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Review

Immune regulation and B-cell depletion therapy in patients with primary Sjögren's syndrome

Wayel H. Abdulahad [a], Frans G.M. Kroese [a], Arjan Vissink [b,*], Hendrika Bootsma [a]

[a] Department Rheumatology and Clinical Immunology, University Medical Center Groningen, University of Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands
[b] Department of Oral and Maxillofacial Surgery, University Medical Center Groningen, University of Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands

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ABSTRACT

Primary Sjögren's syndrome (pSS) is an autoimmune exocrinopathy characterized by chronic inflammation and destruction of the salivary and lacrimal glands. B- and T- lymphocyte infiltrations in the salivary glands with development of germinal center-like structures are characteristic for pSS. Overexpression of soluble factors, such as interferon α (IFNα) and B-cell activating factor (BAFF), are supposed to be important factors in the initiation and continuation of this disorder. The efficacy and success of B-cell depleting therapy in reducing disease activity in pSS patients for about six to nine months supports the notion that B-cells are major key players in disease manifestation of pSS. In addition to B-cells, also Th-cells (mainly Th17) seem to be involved in the pathogenetic process. In this review, we will discuss recent research findings regarding the cytokines IFNα and BAFF as wells as the role of B- and T-cells in pSS. Emphasis will be put on the impact of B-cell depletion therapy as well as on the presumed impact of therapies aimed for targeting BAFF, either as a sole modality or as a combined treatment with B-cell depletion.

1. Introduction

Sjögren's syndrome (SS) is a systemic autoimmune disease characterized by chronic focal inflammation of the exocrine glands, primarily the lacrimal and salivary glands, resulting in dryness of the eyes (keratoconjunctivitis sicca) and mouth (xerostomia) [1]. SS is one of the more common rheumatic diseases; with a prevalence of 1–3%, affecting more women than men (ratio 9:1). SS may occur alone, independently of another autoimmune disease, and is then termed primary Sjögren's syndrome (pSS). It can also present against a background of other connective tissue diseases, such as rheumatoid arthritis and systemic lupus erythematosus, as a secondary disorder (so-called secondary SS). The serological hallmark of this disorder is the presence of circulating autoantibodies directed against soluble nuclear RNA containing antigens Ro/SSA and La/SSB [2].

The etiology of pSS remains undefined and the pathophysiological mechanism is still poorly understood despite decades of research. Several lines of evidence indicate that lymphocytic infiltrates around the glandular ducts of the exocrine glands are associated with glandular destruction. Contrary to the long-held notion that pSS is a T-cell-driven autoimmune disorder, available evidence indicate that B-cells play a central and critical role in the pathogenesis of pSS [3]. Hyperactivity of B-cells has been demonstrated in SS-patients, and this is manifested by increased serum levels of rheumatoid factor, type 2 cryoglobulins, hypergammaglobulinemia, and the presence of anti-SSA and anti-SSB autoantibodies [3]. In addition, a significant increased risk of developing B-cell lymphoma is observed in patients with SS [4,5]. Finally, B depletion therapy with anti-CD20 reagents, appears to be an effective treatment modality for this disorder [6,7]. According to current hypothesis, this B-cell hyperactivity might well be driven by B-cell activating factor (BAFF), which is upregulated by type I interferons (IFNα/β) [8]. Here we will review the current knowledge on the impact of type I interferons (IFNα/β) and BAFF as well as of the aberrations in the T- and B- lymphocyte compartments in pSS disease pathogenesis, in the light of B-cell depletion therapy. Emphasis will be put on the impact of B-cell depletion therapy as well as on the presumed impact of therapies aimed for targeting BAFF, either as a sole modality or as a combined treatment with B-cell depletion.

2. Role of type I interferon (IFNα/β)

Type I interferons (IFNα/β) constitute critical elements of the innate immune system in response to viral infections. Type I interferons can inhibit viral replication in infected cells, but they

* Corresponding author. Tel.: +31 50 3613840; fax: +31 50 3611136.
E-mail address: a.vissink@umcg.nl (A. Vissink).

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also exert important immunomodulatory effects. In most celltypes, the prevalent pathway of the induction of type I IFN is the activation of cytosolic sensors, such as MDA5 and RIG-1. However, cells may also use toll-like receptor (TLR) 3 and TLR4 (macrophages and dendritic cells (DCs)) or TLR7 and TLR 9 (plasmacytoid DCs) for type I IFN production (for review see e.g. [9]). Initial evidence regarding the role of IFNα in pSS disease manifestations came from the clinical observation that treatment of a patient with hepatitis C with IFNα resulted in the development of pSS [10]. This observation was substantiated by the finding that increased levels of IFNα were observed in labial salivary gland biopsies of patients with pSS [11,12]. Most IFNα was present in ductal epithelial cells and in lymphocytic foci. Serum levels of IFNα were increased in only some pSS patients and IFNα-mRNA levels were only slightly elevated in peripheral blood cells compared to controls [11,12]. Plasmacytoid dendritic cells (pDCs) are main producers of IFNα and these cells were demonstrated in the salivary glands of pSS patients, but not in controls [13,14]. Since reduced levels of pDCs were found in peripheral blood from patients with pSS, the findings suggest that pDCs are recruited into the salivary glands and are involved in disease pathogenesis [14]. Whether these cells are the major source of type I IFN in pSS patients is, however, not known and ductal epithelial cells likely contribute to (circulating) type I IFN levels [15]. Salivary gland ductal epithelial cells indeed express the cytosolic receptors MDA5 and RIG-1, and also TLRs that can induce type I IFN production [16].

