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WWOM PROCEEDINGS

WILEY ORAL DISEASES

World Workshop on Oral Medicine VII: Immunobiologics for salivary gland disease in Sjögren's syndrome: A systematic review

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Abstract

Objective: This systematic review evaluated the efficacy of immunobiologics for the management of oral disease in Sjögren's syndrome (SS).

Materials and Methods: MEDLINE®, Embase, Scopus, and the Cochrane Library were searched for evidence on the use of immunobiologics for management of glandular disease in SS. Primary outcomes were xerostomia and salivary gland dysfunction, assessed via visual analogue scales, disease-specific scales for SS, measurement of salivary flow, ultrasound data, and quality of life measures.

Results: Seventeen studies (11 randomized controlled trials and 6 observational studies) met inclusion criteria. Rituximab showed efficacy in improving salivary gland function but not xerostomia. Abatacept showed promise in improving both xerostomia and salivary flow. Belimumab exhibited long-term improvement of salivary flow and subjective measures. The novel agent CFZ533 improved both disease activity and patient-reported indexes.

Conclusions: There is strong evidence pointing to the efficacy of rituximab in the management of oral disease in SS. Future controlled trials may elucidate the efficacy of belimumab and abatacept. The new drug CFZ533 is a promising alternative for the management of SS and its salivary gland involvement. In considering these agents, the promise of efficacy must be balanced against the harmful effects associated with biologic agents.

KEYWORDS
biologic agents, salivary flow, Sjogren's syndrome, xerostomia

1 | INTRODUCTION

Sjögren's syndrome (SS) is an autoimmune disease affecting approximately 3.1 million patients in the United States of America (Carsons et al., 2017). The disease is chronic and often slowly progressive. Early impact occurs in the secretory glands, predominantly the salivary and lacrimal glands. However, SS can also affect the joints, gastrointestinal tract, central nervous system, and other organs, and has been linked to an increased risk for lymphoma (Alunno, Leone, Giacomelli, Gerli, & Carubbi, 2018). The majority of affected patients are diagnosed with SS in the absence of other autoimmune conditions (primary SS—pSS). Some patients, however, may develop secondary SS (sSS) as a sequela of rheumatological conditions including systemic lupus erythematosus and rheumatoid arthritis (Georgakopoulou, Andreadis, Arvanitidis, & Loumou, 2013).

In the oral cavity, SS causes hyposalivation, manifesting as xerostomia, by decreasing saliva production from the major salivary glands. Diminished salivary flow decreases patients' functional ability and increases caries rate (von Bultzingslowen et al., 2007). Decreased salivary flow also has a profound negative impact on quality of life and can cause social isolation, depression, and lack of personal satisfaction. Control of these symptoms can be very challenging (Shiboski et al., 2017; Vivino et al., 2016).

The physical symptoms of SS are treated with a variety of medications, ranging from topical salivary substitutes to systemic agents. Many patients with primarily oral manifestations of SS are managed with cholinergic agents such as pilocarpine or cevimeline, both of which have been found to increase the flow of saliva and improve the patient experience of oral dryness. In addition, some patients are managed with disease-modifying antirheumatic drugs (DMARDs) including azathioprine, hydroxychloroquine, and cyclosporine. Studies focused on these agents have shown mixed results when compared with placebo. The management of SS with non-pharmaceutical therapies has also been investigated, with potential benefit found after use of acupuncture and electrostimulation (Al Hamad, Lodi, Porter, Fedele, & Mercadante, 2019).

A newer and less studied area in SS is the use of immunobiologics for treatment. Immunobiologics, or biologic agents, are defined by the National Cancer Institute at the United States' National Institutes of Health as "a substance made from a living organism or its products and used in the prevention, diagnosis, or treatment of cancer and other diseases. Biologic agents include antibodies, interleukins, and vaccines" (National Cancer Institute, 2019). Since the first biologic agent was approved for patient treatment in 1998, this category of medications has significantly expanded in use and prevalence. A wide variety of agents that target distinct pathways are currently available.

