL FULL OF PEP?	1	2	3	4	5	6
B. HAVE YOU BEEN A VERY NERVOUS PERSON?	1	2	3	4	5	6
C. HAVE YOU FELT SO DOWN IN THE DUMPS THAT NOTHING COULD CHEER YOU UP?	1	2	3	4	5	6
D. HAVE YOU FELT CALM AND PEACEFUL?	1	2	3	4	5	6
E. DID YOU HAVE A LOT OF ENERGY?	1	2	3	4	5	6
F. HAVE YOU FELT DOWNHEARTED AND BLUE?	1	2	3	4	5	6
G. DID YOU FEEL WORN OUT?	1	2	3	4	5	6
H. HAVE YOU BEEN A HAPPY PERSON?	1	2	3	4	5	6
I. DID YOU FEEL TIRED?	1	2	3	4	5	6

10. DURING THE *PAST 4 WEEKS,* HOW MUCH OF THE TIME HAS YOUR PHYSICAL HEALTH OR EMOTIONAL PROBLEMS INTERFERED WITH YOUR SOCIAL ACTIVITIES (LIKE VISITING WITH FRIENDS, RELATIVES, ETC.)?

ALL OF THE TIME	MOST OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
1	2	3	4	5

11. HOW TRUE OR FALSE IS *EACH* OF THE FOLLOWING STATEMENTS FOR YOU.

	DEFINITELY TRUE	MOSTLY TRUE	DON'T KNOW	MOSTLY FALSE	DEFINITELY FALSE
A. I SEEM TO GET SICK A LITTLE EASIER THAN OTHER PEOPLE	1	2	3	4	5
B. I AM HEALTHY AS ANYBODY I KNOW	1	2	3	4	5
C. I EXPECT MY HEALTH TO GET WORSE	1	2	3	4	5
D. MY HEALTH IS EXCELLENT	1	2	3	4	5

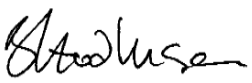
C. Statement of Originality and Authors' Responsibility

Chapter Three

Response to traditional disease-modifying anti-rheumatic drugs in indigent South Africans with early rheumatoid arthritis

	Hodkinson	Musenge	Ally	Meyer	Anderson	Tikly
Conceived and designed the research	✓		✓	✓	✓	✓
Acquired the data	✓		✓	✓		
Performed statistical analysis	✓	✓				
Analysed and interpreted the data	✓	✓	✓	✓	✓	✓
Drafted the manuscript	✓	✓			✓	✓

I hereby certify that all co-authors have provided their consent for the inclusion of the paper in the thesis and that the co-authors accept the candidate's contribution to the paper as described in this Statement of Originality.



Bridget Hodkinson (Candidate) Date: 27 2 2012



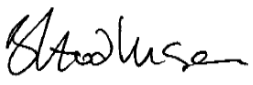
Professor Mohammed Tikly (Supervisor) Date: 27 2 2012

Chapter Four

Functional Disability and Health-Related Quality Of Life in South Africans with Early Rheumatoid Arthritis

	Hodkinson	Musenge	Ally	Meyer	Anderson	Tikly
Conceived and designed the research	✓		✓	✓	✓	✓
Acquired the data	✓		✓	✓		
Performed statistical analysis	✓	✓				
Analysed and interpreted the data	✓	✓	✓	✓	✓	✓
Drafted the manuscript	✓	✓			✓	✓

I hereby certify that all co-authors have provided their consent for the inclusion of the paper in the thesis and that the co-authors accept the candidate's contribution to the paper as described in this Statement of Originality.



Bridget Hodkinson (Candidate) Date: 27 2 2012



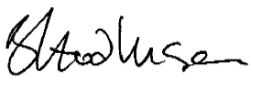
Professor Mohammed Tikly (Supervisor) Date: 27 2 2012

Chapter Five

The diagnostic utility of the aCCP antibody test is no better than rheumatoid factor in South Africans with early rheumatoid arthritis

	Hodkinson	Meyer	Musenge	Ally	Wadee	Anderson	Tikly
Conceived and designed the research	✓	✓		✓	✓	✓	✓
Acquired the data	✓	✓		✓			
Performed statistical analysis	✓		✓				✓
Analysed and interpreted the data	✓	✓	✓	✓		✓	✓
Drafted the manuscript	✓	✓				✓	✓

I hereby certify that all co-authors have provided their consent for the inclusion of the paper in the thesis and that the co-authors accept the candidate's contribution to the paper as described in this Statement of Originality.



Bridget Hodkinson (Candidate) Date: 27 2 2012



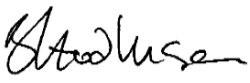
Professor Mohammed Tikly (Supervisor) Date: 27 2 2012

Chapter Six

HLA-DRB1 shared epitope genotyping using the revised classification and its association with circulating autoantibodies, acute phase reactants, cytokines and clinical indices of disease activity in a cohort of South African rheumatoid arthritis patients.

	Meyer	Hodkinson	Ally	Musenge	Wadee	Fickl	Tikly	Anderson
Conceived and designed the research	✓	✓			✓		✓	✓
Acquired the data	✓	✓	✓			✓		
Performed statistical analysis	✓			✓				
Analysed and interpreted the data	✓	✓	✓				✓	✓
Drafted the manuscript	✓	✓					✓	✓

I hereby certify that all co-authors have provided their consent for the inclusion of the paper in the thesis and that the co-authors accept the candidate's contribution to the paper as described in this Statement of Originality.



Bridget Hodkinson (Candidate) Date: 27 2 2012



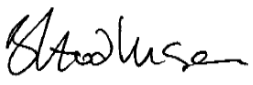
Professor Mohammed Tikly (Supervisor) Date: 27 2 2012

Chapter Seven

Circulating cytokine profiles and their relationships with autoantibodies, acute phase reactants, and disease activity in patients with rheumatoid arthritis.

	Meyer	Hodkinson	Ally	Musenge	Wadee	Fickl	Tikly	Anderson
Conceived and designed the research	✓	✓			✓		✓	✓
Acquired the data	✓	✓	✓			✓		
Performed statistical analysis	✓			✓				
Analysed and interpreted the data	✓	✓	✓				✓	✓
Drafted the manuscript	✓	✓					✓	✓

I hereby certify that all co-authors have provided their consent for the inclusion of the paper in the thesis and that the co-authors accept the candidate's contribution to the paper as described in this Statement of Originality.



Bridget Hodkinson (Candidate) Date: 27 2 2012



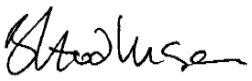
Professor Mohammed Tikly (Supervisor) Date: 27 2 2012

Chapter Eight

Circulating Cytokine profile of early Rheumatoid Arthritis patients with Rheumatoid Nodules

	Hodkinson	Meyer	Musenge	Ally	Anderson	Tikly
Conceived and designed the research	✓					
Acquired the data	✓	✓		✓		
Performed statistical analysis	✓		✓			
Analysed and interpreted the data	✓				✓	✓
Drafted the manuscript	✓				✓	✓

I hereby certify that all co-authors have provided their consent for the inclusion of the paper in the thesis and that the co-authors accept the candidate's contribution to the paper as described in this Statement of Originality.



Bridget Hodkinson (Candidate) Date: 27 2 2012



Professor Mohammed Tikly (Supervisor) Date: 27 2 2012