Inhibitors of T cell Activation in the Treatment of Sjögren's Syndrome

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Published online: 17 July 2015

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This article is part of the Topical Collection on *Sjögren's Syndrome*

Keywords Sjögren's Syndrome · Abatacept · T cell costimulation · Cyclosporine

Opinion statement

Given the hypothesis of an initial exogenous agent attacking/infecting ocular and oral glands in Sjögren's syndrome, we propose a primarily T cell-guided reaction with ensuing recruitment of B cells and finally resulting in auto-antibody production. From an immunological standpoint, the first clinical signs do represent established disease. Nevertheless, targeted therapy should start as early as possible, and they may target B as well as T cells. A primarily local therapy by CsA eye-drops is worthwhile applying in case of strictly ocular involvement only. Otherwise, a short cycle of leflunomide might prove efficient. If not, based on the most possibly underlying pathophysiology of T and B cell interaction and our own experience, a 6-month treatment with abatacept during the early phase of disease can reach the target cells and lead to clinical improvement. In the later stages, especially in case of cryoglobulinemic vasculitis or pulmonary involvement, a B cell depletion therapy may be highly effective. Based on the available data, it would be interesting to initiate a study targeting both cellular arms of the adaptive immune system, i.e., B cell depletion with, e.g., rituximab and T cell inhibition using abatacept. Trials with alefacept have shown T cell-targeted, positive effects on exocrine gland function in a primary SS (pSS)-associated non-obese diabetic (NOD) mouse model. Whether this molecular intervention is beneficial in human disease will have to be shown.

Introduction

A recent meta-analysis of population-based studies in pSS showed estimated pooled incidence rate of around 7 per 100,000 inhabitants and a

pooled prevalence of around 60 per 100,000 inhabitants, representing a rather frequent autoimmune disease [1].

The term Sjögren's syndrome represents two different entities: Primary SS (pSS) is regarded as an independent entity among the autoimmune-mediated connective tissue diseases. It typically affects salivary and lacrimal glands plus other mucous membranes as well as extraglandular organs, posing risks for cryoglobulinemic vasculitis and secondary lymphoma formation, mainly non-Hodgkin lymphoma (NHL). Incidence for NHL in pSS varies across countries and studies within an approximated range of with standard incidence ratios (SIR) reported from 4.9 to 18.8 [2, 3]. Interestingly, in a large nationwide Taiwanese study, the higher NHL incidence was seen in female pSS patients only but not in the respective male counterparts [4]. Secondary SS describes sicca symptoms and reduced exocrine function of mainly the eyes and mouth as a complication of a given autoimmune disease other than pSS, mostly rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), or systemic sclerosis. Sicca symptoms secondary to, e.g., medication and/or smoking are not regarded as a separate entity but as concomitant negatively influencing factors in any of the two Sjögren's syndromes.

Despite growing knowledge about pathogenesis, the etiology of pSS remains obscure, rendering a causative treatment impossible. Histological and serological findings, however, clearly document central roles of T as well as B cells in developing and propagating the inflammation and eventually leading to tissue destruction as found within the salivary glands [5]. Furthermore, therapies using conventional immune-suppressive drugs or biologic agents have shed light on some of the complex underlying molecular pathways.

In early disease, T cell infiltrates mainly consisting of CD4+ cells predominate glandular infiltrates whereas in later stages B cell infiltration prevails, pointing to a Th-2

driven B cell activation and recruitment in the course of disease [5]. These findings strongly suggest a central regulatory role of T cells. In line with this, Th-1 cytokines such as interferon gamma (IFN γ) and TNF-alpha have been addressed therapeutically, but with questionable success. Th-2-derived cytokines like interleukins 4, 5, and 10 have been indirectly addressed by targeting B cells. Yet, B cell depletion using the monoclonal antibody rituximab to target CD-20-expressing B cells was helpful in highly selected patients only [6]. Furthermore, data on the identification of CD4+ TH17 memory cells within the lymphocytic foci of SS mice models and humans point to a somewhat more complex background [7].