Gene expression profiling showed an increase in genes regulated by type I IFN in pSS patients, not only in the (minor) salivary glands [13,17] but also in pDC present in the peripheral blood [18]. This type I IFN signature was particularly enhanced in pSS patients with anti-SSA and/or anti-SSB autoantibodies which suggest a relationship between upregulation of IFNα and presence of autoreactive B-cells [19]. This notion might well be explained by the observation of Båve and coworkers [12] that autoantibodies to RNA-binding proteins from serum of pSS patients, combined with material released by necrotic or late apoptotic cells, are potent inducers of IFNα production by pDCs. Likely, after an initial induction of IFN by virus, the presence of immune complexes containing RNA and autoantibodies sustain the IFNα production by pDCs in the salivary glands [12]. Involvement of virus has been speculated for a long time, but despite the fact that several candidate viruses have been thought to play a role (e.g. Epstein–Barr virus [20,21] and coxsackieviruses [22]), evidence for their contribution in the initiation of the disease is still lacking.

Monoclonal antibodies to IFNα are currently available for clinical application and clinical trials in systemic lupus erythematosus (SLE) and dermatomyositis/polymyositis, but not in pSS, are underway. Given its role of type I IFN in pSS (e.g. stimulation of BAFF production, see below) clinical trials with biologicals directed to IFNα are warranted. Instead of targeting IFNα, yet IFNα itself has been used as a therapeutic agent in pSS, in light of the possible involvement of virus in pSS development. In Phase I and Phase II studies, it was shown that IFNα might increase salivary and lacrimal function in pSS patients [23–25]. These smaller studies were followed by a Phase III RCT on 497 subjects showing that IFNα treatment increased unstimulated whole salivary flow, but not stimulated whole salivary flow and oral dryness [26]. It is currently not clear how the increase in salivary flow following IFNα treatment can be explained.

3. Role of BAFF and APRIL

An important cytokine induced by IFNα is the cytokine B-cell activating factor (BAFF). Together with a proliferation-inducing ligand (APRIL), that share receptors with BAFF, these cytokines play a different but essential role in the regulation of B-cell survival, differentiation and proliferation [27].

The first indication that BAFF may contribute to the development of pSS was derived from studies with BAFF-transgenic mice. Groom et al. [28] showed that BAFF-transgenic mice develop a condition that has interesting similarities to pSS in humans. In these mice, splenic marginal zone B-cells, which exhibit autoreactivity, proliferate in the spleen and later infiltrate the salivary glands, suggesting that cells derived from this compartment potentially participate in exocrine gland tissue damage in pSS. In patients with pSS levels of both BAFF and APRIL are increased [29]. Elevated BAFF levels in pSS patients are held responsible for B-cell hyperactivation and autoantibody production [8]. This is illustrated by the notion that increased serum BAFF/APRIL levels were associated with elevated serum gammaglobulins, IgG, presence of anti-SSA or anti-SSB autoantibodies, and focus score [28,30,31]. In addition, local expression of BAFF was markedly enhanced in inflamed salivary glands that contain germinal center like structures [32]. Transcripts of BAFF were observed in epithelial cells and infiltrating T- and B-cells in salivary glands of pSS patients [33]. BAFF may also participate in the development of abnormal B-cell distribution in pSS patients. This is suggested by the correlation between elevated serum levels of BAFF and the increased number of circulating $CD27^{-}CD38^{++}IgD^{+}$ B-cells [34].

Both virus, type I IFN and (viral) TLR-ligands are able to stimulate BAFF expression in salivary gland epithelial cells, suggesting that viral infection may be responsible for the increase in BAFF production by ductal epithelial cells in patients with pSS [16,35,36]. A recent study based on gene expression modification in labial salivary gland from pSS patients, before and after B-cell depletion by Rituximab (RTX; achimeric monoclonal antibodyagainst CD20), found an increased expression in IFN pathway signaling molecules in pSS patients not-responding to treatment as compared to responders [37]. These observations fit in the concept of type 1-IFN-induced BAFF expression in salivary glands of pSS patients.

Based on the potential role of BAFF in pSS pathogenesis, anti-BAFF therapy is considered to be a serious option. Belimumab, a monoclonal antibody to BAFF, has shown significant benefits for patients with SLE [38]. Similar to pSS patients, SLE patients have also higher serum levels of BAFF and APRIL [39,40]. Data of anti-BAFF therapy are not yet available in pSS patients, but two clinical trials with this biological are underway. Also other BAFF-blocking agents such as A-623, atacicept and briobacept have not been used in clinical trials in pSS yet. BAFF is produced as cell bound cytokine, which is released from the cell surface by proteolytic cleavage. Not all therapeutic reagents available recognize membrane and soluble forms of BAFF with the same affinity, which may result in different outcomes of treatment [32]. Targeting BAFF using one of these agents could not only be beneficial for the pSS patients, but may also shed further light on the pathogenic significance of BAFF in pSS.

4. Role of B-cells

Available evidence indicates that B-cells play a central and critical role in the pathogenesis of pSS. As noted before, B-cell hyperactivity reflected by hypergammaglomulinemia, circulating autoantibodies are major findings in pSS. In addition, B-cells participate in the lymphocyte infiltrate of salivary glands from pSS patients. Ectopic germinal center like structures may be seen in the infiltrates of the salivary glands of some pSS patients, reflecting local B-cell activation, that ultimately may lead to the presence of malignant (MALT) B-cell lymphoma in approximately 5% of the pSS patients. This is further substantiated by Theander et al. [41] who showed that presence of germinal center-like structures, at