Title
WWOM VII: Immunobiologics for Salivary Gland Disease in Sjögren's Syndrome: A Systematic Review

Running title
WWOM VII: Immunobiologics in Sjogren's Syndrome

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ABSTRACT

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

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 Sjögren's syndrome. Primary outcomes were xerostomia and salivary gland dysfunction, assessed via visual analogue scales, disease-specific scales for Sjögren's syndrome, 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 Sjögren's syndrome. Future controlled trials may elucidate the efficacy of belimumab and abatacept. The new drug CFZ533 is a promising alternative for the management of Sjögren's syndrome and its salivary gland involvement. In considering these agents, the promise of efficacy must be balanced against the harmful effects associated with biologic agents.

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 sequel 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 (Vivino et al., 2016; C.H. Shiboski et al., 2017).

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. 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, 2018).

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, 2016). 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: 1) 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 2) 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 randomized clinical trials 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 1) participants – individuals diagnosed with SS according to American-European consensus group (AECG) (Vitali et al., 2002), American College of Rheumatology (ACR) (S.C. Shiboski et al., 2012) or ACR/European League Against Rheumatism (EULAR) (C.H. Shiboski et al., 2017) or other criteria, demographic details including age, gender, disease duration and severity, and indication for treatment with immunobiologics; 2) immunobiologic agent prescribed and any additional treatment; 3) dosage, frequency, route of administration and number of doses; 4) control; 5) outcome measures; and 6) 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 supplementary table 1.

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 (metanalyses 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).

RESULTS

We included seventeen randomized controlled trials (RCTs) and observational studies in this review **(Figure 1)**. Most of the included studies diagnosed subjects according to AECG criteria (9 studies) (Vitali et al., 2002). Eleven papers were identified that reported on seven different RCTs. 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 **(Fig. 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 randomized clinical trial 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 was 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: 4 studies, belimumab and epratuzumab: 1 each), followed by anti-tumor necrosis factor (TNF) agents (infliximab, etanercept: 1 each), costimulatory signal inhibitors (abatacept: 3), and a novel anti CD40 inhibitor (CFZ533: 1). The studies are described below and summarized in supplementary tables 2 and 3.

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 (3 cases of breast cancer). Oral AEs were rarely reported and included stomatitis (abatacept), aphthous-like lesions (belimumab) and dental abscess (epratuzumab).

Anti-B cell agents

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 times. 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 bias 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 was 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 level of evidence of IB (**LOE IB).**

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).**

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).**

Anti-TNF

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 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).**

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)**.

Costimulatory Signal Inhibitors

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 0.1mL/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)**.

Anti-CD40

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 3mg/kg or 10mg/kg CFZ533 in 4 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.

3. 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., 2018; 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 randomized clinical trials and eighteen 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 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, analysis of the entire TEARS cohort showed a stable, but nonsignificant reduction in oral dryness after rituximab treatment (Devauchelle-Pensec et al., 2014). Bowman et al. (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; Devauchelle-Pensec et al., 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., 2013; Gottenberg et al., 2005). 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 post-enrollment. 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 post-enrollment. 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 3mg/kg and 10mg/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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Figure Legends

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

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

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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 label 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 (10mg/kg).	IIB

