REVISTA BRASILEIRA DE REUMATOLOGIA

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SOCIEDADE BRASILEIRA DE REUMATOLOGIA

Review article

Recommendations for the treatment of Sjögren's syndrome☆

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http://dx.doi.org/10.1016/j.rbre.2015.08.002

ARTICLE INFO

Article history:
Received 29 March 2015
Accepted 23 July 2015
Available online 8 September 2015

Keywords:
Sjögren's syndrome
Treatment
Recommendations
Guidelines
Systematic review

ABSTRACT

The recommendations proposed by the Sjögren's Syndrome Committee of the Brazilian Society of Rheumatology for the treatment of Sjögren's syndrome were based on a systematic review of literature in Medline (PubMed) and the Cochrane databases until October 2014 and on expert opinion in the absence of studies on the subject. 131 articles classified according to Oxford & Grade were included. These recommendations were developed in order to guide the management and facilitate the access to treatment for those patients with an appropriate indication, considering the Brazilian socioeconomic context and pharmacological agents available in this country.

Recomendações para o tratamento da síndrome de Sjögren

Palavras-chave:
Síndrome de Sjögren
Tratamento
Recomendações
Diretrizes
Revisão sistemática

RESUM

As recomendações propostas pela Comissão de Síndrome de Sjögren da Sociedade Brasileira de Reumatologia para tratamento da síndrome de Sjögren foram baseadas em uma revisão sistemática da literatura nas bases de dados Medline (PubMed) e Cochrane até outubro de 2014 e opinião de especialistas na ausência de artigos sobre o assunto. Foram incluídos 131 artigos classificados de acordo com Oxford & Grade. Essas recomendações foram elaboradas com o objetivo de orientar o manejo adequado e facilitar o acesso aos tratamentos para aqueles pacientes com adequada indicação de recebê-los, considerando o contexto socioeconômico brasileiro e os medicamentos disponíveis no país.

Introduction

Sjögren's syndrome (SS) is a relatively common autoimmune rheumatic disease, which is most common in women in the fifth decade of life.[1] According to a Brazilian population study, the prevalence of primary SS is 0.17%.[2] SS can occur in association with other autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) in variable rates, up to 22.2% in patients with RA.[3,4]

SS is a slowly progressive chronic disease, characterized by a lymphocytic infiltrate that affects the epithelium of exocrine (mainly salivary and tear) glands, leading to a decreased production of tears and saliva. This is a systemic disease with high risk of transformation to lymphoma that primarily affects the joints, lungs, central nervous system (CNS), peripheral nervous system (PNS) and kidneys in approximately 50% of patients.[5]

More recent studies have shown that there are subgroups of patients with different clinical manifestations, histological patterns (presence of germinative centers), cytokine profile and prognosis.[6,7] In the near future, better genetic[8–10] and phenotypic characterization will be able to determine different treatment patterns. But nowadays it is possible to define treatment strategies based on symptoms (symptomatic treatment), and on the type and severity of systemic manifestations. These guidelines recommend the use of EULAR Sjögren's Syndrome Disease Activity (ESSDAI), a tool validated both internationally[11] and in Brazil,[12] as criteria for disease activity and response to treatment.

These recommendations were developed in order to guide the management and facilitate the access to treatment for those patients with an appropriate indication, considering the Brazilian socioeconomic context and pharmacological agents available in the country. Due to the length of this review, specific topics such as management during pregnancy and treatment of lymphoma associated with SS were not addressed. The recommendations were based on studies on primary Sjögren's syndrome. Considering the lack of studies in patients with association with other autoimmune diseases, these recommendations can be extrapolated to secondary Sjögren's syndrome.

