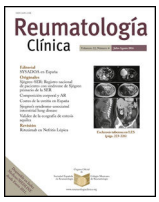
Reumatol Clin. 2019;15(6):315–326

Sociedad Española de Reumatología - Colegio Mexicano de Reumatología

Reumatología Clínica

www.reumatologiaclinica.org



Special Article

SER recommendations on the use of biological drugs in primary Sjögren's syndrome☆

José Luis Andréu Sánchez,[a,*] Mónica Fernández Castro,[b] Petra Díaz del Campo Fontecha,[c] Héctor Corominas,[d] Francisco Javier Narváez García,[e] José Rosas Gómez de Salazar,[f] Íñigo Rua-Figueroa,[g] Miguel Ángel Abad Hernández,[h] María Noelia Álvarez Rivas,[i] Javier del Pino Montes,[j] Félix Manuel Francisco Hernández,[g] María Ángeles Gantes Pedraza,[h] Martín Gerardo Greco Merino,[g] María Vanesa Hernández,[k] María Victoria Navarro Compán,[l] Juan Alberto Paz Solarte,[m] Fredeswinda I. Romero Bueno,[n] Hye Sang Park,[o] Francisca Sivera Mascaró[p]

[a] *Servicio de Reumatología, Hospital Universitario Puerta de Hierro Majadahonda, Majadahonda, Madrid, Spain*
[b] *Servicio de Reumatología, Hospital Universitario Infanta Sofía, San Sebastián de los Reyes, Madrid, Spain*
[c] *Unidad de Investigación, Sociedad Española de Reumatología, Madrid, Spain*
[d] *Unitat Territorial de Reumatología, Hospital Universitari de la Santa Creu i Sant Pau y Hospital Dos de Maig, Barcelona, Spain*
[e] *Servicio de Reumatología, Hospital Universitario de Bellvitge, L'Hospitalet de Llobregat, Spain*
[f] *Servicio de Reumatología, Hospital Marina Baixa, La Vila Joiosa, Alicante, Spain*
[g] *Servicio de Reumatología, Hospital Universitario Dr. Negrín, Las Palmas, Spain*
[h] *Servicio de Reumatología. Hospital Virgen del Puerto, Plasencia, Spain*
[i] *Servicio de Reumatología, Hospital Lucus Augusti Lugo, Lugo, Spain*
[j] *Servicio de Reumatología. Hospital Universitario de Salamanca, Salamanca, Spain*
[k] *Servicio de Reumatología, Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain*
[l] *Servicio de Reumatología, Hospital Universitario La Paz, Madrid, Spain*
[m] *Servicio de Reumatología, Hospital Clínico Universitario de Valencia, Valencia, Spain*
[n] *Servicio de Reumatología, Fundación Jiménez Díaz, Madrid, Spain*
[o] *Servicio de Reumatología, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*
[p] *Servicio de Reumatología, Hospital Universitario de Elda, Elda, Alicante, Spain*

ARTICLE INFO

Article history:
Received 10 July 2018
Accepted 31 October 2018
Available online 15 November 2019

Keywords:
Sjögren's syndrome
Biological therapy
Etanercept
Infliximab
Rituximab
Belimumab
Abatacept
Tocilizumab
Spanish Society of Rheumatology
Recommendations

ABSTRACT

Objective: To formulate SER recommendations for the use of biological agents in primary Sjögren's syndrome (pSS).
Methods: Relevant clinical research questions were identified on the use of biological agents in pSS. The clinical questions were reformulated into 4 PICO questions. A search strategy was designed and a review of the scientific evidence of studies published until May 2017 was carried out. The scientific evidence available was systematically reviewed. The overall level of scientific evidence was assessed using the SIGN evidence levels. After that, specific recommendations were made.
Results: Rituximab is recommended as the biological agent of choice for extraglandular manifestations refractory to conventional treatment. The use of anti-TNF agents is discouraged. The scientific evidence with belimumab and abatacept is scarce, so they should be considered only in cases refractory to rituximab.
Conclusions: Rituximab is the biological agent of choice in severe extraglandular manifestations of pSS. Belimumab or abatacept may be useful in selected cases.

☆ Please cite this article as: Andréu Sánchez JL, Fernández Castro M, Díaz del Campo Fontecha P, Corominas H, Narváez García FJ, Rosas Gómez de Salazar J, et al. Recomendaciones SER sobre la utilización de fármacos biológicos en el síndrome de Sjögren primario. Reumatol Clin. 2019;15:315–326.

* Corresponding author.
E-mail address: jlandreus@gmail.com (J.L. Andréu Sánchez).

Recomendaciones SER sobre la utilización de fármacos biológicos en el síndrome de Sjögren primario

Palabras clave:
Síndrome de Sjögren
Tratamiento biológico
Etanercept
Infliximab
Rituximab
Belimumab
Abatacept
Tocilizumab
Sociedad Española de Reumatología
Recomendaciones

R E S U M E N

Objetivo: Elaborar recomendaciones SER sobre el uso de agentes biológicos en el síndrome de Sjögren primario (SSp).
Métodos: Se identificaron preguntas clínicas de investigación relevantes sobre el uso de agentes biológicos en el SSp. Las preguntas clínicas se reformularon en 4 preguntas PICO. Se diseñó una estrategia de búsqueda y se realizó una revisión de la evidencia científica de estudios publicados hasta mayo de 2017. Se revisó sistemáticamente la evidencia científica disponible. Se evaluó el nivel global de la evidencia científica utilizando los niveles de evidencia del SIGN. Tras ello, se formularon recomendaciones específicas.
Resultados: Se recomienda rituximab como el fármaco biológico de elección para las manifestaciones extraglandulares refractarias al tratamiento convencional. Se desaconseja el uso de agentes anti-TNF. La evidencia científica es escasa con belimumab y abatacept, por lo que deberían considerarse solamente en los casos resistentes a rituximab.
Conclusiones: El rituximab es el fármaco biológico de elección en las manifestaciones graves extraglandulares del SSp. Belimumab o abatacept podrían ser de utilidad en casos seleccionados.

Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterised by the predominant involvement of the exocrine glands, typically the lacrimal and salivary glands. Glandular lymphoplasmocyte infiltration typically occurs, causing progressive destruction, with the consequent dysfunction of secretion and onset of dryness of the eyes, mouth and other mucous membranes. Its clinical spectrum is broad and heterogeneous; on onset and as the disease progresses multiple extraglandular manifestations, such as joint involvement, cutaneous, pulmonary, renal, nervous system and haematological involvement, among others, and certain complications, such as lymphoma can develop, which will determine prognosis.[1,2] Peripheral B lymphocyte hyperactivity is a characteristic phenomenon of the disease, with the consequent production of diverse inflammatory mediators; autoantibodies, such as rheumatoid factor (RF), antinuclear antibodies, antiRo/SSA, anti-La/SSB and the presence of hypergammaglobulinaemia.[3]

Primary Sjögren's syndrome has universal distribution and is one of the most frequent systemic autoimmune diseases, and is therefore of major social and health impact. It predominantly affects females, with a ratio of 9–10:1. The estimated incidence rate of pSS is 6.92 per 100,000 people/year (95%CI: 4.98–8.86) and its prevalence is 60.82 cases per 100,000 inhabitants (95%CI: 43.69–77.94).[4] of Primary Sjögren's syndrome is more frequent between the fourth and fifth decades of life, although onset can be at any age.[5,6]

The European-American Consensus Group (EACG) classification criteria for pSS published in 2002[7] have been the most used since they were drafted until the present day, although in 2016 new pSS classification criteria were published by consensus of the American College of Rheumatology and the European League Against Rheumatism (EULAR).[8]

PSS negatively affects the different variables of health-related quality of life domains of the Short Form Health Survey-36 (SF-36), as shown in a recent meta-analysis.[9]

The lack of disease-modifying drugs (DMARDs) of clearly demonstrated efficacy and the use of different biological agents in other systemic autoimmune diseases that share clinical manifestations and pathogenic mechanisms with pSS have determined the occasional use of biological agents "off-indication" in certain extraglandular manifestations of pSS.

This document constitutes the first consensus of the Spanish Society of Rheumatology (SER) on the use of biological treatments in patients with pSS. It includes recommendations intended to serve as a benchmark to help rheumatologists in therapeutic decision making and for all professionals from the different care and management levels involved in the treatment of patients with pSS. Due to the high cost and safety margins of biological treatment, rational and reflexive use of these drugs is necessary, based on scientific evidence and accumulated clinical experience. Biological treatment must be included in a broad therapeutic strategy that covers all possible actions, pharmacological and non-pharmacological, and that values the opinion of the patient and the sustainability of the health system.

Methods

Design

A qualitative synthesis of the scientific evidence and consensus techniques was used that gathered the agreement of experts based on their clinical experience and scientific evidence.

Phases of the process

1. *Creation of the working group.* Drafting of the document began with the constitution of a panel of experts that comprised 6 rheumatologists, who were SER members. The rheumatologists were chosen through an open call to all members. The SER Clinical Practice Guideline and Recommendations Committee assessed the curriculum vitae of all applicants according to objective criteria of contribution to knowledge on pSS. The clinical and methodological aspects were coordinated, respectively, by one of these rheumatologists, as principal investigator and a specialist in methodology from the SER Research Unit.
2. *Identification of key areas.* All the members of the working group participated in structuring the document and establishing the contents and key aspects. First, the clinical research questions that could most impact the use of biological agents in pSS were identified. The methodology of the drafting process of the recommendations was also defined.
3. *Biological search.* The clinical questions were reformulated into 4 questions in PICO format. In order to answer these questions, a search strategy was designed and a review of the scientific

evidence from studies published until May 2017 was conducted. The PubMed (MEDLINE), EMBASE and Cochrane Library (Wiley Online) databases were used. The process was completed with a manual search for references, posters and conference abstracts that the reviewers and experts considered of interest.

