International Journal of
Rheumatic Diseases

International Journal of Rheumatic Diseases 2014

ORIGINAL ARTICLE

A prospective study of anti-tumor necrosis factor therapy in South African rheumatoid arthritis patients

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Abstract

Objective: To quantify primary and secondary anti-tumour necrosis factor inadequate response (aTNF-IR) and intolerance in South Africans with rheumatoid arthritis (RA) over 1 year.

Methods: Rheumatologists from nine independent private practices monitored RA patients commencing on aTNF therapy (incident cases) or already on aTNF therapy (prevalent cases). Observations at baseline and quarterly intervals recorded discontinuation of therapy for either lack of response or adverse effects.

Results: Of the 98 patients screened, 86 were eligible to participate. Mean time from onset of symptoms of RA to start of aTNF treatment was 9.7 years (range: 0.5–32 years). Only 58 (67.4%) continued on aTNF therapy at 12 months, including five judged to have an aTNF-IR. Overall 12 patients had a secondary aTNF-IR with seven discontinuing for this reason. Seven patients discontinued due to adverse events, four due to funding problems and 10 were lost to follow-up. Infections were the most common adverse events, but only two stopped treatment as a result. No cases of active tuberculosis (TB) were recorded, despite nine patients having a positive tuberculin skin test and one, a past history of pulmonary TB.

Conclusions: Almost a third of patients discontinued aTNF therapy over the 1-year period, with infections and inadequate response to treatment being the main reasons for discontinuation. The study highlights the need for biologics with alternative modes of action for patients with moderate to severe RA in South Africa.

Key words: anti-TNF agents, drug survival, rheumatoid arthritis, South Africa.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease which if inadequately treated, leads to progressive joint destruction.[1–4] In South Africa, patients in the private sector who have an inadequate response to traditional disease-modifying anti-rheumatic drugs (DMARDS), have for more than a decade had limited access to biologic agents, principally the anti-tumor necrosis factor (aTNF) drugs (infliximab, etanercept and adalimumab). Guidance on their use has been determined by the South African Rheumatism and Arthritis Association (SARAA) and these agents, usually in combination with methotrexate, have become established as the standard of care for those unresponsive to DMARDS (DMARDS-IR). However, not all patients with RA respond to aTNFs and about 30% fail to achieve an American College of Rheumatology (ACR)-20 response (primary failure) in large randomized controlled trials.[1–3] In addition, there may be further drug attrition either because of secondary failure or adverse events, including infections such as tuberculosis (TB).[5,6] South Africa is a TB endemic country with the 2010 World Health Organization (WHO) report showing a prevalence rate of 798/100 000, one of the highest rates in the world.[7,8] In spite of screening and

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chemoprophylaxis for active and latent TB infection (LTBI) prior to commencement of aTNF therapy, reactivation of TB continues to be a challenge.

The recent availability of other biological agents with different molecular targets, such as rituximab, tocilizumab and abatacept, provide alternatives for patients who fail aTNFs or have adverse events. In the absence of any post-registration data on aTNF agents in SA, a prospective observational study was undertaken to assess the effectiveness and tolerability of these agents in the private sector.

PATIENTS AND METHODS

This was a prospective observational study over a 1-year period of RA patients, who were either commencing aTNF therapy (incident cases) or already on aTNF therapy (prevalent cases), followed up at nine independent private practices across SA. The Pharma Ethics committee approved this study, which complied with the World Medical Association's Declaration of Helsinki.

Informed consent was obtained from all study participants and patient anonymity was preserved throughout clinical trial conduct.

Consenting patients were included if they met the 1987 ACR classification for RA and were older than 18 years of age at the time of diagnosis. Exclusion criteria included an ACR functional status class IV, taking prednisone doses in excess of 10 mg daily and previous treatment with a biological agent. Treating physicians were independent in their choice of patients for enrolment, selection of aTNF and concomitant therapy. Demographics, smoking history, rheumatoid factor (RF), tuberculin test, chest radiograph (CXR), concomitant medications, date of onset of RA and date of start of aTNF therapy were recorded at baseline. Simplified Disease Activity Index (SDAI), Health Assessment Questionnaire Disability Index (HAQ-DI), and adverse events were recorded with each visit.