Materials and methods

Articles were reviewed in MEDLINE (PubMed) and the Cochrane databases until December 2013. The manual update was held in October 2014. The search strategy was based on structured questions according to PICO (i.e. "Patient", "Intervention", "Controls" and "Outcome") format. These descriptors were used for cross-searching in accordance with the theme proposed in each of PICO questions. For all PICOs, the filter "random" was used, limiting the search to controlled studies. Studies published from January to October 2014 and some case series on extraglandular manifestations were manually included. After analyzing titles and abstracts, 131 articles related to questions that generated the evidence that provided the basis for these guidelines were selected (Fig. 1). The studies

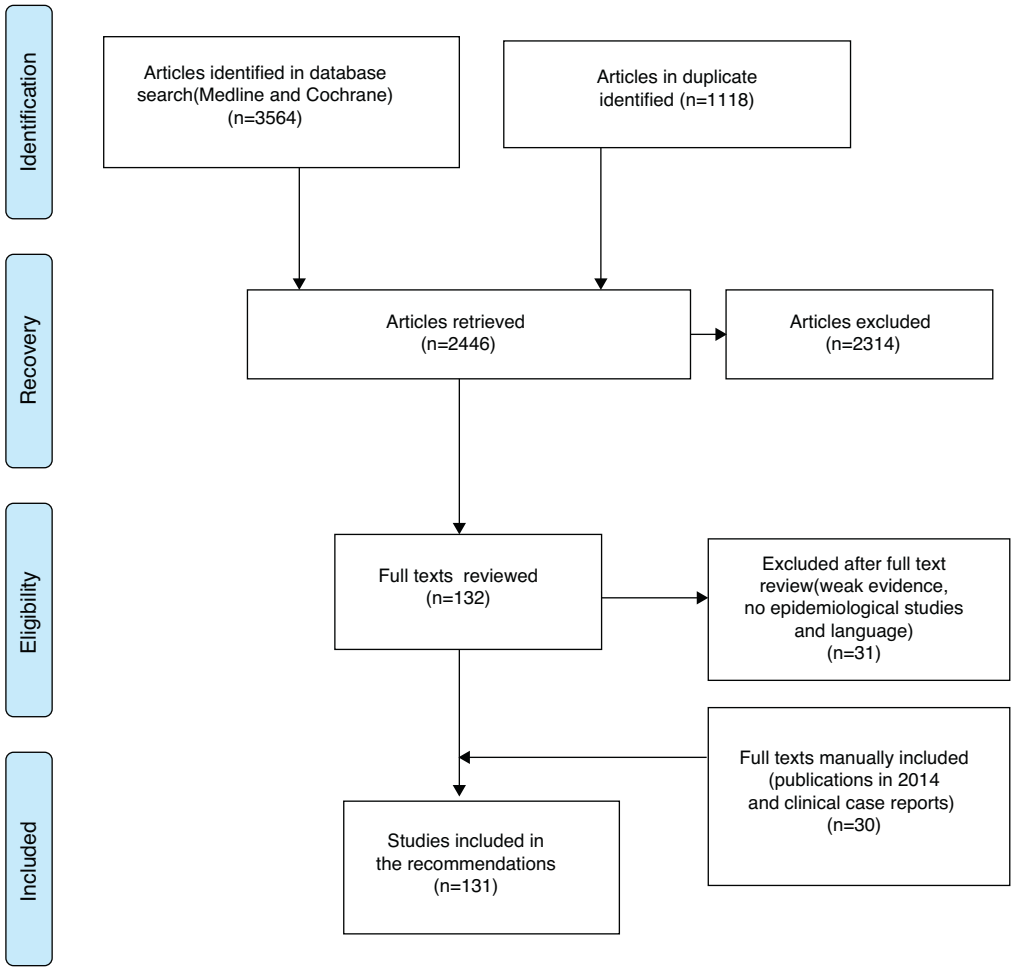

Fig. 1 – Flow diagram of the selection of evidence for Sjögren's syndrome treatment.

were classified according to Oxford & GRADE in degrees of recommendation and strength of evidence as follows:

A: Experimental or observational studies of better consistency.
B: Experimental or observational studies of lower consistency.
C: Case reports (non-controlled studies).
D: Opinion devoid of a critical evaluation, based on consensus, physiological studies, or animal models.

Some recommendations were based solely on the opinion of experts from the Sjögren's Syndrome Scientific Committee of the Brazilian Society of Rheumatology (BSR), in the absence of studies on subjects. These recommendations were also graded as a D level and are not preceded by the reference.