4. *Analysis and synthesis of scientific evidence.* Several rheumatologists, from the working group of reviewers of evidence of the SER, were in charge of systematically reviewing the available scientific evidence. The overall level of scientific evidence was assessed using the SIGN (Scottish Intercollegiate Guidelines Network) levels of evidence.
5. *Formulation of recommendations.* After the critical reading, the principal investigator and the members of the group of experts proceeded to formulate specific recommendations. This formulation was based on "formal evaluation" or "reasoned judgement", with a prior summary of the evidence for each of the clinical questions. The quality, quantity and consistency of the scientific evidence, the generality of the results, their applicability and their clinical impact were also considered. The recommendations were graded using the SIGN system (Annex 1). The recommendations were divided into 4 categories according to the available evidence: anti-TNF agents, rituximab (RTX), belimumab, abatacept and tocilizumab.
6. *Public exposure.* The draft of this SER Recommendations document was subjected to a public exposure process before members of the SER and different interest groups (pharmaceutical industry, other scientific societies and patient associations), in order to gather their evaluation and scientific argumentation on the methodology and recommendations. Full information on this process can be found in an annex on the SER website: www.ser.es, in the section on Research and SER Recommendations.

Prior considerations

Treatment of pSS currently relies principally on symptomatic agents to relieve symptoms of dryness and the use of glucocorticoids (GC), accompanied or otherwise by immunosuppressants if there is relevant systemic involvement (Annex 2). However, evidence on the efficacy of these drugs is scarce.

Therapeutic options

Most of the conventional DMARDs used in rheumatoid arthritis and systemic lupus erythematosus have been used empirically in pSS with mixed results.[10] Analgesics and non-steroidal anti-inflammatory drugs are the first line of treatment for constitutional and musculoskeletal symptoms. GC are used at low doses in arthritis that does not respond to analgesics and non-steroidal anti-inflammatory drugs, in constitutional manifestations and skin involvement, and at medium-high doses in severe extraglandular involvement. There is little evidence to support the use of GC in the treatment of glandular dysfunction in pSS.[11]

Hydroxychloroquine has been successfully used to treat musculoskeletal and constitutional symptoms, as well as non-vascular skin lesions. The use of hydroxychloroquine in pSS has been tested in several studies in recent years, with conflicting results in both glandular and extraglandular areas. In 2017 Wang et al. conducted a systematic review and meta-analysis of the efficacy of hydroxychloroquine in pSS,[12] and found superiority against placebo in the treatment of pain and reduction of erythrocyte sedimentation rate (ESR).

Methotrexate has been used in the polyarticular arthritis of pSS due to its similarity to rheumatoid arthritis, although there are no data of demonstrated efficacy at that or at glandular level.[13] Leflunomide and D-penicillamine have also been trialled in open studies.[14,15] Azathioprine at low daily doses has not shown efficacy for the symptoms, signs, serology or activity of the disease.[16] Cyclosporine-A achieved a significant improvement in oral dryness and in an old randomised clinical trial (RCT) with a small sample size (20 patients).[17] Interferon α has been tested in one RCT and achieved significant improvement in unstimulated whole salivary flow (UWSF) and in some symptoms of oral dryness.[18] In 2007, an open study evaluated the use of mycophenolate mofetil in 11 patients with pSS resistant to other immunosuppressants. Improvement was found in the symptoms of dry eye and significant improvement in laboratory parameters.[19]

Cyclophosphamide treatment is used in severely affected patients, such as glomerulonephritis, motor polyneuropathy, myelopathy, purpura or vasculitis, despite the absence of controlled studies analysing its effect. In acute and severe situations, the use of intravenous immunoglobulins and plasmapheresis is also considered.[10] There is currently no systemic therapy to modify the course of the disease that has proven effective in the treatment of the glandular manifestations of pSS, perhaps because most glandular manifestations are usually due to established damage rather than disease activity. Management is primarily based on relieving the patient's symptoms with the use of lacrimal and salivary substitutes, tear and saliva stimulating agents such as pilocarpine, and other topical alternatives for dry eye such as opthalmic GC, ophthalmic cyclosporine-A, the autologous serum, topical lifitegrast, newly approved by the Food and Drug Administration, or techniques that reduce tear loss, such as tear point occlusion, among other surgical alternatives, and amniotic membrane transplantation.[20,21] In the treatment of dry mouth, it is essential to optimise the patient's dietary habits, oral hygiene and prevent the onset of cavities, with specific products. There are other, more complex and costly alternatives, such as vibrotactile stimulation, for which the current evidence of efficacy is limited.[22]

There is no universally accepted definition of resistant pSS. It is usually understood as not having responded adequately to conventional treatment or requiring an unacceptably high chronic dose of GC to maintain remission or low disease activity status. Before deciding that a treatment is not effective, poor adherence to the treatment or the existence of accumulated damage that cannot be reversed by anti-inflammatory or immunosuppressive agents should be ruled out. The panel of experts proposes a definition of resistant pSS for each organ or system that is detailed in Annex 2.

Assessment of the disease

Tables 1 and 2 summarise the assessment tools, some not yet fully validated, of the different clinical domains in patients with pSS, and the classification criteria of the disease.

Predictive factors of progression to lymphoma or mortality

In 2015, a systematic review of the literature with a total of 15,000 patients with pSS identified lymphadenopathy, parotiditis, palpable purpura, low complement C4 levels, and cryoglobulinaemia as major predictors of the development of non-Hodgkin's lymphoma/lymphoproliferative disease. In addition, it was found that some studies also describe low complement C3 levels, lymphopenia and neutropenia as predictors. Detection of germ-like structures on minor salivary gland biopsy has also been proposed as a highly predictive factor for non-Hodgkin's lymphoma.[23] A recent study with 1045 patients indicates an increased risk of death in

Table 1
Disease assessment procedures.

Disease assessment	Subjective	Objective	Indices/questionnaires
Assessment of glandular involvement[7,8,70–74]	VAS of global dryness[a] VAS of oral dryness VAS of ocular dryness	1. Ocular involvement: Schirmer's test - Pink Bengal staining - TBUT - OSS: - Lisamine green staining - Fluorescein staining 2. Oral involvement: - USF - SSF - Minor salivary gland biopsy: FS	ESSPRI Ocular involvement: OSDI
Assessment of systemic involvement[73,75–77]	VAS of disease activity VAS of pain	- ESR -CRP	ESSPRI ESSDAI DAS28
Assessment of B lymphocyte hyperactivity		- Antinuclear antibodies - Anti-Ro - Anti-La - Impaired immunoglobulins - RF - Hypocomplementaemia - Elevated β2-microglobulin - Elevated cryoglobulins	
Assessment of fatigue	VAS of fatigue		ESSPRI PROFAD MFI
Assessment of quality of life[9]			SF-36

DAS28: Disease Activity Score; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI: EULAR Sjögren's Syndrome Patient reported index; includes 3 VAS, dryness, pain, fatigue; VAS: visual analogue scale; FS: focus score; SSF: stimulated salivary flow; USF: unstimulated salivary flow; MFI: Multidimensional fatigue inventory score; OSDI: Ocular Surface Disease Index; OSS: Ocular Staining Score, includes lisamine green and fluorescein staining; PROFAD: Profile of Fatigue and Discomfort; SF-36: Short Form Health Survey-36; TBUT: tear film break-up time.

[a] Global dryness: oral, ocular, cuteaneous, genital, bronchial.

Table 2
Criteria of the 2002 European-American Consensus Group for the classification of primary Sjögren's syndrome.

I. Ocular symptoms (a positive response to at least one of the following):
Have you had daily, persistent, dry eyes for more than 3 months?
Do you have a recurrent sensation of sand or grit in the eyes?
Do you use tear substitutes more than three times a day?

II. Oral symptoms: (a positive response to at least one of the following):
Have you had a daily feeling of dry mouth for more than 3 months?
Have you had recurrently or persistently swollen salivary glands as an adult?
Do you frequently drink liquids to aid in swallowing dry food?

III. Ocular signs (objective evidence of ocular involvement defined as a positive result for at least one of the following):
a) Schirmer's test I, performed without anaesthesia (≤5 mm in 5 minutes).
b) Rose Bengal ocular stain (score≥4, according to van Bijsterveld's scoring system)

IV. Histopathology: In minor salivary glands/obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score>1, defined as a number of lymphocytic foci (adjacent to normal-appearing mucous acini and containing more than 50 lymphocytes) per 4 mm^2 of glandular tissue

V. Salivary gland involvement (objective evidence of salivary gland involvement defined by a positive result for at least one of the following):
Unstimulated salivary flow (≤ 1.5 ml in 15 min)
Parotid sialography with diffuse sialecasias (punctate, cavitary or destructive pattern),without evidence of obstruction in the major ducts
Salivary scintigraphy showing delayed uptake, reduced concentration or delayed excretion of radio tracer

VI. Autoantibodies (presence in the serum of the following autoantibodies): anti-Ro or anti-La or both

Revised standards for classification.
Primary Sjögren's syndrome.
The patient has a positive biopsy or autoantibodies and meets a total of 4 of the 6 items (97% sensitivity; 90% specificity).
The patient meets 3 of the 4 objective criteria (i.e., groups III, IV, V, VI) (84% sensitivity 95% specificity).
Secondary Sjögren's syndrome.
Patients with a potentially associated disease (another defined connectivopathy), the presence of groups I or II plus a further 2, of groups III, IV and V, could be considered indicative of secondary Sjögren's syndrome.
Exclusion criteria.
Previous head or neck radiotherapy, HCV, HIV infection, pre-existing lymphoma, sarcoidosis, graft-versus-host disease, recent use of anticholinergic drugs.

patients with an ESSDAI (EULAR Sjögren's Syndrome Disease Activity Index) score ≥ 14.[24]

Results

The set of 6 recommendations formulated on the use of biological agents in primary Sjögren's syndrome is shown in Table 3.

