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# Equal rights in autoimmunity: is Sjögren`s syndrome ever ‘secondary’?

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## **Abstract**

Sjögren's syndrome (SjS) accompanied by other systemic autoimmune rheumatic connective tissue diseases has historically been termed 'secondary' in contrast to 'primary' SjS as a standalone entity. However it is a matter of a long-standing debate whether the prefixes 'primary' and 'secondary', notably including a temporal component, are obsolete in the terminology of SjS. We review the history and the pathophysiological, chronological, genetic, histological and clinical data underlying the concept of 'secondary' SjS. There are important unintended consequences of the nomenclature; notably 'secondary' SjS has been much less researched and is often excluded from clinical trials. We argue for further research, a change in terminology and more stringent classification. Further we highlight possible opportunities for trials in SjS and other systemic autoimmune diseases that might contribute to an advance in care for all patients with SjS.

## **Keywords**

Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, clinical trials, anti-Ro antibodies, genetics, histology, salivary glands

## **Key messages**

- Evidence underlying a distinction between 'primary' and 'secondary' SjS is uncertain
- 'Secondary' SjS is much less researched and often excluded from trials
- Inclusion of 'secondary' SjS, and analysis of SjS outcomes in non-SjS trials, could provide therapeutic insights

## Introduction

The occurrence of more than one autoimmune disease, which has been termed polyautoimmunity, is very common in Sjögren's syndrome (SjS), affecting approximately one third of patients. [1]. SjS accompanied by systemic lupus erythematosus (SLE), systemic sclerosis (SSc), or rheumatoid arthritis (RA) has historically been termed 'secondary' in contrast to 'primary' SjS as a standalone entity. However it is a matter of a long-standing debate whether the prefixes 'primary' and 'secondary', notably including a temporal component, are obsolete in the terminology of SjS, with the Sjögren's Syndrome Foundation recently arguing for a single, unifying definition [2]. Furthermore, there are important unintended consequences of the nomenclature; notably 'secondary' SjS has been much less researched and is often excluded from clinical trials.

Former classification criteria for SjS handled this controversy in different ways (see Table 1). Interestingly enough, the initial classification of SjS in 1965 included patients who subsequently would have been largely classified as 'secondary': 'keratoconjunctivitis sicca, xerostomia and rheumatoid arthritis or other connective tissue disease' [3]. The most recent specific classification criteria for secondary SjS were published in 2002 by the American-European Consensus Group (AECG) [4]. Remarkably, neither antibodies against SSA/Ro or SSB/La, nor a corresponding histopathology were necessary to classify 'secondary' SjS; whereas for primary SjS a positive serology or histopathology were defined as *sine qua non* [4]. The provisional American College of Rheumatology (ACR) classification criteria, published in 2012, advocated abandoning the terminology 'secondary' and 'primary' and to employ the same criteria for all patients including those with another systemic autoimmune disease; however, they excluded patients with SLE, RA, SSc, or other connective tissue diseases from their analysis [5]. The current classification criteria, published in 2016, are completely focused on 'primary' SjS, based on the argument that patients with 'secondary' SjS are typically not eligible for clinical trials [6] (for classification criteria see Table 1).

In order to clarify the pros and cons of this terminology and the consequences for clinical trials and future treatment opportunities, it is necessary to step back and to revisit how this terminology evolved.

## Arguments for a distinction between 'primary' and 'secondary' SjS examined

### Pathophysiology

Historically the term 'secondary' SjS arose from a concept of chronically 'pre'-activated lymphocytes causing nonspecific and antigen independent infiltration of the salivary and lacrimal glands, which were thought to be prone for a breach in immune tolerance (reviewed in [7, 8]). Firstly, this was based on the fact that patients with chronic graft-versus-host disease

(cGvHD) after allogeneic bone marrow transplantation can develop sicca symptoms, with histopathological changes of the salivary glands that show some similarity to SjS, but in the absence of autoantibodies [9]. A recent study investigating 101 patients with cGvHD, showed that sicca symptoms occur in approximately 70% of cases, with only one patient being positive for anti-SSA/Ro autoantibodies. Minor salivary gland histology was analyzed in 36 of these patients, revealing some similarities but considerably less lymphocyte infiltration and more fibrosis than one might expect in SjS [10]. Notably, there was no direct comparison to SjS histopathology in this study. However, as differences could be observed on a gross histopathological level, it seems possible that further differences between the pathophysiology of these entities might be shown if more detailed cellular and transcriptomic approaches to tissue analysis were to be utilised.

