Review

Infections in Sjögren's disease: a clinical concern or not?

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ABSTRACT

Patients with autoimmune diseases are particularly prone to infections due to both the underlying immune dysfunction and the use of immunosuppressive therapies. Sjögren's disease (SjD) serves as a valuable model for studying the complex interplay between autoimmunity and infections. This review focuses on the infection risks associated with SjD, emphasising key areas such as oral, respiratory, and urogenital infections, along with complications arising from systemic infections. The role of infections in SjD-associated lymphoma treatment complications is also addressed. Additionally, the recent COVID-19 pandemic has highlighted the vulnerability of autoimmune patients to severe viral infections, complicating disease management. While biologic therapies, including predominantly rituximab and belimumab have become increasingly utilised, they carry inherent risks of infections due to their immunosuppressive effects. Emerging therapies, such as ianalumab, iscalimab, dazodalibep, and remibrutinib, show efficacy in reducing disease activity but also present infection risks, with reports of upper respiratory infections and serious cases, including pneumonia and COVID-19. By exploring these infection-related challenges, this review underscores the importance of understanding the infection-autoimmunity relationship to improve outcomes for patients with SjD and similar autoimmune conditions.

Autoimmune diseases and infections

The immune system is a complex network of biological processes designed to protect us against infectious pathogens and tumour cells. While it is meticulously equipped to tackle different potential invaders (viruses, bacteria, fungi, helminths), its overactivation or dysregulation can result in the misidentification of the body's own components as foreign threats, leading to the genesis of autoimmunity. For autoimmunity to develop, a combination of genetic, immunologic, hormonal, and environmental factors is necessary, often referred to as the "mosaic of autoimmunity" (1). A significant and well-recognised component of this mosaic is infections, which paradoxically serve a dual role: they can be the endpoint of the immune response while simultaneously acting as triggers for autoimmune processes. The mechanisms by which infections induce a breakdown in immune tolerance are well documented and include molecular mimicry, epitope spreading, and bystander activation (1-5).

However, the modern understanding of autoimmune diseases has introduced another paradox: patients with autoimmunity are particularly susceptible to infections. This was first highlighted in the mid-20th century when a large observational cohort study of rheumatoid arthritis patients revealed that 25% of them died from infections, raising significant concern among physicians (6). More recent data have shown that patients with autoimmune diseases are at least twice as likely to acquire or experience reactivation of infections compared to the general population (7).

A key factor contributing to this susceptibility is the immunomodulatory therapies commonly used to treat autoimmune diseases. These treatments often result in immunosuppression, which understandably leads to a higher incidence of both common and opportunistic infections. Apart from the treatments, the hyperactive immune system that characterises autoimmunity creates a conducive environment for infections. This misallocation of immune responses often results in the immune system focusing on self-tissues instead of effectively combating pathogens. In

addition, chronic inflammation seen in autoimmune diseases can lead to immune exhaustion particularly of the T cell component (8). Another aspect of immune dysregulation is evidenced by lymphopenia, which is commonly observed in conditions such as systemic lupus erythematosus (SLE) and Sjögren's disease (SjD) (9). An additional mechanism implemented is the production of neutralising autoantibodies against key defensive components, such as the cytokines. This can impair the immune system's ability to clear pathogens and diminish its protective effects against infections (8). Complement deficiency, another common immunological abnormality observed in SLE and SjD, might also contribute to the increased susceptibility to infections (10).

SjD could serve as an excellent prototype disease for studying the relationship between autoimmunity and infections. SjD is characterised by immune alterations in topical and systemic level, beginning from the exocrine glands that are primarily affected and extending systemically with a broad spectrum of clinical manifestations (11, 12). It is characterised by a persistent inflammatory state disrupting both the innate and adaptive arms of the immune response and is characterised by epithelial cell activation, B cell hyperactivation and T cell anergy (13, 14). In addition, the fact that the use of immunosuppressive therapies is relatively sparse, contrary to other autoimmune diseases, could allow researchers to better isolate the effects of the disease *per se* on infection susceptibility. Previous cohort studies in SjD have not identified infections as a significant clinical concern (15-17). In recent years however, two major advances have been achieved: 1) Patients with the most severe disease outcomes, such as non-Hodgkin's lymphoma (NHL) may survive for many years (18), but often face a wide range of complications, and 2) with the advent of targeted therapies for the disease, the incidence of infections has increased contributing to increased morbidity. These two reasons underscore the importance of exploring the true impact of infections on morbidity and mortality in SjD. In addition, several recent studies investigating the clinical phenotype of the disease revealed differences based on age, gender and minor salivary gland biopsy (MSGBx) Focus Score (19-22), making the search for potential infections in these subgroups more imperative. In the current review, the complex relationship between SjD and infections will be explored. For the sake of clarity in the following sections, we will divide the discussion into distinct categories including, epithelial infections, pulmonary infections, common viral infections such as SARS-COV2 and systemic infections related to underlying lymphoma or targeted treatments.

