

# Response to Traditional Disease-Modifying Anti-Rheumatic Drugs in Indigent South

## Africans with Early Rheumatoid Arthritis

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### Abstract

**Objective:** To investigate clinical response to traditional disease modifying anti-rheumatic drugs (DMARDs) in indigent South Africans with early RA. **Methods:** A cohort of patients with early ( $\leq 2$  years) RA who were DMARD-naïve at inception were prospectively assessed for response to DMARDs using the simplified disease activity index (SDAI) over a 12-month period. Patients with low disease activity (LDA) at 12 months were compared to those with moderate and high disease activity with respect to demographic, clinical, autoantibody and radiographic features. **Results:** The 171 patients (140 females) had a mean (SD) age of 47.1 (12.4) years, symptom duration of 11.7 (7.1) months and baseline SDAI of 39.4 (16.2). There was a significant overall improvement in the

SDAI and its components in the 134 (78.4%) patients who completed the 12 months visit, but only 28.4% of them achieved LDA. The majority of patients (91%) were treated with methotrexate as monotherapy or in combination with chloroquine and/or sulphasalazine. Baseline features that independently predicted a LDA state at 12 months were lower HAQ-DI ( $p=0.023$ ) and a higher haemoglobin level ( $p=0.048$ ). Receiver operating characteristic curve analysis showed that the 6-months SDAI was better than the baseline SDAI in predicting the 12-month SDAI (area under the curve of 0.69 vs. 0.52, respectively,  $p=0.008$ ). **Conclusion:** Less than a third of patients achieved low disease activity at 12 months on traditional DMARDs. Patients who have an inadequate response to traditional DMARDs at 6 months are unlikely to show further improvement on traditional DMARDs at 12 months. These findings underscore the need for better disease control by an aggressive tight control strategy, including intense patient education and biologic therapy.

**Keywords:** Rheumatoid Arthritis, response to therapy, DMARDs, anaemia, South Africa

Rheumatoid arthritis (RA) is a chronic inflammatory arthritis that occurs worldwide, and is characterized by joint inflammation and destruction. It is now well-established that early intervention with disease modifying anti-rheumatic drugs (DMARDs) to suppress inflammation and achieve a low disease activity state prevents radiographic damage and disability<sup>1,2</sup>. The varying course of the disease from a mild intermittent syndrome to an aggressive systemic disease, coupled with the wide choice of therapies that are now available for RA, make prediction of early response to traditional DMARD therapy a key issue. This may allow treatment to be tailored for the individual patient with RA<sup>3</sup>.

Health services in sub-Saharan Africa, including South Africa, are overwhelmed by the burden of infectious diseases, but there is mounting evidence that the prevalence of non-communicable diseases is increasing<sup>4,5</sup>. The lower socio-economic groups bear the brunt of these illnesses. Cross sectional and retrospective studies in recent years indicate that RA in Africa is often severe and associated with high levels of functional disability<sup>6,7</sup>.

To date there are no published prospective longitudinal studies of early RA in sub-Saharan Africa. In this resource-constrained setting, characterizing patients who are likely to respond to relatively inexpensive traditional DMARD therapy is important so that aggressive treatment with costly biologics can be reserved for those who clearly need it. We therefore undertook a prospective observational study of early RA in search of clinical, biochemical or radiographic predictors of response to traditional DMARD therapy. This study was approved by the University of the Witwatersrand Committee for Research on Human Subjects.

## PATIENTS AND METHODS

### *Patients*

The Gauteng Region Early Arthritis (GREAT) registry is an ongoing multi-dimensional project at two state-funded tertiary hospitals in Gauteng, South Africa that service a predominantly Black African indigent urban and peri-urban population. Consenting patients who met the 1987 revised American College of Rheumatology (ACR) classification criteria for RA <sup>8</sup>, had early disease (defined as symptom duration  $\leq 2$  years), and were DMARD-naïve were enrolled between mid-2005 and mid-2008. Standard of care was provided with DMARDs and patients were assessed at routine follow-up visits at 2 to 4-monthly intervals.