Primary aTNF-IR is widely accepted as failure to achieve a targeted response, either remission or low disease activity (LDA) within 3–6 months of treatment initiation[9,10] For the purpose of this study primary aTNF-IR was defined as an improvement of < 15 points in the SDAI score within the first 6 months of treatment. The definition of secondary aTNF-IR, according to the SARAA guidelines is a loss in treatment response after 6 months.[11] For uniformity in the study secondary aTNF-IR was defined as a deterioration of at least 10 points in the SDAI score, over two successive visits, following an initial adequate response.

Statistical analysis

The data were entered in Epi-Info version 3.5.2 (http://epi-info.software.informer.com/) by two independent data capturers and verified by two of the authors for consistency and accuracy. Descriptive statistics for numerical as well as categorical variables were performed on the data. Measures of location (mean) and measures of variability (standard deviations and ranges) were used to describe the numerical data of interval and ratio scales. Pictographically the box and whisker plots were used for numerical data. Categorical data of nominal and ordinal scales were described by frequency. The analysis was done using STATA Version 10.0 (StataCorp, College Station, TX, USA).

RESULTS

Demographic and clinical characteristics

Recruitment was from February to July 2010, and included a baseline visit and four quarterly visits thereafter.

Of the 98 patients screened, 12 were excluded as they failed to meet the inclusion/exclusion criteria (Fig. 1). The cohort comprised predominantly White (91%) females, of whom the majority (76%) was RF positive.

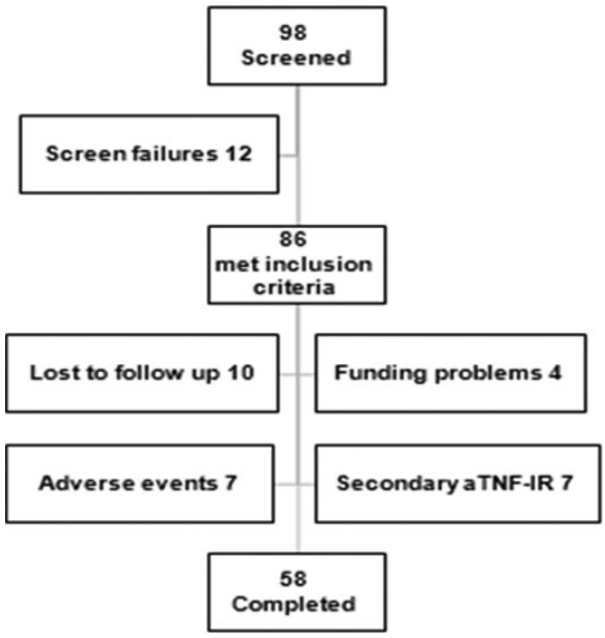

Figure 1 Enrolment and follow-up of patients with rheumatoid arthritis on anti-tumor necrosis factor therapy from South Africa.

Table 1 Baseline demographic and clinical features of 86 rheumatoid arthritis patients

	n (%)
Gender	
Males	18 (20)
Females	68 (80)
Race	
White	78 (91)
Black	2 (2)
Other	6 (7)
Smokers	12 (14)
RF+	65 (76)
TST+	9 (10)
Concomitant medication	
Methotrexate	76 (88)
Oral prednisone	34 (40)
aTNF choices	
Infliximab	39 (45)
Adalimumab	26 (30)
Etanercept	21 (25)
Incident cases	27 (31)
	Mean (range)
Age at baseline (years)	57 (29–77)
SDAI at initiation of aTNF	42.3
Time from diagnosis to initiation of aTNF therapy (years)	9.7 (0.5–32)

RF, rheumatoid factor; TST, tuberculin skin test; SDAI, simplified disease activity index; aTNF, anti-tumour necrosis factor.

Anticyclic citrullinated peptide antibody (anti-CCP) results were not collected. The mean age of the cohort was 53 years (range 29–77 years).

Seventy-six patients (88%) were on methotrexate (mean dose 15 mg) and 34 (40%) were taking oral prednisone (mean dose 6.8 mg). Nine patients (10.5%) had a positive tuberculin skin test (TST) at initiation of aTNF therapy and one had a past history of pulmonary TB. No CXR reported any evidence of TB. All TST positive patients were treated for latent TB with isoniazid.