### Chronology

Related to the concept above, the prefix 'secondary' was based on data showing that, in patients with concomitant RA and SjS, the SjS most commonly developed after the onset of RA. In 1978 Moutsopoulos and colleagues reported that in 16 out of 21 patients the onset of RA predated the diagnosis of SjS (*by 2-40 years*) [11]. In a more recent study investigating 74 patients with RA and SjS 62.2% (n=46) were diagnosed with RA first and 21.6% (n=16) with SjS [12]. Notably, there might be a considerable bias underlying these observations as sicca symptoms alone may not trigger a clinical visit as effectively as RA-related joint pain and there is a well-recognised delay in the diagnosis of SjS. Furthermore, for SjS/SLE it has been shown that in 18 out of 26 patients (69.2%) SjS preceded the onset of SLE (*-4 years, range: -15 to +3*) [13]. Therefore SjS antedates the diagnosis of RA or SLE in a considerable proportion of patients; rendering the chronological justification for the current terminology of 'secondary' SjS debatable.

### Genetics

In 1979 genetic differences between SjS and SjS/RA were employed to support the sub-classification into 'primary' and 'secondary' SjS [11]. Thus, a higher prevalence of HLA-B8, HLA-DR3, and HLA-Dw2 and a lower prevalence of HLA-DR4 have been found in Caucasian patients with SjS as compared to patients with SjS associated to RA [14, 15]. In comparison to SLE or RA, genetic studies in SjS are in their infancy. However, there are common factors in HLA and non-HLA genes overlapping between RA and SjS, and between SLE and SjS especially [16]; e.g. female predominance in all three disorders, X chromosomal abnormalities described for SLE and SjS [17, 18], familial aggregation, and promising candidate genes like STAT4 and IRF5, which may be relevant in both SLE and SjS [19, 20]. When focusing on the differences between patients with SjS associated with SLE, RA, or SSc, and patients with SjS

alone, genetic studies are rare and considerably complicated by the genetic overlap between these diseases. However similarities have been suggested for SjS/SLE and SjS as shown by the high frequency of HLA-DR3 in both subsets [13]. On the basis of this limited evidence for genetic differences between SjS and SjS/RA, and also in the light of the strong overlap of genetic abnormalities particularly in SLE and SjS as single entities, and autoimmune diseases in general – also known as autoimmune tautology [21] – it is hard to justify a dichotomous nomenclature separating SjS from SjS associated to any systemic autoimmune disease on genetic reasons alone. Indeed, genome-wide pairwise-association analyses suggest a closely shared genetic susceptibility between SjS and SSc, and to a lesser extent between SjS and SLE [22].

### Histology

More recently, histopathological differences have been reported between SjS and SjS associated with SLE and SSc. Although most patients with SjS/SLE showed the typical periductal infiltrates as observed in SjS, some patients exhibited perivascular infiltrates, which were correlated with the presence of anti-cardiolipin antibodies suggesting an antiphospholipid-associated vasculopathy [13]. In patients with SjS associated with SSc and a history of pregnancy with a male baby, male DNA could be found in salivary gland cells. In contrast, patients with SjS alone did not show this microchimerism [23]. However, microchimerism has been frequently observed in SSc and may be a part of its pathogenesis. Overall similarities seem to outweigh differences between gland histopathology in SjS versus SjS associated to SLE or SSc, particularly when taking into account case ascertainment bias [13, 23, 24], albeit more detailed molecular and cellular studies are lacking. Moreover, the observed differences in the histopathology of ‘primary’ and ‘secondary’ SjS may be mainly related to an overlap of disease manifestations when occurring in the context of other autoimmune diseases, rather than a fundamental difference in SjS pathogenesis. Notably, sicca manifestations in SSc may arise through a primary fibrotic process or through SjS, the latter being associated with limited cutaneous SSc and anti-centromere antibodies [25]. Thus an overlap of these features might be possible especially in established disease, but this observation also emphasizes the importance of biopsy for correct classification.

