PROTOCOL

STUDY TITLE: South African Rheumatism and Arthritis Association (SARAA) Registry of patients on Biologic Disease modifying anti-rheumatic therapies (DMARDS) for rheumatic diseases

PROTOCOL NUMBER: SABIO 001

SPONSOR: South African Rheumatology and Arthritis Association

Biologic disease modifying drugs (DMARDS) have demonstrated superior efficacy to the conventional treatments in patients with rheumatic diseases [1-3]. However there are concerns about the safety of these drugs most specifically the risk of tuberculosis (TB) with the anti-TNF therapies [4]. Patients with rheumatoid arthritis (RA) are more susceptible to TB than the general population [5], independent of treatment, and the risk is further increased with anti-TNF therapy [4]. Older age, past history of TB, prednisone dose >10 mg [6] and being born in an endemic area [7] have been identified as risk factors. There is also evidence that in patients with ankylosing spondylitis the risk of TB is increased [8]. Over 50% of reported TB cases associated with anti TNF alpha treatments are extra pulmonary [9]. In South African (SA) Mycobacterium Tuberculosis is endemic, with regional variations. WHO estimates the incidence of TB in SA as 981/100 000 (including HIV positive patients), one of the highest rates in the world, with mortality of 50/100 000 in 2010 (WHO TB Data). The risk of TB in patients with rheumatic diseases on conventional therapies as well as biologic therapies, specifically anti TNF therapy, in a TB endemic country is of fundamental importance and needs to be documented.

South Africa is a developing country, which has a 2 tier health care system. Approximately 7 million people in South Africa are on medical insurances (ref), and their care is managed in the private health care sector. These patients are generally socio-economically more advantaged and probably at lower risk of TB. The majority of South Africans (42 million) are dependent on State health sector, where resources are limited and there are many challenges in terms of access to health care, personnel shortages and treatment shortages[10]. Biological DMARDS use in South Africa is mainly in the private health care sector. These high cost drugs, although effective, poses health economic challenges in both the private as well as the state sector in a country with limited resources.

Biologic DMARDS have been licensed in South Africa for severe refractory rheumatoid arthritis, refractory ankylosing spondylitis and severe refractory psoriatic arthritis that is not responsive to conventional DMARDS. The South African Rheumatism and Arthritis Association (SARAA) have published recommendation about the use of these biologics DMARDS (http://saraa.co.za/F_BioGuides.asp). Currently there are 6 biologic DMARDS licensed for rheumatic diseases. These include 3 anti-TNF alpha blockers – infliximab, etanercept, adalimumab – which are licensed for RA, ankylosing spondylitis and psoriatic arthritis. Other biological DMARDS that have been licensed for RA include rituximab (B cell depletion), abatacept (T cell co-stimulation) and tocilizumab (IL 6 receptor antagonist).

Most countries have established biologic registries to assess adverse events and safety of the biologic DMARDS. To address the safety of biologic DMARDS in South Africa, SARAA will establish a post marketing surveillance register. Any patient who is on a biologic DMARD or initiating a biologic DMARD for a rheumatic disease will be invited to be enrolled on this register. A cohort of biologic naive RA patients with moderate to severe active disease will also be recruited in parallel to provide a comparison cohort. The incidence and relative risk of adverse events in patients on biologic therapies will be compared to the cohort of RA patients who are on conventional therapies.

Study Design
This is a prospective post marketing study assessing the risk of adverse events in patients commencing a biologic DMARDS for a rheumatic disease compared to a comparison cohort of patients with RA who have moderate to active disease on conventional DMARDS

Primary Objective
To assess the incidence of developing an adverse event (hospitalisation, infections, malignancy, death, pregnancy and congenital abnormalities) in patients on biologic therapies compared to a cohort of patients with RA patients treated with conventional therapies

Secondary Objectives
1 To assess the clinical effectiveness on biologic therapies – change in SDAI, BASDAI
2 To assess the pattern of biologic DMARD uses
3 To assess the LTBI results and prophylaxis in the biologic cohort.

Inclusion Criteria
Biologic cohort

1. Patients with a rheumatic disease who are currently on or commencing a biologic DMARD. The patients will have to satisfy the classification criteria for the respective diseases - rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis
2. Willingness by the patient to give informed consent.

RA Cohort on conventional therapy

1. Patients with rheumatoid arthritis – fulfilling the ACR 1987 classification criteria
2. Moderate/severe disease at the time of consent SDAI of ≥11
3. Disease duration of ≥ 6 months
4. Methotrexate ≥ 12.5 mg – current or past use

SAMPLE SIZE
It is likely that the number of subjects that will be treated with a biologics will vary, depending on the clinical indication. The factor that is under the control of the register is the size of the comparison RA biologic naive cohort . The calculation for

the sample was based on a two – fold increase in the in tuberculosis in the subjects on biologics. Since no tuberculosis prevalence data for patients who have RA and are on synthetic DMARDS are available, a population proportion π1 of 0.01 can be assumed based on the 2010 WHO estimate of the incidence of TB (981/100 000) in South Africa. Based on studies in Hong Kong , Spain, Sweden, Japan, Korea and Canada, there is an increased risk of TB infection ranging from 2 to 11 in RA patients; sample sizes are thus also provided for a two - fold increased relative risk for the RA biologic naïve group (relative to the South African population) – see table 1 below. The sample sizes were calculated a 5% level of significance with 90% power to detect the difference between the two groups.

