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Review

Medical and Oral Care in the 21st Century by the Department of Oral Medicine

– A novel Therapeutic Strategy for Dry Mouth on the Basis of Molecular Mechanisms Involved in the Onset of the Disease –

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Keywords: Department of Oral Medicine, Medical and oral care, dry mouth, Sjögren's syndrome

Abstract: Japan became a super-aging society in 2007, and the aging rate is expected to increase further. This rapid aging of the population has impacted the structure of disease. In terms of oral health, this has resulted in an urgent need to shift from conventional "curative treatment", which focuses on restoring dental morphology, to "curative and supportive treatment", which focuses on restoring oral function in elderly and diseased patients. Diseases treated by the Department of Oral Medicine include oral mucosal diseases, salivary gland diseases (such as dry mouth), inflammatory diseases, neurological diseases, oral psychosomatic disorders, and taste disorders, among others. As many oral diseases are related to systemic diseases, the Department of Oral Medicine is a dental field adjacent to medical science. Therefore, the Department of Oral Medicine is responsible for perioperative oral function management and oral screening prior to the introduction of bone-modifying drugs in collaboration with medical doctors, and it also plays an important role in developing oral management plans according to the patient's disease and condition. The importance of the Department of Oral Medicine will continue to increase further. This review article focuses on dry mouth, a rising issue in the super-aging society, and describes research on developing novel treatments for Sjögren's syndrome (SS). C-X-C motif chemokine ligand 10 (CXCL10) is overexpressed in the labial salivary glands (LSGs) of patients with primary SS (pSS). Studies using human salivary gland cells have demonstrated that CXCL10 is secreted via the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway through interferon-γ stimulation in ductal cells. The potential of JAK inhibitors as therapeutic agents for pSS was evaluated by analyzing the LSGs of patients with pSS and immortalized normal human salivary gland cell lines. The results suggested that JAK inhibitors may be effective for treating dry mouth in patients with pSS. Treating dry mouth may improve the quality of life and contribute to a long and healthy life.

I. Introduction

The rapid aging of the population in Japan has impacted the structure of disease, with an increase of chronic diseases such as sarcopenia, and frailty, dementia, which has become a social problem. In terms of oral health, this has resulted in an urgent need to shift from conventional "curative treatment", which focuses on restoring dental morphology, to "curative and supportive treatment", which focuses on restoring oral

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function in elderly and diseased patients. Furthermore, a medical team and collaboration between hospitals and clinics should be promoted to improve medical efficiency, effectiveness, and safety. The importance of the Department of Oral Medicine is expected to increase.

In Japan, the Department of Oral Medicine is defined as "a medical science that does not focus solely on the oral cavity of a dental patient, but rather takes a holistic perspective and diagnoses and treats oral diseases in consideration of the systemic background, without relying primarily on surgical approaches"[1]. This department deals with a wide range of diseases, including oral mucosal diseases, salivary gland diseases (such as dry mouth), inflammatory diseases, neurological diseases, oral psychosomatic disorders, and taste disorders. As many oral diseases are related to systemic diseases, the Department of Oral Medicine is considered to be a field of dentistry that is closely related to medicine. Therefore, the Department of Oral Medicine is responsible for perioperative oral function management and oral screening prior to the introduction of bone-modifying drugs in collaboration with medical doctors, and also plays an important role in developing oral management plans according to the patient's disease and condition. This review article focuses on dry mouth, a rising issue in the super-aging society, and describes research on developing novel treatments for Sjögren's syndrome (SS).

II. Dry mouth

Dry mouth is a pathological condition in which saliva in the oral cavity is insufficient. Saliva has physical effects, such as moisturizing, lubricating, and purifying the oral cavity, and protecting teeth and mucous membranes; chemical effects, such as digestion of food and buffering; and biochemical effects, such as antibacterial, antiviral, and promoting wound healing[1]. Dry mouth causes various symptoms, like xerostomia, tongue pain, dysgeusia, oral candidiasis, halitosis, dental caries, periodontal disease, and dysphagia, which significantly impair the quality of life (Figure 1). Early diagnosis and treatment of dry mouth are important for dentists to ensure a healthy and enriched social life.

