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# The $A_3$ Adenosine Receptor as a Biological Predictive Marker in Rheumatoid Arthritis: Lessons from Phase II Clinical Studies

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**Background.** The Gi protein associated $A_3$ adenosine receptor ($A_3AR$) is highly expressed in the inflammatory tissues and peripheral blood mononuclear cells (PBMCs) of patients with Rheumatoid Arthritis (RA). The $A_3AR$ selective agonist CF101 has been shown to possess robust anti-inflammatory effect via de-regulation of the NF-κB signaling pathway and induction of inflammatory cell apoptosis.

**Objectives.** To evaluate the correlation between $A_3AR$ expression at baseline and the response of RA patients to CF101 treatment. CF101 was given as a monotherapy (Phase IIa) or in combination with methotrexate (MTX, Phase IIb).

**Methods.** The trials were multi-center, randomized, double-blind, parallel group dose-ranging (Phase IIa, n=74) or placebo controlled (Phase IIb, n=223) enrolling patients with active RA who failed MTX treatment. In the Phase IIa study, CF101 was given as a monotherapy, at doses of 0.1mg, 1.0mg or 4.0mg, after one month of washout from MTX. In the Phase IIb, CF101 at doses of 0.1mg, 1.0mg or placebo were added to stable doses of MTX. In both trials, CF101 was given orally, twice daily for 12 weeks. The primary efficacy endpoint was ACR20 response and secondary end point were ACR 50/70. To evaluate $A_3AR$ protein expression levels in the PBMCs at baseline, blood samples were withdrawn from 18 patients (Phase IIa) and from 60 patients (Phase IIb). $A_3AR$ expression levels were tested by western blot analysis and compared to that of healthy subjects (control).

**Results.** The Phase IIa study reached, whereas the Phase IIb study missed the primary efficacy end points. $A_3AR$ expression levels at baseline were <u>up-regulated</u> in the Phase IIa and similar to control in the Phase IIb (2.46±0.0.398 and 1.29±0.125 fold vs. control, respectively).

**Conclusion.** $A_3AR$ over-expression at baseline in the Phase IIa study was found to be directly correlated to the success of the response, whereas in the phase IIb study low $A_3AR$ expression levels were associated with lack of response. It thus seems that $A_3AR$ can be utilized as a biological marker to predict patient response to CF101.