### *Clinical and Serological Assessments for study*

Data for the study was collected at baseline, 6 months and 12 months, independent of routine clinic visits. Demographic features of current employment status, highest level of education and smoking history were obtained. At each visit the 28-joint swollen (SJC) and tender (TJC) counts, pain score, patient global and physician global assessment scores, the health assessment disability index (HAQ-DI) <sup>9</sup>, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), haemoglobin (Hb) level and platelet count were documented. Anaemia was defined as Hb  $< 12$  in females and  $< 13$  in males <sup>10</sup>. At inception, rheumatoid factor (RF) (composite IgM, IgG, IgA) was assayed by nephelometry (Siemens Healthcare Diagnostics, USA) and anti-cyclic citrullinated peptide antibodies (aCCP) were measured by a second generation assay (Phadia AB, Sweden). Values of 15 IU/ml and 10 U/ml, respectively, were considered positive. Response to therapy was defined in terms of the simplified disease activity index (SDAI) as follows: remission  $\leq 3.3$ , low disease activity (LDA)  $\leq 11.0$ , moderate disease activity (MDA)  $> 11 \leq 26$  and high disease activity (HDA)  $> 26$  <sup>11</sup>. Based on the 12-month SDAI, patients with LDA (“LDA-12”) were compared to those with MDA and HDA (“MDA/HDA-12”).

### *Radiographic assessment*

Plain radiographs of the hands and feet taken at inception were scored for radiographic damage using the modified Larsen method where the maximum obtainable score was 200 <sup>12</sup>, and patients were classified as having “erosive” disease if one or more marginal erosion was observed.

### *Medical therapy*

Oral methotrexate (MTX), sulphasalazine (SSZ) and chloroquine sulphate (CQ) were prescribed as either monotherapy or combination therapy, with or without low dose oral prednisone ( $\leq 7.5$ mg/day). Therapy was

adjusted by the attending physician, based on the clinical response and adverse effects. No patients were 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.

### *Statistical analysis*

The Student's t-test was applied to compare continuous variables between groups. In the case of categorical variables, the Pearson's Chi-Square test, or where indicated, the 2-tailed Fishers' Exact test was used. Multivariate analysis was performed using stepwise logistic regression, and any demographic or baseline variable with a p-value  $\leq 0.15$  in the univariate analysis were included in the model. Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive value of the baseline and the 6-month SDAI. Stata 10 software (StataCorp, USA) was used. A p value of less than 0.05 was considered significant.

## **RESULTS**

### *Baseline features and improvement*

At inception, the 171 patients (140 females) had a mean age of 47.1 years and symptom duration of 11.7 months (range 2-24 months) (Table 1). Only 25.7% of patients had a symptom duration of less than 6 months. The majority (55.0%) of patients were unemployed, and the mean number of school years completed was only 8.9 years (range 0-14 years). No patients received tertiary education. Rheumatoid nodules were observed in a fifth of patients and RF and aCCP were positive in 83.6% and 80.1% of patients respectively. Disease activity was high as reflected by a mean SJC of 10.1, a mean SDAI of 39.4 and moderate to severe functional disability with a mean HAQ-DI of 1.7. Sixty-two patients (36.3%) were anaemic. The mean Larsen score was 22.2 and 50.9% of patients had erosive disease.