A developing body of literature has investigated the use of biologic agents in the treatment of SS, particularly in patients with severe systemic complications (Sambataro, Sambataro, Dal Bosco, & Polosa, 2017). Existing literature has focused on the use of rituximab, with a weak recommendation for the use of rituximab to treat sicca symptoms and moderate recommendation for use of rituximab to treat systemic disease (Letaief et al., 2018; Saraux, 2010; Souza, Porfirio, Andriolo, Albuquerque, & Trevisani, 2016; Verstappen, van Nimwegen, Vissink, Kroese, & Bootsma, 2017). The World Workshop on Oral Medicine VII reviewed the literature relating to the use of biologic agents on oral signs and symptoms in SS. Existing literature has not been combined into a consensus on the use of rituximab for treatment of SS, particularly where oral signs and symptoms are concerned. In addition, limited evidence exists on use of other immunobiologics in SS. Given these points, we performed a systematic review with two objectives: (a) to determine the efficacy of rituximab as compared to placebo treatment for the treatment of oral disease related to pSS, as measured through symptomatic improvement and objective change in salivary measures and (b) to determine the evidence available for use of other biologic agents to treat the oral component of SS.

2 | METHODS

We searched the English language literature for studies and reviews in MEDLINE® (via PubMed), Embase, Scopus, and the Cochrane Library from date of database inception through October 25, 2018, using general terms for biologics, or terms for specific drugs or drug classes combined with terms for SS. We used either medical subject headings (MeSH) or Embase subject headings (Emtree) where available and keywords when applicable. We searched for conference papers in Embase and Scopus and unpublished clinical trials using ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform. This study was structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Our literature search initially included case reports, case series, narrative reviews, observational studies, and randomized clinical trials (RCTs) where full text was available and any abstracts that contained sufficient data for analysis. For this systematic review, inclusion criteria were restricted to RCTs and observational studies, either in full text or abstract form, that discussed the use of biologic agents in SS and were published after January 1, 2002. No restrictions were imposed on the duration of follow-up. Exclusion criteria included papers not in English, where the full text was not available, and the abstract did not contain sufficient information, those that reported on interventions other than biologic agents, and papers that did not include sufficient information about oral outcomes.

Titles and abstracts of all references were screened by two independent reviewers (LAG and KF). Any disagreement was resolved

through discussion and consensus. Full text of all potentially relevant papers was reviewed and screened in duplicate. Discordances were resolved through discussion. Ineligible studies were sorted according to exclusion criteria. Relevant data from included articles was extracted into a standardized form by either LAG or KF and independently verified by the other. Information from each included study was then collected including but not limited to (a) participants—individuals diagnosed with SS according to American-European consensus group (AECG) (Vitali et al., 2002), American College of Rheumatology (ACR) (Shiboski et al., 2012) or ACR/European League Against Rheumatism (EULAR) (Shiboski et al., 2017) or other criteria, demographic details including age, gender, disease duration and severity, and indication for treatment with immunobiologics; (b) immunobiologic agent prescribed and any additional treatment; (c) dosage, frequency, route of administration, and number of doses; (d) control; (e) outcome measures; and (f) adverse events. Observational studies were considered when there was no evidence available from RCTs on a particular agent. Risk of bias for randomized controlled studies was assessed using the Cochrane Collaboration tool and included random sequence generation and selection, allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment in patient-related outcomes (detection bias), blinding of outcome assessment for mortality (detection bias), incomplete short-term (2–6 weeks) outcome data addressed (attrition bias), incomplete long-term (>6 weeks) outcome data addressed (attrition bias), and selective reporting (reporting bias) (Higgins et al., 2011). Risk of bias from observational studies was assessed and is included as Supporting Information Table S1.

The primary outcomes in this study were xerostomia and salivary gland function as measured by unstimulated and stimulated salivary flow rates. Secondary outcomes included: visual analogue scales (VAS) for oral dryness, overall dryness, and global measures, the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) (Seror et al., 2010), symptomatic changes evaluated through the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) (Seror et al., 2011), and quality of life measures. A qualitative synthesis was planned to combine any outcome measures reported homogenously across included studies.

The level of evidence (LOE) was assessed according to the Somerfield criteria (Somerfield et al. 2000), which considers and scores the type of evidence from I (meta-analyses and well-designed RCTs) to V (case reports) and provides a grade for the recommendation (ranging from A to D based on the strength of the conclusions).