The causes of dry mouth include the loss of moisture from the oral mucosa and decreased salivary secretions. According to the classification proposed by the Japanese Society of Oral Medicine[2], the causes can be broadly divided into: (1) dysfunction of salivary glands, (2) neurological or drug-related causes, and (3) systemic or metabolic causes. When the cause is a dysfunction of the salivary glands, SS, an autoimmune disease, and radiation-induced xerostomia, a late adverse event of radiation therapy for head and neck cancer, produce particularly severe xerostomia symptoms.

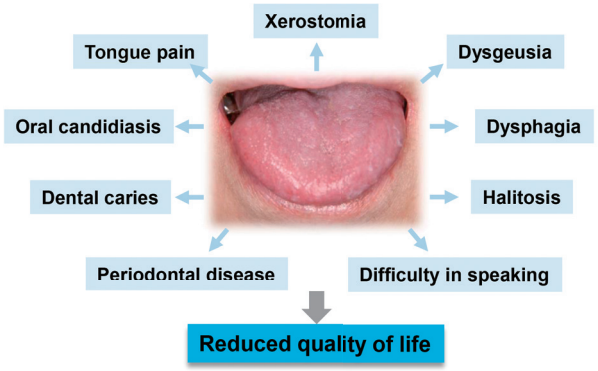

Fig. 1 Symptoms caused by dry mouth

III. Sjögren's syndrome (SS)

SS is an autoimmune disease that specifically affects exocrine glands such as the lacrimal and salivary glands. While the exact pathogenesis of SS is unknown, it is caused by specific genetic factors, exposure to pathogens, and the complex crosstalk between target organs, various immune cells, and the cytokines and chemokines they produce. Histopathologically, the lacrimal and salivary glands exhibit various features, including marked lymphocytic infiltration around the ducts, atrophy or disappearance of the acini, fibrosis in the intralobular and interlobular interstitium, and fatty degeneration. Among the infiltrating lymphocytes, $CD4^+$ T cells are predominant in the early stages of the disease. As the disease progresses, $CD8^+$ T cells and B cells become predominant, and various immune cells, such as plasma cells, macrophages, and dendritic cells, are infiltrated. Currently, only supportive treatment is available for SS, and effective treatment has hardly been established.

Biological drugs (molecular-targeting drugs) have brought about a paradigm shift in the treatment of rheumatoid arthritis (RA) by alleviating inflammation and inhibiting joint destruction. While they do not significantly improve glandular symptoms (dry symptoms) in SS, some improvement in extraglandular symptoms has been observed[3-8]. Many biologics including infliximab[3], etanercept[4], tocilizumab[5], abatacept[6], rituximab[7], and baminercept (lymphotoxin β receptor fusion protein)[8] have failed to obtain an increase in saliva secretion in current RCTs. There have been no study examining at the molecular level why these are not effective against glandular symptoms, and the mechanism is unclear. The pathogenesis of primary SS (pSS) involves complex interactions among many immune cells, salivary gland cells, hormones, and other factors. Due to the diversity of phenotypes and endotypes of pSS, biologics targeting single molecules may have interfered with significant improvement in glandular symptoms.