Oral and oropharyngeal infections

Most orofacial manifestations of SjD are primarily a result of salivary gland hypofunction. Saliva plays an important role, among others, in providing lubrication, buffering, remineralising enamel and aiding in host defences against infections. Several saliva proteins such as lysozyme, defensins, histatins, facilitate the last procedure. Hyposalivation that characterises SjD, results in a modified oral microflora and leads to increased bacteria colonisation of periodontal pathogens (23, 24). Infections of the area include mainly periodontal disease and oral candidiasis.

Dental caries and periodontal disease

Xerostomia (Fig. 1) results in a decrease in secretory IgA, an antibody responsible for mucosal immunity, thereby weakening the defence system against dental caries. Individuals with SjD have a much lower pH which in combination with the decreased salivary flow rate, is associated with increased levels of dental decay (23). Specifically, low saliva flow has been associated with high bacterial levels of *Lactobacillus acidophilus* and S mutans, which has been postulated to explain the increased caries rate in patients with SjD (25, 26). Reduction of saliva in association with saliva qualitative changes, lead to an impairment of defensive salivary capacity. The inability to prevent the formation of dental plaque may account for possible increases in calculus formation and periodontal disease. Conflicting evidence exists regarding whether patients with SjD are at increased risk for periodontal disease. Several studies have reported a link between SjD and periodontal disease (27). Chuang *et al*. (28), found that the prevalence (74.6% *vs*. 63.0%, p=0.001) and frequency (median 5.37 *vs*. 1.45 per year, p<0.001) of dental visits were found higher in patients with SjD and the risk of gingivitis and periodontitis was also significantly higher. This finding is coherent with an earlier study which suggested that SjD may affect bacterial colonisation in plaque and contribute to increased periodontal disease (29). However, early studies in the literature found no significant differences in the periodontal status of patients with SjD compared to those with other autoimmune diseases or to individuals who were otherwise healthy (30-33).

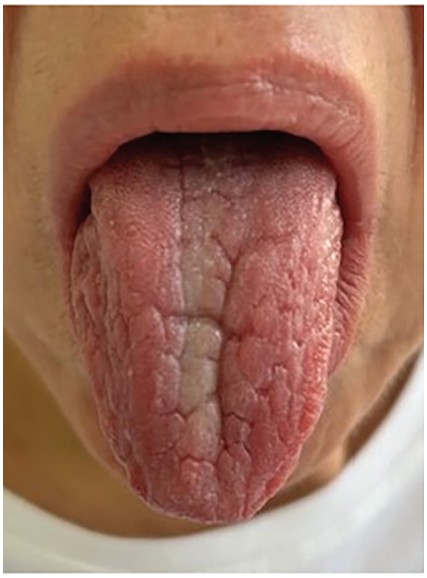

Fig. 1. A representative picture of a patient with Sjögren's disease with severe oral dryness.

Candidiasis

Oral candidiasis is the most frequent fungal infection affecting the human oral cavity. Intraorally, *Candida* infection may present as erythematous mucosal lesions (chronic erythematous candidiasis), denture stomatitis, tongue fissuring and angular cheilitis (34). Contributory role to oral candidiasis plays several local and systemic co-factors, such as a reduced salivary

flow rate, oral mucosal erosion, vitamin deficiency, and generalised immune suppression. Patients with SjD have an increased occurrence of fungal infections, with C. *albicans* infections more frequent than the general population (23). An observational cross-sectional study conducted in 61 SjD patients described an inverse relationship between salivary flow rates (unstimulated whole saliva (UWS) and stimulated whole saliva (SWS) and clinical oral *Candida* infection (35). Tapper-Jones and colleagues forty years earlier had indicated the same association (36). This is secondary to decreased buffering capacity and salivary output, and the immunocompromised status of patients with SjD. Furthermore, another retrospective study investigating the characterisation of oral candidiasis and the profile of *Candida* species among patients with oral mucosal diseases found that the second most common comorbidity in patients with oral candidiasis was SjD(37). The prevalence of oral *Candida* carriage in SjD individuals is found to be higher than in healthy individuals, ranging from 54.2% to 87%, (38-41, 27), presuming an inverse relationship between the mean salivary flow and the load of candida caries. Yan et al (38) found that although *Candida albicans* was the most frequently isolated species, other, less common species were also detected, either alone or in combination. Notably, the study revealed a high level of resistance to azoles, with significant cross-resistance observed between fluconazole and itraconazole.