3 | RESULTS

We included 17 randomized controlled trials (RCTs) and observational studies in this review (Figure 1). Most of the included

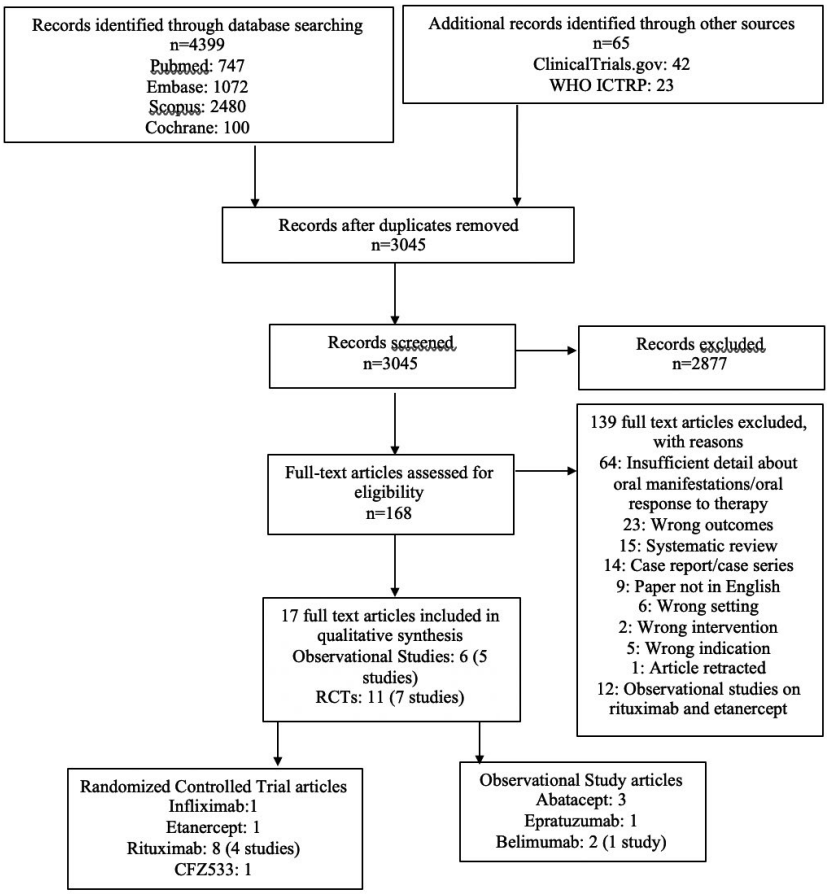

FIGURE 1 Flow chart of study selection according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard

studies diagnosed subjects according to AECG criteria (nine studies) (Vitali et al., 2002). Eleven RCTs were identified that reported on seven studies. Of these, four studied the use of rituximab, while one each studied infliximab, etanercept, and the novel agent CFZ533. Six papers reported on five observational studies using abatacept, epratuzumab, and belimumab. Observational studies covering agents evaluated in the included RCTs (11 papers on rituximab and 1 paper on etanercept) were not included in this report (Figure 1a).

In terms of outcomes, six studies measured xerostomia via a VAS. ESSPRI, which includes xerostomia, was examined in two studies. Salivary gland function was assessed using unstimulated salivary flow (n = 12 papers) and stimulated salivary flow (n = 4 papers). Studies also assessed objective measures using ESSDAI. Salivary gland morphology and volume, measured by ultrasonography, were evaluated in three studies. Most studies reported a low rate of side effects, and none reported any side effects specific to the oral cavity. There was significant heterogeneity in how xerostomia and salivary gland-related outcomes were reported between the studies, preventing a metanalysis from being performed.

Risk of bias for the RCT reports is shown in Figure 2. Nine of the reports showed both adequate sequence generation and allocation concealment. Blinding of treatment was observed in 8 of 11 papers, but outcome assessors were clearly blinded in only one paper. Outcome data were complete in 7 of the manuscripts, and 8 of 11 were free from selective reporting.

The majority of the included studies investigated the use of anti-B-cell agents (rituximab: four studies, belimumab and epratuzumab: one each), followed by anti-tumor necrosis factor (TNF) agents (infliximab, etanercept: one each), costimulatory signal inhibitors (abatacept: 3), and a novel anti CD40 inhibitor (CFZ533: 1). These studies are described below and summarized in Supporting Information Tables S2 and S3. A summary of the evidence from all included studies is described in table 1.

No deaths secondary to treatment with immunobiologics were reported by any included study. Although AEs were commonly observed, they were often mild and self-limited. Infectious AEs were frequent, but severe infection was rarely observed. Cancer was a significant AE reported occurring in six patients (three cases of breast cancer). Oral AEs were rarely reported and included stomatitis (abatacept), aphthous-like lesions (belimumab), and dental abscess (epratuzumab).