Table 1 The top 10 genes in DNA microarray analysis of LSGs with pSS

	FC	Gene symbol	Gene title
1	9.15	IFI6	interferon, alpha-inducible protein 6
2	8.82	CXCL9	chemokine (C-X-C motif) ligand 9
3	8.79	IFI27	interferon, alpha-inducible protein 27
4	6.61	CXCL10	chemokine (C-X-C motif) ligand 10
5	6.54	IFI44	interferon-induced protein 44
6	6.53	LOC10029	similar to hCG1686089
7	6.47	XAF1	XIAP associated factor 1
8	6.45	CMPK2	cytidine monophosphate (UMP-CMP) kinase 2
9	6.23	CCL4	chemokine (C-C motif) ligand 4
10	6.07	TRA	T cell receptor alpha locus

LSG samples were obtained from 6 Japanese patients with pSS and 6 healthy controls who had been followed up at Tokushima University Hospital. All subjects were women and had not been treated with corticosteroids, immunosuppressive agents, or biologic agents.
LSGs: labial salivary glands.

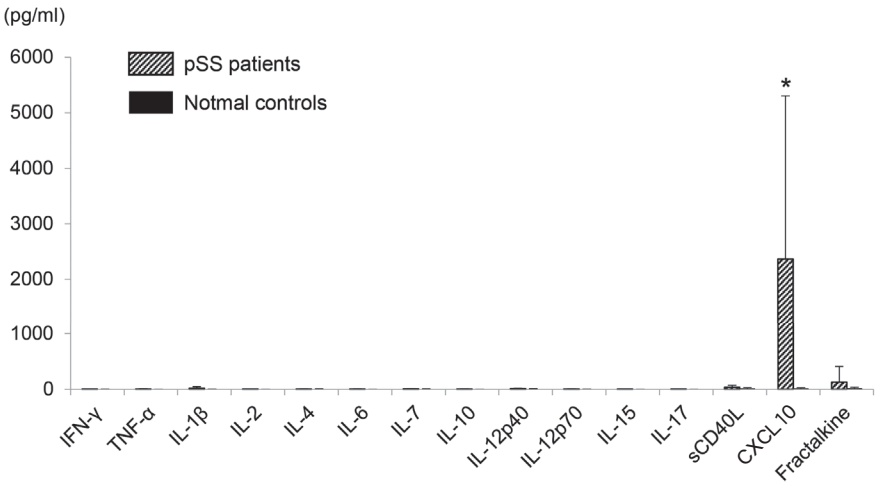

Fig. 2 Multiplex cytokine analysis of saliva with pSS
Saliva samples were obtained from 12 Japanese patients with pSS and 6 healthy controls who had been followed up at Tokushima University Hospital. All subjects were women and had not been treated with corticosteroids, immunosuppressive agents, or biologic agents. The assay was measured by a Luminex 100™ instrument.

IV. Sjögren's syndrome and CXCL10 expression

Recently, a comprehensive genetic analysis of salivary glands of patients with pSS revealed overexpression of interferon (IFN)-related molecules and C-X-C motif chemokine ligand 10 (CXCL10) (also known as IFN-γ-induced protein 10, IP-10)[9]. In 2002, CXCL10 was reported to be produced in salivary gland ducts in pSS and involved in T cell migration[10]. Furthermore, CXCL10 was overexpressed in patients with pSS than in controls in DNA microarray analysis using labial salivary glands (LSGs) (Table 1). In addition, multiplex cytokine analysis using saliva revealed significantly higher expression of CXCL10 in patients with pSS than in controls (Figure 2). Based on these results, I hypothesized that CXCL10 plays an important role in the pathogenesis of salivary glands in pSS.