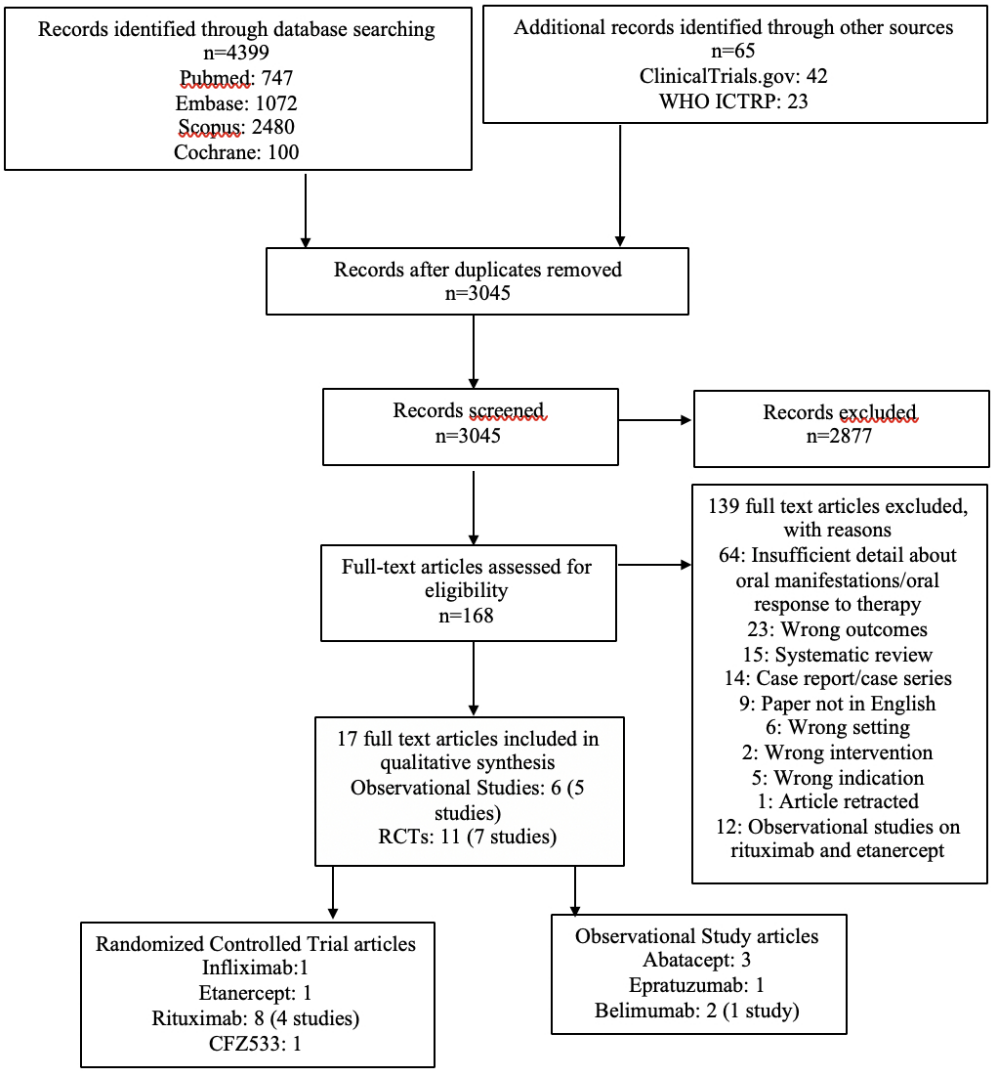

Figure 1. Flow chart of study selection according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard.

180x195mm (144 x 144 DPI)