At baseline 27 patients were on aTNF therapy for 3 months or less. The mean SDAI at initiation of aTNF therapy was 42.3. The mean time interval from when patients were diagnosed with RA to initiation of aTNF therapy was 9.7 years (range 0.5–32 years) and from commencement of aTNF therapy to baseline was 1.8 years (range 0–9.5 years). Mean duration of aTNF therapy in prevalent cases at baseline was 2.6 years (range 3 months to 9.7 years). Baseline characteristics are shown in Table 1.

Simplified Disease Activity Index and HAQ-DI scores at initiation of aTNF therapy, at baseline and with each 3-monthly visit show a statistically significant ($P < 0.05$ for both scores) reduction, indicative of RA disease improvement (Figs 2,3, respectively).

After 1 year, 12 patients had a secondary aTNF-IR, of whom seven stopped therapy and the balance continued on treatment. No patient had a primary aTNF-IR. The mean methotrexate doses were similar in the aTNF-IR and TNF responder group (14.1 *vs.* 15.2 mg, respectively, $P = 0.29$). No statistical difference was demonstrated in the ages between the aTNF-IR and TNF responder group (54 *vs.* 53 years, $P = 0.9558$). Seven withdrew due to adverse events, four for funding reasons and 10 were lost to follow-up. In all, only 58 patients remained on treatment at 1 year.

Infections were the most common adverse events (Table 2) although they only resulted in two discontinuations (appendicitis, septic finger). Other discontinuations due to adverse events included subarachnoid hemorrhage (one), malignant melanoma (one), infu-

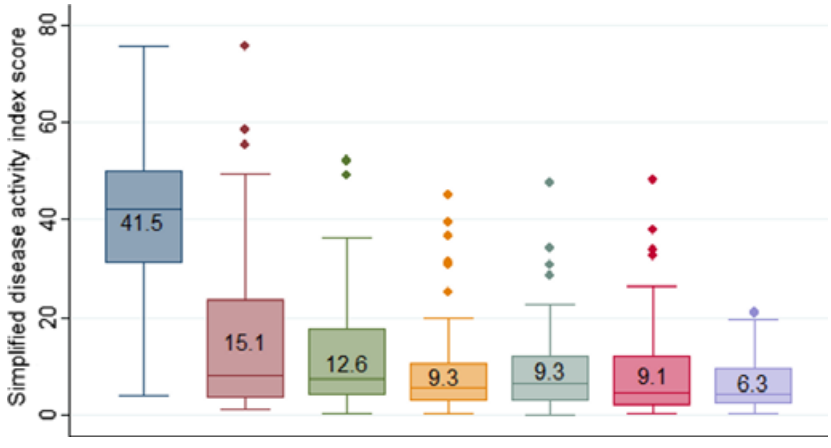

Figure 2 Simplified Disease Activity Index scores at initiation of anti-tumor necrosis factor therapy, baseline and quarterly visits. ■, SDAI at start of aTNF; ■, SDAI at last visit before trial; ■, Baseline SDAI; ■, Visit 1 SDAI; ■, Visit 2 SDAI; ■, Visit 3 SDAI; ■, Visit 4 SDAI.

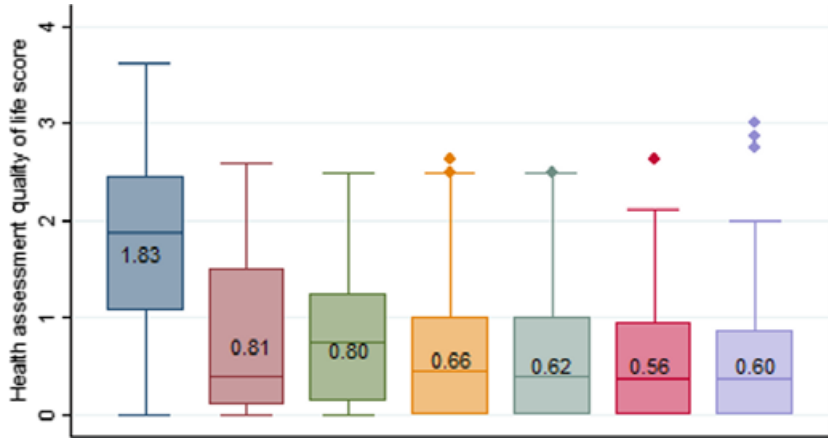

Figure 3 Health Assessment Questionnaire scores at initiation of anti-tumor necrosis factor therapy, baseline and quarterly visits. ■, HAQ at start of aTNF; ■, HAQ at last visit before trial; ■, Baseline HAQ; ■, Visit 1 HAQ; ■, Visit 2 HAQ; ■, Visit 3 HAQ; ■, Visit 4 HAQ.