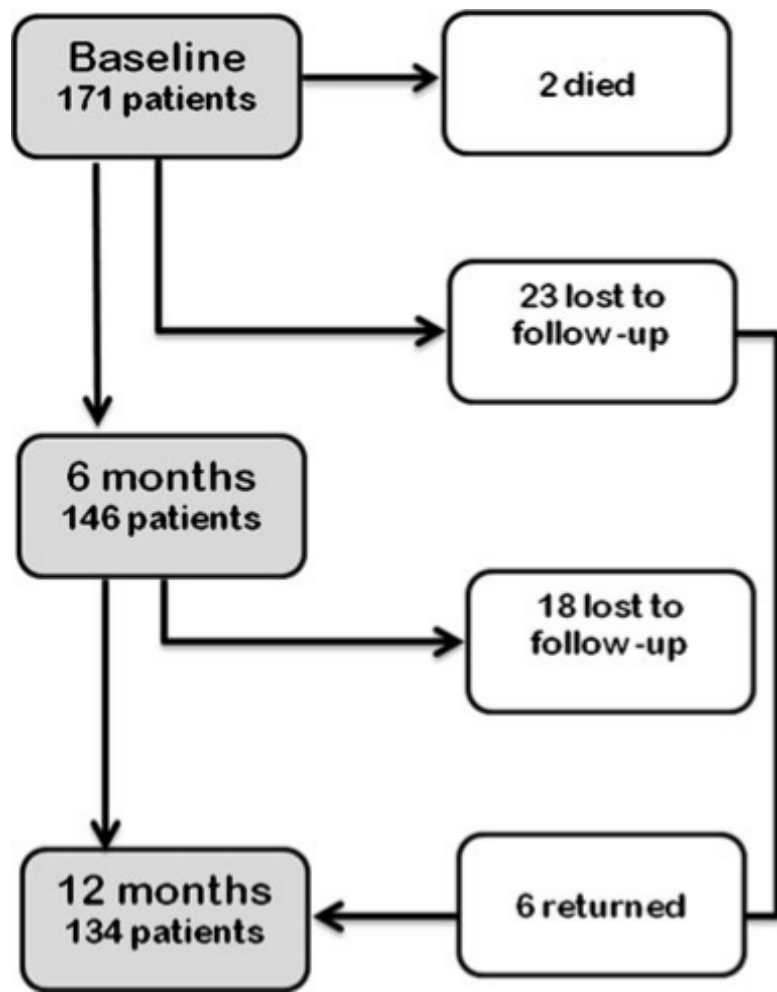
At 12 months, data was available for 134 patients (Figure 1). In these patients the mean SDAI was 17.1, a significant improvement from baseline ( $p < 0.001$ ); 28.4% of patients achieved LDA (of these 10.4% of patients were in remission), 54.5% had MDA and 17.2% patients had HDA (Table 2). Over the 12 month period, 85 patients (63.4%) received MTX monotherapy, 37 (27.6%) were on a combination of MTX and CQ, 8 (6.0%) on SSZ and 4 (3.0%) received CQ monotherapy. The starting dose of MTX was between 7.5 and 15mg/week (mean (SD) dose 13.1 (3.2) mg/week), and the drug was increased gradually to a maximum of 25mg/week (mean (SD) dose 20.0 (4.3) mg/week) at 12 months. Low dose prednisone (5-7.5mg/day) was prescribed in 52.2 % of patients.

**Table 1:** Baseline clinical and demographic features of 171 early rheumatoid arthritis patients

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Black ethnicity (%)	152 (88.9)
Females (%)	140 (81.9)
Age in years – mean (SD)	47.1 (12.4)
Symptom duration in months – mean (SD)	11.7 (7.1)
Smoking history (%)	40 (23.4)
Unemployed (%)	94 (55.0)
Schooling completed in years – mean (SD)	8.9 (3.1)
Rheumatoid nodules (%)	34 (20.0)
Swollen joint count – mean (SD)	10.1 (6.4)
Tender joint count – mean (SD)	13.5 (7.9)
ESR (mm/hr) – mean (SD)	46.0 (30.8)
CRP (mg/l) – mean (SD)	30.2 (38.7)
Haemoglobin (g/dl) – mean (SD)	12.5 (1.6)
Anaemia (%)	62 (36.3)
Platelet count ( $\times 10^9/l$ ) – mean (SD)	366.8 (122.6)
Simplified Disease Activity Index – mean (SD)	39.4 (16.2)
Health Assessment Questionnaire Disease Index – mean (SD)	1.7 (0.8)
modified Larsen score – mean (SD)	22.2 (13.0)
Erosive disease (%)	87 ( 50.9)
Rheumatoid factor positive (%)	143 (83.6)
Anti-cyclic citrullinated peptide antibody positive (%)	137 (80.1)

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**Figure 1:** Flow diagram of patients participating in 12 month study

**Table 2:** Changes in Simplified Disease Activity Index (SDAI) from baseline to 12 months in early RA patients

	SDAI category	Baseline n=171	12 months n=134
Remission (%)	≤3.3	0	14 (10.4)
LDA (including remission) (%)	≤11	4 (2.4)	38 (28.4)
MDA (%)	>11 ≤ 26	37 (21.6)	73 (54.5)
HDA (%)	>26	130 (76.0)	23 (17.2)

LDA: low disease activity, MDA: moderate disease activity, HDA: high disease activity.

Chi-squared test for trend  $p < 0.001$ .