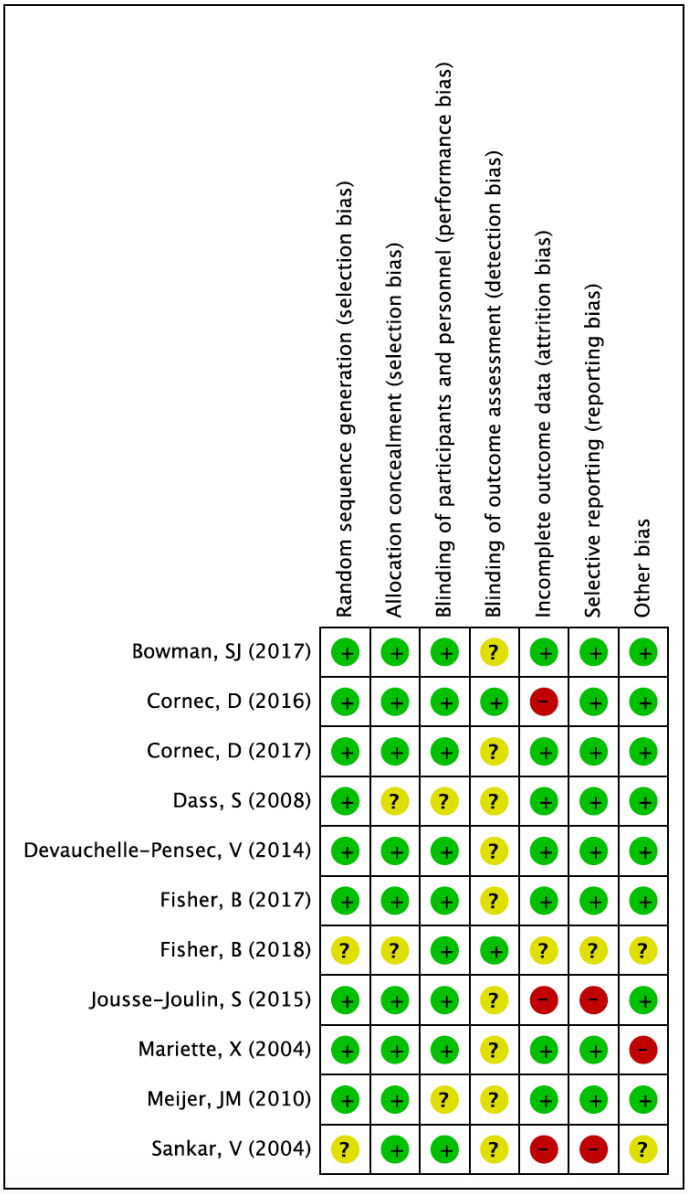

Figure 2. Risk of bias evaluation of randomized clinical trials according to Cochrane Collaboration risk of bias tool.

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Complementary table 1. Assessment of the methodological quality of observational studies (Dows and Black scale).

Observational studies on biologics in SS (excluding the agents evaluated by RCTs) (N=6)				
Anti-B cells				
Author:	**Agent:**			**Notes/justification**
Steinfeld et al, 2006	**Epratuzumab**			
Reporting	0	1	2	
1. Is the hypothesis/aim/objective of the study clearly described?		Y	-	
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?		Y	-	Outcomes were detailed at the "Clinical Assessment" section
3. Are the characteristics of the patients included in the study clearly described ?		Y	-	Inclusion and exclusion criteria were clearly stated.
4. Are the interventions of interest clearly described?		Y	-	Drug administration protocol was clearly detailed.
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	N			There was no comparison group, so confounders were not described.
6. Are the main findings of the study clearly described?		Y	-	Response rates were described and graphically presented.
7. Does the study provide estimates of the random variability in the data for the main outcomes?		Y	-	Data was reported using mean and standard deviation.
8. Have all important adverse events that may be a consequence of the intervention been reported?		Y	-	Adverse events were adequately reported.
9. Have the characteristics of patients lost to follow-up been described?	N		-	Only the number of patients lost to follow up were described.
10. Have actual probability values been reported(e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	N		-	Only the descriptive analysis was reported.
External validity				
All the following criteria attempt to address the representativeness of the findings of the study and whether they may be generalized to the population from which the study subjects were derived.				
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?		y		All patients from 2 centers were invited to enroll the study.

12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	N			Unable to determine the proportion of patients who agreed to participate the study.
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	N			Unable to determine the source population.
Internal validity - bias				
14. Was an attempt made to blind study subjects to the intervention they have received ?	N			The study was not blind.
15. Was an attempt made to blind those measuring the main outcomes of the intervention?	N			The study was not blind.
16. If any of the results of the study were based on "data dredging", was this made clear?	N			Data dredging was not performed.
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls ?		Y		Adjusted for different lengths of follow up.
18. Were the statistical tests used to assess the main outcomes appropriate?		Y		
19. Was compliance with the intervention/s reliable?		Y		
20. Were the main outcome measures used accurate (valid and reliable)?		Y		Outcome measures were clearly described.
Internal validity - confounding (selection bias)				
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	N			No control group.
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	N			Unable to determine.
23. Were study subjects randomized to intervention groups?	N			No control group.