Anti-tumour necrosis factor agents

In patients with pSS, what is the efficacy of anti-TNF in the treatment of ocular and oral dryness, and the systemic manifestations, including fatigue?

Recommendation. The use of anti-TNF-α drugs is not recommended in the treatment of pSS *(grade B recommendation).*

Table 3
SER recommendations on primary Sjögren's syndrome.

Recommendations	G R
Anti-TNF agents	
Recommendation: The use of anti-TNF alpha drugs in the treatment of primary Sjögren's syndrome is not recommended	B
Rituximab	
Recommendation: rituximab is recommended for patients with primary Sjögren's syndrome and clinically relevant extraglandular manifestations or parotidomegaly who have not responded to treatment with DMARDs or chemical immunosuppressants	*D*
Recommendation: rituximab could be considered for use in selected patients with clinically relevant ocular or oral dryness, resistant to conventional treatment, especially those with disease of short duration and glandular reserve	√
Belimumab	
Recommendation: The panel proposes considering the use of belimumab in selected patients with primary Sjögren's syndrome (especially patients with positive anti-Ro/SSA or anti-La/SSB antibodies, with joint involvement or parotidomegaly) in whom biological treatment is proposed and who do not respond or tolerate RTX, or for whom it is contraindicated	√
Abatacept and tocilizumab	
Recommendation: The panel proposes considering the use of abatacept in selected patients with primary Sjögren's syndrome (especially with joint manifestations) in whom biological treatment is considered and who do not respond to or tolerate rituximab, or for who it is contraindicated	√
Recommendation: Given the absence of evidence, the use of tocilizumab is not recommended for the treatment of primary Sjögren's syndrome	√

DMARDs: disease-modifying anti-rheumatic drugs; GR: grade of recommendation (see Annex 1).

TNF α, together with interleukin-1 (IL-1) and interferons α and γ, plays an important pathogenic role in the early stages of pSS. In response to an unknown antigenic stimulus, glandular epithelial cells express various cytokines that induce migration to glandular tissue of innate immune response cells that produce IL-1, TNF α and interferon.[25] This inflammatory response allows the presentation of autoantigens to Th0 lymphocytes. Based on this evidence and the excellent results obtained in other rheumatic diseases, treatment with TNF-α antagonists has been trialled in pSS.

To date, data from 2 controlled trials in pSS have been published, one with etanercept and one with infliximab, as well as other non-randomised prospective studies with these drugs.

Results with etanercept

Sankar et al.[26] evaluated the safety and efficacy of etanercept at doses of 25 mg twice a week in a double-blind, placebo-controlled RCT. Twenty-eight patients with pSS classified according to the 2002 EACG criteria, with symptoms of dryness and evidence of disease activity (arbitrarily considered as elevated ESR or hypergammaglobulinaemia) were included. They were divided into 2 groups of 14 patients. In both, 11 had pSS and 3 SS associated with other systemic autoimmune diseases, mainly rheumatoid arthritis.

The duration of the study was 12 weeks and the main outcome of efficacy was the proportion of patients achieving improvement ≥20% in 2 of the 3 domains assessed: (1) oral dryness measured by visual analogue scale (VAS) or by stimulated salivary flow (SSF); (2) eye dryness measured by VAS, Schirmer's test or van Bijsterveld score and (3) biological activity, reflected in a reduction in immunoglobulin levels or a decrease in ESR.

Three patients treated with etanercept and one who received placebo did not complete the study. At the end of the 12 weeks, no statistically significant differences were found between the groups in the main efficacy variable, in either ocular or oral dryness. In laboratory tests, a significant decrease in acute phase reactants was detected in the etanercept treated group, but not in immunoglobulin levels. No differences were observed in the other secondary efficacy variables (*level of evidence 1−*).

These results are consistent with those of another non-randomised prospective study conducted by Zandbelt et al.[27] in 25 patients, who also failed to demonstrated histological improvement on minor salivary gland biopsy after 12 weeks of treatment with etanercept. Its effect on arthritis or other extraglandular manifestations was not studied.

Results with infliximab

Mariette et al.[28] assessed the safety and efficacy of infliximab in a multi-centre, double-blind, placebo- controlled RCT in the Trial of Remicade In Primary Sjögren's Syndrome (TRIPSS). One hundred and three patients with pSS were included, classified according to 2002 EACG criteria and active disease, randomised to receive infusions of infliximab (5 mg/kg) or placebo at weeks 0, 2 and 6, with follow-up to 22 weeks.

Disease activity was assessed primarily in 3 domains: pain, fatigue and dryness, measured by VAS. The VAS of dryness included the patient's self-reported assessment of oral, ocular, cutaneous, vaginal and bronchial dryness. Active disease was defined when the score was > 50 mm in 2 of the 3 domains. The main outcome of efficacy was the proportion of patients who achieved an improvement ≥ 30% in 2 of the 3 domains assessed at week 22. Secondary variables included the number of painful and swollen joints, USF, the focus score of the labial salivary gland biopsy, Schirmer's test, quality of life measured by SF-36 questionnaire and acute phase reactant values.

At the end of the follow-up period no significant differences were observed between the groups in the principle efficacy variable, or in the domains of pain, fatigue and dryness analysed individually, or in any of the secondary efficacy variables (*level of evidence 1+).*

The results of this RCT questioned data from 2 previously published studies by Steinfeld et al.,[29,30] who highlighed a beneficial effect on glandular function, pain and fatigue after infliximab treatment. Eleven years later, the authors recanted the conclusions of their studies and acknowledged major methodological shortcomings that invalidated their results.[31]

The results of the different valid studies identified are consistent and demonstrate the inefficacy of the anti-TNF drugs assessed (etanercept and infliximab) in pSS. Therefore, the panel of experts agreed not to recommend the use of anti-TNF, since the efficacy data from RCTs have not demonstrated significant clinical benefit. The panel of experts assumes that all anti-TNF agents available on the market have similar efficacy in pSS due to their class effect and preferred to make a grade B recommendation regardless of the quality of the studies, taking into account that these were performed in patients with highly evolved disease. Furthermore, the effect of etanercept on arthritis or other extraglandular manifestations was not studied.

Rituximab

In patients with pSS, what is the efficacy of RTX in the treatment of ocular and oral dryness, and the systemic manifestations, including fatigue?

Recommendation. The use of RTX is recommended in patients with pSS and clinically relevant extraglandular manifestations

or parotidomegaly who have not responded to treatment with DMARDs or chemical immunosuppressants *(grade D recommendation)*.

Recommendation. The use of RTX could be considered in selected patients with clinically relevant ocular or oral dryness, resistant to conventional treatment, especially those with short-term disease progression and glandular reserve *(grade √ recommendation)*.

B lymphocytes are essential in the pathogenesis of pSS. B-lymphocyte hyperactivity is the consequence of the coordinated and integrated action of B-lymphocyte receptors, CD40 signals and TLR (toll-like receptor) signals in the presence of appropriate cytokines. B lymphocytes are detected in certain regions in ectopic lymphoid structures, as are dendritic cells and T lymphocytes, probably due to increased expression of ectopic chemokines, such as CXCL13 by the salivary gland epithelial cells. The scientific evidence supports the role of B lymphocytes in the development, maintenance and progression of the disease and open studies indicate the benefits of B-lymphocyte depletion in patients with pSS.[32,33] B-lymphocyte hyperactivity, salivary gland lymphocyte infiltrate and the development of B lymphocyte follicles containing germinal centre-type structures are the fundamental characteristics of the disease. It seems reasonable, therefore, to investigate the pathways available that make the B lymphocyte a target for therapeutic purposes. RTX is an anti-CD20 chimeric monoclonal anti-CD20 antibody approved for use in various immune-mediated diseases, such as rheumatoid arthritis, microscopic polyangeitis and granulomatosis with polyangeitis. RTX causes depletion of B lymphocytes.

Most of the scientific evidence found on the efficacy of RTX in pSS comes from heterogeneous studies in terms of quality, with a predominance of low-level studies that also include few patients. We have identified 2 meta-analyses, 4 RCTs, one open trial, 3 observational studies and a sub-analysis of one of the RCTs.

The first meta-analysis that assesses the efficacy and safety of RTX at 24 weeks includes 4 RCTs, with 276 patients (145 treated with RTX and 131 treated with placebo) with pSS, meeting the EACG criteria of 2000.[34] Its aim was to assess the efficacy and safety of RTX in salivary gland involvement, lacrimal gland involvement and fatigue in patients with pSS. In the studies included, of low-moderate quality of evidence, treatment with RTX resulted in improved salivary flow. However, no differences were observed at 24 weeks in parameters such as Schirmer's test, oral dryness measured by VAS, fatigue (changes in VAS of 30%), quality of life (mental component of SF-36), disease activity (measured by ESSDAI) or serious side effects *(level of evidence 1+)*.

One of the RCTs included in the meta-analysis assessed the efficacy of RTX on fatigue in 17 patients.[35] Its primary objective was to achieve a 20% improvement in the VAS of fatigue after 6 months of treatment. The patients included had to score > 50 on the fatigue scale (VAS 0–100) and be positive for anti-Ro/SSA or anti-La/SSB. They received 2 infusions of one gram of RTX, on days 1 and 15, and 100 mg methylprednisolone beforehand. Twelve patients were also treated with GC at high doses, in a tapering regimen, from 60 mg to 30 mg in the 14 days following the infusion. At 6 months after treatment, a significant improvement compared to baseline was found in the VAS of fatigue in the RTX group (mean improvement of 36.8; $P < .001$) versus placebo (P 17.3; $P = .147$). The overall assessment of the disease by VAS also improved significantly in the RTX group ($P = .021$), compared to placebo ($P = .96$). In addition, there were significant differences in the RTX group in the Profile of Fatigue and Discomfort (PROFAD) index ($P = .026$). At 6 months, significant differences were also found in the social functional score of the SF-36 ($P = .01$), in reduction of RF and in the mean decrease of immunoglobulins in the RTX group. By contrast, there were no significant differences in the glandular manifestations, in the Schirmer's test or USF *(level of evidence 1−)*.