Table 1

	Group 1 proportion π_1	**Group 2 proportion π_2**	**Number per group**
Doubled risk	0.01	0.02	657

Method

The logrank test will be used to determine whether the two survival curves of the biologic RA patients and the biologic naïve RA patients are significantly different. This test compares the number of observed occurrences of the outcome (event of interest is TB) and is suitable for progressively censored data (i.e. where patients do not enter the study at the same time). The level of significance for the test is specified as 5%. The hazard ratio will be reported together with the test.
The survival time of the patients (i.e. until occurrence of TB) will be modelled using the Cox proportional hazard model. This technique allows the inclusion of confounding variables and the Cox regression coefficients can be used to determine the relative risk associated with each covariate, adjusted for the effect of all other variables in the equation. Variables that have been identified as possible confounders include age, sex, disease activity (SDAI), past history of TB, prednisone dose and ethnicity.

Recruitment

All clinicians who commence a patient on a biologic therapy in South Africa will be advised to notify the registry. Rheumatology sites representing the different geographic regions and socio-economic classes will be invited to recruited RA patients on conventional DMARDS. Any clinician who is willing to participate will be asked to sign the Doctor consent form (Appendix D). The clinician will be responsible for obtaining patient consent and providing the patient information leaflet APPENDIX E). The protocol, doctor consent, patient consent and patient information leaflets will be available on the SARAA website.
The current number of new patients going onto biologics is estimated to be 30 per month. Hence the recruitment time is estimated to be at least 2 years.

BASELINE DATA

The baseline data will be collected by the clinician on standardised form. (Appendix A1, A2, A3)

Demographics- Age, Gender, Race, Medical aid and plan, address, employment status

Disease: Diagnosis (classification criteria), Duration of disease (calculated from symptom onset)

Comorbid diseases

Smoking status – never smoked, exsmoker, current smoker – duration of smoking

Previous DMARD history – start date, stop date, maximum dose and reason for discontinuation

Current DMARD – start date and dose.

Steroid use – start date and dose

Disease activity - SDAI (28 SJC, 28 TJC, Physician global assessment VAS 100mm, patient global assessment VAS 100mm, CRP) in patients with RA and Psoriatic arthritis. BASDAI and spinal pain in AS.

Functional assessment - RA and Psoriatic arthritis patients HAQ. In AS – BASFI

TB risk: past history of TB, previous treatment for TB or LTBI, current TB exposure

Assessment of LBTI (only in the patients on biologics therapy)

PPD (if positive - size of induration)/TB quantiferon (positive, negative)

CXR results – clear, evidence of LTB or active TB

TB prophylaxis drug/s and duration of prophylaxis

In addition contact details will be collected for each patient recruited

Follow up data

This will be co-ordinated and collected by SARAA at 6 months, 12 months and then annually. Follow up information will be collected from the clinician using standardised forms (Appendix B1, B2, B3)

Development of adverse events – date of onset, serious, related to biologic, treatment. The clinician will be asked to provide supporting evidence where possible in the case of TB or infections.

Change in therapies – DMARDs, NSAIDS, corticosteroid and biologics DMARDS

Change in disease activity – SDAI and BASDAI

Change in functional assessments – HAQ and BASFI

In addition patients will be contacted every 6 months for the first year and then annually to assess any adverse event. This will be conducted by SARAA study co-ordinator either telephonically or via email. (Appendix C).

The notification of adverse event to SARAA will not exempt the rheumatologist from the obligation of notifying the events to the usual drug monitoring authority and the company concerned.

ANALYSIS

The initial analysis will compare the baseline data between the 2 cohorts. The final analysis will be based on comparing the risk of developing a primary end point over time, taking into consideration the difference in between groups and the potential confounders.
Incident rate of an adverse event will be presented as events/100000 patient year's exposure.

SARAA has set up a Biologics steering committee which is responsible for the overall management of the study. There are 2 subcommittees for the data analysis and safety adjudication. These committees will be independent of any involvement from the pharmaceutical industry. The safety adjudication committee will include 2 rheumatologists and 1 physician with and interest in infectious diseases. The data monitoring committee will include 3 rheumatologists and a statistician.

ROLE OF THE PHARMACEUTICAL INDUSTRY

The establishment of the register is of mutual importance to the pharmaceutical industry and rheumatologists. The pharmaceutical industry provides sponsorship to SARAA for the maintenance of the Registry and the database. The industry however will not have any direct involvement in the register. The analysis, interpretation of data and publications will be independent of any industry contribution. Individual identifiable patient data will not be released to industry, however overall data relating to specific product may be shared with the industry.

ROLE OF SARAA

SARAA will be the owner of the biologics registry and the data that emerges from the registry. The SARAA register and study will be managed by the biologics steering committee. The Chairperson of the steering committee, as appointed by SARAA, will be responsible for reporting to pharma-ethics and other regulatory authorities as appropriate.

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