Local TACI-Ig Gene Therapy of the Salivary Gland of NOD Mice Reduces Auto-Immune Inflammation by Affecting the B Cell Compartment

Nienke Roescher, MD, MSc[1], *Jelle L Vosters[1],Marco Guadagnoli[1],Jan P Medema[1],Gabor G Illei, MD[2],John A Chiorini[3],Paul P Tak, MD, PhD[4]. [1]Academic Medical Center-University of Amsterdam,[2]Sjogren's Clinic, NIDCR/ NIH, Bethesda, MD,[3]National Insitutes of Health-National Institute of Dental and Craniofacial Research,[4]Clinical Immun/Rheumatology, Academic Med Ctr/Univ of Amste, Amsterdam*

Background:

Sjögren's syndrome (SjS) is characterized by inflammatory autoimmune exocrinopathy in which B cells and B cell-related factors are important. Some patients have benefited from the use of the pan B cell depleting agent rituximab, validating the B cell compartment as a therapeutic target. An alternative therapeutic approach could be to use the soluble receptor TACI, which binds BAFF and APRIL, factors important in B cell survival and activation. Overexpression of BAFF in mice leads to a SjS-like syndrome and BAFF and APRIL are aberrantly expressed in salivary glands (SG) of patients with SjS. Therefore, we evaluated the effect of blockade of APRIL and BAFF using local gene transfer of a gene encoding for a TACI-Ig fusion protein in the SG of Non-Obese Diabetic (NOD) mice that spontaneously develop a SjS-like disease.

Material and Methods:

An adeno-associated virus serotype 2 (AAV2) vector encoding the TACI fusion protein was constructed by cloning of the extra-cellular domain of mouse TACI coupled to the Fc-part of mouse immunoglobulin (Ig) G1. Expression of this gene was driven by the CMV promoter. The TACI-Ig vector or a control vector expressing beta galactosidase (LacZ) was administered once locally into the SG of NOD mice at the age of 10 weeks. Stimulated saliva flow was determined 10 weeks post-vector delivery. Gene transfer was measured by QPCR and protein analysis of the transduced SG. Inflammation was assessed by quantitative immunohistochemisty as well as by analysis of Ig and cytokine levels in the SG and in serum.

Results:

TACI-Ig was highly expressed following transduction of 293T cells, and media from transduced cells could block BAFF induced B cell proliferation in vitro. In vivo, retrograde canulation of mouse SG also resulted in stable transduction and expression of TACI-Ig as determined by QPCR and ELISA. No change in stimulated saliva flow was observed between TACI treated and control mice. However, TACI-Ig treated mice had reduced SG inflammation as determined by the number of inflammatory foci per cross sectional surface area of the SG (LacZ 3.8 vs TACI-Ig 2.6, $p < 0.01$) and pro-inflammatory cytokines levels (IL-2, IL1β, IFN gamma) in the SG tended to be lower compared with control mice. Moreover, the numbers of B and plasma cells, were significantly lower ($p<0.05$) in the SG of treated mice, as well as IgG and IgM levels (50% and 41% reduction respectively, $p<0.05$). IgA levels did not change resulting in a significant improvement of the IgG/IgA ratio for the treated mice. Systemically, no significant changes in Ig-subtypes or cytokine levels were observed.

Discussion:

The results presented here suggest that local B-cell targeted therapies may be beneficial in the treatment of SjS. The expression of a soluble TACI-Ig fusion protein in SG of NOD mice decreased autoimmune inflammation by reducing the number of B and plasma cells locally. The observed changes in IgG and IgM and the reduced IgG/IgA ratio levels suggest restoration of the balance of the mucosal immune system. When tested in patients with SjS, the timing of administration of the gene construct in the disease process may be critical in determining the outcome for salivary flow.