**Table 3:** Clinical, biochemical and radiographic features of 134 early RA patients classified according to SDAI at 12 months - univariate analysis

		LDA-12 (SDAI ≤11) n=38	MDA/HDA-12 (SDAI >11) n=96	p value
Demographics	Black Ethnicity (%)	37 (94.4)	83 (86.5)	ns
	Age (years)-mean (SD)	43.9 (13.0)	48.9 (12.3)	0.04
	Female gender (%)	29 (76.3)	80 (83.3)	ns
	Symptom duration (months) -mean (SD)	9.9 (6.9)	11.7 (6.8)	ns
	Smoker (ever) (%)	7 (18.4)	24 (25.0)	ns
	Unemployed (%)	19 (50.0)	54 (56.2)	ns
	Schooling completed (years)-mean (SD)	9.8 (8.8)	8.6 (7.9)	0.06
Baseline Clinical Assessment	SJC -mean (SD)	9.8 (7.3)	10.2 (6.1)	ns
	TJC -mean (SD)	12.7 (8.4)	14.5 (7.5)	ns
	PAIN (mm) -mean (SD)	53.4 (23.5)	66.7 (22.8)	0.006
	PGDA (mm) -mean (SD)	64.5 (25.1)	72.8 (24.1)	0.08
	MDGA (mm) -mean (SD)	52.0 (23.5)	60.4 (20.1)	0.04
	ESR -mean (SD)	38.2 (25.6)	49.8 (29.9)	0.04
	SDAI -mean (SD)	36.6 (18.2)	41.5 (15.6)	ns
	Haemoglobin (g/dl)- mean (SD)	13.0 (1.5)	11.8 (1.6)	0.009
	Platelet count ( x10 <sup>9</sup> /l) - mean (SD)	327.9 (93.0)	377.8 (115.0)	0.02
	HAQ-DI -mean (SD)	1.4 (0.8)	1.8 (0.8)	0.02
Radiology at baseline	Presence of erosions (%)	23 (60.5)	50 (52.1)	ns
	modified Larsen score -mean (SD)	20.8 (10.1)	22.4 (13.7)	ns
Serology	RF positive (%)	33 (86.8)	79 (82.3)	ns
	aCCP positive (%)	34 (89.5)	78 (81.3)	ns
Therapy	Poor adherence to treatment (%)	9 (23.7)	24 (25.0)	ns
	Corticosteroid prescribed (%)	21 (55.3)	49 (51.0)	ns
6 month Clinical Assessment	SJC -mean (SD)	1.9 (2.1)	3.9 (4.4)	0.02
	TJC -mean (SD)	2.8 (3.8)	6.5 (6.7)	0.005
	PAIN (mm)-mean (SD)	40.3 (24.8)	47.8 (25.9)	ns
	PGA (mm)-mean (SD)	38.2 (21.10)	50.5 (26.2)	0.02
	MDGA (mm)-mean (SD)	20.0 (19.9)	41.0 (26.6)	<0.001
	ESR -mean (SD)	26.9 (16.6)	35.2 (26.2)	0.08
	SDAI -mean (SD)	11.7 (8.5)	21.1 (14.0)	0.001
	Haemoglobin (g/dl)- mean (SD)	13.8 (1.3)	12.6 (2.0)	0.007
Platelet count (x10 <sup>9</sup> /l)- mean (SD)	317.8 (65.6)	337.2 (102.1)	0.02	
HAQ-DI -mean (SD)	0.6 (0.3)	0.8 (0.4)	0.01	

**LDA-12:** low disease activity at 12 months, **MDA/HAD-12:** moderate or high disease activity at 12 months, **SDAI:** Simplified Disease Activity Index, **SJC:** 28-joint swollen joint count, **TJC:** 28-joint tender joint count, **PGA:** Patient global disease activity assessment, **MDGA:** Physician global disease activity assessment, **ESR:** Erythrocyte, Sedimentation Rate, **HAQ-DI:** Health Assessment Questionnaire Disability Index, **RF:** Rheumatoid factor, **aCCP:** Anti-cyclic citrullinated peptide antibody, **ns:** not significant

### *Predictors of response*

Compared to the MDA/HDA-12 group, the LDA-12 group was significantly younger, had completed more schooling, scored better in baseline pain and physician and patient global scores, and had higher Hb levels and lower platelet counts (Table 3). There was no difference in auto-antibody positivity or titre between the groups, and smokers did not fare worse. Neither the baseline radiographic score or presence of erosions, nor the type of DMARD therapy prescribed nor whether or not the patient received oral corticosteroids were predictive of disease activity at 12 months. Good responses at the 6-months visit of the TJC and SJC, global patient and physician assessments, ESR, SDAI and HAQ-DI were strongly predictive of LDA-12.