24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	N			No randomization was performed.
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	N			No control group
26. Were losses of patients to follow-up taken into account?		y		Losses described and considered for analysis.
Power				
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	N			N=16, single-arm.
Author:	**Agent:**			**Notes/justification**
Mariette et al., 2015	**Belimumab**			
Reporting	0	1	2	
1. Is the hypothesis/aim/objective of the study clearly described?		Y		Abstract and introduction clearly describe the objectives of the study.
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?		Y		The methods section has a subsection (endpoints) that describes the outcomes in detail.
3. Are the characteristics of the patients included in the study clearly described ?		Y		Eligibility criteria was clearly described.
4. Are the interventions of interest clearly described?		Y		The study described how and when belimumab was administered.
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	N			There was only 1 group.
6. Are the main findings of the study clearly described?		Y		Response to primary outcomes were described.
7. Does the study provide estimates of the random variability in the data for the main outcomes?		Y		The study used mean and ./standard deviation.
8. Have all important adverse events that may be a consequence of the intervention been reported?		Y		The result section has a subsection (tolerance) that described the adverse events.
9. Have the characteristics of patients lost to follow-up been described?		Y		Clinical details of the patients lost to follow up were described.

10. Have actual probability values been reported(e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?		Y		The actual probability values were reported.
External validity				
All the following criteria attempt to address the representativeness of the findings of the study and whether they may be generalized to the population from which the study subjects were derived.				
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	N		-	It was not clear if consecutive patients were included.
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	N			The proportion of those asked who agreed to participate the study was not stated.
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	N			The study was performed in specialized unit in 2 hospital centers.
Internal validity - bias				
14. Was an attempt made to blind study subjects to the intervention they have received ?	N			It was an open label study.
15. Was an attempt made to blind those measuring the main outcomes of the intervention?	N			It was an open label study.
16. If any of the results of the study were based on “data dredging”, was this made clear?		Y		No retrospective unplanned analysis was performed.
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls ?		Y		Primary endpoints were analyzed at week 28.
18. Were the statistical tests used to assess the main outcomes appropriate?		y		Statistical analysis was simple but adequate.
19. Was compliance with the intervention/s reliable?		Y		No contamination of the study group.
20. Were the main outcome measures used accurate (valid and reliable)?		Y		Outcomes were clearly described
Internal validity - confounding (selection bias)				

21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	N			Patients were recruited in 2 hospital centers.
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	N			The period for patients recruitment was not stated.
23. Were study subjects randomized to intervention groups?	N			It was an open label study.
24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	N			The study was not randomized.
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	N			The effect of confounding factors were not considered.
26. Were losses of patients to follow-up taken into account?		Y		Losses were justified and considered for analysis.
Power				
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	N			N=30, single-arm.
Author:	**Agent:**			**Notes/justification**
De Vita et al., 2015	**Belimumab**			
Reporting	**0**	1	2	
1. Is the hypothesis/aim/objective of the study clearly described?		Y		It was stated in the abstract and introduction.
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?		Y		It was an additional analysis of the BELISS study (Mariette et al., 2015)
3. Are the characteristics of the patients included in the study clearly described ?		Y		Eligibility criteria was as part of the BELISS study.
4. Are the interventions of interest clearly described?		Y		Efficacy at week 52.

5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	N			There was only 1 group.
6. Are the main findings of the study clearly described?		Y		Outcome data was reported accordingly.
7. Does the study provide estimates of the random variability in the data for the main outcomes?		Y		Data was described by using mean ad standard deviation.
8. Have all important adverse events that may be a consequence of the intervention been reported?		Y		Tolerance/safety was described in detail.
9. Have the characteristics of patients lost to follow-up been described?	N			The study considered only the patients evaluated at W52 (19 patients), but do not comment on those lost to follow up from W28 to w52.
10. Have actual probability values been reported(e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?		Y		The actual probability values were reported.
External validity				
All the following criteria attempt to address the representativeness of the findings of the study and whether they may be generalized to the population from which the study subjects were derived.				
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?		Y		Patients from the BELISS study
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	N			The proportion of those asked who agreed to participate was not reported.
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	N			The study was performed in specialized unit in 2 hospital centers.
Internal validity - bias				
14. Was an attempt made to blind study subjects to the intervention they have received ?	N			It was an open label study.