Vaginal and urinary tract infections

SjD predominantly affects women and vaginal involvement is often a major clinical problem impacting sexual function and eventually the lives of the patients (42, 43). The predominant clinical finding is called dyspareunia that is pain during sexual intercourse caused by vaginal dryness. However, dyspareunia is also a common finding in patients with vaginal infections. Therefore, dyspareunia is at the crossroads of autoimmunity related manifestations due to SjD and infections. Because of this overlap, patients with deteriorating or recent appearance of dyspareunia should be advised to visit a gynaecologist for the exclusion of a local infection. Some studies indicate that the pH and composition of the vaginal microbiota are similar between reproductive-age SjD patients and healthy controls and the most prevalent genera in this flora (*Lactobacillus, Gardnerella,* and *Streptococcus*) are equally found in both cases (43). In contrast, the changes in vaginal microbiota that occur postmenopausaly can be explained by hypoestrogenism and worsened by sicca due to SjD. *Lactobacilli* use the breakdown products of glycogen to produce lactic acid, which contributes to low vaginal pH and thereby inhibits the growth of other bacteria. This phenomenon occurs through the influence of estrogen (premenopausal) and makes the health of this epithelium less dependent on dryness (44, 45). Although one study suggested that SjD-associated vaginal dryness in premenopausal women does not negatively influence homeostasis of the vaginal ecosystem (46), the urinary tract system which is adjacent to the genital, seems to be affected by infections. Tishler *et al*. (47) highlighted in their study that recurrent UTIs are more frequent in patients with SjD. Of seven patients with vaginal sicca symptoms, six had recurrent urinary tract infection. The increased risk of infection was connected to defects in the urinary protective mechanisms, mucosal atrophy, and decreased urinary immunoglobulin A secretion. According to Çetin *et al*., the most common pathogen responsible for UTIs in SjD, was *Escherichia Coli* similarly to the general population (48). In the same study where patients with SjD, rheumatoid arthritis and healthy individuals were compared, a higher incidence of recurrent UTIs in SjD group was highlighted. This may have led to a more frequent use of antibiotics and finally to the presence of ESBL strains, as the authors propose.

Respiratory infections

Respiratory tract is affected in SjD in various ways. Tracheobronchial disease is common in SjD, characterised by diffuse lymphocytic infiltration of the airway. It is sometimes responsible for a crippling chronic cough. It can also present in the form of bronchial hyperresponsiveness, bronchiectasis, bronchiolitis or recurrent respiratory infections (49). Apart from that, interstitial lung disease (ILD) accounts for a major extra-glandular manifestation of SjD (50). A large national U.S. study examined the epidemiology, time-trends and outcomes of serious infections in hospitalised patients with SjD. Of the serious infections, the most common during the study period 1998-2016 were pneumonia and sepsis: opportunistic infections 3%, skin and soft tissue infections (SSTI) 19%, UTIs 6.4%, pneumonia 37%, and sepsis 34% (51). In accordance, another nationwide incidence study from France (52) reported the increased hospitalisation risk for community infections. More specifically, SjD patients had a significantly higher incidence rate of hospitalisation for bronchopulmonary infections compared to matched controls. A limitation of the study is that it is not reported whether the study population were receiving immunosuppressive treatment prior to the hospitalisation, so we cannot safely substantiate SjD as an independent risk factor for serious respiratory infections. However, both studies highlight the burden of respiratory infections on the hospitalisations of SjD patients, constituting an important cause of morbidity. Interstitial lung disease in the setting of SjD is a separate clinical entity, predisposing independently to respiratory infections. Recurrent pulmonary infections, particularly pneumonia, have been documented in 10–35% of SjD-ILD patients due to factors such as abnormal mucociliary clearance, sputum abnormalities, compromised local immunity, gastro-oesophageal reflux, bronchiectasis, periodontopathy, and the use of immunosuppressive drugs. Bacteria constituted the most prevalent pathogens at 64.15%, followed by co-infections at 20.75% and fungal infections at 7.55% according to a retrospective study from Zhou *et al*. (53). The investigators report that patients with infections compared to those without had significantly higher average EULAR SS disease activity index scores

Table I. Prevalence and outcome of SARS-COV2 infection in Sjögren's disease.

Study	Cohort size (n)	Mean age	Prevalence of COVID-19	Comorbidities	Hospitalisation	mortality	Baseline Tx	Ref
Brito-Zeron *et al*.	51	60	0.62%	CVD 15,7% Obesity 13.7% CLD 33.3% Other diseases 7.8%	49%	7.8%	HCQ 37.3%, GCs 17.6%, other 21.5%	(64)
Giardina *et al*.	150	62	4% with reported symptoms	70% overall with DM, HTN, CVD, DLD, lung disease	0%	0%	HCQ 18%, GCs 8% other 8.6%	(94)
Carubbi *et al*.	102	n/a	1.9%	N/A	0.9%	N/A	HCQ 38%, GCs N/A, other N/A	(63)
Torgashina *et al*.	387	56 (RTX group), 50 (non-RTX group)	36.7%	26% overall with DM, HTN, CVD	30.9% overall (36% in the RTX group, 23% in the control group)	N/A	RTX 60.5%	(95)
Alunno *et al*.	9462 (129)	52	14% (SjD) *vs*. 19% (HC)	N/A	17% (in pre-vaccine era) 0.7% (after-vaccine)	N/A	N/A	(65)

SjD: Sjögren's disease; HC: healthy controls; CVD: cardiovascular disease; CLD: chronic liver disease; HTN: hypertension; DM: diabetes mellitus; DLD: dyslipidaemia; RTX: rituximab; HCQ: hydroxychloroquine; GCs: glucocorticoids.

