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RESEARCH TOPIC:

Tobacco usage, clinical and systematic biomarker profiles in the detection of cardiovascular disease in at-risk patients with Rheumatoid Arthritis.

RESEARCH PROPOSAL ABSTRACT

In some, but not all, developed countries mortality among rheumatoid arthritis (RA) patients has declined over time largely due to earlier diagnosis and aggressive implementation of disease-modifying therapies. Nonetheless, mortality in those afflicted with RA remains unacceptably high with 40–50% more deaths occurring among RA patients relative to the general population. The predominant cause of death, accounting for about 40% of cases, is cardiovascular disease (CVD), which has clear associations with factors linked to severity of RA, specifically genotype (HLADRB1/shared epitope), seropositivity (rheumatoid factor – RF; anti-citrullinated peptide/protein antibodies – ACPA), persistent systemic inflammation, and cigarette smoking.

In South Africa and other developing countries, RA remains a seriously under-prioritised disease, particularly among the underprivileged, often resulting in presentation of patients late in the course of their disease, further complicated by limited therapeutic options, and inconsistent follow-up. The consequences are often severe and irreversible disability, increased frequency of co-morbidities, especially CVD, and higher mortality rates, relative to developed countries. In this context, the applicant and his collaborators through their involvement in the Gauteng Rheumatoid Evaluation and Assessment Trial (GREAT) have reported that Black South African RA patients share the same genetic (shared epitope) and immunological determinants (high frequency of dual seropositivity for RF and ACPA) of disease severity and mortality as their European and North American counterparts. Of considerable concern, however, is the finding that South African patients have a particularly high disease burden at presentation which is evident even after 1 year of routine therapy, potentially heightening the risk for development of CVD.

The prevalence of CVD in the context of RA in South Africa is unknown. Addressing this, as well as the impact of early diagnosis and therapy on CVD and the relationship thereof with HLADRB1 genotype, autoantibody type, and biomarkers of systemic inflammatory status, represent the primary objectives of the proposed study, an important extension of the GREAT initiative.

The envisaged translational outcomes are:

- documentation of the prevalence of CVD in a cohort of patients with RA.
- prioritisation of patients for aggressive therapy through identification of clinical and laboratory determinants most strongly associated with high risk. The latter includes genotype, autoantibody type (RF, citrullinated, carbamylated, amylated, etc.), systemic biomarkers of neutrophil/monocyte, platelet and endothelial activation, biomarkers of myocardial dysfunction.
- identification of disease-modifying anti-inflammatory therapies which are also effective in countering CVD in RA and potentially applicable to other inflammatory disorders.

This collaboration involves the Rheumatology Units of the Departments of Internal Medicine of Steve Biko Academic Hospital/University of Pretoria and Chris Hani Baragwanath Hospital/University of the Witwatersrand, and Dept of Immunology NHLS/University of Pretoria(UP). Professors M. Ally and M. Tikly are the respective senior clinical investigators supported by senior scientists Dr P.W.A. Meyer and Prof R. Anderson of the Department of Immunology, University of Pretoria.