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RESULTS OF THE FIRST CELL-BASED IMMUNOTHERAPY TRIAL WITH IL-10 PRODUCING REGULATORY (TR1) CELLS IN CROHN'S DISEASE

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INTRODUCTION: Adoptive transfer of antigen-specific IL-10 producing Treg (Tr1) 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.

AIMS & METHODS: CATS1 is an open label, 12-week multicenter, single injection, ascending dose, phase I/II study in 20 patients with severe CD patients presenting active inflammation. Autologous ovalbumin-specific IL-10 producing Tr1 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 CDAI (response: decrease ≥100; remission: <150) and CRP.

RESULTS: The ovalbumin-specific IL-10 producing cells injected by i.v. into patients displayed the characteristic profile of Tr1 cells producing IL-10 and IFN-γ 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 negative. The treatments were well tolerated with 66 adverse events (17 possibly and 3 related) and 14 serious adverse events (3 possibly related), all recovered. Clinical response was observed in 40% (8/20) of the patients at weeks 5 and 8. In the best dose group (10^6 cells), response was 75% (6/8) at both time points; remission was 38% (3/8) and 25% (2/8) with a mean CDAI reduction of 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) at week 5 and 93.05±38.11 (p=0.0266) at week 8. Several patients were infused a second time with the same product and a CDAI response was seen in the 3 patients that received a re-injection with 10^6 cells. C reactive protein dropped to normal values in 58% (5/8) of the patients at the 10^6 dose. All were responders.

CONCLUSION: Cell based immunotherapy of Crohn's disease using autologous antigen specific IL-10 producing Tregs (Tr1 cells) is well tolerated and shows a positive dose related efficacy in severe refractory patients and a possible novel therapeutic opportunity in this unmet medical need. These positive results support further development of Tr1 cell-based treatment of Crohn's Disease patients and other autoimmune/chronic inflammatory diseases.