PICOs were structured by a multidisciplinary team that was comprised of nine rheumatologists, members of the Sjögren's Syndrome Scientific Committee of BSR, with eight professionals from different areas (dentists, ophthalmologists, pathologists and physiotherapists); all were members of the Expanded Study Group on Sjögren's Syndrome (*Grupo Ampliado de Estudos em Síndrome de Sjögren* – GAESS – Brazil). The recommendations were formulated mainly based on evidence and reviewed by all participants at two meetings and several rounds of communication via the Internet, from April 2013 until October 2014.

Recommendations

Based on those 14 PICOs used in this survey, we organized didactically 16 questions with 44 recommendations, divided into three major topics and summarized in Figs. 2–5:

Part 1. General and patient education recommendations.
Part 2. Symptomatic management of dryness.
Part 3. Systemic treatment for glandular and systemic manifestations.

Part 1. General and patient education recommendations

Q1. What are the general recommendations based on expert opinion?

1. The management of SS must be performed by a multidisciplinary team including at least a rheumatologist, a dentist and an ophthalmologist. The rheumatologist is the reference specialist in the management of SS **(D)**.

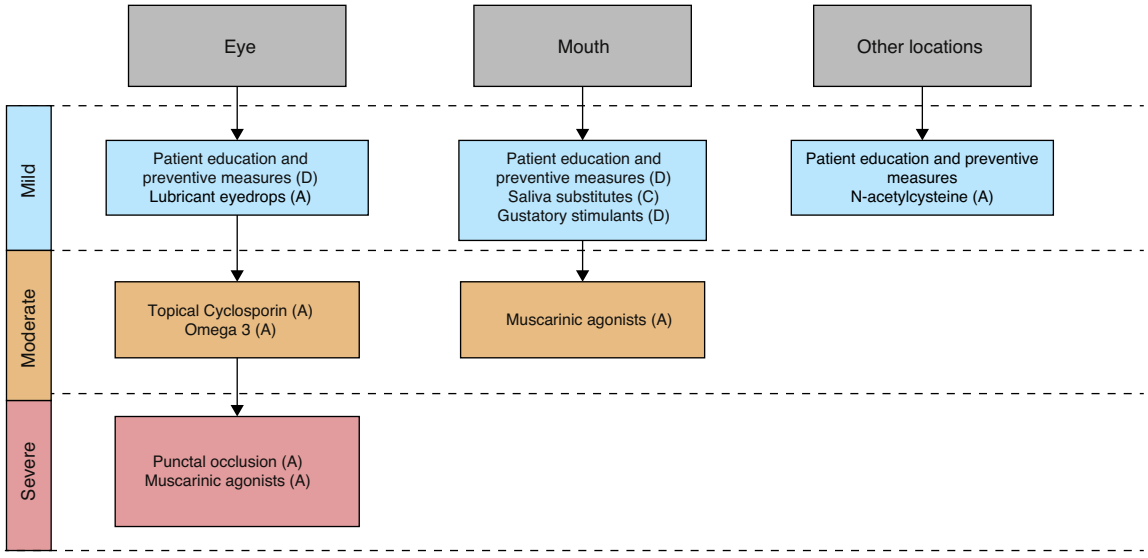

Fig. 2 – Flowchart for the symptomatic treatment of dryness of SS.

2. Patients with early diagnosis and improved glandular reserve show a better response to treatment **(D)**.
3. It is recommended that treatment strategies of systemic manifestations are stratified according to disease severity, based not only on clinical impression of the specialist, but also with the use of ESSDAI. Systemic treatment should be instituted in the face of a moderate ESSDAI (≥5). A response to treatment was considered where a decrease of ESSDAI ≥3 points was detected **(D)**.
4. Patients with SS should avoid the use of caffeinated drinks, alcohol and tobacco **(D)**.
5. It is recommended that patients receive general education for hygiene and measures to prevent dehydration and irritation of mucous membranes (Table 1) **(D)**.

Q2. Exercise is effective in treating patients with SS?

6. Women with SS have a lower physical ability,[13] and the practice of aerobic exercise at moderate to high intensity leads to the improvement of aerobic capacity, fatigue, perceived exertion and depression.[14] **(B)**

Q3. What are the effectiveness and safety of vaccines in patients with SS?