Another RCT included in the meta-analysis, the Tolerance and Efficacy of Rituximab in Primary Sjögren's Syndrome (TEARS) study, assessed the efficacy and safety of RTX in 120 patients with active disease defined by a mean of ≥50 mm in at least 2 of the 4 VAS (global assessment of disease, pain, fatigue and dryness) and "recent" onset of the disease (<10 years), biologically active (presence of autoantibodies – anti-Ro/SSA or RF – or B lymphocyte activation markers (cryoglobulinaemia, hypergammaglobulinaemia, elevated β2-microglobulinaemia or hypocomplementaemia) or pSS with systemic involvement (at least one extraglandular manifestation, including inflammation of the parotid gland).[36] One gram of RTX was administered on two occasions, 15 days apart. The primary objective was an improvement of at least 30 mm on 2 of the 4 VAS scales at 24 weeks. No significant differences were detected between the groups at 24 weeks in the main variable. However, the proportion of patients with an improvement ≥30 mm in at least 2 of the 4 VAS was greater in the RTX group at week 6 ($P = .036$). Likewise, an improvement ≥30 mm in the VAS of fatigue was more frequent in the RTX group at week 6 ($P = .001$) and at week 16 ($P = .012$); as was an improvement in fatigue compared to baseline at week 24. Furthermore, there was a greater decrease in immunoglobulin levels (IgG, IgM, IgA) and β2-microglobulin in the RTX group. There was an increased frequency of infusional reactions. The rate of infection and severe infection was similar in the 2 groups *(level of evidence 1+)*.

The following RCT included in the meta-analysis evaluated the efficacy and safety of RTX in 30 patients (RTX *n*: 20; placebo *n*: 10) who had to have a SSF > .15 ml/min and positivity for antibodies (RF ≥ 10 IU/ml and anti-Ro/SSA or anti-La/SSB) and have undergone a minor salivary gland biopsy with typical characteristics of pSS in the previous 12 months.[37] Patients in the RTX group received 2 doses of one gram separated by 2 weeks and, beforehand, 100 mg intravenous methylprednisolone; in addition, during the 5 days after the infusion, they received oral prednisone in a tapering regimen from 60 mg to 15 mg daily. The primary objective was to assess change in overall SSF (parotid and submandibular/sublingual) at 48 weeks. The RTX group obtained significant differences in: (a) overall SSF up to week 12 ($P = .038$); (b) ocular involvement with lysamine green stain at week 24 and in the VAS of ocular dryness at weeks 24, 36 and 48 (but there was no difference in Schirmer's test result or tear break-up time); (c) subjective variables, such as the Multidimensional Fatigue Inventory score (MFI), which showed a decrease in the disease activity index from baseline to week 36 ($P = .023$) and in the motivation domain from baseline to week 12 ($P = .039$); SF-36, which showed significant improvement in the vitality domain from baseline to 36 weeks ($P = .013$) and the VAS of oral dryness (the RTX group reported improvement in dry mouth at 24, 36 and 48 weeks); (d) decrease in RF levels between 5 and 36 weeks, and in the absolute number of B lymphocytes at 5, 12, 24, 36 and 48 weeks. With regard to safety, one patient treated with RTX presented symptoms compatible with serum disease. The infection rate per 100 patients/year was 76 and 65 in the placebo group and RTX group, respectively (*level of evidence 1+*).

A prospective study in 2 centres compared the efficacy and safety of RTX against synthetic DMARDs in 41 patients (RTX *n*: 19 and placebo *n*: 22) with early pSS (defined as a maximum disease duration of 2 years) over 120 weeks.[38] The patients had to meet the EACG criteria for pSS, including the histopathological criterion, in addition to presenting active disease, defined as >50 mm for 2 out of 4 VAS (global disease activity-including extraglandular manifestations-, pain, symptoms of dryness and fatigue) and an ESSDAI ≥ 6. One of the centres included patients on RTX treatment and the other on DMARDs (hydroxychloroquine, methotrexate or cyclosporine). The patients in the RTX group received 2 doses of one gram, 15 days apart every 24 weeks (6 cycles in total). The primary objective was to assess the variation in ESSDAI and the

safety of RTX infusion. The secondary objectives included the subjective response of both treatments to fatigue, salivary and ocular secretion and the effect of RTX on the salivary biopsy at the end of the study. The RTX group behaved better than the DMARD group and achieved a significant decrease in ESSDAI and significant improvement of the subjective data measured by VAS (global disease activity, pain and physician overall assessment). The VAS of dryness and fatigue in the RTX group improved progressively from baseline until week 120; however, in the DMARD group only a slight improvement was observed until week 12. Likewise, significant improvement was seen in the Schirmer's test and USF in week 12 and a significant reduction of glandular lymphocytic infiltrate (focus score) and of germinal centres was observed in the labial biopsy at the end of the treatment. A decrease in the percentage of CXCR4+ and CXCR5+ cells was observed compared to the baseline. No differences were detected in immunoglobulin levels, antinuclear antibodies, RF, anti-Ro/SSA or anti-La/SSB. None of the patients treated with RTX had an infusional reaction or had to discontinue treatment due to side effects *(level of evidence 1−)*.

An open uncontrolled trial assessed the efficacy and safety of RTX in 8 patients with early pSS (disease duration of less than 4 years) and B-lymphocyte hyperactivity (IgG >15 g/l) and presence of antibodies (RF, anti-Ro/SSA, anti-La/SSB) and in 7 patients with MALT lymphoma and pSS.[39] The patients received 4 weekly infusions of 375 mg/m^2. The response was assessed at 5 and 12 weeks post infusion. Significant differences were detected in: (1) SSF at submandibular/sublingual level, in the patients with salivary reserve; (2) at ocular level with Rose Bengal staining and tear break up time and (c) improvement in subjective parameters: oral dryness reported by the patient, arthralgia, physical function, vitality, and in most of the MFI domains. Of the 7 patients with MALT, full remission was observed in 3 patients, stability in 3 and progression in one. In the early pSS group anti-RTX antibodies were detected in 50% and 2 patients had an infusional reaction *(level of evidence 3)*.

One retrospective study included 16 patients diagnosed with pSS according to the 2002 EACG criteria, of whom 5 presented lymphoma and 11 had systemic manifestations, with an average disease duration of 9.5 years and follow-up of 14.5 months.[40] There was subjective improvement in glandular dryness, but not in Schirmer's test result or USF. The parotidomegaly of three patients improved. Four of the 5 patients with lymphoma achieved clinical remission and 9 of the 11 patients with systemic manifestations improved. The GC dose, RF level (35% negative), ESR, C-reactive protein, gammaglobulins and β2-microglobulin levels reduced significantly, and cryoglobulins were negatively affected *(level of evidence 3)*.

Another uncontrolled retrospective study assessed the efficacy of RTX in patients with pSS and peripheral nervous system involvement in 17 patients, of whom 9 had cryoglobulinaemia or vasculitis (group 1) and 7 did not (group 2), with a mean follow-up of 33 months.[41] Eighty-eight percent received GC and the other 29% concomitant immunosuppressants. The patients of group 1 had significantly higher ESSDAI, skin involvement and hypocomplementaemia. At 3 and 6 months of treatment, significant neurological improvement was observed in 90% of the patients in group 1 and only 30% of the patients in group 2 improved. Improvement was significantly greater in multiple mononeuritis and in motor sensory neuropathy. The ESSDAI significantly decreased in group 1 and did not improve in group 2. One patient had an infusional reaction on second administration, another patient had a severe skin infection, and one patient with hypogammaglobulinaemia, treated with mycophenolate mofetil, had a cytomegalovirus infection 18 months after receiving RTX *(level of evidence 3)*.

A final retrospective study assessed the efficacy of RTX in 78 patients with pSS from a French registry, with a mean disease duration of 11.9 years and 34.9 months follow-up.[42] The indication for treatment was systemic involvement (joint, neurological, pulmonary, vasculitis, kidney, muscular, pancreatic or haematological) in 74 patients and glandular inflammation in 4. Seventeen patients received concomitant immunosuppressive treatment. After the first course of treatments improvement was observed, according to the physician's assessment, in 60% of the cases. The decrease in the median ESSDAI was significant ($P < .001$), from 11 to 7.5. Fifty-three percent were retreated with RTX, with a mean of 2.3 retreatments, at an average 11 months from the first cycle. Four patients had an infusional reaction, one patient manifested serum disease, and 3 patients had a severe infection (severe infection rate: 1.3/100 patients/year) *(level of evidence 3)*.

In a second meta-analysis, Letaief et al.[43] assessed the efficacy and safety of biological treatment in pSS and conducted a meta-analysis of 4 of the abovementioned studies.[35–37,44] Three hundred patients were included. No significant differences were observed at 24 weeks between the two groups in the assessment by VAS of fatigue and oral dryness, or salivary flow and Schirmer's test. However, the authors point out that, prior to the meta-analysis, they reconverted all the salivary flow scales to make them homogeneous and analysed them at 24 and 48 weeks. These facts may explain the differences in salivary flow from the first meta-analysis.[34] RTX was considered relatively safe versus placebo.[43]

The Trial of Anti B cell Therapy in Patients with Primary Sjogren's Syndrome (TRACTISS), published by Bowman en 2017,[44] assessed the efficacy of RTX in improving fatigue and oral dryness in 133 patients with pSS (RTX: 67 patients; placebo: 66 patients), after 2 cycles of treatment (weeks 0, 2, 24, 26). Patients with positive anti-Ro/SSA and USF > 0, and on a Likert scale >5 cm in symptoms of fatigue and worsening of oral dryness were included. There was no significant difference in the primary outcome measures: achieving an improvement of 30% in fatigue or oral dryness between the groups. Neither were there significant differences between the groups in other VAS (global dryness, ocular dryness, pain, global disease assessment), on the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), ESSDAI, SF-36 or PROFAD-SSI. A difference was observed between the groups in USF: in the patients in the placebo group deterioration over time was observed, which in the RTX group remained constant. Although this difference did not reach statistical significance ($P = .066$) by week 24, it did by weeks 36 and 48 ($P = .0103$ and $P = .0015$, respectively). No differences were found in USF or tear flow. There were 10 serious side effects in 9 patients from each group *(level of evidence 2+)*.

