RESULTS OF THE FIRST CELL THERAPY TRIAL WITH ANTIGEN-SPECIFIC IL-10 PRODUCING REGULATORY T CELLS IN CROHN'S DISEASE

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INTRODUCTION: Adoptive transfer of antigen-specific IL-10 producing Treg cells inhibits inflammation in a wide range of inflammatory disorders in mice including chronic colitis. The tolerability and efficacy of this therapeutic strategy was assessed in a phase I/II clinical study in severe Crohn's Disease (CD) patients using autologous ovalbumin-specific IL-10 producing Treg cells (OVASAVE^{TM})

AIMS & METHODS: CATS1 (Crohn And Treg Study) is an open label, 12-week multicenter, single injection, ascending dose, phase I/II study in 20 patients with severe CD presenting active inflammation. Autologous ovalbumin-specific IL-10 producing Type 1 Treg cells were induced from patient PBMC, exposed to ovalbumin followed by cell cloning and expansion using feeder cells prior to formulation for intravenous administration. Patients were distributed in 4 dose groups (10^6 cells: 8 pts; 10^7: 3 pts; 10^8: 3 pts; 10^9: 6pts). Safety was assessed with clinical and laboratory parameters and efficacy with Crohn's Disease Activity Index (CDAI, response: decrease ≥100; remission: <150) and CRP. Patient's peripheral blood was collected before and 1, 3, 8 and 12 weeks after cell administration. Change in peripheral blood immune cell populations was evaluated by flow cytometry. The impact of the treatment on the proliferative response of patients' PBMC (peripheral blood mononuclear cells) to ovalbumin in vitro was also evaluated.

RESULTS: Cells composing OVASAVE^{TM} displayed the characteristic profile of Type 1 Treg cells with IL-10 and IFN-γ production in the absence of IL-4. Cells expressed high levels of Granzyme B, IL-13, VLA-4 and LFA-1. Foxp3 and CD25 expression were inducible by TCR activation signals. CD62L and CD127 expression were low. OVASAVE^{TM} was well tolerated. Clinical response was observed in 40% (8/20) of overall patients. In the best dose group (10^6 cells), response was 75% (6/8) 5 and 8 weeks after treatment; remission was 38% (3/8) and 25% (2/8) and the mean CDAI reduction was 143.4±105 (p=0.0062) and 114.3±77.9 (p=0.0043) at weeks 5 and 8, respectively. The difference in CDAI reduction for the 10^6 dose group vs all other groups was 101.79±37.71 (p=0.0147) and 93.05±38.11 (p=0.0266) at weeks 5 and 8, respectively. Immunomonitoring studies revealed that blood CD16+ pro-inflammatory monocytes, one of the main contributors of mucosal inflammation, were selectively decreased in the group of responder patients 3 weeks after administration. In this group of patients, the proliferative response of PBMC to ovalbumin in vitro was reduced 3 weeks after treatment, suggesting a direct suppression of ovalbumin-specific immune response in patients mediated by OVASAVE^{TM}.

CONCLUSION: OVASAVE^{TM}, antigen-specific Treg cell therapy is well tolerated and shows a positive dose related efficacy in severe CD patients. The immune responses support the mechanism of action and correlate with the clinical efficacy results. The consistency of the results across different methods is supportive of an efficacy in CD patients and warrant further clinical and mechanistic studies.