7. It is recommended that general guidelines for vaccination in patients with autoimmune diseases are followed[15] **(C)**, and the vaccination status of the patient must be checked at the patient baseline assessment. It is also recommended

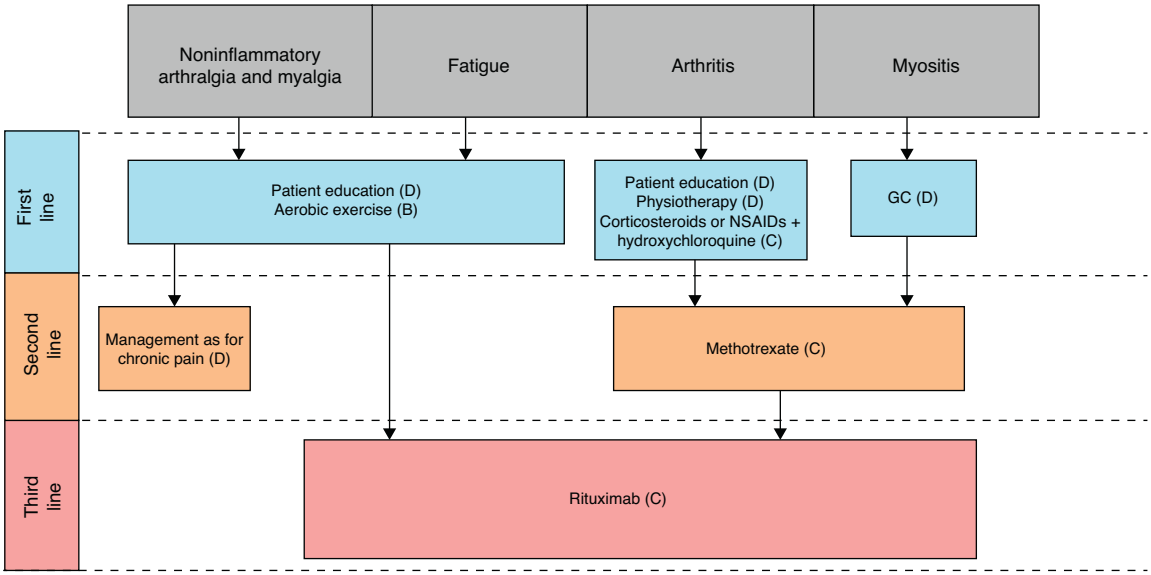

Fig. 3 – Flowchart for the treatment of musculoskeletal symptoms. NSAIDs, non-steroidal anti-inflammatory drugs; GC, glucocorticoids.

