THERAPEUTIC POTENTIAL OF IL-10 PRODUCING REGULATORY (TR1) CELLS IN SEVERE RHEUMATOID ARTHRITIS PATIENTS.

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Background: IL-10 producing regulatory T (Tr1) lymphocytes have been shown to inhibit chronic inflammation in a wide range of animal models such as chronic colitis, type 1 diabetes, experimental encephalomyelitis and allergy. A phase I/IIa clinical study has recently shown promising results on the use of these cell population for treating severe refractory Crohn's Disease patients.
Objectives: The aim of this study is to address the feasibility of using Tr1 cells for the treatment of severe Rheumatoid Arthritis (RA).
Methods: We assessed the efficacy of collagen-specific Tr1 cells in two models of arthritis in mice (CIA:Collagen-Induced-Arthritis and CAIA: Collagen-Antibody-Induced-Arthritis) and studied the phenotype and function of collagen-specific Tr1 cells in the peripheral blood of RA patients.
Results: Mouse Tr1 cells specific for Collagen-II were differentiated *in vitro* and infused into DBA-1 mice developing CIA. The infused cells migrated rapidly to the inflamed joints and inhibited both the incidence and the severity of the disease at doses ranging from 1 to 3 million of transferred cells. Treatment of arthritic mice with 10 millions of Tr1 cells did not show the same beneficial effect, despite an equivalent migration to the joints. Control of arthritis was correlated with inhibition of both cellular collagen II-specific Th17 as well as humoral collagen-II antibody responses. In addition, the therapeutic action of collagen-II specific Tr1 cell infusion was confirmed in acute CAIA, in which migration to inflamed joints and inhibition of disease severity with 1 million cells was also observed.
In order to demonstrate the feasibility of the approach in humans, we isolated collagen-II specific Tr1 cells from the blood of severe RA patients, who are refractory to Methotrexate and anti-TNF agents. We showed upon in vitro activation that these cells display unaltered phenotype (Foxp3, GITR, CTLA4) and cytokine secretion profile ($IL\text{-}10^{high}$, $IL\text{-}4^{low}$, $IFNg^{int}$). Importantly, the *in vitro* suppressive capacity on bystander T cell proliferation was also demonstrated on patients' cells.
Conclusion: Altogether, these results demonstrate that cell therapy of severe RA using autologous collagen-II Tr1 cells may be an important novel therapeutic strategy for the treatment of patients that are refractory to conventional treatments.

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