(20 *vs*. 13 points), significantly lower levels of DLCO (60.1 *vs*. 74.2 units), and were significantly more likely to have PAH, at 62.3% *versus* 32.1%.

COVID-19 infection in Sjögren's disease

COVID-19 pandemic has had an overwhelming impact on the management of patients with chronic diseases. Autoimmune diseases (ADs), including SjD, characterised by immune dysregulation affecting several organs in variable severity, have been of particular interest given the accelerated phase of the immune response in the course of SARS-CoV-2 infection leading to the acute inflammatory response and respiratory distress syndrome or multi-organ failure. Since the start of COVID-19 pandemic several studies have assessed the risk of infection, the morbidity and mortality in patients with ADs. Autoimmune diseases predispose to a higher prevalence of COVID-19 infection (54, 55). Prolonged glucocorticoid exposure in patients with autoimmune diseases is associated with a more severe course of SARS-COV2 infection by means of need for hospitalisation (54, 56-59). Anti-TNF use was associated with a decreased odds of hospitalisation in patients with autoimmune diseases (57) while on the other hand rituximab, a frequently used therapy in SjD, is a predisposition factor for severe COVID-19 infection (59),(60). Regarding the outcome in patients with autoimmune diseases and COVID-19, several studies suggest that autoimmunity is not an independent risk factor for mortality but the higher COVID-19 mortality rate seen in ADs patients is related to the higher burden of comorbidities, secondary to direct organ damage and sequelae of their condition (54, 61, 62). Conversely, researchers found that patients with autoimmune diseases (ADs) faced a threefold higher risk of intensive care admission and mechanical ventilation compared to those without ADs, indicating significant challenges in managing this subgroup (62).

Data addressing specifically the severity of COVID-19 infection in SjD is scarce with the majority of studies being conducted in the entire group of ADs. Data from studies focused on patients with SjD and SARS-COV2 infection are presented in Table I. One of the first studies, included 102 SjD patients that were evaluated for the disease status, ongoing treatment and symptoms/diagnosis of COVID-19. Thirteen (13%) patients experienced symptoms that could be related to COVID-19 (*e.g*. sore throat, non-productive cough). All of them were tested for SARS-CoV-2 infection by nasopharyngeal swab but only 2 had proven SARS-CoV-2 infection. In our opinion this study is of limited value. As it was conducted during the first lockdown, patients were evaluated via telephone consultation and the clinical aspects of their disease and COVID-19 symptoms were subjectively recorded. Moreover testing for SARS-COV-2 infection was performed only to the patients reporting symptoms clearly related to COVID-19 (63). The largest study on SjD and SARS-CoV-2 infection comes from an international registry identifying patients with SjD and confirmed or highly likely SARS-CoV-2 infection, both hospitalised and primary care patients were included. The estimated infection rate (0.62%) was similar to that in the general population and baseline characteristics associated with more severe disease were also similar to those identified in the wider spectrum of ADs *i.e*. older age, male gender, chronic comorbidities, there was no association between underlying therapies for SjD and hospitalisation (64). Similarly with the aforementioned study the infection rate was evaluated through questionnaires rather than nasopharyngeal swabs. However, the only study that compares the spectrum and severity of breakthrough COVID-19 infections between patients

with SjD, other autoimmune diseases and healthy controls is by Alunno *et al*. As expected their data demonstrate that breakthrough infections in patients with SjD are less severe compared to those observed before vaccination (65). Interestingly in a large cohort retrospective study that evaluated outcomes from SARS-CoV-2 infection among patients with different ILD subtypes it was found that all ILDs increase mortality from SARS-CoV-2, with the exception of SjD, which had a lower mortality than control subjects (66).

Tuberculosis

One notable infection linked to SjD is tuberculosis. A nationwide population-based study in Taiwan by Chang *et al*. (67) found that the risk of *Mycobacterium tuberculosis* (TB) infection was higher in the SjD cohort compared to a control group. The increased incidence of TB in SjD patients was associated with age (≥60 years) and corticosteroid use, with a dose-dependent effect (prednisolone dose ≥5 mg/day). Additionally, the study revealed a higher risk of mortality in SjDpatients with tuberculosis compared to those without the infection. Regarding non-tuberculous mycobacterial infections, Chao *et al*. (68), using the same database, observed that the risk of these infections only increased in SjD patients receiving immunosuppressive treatment throughout the follow-up period. These studies suggest that in this endemic region of the Far East, the heightened risk of both types of mycobacterial infections in SjD patients is more closely related to the treatments they receive than to the disease itself.