In a histopathological analysis of LSGs from patients

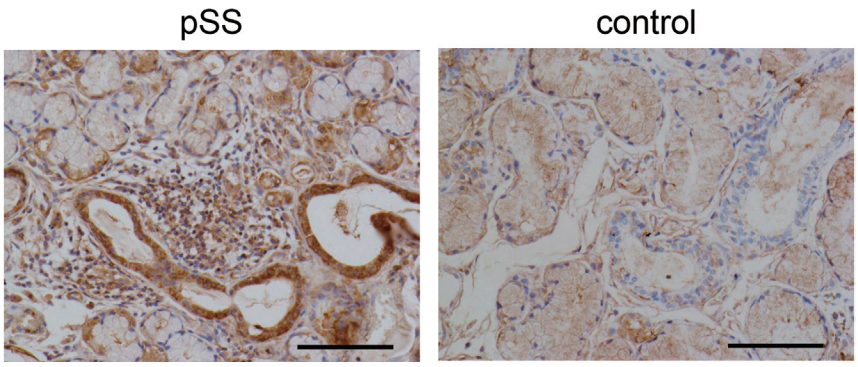

Fig. 3 Expression of CXCL10 in LSG sections from pSS patients and healthy controls. Representative images are shown. Scale bars: 100 μm.

with pSS, CXCL10 was strongly expressed in ductal cells (Figure 3)[11], consistent with previous reports[10]. CXCR3, a CXCL10 receptor, was expressed in $CD3^+$ T cells and $CD163^+$ M2 macrophages[11]. Hence, I analyzed the precise molecular mechanisms by which CXCL10 was overexpressed in pSS salivary glands using an immortalized normal human salivary gland cell line[12]. Although the cause of SS onset is still unknown, it has been reported that immune cell-derived cytokines such as IFN-α, IFN-γ, tumor necrosis factor (TNF)-α, and interleukin (IL)-1β are involved in SS pathogenesis[13-16]. Therefore, these cytokines were added to a normal human salivary gland acinar cell line (NS-SV-AC) and ductal cell line (NS-SV-DC), after which the expression of CXCL10 mRNA and protein was examined. CXCL10 mRNA was markedly upregulated after stimulation with IFN-γ in NS-SV-DC, but not with IFN-α, TNF-α, and IL-1β (Figure 4A)[17]. The CXCR3 ligands CXCL9 and CXCL11, as well as CXCL10, were also upregulated only with IFN-γ stimulation (Figure 4A)[17]. Analysis at the protein level showed that CXCL10 was significantly secreted by NS-SV-DC upon IFN-γ stimulation (Figure 4B)[17]. These results are consistent with a previous report that type I IFN-related molecules are significant in the peripheral blood of patients with pSS, whereas type II IFN-related molecules are significant in the salivary glands[13]. On the contrary, CXCL10 mRNA and protein expression was induced upon TNF-α stimulation in NS-SV-AC, although to a lesser extent than in NS-SV-DC[17]. Analysis of the signal transduction pathway leading to CXCL10 overproduction in NS-SV-DC revealed that IFN-γ activates both the Janus kinase/signal transducers and activator of transcription (JAK/STAT) pathway as well as the NF-κB pathway[17]. However, analyses using STAT1 and NF-κB inhibitors showed that the suppressive effect of STAT1 inhibitors on IFN-γ-induced CXCL10 expression was significantly higher than that of NF-κB inhibitors; the transmission pathway was the JAK/STAT pathway[17].

In summary, in the SS salivary gland, IFN-γ-stimulated salivary ductal cells markedly secrete CXCL10 mainly through the JAK/STAT signaling pathway, which recruits $CXCR3^+$ immune cells to form an inflammatory pathology in SS salivary glands. These results suggest that JAK, an important intracellular signaling molecule involved in CXCL10 production, may be a potential therapeutic target in SS.

V. JAK inhibitors

JAKs are intracellular tyrosine kinases that specifically bind to cytokine receptors (Table 2). Binding of cytokines to the receptor induces the phosphorylation of JAK and the transcription factor STAT; the phosphorylated STAT forms a dimer and translocates to the nucleus to initiate gene transcription[18]. Four types of JAK (JAK1, JAK2, JAK3, and TYK2) and seven types of STAT have been identified, and JAK-STAT activation reportedly depends on the type of cytokine that induces different cellular functions[18, 19].

