Abatacept (CTLA-4Ig) treatment reduces T cell apoptosis and regulatory T cell suppression in patients with rheumatoid arthritis (RA).

Bonelli M[1], Göschl L[1], Blüml S[1], Karonitsch T[1], Steiner G[1], Smolen JS[1] and Scheinecker C[1].

ABSTRACT

OBJECTIVE:
Abatacept (CTLA-4Ig) blocks CD28-mediated T cells activation by binding to the costimulatory B7 ligands CD80/CD86 on antigen presenting cells (APC). Costimulatory molecules, however, can also be expressed on T cells upon activation. We therefore analysed whether CTLA-4Ig directly affects distinct T cell subsets in RA patients.
METHODS:
Phenotypic and functional analyses of $CD4^+$ T cells, including $CD4^+FoxP3^+CD25^+$ regulatory T cells (Treg), from RA patients were performed before and during CTLA-4Ig therapy. In addition T cells from HC were analysed upon in vitro culture with CTLA-4Ig or anti-CD80 and anti-CD86 antibodies. Apoptotic DNA fragmentation in $CD4^+$ and $CD4^+FoxP3^+$ T cells was measured by TUNEL staining.
RESULTS:
We observed an increase in T cells, including Treg cells, after initiation of CTLA-4Ig therapy, which was linked to a downregulation of activation associated marker molecules and CD95 on $CD4^+$ T cells and Treg cells. CTLA-4Ig decreased CD95-mediated cell death in vitro in a dose dependent manner. Functional analysis of isolated Treg cells from RA patients further revealed a diminished suppression of responder T cell proliferation. This was found to be due to CTLA-4Ig mediated blocking of CD80 and CD86 on responder T cells that led to a diminished susceptibility for Treg cell suppression.
CONCLUSION:

CTLA-4Ig therapy in RA patients exerts effects beyond the suppression of T cell activation, which has to be taken into account as an additional mechanism of CTLA-4Ig treatment.