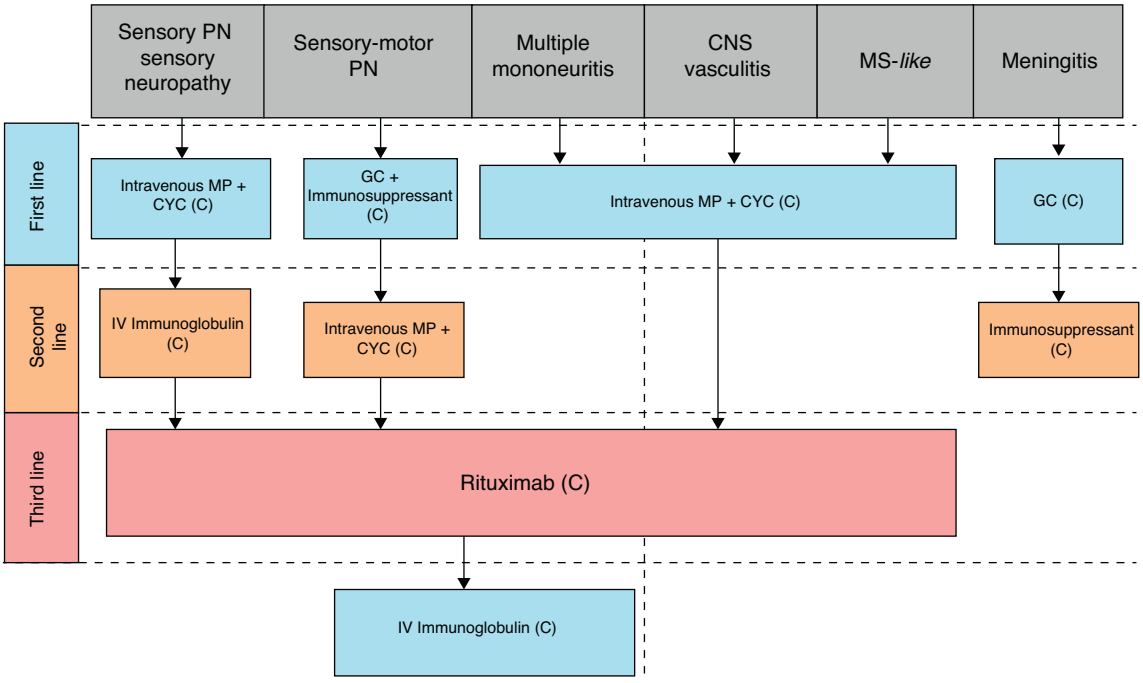

Fig. 4 – Flowchart for the treatment of neurological systemic manifestations. PN, peripheral polyneuropathy; CNS, central nervous system; MS, multiple sclerosis; GC, glucocorticoids; MP, methylprednisolone; CYC, cyclophosphamide.

to administer vaccines in stable periods of the disease; live attenuated vaccines should be avoided. Immunization against influenza[16,17] **(A)** and *Pneumococcus* are indicated,[18] **(A)** with application of other vaccines according to the immunization schedule **(D)**.

Q4. SS patients should receive supplementation with vitamin D?

8. Vitamin D deficiency should be investigated and, if necessary, its supplementation should be instituted[16–23] **(C)**.

Part 2. Symptomatic management of dryness

Q5. What is the topical treatment for dry mouth?

9. Saliva substitutes improve comfort[24–31] **(C)** and ideally should contain fluoride, bactericides and buffered solutions that help to combat biofilm, the formation of caries and candidiasis[32] **(D)**.
10. Mechanical and/or chemical gustatory stimulating agents, for instance, hard candies and sugar-freechewing

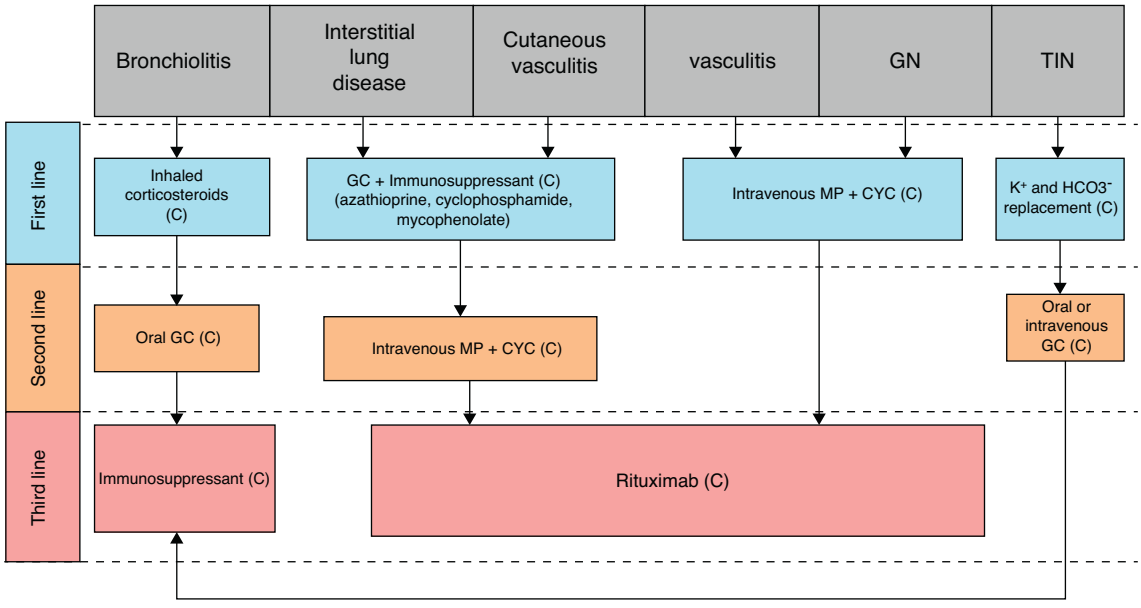

Fig. 5 – Flowchart for the treatment of systemic kidney, lung and vasculitis manifestations. GN, glomerulonephritis; TIN, tubulointerstitial nephritis; GC, glucocorticoids; MP, methylprednisolone; CYC, cyclophosphamide.