JAK inhibitors can simultaneously suppress multiple cytokine signals via intracellular kinase inhibition by competitively binding to the ATP-binding site of JAK within the cells, whereas other biological drugs (molecular-targeted drugs) target a single molecule. This is a major advantage of JAK inhibitors. Simultaneous suppression of multiple cytokines is a major advantage of JAK inhibitors. In Japan, JAK inhibitors were first approved in 2013 for the treatment of RA and have demonstrated efficacies comparable to those of biological drugs. Furthermore, as JAK inhibitors are low-molecular-weight compounds, they have the advantages of being orally ingestible and inexpensive, unlike biological preparations. As of 2022, six types of oral JAK inhibitors with different JAK-inhibiting properties have been approved for use in Japan (Table 3).

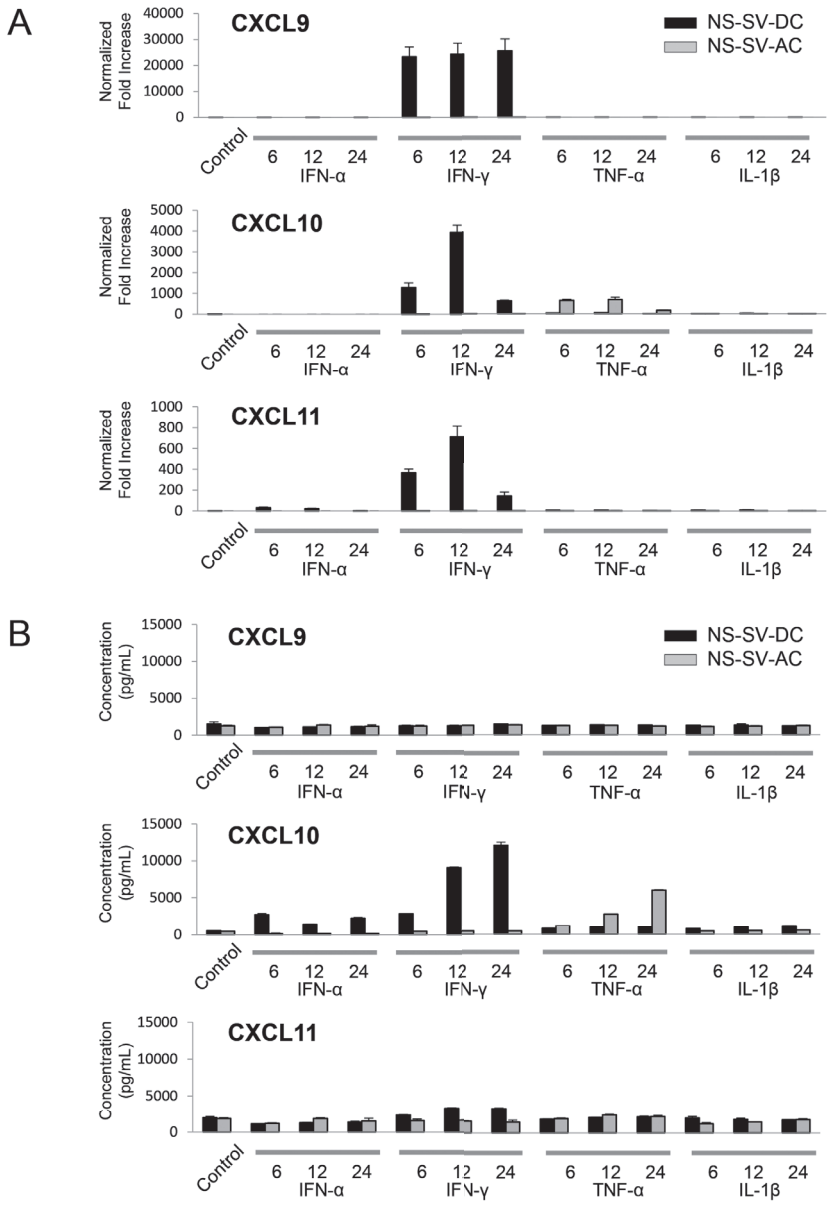

Fig. 4 Expressions of CXCL9, CXCL10, and CXCL11 mRNA and protein following IFN-α, IFN-γ, TNF-α or IL-1β stimulation in NS-SV-DC and NS-SV-AC cells.