Fisher et al.[45] conducted a subanalysis of the TRACTISS, published in 2018, in which they evaluated 52 patients who underwent salivary gland ultrasound at baseline, 16 and 48 weeks. The patients were randomised to RTX ($n = 26$) or placebo ($n = 26$) and received an infusion at weeks 0, 2, 24 and26. Significant improvement was found in the salivary gland ultrasound after RTX compared to placebo, with an odds ratio in the RTX group of 6.8 (95% CI: 1.1–43.0; $P = .043$) in week 16 and 10.3 (95%CI: 1.0–105.9; $P = .05$) in week 48.

Sponsored by the Sjögren's Syndrome Foundation, a clinical practice guideline for the treatment of pSS[42] has recently been published. In the section on RTX, the possibility of use of the drug in xerophthalmia and xerostomia is recommended, in patients in whom salivary glandular reserve has been demonstrated, with a weak level of agreement, and in patients in whom conventional treatments have failed. However, they recommend the use of RTX, with a moderate level of agreement, in the presence of systemic manifestations: vasculitis, cryoglobulinaemia, parotidomegaly, arthritis, lung disease and peripheral neuropathy, especially multineuritis.

The drafting group took into account that the 2 meta-analyses, with low quality studies and a low number of patients, indicate that

RTX versus placebo does not significantly improve ocular dryness, fatigue or disease activity at 24 weeks in patients with pSS. However, in their meta-analysis, Souza et al.[34] indicate that salivary flow can increase at 24 weeks in patients with glandular reserve.

Nevertheless, it should be noted that none of the meta-analyses include the abovementioned study by Carubi et al.,[38] in which RTX produced significant improvement in ESSDAI (from the second infusion), Schirmer's test, salivary flow and fatigue, and also demonstrated objective improvement on labial biopsy, with reduction of focus score and germinal centres.

The drafting group considers that the results of the studies identified directly apply to our health system.

Belimumab

In patients with pSS, what is the efficacy of belimumab in the treatment of ocular and oral and systemic manifestations, including fatigue?

Recommendation. The panel proposes that the use of belimumab be considered in selected patients with pSS (especially patients with anti-Ro/SSA or anti-La/SSB, with joint involvement or parotidomegaly) in whom biological treatment is being considered and who do not respond to or tolerate RTX, or who for whom it is contraindicated *(grade √ recommendation).*

Two of the most important cytokines related to B cell survival and activation are B cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL), both members of the TNF family. BCAF, also called B-lymphocyte stimulator (BLyS), is involved in B-lymphocyte survival and humoral immune response, which plays a critical role in B lymphocyte homeostasis. BAFF plays a key role in B lymphocyte overstimulation, a fundamental characteristic of pSS. An increase of this cytokine in peripheral blood and in the salivary glands of patients with pSS has been consistently demonstrated, which also correlates with autoantibody titres.[46] High levels of BAFF have also been associated with lymphoproliferative complications of pSS[47] and could be implicated in resistance to anti-B lymphocyte therapies.[48] Belimumab is an anti-BAF monoclonal antibody that has shown efficacy in systemic lupus erythematosus, for which there is clinical experience.[49,50] Therefore, there is a rational basis for studying anti-BAFF drugs, such as belimumab, in pSS.

The scientific evidence identified to answer this clinical question is very limited. The 3 articles found correspond to the design of an experimental study with no control group or randomisation and show data from the same study[46] assessing different variables at different follow-up points: at week 28, week 52, and after discontinuing treatment.

The BELISS study assessed the efficacy and safety of belimumab in 30 patients with pSS classified according to the 2002 EACG criteria, with anti-Ro/SSA or anti-La/SSB and at least one of the following 3: (a) systemic involvement or salivary glandular inflammation, (b) early disease (<5 years of disease duration) or (c) with biomarkers of B lymphocyte activation.[51] Belimumab was administered at a dose of 10 mg/kg, in the standard regimen for systemic lupus erythematosus, up to week 24, and response was assessed at week 28. The primary objective was achieved in 60% of the patients, with significant improvement in mean ESSDAI (from 8.8 to 6.3; $P = .0015$), ESSPRI (6.4 to 5.6; $P = .0174$) and VAS of dryness (from 7.8 to 6.2; $P = .0021$). The VAS of physician assessed systemic activity improved by 43%. The objective measures of glandular function (Schirmer's and salivary flow) did not change. Ten out of 13 patients (77%) with parotid inflammation improved. A significant improvement in B lymphocyte biomarkers was also noted in 73% of the patients. Tolerance to the drug was good *(level of evidence 3).*

In an extension study, follow-up of these patients at 52 weeks showed treatment survival in 19 of the 30 patients, with a tendency to further improvement of ESSDAI and ESSPRI.[52] A significant change was observed in the mean VAS of disease activity perceived by the physician. It is worth highlighting the response obtained in the 4 patients who were non-responders at week 28. In 3 of these patients, the primary objective was achieved at week 52. In some domains, such as glandular, joint and lymphadenopathy, improvement was more noticeable. No relevant safety problems were detected *(level of evidence 3).*

It is also interesting to note that discontinuing treatment with belimumab, in a subsequent discontinuation study performed with BELISS responders, led to a worsening of ESSDAI and an increase in BAFF and serum markers (RF, IgM) in the 12 months following completion of treatment.[53] Two cases of B lymphocyte lymphoma were observed 2 years after the end of the trial *(level of evidence 3).*

A study was also identified, not included in the body of evidence because it did not specifically answer the question, which is a mechanistic analysis of the BELISS study and which indicates that in patients responding to belimumab the type-I interferon-BAFF-B lymphocyte axis predominates compared to the non-responders, in which the interferon II- NK lymphocytes axis would be predominant.[54]

The drafting group took into account the methodological limitations of the BELISS studies (no control group or randomisation and small sample size); however, controlled-randomised trials being necessary, the worsening after discontinuing belimumab strongly indicates that this biological drug is effective in pSS, and that it is unlikely that the improvement achieved in the BELISS study is attributable to the natural course of the disease.

Although BELISS included some patients with extraglandular manifestations, its low number and heterogeneity do not enable relevant conclusions to be drawn. Therefore, no data are available on the efficacy of belimumab in the extraglandular manifestations of pSS. Neither are data available on its possible usefulness as a GC sparing agent.

The results of the studies identified can be directly applied to our health system, as belimumab is routinely used in rheumatology units and services in patients with systemic lupus erythematosus.

Abatacept/tocilizumab

In patients with pSS, what is the efficacy of abatacept and tocilizumab in the treatment of ocular and oral dryness and systemic manifestations, including fatigue?

Recommendation. The panel propose considering the use of abatacept in selected patients with pSS (especially with joint manifestations) in whom biological treatment is considered and who do not respond or tolerate RTX, or for whom it is contraindicated *(grade √ recommendation).*

Recommendation. Given the lack of evidence, the use of tocilizumab for treatment of pSS is not recommended *(grade √ recommendation).*

The main pathogenic characteristics of pSS are B- lymphocyte hyperstimulation and exocrine glandular infiltration by T lymphocytes. For this reason, biological treatments targeting the T lymphocyte, such as abatacept, have also been trialled in this disease.

Another potential target in pSS is IL-6. IL-6 is a potent proinflammatory cytokine that participates in the response mediated by B and T lymphocytes. Elevated levels of IL-6 in serum, tear and saliva from pSS have been demonstrated, as well as IL-6 expression in salivary glands and corneal epithelium from these patients[55–62]; therefore there is a rational basis for trialling treatment with tocilizumab, a human monoclonal antibody targeting the IL-6 receptor, in pSS.

Abatacept

Abatacept is a fusion protein that depresses T-cell activation. The efficacy of abatacept in pSS has been evaluated in 2 proof-of-concept studies to date, with a small sample size and no control group.

The independent, prospective and open Study to Assess the efficacy and Safety of Abatacept in patients with Primary Sjögren's syndrome (ASAP) assessed the efficacy and safety of treatment with abatacept (10 mg/kg intravenously in weeks 0, 2, 4 and then every 28 days) over 24 weeks.[63] After these 6 months of treatment, there was a follow-up period of a further 24 weeks, with a total study duration of 48 weeks. Fifteen patients with pSS were included according to the 2002 EACG criteria, without prior treatment with DMARDs (except hydroxychloroquine) or other biological drugs. The patients had to have a disease duration of ≤5 years, and an SSF ≥ .10 ml/min. The mean ESSDAI score was 11 (range 8–14) and ESSPRI 7.5 (range 6–8). Treatment with GC and hydroxychloroquine was discontinued at least one month before the start of the study.

At the end of the treatment period a statistically significant decrease in ESSDAI, ESSPRI and VAS scores was observed in physician-assessed disease activity. In the ESSDAI, the greatest improvement occurred in the joint, biological, glandular and constitutional domains. In the ESSPRI, significant improvement was observed in pain and fatigue, but not in dryness. An improvement in health-related quality of life (subscale of SF-36) and a decrease in RF titres, anti-Ro52/60 antibodies and IgG levels were also documented. By contrast, no statistical differences were observed in the VAS of disease activity by the patients, or in tear function (assessed by Schirmer's test and tear film break-up time), or in salivary function (quantified by SSF and USF).