Table 1 – Patient education: measures for hygiene and hydration of mucous membranes.

SS patients should be encouraged to drink fluids frequently, preferably water.
SS patients should be informed that tobacco, caffeine and various medications such as diuretics, beta blockers, antidepressants and anxiolytics, are known causes of dryness and can worsen the glandular symptoms.
To prevent tear evaporation, the patient must avoid dry environments, air conditioning, wind, and also activities that decrease eye blinking, such as using the computer or reading for a long period of time.
Patients with symptomatic dry eye should use environment humidifiers, and glasses with side shields during exposure to wind or when practicing outdoor sports.
Preventive measures for oral health aim to control biofilm, caries, loss of teeth and oral candidiasis. For this purpose, it is important to maintain a good oral hygiene, keeping intraoral pH (basic) with the use of buffers and restricting consumption of sugar.
Careful oral hygiene includes the same recommendations for the general population, with special attention to prosthesis hygiene and choosing less abrasive products, avoiding products that increase dryness of the mucosa, for example, toothpastes containing sodium lauryl sulfate and the use of alcohol-containing mouth rinse.
Removable total dental prosthesis users should daily cleaned their dentures using a dental brush with stiff bristles with toothpaste, switching to a soft bristles brush for oral mucosa cleaning. Once a week, the prosthesis must be immersed in an aqueous solution containing 1% sodium hypochlorite solution during 30 min; then the prosthesis should be rinsed in running water. One can obtain this concentration of sodium hypochlorite by diluting a tablespoon of chlorine bleach in a glass containing 300 mL of filtered water.

gum,[32] **(D)** may be helpful. Solutions or mouthwashes containing malic acid, fluoride and xylitol have similar efficacy to traditional stimulating agents containing citric acid, but with the advantage of maintaining a less acid pH.[33] **(B)**

Q6. What is the topical treatment for dry eye?

11. The frequent use of lubricant eyedrops containing glucans or carboxymethylcellulose improves comfort and functional tests[34–40] **(A)**. These eyedrops should be preservative-free, hypotonic, higher colloidal osmolality products.[37,41] **(A)** Gel formulations are of longer duration and generate greater relief, but may cause temporary blurred vision.
12. Topical cyclosporin 0.05% bid for 6–12 weeks is effective for symptomatic and functional improvement of dry eye[42–56] **(A)**. The occurrence of eye irritation is common; thus, this drug is recommended at the lowest effective concentration (0.05%)[55] **(A)**.
13. Topical glucocorticoids can be used for the most symptomatic cases[57,58] **(A)** for a limited period, because of the risk subcapsular cataract, glaucoma and infection[34] **(D)**. Non-steroidal anti-inflammatory drugs (NSAIDs) must not be routinely used, due to the high risk of corneal perforation[59,60] **(D)**.
14. Lacrimal puncta occlusion improves symptoms and outcomes of ocular tear tests. This strategy is superior to lubricant eyedrops, and is indicated in severe cases refractory to topical treatment with eyedrops[61–65] **(A)**.

Q7. What are the effectiveness and safety of muscarinic agonists and mucolytics in systemic symptomatic treatment of dryness?

