Cytokines in Sjogren's syndrome: potential therapeutic targets

Roescher, N.; Tak, P.P.; Illei, G.G.

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Cytokines in Sjögren’s syndrome: potential therapeutic targets

Nienke Roescher,1,2 Paul P Tak,2 Gabor G Illei1

ABSTRACT
The dysregulated cytokine network in Sjögren’s Syndrome (SS) is reflected by local and systemic overexpression of pro-inflammatory cytokines and absent or low levels of anti-inflammatory cytokines. To date, the use of cytokine-based therapies in SS has been disappointing. Oral administration of low dose interferon (IFN)α showed inconsistent efficacy in various studies and failed to achieve the primary endpoint in a pivotal randomised controlled trial. Similarly, neither of the two tumour necrosis factor (TNF)-α blockers tested (etanercept and infliximab) showed efficacy in placebo controlled trials. Although the rationale for low dose oral IFN treatment has not been firmly established, TNF blockade was based on solid preclinical data. Therefore, the reason for the lack of efficacy is unclear, but recent data suggest that unexpected biological effects of TNF antagonists may have contributed to this. Cytokines, given their central role in the pathogenesis of SS, remain attractive targets for future treatments, despite the disappointing early results. Inflammatory cytokines are obvious candidates, and agents against several of them are available or under development for other autoimmune diseases similar to SS. New candidate cytokines such as IL-17 and IL-12 have low levels of circulating IFNα (a view that has since been challenged) and reduced sensitivity of natural killer cells, indicating a potentially reduced antiviral response.1 2 3 Early small studies used high-dose parenteral IFNα with overall positive results on salivary function and focus score.4 5 At the same time, several groups showed that oromucosal administration of low-dose IFNα was biologically and clinically effective in animal models of autoimmune diseases.6 These observations and the concern about potential toxicities associated with high-dose IFNα led to studies evaluating low-dose oral IFNα. Initial studies showed an improvement in some but not the same outcome measure of salivary function7 8 and focus score.7 A phase III study with 497 patients treated with placebo or IFNα lozenges chose stimulated salivary flow and subjective oral dryness as the co-primary outcomes. This study was negative for these primary endpoints because both the placebo and the IFN-treated groups showed significant but similar improvement in stimulated saliva.5 Interestingly, compared with placebo recipients those treated with IFNα had a significantly greater improvement in unstimulated salivary flow and showed improvement in several other subjective secondary endpoints.9

Preliminary studies with TNF blocking agents were also encouraging, with positive outcome in both objective and subjective parameters after infliximab treatment.10 However, a larger randomised, double-blind, placebo-controlled study of infliximab with 103 SS patients showed no difference in response between the placebo versus the infliximab-treated group.11 Similarly, etanercept was also no more effective than placebo in a 12-week placebo-controlled study.12

A major limitation of these studies is that they do not provide an explanation for the disappointing results. The negative results could be due to suboptimal study design, ineffective dosing, insensitive outcome measures, biological inefficacy or a combination of these factors. Patient selection is important and should be tailored to the goal of the therapy. If improving salivary flow is the goal, including only patients who have some salivary function will improve the chance to show an effect, because patients who may not have any functional tissue left due to fibrosis or atrophy will be excluded. The importance of this consideration has already been shown in a study with rituximab.13 Alternatives to traditional outcome measures of saliva and tear flow are much needed, because our current measures are both insensitive and non-specific and do not distinguish between disease activity and damage. Most importantly, early clinical studies should address the biological effects

1Molecular Physiology and Therapeutics Branch, National Institute of Dental and Craniofacial Research, National Institutes of Health, DHHS, Bethesda, Maryland, USA
2Division of Clinical Immunology and Rheumatology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Correspondence to Dr Nienke Roescher, Molecular Physiology and Therapeutics Branch, National Institute of Dental and Craniofacial Research, National Institutes of Health, DHHS, 10 Center Drive, Bethesda, MD 20892-1190, USA; roeschm@mail.nih.gov

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THE CYTOKINE IMBALANCE IN SJÖGREN’S SYNDROME
Dysregulation of the cytokine network contributes to both systemic and exocrine manifestations of Sjögren’s syndrome (SS) (reviewed in Roescher et al).1 In the exocrine glands, proinflammatory cytokines, such as interferon (IFN)α and γ, tumour necrosis factor (TNF)α, interleukin (IL)-12 and IL-18, along with other cytokines important in T and B cell activation and autoantibody production, such as IL-6 and B cell activating factor (BAFF), are over-expressed. In contrast, important anti-inflammatory cytokines, such as IL-4 and transforming growth factor (TGF)β, are expressed at low levels. The effects of other cytokines important in chronic inflammation, such as IL-1β, IL-17 and IL-23, have not been adequately studied (figure 1). The peripheral blood is characterised by overexpression of the IFN-regulated genes,2 high immunoglobulin levels and the presence of autoantibodies, indicating concomitant activation of the innate and adaptive immune system.