A: NS-SV-DC and NS-SC-AC cells were treated with IFN-α (1000 IU/mL), IFN-γ (10 ng/mL), TNF-α (10 ng/mL) or IL-1β (1 ng/mL) for 6, 12, or 24 h. Total RNAs were prepared, and the quantification of mRNA levels was evaluated by RT-qPCR. Unstimulated cells were used as a control. Bar: mean ± SD.

B: NS-SV-DC and NS-SC-AC cells were treated with IFN-α (1000 IU/mL), IFN-γ (10 ng/mL), TNF-α (10 ng/mL) or IL-1β (1 ng/mL) for 6, 12, or 24 h. An ELISA was performed to measure CXCL9, CXCL10, and CXCL11 protein in the conditioned medium. Unstimulated cells were used as a control. Bar: mean ± SD.

Tofacitinib, a selective JAK1/JAK3 inhibitor first approved for RA in Japan, was effective against ulcerative colitis[20] and was subsequently approved in 2018. Currently, a phase II clinical study is ongoing for pSS, ankylosing spondylitis, and systemic juvenile idiopathic arthritis. Baricitinib, a selective JAK1/JAK2 inhibitor, was the second JAK inhibitor approved for RA in 2017 and the first drug suggested to have a therapeutic efficacy superior to that of TNF inhibitors in treating RA[21]. It was also approved and indicated for atopic dermatitis in 2020, and for pneumonia caused by

Table 2 JAKs that bind to cytokines

Cytokines	JAKs
IL-2, IL-4, IL-7, IL-9, IL-15, IL-21	JAK1, JAK3
IFN-α, IFN-β	JAK1, TYK2
IL-6, IL-11, IL-13, IL-10, IL-19, IL-20, IL-22	JAK1, JAK2, TYK2
IFN-γ	JAK1, JAK2
IL-12, IL-23	JAK2, TYK2
IL-3, IL-5, GM-CSF, EPO, TPO, G-CSF	JAK2

EPO: erythropoietin, G-CSF: granulocyte-colony stimulating factor, GM-CSF: granulocyte-macrophage colony-stimulating factor, IFN: interferon, IL: interleukin, TPO: thrombopoietin.

Table 3 JAK inhibitors approved for use in Japan (2022)

	Tofacitinib	Baricitinib	Peficitinib	Upadacitinib	Filgotinib	Abrocitinib
Indication	RA, UC	RA, AD, COVID-19	RA	RA, PsA, AD	AD, UC	AD
JAK/Target	JAK1/JAK2/JAK3	JAK1/JAK2	Pan-JAK	JAK1	JAK1	JAK1

AD: atopic dermatitis, PsA: psoriatic arthritis, RA: rheumatoid arthritis, UC: ulcerative colitis.

SARS-CoV-2 in 2021. Clinical trials targeting systemic lupus erythematosus, idiopathic inflammatory myositis, and alopecia areata are currently ongoing. Although clinical study of tofacitinib is ongoing for pSS, there are currently no studies suggesting the therapeutic effects of JAK inhibitors on pSS from a molecular pathological perspective. Therefore, an in vitro study was conducted to evaluate the potential of JAK inhibitors as therapeutic agents for pSS.