In contrast to many systemic autoimmune diseases which can be controlled targeting a single pathogenic pathway, pSS appears to be more resistant or more complex. One option to interfere at more than one cell type is to target the T/B cell costimulation [8, 9]. In this context, the CD 40 ligand plays an important role. Interference within the CD40 pathway is described to ameliorate inflammation in some disease models. In non-obese diabetic (NOD) mice as a mouse model for pSS, endogenous CD40 was expressed on either inflammatory foci of salivary glands, and as well in addition on cultured epithelial cells from SS patients. Yet, first therapeutic attempts by local administration of CD40 coupled to a human FC domain neither reduce inflammation nor improve salivary gland function [10].

Taken together, T cell activation—in whatever way—remains a focus of interest in the pathogenesis of pSS. We address current T cell-targeted medication in treating pSS and give a short outlook on possible options in the near future.

Treatment

Diet and lifestyle

Lifestyle changes might be directed towards avoiding or reducing any dryness-provoking means as smoking, low fluid intake, use of anti-depressants, and sicca-inducing anti-hypertensives as, e.g., beta-blockers and diuretics. Symptomatic relief can be achieved by tear and saliva substitutes and/or saliva-inducing medication. Prospectively assessing the use of drugs with frequent and/or profound side effects on saliva secretion identified more than 50 % of patients taking such drugs on a regular basis. Most of the patients were not informed about correct handling of sicca problems (evaluation of the Bernese Sjögren population, data not published).

Pharmacologic treatment

Drug therapy in general aims at relieving symptoms of dryness and fatigue, prohibiting visual loss, avoiding and/ treating extraglandular manifestations and—if at all possible—reducing the risk for lymphoma development. Unfortunately, there is no such drug or drug combination available comprising all specific needs. Miscellaneous classes of drugs were used with various outcomes.

In this review, we focus on the use of topical and systemic T cell activation inhibitors in Sjögren's syndrome.

Topical therapy

The calcineurin inhibitors (CNI) cyclosporine A (CsA) and tacrolimus (TAC) have both been used in the therapy of SS-associated dry eye problems with partly contradictory results. A recent study evaluated topical 0.05 % cyclosporine A emulsion applied for keratoconjunctivitis sicca in a dosage of one drop twice a day [11•]. All patients showed significant improvement in redness, Schirmer's test, and tear break up time during a 1-month follow-up. Initial local side effects of, e.g., burning and pain waned already 1 week after start of therapy. Overall, CsA showed consistent improvement over a 6-month period, e.g., in large phase III trials [12]. Finally, a recent consensus panel evaluation recommends CsA in SS-associated dry eyes with a level II to III evidence [13].

Evidence for topical TAC is scarce, yet, a recent prospective double-blind randomized controlled trial used 0.03 % TAC in pSS in a dosage of one drop twice daily in 16 eyes with promising results and significant improvements in objective measurements for exocrine gland function [14].

Nevertheless, CNI seem effective mostly in mild to moderate local disease, outcome measures differ widely between studies, and patients with corneal lacerations appear ineligible due to possibly increased topic side effects. Patients with severe ocular dryness are reluctant to use CsA because of strong burning pain. A comparison of both CNI was performed only in dogs with dry eye symptoms favoring TAC [15].

Systemic non-biologic therapy

Introduced into organ transplantation in the 1980s, cyclosporine A as systemic therapy has been used in autoimmune diseases mainly as a T lymphocyte immunomodulatory agent with various results. Due to its immunological target of activated T cells, effects in pSS were expected. Histological studies 6 months after CsA in a dosage of 5 mg/kg/day divided into two daily applications showed decreased T lymphocytes and T helper cells in minor salivary glands yet clinical effects were described as marginal [16]. Further studies have so far not been performed until in 2015 a Chinese group demonstrated a suppression of TH-17 cell activation by CsA at concentrations of 80 ng/ml in active pSS but not in inactive pSS patients or healthy controls [17]. Unfortunately, clinical effects were not described.