After discontinuing treatment, in week 48 the ESSDAI, ESSPRI and physician-assessed disease activity VAS scores had worsened to values similar to baseline. In addition, the RF and autoantibody titres again increased, and a slight decrease in SSF was observed ($P = .018$).

No serious side effects were observed and the safety profile was similar to that described in patients with rheumatoid arthritis *(level of evidence 3).*

A second study,[64] also independent, included 11 patients with pSS according to the 2002 EACG criteria. All the patients had undergone a minor salivary gland biopsy, had not received any previous treatment with DMARDs or other biological drugs and their treatment with GC had been discontinued 6 months previously. The duration of treatment with abatacept was also 24 weeks, with the same dosage as in the previous study. In this case, assessment of drug response focused solely on salivary gland involvement.

At the end of the 24 weeks of treatment, histological improvement was demonstrated (decrease in glandular inflammation on repeated minor salivary gland biopsy, with a reduction in the total number of lymphocytic foci and germinal centres, as well as the number of FoxP3+ regulatory T lymphocytes) and a significant increase in USF, although only when this was assessed adjusted for the duration of the disease (the shorter the duration of the pSS, the more it increased).

Regarding serology, a decrease in total immunoglobulin levels, changes in lymphocyte subpopulations in peripheral blood (decrease in effector memory population), and a reduction of lymphocyte-related cytokines (IL-21 and CXCL13) were also observed. The documented side effects were few and mild *(level of evidence 3).*

These authors subsequently published a subanalysis of this same study focused on specifically assessing the efficacy of abatacept in joint involvement.[65] Of the 15 patients with pSS included, 13 had arthritis with a baseline DAS28-ESR ≥ 3.2 (mean 4.5; interquartile range 3.9–5.9). At the end of the 24 weeks of treatment, a statistically significant improvement in DAS28-ESR levels (mean 2.4) was observed, with a standardised mean response of 1.31. The improvement in the DAS28 occurred mainly at the expense of the number of painful and swollen joints, with no evidence of a significant decrease in the values of ESR. This improvement was also reflected in the joint domain of the ESSDAI (10 patients with no activity, one with low activity and one with moderate activity at week 24). As noted above, after abatacept was discontinued, at the end of the follow-up period (week 48) a progressive worsening of joint symptoms, that returned to similar values to baseline, both in the DAS28 and in the ESSDAI (*level of evidence 3).*

In conclusion, based on the results of these preliminary studies, treatment with abatacept for 24 weeks does not result in a significant improvement in oral dryness or self-reported ocular dryness. Nor does it conclusively improve tear function, whereas salivary function can improve mildly in cases with early pSS, although the data are contradictory. It might also have a beneficial effect in preserving salivary function, given that significant histological improvement has been demonstrated after treatment, as well as an improvement in biological and serological activity.

However, it does appear to be an effective treatment to improve joint and constitutional symptoms, fatigue, disease activity and quality of life in these patients.

When evaluating these results, the limitations of these studies should not be forgotten: experimental proof-of-concept studies, with a small sample size and no control group, as well as other methodological limitations. Despite these limitations, these preliminary results have been promising enough to launch 2 phase III RCTs which are currently in the recruitment phase.[66,67] The results of the studies identified can be directly applied to our health system, since the therapeutic agent assessed is commonly used in rheumatology units and services.

Tocilizumab

No studies specifically designed to answer the clinical question were found. Only 2 observational studies on case reports of patients with refractory pneumonitis or pSS-associated neuromyelitis and describing the successful use of tocilizumab in extraglandular involvement were found. Justet et al.[68] described a case of refractory organised pneumonia with a favourable response to tocilizumab, at a dose of 8 mg/kg, which, after 8 months, showed a relevant improvement in the ESSDAI, lung function tests and high-resolution helical computed axial tomography. In addition, Komai et al.[69] described an isolated case of neuromyelitis in a patient with pSS who also responded well to tocilizumab.

In view of these results, the drafting group considers that there is no evidence to justify the use of tocilizumab in pSS and decided not to make a recommendation in this regard.

Conclusions

We present the first official SER document with recommendations on the use of biological treatment in patients with pSS. These recommendations were made through a strict and validated methodology of systematic reviews of the scientific literature and consensus techniques among the panel of experts. In addition, these are recommendations that can be directly applied to the Spanish healthcare system, as the recommended biological agents are available in our healthcare environment. The absence of cost-effectiveness studies on the use of biological agents in pSS should also be taken into account.

The systematic review of the literature highlighted the scarcity of controlled studies in the field of pSS, and therefore the recommendations are largely based on the opinion of experts. PSS is a complex disease with varied involvement and different levels of severity in each individual patient, and therefore the therapeutic

decisions in routine clinical practice and the design of clinical trials are particularly complex and difficult.

There are 2 therapeutic challenges facing the rheumatologist in managing a patient with pSS: whether to preserve or restore exocrine function, particularly tear and saliva production, and controlling the extraglandular manifestations of the disease, suppressing inflammation and recovering the patient's function and quality of life. Although there are no conclusive data on the effect of any biological drug on exocrine function, the panel of experts leaves open the possibility of using RTX in selected patients with clinically relevant ocular or oral dryness, resistant to conventional treatment, especially those with disease of short duration and glandular reserve. Likewise, the panel recommends RTX as the first biological drug that should be used to control extraglandular manifestations of clinically relevant parotidomegaly refractory to conventional treatment.

The use of anti-TNF α agents is formally discouraged, as there are 2 controlled clinical trials, one with infliximab and the other with etanercept, which did not demonstrate efficacy. Similarly, the practical absence of data on the use of tocilizumab means that the panel of experts does not recommend its use.

Both in the case of belimumab and abatacept, there is little published scientific evidence and controlled studies on the use of both agents are lacking, therefore the drugs should only be considered in cases where RTX has not been effective or there are safety problems or contraindications for their use. Certain patient profiles may require the use of one or other agent. Thus, in patients with anti-Ro/SSA or anti-La/SSB positive antibodies the use of belimumab might be favoured, whereas abatacept could be useful in patients in whom refractory polyarthritis is the indication for use of the biological drug.

The need is evident for more clinical research to guide the use of biological agents in patients with pSS. These recommendations are derived from the currently available data and should be considered an aid to decision making for the clinician who is directly involved in the care of patients with pSS. The recommendations should not be considered as restrictive rules for use but as suggestions for action, since the decision of the clinician with expertise in pSS shared with the patient must always prevail over general recommendations.

Funding

Spanish Rheumatology Foundation.

Conflict of interest

José Luis Andreu Sánchez has received funding from Abbvie, Gebro, MSD and Pfizer for course/congress attendance; fees from Abbvie, Antares, GSK, MSD, Novartis, Sanofi, and UCB for papers and has received funding from Abbvie, AstraZeneca, Biogen, Celltrion, Pfizer and Regéneron for participating in research and in a consultancy capacity for pharmaceutical or other technology companies.

Mónica Fernández Castro has received funding from Pfizer, Abbvie, MSD, UCB, Novartis, Lilly, Janssen and Roche to attend courses/congresses, as a speaker and as an expert consultant for some of the pharmaceutical companies named.

Hector Corominas Macias has received funding from Abbvie, Roche, Bristol and Pfizer for attending courses/congresses and as a speaker; MSD fees for conducting educational programmes or courses and has received funding from Abbvie for participating in research.

Francisco Javier Narváez García has received funding from Abbvie, MSD, GSK, UCB, Bristol and Roche for attending courses/congresses; fees from Abbvie, MSD, Bristol, UCB and Roche as a speaker; he has received funding from Pfizer for participating in research; and has received financial support from Roche, Abbvie and Lilly as a consultant for pharmaceutical or other technology companies.

José Rosas Gómez de Salazar has received funding from Pfizer and Abbvie for attendance at courses/congresses; fees from Pfizer, Abbvie, Bristol, Gebro, MSD and Lilly as a speaker; funding from Gebro, Jansen, Lilly and Roche for participating in research; and financial support from Abbvie for significant contribution of material to the unit or service.

Íñigo Rua-Figueroa Fernández de Larrinosa has received funding from UCB, Roche and GSK to attend courses/congresses; fees from GSK as a speaker and has received funding from UCB, Lilly and GSK for participating in research.

Acknowledgements

The group of experts of this study wish to express their gratitude to Mercedes Guerra Rodríguez, SER documentalist, for her collaboration in the search strategies for evidence and Dr. Mónica Fernández Castro and Dr. Hye Sang Park for their collaboration in the reviews of the RS reports. They would also like to thank Dr. Federico Díaz Gonzñalex, Director of the SER Research Unit, for his participation in the review of the final manuscript and for contributing to preserving the independence of this document.

Annex 1.

RBE group of evidence reviewers:

María Noelia Álvarez Rivas. Rheumatology Department, Lucus Augusti Hospital (Lugo).

Javier del Pino Montes. Rheumatology Department, University Hospital of Salamanca (Salamanca).

María Ángeles Gantes Pedraza. Rheumatology Department, Virgen del Puerto Hospital (Plasencia).

Martín Gerardo Greco Merino. Rheumatology Department, University Hospital of Gran Canaria Dr. Negrín (Las Palmas de Gran Canaria).

María Vanesa Hernández. Rheumatology Department, Hospital Universitario de Canarias, (La Cuesta, Santa Cruz de Tenerife).

Juan Alberto Paz Solarte. Rheumatology Department, Hospital Clínico Universitario de Valencia (Valencia).

Fredeswinda I. Romero Bueno. Rheumatology Department, Jiménez Díaz Foundation (Madrid).

Hye Sang Park. Rheumatology Department, Hospital de la Santa Creu i Sant Pau (Barcelona).

Miguel Ángel Abad Hernández. Rheumatology Department, Virgen del Puerto Hospital (Plasencia, Cáceres).