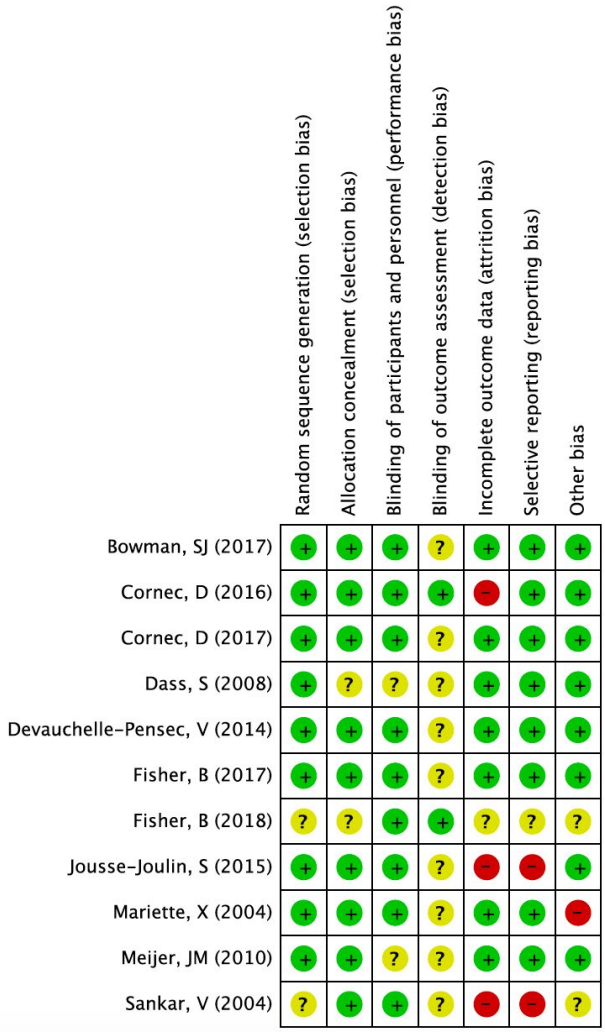

FIGURE 2 Risk of bias evaluation of randomized clinical trials according to Cochrane Collaboration risk of bias tool

3.1 | Anti-B-cell agents

3.1.1 | Rituximab

Rituximab is a chimeric monoclonal antibody that targets CD20 on the surface of B cells and causes apoptosis. Rituximab use in Sjögren's syndrome was investigated in four RCTs and reported in eight manuscripts.

Dass et al. (2008) completed the first RCT on patients with pSS. Although the primary outcomes of this trial were global disease ratings, the authors did evaluate unstimulated salivary flow rate before and after treatment. Rituximab did not improve the unstimulated salivary flow compared to placebo. This study was found to have a low to unclear risk of bias.

Meijer et al. (2010) evaluated both stimulated and unstimulated salivary flow rates, as well as oral dryness via VAS. They found a reduction in oral dryness ratings in the rituximab group. Oral dryness during the night showed a sustained response during follow-up for 48 weeks. Rituximab promoted the improvement of both stimulated and unstimulated whole saliva, as well as salivary flow in both the parotid and submandibular/sublingual glands. In contrast, patients treated with placebo exhibited a reduction in salivary flow over the treatment period. Their study showed a low risk of bias in the majority of domains.

The Tolerance and Efficacy of Rituximab in Primary Sjögren's Syndrome (TEARS) study was reported on multiple studies. Devauchelle-Pensec et al. (2014) showed that after treatment with rituximab, oral VAS and salivary flow rate did not significantly improve. ESSDAI decreased, but this effect was only significant at week 6. This

report was at low risk of bias. Jousse-Joulin et al. (2015) evaluated ultrasonographic findings in these patients and reported a reduction in salivary gland swelling during treatment. In this report, both outcome data and reporting measures were found to be at high risk of bias. Cornec et al. (2016) also evaluated ultrasonographic findings and reported a decrease in hypoechoic areas in those patients who reported at least a 30% improvement in oral dryness (responders). In addition, rituximab responders had higher baseline unstimulated whole salivary flow rates (more mild disease) than non-responders. In this study, only attrition exhibited high risk of bias. Cornec et al. (2017) correlated quality of life measures as determined by the Short Form 36 (SF-36) with ratings of SS disease activity. They found that patient ESSPRI ratings, measuring subjective symptoms, were strongly correlated with SF-36, with significant correlations between ESSPRI rating and each individual domain of the SF-36. The ESSDAI ratings did not correlate with the overall SF-36 score or with the majority of reported domains. This study showed a low overall risk of bias.