15. Muscarinic agonists such as pilocarpine (5 mg bid, qid) and cevimeline (30 mg, tid), are more beneficial in the symptomatic treatment of dry mouth[66–69] **(A)**, but they may also be useful in treating moderate to severe[41] **(D)** dry eye[66,67,69–73] **(A)**.
16. It is recommended that the dose and the range of pilocarpine be adjusted as tolerated[66,67] **(A)**.
17. Although not available in Brazil, cevimeline is the safest muscarinic agonist, with lower rates of side effects and of treatment discontinuation, thanks to a more selective action on M3 receptors[74,75] **(C)**.
18. The most frequent side effect of muscarinic agonists is sweating[69,72,74] **(A)**. One should be aware of the contraindications for the use of muscarinic agonists, especially pilocarpine, in asthma and cardiac disease patients[41] **(D)**.
19. The mucolytic agent N-acetylcysteine, at a dose of 200 mg tid, may be an option for muscarinic agonists in patients with intolerance, and also in patients with dryness in other places, such as the skin, vagina and airways[76] **(A)**.

Q8. What are the effectiveness and safety of supplementation with fatty acids in patients with SS?

20. Supplementation of fatty acids (omega-3) can be used, since this is a low-risk intervention and promotes the improvement of symptoms and of functional dry eye tests, although the results have been controversial in different studies[77–82] **(A)**.

Part 3. Systemic treatment for glandular and systemic manifestations

Q9. What are the effectiveness and safety of hydroxychloroquine and immunosuppressants in the treatment of patients with SS?

21. There is no evidence of significant improvement in glandular symptoms with the use of hydroxychloroquine in SS. However, there is improvement of laboratory and inflammatory parameters[83–90] **(A)**.
22. There is no evidence for the use of systemic immunosuppressants in treating symptoms of dryness. While some open and controlled studies have shown improvement in laboratory and inflammatory parameters, a high frequency of adverse events precluded their use for dry syndrome[91–98] **(B)**.
23. The choice of immunosuppressive drug treatment for systemic manifestations will depend on the affected organ and severity[60] **(D)**.

Q10. What are the effectiveness and safety of biologic therapies in the treatment of patients with SS?

24. Anti-TNF therapy is not indicated for the treatment of glandular or systemic manifestations of SS[99–102] **(A)**.
25. Rituximab is effective in improving many manifestations in SS, as glandular involvement **(A)**, fatigue **(A)**, disease activity **(C)**, immunological parameters **(A)**, glandular lymphocytic infiltration, systemic manifestations, and quality of life[103–105]
26. Rituximab is not indicated as sole treatment of the symptoms of dryness. This drug is a therapeutic option for systemic manifestations that failed conventional treatment[103–106] **(C)**. By clinical criteria, in selected cases, rituximab can be considered for serious and specific glandular manifestations, such as refractory parotiditis[62] **(D)**.
27. Abatacept[106–109] **(C)** and belimumab[110] **(C)** are promising drugs to improve disease activity, immunological profile and quality of life. These drugs can be considered in the treatment of SS in refractory cases and with high systemic disease activity.

Q11. What is the treatment of articular manifestations, myositis and fatigue in patients with SS?

28. Initial treatment of arthritis resulting from SS can be carried out with hydroxychloroquine, with or without low doses of glucocorticoids or NSAIDs for symptomatic relief[83] **(C)**. In case of treatment failure with hydroxychloroquine, this drug can be replaced or associated with methotrexate[60,96] **(D)**. In those rare refractory cases under an optimal methotrexate dosage, the use of rituximab is recommended[106] **(C)**.
29. Myositis characterized by weakness, elevated creatine kinase (CK) and electroneuromyographic changes should initially be treated with prednisone. In those rare refractory cases, methotrexate is recommended **(D)**.
30. Noninflammatory pattern arthralgia with diffuse pain in the absence of myositis should be treated as a painful amplification syndrome, with analgesia and exercise, with attention to the potential risk of worsening of dryness, caused by a pharmacological adverse effect **(D)**.
31. The treatment of fatigue includes the prescription of aerobic exercise of moderate to high intensity [14] **(B)**, and a proper management of the underlying disease. Different classes of drugs have been tested and have not proved to be effective or safer, because they have unacceptable rates of adverse events, such as dehydroepiandrosterone (DHEA)[111] **(A)**, fatty acids[82] **(A)**, hydroxychloroquine[89,90] **(A)**, azathioprine[94] **(A)**, leflunomide[97] **(A)**, mycophenolate[98] (A) and anti-TNF agents[102] **(A)**. At the discretion of the clinician, rituximab[103–105,112] **(A)** may be a therapeutic option, considering the evidence of inflammation and the impact on functional capacity and quality of life.