15. Was an attempt made to blind those measuring the main outcomes of the intervention?	N			It was an open label study.
16. If any of the results of the study were based on “data dredging”, was this made clear?	N			No retrospective unplanned analysis was performed.
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls ?		Y		The study considered the patients followed until W52.
18. Were the statistical tests used to assess the main outcomes appropriate?		Y		They used paired tests to compare the results with w28.
19. Was compliance with the intervention/s reliable?		Y		No contamination of the study group.
20. Were the main outcome measures used accurate (valid and reliable)?		Y		Outcome measures were clearly described.
Internal validity - confounding (selection bias)				
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	N			Patients were recruited in 2 hospital centers.
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	N			The period for patients recruitment was not stated.
23. Were study subjects randomized to intervention groups?	N			It was a single-group open label study.
24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	N			It was a single-group open label study.
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	N			The effect of confounding factors were not considered.

26. Were losses of patients to follow-up taken into account?	N			Patients who dropped the study after W28 were not described.
Power				
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	N			There was no sample size calculation.
Costimulatory Signal Inhibitors				
Author: 4	**Agent:**			**Notes/justification**
Adler et al., 2013	**Abatacept**			
Reporting	0	1	2	
1. Is the hypothesis/aim/objective of the study clearly described?		Y	-	Objective is described in the abstract and introduction sections.
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?	N		-	The study evaluated several endpoints, but primary endpoints were not reported.
3. Are the characteristics of the patients included in the study clearly described ?		Y	-	Eligibility criteria was reported on methods section.
4. Are the interventions of interest clearly described?		Y	-	The subsection “Medication” describes the intervention in detail.
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	N			There was only 1 group.
6. Are the main findings of the study clearly described?		Y	-	The study describes the main findings properly.
7. Does the study provide estimates of the random variability in the data for the main outcomes?		Y	-	The median and range was described for numeric variables.
8. Have all important adverse events that may be a consequence of the intervention been reported?		Y	-	Results section describes the adverse events in the “side effects” subsection.
9. Have the characteristics of patients lost to follow-up been described?		Y	-	All patients (n=11) completed the study.
10. Have actual probability values been reported(e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?		Y	-	Actual probability values were reported.
External validity				

All the following criteria attempt to address the representativeness of the findings of the study and whether they may be generalised to the population from which the study subjects were derived.				
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	U			Unable to determine
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	U			Unable to determine
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	U			Unable to determine
Internal validity - bias				
14. Was an attempt made to blind study subjects to the intervention they have received ?	N			It was an open label study.
15. Was an attempt made to blind those measuring the main outcomes of the intervention?	N			It was an open label study.
16. If any of the results of the study were based on “data dredging”, was this made clear?		Y		No retrospective analysis was performed.
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls ?		Y		Follow up was the same for all the patients.
18. Were the statistical tests used to assess the main outcomes appropriate?		Y		Statistical analysis was adequate.
19. Was compliance with the intervention/s reliable?		Y		No contamination of the study group.
20. Were the main outcome measures used accurate (valid and reliable)?		Y		Main outcomes were not clear.
Internal validity - confounding (selection bias)				

21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?		Y		Patients were recruited from the same population.
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	N			There was only 1 group.
23. Were study subjects randomized to intervention groups?	N			It was an open label study.
24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	N			It was an open label study with a single group.
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?		Y		The authors used a "repeated-measures analysis of variance to adjust analysis of time effects for possible confounding by age and disease duration."
26. Were losses of patients to follow-up taken into account?		Y		There were no losses.
Power				
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	N			N=11, single-arm.
Author:	**Agent:**			**Notes/justification**
Meiners et al., 2014	**Abtacept**			
Reporting	0	1	2	
1. Is the hypothesis/aim/objective of the study clearly described?		Y	-	It is described in the abstract and introduction.
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?		Y	-	Outcomes were described in the methods section.
3. Are the characteristics of the patients included in the study clearly described ?		Y	-	Eligibility criteria were described in methods section.
4. Are the interventions of interest clearly described?		Y	-	Intervention was described in the methods section.