Finally, the TRial of Anti-B-Cell Therapy In patients with primary SS (TRACTISS) study was reported in two publications (Bowman et al., 2017; Fisher et al., 2018). Bowman et al. (2017) reported no difference between rituximab and placebo in the number of patients with at least a 30% reduction in their ratings of fatigue and oral dryness. The mean unstimulated salivary flow difference between groups was, however, statistically significant. Fisher et al. (2018) evaluated salivary gland ultrasounds at baseline and at least once after that. They scored improvement as Total Ultrasound Score (TUS), a combined measure of echogenicity, consistency, definition, glands involved, and size of hypoechoic foci. TUS reduction at weeks 16 and 48 was significant and stable over time. The glandular characteristics displayed statistically significant improvement at week 16 and continued improvement at week 48. TUS alteration was not associated with ESSDAI or salivary flow rates at any time points. Both of these studies showed a low risk of bias.

These results show mixed evidence for the use of rituximab in SS, with a combined LOE of IB (LOE IB).

3.1.2 | Epratuzumab

There was one observational study on Epratuzumab. This is a human monoclonal antibody that targets the CD22 protein on mature B cells. In their 2006 study, Steinfeld and colleagues investigated the use of epratuzumab in pSS (Steinfeld et al., 2006). Throughout the study period, successively larger percentages of patients exhibited subjective improvement as measured by at least 20% improvement in VAS for dry mouth over baseline (LOE IIIB).

3.1.3 | Belimumab

There was one observational study reported in two papers assessing belimumab's efficacy for treatment of SS. Belimumab is a human monoclonal antibody targeting B-cell-activating factor (BAFF). Mariette et al. (2015) evaluated the efficacy of belimumab in pSS. They showed a significant reduction in VAS for dry mouth, ESSDAI, and ESSPRI. No change in salivary flow rate was observed. De Vita et al. (2015) also reported on this trial. They noted that those patients responding at week 28 maintained or improved their subjective and objective measures at week 52 (LOE: IIIB).

3.2 | Anti-TNF

3.2.1 | Infliximab

Infliximab is a chimeric anti-TNF agent targeting TNF-α that was explored in the Trial of Remicade in Primary Sjögren's Syndrome (TRIPSS), an RCT. Mariette et al. (2004) published the results in 2004. There was no sustainable response to treatment and no significant

TABLE 1 Summary of efficacy of the immunobiologics in the management of salivary gland disease of Sjögren's syndrome

Category of agent	Medication	Type of study	Summary of evidence	LOE
Anti-B cell	Rituximab	RCTs	Improvement of unstimulated salivary flow rate, effect on xerostomia not demonstrated. Significant improvement in glandular parenchyma in two studies.	IB
	Epratuzumab	Single group open trial	Improvement in unstimulated flow (36% of patients at week 18 and in 64% of patients at week 32).	IIIB
	Belimumab	Single group open trial	Reduction in VAS dryness, ESSPRI and ESSDAI, with evidence of sustained response (52 weeks). No improvement in salivary gland function. Reduction in non-malignant salivary gland swelling.	IIIB
Anti-TNF-α	Infliximab	RCT	No difference in salivary flow rates or xerostomia. No changes in microscopic aspects of minor salivary glands.	IIB
	Etanercept	RCT	No difference in VAS dryness. No improvement in salivary gland function.	IIB
Costimulatory Signal Inhibitors	Abatacept	Single group open trials	Two of three papers demonstrated improvement in salivary gland function. Reduction of ESSPRI and ESSDAI was observed until 24 weeks but not after 48 weeks. Improvement of xerostomia was noted.	IIIB
Anti-CD40	CFZ533	RCT	ESSPRI and ESSDAI improved with the higher dose (10 mg/kg).	IIB

difference between groups in VAS. There was no significant change in focus score or salivary flow rate after treatment. This study was at low risk of bias except as related to funding sources (LOE: IIB).

3.2.2 | Etanercept

Etanercept is a fusion protein that binds to TNF-α. Sankar et al. (2004) completed an RCT to evaluate its efficacy in SS and failed to show evidence of improvement in any oral or general outcomes. This trial did show high risk of bias in both attrition and reporting and uncertain risk in multiple other domains (LOE IIB).