Sjögren's disease associated lymphoma

Lymphoproliferation is an intrinsic factor in SjD, with studies indicating that 5–10% of patients may develop a lymphoproliferative disorder over the course of their disease due to the constant aberrant antigenic stimulation (69). The majority of these lymphomas are of the mucosa-associated lymphoid tissue (MALT) type, which is generally considered indolent and associated with a favourable overall prognosis. However, patients with MALT lymphoma related to SjD face a complex disease trajectory marked by various challenges and complications(18). In our cohort of over 90 patients with SjD-associated MALT lymphomas, we observed that six patients died due to treatment-related reasons, with four of these cases linked to significant infections (unpublished data). This highlights the pressing need for further research into the impact of infections both in patients that are undergoing treatment and in patients that are being closely monitored.

Therapies in SjD and infection

The current therapeutic approach of SjD is mainly symptomatic aiming to alleviate symptoms and prevent complications, whereas disease-modifying therapy is reserved for patients with systemic involvement. Immunosuppressive biologic therapies and steroid usage are common treatments used in SjD and have been unequivocally identified as risk factors for infections. Data regarding infectious adverse events of biologic treatments tested in randomised control trials (RCTs) are presented in Table II.

Rituximab

One of the most commonly used biologic therapies is rituximab (RTX), a chimeric anti-CD20 antibody that leads to B-cell depletion by diverse mechanisms. RTX is widely used in the treatment of SjD-related lymphoma, often in combination with cyclophosphamide and prednisone. B-cell depleting therapy is also regularly used off-label for SjD patients with severe extraglandular manifestations (70). Most data concerning the safety of B cell–targeted therapies are derived from randomised trials and open-label studies of rituximab.

The first pilot RCT by Dass *et al*. (71) that randomised 17 patients in order to evaluate the efficacy and safety of rituximab, reported three serious adverse events (SAEs) in the rituximab arm (8 pts). One of them was admission to the hospital due to gastroenteritis. In another randomised double-blind, placebo-control trial by Meier *et al*. (72) that enrolled 30 patients reported similar infection rates between rituximab and placebo group. None of them required hospitalisation. Similarly in TEARS trial by Devauchelle-Pensec *et al*. (120 patients enrolled) (73) rates of infection and severe infection were similar between groups (bronchitis and urinary and cutaneous infections were the more frequent manifestations in both groups). In both trials no opportunistic infections occurred. TRACTISS, the largest, randomised, placebo-controlled, trial of rituximab in 133 patients with SjD (74) reported two serious infection events in the rituximab group (one sepsis and one urinary tract infection) while one serious chest infection occurred in the control group. In general, data derived from RCTs, concerning the safety of B-cell depleting therapy suggest that rituximab is a safe therapy option in SjD. The most commonly reported side effects in the studies include infusion-related reactions, both immediate and delayed, while infections were reported less frequently.

In a Cochrane review (75) of the safety profile of biologics for the treatment of several diseases, rituximab showed the lowest odds for serious infections compared to control treatment (OR 0.26, 95% CI 0.03 to 2.16). These results were confirmed by a prospective registry of patients with systemic autoimmune diseases treated with rituximab (AIR registry) (76) , comprising 78 SjD patient with a median follow up of 34.9 months. According to the AIR registry, the rate of serious infections during rituximab treatment was lower in SjD than in SLE (1.3/100 patient years *vs*. 6.6/100 patient years, respectively).

In a case-control study, Carubbi *et al*. (77) compared the therapeutic effect of rituximab (n=22) to conventional immunosuppressive therapy (n=19) in SjD. In both treatment groups, no adverse events were reported. More importantly, no adverse events, judged by the investigator to be possibly, probably, or definitely related to RTX therapy, were observed in the 120-week follow-up period. In line with these results was a small open-lapel trial by Clair *et al*. (78), where 12 patients treated with rituximab had no infectious adverse events. A more recent cohort study enrolling 35 SjD patients treated with RTX between 2008 and 2019 aimed to

Table II. Summary of Sjögren's disease biologic treatments and their documented infections in RCTs.