Since its first use in animal models of autoimmune diseases in the 1980s and introduced into clinical use in the late 1990s, leflunomide (LEF) has been successfully prescribed to suppress autoimmune activities in RA, psoriatic arthritis, and SLE. Its use in pSS is anecdotal, few studies and case reports of LEF did not show convincing results [18–20]. Of interest is a recent publication which reports an inhibition of IFN γ by LEF which was related to improvement of saliva production [21]. Thirteen early pSS patients with a mean symptom

duration of 3.3 years received 20 mg leflunomide daily for a 24-week period. Unfortunately, response was counted as either subjective improvement in oral and clinical symptoms measured by visual analogue scales or as amelioration in objective parameters, which—in pSS—might differ to a great extent. Nevertheless, significant increases in stimulated salivary flow were observed in 5/13 patients and correlated well with decreases of IFN γ production, thus clearly supporting the Th-1-related pathogenesis. Furthermore, in 5/13 patients, leflunomide downregulated CD40 ligand-expressing cells and an increased expression of the interleukin 7-receptor (IL-7R) alpha on CD4 T cells pointing to the demonstrated correlation of, e.g., IL-7R alpha with pSS disease activity.

Systemic biologic therapy

As outlined above, targeting one cell type or one mediator such as a cytokine proved not to be sufficient to induce clinically relevant improvement of salivary gland function. Inhibition of cell-crosstalk, however, bears the potential to more profoundly interfere with pathogenic events. Abatacept is a molecule which inhibits activation of T cells by blocking the cross talk between the antigen-presenting cell and the T lymphocyte (Fig. 1). Abatacept, primarily approved for RA treatment, represents a soluble fusion protein of the human cytotoxic T lymphocyte-associated antigen 4 linked to the modified portion of human IgG1 (CTLA4-Ig). As CTLA4 was shown to be involved in controlling CD4 proliferation and downregulating of T cell activation in SS, CTLA4-Ig application in clinical use was demonstrated in few clinical trials [9•, 23•].

Fig. 1. Mode of action of abatacept. By binding to CD80/86, abatacept blocks the interaction of CD80/86 and CD28 on the APC and T cell, respectively. The co-stimulatory pathway leading to T cell activation is inhibited and processes in the inflammatory cascade are downregulated, resulting in normalized levels of cytokines and autoantibodies, and inhibition of osteoclast activity. APC antigen presenting cell (e.g., macrophages, dendritic cells, B cells), MHC major histocompatibility complex, TCR T cell receptor, RF rheumatoid factor, TNF tumor necrosis factor, IFN interferon, IL interleukin, anti-CCP anti-cyclic citrullinated peptide, RANK receptor activator of NF- κ B, MMPs matrix metalloproteinases [22].

Within the first study [4], 11 patients received RA-adapted, 8 body-weight defined doses of abatacept with pre- and post-therapy evaluations of clinical, serological, and histological parameters. Remarkably, a significant reduction in glandular inflammation could be demonstrated alongside with an increase in saliva production when adjusted for disease duration. Furthermore, a secondary effect on the B cell pool by abatacept can be assumed as naïve B cells increased at the end of the study. In another abatacept study [15] in well characterized pSS patients with short median disease duration of 11 months, the same application scheme was given, focusing on SS disease activity, SS patient-reported symptom index, and ocular and salivary gland secretion. While disease activity decreased and patient-reported symptoms ameliorated, only a slight post-treatment effect was seen regarding stimulated whole saliva production. As the study was not blinded and the read-out was patient-related, reported positive effect would have to be confirmed by a RCT. Of note, in both study groups 1 and 2, respectively, patients developed cutaneous lupus symptoms but no other side effects. Overall, abatacept proved to be a safe and valuable option to decrease pSS disease activity, demonstrate T cell changes on a structural level, and increase salivary gland function.