VI. Potential of JAK inhibitors as therapeutic agents for pSS

Among the JAK family members, JAK1, JAK2, and TYK2 are expressed in a wide range of cells, whereas JAK3 expression is restricted to hematopoietic cells such as lymphocytes[17]. The expression of JAK1, JAK2, phosphorylated JAK1, and phosphorylated JAK2 in the LSGs of patients with pSS was analyzed via immunohistochemical staining (Figure 5)[22]. JAK1 was expressed in the ducts but was slightly expressed in the acini. Phosphorylated JAK1 was expressed in the ducts to the same extent as JAK1 but was expressed basolaterally in the acini. In contrast, JAK2 was less expressed in the ducts and acini compared to JAK1. Phosphorylated JAK2 was significantly upregulated in the ducts and strongly expressed in lymphocytes infiltrating the ducts. These results suggest that phosphorylation of JAK1 and JAK2 is upregulated in the LSGs of patients with pSS, and

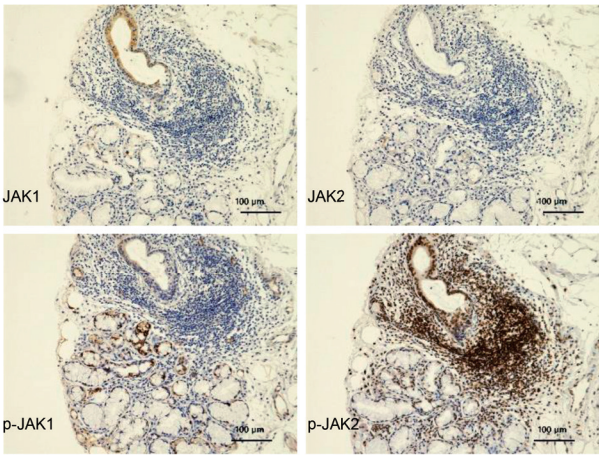

Fig. 5 Expressions of JAK1, JAK2, phosphorylated JAK1 (p-JAK1) and phosphorylated JAK2 (p-JAK2) in LSG sections from pSS patients.
Representative images are shown. Scale bars: 100 μm.

that molecular targeting of JAK1 and JAK2 may be effective in suppressing CXCL10 production from ductal cells and activation of immune cells. Therefore, an in vitro analysis was performed using baricitinib, a JAK1/JAK2 selective inhibitor.

The effect of baricitinib on IFN-γ-induced CXCL10 expression in NS-SV-DC was analyzed using real time-quantitative polymerase chain reaction and enzyme-linked