Q12. What is the treatment of neurological manifestations in the peripheral nervous system in patients with SS?

32. For the treatment of PNS involvement, the combination of high-dose glucocorticoids (with subsequent tapering) and an immunosuppressant (azathioprine, cyclophosphamide, mycophenolate) is recommended[60,113,114] **(C)**.
33. Patients with mononeuritis multiplex should start a scheme of intravenous methylprednisolone and cyclophosphamide[113] **(C)**.
34. Patients with ataxic polyneuropathy and sensory ganglioneuronopathy have poorer responses to all treatments[113] **(C)**. Therefore, for these patients, the association of IVIG to the therapeutic regimen with glucocorticoids and immunosuppressive drugs is recommended, in an attempt to achieve a better clinical response[115] **(C)**.
35. When no clinical improvement is observed in the initial treatment, rituximab is recommended[116] **(C)**. Patients with vasculitis and cryoglobulinemia have better responses to rituximab[116] **(C)**.
36. IVIG is a therapeutic option for all types of PNS involvement, when previous schemes failed[115,117,118] **(C)**.
37. Plasmapheresis should be reserved for severe cases refractory to all previous measures, since no studies were published justifying its routine use[119] **(C)**.

Q13. What is the treatment of neurological manifestations in the central nervous system in patients with SS?

38. For the treatment of CNS involvement, a combination of glucocorticoids and cyclophosphamide at high doses is recommended[113,120–124] **(C)**. In the face of no clinical improvement, rituximab is recommended[60,125] **(C)**.
39. Subacute febrile aseptic meningitis can be treated initially solely with glucocorticoids, depending on the clinical condition[122] **(C)**.

Q14. What is the treatment of pulmonary (parenchymal and lower airways) manifestations in patients with SS?

40. In the presence of symptomatic interstitial pulmonary disorder, treatment with glucocorticoids plus an immunosuppressive agent (azathioprine or cyclophosphamide) is recommended[126–129] **(C)**. Mycophenolate mofetil is an option in refractory cases or in those patients with contraindication to other immunosuppressive agents[130] **(C)**. Rituximab may be considered in refractory cases of interstitial pneumonia, and overtreatment of fibrotic changes related to the sequel should be avoided[106] **(C)**.
41. Bronchiolitis respiratory tract manifestations may be mild, justifying only the use of inhaled and/or systemic corticosteroid therapy[131] **(C)**. Immunosuppressive drugs should be according to specialist opinion[60] **(D)**.

Q15. What is the treatment of glomerular and tubulointerstitial renal manifestations in patients with SS?

42. Considering clinician opinion high-dose glucocorticoids might be indicated, with or without association with other immunosuppressive agents[132–137] **(C)**.
43. In GNs, intravenous methylprednisolone in association with cyclophosphamide is recommended[132,133] **(C)**. Azathioprine and cyclosporine may be options in mild to

moderate cases[132] (C). Rituximab should be considered in refractory cases[106,132,137] (C).

Q16. What are the effectiveness and safety of drug therapy in the treatment of vasculitis in patients with SS?

44. The recommended treatment for vasculitis, regardless of the organ involved, is immunosuppression with high-dose intravenous methylprednisolone for three days, in combination with immunosuppressants (azathioprine, mycophenolate mofetil, or cyclophosphamide); cyclophosphamide has been the most commonly used immunosuppressant[138–141] (C). Treatment of cutaneous vasculitis may be initially carried out with an oral glucocorticoid (0.5–1 mg/kg/day) or with intravenous methylprednisolone (depending on the severity of the condition) plus an immunosuppressant. Cases refractory to initial treatment can be treated with rituximab[142,143] (C).

Funding

Brazilian Society of Rheumatology.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

The authors acknowledge Walber Vieira Pinto (President of SBR in the biennium 2012-2014) and César Emile Baaklini (President of SBR in the biennium 2014-2016), for supporting the development of these guidelines.

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