5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	N			It was single group open label study.
6. Are the main findings of the study clearly described?		Y	-	Table 2 describes the min results.
7. Does the study provide estimates of the random variability in the data for the main outcomes?		Y	-	Authors reported mean, standard devition and median.
8. Have all important adverse events that may be a consequence of the intervention been reported?		Y	-	Adverse events were described in the results section.
9. Have the characteristics of patients lost to follow-up been described?		Y	-	All patients completed follow up.
10. Have actual probability values been reported(e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?		Y	-	Actual probability values were reported.
External validity				
All the following criteria attempt to address the representativeness of the findings of the study and whether they may be generalized to the population from which the study subjects were derived.				
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	N		-	The source population was not clear.
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	N		-	The source population was not clear.
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	N		-	It was an open label study.
Internal validity - bias				
14. Was an attempt made to blind study subjects to the intervention they have received ?	N		-	It was an open label, single-arm study.
15. Was an attempt made to blind those measuring the main outcomes of the intervention?	N			It was an open label, single-arm study.

16. If any of the results of the study were based on "data dredging", was this made clear?		Y	-	All analysis were previously planned.
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls ?		Y	-	All patients completed follow-up.
18. Were the statistical tests used to assess the main outcomes appropriate?		Y	-	Statistical tests were adequate. They used generalized estimating equations to analyze variables over time within subjects
19. Was compliance with the intervention/s reliable?		Y	-	All patients performed the interventions accordingly.
20. Were the main outcome measures used accurate (valid and reliable)?		Y	-	Outcome measures were clearly described or referred other studies.
Internal validity - confounding (selection bias)				
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	N		-	The site/city of recruitment was not clear.
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?		Y	-	Patients were recruited for a single-arm study from August/2010 to May/2012.
23. Were study subjects randomized to intervention groups?	N		-	It was an open label, single-arm study.
24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	N		-	It was an open label, single-arm study.
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	N			It was not reported.
26. Were losses of patients to follow-up taken into account?		Y		There were no losses.
Power				

27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	N			N=15, single arm.
Author:	**Agent:**			**Notes/justification**
Tsuboi et l., 2016	**Abatacept**			
Reporting	0	1	2	
1. Is the hypothesis/aim/objective of the study clearly described?		Y	-	Objectives were described in the abstract and introduction.
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?		Y	-	Outcome measures were described in the methods section.
3. Are the characteristics of the patients included in the study clearly described ?		Y	-	Eligibility criteria were adequately described.
4. Are the interventions of interest clearly described?		Y	-	The “medication” subsection of the “Methods” section described the intervention properly.
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	N			It was a single-group open label study.
6. Are the main findings of the study clearly described?		Y	-	The authors describe the efficacy for both rheumatoid arthritis and SS.
7. Does the study provide estimates of the random variability in the data for the main outcomes?		Y	-	Results used mean and standard deviation.
8. Have all important adverse events that may be a consequence of the intervention been reported?		Y	-	The study also aimed to describe the safety of the intervention, and described the adverse events in the results section.
9. Have the characteristics of patients lost to follow-up been described?		Y	-	Adherence was described in the methods section.
10. Have actual probability values been reported(e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?		Y	-	Actual probability values were reported.
External validity				
All the following criteria attempt to address the representativeness of the findings of the study and whether they may be generalized to the population from which the study subjects were derived.				

11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	N			The entire population was not clearly described.
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	N			The proportion of those asked who agreed to participate was not reported.
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	N			It was an open label study.
Internal validity - bias				
14. Was an attempt made to blind study subjects to the intervention they have received ?	N			It was an open label study.
15. Was an attempt made to blind those measuring the main outcomes of the intervention?	N			It was an open label study.
16. If any of the results of the study were based on “data dredging”, was this made clear?		Y		The study performed only planned analysis.
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls ?		Y		Follow-up was the same for all the patients.
18. Were the statistical tests used to assess the main outcomes appropriate?		Y		Statistical analysis was performed accordingly.
19. Was compliance with the intervention/s reliable?		Y		Compliance was reliable.
20. Were the main outcome measures used accurate (valid and reliable)?		Y		Outcome measures were clearly described.
Internal validity - confounding (selection bias)				
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	N			It was a single arm study.