### Serology

The sub-classification of ‘primary’ and ‘secondary’ SjS was also based on the serological differences which were first reported in 1979, showing a lower frequency of anti-Ro/SSA and anti-La/SSB antibodies in SjS/RA patients [8]. Notably, these differences are highly dependent on the classification criteria employed (see also Table 1); and could not be confirmed in recent studies, which revealed no differences between patients with SjS and SjS/RA regarding the

prevalence of anti-Ro/SSA antibodies, anti-La/SSB antibodies, ANAs, or hypergammaglobulinaemia [12]. Also for SjS associated with SLE, no differences have been found in the prevalence of anti-Ro/SSA, anti-La/SSB, or RF when compared to SjS alone, whereas anti-dsDNA and anti-cardiolipin antibodies were more frequent, but did not differ between patients with both SjS and SLE and SLE alone [13]. Although anti-La/SSB antibodies seemed to be lower in SjS/SSc as compared to SjS there were no statistically significant differences in the prevalence of autoantibodies between SjS and SjS/SSc reported [26]. To summarize, the autoantibody profile between patients with SjS alone and those with an accompanying systemic autoimmune disease seems to be very similar.

### Clinical Phenotype

The 'primary/secondary' sub-classification was originally based on differences between the clinical SjS phenotype in SjS and SjS/RA patients, showing that patients with SjS alone had a higher frequency of parotitis, Raynaud's phenomenon (RP), purpura, lymphadenopathy, myositis, and renal involvement [11]. Recently, these differences could not be entirely confirmed (Table 2), showing no differences for lymphadenopathy, renal involvement, or RP. However, an increased prevalence of rash and parotid gland enlargement has been reported in SjS alone, and a higher incidence of interstitial lung disease (ILD) and arthritis in SjS/RA [12]. Accordingly, patients with SjS/RA revealed a higher EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI), presumably due to RA-related arthritis (although features due to another disease should not be calculated) and also to the higher prevalence of ILD, which was considered to be associated with both SjS and RA [12]. In patients with SjS/SSc the SjS phenotype was similar to SjS as standalone entity [26], whereas patients with SjS/SLE showed a higher prevalence of RP, arthritis, and central nervous system involvement, and a lower frequency of lymphadenopathy, whereas there were no differences for lymphopenia, myositis, purpura, peripheral nervous system, lung, or kidney involvement, when compared to SjS alone [13].

Interestingly, the presence of SjS may also have an impact upon the phenotype of the associated autoimmune disease. Accordingly, it has been shown that SSc is rather mild, with a lower frequency of lung fibrosis when compared to SSc without SjS [26]. Also for SjS/SLE a milder SLE phenotype has been demonstrated, showing a lower prevalence of renal involvement, thrombocytopenia, and lymphadenopathy, but a higher frequency of RP [13]. It is well-known that patients with SjS normally do not develop bone erosions in contrast to patients with SjS/RA or RA [27]. However, in a study comparing 85 patients with SjS/RA to 744 patients with RA alone, it has been shown that patients with SjS/RA had higher levels of joint damage as measured by the Sharp score irrespective of RA disease duration, age, or seropositivity [28]. Another study comparing 435 patients with RA to 74 patients with SjS/RA showed that

patients with SjS/RA are characterized by more systemic complications and a higher disease activity score 28 (DAS28) [12].

Taken together, the SjS phenotype may differ between patients with SjS as a standalone entity and patients with an additional systemic autoimmune disease, but also the other systemic autoimmune disease differs when associated with SjS (see Table 2). These differences seem to be mainly attributable to an overlap of the symptomatology, but there might also be factors linked to involved pathways and underlying genetics in distinct subsets. Notably, patient numbers in all these studies are small, and thus, the significance of differences or similarities may change when investigating larger cohorts. However, SLE, SSc, and RA influence the clinical presentation of SjS in diverse ways, which makes it difficult to justify an overarching and oversimplified dichotomous sub-classification for SjS rather than speaking about SjS 'in association' with the other autoimmune disease. This doesn't imply that the associated autoimmune diseases should be neglected, neither from a clinical nor from a scientific perspective, but on the contrary, the second autoimmune disease should be emphasized by including both disease names in the nomenclature.

'Secondary' SjS can be overshadowed by the associated systemic autoimmune disease and is often judged as secondary in terms of disease severity also. However, this can be misleading as SjS-related symptoms have an important impact upon quality of life [29, 30]. Moreover, a recent study analyzing quality of life in RA, SLE and SjS, revealed that patients with SjS have the lowest levels in certain domains of the 36-Item Short Form Health Survey (SF-36) (vitality, social function) and the second lowest levels after SSc in the total score of the Short Form Six-Dimensional health index (SF-6D) and three-level version of the EuroQol Five-Dimensional descriptive system (EQ-5D-3L) [31]. This shows that SjS should not be under-estimated in comparison to other systemic autoimmune diseases and, in certain patients, quality of life might even be determined by so called 'secondary' SjS. However, when symptoms of the associated autoimmune disease predominate, or in the case of severe systemic features related to the associated autoimmune disease, then management of that disease should take priority and guide initial therapeutic choices, taking SjS into account as a stratifying factor when such evidence becomes available (see above).