CURRENT EXPERIENCE WITH CYTOKINE-DIRECTED THERAPIES
IFNα was the first cytokine used in a therapy for SS patients based on the observation that SS patients have low levels of circulating IFNα (a view that has since been challenged) and reduced sensitivity of natural killer cells, indicating a potentially reduced antiviral response.1 2 3 Early small studies used high-dose parenteral IFNα with overall positive results on salivary function and focus score.4 5 At the same time, several groups showed that oromucosal administration of low-dose IFNα was biologically and clinically effective in animal models of autoimmune diseases.6 These observations and the concern about potential toxicities associated with high-dose IFNα led to studies evaluating low-dose oral IFNα. Initial studies showed an improvement in some but not the same outcome measure of salivary function7 8 and focus score.7 A phase III study with 497 patients treated with placebo or IFNα lozenges chose stimulated salivary flow and subjective oral dryness as the co-primary outcomes. This study was negative for these primary endpoints because both the placebo and the IFN-treated groups showed significant but similar improvement in stimulated saliva.5 Interestingly, compared with placebo recipients those treated with IFNα had a significantly greater improvement in unstimulated salivary flow and showed improvement in several other subjective secondary endpoints.9

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Table 1  Cytokines as therapeutic targets for the treatment of SS based on the availability and/or development of cytokine-directed drugs

<table>
<thead>
<tr>
<th>Target</th>
<th>Main effect</th>
<th>Rationale for blocking in SS</th>
<th>Stage of drug development</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFNα</td>
<td>Antiviral, pro and anti-inflammatory, important for NK cell activity</td>
<td>Decreasing inflammation, reverse Th1 type immune response. Administration: enhancing NK cell activity?</td>
<td>Anti-IFNα monoclonal antibody: single dose suppressed IFN signature in SLE, multiple dose phase I study completed Administration: multiple parenteral formulations approved, oral lozenge in clinical studies</td>
</tr>
<tr>
<td>BAFF</td>
<td>B-cell development, maturation, survival</td>
<td>Decreasing B-cell activation, prevention of GC formation and lymphoma-genesis, reduction of autoantibodies</td>
<td>Phase III studies have shown efficacy in SLE</td>
</tr>
<tr>
<td>IL-6</td>
<td>B-cell proliferation and plasma cell formation, acute phase response, T-cell stimulation and recruitment</td>
<td>Decreasing systemic and local inflammation, decreasing B-cell activation, decreasing plasma cell formation, reduction of autoantibodies</td>
<td>Phase III studies in RA successfully completed, pilot study in SLE showed normalisation of B-cell repertoire</td>
</tr>
<tr>
<td>IL-12/IL-23</td>
<td>Differentiation into Th1 type immune response</td>
<td>Decreasing inflammation, reduction of GC formation and lymphoma genesis</td>
<td>Phase III clinical trial in psoriasis successfully completed, phase II for Crohn’s disease currently undertaken</td>
</tr>
<tr>
<td>IL-17</td>
<td>Proinflammatory, clearing of extracellular pathogens, major role in autoimmunity</td>
<td>Reverse autoimmunity, reducing inflammation</td>
<td>Phase II clinical trial for RA, Crohn’s disease and psoriasis currently undertaken</td>
</tr>
</tbody>
</table>

BAFF, B-cell-activating factor; GC, germinal centre; NK, natural killer; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS, Sjögren’s syndrome; Th1, T-helper type 1.

Figure 1  The effect of key cytokines on the different aspects of Sjögren’s syndrome (SS). An imbalance in the local expression of pro and anti-inflammatory cytokines leads to chronic inflammation and salivary gland dysfunction. Proinflammatory cytokines are shown in dark grey, anti-inflammatory in green boxes. IL-10 is a bipolar cytokine with known pro- and anti-inflammatory characteristics, shown in green and grey. The effect of cytokines on the most important pathological processes (white ovals) are shown by blue arrows. The effect of some cytokines on each other is shown in orange arrows. IL-4 and transforming growth factor (TGF) beta are expressed at low levels or are not detectable in SS. IL-17 and IL-23 (in orange) may play a role in SS (dotted lines) but data on this are not yet available. Cytokines in the red framed boxes depict cytokines that may provide a good target for therapy. BAFF, B-cell-activating factor; DC, dendritic cell; TNFα, tumour necrosis factor alpha.

of the treatments. For example, it is not known whether the lack of efficacy of TNF inhibitors was due to suboptimal doses, which were insufficient to suppress TNF in the target organs, or if effective suppression of TNF was achieved but other mechanisms of the underlying pathophysiology negated the benefit of TNF blockade. This latter mechanism is supported by recent observations showing a paradoxical elevation of TNFα,14 IFNα and BAFF15 after etanercept treatment.