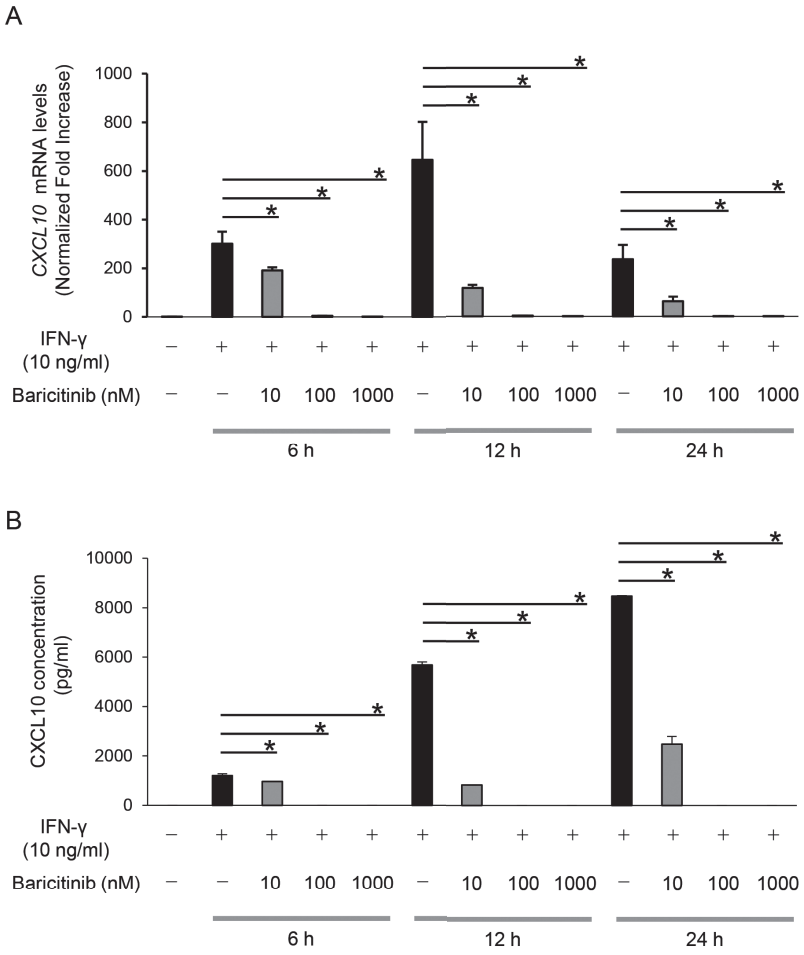

Fig. 6 Effects of baricitinib on CXCL10 expression and protein secretion in IFN-γ-stimulated NS-SV-DC cells.
A: Histogram showing relative changes in CXCL10 mRNA levels in NS-SV-DC cells treated for 6, 12, or 24 h with 10 ng/mL IFN-γ in the presence or absence of baricitinib (10, 100, or 1000 nM). Untreated cells were used as a control. Fold changes in mRNA levels were evaluated by RT-qPCR using GAPDH mRNA as an internal reference. Data represent the mean ± SD of three independent experiments. *$p < 0.05$, two-tailed Mann–Whitney U test.
B: Histogram showing the concentration of CXCL10 measured by ELISA in the supernatants of NS-SV-DC cells treated for 6, 12, or 24 h with 10 ng/mL IFN-γ in the presence or absence of baricitinib (10, 100, or 1000 nM). Untreated cells were used as a control. Data represent the mean ± SD of three independent experiments. *$p < 0.05$, two-tailed Mann–Whitney U test.

immunosorbent assay. IFN-γ-induced CXCL10 mRNA expression and CXCL10 protein secretion were significantly inhibited by the addition of baricitinib to the NS-SV-DC culture medium. The inhibitory effect of baricitinib on CXCL10 expression was concentration-dependent (Figure 6)[22]. The effect of baricitinib on IFN-γ-induced JAK-STAT signaling was analyzed using Western blotting. When IFN-γ was added to the NS-SV-DC culture solution, phosphorylation of STAT1 and STAT3 occurred 5 min later, but the addition of baricitinib suppressed this phosphorylation[22]. These results indicate that baricitinib competitively inhibits JAK1 and JAK2 in ductal cells, and blocks IFN-γ signal transduction, thereby inhibiting the transcription of CXCL10 in the nucleus, protein synthesis, and secretion.

VII. Summary

There has been remarkable progress in the treatment of RA with biological agents targeting cytokines and cell surface antigens, particularly anti-TNF antibodies and anti-IL-6 receptor antibodies. Although large-scale clinical trials using various biological agents have been conducted worldwide for pSS, the glandular lesions have not improved, and no

treatment has been established yet.

This review focused on the effects of baricitinib, a JAK1/JAK2 selective inhibitor, on JAK expression analysis in the LSGs of patients with pSS. Baricitinib was found to suppress IFN-γ-induced CXCL10 secretion in salivary gland duct cells via JAK/STAT signaling regulation, which likely improves the inflammatory conditions in pSS salivary glands. Furthermore, because the expression of phosphorylated JAK2 is upregulated in infiltrating T lymphocytes in the LSGs of patients with pSS, baricitinib may also suppress the activation of immune cells. Although baricitinib was selected for this study, individualized medicine for pSS could be established by examining JAK expression in the LSGs of patients with pSS and subsequently selecting a JAK inhibitor that corresponds to the specific JAK whose phosphorylation is increased. This may improve the beneficiary effects on glandular symptoms.

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Disclosure

The author declares no conflict of interest regarding this article.

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