22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	N			It was a single arm study.
23. Were study subjects randomized to intervention groups?	N			It was an open label study.
24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	N			It was an open label study.
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	N			It was not reported.
26. Were losses of patients to follow-up taken into account?	N			The study did not describe if the losses were considered in analysis.
Power				
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	N			N=36, single arm.

Suplementary table Table 2. Characteristics of randomized controlled trials investigating the use of biologics for xerostomia and/or hyposalivation in Sjögren's syndrome.

Category of Agent	Medication	Author & Study name if applicable	Sample size (# receiving biologic agent)	Oral Outcome	Xerostomia	Salivary gland function
Anti-B cell	Rituximab 1g at days 1	Dass, S (2008)	17 (8)	Unstimulated salivary flow rate	Not evaluated	No change in unstimulated salivary flow rate after treatment

		Meijer, JM (2010)	30 (20)	Stimulated and unstimulated whole saliva; VAS oral dryness	Significant improvement in mean VAS for oral dryness in the rituximab group; improvement in nocturnal dry mouth at weeks 24, 36, and 48	Significant improvement to stimulated whole saliva, unstimulated whole saliva, and submandibular/sublingual flow rate from baseline in rituximab group. The placebo group saw decreases in salivary flow measures.
		Devauchelle-Pensec, V (2014), TEARS	122 (63)	Oral dryness VAS, success defined as 30mm change; unstimulated salivary flow rate	No significant difference in percent of patients with 30mm improvement to oral dryness at any time point.	No significant difference in salivary flow rate between placebo and rituximab groups at weeks 6, 16 and 24.

		Jousse-Joulin S (2015), TEARS	28 (14)	Changes in salivary gland size, resistive index, and echostructure.	Not evaluated	Significantly greater improvement in salivary gland echostructure with rituximab, no significant differences in size or resistive index between groups.
		Cornec, D (2016), TEARS	28 (14)	SSRI-30; salivary gland ultrasound; MSG biopsy; unstimulated whole salivary flow	Improvement in oral dryness was more often seen in patients with lower salivary gland function.	Non-responders to rituximab began with lower unstimulated whole salivary flow. No reliable response to rituximab.

		Cornec, D (2017), TEARS	28 (14)	ESSDAI, ESSPRI, VAS for oral dryness, unstimulated whole salivary flow, salivary gland biopsy focus score >1	ESSPRI positively correlated with disease activity, SF-36, moderate correlation between oral dryness and social functioning, physical functioning, and general health ratings	Moderate correlation between ESSDAI and ESSPRI/VAS scores, no correlation with SF-36 composite score (0.092, p=0.491)
	Rituximab 1g at weeks 0,2,24,26	Bowman, SJ (2017), TRACTISS	133 (65)	Unstimulated and stimulated salivary flow; 30% reduction in oral dryness via VAS	Rituximab did not significantly improve patient-reported oral dryness over placebo.	Significant improvement in unstimulated but not stimulated salivary flow by the end of the study period.

		TRACTISS Fisher, BA (2018),	52 (26)	Total ultrasound score (TUS)	Not evaluated.	Rituximab diminished TUS at weeks 16 and 48. The glandular definition of TUS was also improved at weeks 16 and 48. Improvement of ≥1 point in TUS was not associated with improvement in unstimulated or stimulated salivary flow rates, ESSDAI, ESSPRI or VAS dryness.