Several questions remain unanswered: Would higher doses or prolonged treatments lead to a histological remission with more profound effect on saliva production? Would combination therapies, e.g., targeting B and T cells lead to more rapid and substantial improvement? It is conceivable that an intensified treatment would lead to a complete remission which could be maintained using conventional doses of a single agent. These considerations have to be put into equation when it comes to discussion about cost-effectiveness. As it stands, abatacept definitely represents a cost-intensive option, yet, rituximab, displaying similar effects and more widely used, compares well.

Indirect interaction with T cell activation and reactivation was expected from efalizumab, a humanized monoclonal antibody targeting the CD11a component of leucocyte function-associated antigen-1 (LFA-1) and initially being approved for psoriasis, demonstrating positive effects in TNF-alpha refractory patients [24]. A possible role in controlling lymphocyte migration into exocrine glands [25] led to the initiation of an efalizumab trial in pSS patients. Started in 2006, it had to be stopped due to potential risks of progressive multifocal leukoencephalopathy [26]. In 2009, efalizumab has been withdrawn from the market completely.

Emerging therapies

Alefacept—a dimeric fusion protein—interferes with lymphocyte activation by specifically binding to the lymphocyte antigen, CD2, and inhibiting the LFA-3/CD2/ interaction. It therefore indirectly modulates activation and proliferation of memory effector T cells [27]. As well primarily used in psoriasis, it herein has shown the most sustained effects within the group of biologic drugs [28]. Yet, due to forced but dose-dependent T lymphocyte depletion, a severe drop in CD4+ and CD8+ cells poses a major concern [28]. A recent trial of alefacept in diabetes type I, given in a standard dosing scheme of 15 mg i.m. per week, showed promising results without major side effects: even though the aimed change in C-peptide was not achieved, insulin use was lowered and hypoglycemic events were decreased, indicating a possible restoration in exocrine

Table 1. T cell targeted therapies

Application/drug	Dosage	Frequency	Indication
Topical			
Cyclosporine A	0.05 %	1 drop twice daily	Dry eye symptoms in SS
Systemic			
Leflunomide	20 mg	p.o. daily	Early pSS
Abatacept	Weight-adapted	i.v. monthly	Early pSS
Alefacept	15 mg (or still to be defined in pSS)	i.m. weekly	To be defined

function [29]. Therefore, in possible analogy to the underlying pathomechanism of immune-mediation by effector memory T cells, its use in pSS seems worthwhile studying—with given precautions.

Another target might be the M3 muscarinic acetylcholine receptor (M3R): being expressed in exocrine glands, it plays an important role in the exocrine secretion. Furthermore, M3R reactive T cells were detected in the peripheral blood of SS patients, indicating a possible role in the T cell activation cascade. A recent study in experimental SS-like sialadenitis indirectly showed its effects by inducing anergy of M3R reactive CD4+ T cells, hereby suppressing IFN γ in vitro and reducing sialadenitis in vivo [30]. Yet, so far, clinical data are lacking.

Expression of CD40 and further CD40-related induction by IFN γ has been found in cultured salivary gland epithelial cells, inducing and maintaining lymphocytic infiltration in pSS patients [31]. Identified primarily as B cell antigen, it was recognized that its ligand is expressed on activated CD4+ T cells. As interference with the CD40 pathway has shown beneficial effects in some disease models, a NOD mouse model analogous to pSS was used for proof of concept. Unfortunately, the local delivery of CD40 coupled to a human Fc domain (CD40:Fc) into the salivary glands could neither improve inflammation nor increase saliva production. The authors conclude that targeting the CD40 alone might not be helpful, and a redundancy in the CD40 pathway might be proposed [10] (Table 1).

Overall, an approach to T cell targeted therapy might be guided as proposed in the table.

Compliance with Ethics Guidelines

Conflict of Interest

Peter Villiger declares that he has no conflict of interest.

Sabine Adler declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by either of the authors.

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