3.3 | Costimulatory signal inhibitors

3.3.1 | Abatacept

There were three observational studies assessing abatacept efficacy in SS. Abatacept is a fusion protein that targets CD80 and CD86 on T cells, preventing activation. Adler et al. (2013) studied the histologic, serologic, and clinical response of 11 pSS patients to abatacept. The authors observed a significant increase in saliva secretion, a reduction in focus scores on minor salivary gland biopsy, and a decreased density of infiltrating lymphocytes within the foci after treatment.

Meiners et al. (2014) evaluated the efficacy of abatacept in 15 patients with early and active pSS. Patients were required to exhibit a stimulated whole salivary flow rate higher than 0.1 mL/min for inclusion. Median ESSDAI decreased at week 24 but returned to baseline by week 48. ESSPRI decreased during treatment and did not rebound. Unstimulated salivary flow did not change during or after treatment, while stimulated salivary flow was stable during treatment and decreased significantly post-treatment.

Tsuboi et al. (2016) evaluated the efficacy of abatacept in patients with SS and rheumatoid arthritis (sSS) using salivary gland biopsy and salivary flow rate. Patients with a less notable minor salivary gland inflammatory infiltrate at baseline exhibited an increase in salivary flow rate at week 24.

These combined results show a trend toward increased salivary flow and improved subjective measures after treatment with abatacept (LOE IIIB).

3.4 | Anti-CD40

3.4.1 | CFZ533

CFZ533 is a potent inhibitor of CD40 stimulation, limiting the formation of ectopic germinal centers. Fisher et al. (2017) performed an RCT to evaluate the effect of either 3 mg/kg or 10 mg/kg CFZ533 in four doses over 3 weeks for pSS. The higher dose was shown to reduce the ESSDAI most effectively. ESSPRI and serum levels of CXCL13 (a germinal center-related biomarker) were also reduced (LOE: IIB). This study is currently only published in abstract form, leaving most categories at uncertain risk of bias.

4 | DISCUSSION

Immunobiologics have been clinically tested and used in the off-label management of SS and its systemic complications for more than a decade (Zandbelt et al., 2004). Some systematic reviews have assessed the use of these drugs in the management of systemic disease in SS (Al Hamad et al., 2019; Souza et al., 2016), but this is the first systematic review to assess the efficacy of immunobiologics in the management of oral disease. We determined efficacy by considering several outcomes including salivary flow, xerostomia, and ultrasonographic pattern of major salivary glands. Eleven RCTs and 18 observational studies were included, reporting on four classes of biologics—anti-B cell (rituximab, epratuzumab, and belimumab), anti-TNF (infliximab and etanercept), inhibition of costimulatory signal (abatacept), and anti-CD40 (CFZ533) therapy. RCTs included 477 patients (253 on biologics) and observational studies included 127 patients on biologics. Oral outcomes were clearly described in each study. Overall, these studies showed a very low rate of adverse effects, but recognized complications from the use of biologic agents should be thoroughly discussed with patients before treatment with these drugs. Rituximab has been evaluated most extensively, allowing for more conclusions on this agent.

Our results clearly show, based on two RCTs, that infliximab and etanercept are ineffective for the management of salivary gland disease in SS (Mariette et al., 2004; Sankar et al., 2004). Treatment with these medications produced no difference in oral dryness or salivary flow.

On the other hand, abatacept, an agent that prevents the antigen-presenting cells from delivering the costimulatory signal, showed promise in three open-label studies (Adler et al., 2013; Meijer et al., 2010; Tsuboi et al., 2016). In these studies, improvements to xerostomia and salivary flow rates (both unstimulated and stimulated) were observed, as was as a reduction in the inflammatory infiltrate in minor salivary glands. Since these studies had an open-label design, however, RCTs are required to confirm these findings.

Anti-B-cell treatment has been most commonly used to reduce SS disease activity and manage systemic complications. However, studies on rituximab show mixed evidence on the agent's efficacy for treating oral disease in SS. The RCTs studying rituximab were mostly at low risk of bias, with some areas of each exhibiting unclear risk of bias, and with selected domains at high risk of bias in two studies (Cornec et al., 2016; Jousse-Joulin et al., 2015). The TEARS and TRACTISS studies have demonstrated that rituximab was able to improve salivary gland echostructure by modifying glandular patterns after treatment (Fisher et al., 2018; Jousse-Joulin et al., 2015). On the other hand, there are conflicting data regarding its efficacy on xerostomia and salivary flow. Meijer et al. (2010) reported benefit from rituximab in the improvement of oral dryness. They included patients with residual stimulated salivary flow at baseline, which may be the key to a clinically relevant response. As part of the TEARS study, Cornec et al. (2016) evaluated those patients who had salivary gland ultrasound data available at baseline and also reported an improvement of xerostomia. They

