Combined Immune Parameters and X-ray data in Early Prediction of Anti-Tuberculosis Chemotherapy Response

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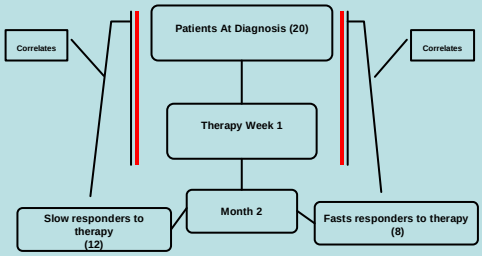
Objective: To investigate the combined predictive value of different circulating immune factors, selected flow cytometric parameters on whole blood and chest radiography for month two sputum culture conversion during anti-tuberculous chemotherapy

Setting: 20 tuberculosis (TB) patients with Bactec culture positivity for *Mycobacterium* tuberculosis (Mtb) at diagnosis were treated with directly observed short course anti-tuberculosis chemotherapy. Serum samples were collected at diagnosis, week 1, 5, 13 and 26 after the initiation of chemotherapy. After the 2-month intensive phase of treatment, 12 patients remained sputum culture positive (slow-responders) and 8 patients were culture negative (fast responders).



Methods: All patients had their postero-anterior and lateral chest X-ray radiography taken at the beginning of chemotherapy and grade for extension of disease. Flow cytometric peripheral blood immune phenotyping was performed and soluble intercellular adhesion molecule-1 (sICAM-1), and soluble urokinase plasminogen activator receptor (suPAR) concentrations measured in serum by ELISA. Tumour necrosis factor receptor two (sTNFRII) was measured using cytokine beads beads base Immuno assay.

Results: The level of sTNFRII rose in all patients from diagnosis to week 1 of chemotherapy and was significantly higher in fast responders both at diagnosis and week 1 of treatment (Anova, $p<0.044$). Slow responders displayed a significant decline in circulating ICAM levels after one week (Anova, $p< 0.0063$,) whereas fast responders showed no change.Overall, suPAR levels decreased between diagnosis and week 1 in both slow and fast responders but changes between and within the groups were not significant. General discrimination analysis indicated that the presence of multiple cavities on X-ray, TNFRII level at diagnosis, the change in sICAM levels during the first week of therapy and the presence of CD3dim/CD56+ NKT cells at diagnosis as the best set of markers predictive of sputum conversion at month 2, with 91.66% correct classification of fast responders and 100% correctly classify slow responder (91.66% and 87,50% % after cross validation, respectively). The support vector machine analysis identified TNFR II level at diagnosis and week1, suPAR level changes during the first week of therapy and the presence of CD3dim/CD56+ NKT cells at diagnosis as the best set of markers predictive with 100% correct classification of the patients after cross validation.

Table 1. General Discrimination Classification Matrix based on the change in sICAM concentration after the first week of treatment, the concentration of sTNFRII at diagnosis, the Absolute CD3dim/CD56+ NKT cells count at diagnosis and the presence or absence of multiple cavities

General Discriminant Analysis Based Classification Model (sICAM; sTNFRII ;CD3dim/CD56+ NKT cells; Multiple cavities)		
	Correct Classification	
	Fast Responders	*Slow Responders*
Classification after Cross validation	87,50%	91,66%

Table 2. Support Vector machine Classification Matrix based on The difference in suPAR concentration between diagnosis and week 1, the Absolute.CD3dim/CD56+ NKT cells count at diagnosis, sTNFRII concentration at diagnosis and week 1

Support Vector machine Based Classification Model (suPAR; sTNFRII; CD3dim/CD56+ NKT cells)		
	Correct Classification	
	Fast Responders	*Slow Responders*
Classification after Cross validation	100%	100%

Discussion: This study showed that the pathophysiological features of patients with active tuberculosis at diagnosis (sTNFRII profile, occurence of CD3dim/CD56+ NKT cells and presence of multiple cavities on X-ray) and the modulation of sICAM and suPAR after the first week of anti-tuberculous chemotherapy can be combine in a model differentiating fast from slow responders to TB therapy early during the course of treatment suggesting that predictive models for differential treatment responses using combinations of host markers hold promise.

The study was funded by GlaxoSmithKline Action TB and the South African MRC