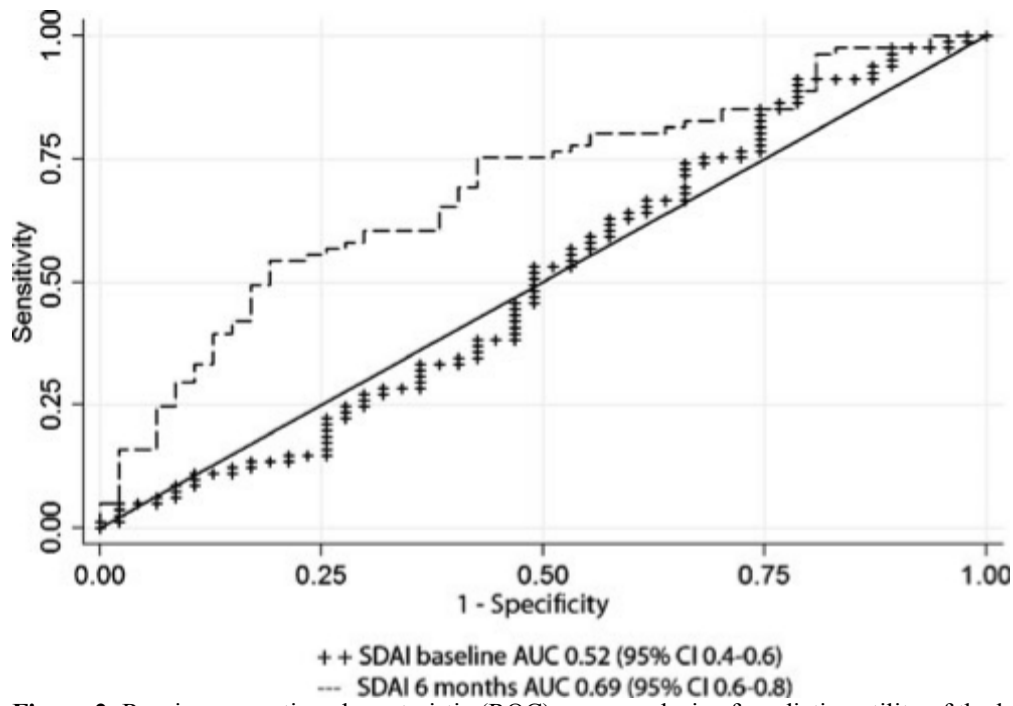
**Table 4:** Multivariate analysis of baseline predictors of low disease activity state at 12 months.

	<b>OR (95% CI)</b>	<b>p value</b>
HAQ-DI	1.89 (1.09-3.27)	0.023
Haemoglobin	0.75 (0.56-0.99)	0.048
Age	1.03 (1.00-1.06)	0.072
Platelet count	1.05 (1.00-1.10)	0.070

HAQ-DI- Health Assessment Questionnaire Disability Index

Independent baseline predictors of LDA-12 by multivariate analysis were the HAQ-DI score and Hb, with age and platelet count showing a trend that did not reach statistical significance (Table 4). ROC curve analysis showed that the area under the curve (AUC) for the 6 months SDAI had significantly better predictive utility than the AUC for the baseline SDAI for LDA-12, (0.69 vs 0.52,  $p=0.008$ ) (Figure 2).





**Figure 2:** Receiver operating characteristic (ROC) curve analysis of predictive utility of the baseline and 6-month SDAI for achievement of low disease activity state at 12 months. The increasing area under the curve (AUC) corresponds to better predictive utility of the 6-months SDAI compared to the baseline SDAI (p=0.008).

SDAI = Simplified Disease Activity Index

#### *Patients lost to follow-up*

Two patients died within the first 6 months of DMARD therapy of respiratory infections and 35 (20.5%) patients were lost to follow-up over the 12 months period: 17 before the 6 months visit, and a further 18 before the 12 months visit. At baseline, the ‘lost-to-follow-up’ group differed from those that attended the 12 months visit in that they had a higher mean CRP (43.3mg/dl vs. 26.8mg/l, p= 0.03), a trend towards a higher mean SDAI score (42.1 vs. 32.6, p=0.06) and longer mean disease duration (13.6 months vs 11.2 months, p= 0.05). No significant differences were observed with respect to level of education, employment status, HAQ-DI scores, or radiographic damage. The group of patients who completed the 6 months visit but missed the 12 months visit fared worse at the 6 months visit than the compliant group, with a higher mean SDAI (24.3 vs. 18.1, p = 0.02). Within the group who attended all their study visits, 33 patients (24.6%) were deemed to be poorly adherent to therapy, but were otherwise indistinguishable from the rest of the group.