Félix Manuel Francisco Hernández. Rheumatology Department, Hospital Universitario de Gran Canaria Dr. Negrín (Las Palmas de Gran Canaria).

María Victoria Navarro Compán. Rheumatology Department, Hospital Universitario La Paz (Madrid).

Fran Sivera Mascaró. Rheumatology Department, Elda University Hospital (Elda, Alicante).

Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.reumae.2018.10.017.

References

1. Brito-Zeron P, Baldini C, Bootsma H, Bowman SJ, Jonsson R, Mariette X, et al. Sjogren syndrome. Nat Rev Dis Primers. 2016;2:16047.

2. Goules AV, Tzioufas AG. Primary Sjogren's syndrome: clinical phenotypes, outcome and the development of biomarkers. Immunol Res. 2017;65:331–44.
3. Fayyaz A, Kurien BT, Scofield RH. Autoantibodies in Sjogren's syndrome. Rheum Dis Clin North Am. 2016;42:419–34.
4. Qin B, Wang J, Yang Z, Yang M, Ma N, Huang F, et al. Epidemiology of primary Sjogren's syndrome: a systematic review and meta-analysis. Ann Rheum Dis. 2015;74:1983–9.
5. Ramos-Casals M, Solans R, Rosas J, Camps MT, Gil A, Del Pino-Montes J, et al. Primary Sjogren syndrome in Spain: clinical and immunologic expression in 1010 patients. Medicine (Baltimore). 2008;87:210–9.
6. Fernandez Castro M, Andreu JL, Sanchez-Piedra C, Martinez Taboada V, Olive A, Rosas J, et al. Sjogren SER: national registry of the Spanish Society of Rheumatology of patients with primary Sjogren syndrome: objectives and methodology. Reumatol Clin. 2016;12:184–9.
7. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, et al. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis. 2002;61:554–8.
8. Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, et al. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjogren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. Ann Rheum Dis. 2017;76:9–16.
9. Zhang Q, Wang X, Chen H, Shen B. Sjogren's syndrome is associated with negatively variable impacts on domains of health-related quality of life: evidence from short form 36 questionnaire and a meta-analysis. Patient Prefer Adherence. 2017;11:905–11.
10. Fernandez Castro M, Silva L, Oton T, Andreu JL. Etiologic treatment of sicca syndrome. What can the rheumatologist offer? [artículo en español]. Reumatol Clin. 2010;6 Suppl. 2:1–5.
11. Miyawaki S, Nishiyama S, Matoba K. Efficacy of low-dose prednisolone maintenance for saliva production and serological abnormalities in patients with primary Sjogren's syndrome. Intern Med. 1999;38:938–43.
12. Wang SQ, Zhang LW, Wei P, Hua H. Is hydroxychloroquine effective in treating primary Sjogren's syndrome: a systematic review and meta-analysis. BMC Musculoskelet Disord. 2017;18:186.
13. Skopouli FN, Jagiello P, Tsifetaki N, Moutsopoulos HM. Methotrexate in primary Sjogren's syndrome. Clin Exp Rheumatol. 1996;14:555–8.
14. Van Woerkom JM, Kruize AA, Geenen R, van Roon EN, Goldschmeding R, Verstappen SM, et al. Safety and efficacy of leflunomide in primary Sjogren's syndrome: a phase II pilot study. Ann Rheum Dis. 2007;66:1026–32.
15. ter Borg EJ, Haanen HC, Haas FJ, Bistervels JH, Huisman FW, Kerckhaert JA, et al. Treatment of primary Sjogren's syndrome with D-penicillamine: a pilot study. Neth J Med. 2002;60:402–6.
16. Price EJ, Rigby SP, Clancy U, Venables PJ. A double blind placebo controlled trial of azathioprine in the treatment of primary Sjogren's syndrome. J Rheumatol. 1998;25:896–9.
17. Drosos AA, Skopouli FN, Costopoulos JS, Papadimitriou CS, Moutsopoulos HM. Cyclosporin A (CyA) in primary Sjogren's syndrome: a double blind study. Ann Rheum Dis. 1986;45:732–5.
18. Cummins MJ, Papas A, Kammer GM, Fox PC. Treatment of primary Sjogren's syndrome with low-dose human interferon alfa administered by the oromucosal route: combined phase III results. Arthritis Rheum. 2003;49:585–93.
19. Willeke P, Schluter B, Becker H, Schotte H, Domschke W, Gaubitz M. Mycophenolate sodium treatment in patients with primary Sjogren syndrome: a pilot trial. Arthritis Res Ther. 2007;9. R115.
20. Ciurtin C, Ostas A, Cojocaru VM, Walsh SB, Isenberg DA. Advances in the treatment of ocular dryness associated with Sjogrens syndrome. Semin Arthritis Rheum. 2015;45:321–7.
21. Foulks GN, Forstot SL, Donshik PC, Forstot JZ, Goldstein MH, Lemp MA, et al. Clinical guidelines for management of dry eye associated with Sjogren disease. Ocul Surf. 2015;13:118–32.
22. Lopez-Pintor RM, Fernandez Castro M, Hernandez G. Oral involvement in patients with primary Sjogren's syndrome. Multidisciplinary care by dentists and rheumatologists. Reumatol Clin. 2015;11:387–94.
23. Nishishinya MB, Pereda CA, Munoz-Fernandez S, Pego-Reigosa JM, Rua-Figueroa I, Andreu JL, et al. Identification of lymphoma predictors in patients with primary Sjogren's syndrome: a systematic literature review and meta-analysis. Rheumatol Int. 2015;35:17–26.
24. Brito-Zeron P, Kostov B, Solans R, Fraile G, Suarez-Cuervo C, Casanovas A, et al. Systemic activity and mortality in primary Sjogren syndrome: Predicting survival using the EULAR-SS Disease Activity Index (ESSDAI) in 1045 patients. Ann Rheum Dis. 2016;75:348–55.
25. Kiripolsky J, McCabe LG, Kramer JM. Innate immunity in Sjogren's syndrome. Clin Immunol. 2017;182:4–13.
26. Sankar V, Brennan MT, Kok MR, Leakan RA, Smith JA, Manny J, et al. Etanercept in Sjogren's syndrome: a twelve-week randomized, double-blind, placebo-controlled pilot clinical trial. Arthritis Rheum. 2004;50:2240–5.
27. Zandbelt MM, de Wilde P, van Damme P, Hoyng CB, van de Putte L, van den Hoogen F. Etanercept in the treatment of patients with primary Sjogren's syndrome: a pilot study. J Rheumatol. 2004;31:96–101.
28. Mariette X, Ravaud P, Steinfeld S, Baron G, Goetz J, Hachulla E, et al. Inefficacy of infliximab in primary Sjogren's syndrome: results of the randomized, controlled Trial of Remicade in Primary Sjogren's Syndrome (TRIPSS). Arthritis Rheum. 2004;50:1270–6.
29. Steinfeld SD, Demols P, Salmon I, Kiss R, Appelboom T. Infliximab in patients with primary Sjogren's syndrome: a pilot study. Arthritis Rheum. 2001;44:2371–5.
30. Steinfeld SD, Demols P, Appelboom T. Infliximab in primary Sjogren's syndrome: one-year followup. Arthritis Rheum. 2002;46:3301–3.
31. Steinfeld SD, Demols P, Salmon I, Kiss R, Appelboom T. Notice of retraction of two articles («Infliximab in patients with primary Sjogren's syndrome: a pilot study» and «Infliximab in patients with primary Sjogren's syndrome: One-year followup»). Arthritis Rheum. 2013;65:814.
32. Cornec D, Devauchelle-Pensec V, Tobon GJ, Pers JO, Jousse-Joulin S, Saraux A. B cells in Sjogren's syndrome: from pathophysiology to diagnosis and treatment. J Autoimmun. 2012;39:161–7.
33. Nocturne G, Mariette X. Sjogren Syndrome-associated lymphomas: an update on pathogenesis and management. Br J Haematol. 2015;168:317–27.
34. Souza FB, Porfirio GJ, Andriolo BN, Albuquerque JV, Trevisani VF. Rituximab effectiveness and safety for treating primary Sjogren's syndrome (pSS): systematic review and meta-analysis. PLOS ONE. 2016;11, e0150749.
35. Dass S, Bowman SJ, Vital EM, Ikeda K, Pease CT, Hamburger J, et al. Reduction of fatigue in Sjogren syndrome with rituximab: results of a randomised, double-blind, placebo-controlled pilot study. Ann Rheum Dis. 2008;67:1541–4.
36. Devauchelle-Pensec V, Mariette X, Jousse-Joulin S, Berthelot JM, Perdriger A, Puechal X, et al. Treatment of primary Sjogren syndrome with rituximab: a randomized trial. Ann Intern Med. 2014;160:233–42.
37. Meijer JM, Meiners PM, Vissink A, Spijkervet FK, Abdulahad W, Kamminga N, et al. Effectiveness of rituximab treatment in primary Sjogren's syndrome: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2010;62:960–8.
38. Carubbi F, Cipriani P, Marrelli A, Benedetto P, Ruscitti P, Berardicurti O, et al. Efficacy and safety of rituximab treatment in early primary Sjogren's syndrome: a prospective, multi-center, follow-up study. Arthritis Res Ther. 2013;15. R172.
39. Pijpe J, van Imhoff GW, Spijkervet FK, Roodenburg JL, Wolbink GJ, Mansour K, et al. Rituximab treatment in patients with primary Sjogren's syndrome: an open-label phase II study. Arthritis Rheum. 2005;52:2740–50.
40. Seror R, Sordet C, Guillevin L, Hachulla E, Masson C, Ittah M, et al. Tolerance and efficacy of rituximab and changes in serum B cell biomarkers in patients with systemic complications of primary Sjogren's syndrome. Ann Rheum Dis. 2007;66:351–7.
41. Mekinian A, Ravaud P, Hatron PY, Larroche C, Leone J, Gombert B, et al. Efficacy of rituximab in primary Sjogren's syndrome with peripheral nervous system involvement: results from the AIR registry. Ann Rheum Dis. 2012;71:84–7.
42. Gottenberg JE, Cinquetti G, Larroche C, Combe B, Hachulla E, Meyer O, et al. Efficacy of rituximab in systemic manifestations of primary Sjogren's syndrome: results in 78 patients of the autoimmune and rituximab registry. Ann Rheum Dis. 2013;72:1026–31.
43. Letaief H, Lukas C, Barnetche T, Gaujoux-Viala C, Combe B, Morel J. Efficacy and safety of biological DMARDs modulating B cells in primary Sjogren's syndrome: Systematic review and meta-analysis. Joint Bone Spine. 2018;85:15–22.
44. Bowman SJ, Everett CC, O'Dwyer JL, Emery P, Pitzalis C, Ng WF, et al. Randomized controlled trial of rituximab and cost-effectiveness analysis in treating fatigue and oral dryness in primary Sjogren's syndrome. Arthritis Rheumatol. 2017;69:1440–50.
45. Fisher BA, Everett CC, Rout J, O'Dwyer JL, Emery P, Pitzalis C, et al. Effect of rituximab on a salivary gland ultrasound score in primary Sjogren's syndrome: results of the TRACTISS randomised double-blind multicentre substudy. Ann Rheum Dis. 2018;77:412–6.
46. Mariette X, Roux S, Zhang J, Bengoufa D, Lavie F, Zhou T, et al. The level of BLyS (BAFF) correlates with the titre of autoantibodies in human Sjogren's syndrome. Ann Rheum Dis. 2003;62:168–71.
47. Quartuccio L, Salvin S, Fabris M, Maset M, Pontarini E, Isola M, et al. BLyS upregulation in Sjogren's syndrome associated with lymphoproliferative disorders, higher ESSDAI score and B-cell clonal expansion in the salivary glands. Rheumatology (Oxford). 2013;52:276–81.
48. Quartuccio L, Fabris M, Moretti M, Barone F, Bombardieri M, Rupolo M, et al. Resistance to rituximab therapy and local BAFF overexpression in Sjogren's syndrome-related myoepithelial sialadenitis and low-grade parotid B-cell lymphoma. Open Rheumatol J. 2008;2:38–43.
49. Furie R, Petri M, Zamani O, Cervera R, Wallace DJ, Tegzova D, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum. 2011;63:3918–30.
50. Navarra SV, Guzman RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet. 2011;377:721–31.
51. Mariette X, Seror R, Quartuccio L, Baron G, Salvin S, Fabris M, et al. Efficacy and safety of belimumab in primary Sjogren's syndrome: results of the BELISS open-label phase II study. Ann Rheum Dis. 2015;74:526–31.
52. De Vita S, Quartuccio L, Seror R, Salvin S, Ravaud P, Fabris M, et al. Efficacy and safety of belimumab given for 12 months in primary Sjogren's syndrome: the BELISS open-label phase II study. Rheumatology (Oxford). 2015;54:2249–56.
53. Quartuccio L, Salvin S, Corazza L, Gandolfo S, Fabris M, de Vita S. Efficacy of belimumab and targeting of rheumatoid factor-positive B-cell expansion in Sjogren's syndrome: follow-up after the end of the phase II open-label BELISS study. Clin Exp Rheumatol. 2016;34:311–4.
54. Seror R, Nocturne G, Lazure T, Hendel-Chavez H, Desmoulins F, Belkhir R, et al. Low numbers of blood and salivary natural killer cells are associated with a better response to belimumab in primary Sjogren's syndrome: results of the BELISS study. Arthritis Res Ther. 2015;17:241.