### **Implications for Clinical Trials**

#### **Sjögren's trials**

Classification is relevant to clinical trials and, in particular, approvals for new therapies in SjS. One could ask whether drugs which might get approval for 'primary' SjS (according to the new classification criteria [6]) will also be licensed and funded by payers for patients with 'secondary' SjS. This question hasn't ever been raised for RA, where none of the approved



therapies are linked to the presence or absence of SjS; but, in RA trials patients with concomitant SjS were not generally excluded. The issue is complicated by the arguably less stringent classification criteria being applied to 'secondary' as opposed to 'primary' SjS.

Given the observed similarities and current absence of a robust distinction between 'primary' and 'secondary' SjS, from an equality perspective it doesn't seem reasonable to exclude patients with 'secondary' SjS from new therapies which might in future be available. However, as regulatory bodies might have to analyze this soon in detail, there is a compelling case to further understand disease pathogenesis in patients with SjS associated with other systemic autoimmune disease. Furthermore, the issue of clinical trials highlights a pragmatic argument for distinguishing between 'primary' and 'secondary' SjS given the perceived difficulties of studying disease outcomes in the presence of co-morbid autoimmune diseases and the concomitant medications associated with them. This is especially true given that the primary outcome in most current SjS trials is the EULAR Sjögren's syndrome Disease Activity Index (ESSDAI). This is primarily a measure of systemic disease activity incorporating 12 domains, several of which could be influenced by disease activity arising from the concomitant autoimmune disease. Whilst the relative importance of this could be debated given that many drugs currently under investigation target pathways of relevance to multiple autoimmune diseases, it could make interpretation of data more challenging. However, even within 'primary' disease the pathogenic mechanisms underlying the various extraglandular manifestations may differ, and in a few cases it is unclear whether they should be attributed to SjS or to another co-existent disease; an example of this is transverse myelitis, long-considered a rare central nervous system manifestation of SjS, but which has now been associated with the presence of anti-aquaporin 4 antibodies, raising the question of whether its occurrence is more likely due to concomitant neuromyelitis optica, rather than to SjS [29, 30]. Nevertheless, including patients with SjS associated with another autoimmune rheumatic disease in SjS clinical trials would require careful attention to outcome measures, classification of cases and statistical modeling. A focus of such a trial could be on glandular and symptomatic outcomes, and indeed dryness and fatigue may have more impact upon health-related quality of life than systemic disease activity [31, 32]. A second important barrier is the use of concomitant medications for the associated autoimmune disease and such a trial may not be suitable for all experimental therapies or at all stages of development.

### Non-Sjögren's trials

The opportunities of focusing on both autoimmune diseases in clinical trials has been impressively shown by a recent *post-hoc* analysis of the EMBODY trials, investigating the effectiveness of epratuzumab, targeting CD22, in SLE patients [33]. Although these large phase III trials did not demonstrate any overall efficacy of epratuzumab for SLE, the authors

could retrospectively show a significant reduction of disease activity and biological activity in the subgroup of SLE patients with associated SjS. They concluded that differences in B cell biology may account for the observed effect in SjS/SLE as compared to SLE alone [33]. Even back in the era of gold therapy in RA, differences between patients with RA alone and those with associated anti-SSA/Ro antibodies have been shown by increased skin side effects in the latter [34, 35]. Moreover, it has been shown that anti-Ro antibodies in RA are associated with a poorer clinical response to infliximab (n=111) [36]. Clinical trials of anti-TNF therapy (etanercept, infliximab) in SjS showed no clinical benefit [37, 38] but rather a tendency towards rising immunoglobulins [37]. Indeed, plasma from etanercept treated SjS patients showed higher IFN $\alpha$  activity, which correlated with the rise in IgG, as well as higher levels of B cell activating factor (BAFF) [39].