Anti-TNFα	Infliximab 5mg/kg at weeks 0,2,6	Mariette, X (2004), TRIPSS	103 (54)	Dryness (VAS); salivary flow rate; MSG biopsy	No difference based on 30% decrease in dryness VAS at weeks 10 and 22	No difference in salivary flow rate at weeks 10 and 22, biopsy specimens showed no difference after treatment.
	Etanercept 25mg twice weekly	Sankar, V (2004)	28 (14)	>20% improvement in the patient's assessment of dry mouth by VAS or >20% improvement in total stimulated salivary flow	No significant difference in dry mouth VAS after treatment.	Total stimulated saliva flow did not show >20% improvement.
Anti-CD40	CFZ533 3 or 10 mg/kg, four doses in 12 weeks	Fisher, B (2017)	44 (29)	ESSDAI, ESSPRI	ESSPRI showed improvement after treatment with 10 mg/kg	ESSDAI showed significant improvement only in the group treated with 10 mg/kg IV

Suplementary Table 3. Characteristics of observational studies investigating the use of biologics for xerostomia and/or hyposalivation in Sjögren's syndrome.

Category of Agent	Medication	Author (Year), study type, & name if applicable	Sample size (# receiving biologic agent)	Oral Outcome	Xerostomia	Salivary gland function
Anti-B cell	Epratuzumab	Steinfeld et al. (2006), Open Label	16 (16)	Unstimulated whole salivary flow, improvement defined as 20% change in flow	Not evaluated	Improvement in unstimulated flow seen in 36% of patients at 18 weeks and in 64% of patients at week 32.

Belimumab	Mariette et al. (2013), Open Label, BELISS	30 (30)	From baseline to week 28: ≥30% reduction in dryness VAS; unstimulated salivary flow; ESSDAI; ESSPRI	At week 28, 37% of patients showed reduced VAS dryness (mean (SD) from 7.8 (1.8) to 6.2 (2.9), p=0.0021). ESSPRI also showed a decrease from 6.4 (1.1) to 5.6 (2.0), p=0.0174.	No change in unstimulated whole salivary flow, but mean ESSDAI score decreased from 8.8 (7.4) at baseline to 6.3 (6.6) at week 28, p=0.0015. 10/13 patientys showed improvement in non-malignant salivary gland swelling.

	De Vita et al. (2015), Open Label, BELISS	19 (19)	From W28 to W52: ≥30% reduction in dryness VAS; unstimulated salivary flow; ESSDAI; ESSPRI	Thirteen of the 15 responders at W28 also responded at W52 (86.7%). Improvement of >30% in the VAS dryness score remained unchanged.	ESSDAI and ESSPRI. showed a trend of improvement from W28 toW52. No statistical differences were reported from W28 to W52 for the whole unstimulated salivary flow rate.

Costimulatory Signal Inhibitors	Abatacept	Adler et al. (2013), Open Label	11 (11)	Stimulated whole saliva; salivary gland biopsy	Not evaluated	Significant increase in stimulated whole saliva from 1.61 to 1.74 gm/2 minutes (p=0.029 after adjusting for disease duration). There was also a signficant decrease in the number of lymphocytic foci found in minor salivary gland biopsy (4.4 to 2.1, p=0.041).

		Meiners et al. (2014), Open Label, ASSAP	15 (15)	ESSDAI, ESSPRI, unstimulated and stimulated parotid saliva and submandibular/sublingual saliva	Median ESSPRI showed a significant decreased from 7.5 at baseline to 5.8 when active treatment was completed at week 24 (p=0.015), and increased in follow up to 7.0 at week 48 (p=0.151).	Baseline and week 24: median ESSDAI decreased from 11 to 2 (p<0.001). Baseline and week 48: ESSDAI did not differ (p=0.137). Salivary flow (stimulated and unstimulated) did not change significantly during or after treatment.

		Tsuboi et al., (2016), Open Label, ROSE	36 (36)	VAS for dry mouth and parotid pain; saliva volume via Saxon's test	Significant reduction in dry mouth VAS = 49.8±26.5 at baseline to 39.5±31.3 at 24 weeks (p<0.05). No improvement in VAS for parotid pain.	Saliva volume increased from 2136±1809 mg/2 min at week 0 to 2397±1878 mg/2 min at 24 weeks (p<0.05).