Treatment	Type of study	Number of subjects	Duration	Documented infections	Ref
RTX	RCT (Dass *et al.)*	17	6 months	1 event of gastroenteritis	(72)
RTX	RCT (Clair *et al.)*	12	52 weeks	none	(78)
RTX	RCT (Devauchelle-Pensec *et al.)*	120	24 weeks	Similar rates of infection between placebo and RTX group (bronchitis, urinary and cutaneous infections)	(74)
RTX	RCT (TRACTISS) Bowman *et al.*	133	48weeks	2 serious infection events in the rituximab group (one sepsis and one urinary tract infection)	(75)
Belimumab	RCT (BELISS)	30	1 year	1 pneumococcal meningitis	(80)
Belimumab followed by RTX	RCT (Mariette *et al.)*	86	68 weeks	2 (8.3%) patients in the belimumab + rituximab group (enterocolitis infectious and pyelonephritis), 1 (4.2%) patient in the belimumab group (pneumonia), and 1 (4.0%) patient in the rituximab group	(81)
Tocilizumab	RCT (Felten *et al.)*	110	24weeks	none	(83)
Abatacept	RCT (Meiner's *et al.)*	15	48 weeks	18 self-reported infections were seen in 10 patients (67%) most common upper respiratory tract infections	(84)
Abatacept	RCT (ASAP III)	80	24weeks	29 (73%) patients in the abatacept group and in 28 (70%) in the placebo group	(85)
Abatacept	RCT (Baer *et al.)*	165	169 days	1 SAE bacterial pneumonia	(86)
Abatacept	RCT (ROSE I&II)	68	52weeks	22.1% of enrolled patients experienced AEs of which 40.9% were infections (2 urinary tract infections, 1 infectious cornea ulcer, 1 bronchitis, 1 herpes zoster, 1 sinusitis, 1 upper respiratory tract infection, 1 pharyngitis, and 1 suspected cellulitis of the left lower leg)	(87)
Ianalumab	RCT (Dorner *et al.*)	27	24 weeks	no increase in infections other than nasopharyngitis in the ianalumab group *vs.* placebo group (6 cases with nasopharyngitis, 1 GI infection, 2 cases with influenza, 1 case with sinusitis, 1 case with tooth infection)	(88)
Ianalumab	RCT (Bowman *et al.)*	190	24 weeks	Infections in 70 [50%] of 141 patients in the ianalumab groups. Nasopharyngitis: slightly more frequent in the ianalumab 300 mg group than in the placebo group, sinusitis, upper respiratory tract infections and urinary tract infections: all slightly less frequent in the ianalumab 300 mg group than in the placebo group	(89)
Iscalimab	RCT (Fisher *et al.*)	44 (n=12 cohort 1, n=32 cohort 2)	32 weeks	most frequent AE: upper respiratory tract infection (cohort 1, two [25%] for iscalimab *vs.* two [50%] for placebo; cohort 2, two [10%] for iscalimab *vs.* two [18%])	(90)
Iscalimab	RCT (TWINSS)	273 (N=173 cohort 1, n=100 cohort 2)	24 weeks	Nasopharyngitis was more frequent in all iscalimab groups. SAEs related to infections: 4 in iscalimab groups (retroperitoneal abscess, postoperative wound infection, appendicitis, pneumonia, *vs.* 1 in placebo	(91)
Dazodalibep	RCT (Clair *et al.)*	183	169 days	Most frequently reported infectious AEs occurring in ≥5% of DAZ-treated participants were COVID-19 infection, upper respiratory tract infections, nasopharyngitis and urinary tract infections	(91)
Remibrutinib	RCT (Dörner *et al.*)	73	24 weeks	Infections were more frequent in the remibrutinib bid-arm (54.2%) *vs.* remibrutinib qd-arm (28.0%) and placebo (41.7%) arm. Most reported infections: upper respiratory tract (nasopharyngitis (6.1% remibrutinib *vs.* 12.5% placebo) and upper respiratory tract infection (6.1% remibrutinib *vs.* 8.3% placebo)	(92)
Etanercept	RCT (Moutsopoulos *et al.*)	28	12 weeks	No reference in infections	(96)
Etanercept	RCT (Sankar *et al.*)	28	12 weeks	No reference in infections	(97)
Epratuzumab	RCT (EMBODY-Gottenberg *et al.*)	113 sSS-SLE	52 weeks	No reference in infections	(98)
Telitacicept	RCT (Xu *et al.*)	42	24 weeks	No increased risk of infections: placebo group: 57.1%, telitacicept 160mg group: 64.3%, telitacicept 240mg group: 35.7%. 1 SAE acute pyelonephritis	(99)
Infliximab	RCT (TRIPSS Mariette *et al.*)	103	22 weeks	1 pneumococcal septicaemia (SAE) in infliximab group	(100)
Filgotinib, lanraplenib and tirabrutinib	RCT (Price *et al.*)	150	52 weeks	Infection-AEs occurred in 17 patients in the filgotinib group (44.7%), 12 in the lanraplenib group (32.4%), 17 in the tirabrutinib group (43.6%) and 18 receiving placebo (50.0%). Only 1 serious infection (filgotinib group)	(101)

RCT: randomised control trial; RTX: rituximab.

evaluate the safety of long-term RTX treatment. Among the 13 patients who discontinued the RTX treatment, seven were due to hypogammaglobulinaemia. The time from starting RTX and withdrawal was 35.86±28.79 months, with an average of 7 treatment courses. 2 out of 7 patients had concomitant severe infection. One patient developed pyelonephritis, and one patient developed an ocular infection caused by cytomegalovirus (79). In general, published data from RCTs and open label studies suggest that long term administration of rituximab is a safe therapeutic option in patients with SjD.