This, together with other data [40, 41], points to a counter-regulatory role of TNF $\alpha$  on type I IFN mediated pathology in SjS and raises the question of whether in some patients with RA and SjS, anti-TNF may have lesser efficacy or might exacerbate sicca symptoms. Other than the lower response rate to rituximab seen in RA patients who are autoantibody negative, there are no clinically useful biomarkers guiding treatment decisions in RA. The possibility of concomitant SjS being another such biomarker to help personalize treatment in RA should be further explored. Assessing SjS endpoints alongside those of the associated autoimmune disease might facilitate drug development; one example of this is the ROSE trial, where treatment with abatacept showed effects not only for RA but also for SjS endpoints (saliva volume, Schirmer's test) [42]. Again, however, such an approach would require careful attention to classification and endpoints.

Nevertheless it seems like we have missed multiple opportunities in former RA, SLE, and SSc trials, either to separately assess subgroups associated to SjS to examine for differential efficacy in these subsets; or even to measure SjS related outcomes, like sicca symptoms or tear and saliva production, in patients with associated SjS, as a signpost towards possible efficacy in SjS itself. Only in the last few years has there been a welcome upsurge in clinical trials for SjS, but thousands of patients with SjS will have received novel therapeutics in the context of trials for their associated autoimmune disease, but with no assessment of the effects on SjS.

## **Conclusion**

SjS is associated with other systemic autoimmune diseases, which impacts the SjS systemic phenotype, mainly due to an overlap of disease manifestations, but which may also alter the phenotype of the associated autoimmune disease. There is, however, remarkably little evidence to substantiate a difference in glandular pathology between patients with and without

an associated autoimmune rheumatic disease. From a chronological perspective it seems that SjS might predate RA, SSc, and SLE in a considerable proportion of patients, and doesn't always come 'second'.

The consequences of the 'primary' and 'secondary' nomenclature has been that SjS associated with other autoimmune diseases has been under-recognised, under-researched and possibly under-treated, with the very real risk that such patients will be left-behind by current progress in drug development and consequently have their future therapeutic options curtailed.

Furthermore we have missed potential SjS-relevant therapeutic insights from past drug development for the associated autoimmune diseases, and left unexplored the possibility that SjS itself may be a biomarker to help select choice of therapy for the associated rheumatic autoimmune disease.

The focus of SjS research on 'primary' disease has to a large extent been pragmatic given the perceived complexities of studying SjS in the presence of other autoimmune diseases. Ultimately, the suggestion that the phenotype and responsiveness to treatment of the associated autoimmune disease may be different in the presence of SjS, supports current efforts to investigate a molecular stratification of rheumatic autoimmune disease, rather than relying on 20<sup>th</sup> century phenotypic classifications. In future we might be treating pathogenic pathways or individual autoimmune manifestations e.g. arthralgia or interstitial lung disease, rather than overarching and outmoded diagnostic labels. It has been suggested, for example, that the importance of the type I interferon pathway in several autoimmune connective tissue diseases such as SjS and SLE might allow us to define a subset of such patients with 'acquired type I interferonopathy'. However, we believe that more evidence is required before such a classification is possible, as for example, it has been shown that hydroxychloroquine down-regulates the interferon signature and improved laboratory abnormalities, but was not associated with clinical improvement in either European League against Rheumatism (EULAR) Sjögren's Syndrome disease activity index (ESSDAI) or EULAR Sjögren's Syndrome patient reported index (ESSPRI) [43]. Although there is an opportunity to stratify clinical trials by this pathway, it is still not clear whether [type I IFN alone is sufficient to characterize patients in a way that is meaningful in regard to](#) targeted therapies and personalized medicine.

Further research into the pathogenesis of SjS in the presence or absence of an associated autoimmune disease should be encouraged. In tandem, the use of classification criteria pertaining to 'secondary' SjS should be reviewed, to make such comparisons rigorous and meaningful. However, until clear evidence of a distinction in glandular pathogenesis is produced, we suggest abandoning the term 'secondary' SjS in favour of SjS (in association

with). This would not only emphasize the associated autoimmune disease by including it into the nomenclature, but also give due regard to SjS when associated with other autoimmune diseases. Autoimmune diseases sometimes come in baskets, and we could take this opportunity to evaluate new drug candidates in a more efficient way.