## **DISCUSSION**

In spite of an overall reduction in disease activity over the 12 months with traditional DMARD therapy in this cohort of indigent patients with early RA, less than a third of patients reached a LDA state, and only 10%

achieved remission. Even though our findings are not dissimilar to those reported in a mixed US and Mexican cohort and a Swedish cohort in whom 32% and 34% of patients, respectively, achieved a LDA state at 12 months with traditional DMARD treatment<sup>13,14</sup>, the poor response rate in our patients is, at least in part, reflective of their poor socio-economic status. Low levels of formal education and poor socio-economic status have been identified as risk factors for poorer outcome in RA<sup>15-17</sup>. Our patients overall had a low level of education, with those with fewer years of schooling fared worse, and more than half the patients were unemployed at inception. 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.

Low disease activity and low HAQ-DI scores at baseline are predictive of better SDAI scores at 12 months in the present study. Similar findings have been reported previously in early and established RA where lower joint counts and less functional disability were good prognostic markers for long term low disease activity or remission<sup>18,19</sup>. We also observed that higher baseline Hb level, and a lesser extent lower platelet count, was predictive of a better outcome at 12 months. A recent study supports this finding that RA patients with anaemia have more severe disease<sup>20</sup>. This is most likely on the basis of anaemia of chronic inflammation, mediated by inflammatory cytokines, in particular interleukin (IL)-6<sup>21</sup>. Similarly, a reactive thrombocytosis associated with active RA is thought to be due to the pro-inflammatory effects of IL-1 $\beta$  and IL-4<sup>22,23</sup>.

The 6-month SDAI was strongly predictive of disease activity at 12 months. The concept that response to DMARDs is evident within 3-6 months of initiating therapy has been described previously<sup>24</sup> and emphasizes the importance of escalating DMARD therapy early and rapidly in patients who fail to achieve at least LDA. These findings call for a more aggressive approach to the use traditional DMARDs, and an intense “treat-to-target” strategy such as used in the TICORA and FIN-RACo studies, needs to be explored in this setting<sup>25,26</sup>. Notwithstanding the likely gains from a more aggressive approach with traditional DMARDs, judging from experience elsewhere, there will be a need for biologics, despite their cost, for a select group of patients who fail to achieve LDA on traditional DMARDs<sup>27</sup>.

In the present study, neither gender, smoking (past or present) nor auto-antibody status had influence on the outcome, where other studies have reported a more severe disease course in females, smokers, and in those with RF or aCCP<sup>28-30</sup>. The relatively small cohort and short follow-up period might explain our results. Neither baseline radiographic scores nor the presence of erosions were of prognostic importance, but these factors may prove to be of significance when we assess radiological outcome rather than clinical disease activity.

A disquieting limitation of this study was that about a fifth of patients were lost to follow-up. There is no obvious explanation why this group, which had more active disease at baseline but no significant differences in socio-demographic features compared to the group that completed the 12 months visit, defaulted treatment. It might be a reflection of financial difficulties that preclude these patients from returning for their follow-up visits. It is possible that some of these patients, dissatisfied with their high pain and disability despite commencing treatment at our hospital, may have attended other hospitals or consulted a traditional healer. Another issue of concern is the poor adherence to DMARD therapy in about a quarter of the patients. Both these issues speak to the need for more effective and intense RA education programmes, at both hospital and community levels, to improve outcomes.

It could be argued that symptom duration of 24 months is not “early” disease. This is reinforced by the fact that over half of our patients had erosive disease on plain radiographs at inception. This reflects the patchy and erratic primary care services in many parts of South Africa and underscores the need for training of primary health care workers to recognize and rapidly refer patients with early inflammatory arthritis. A further limitation was the variation in clinical expertise of the attending physicians in assessing disease activity and prescribing DMARDs. This may be an additional reason that better response rates were not achieved.

In summary, a combination of poor socio-economic factors including a low level of formal education, together with older age, high baseline disease activity and functional disability, with a lower haemoglobin level and high platelet count, bodes a poorer prognosis. The study highlights the huge challenge to effectively control disease and reduce disability. The role of tight monitoring and control with both traditional DMARDs and biologics, together with ongoing intense nurse-based patient education need to be explored.

### **Acknowledgements**

Funding for this study was obtained from the Connective Tissue Diseases Research Fund, University of the Witwatersrand and the Medical Research Council of South Africa.

### **Conflict of interest**

Hodkinson B: none

Musenge E: none

Ally M: none

Meyer PWA: none

Anderson R: none

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