Belimumab

B-cell activating factor (BAFF) blockade by belimumab, inhibits survival of autoreactive B-cells and could therefore be beneficial in diseases characterised by B-cell hyperactivity such as SjD. However published evidence to determine the efficacy and safety of belimumab in SjD is limited. The single open label phase 2 study BELISS (80) enrolled 30 patients with SjD who were treated with belimumab 10mg/kg (weeks 0, 2 and 4, and then every 4 weeks until week 24). With respect to the safety profile, only one serious adverse event was reported (pneumococcal meningitis) after six drug infusions. Interesting results were highlighted in the randomised phase II study of sequential belimumab and rituximab in SjD by Mariette *et al*. (81). 86 patients with active SjD were divided into 4 different treatment arms (placebo, s.c. belimumab, i.v. rituximab, or sequential belimumab + rituximab), and beyond efficacy, the safety profile was assessed. One of the most common adverse events were infections, primarily nasopharyngitis. However, the incidence rates of infections were similar between the groups. Infectious SAEs were reported in 2 (8.3%) patients in the belimumab + rituximab group (enterocolitis infectious and pyelonephritis), 1 (4.2%) patient in the belimumab group (pneumonia), and 1 (4.0%) patient in the rituximab group. The overall safety of belimumab, rituximab, and belimumab + rituximab sequential treatment in this study was consistent with the known individual safety profiles for belimumab and rituximab. Although the already published data about safety are scarce (82), we can assume that belimumab is in general a safe therapeutic option. However, in order its safety to be established, further prospective studies should be conducted.

Tocilizumab

Elevated levels of IL-6 in the serum, saliva, and tears of patients with SjD highlight the cytokine's critical role in the disease's pathophysiology. IL-6 plays a significant part in B cell activation, T cell differentiation, and is linked to fatigue. Tocilizumab, a monoclonal antibody, blocks the IL-6 receptor, thereby inhibiting IL-6 signalling. This makes tocilizumab a promising therapeutic option for SjD, as it can effectively disrupt IL-6-driven inflammatory responses. A large randomised double-blind placebo-controlled trial that included 110 patients with SjD (83) failed to show superiority of tocilizumab over the placebo drug in improving systemic involvement and symptoms over 24 weeks of treatment. However, no related infections were described in the trial.

Abatacept

T cell-targeted therapies, exemplified by abatacept, have gained prominence for their significance in the complex landscape of SS pathogenesis. Abatacept, a soluble fusion protein comprising the extracellular domain of human cytotoxic T lymphocyte-associated antigen 4 and the modified Fc portion of human IgG1, has been approved for rheumatoid arthritis. Research has shown that human cytotoxic T-lymphocyte-associated antigen 4 contributes to T cell CD4 proliferation control and down-regulates T cell activation in SS. This entanglement of CTLA-4 has led to the conduction of open label studies regarding the efficacy and safety of abatacept in SjD. In the abatacept pilot study by Meiner *et al*. (84), 15 DMARD-naive patients were included and treated with eight intravenous abatacept infusions on days 1, 15 and 29 and every 4 weeks thereafter. During treatment, 18 self-reported infections were seen in 10 patients (67%), the most common being upper respiratory tract infections. No infection required hospitalisation. The ASAP III study (85), a single centre placebo-control trial, enrolled 40 patients in each arm of the study (80 in total). In this trial the biological effect of abatacept did not translate into improvement of systemic disease activity. Regarding the adverse events of infections, no significant differences between the two arms of the study were found. Infections occurred in 29 (73%) patients in the abatacept group and in 28 (70%) in the placebo group. Similar results were shown in the RCT conducted by Baer *et al*. (86) where the primary analysis failed to show a statistically significant difference in the primary endpoint and no new safety signals were identified compared with the known abatacept safety profile. Only one serious infection adverse event related to the study-drug was recorded that was a bacterial pneumonia. On the other hand, the effectiveness and safety of abatacept for patients with Sjögren's associated with RA was confirmed in the ROSE and ROSE II trials (n=68) (87). 22.1% of enrolled patients experienced AEs of which 40.9% were infections (2 urinary tract infections, 1 infectious cornea ulcer, 1 bronchitis, 1 herpes zoster, 1 sinusitis, 1 upper respiratory tract infection, 1 pharyngitis, and 1 suspected cellulitis of the left lower leg). Although many infectious events were common and not specific for patients with Sjögren's associated with RA, one case developed infectious cornea ulcer, which could be related with dry eye and keratoconjuctivitis sicca.

