Sun Pharma Science Foundation Clinical Research Fellowship

Title - To develop a multi-biomarker panel to predict cardiovascular risk and treatment response in patients with early axial-spondyloarthritis (axSpA) in Eastern India.

Introduction – Subclinical atherosclerosis is a common complication in axial SpA, often underdiagnosed and inadequately treated. Many molecules interplay in SpA with different mechanisms, resulting in a robust inflammatory response and cardiovascular risk. Since the sizable cardiovascular risk is widely recognised in patients with axSpA, various biomarkers are suggested in the literature with conflicting reports. Different studies used serum CRP, complement component C3, visfatin, osteoprotegerin, sclerostin, and serum calprotectin to identify and improve cardiovascular outcomes in such patients. In rheumatoid arthritis (RA), there is a growing interest in multi-biomarker panels to predict CV risk; however, in axial SpA, especially in Asian populations, studies regarding panels of serum biomarkers are limited.

Study Objectives -

A. Primary objective - To compare different serum biomarker values with varied modes of action to predict subclinical atherosclerosis (measured by carotid ultrasound) in axSpA and build a multi-biomarker prediction model.

B. Secondary objectives -

1. To evaluate the correlation between different biomarker levels and baseline clinical disease activity
2. To assess the predictive value of multiple biomarker panels for treatment response at three and 6-month
3. To correlate different biomarker values with the degree of inflammation in MRI of the sacroiliac joint

Methodology

1. **Study design -** Institution-based observational, longitudinal study. We will include patients of axSpA by ASAS criteria as cases. (n= 100)

2. **Study criteria** –

A. Inclusion criteria –

1. Disease duration less than five years (first symptom within five years of data entry)
2. Patients with NSAIDs or conventional DMARD at the time of study entry but not on biological DMARD or target synthetic molecule.
3. Patients should have axial involvement. However, peripheral joint involvement and enthesitis can also be present.
4. The following subgroup of patients will be considered -

B. **Exclusion criteria**: Undifferentiated arthritis, enthesitis-related arthritis, psoriatic arthritis, IBD-associated arthritis, Disease duration for more than five years, and other known comorbidities, including hypertension, diabetes mellitus, and dyslipidemia.

3. Study variables -

A. Blood Parameters - Following serum biomarker level will be assessed

1. Acute phase response - hsCRP, CRP to albumin ratio
2. Adipokines - serum Visfatin
3. Metabolic biomarker- Lipid profile, homocysteine, monocyte to HDL ratio
4. Bone formation marker - Osteoprotegerin
5. Complement - C3, C4

B Imaging -1. Conventional radiography of the pelvis with both hips for all patients, 2.MRI sacroiliac joint (T1 & STIR sequence) for all patients, 3. Carotid US - Ultrasonographic (US) measurements will be made by a radiologist using high-resolution linear transducers.

Sample size calculation—In a study on rheumatoid arthritis, the multi-biomarker disease activity score was compared with DAS28, and the total study population was 92. Another quantitative proteomic sequencing-based study considered 80 cases with 60 spondyloarthritis patients. Based on this limited information, we will evaluate 100 patients with axSpA.

Statistical analysis -We will first examine the biomarker values, calibrating ones that have been measured simultaneously using two methods and trimming outliers. In a series of adjusted linear regression models, we will assess the associations between each candidate biomarker Z score value (number of SDs from the mean) at baseline CIMT and plaque status.

Expected Outcome —This study will help formulate cardiovascular risk prediction models in axSpA, increasing the sensitivity and specificity of cardiovascular risk assessment scores in routine practice. We can also develop a biomarker-based disease activity measure with better sensitivity and specificity than commonly used disease activity parameters.

Timeline

	Task	0-3rd month	4^{th}- 9^{th} month	11^{th}-12^{th} month
1	Serum biomarker and carotid US at baseline			
2.	Follow up (6^{th} and 9^{th} month)			
3.	Result analysis and manuscript writing			