showed that patients who presented at least 30% improvement in oral dryness VAS had fewer salivary gland ultrasound alterations at baseline, reinforcing the hypothesis that a measurable salivary gland function at baseline is important to clinical response. However, the analysis of the entire TEARS cohort showed a stable, but non-significant reduction in oral dryness after rituximab treatment (Devauchelle-Pensec et al., 2014). Bowman et al. (2017) also failed to show changes in oral dryness at any time point in the TRACTISS study. Their inclusion of patients with severe glandular disease may have influenced this outcome.

The effect of rituximab on xerostomia was also evaluated in seven observational studies, each of which showed a positive effect (Carubbi et al., 2013; Devauchelle-Pensec et al., 2011, 2007; Galarza et al., 2008; Gottenberg et al., 2005; Pijpe et al., 2005; St Clair et al., 2013), although the uncontrolled nature of these studies may have influenced the results (Concato, Shah, & Horwitz, 2000). These data also showed improvement of parotid gland swelling in small numbers of affected patients (Galarza et al., 2008; Gottenberg et al., 2005, 2013). In addition, not all studies commented on the timing of treatment or salivary gland function at baseline of included subjects, which may explain some variation in the reported results.

Our results, therefore, suggest that rituximab is effective in improving the salivary flow rate in SS. Meijer et al. (2010) and the TRACTISS study (Bowman et al., 2017) each reported improvement, while the TEARS study (Devauchelle-Pensec et al., 2014) showed no change in flow. However, the TEARS study included patients up to 10 years after initial diagnosis, and patients received two doses of rituximab on weeks 0 and 2 postenrollment. In contrast, Meijer et al. (2010) evaluated patients with at least some residual saliva (stimulated whole saliva ≥ 0.15 ml/minute). The TRACTISS study was primarily designed to evaluate the effect of rituximab on oral dryness and four doses were administered at weeks 0, 2, 24, and 26 postenrollment. These additional doses, along with a measurable baseline salivary flow, may be responsible for the sustained improvement.

Other anti-B-cell therapies have also shown some benefit in the management of oral disease in SS. Preliminary results on the use of belimumab from one uncontrolled trial suggest some efficacy as measured by xerostomia, parotid gland swelling, and ESSDAI. The results were particularly promising for the glandular domain of this scale. However, no effect on salivary flow was observed (De Vita et al., 2015; Mariette et al., 2015).

Epratuzumab is an anti-CD22 drug that causes less B-cell depletion than rituximab, and its use in SS patients showed a clinically significant improvement of salivary flow in more than 60% of the patients studied in one observational trial (Steinfeld et al., 2006).

Recently, a new intervention was proposed to treat SS. CFZ533, a drug that selectively blocks CD40 costimulation and reduces germinal center formation, was tested in an RCT in 3 mg/kg and 10 mg/kg doses. This trial showed that the drug was safe and well tolerated, and the higher dose was more effective in reducing ESSDAI and ESSPRI (Fisher et al., 2017).

In summary, the use of biologics in SS represents a new frontier in the management of this disease. Anti-B-cell therapies are the leaders of immunobiologics for treatment of SS. Here, we show that rituximab has the most evidence in the treatment of xerostomia and stimulation of salivary flow improvement in SS, especially with continuous treatment. Abatacept, belimumab, epratuzumab, and CFZ533 are promising alternatives, and additional head-to-head RCTs may clarify their benefit and define cost-effectiveness.

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AUTHOR CONTRIBUTION

Luiz Alcino Gueiros and Katherine France screened the included papers, worked on the study protocol, and wrote this report. Rachael Posey selected the abstracts and provided guidance on the paper selection process. Jacqueline W. Mays and Barbara Carey worked on paper selection and defining the study protocol. Thomas P. Sollecito, Jane Setterfield, Sook Bin Woo, Donna Culton, and Aimee S. Payne reviewed the drafts and provided technical guidance. Giovanni Lodi worked on the study protocol and reviewed the final draft. Martin S. Greenberg and Scott De Rossi worked on the study protocol, reviewed drafts, and approved the final version.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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