Emerging therapies

Ianalumab

Ianalumab (VAY736) is a human IgG1/κ monoclonal antibody designed to target human BAFF-Receptor, thereby blocking BAFF-R-mediated signalling in B cells which seems to play a pivotal role in modulating B cell activity in SjD. A single centre RCT assessed the therapeutic efficacy, tolerability and safety of a single ianalumab intravenous infusion in patients with SjD (88). A total of 27 patients were enrolled and randomised in three differ-

ent treatment arms: 3 mg/kg ianalumab (n=6), 10 mg/kg ianalumab (n=12), placebo (n=9). The safety analysis of the study showed no increase in infections other than nasopharyngitis in the ianalumab group versus placebo group, nor in the incidence of other AEs over the 24-week, blinded study period. Another larger phase 2b clinical trial (89), evaluating the impact of different subcutaneous doses of ianalumab in subjects (n=190) with moderate to severe SjD met its primary objective, showing a dose-related decrease in disease activity as measured by ESSDAI at week 24. Overall, ianalumab was well tolerated and safe. Among the common infections, only nasopharyngitis occurred slightly more frequently in the ianalumab 300 mg group compared to the placebo group, while sinusitis, upper respiratory tract infections, and urinary tract infections were somewhat less common in the ianalumab 300 mg group. Overall, infections occurred in 70 (50%) of the 141 patients receiving ianalumab, and most of them were mild or moderate, with only one severe adverse event reported. There were four serious infection-related adverse events: pneumonia and gastroenteritis in the placebo group, and appendicitis along with a tubo-ovarian abscess in one patient from the ianalumab 50 mg group, which were considered related to the treatment.

Iscalimab

Iscalimab, an anti-CD40 monoclonal antibody that has been reported to significantly improve the ESSDAI when compared with placebo in a proof-of-concept RCT targeting SjD (90). Upper respiratory tract infections consisted of the most frequent adverse event in both iscalimab and placebo arm of the study. No major safety signals during the iscalimab treatment open-label period were observed. The efficacy of iscalimab was confirmed in the much larger TWINSS study (91) where a significant dose–response relationship with iscalimab in terms of disease activity at week 24 was demonstrated. Among the infections nasopharyngitis was more frequent in all iscalimab groups. Overall, up to week 24 the observed adverse events neither yielded a safety signal nor a dose-response relationship yet infections were numerically higher in the active treatment groups compared with the placebo group.

Dazodalibep

Dazodalibep (DAZ) is a CD40 ligand antagonist that disrupts costimulatory signalling between T cells, B cells, and antigen-presenting cells, potentially suppressing the broad range of cellular and humoral immune responses that fuel autoimmunity in SjD. In a large phase-2 RCT with two clinically distinct populations of SjD patients (total n=183), dazodalibep was found to be both efficacious and safe for administration (92). However, some infections were reported in DAZ-treated participants during the follow up period, which occurred more frequently than in participants receiving placebo. The most frequent were COVID-19 infection, upper respiratory tract infections, nasopharyngitis and urinary tract infections. More specifically two serious adverse events (SAEs) regarding infections were reported: the first was a COVID-19 infection with subsequent death of unknown cause 46 days following the last administration of DAZ (12 days after COVID-19 diagnosis) and the second was pneumonia influenza both in DAZ-groups. All SAEs were deemed by investigators to be unrelated to study medication.

Remibrutinib

Remibrutinib, a selective covalent BTK inhibitor, has lately emerged as a promising therapeutic option for SjD through interference with B-cell receptor signalling. Dörner *et al*. (93) evaluating its efficacy and safety in a phase-2 trial, found that remibrutinib had a favourable safety profile in patients with SjD over 24 weeks. The incidence of infections was comparable between any remibrutinib (40.8%) and placebo group (41.7%). Numerically, infections were more frequent in the remibrutinib two times a day arm (54.2%) *versus* remibrutinib one time a day arm (28.0%) and placebo (41.7%) arm with no specific infection driving the difference. The most reported infections were infections of upper respiratory tract, including nasopharyngitis (6.1% remibrutinib *vs*. 12.5% placebo) and upper respiratory tract infection (6.1% remibrutinib *vs*. 8.3% placebo). Regarding the SAEs, one patient in the remibrutinib one time a day arm experienced Herpes Zoster (moderate), one patient in the remibrutinib two times a day arm experienced COVID-19 pneumonia (moderate) and one male patient treated in the placebo arm experienced pneumonia (moderate).

Conclusion

SjD, an autoimmune disorder primarily affecting the exocrine glands, leads to chronic dryness of the mucosal surfaces, including the eyes, mouth, and respiratory tract. This disruption in the natural barrier functions of these tissues predisposes patients to a higher risk of infections. Salivary and tear fluid reduction diminishes the antimicrobial properties normally protecting against pathogens, increasing susceptibility to conditions like dental infections, oral candidiasis, and respiratory tract infections. Additionally, the immune system dysregulation that accompanies SjD may further impair the body's ability to mount an effective response to infections. Treatment options, particularly with biologic agents, aim to strike a balance between controlling autoimmune activity, which can lead to severe extraglandular manifestations, and minimising the risk of infections. While current therapies are generally considered safe for SjD, further studies on their safety concerning infections may yield more definitive conclusions.

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