FUTURE TARGETS
Despite the disappointing clinical results to date, cytokines remain attractive albeit challenging therapeutic targets. The pharmaceutical industry shows little interest in developing biological therapies primarily for SS; therefore we will focus on cytokines that could be targeted with biological agents that are available or are in clinical testing for other indications (table 1).

IFN-regulated genes are overexpressed in both the exocrine glands and peripheral blood in SS, suggesting an exaggerated IFN response.16 17 Suppressing IFNα represents an appealing therapeutic target, but the clinical significance of the IFN signature and the role of IFNα in SS in general is not yet understood. First, the IFN signature showed no association with any clinical manifestations other than the presence of anti-SSa and SSb antibodies in SS16 and, as discussed above, therapeutic trials with IFNα showed no harmful effects and may have had some benefit. So, on the one hand, although conventional wisdom overwhelmingly supports the blockade of IFNα as a treatment option in SS, based on the available clinical data of IFNα treatment of patients with established SS, it should not be dismissed as a potential therapy. On the other hand, the majority of experts support the idea of blocking IFNα to treat SS. Several IFN-blocking agents are under development. The single administration of an anti-IFNα monoclonal antibody in systemic lupus erythematosus (SLE) successfully suppressed the IFN signature.18 Further studies are required to test whether this translates into clinical benefit. Multiple dosing studies are underway and if they show a reasonable safety profile IFN-blocking agents should be tested in SS.

A more recently described cytokine implicated in SS is BAFF, a major promotor of B-cell survival. In patients with SS BAFF levels are elevated in the serum, saliva and exocrine glands.19 BAFF is upregulated in salivary gland epithelial cells in vitro
after viral infection and after treatment with IFNα, suggesting that it may represent a link between innate and adaptive immunity. Moreover, BAFF seems to be involved in the formation of ectopic germinal centres in the salivary glands, which may be an important step in lymphomagenesis. Several anti-BAFF agents are currently being tested in autoimmune diseases. In SS, studies with belimumab, an anti-BAFF monoclonal antibody, which showed efficacy in SLE, are planned.

IL-6, a potent proinflammatory cytokine, is involved in acute phase reactions and both B and T-cell responses. It was found to be consistently high in saliva and serum and is highly expressed in the salivary glands of SS patients but not in subjects with xerostomia only. A monoclonal antibody against the IL-6 receptor exhibited efficacy and a good safety profile in rheumatoid arthritis (RA). The same antibody led to normalisation of the abnormal peripheral B-lymphocyte repertoire in a pilot study in patients with SLE. B-cell abnormalities are similar between SS and SLE and are characterised by a shift to increased plasma cell and memory B-cell populations; therefore, blocking IL-6 or its receptor may have a beneficial effect on both the local inflammatory process and systemic autoimmunity in SS.

Overexpression of IL-12 and IL-18 is associated with inflammation and decreased function in the gland as well as lymphomagenesis. Limited preliminary studies with an IL-18-binding protein were performed in RA and psoriasis. A monoclonal antibody against the p40 subunit of IL-12 showed beneficial effects in Crohn’s disease and psoriasis. As the p40 subunit is shared with the recently discovered IL-23, it is likely that, at least some of the beneficial effects are due to blocking IL-23. IL-23 was found at higher levels in the salivary gland in SS, and if its role in chronic inflammation were to be confirmed, blocking the shared p40 subunit of IL-12 and IL-23 would be appealing. IL-17 secreting CD4 T cells have recently been identified as a specific subset with an important role in inflammation and autoimmunity. SS patients have increased expression of IL-17 in the salivary glands and higher levels in the serum. Further studies are needed to establish the role of IL-17 in humans but it may represent an exciting future target.

Successful cytokine-based therapies must have a reasonable safety profile, should reduce inflammation systemically and locally and should restore the secretory function. Because of the redundancy of the cytokine network, targeting a single candidate may not achieve all criteria. Therefore, for an effective therapeutic response, it may be necessary to use a combination of cytokine targets concomitantly or sequentially or target downstream effector molecules shared by several cytokines. A major limitation of these approaches is the increased risk of potentially severe side effects, which is not justified for many SS patients. Because the salivary glands are relatively easily accessible, an alternative to systemic treatment, which would greatly improve the risk benefit ratio of cytokine-based therapy for SS patients, would be the local delivery of cytokines or their inhibitors, for example by gene therapy, successfully applied to animal models of SS. The increasing availability of biological agents and the potential of gene therapy are exciting, but identifying the right target remains a challenge that can only be overcome by a better understanding of the pathogenesis of SS. Well-designed proof-of-concept studies addressing the biological effects of cytokine-directed therapies will facilitate the identification of targets that can be tested for clinical efficacy. As SLE and SS share many pathophysiological similarities, and a large proportion of SLE patients have coexisting SS, SLE patients enrolled in studies with biological agents that may work in SS should also be evaluated for SS. This could be done relatively easily and would provide significant information about the potential value of various cytokines as potential targets in SS.

Competing interests None.

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