Table 2 Adverse events encountered by subjects over 1 year on aTNF therapy

Adverse events	RA cohort $n = 86$
Infections (total)	(18)
Upper respiratory tract infection	8
Chest infection	3
Shingles	2
Urinary tract infection	1
Dental abscess	1
Appendicitis	1
Cholecystitis	1
Finger infection	1
Dermatological	(7)
Urticaria	2
Vasculitis	1
Fever blisters/mouth ulcers	2
Scaly patches (legs, scalp and wrist)	1
Malignant melanoma	1
Ophthalmic	(2)
Dry eyes	1
Keratoconjunctivitis	1
Neurological	(4)
Headaches	1
Tinnitus	1
Depression	1
Subarachnoid hemorrhage	1
Other	(7)
Neutropenia	1
Elevated liver function tests	1
Hypertension exacerbation	1
Infusion reaction	1
Injection site reaction	1
Bowel prolapse	1
No specific symptoms	1

aTNF, anti-tumor necrosis factor; RA, rheumatoid arthritis.

sion reactions (two) and non-specific symptoms (one). Of note, there were no reported cases of TB.

Of the 27 incident patients, three withdrew due to adverse events, two due to an aTNF-IR, one due to funding issues and two were lost to follow-up, which did not differ significantly compared to the prevalent cases.

DISCUSSION

This is the first study from South Africa evaluating the drug survival for aTNF agents in RA patients. In this cohort of private patients with average disease duration of almost a decade before commencement of aTNF therapy, there was no primary aTNF-IR and patients had a good initial response. However, almost a third stopped therapy, mainly due to secondary aTNF-IR or adverse events, with no significant difference in drug adherence between incident and prevalent cases. These rates correlate with results from large registries, such as the Danish DANBIO Registry, showing that after 48 months, the unadjusted drug survival rate was 52% for adalimumab, 56% for etanercept and 41% for infliximab.[12]

Infection was the most common adverse event; however only two stopped therapy for this reason and there were no cases of active TB. Nine patients (10.5%) tested TST positive at aTNF initiation and one patient had a past history of pulmonary TB. The prevalence of LTBI in this cohort is high, considering that selected patients were predominantly Caucasians from higher socioeconomic classes. However, it does attest to the background burden of TB in South Africa as demonstrated by total TB notifications in Cape Town, a city of 3.2 million people, which reached 27 000 in 2006.[13] However, the distribution of TB cases within this population is very unequal with unprecedented high burdens in

the crowded and socially deprived African townships.[14,15] Here TB annual notifications exceeded 1500 per 100 000 in 2006.[16,17] A cross-sectional survey in human immunodeficiency virus (HIV) negative individuals in these areas, using a TST diameter of $\geq$ 10 mm to indicate LTBI, showed LTBI prevalence rates in subjects aged between 17–40 years to be 69%.[18] South Africa is indeed a land of stark contrasts and this explains our TST findings. There are no publications on the risk of TB in methotrexate-exposed RA patients in South Africa.

Limitations of the study include the relatively small sample size, which limited comparisons between inception and prevalent cases and the high dropout rate for non-medical reasons.

Notwithstanding the limitations, this study provides evidence that while aTNF agents are effective in South Africans with RA, the high background LTBI, infection risks and attrition rates demonstrate an unmet need for effective and safe alternative therapies for RA in South Africa. The study also underscores the need for a national biologics registry.

ACKNOWLEDGEMENTS

The following investigators were involved in the study: A. Halland, F. Khatib, I. Louw, A. Maharaj, C. Pettipher, J. Potts, B. Sarembock, C. Spargo, E. van Duuren and H. Reuter.

DISCLAIMERS AND SUPPORT

C. Pettipher has done consultancy work for Roche, Abbott and Jansen. R. Rudolph is an employee of Roche Products (Pty) Ltd. M. Tikly has done consultancy work for Roche, Abbott and Pfizer. E. Musenge has done consultancy work for Roche. The study was funded by Roche Products (Pty) Ltd.

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