55. Halse A, Tengner P, Wahren-Herlenius M, Haga H, Jonsson R. Increased frequency of cells secreting interleukin-6 and interleukin-10 in peripheral blood of patients with primary Sjogren's syndrome. Scand J Immunol. 1999;49:533–8.
56. Tishler M, Yaron I, Shirazi I, Yossipov Y, Yaron M. Increased salivary interleukin-6 levels in patients with primary Sjogren's syndrome. Rheumatol Int. 1999;18:125–7.
57. Tishler M, Yaron I, Geyer O, Shirazi I, Naftaliev E, Yaron M. Elevated tear interleukin-6 levels in patients with Sjogren syndrome. Ophthalmology. 1998;105:2327–9.
58. Grisius MM, Bermudez DK, Fox PC. Salivary and serum interleukin 6 in primary Sjogren's syndrome. J Rheumatol. 1997;24:1089–91.
59. Hulkkonen J, Pertovaara M, Antonen J, Pasternack A, Hurme M. Elevated interleukin-6 plasma levels are regulated by the promoter region polymorphism of the IL6 gene in primary Sjogren's syndrome and correlate with the clinical manifestations of the disease. Rheumatology (Oxford). 2001;40:656–61.
60. Szyszko EA, Brokstad KA, Oijordsbakken G, Jonsson MV, Jonsson R, Skarstein K. Salivary glands of primary Sjogren's syndrome patients express factors vital for plasma cell survival. Arthritis Res Ther. 2011;13. R2.
61. Sugaya S, Sakimoto T, Shoji J, Sawa M. Regulation of soluble interleukin-6 (IL-6) receptor release from corneal epithelial cells and its role in the ocular surface. Jpn J Ophthalmol. 2011;55:277–82.
62. Benchabane S, Boudjelida A, Toumi R, Belguendouz H, Youinou P, Touil-Boukoffa C. A case for IL-6, IL-17A, and nitric oxide in the pathophysiology of Sjogren's syndrome. Int J Immunopathol Pharmacol. 2016;29:386–97.
63. Meiners PM, Vissink A, Kroese FG, Spijkervet FK, Smitt-Kamminga NS, Abdulahad WH, et al. Abatacept treatment reduces disease activity in early primary Sjogren's syndrome (open-label proof of concept ASAP study). Ann Rheum Dis. 2014;73:1393–6.
64. Adler S, Korner M, Forger F, Huscher D, Caversaccio MD, Villiger PM. Evaluation of histologic, serologic, and clinical changes in response to abatacept treatment of primary Sjogren's syndrome: a pilot study. Arthritis Care Res (Hoboken). 2013;65:1862–8.
65. Moerman RV, Arends S, Meiners PM, Vissink A, Spijkervet FK, Kroese FG, et al. Detailed analysis of the articular domain in patients with primary Sjogren syndrome. J Rheumatol. 2017;44:292–6.
66. A study to assess the efficacy and safety of abatacept in adults with active primary. Sjogren's syndrome. Available from: https://clinicaltrials.gov/ct2/show/NCT02915159 [accessed 28.12.17].
67. Randomized D-b, placebo-controlled phase III study to assess the efficacy and safety of abatacept in patients with primary Sjögren's syndrome (ASAP III Study, Abatacept Sjögren Active Patients Phase III Study). Available from: https://clinicaltrials.gov/ct2/show/NCT02067910 [accessed 28.12.17].
68. Justet A, Ottaviani S, Dieude P, Taille C. Tocilizumab for refractory organising pneumonia associated with Sjogren's disease. BMJ Case Rep. 2015, http://dx.doi.org/10.1136/bcr-2014-209076.
69. Komai T, Shoda H, Yamaguchi K, Sakurai K, Shibuya M, Kubo K, et al. Neuromyelitis optica spectrum disorder complicated with Sjogren syndrome successfully treated with tocilizumab: a case report. Mod Rheumatol. 2016;26:294–6.
70. Seror R, Ravaud P, Mariette X, Bootsma H, Theander E, Hansen A, et al. EULAR Sjogren's Syndrome Patient Reported Index (ESSPRI): development of a consensus patient index for primary Sjogren's syndrome. Ann Rheum Dis. 2011;70:968–72.
71. Fisher BA, Jonsson R, Daniels T, Bombardieri M, Brown RM, Morgan P, et al. Standardisation of labial salivary gland histopathology in clinical trials in primary Sjogren's syndrome. Ann Rheum Dis. 2017;76:1161–8.
72. Guellec D, Cornec D, Jousse-Joulin S, Marhadour T, Marcorelles P, Pers JO, et al. Diagnostic value of labial minor salivary gland biopsy for Sjogren's syndrome: a systematic review. Autoimmun Rev. 2013;12:416–20.
73. Seror R, Bootsma H, Saraux A, Bowman SJ, Theander E, Brun JG, et al. Defining disease activity states and clinically meaningful improvement in primary Sjogren's syndrome with EULAR primary Sjogren's syndrome disease activity (ESSDAI) and patient-reported indexes (ESSPRI). Ann Rheum Dis. 2016;75:382–9.
74. Wolffsohn JS, Arita R, Chalmers R, Djalilian A, Dogru M, Dumbleton K, et al. TFOS DEWS II Diagnostic Methodology report. Ocul Surf. 2017;15:539–74.
75. Hammitt KM, Naegeli AN, van den Broek RWM, Birt JA. Patient burden of Sjogren's: a comprehensive literature review revealing the range and heterogeneity of measures used in assessments of severity. RMD Open. 2017;3, http://dx.doi.org/10.1136/rmdopen-2017-000443, e000443.
76. Seror R, Bowman SJ, Brito-Zeron P, Theander E, Bootsma H, Tzioufas A, et al. EULAR Sjogren's syndrome disease activity index (ESSDAI): a user guide. RMD Open. 2015;1, http://dx.doi.org/10.1136/rmdopen-2014-000022, e000022.
77. Seror R, Theander E, Brun JG, Ramos-Casals M, Valim V, Dorner T, et al. Validation of EULAR primary Sjogren's syndrome disease activity (ESSDAI) and patient indexes (ESSPRI). Ann Rheum Dis. 2015;74:859–66.