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### **Competing interests**

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## References

1. Amador-Patarroyo, M.J., et al., *Sjögren's syndrome at the crossroad of polyautoimmunity*. Journal of Autoimmunity, 2012. **39**(3): p. 199-205.
2. Hammitt, K.M., et al., *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**(2): p. e000443.
3. Bloch, K.J., et al., *Sjogren's syndrome. A clinical, pathological, and serological study of sixty-two cases*. 1965. Medicine (Baltimore), 1992. **71**(6): p. 386-401; discussion 401-3.
4. Vitali, C., 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**(6): p. 554-8.
5. Shiboski, S.C., et al., *American College of Rheumatology classification criteria for Sjogren's syndrome: a data-driven, expert consensus approach in the Sjogren's International Collaborative Clinical Alliance cohort*. Arthritis Care Res (Hoboken), 2012. **64**(4): p. 475-87.
6. Shiboski, C.H., 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**(1): p. 9-16.
7. *Primary and secondary Sjogren's syndrome*. Lancet, 1984. **2**(8405): p. 730-1.
8. Moutsopoulos, H.M., et al., *Sjogren's syndrome (Sicca syndrome): current issues*. Ann Intern Med, 1980. **92**(2 Pt 1): p. 212-26.
9. Gratwohl, A.A., et al., *Sjogren-type syndrome after allogeneic bone-marrow transplantation*. Ann Intern Med, 1977. **87**(6): p. 703-6.
10. Imanguli, M.M., et al., *Salivary gland involvement in chronic graft-versus-host disease: prevalence, clinical significance, and recommendations for evaluation*. Biol Blood Marrow Transplant, 2010. **16**(10): p. 1362-9.
11. Moutsopoulos, H.M., et al., *Differences in the clinical manifestations of sicca syndrome in the presence and absence of rheumatoid arthritis*. Am J Med, 1979. **66**(5): p. 733-6.
12. He, J., et al., *Characteristics of Sjogren's syndrome in rheumatoid arthritis*. Rheumatology (Oxford), 2013. **52**(6): p. 1084-9.
13. Manoussakis, M.N., et al., *Sjogren's syndrome associated with systemic lupus erythematosus: clinical and laboratory profiles and comparison with primary Sjogren's syndrome*. Arthritis Rheum, 2004. **50**(3): p. 882-91.
14. Moutsopoulos, H.M., et al., *Genetic differences between primary and secondary sicca syndrome*. N Engl J Med, 1979. **301**(14): p. 761-3.
15. Manthorpe, R., et al., *HLA-D antigen frequencies in Sjogren's syndrome. Differences between the primary and secondary form*. Scand J Rheumatol, 1981. **10**(2): p. 124-8.
16. Cobb, B.L., et al., *Genes and Sjogren's syndrome*. Rheum Dis Clin North Am, 2008. **34**(4): p. 847-68, vii.
17. Liu, K., et al., *X Chromosome Dose and Sex Bias in Autoimmune Diseases: Increased Prevalence of 47,XXX in Systemic Lupus Erythematosus and Sjogren's Syndrome*. Arthritis Rheumatol, 2016. **68**(5): p. 1290-1300.
18. Sharma, R., et al., *Rare X Chromosome Abnormalities in Systemic Lupus Erythematosus and Sjogren's Syndrome*. Arthritis Rheumatol, 2017. **69**(11): p. 2187-2192.
19. Korman, B.D., et al., *Variant form of STAT4 is associated with primary Sjogren's syndrome*. Genes Immun, 2008. **9**(3): p. 267-70.
20. Nordmark, G., et al., *Additive effects of the major risk alleles of IRF5 and STAT4 in primary Sjogren's syndrome*. Genes Immun, 2009. **10**(1): p. 68-76.
21. Anaya, J.M., *The autoimmune tautology. A summary of evidence*. Joint Bone Spine, 2017. **84**(3): p. 251-253.

22. Li, Y.R., et al., *Meta-analysis of shared genetic architecture across ten pediatric autoimmune diseases*. Nat Med, 2015. **21**(9): p. 1018-27.
23. Aractingi, S., et al., *Presence of microchimerism in labial salivary glands in systemic sclerosis but not in Sjogren's syndrome*. Arthritis Rheum, 2002. **46**(4): p. 1039-43.
24. Hernandez-Molina, G., et al., *Similarities and differences between primary and secondary Sjogren's syndrome*. J Rheumatol, 2010. **37**(4): p. 800-8.
25. Avouac, J., et al., *Systemic sclerosis-associated Sjogren's syndrome and relationship to the limited cutaneous subtype: results of a prospective study of sicca syndrome in 133 consecutive patients*. Arthritis Rheum, 2006. **54**(7): p. 2243-9.
26. Salliot, C., et al., *Sjogren's syndrome is associated with and not secondary to systemic sclerosis*. Rheumatology (Oxford), 2007. **46**(2): p. 321-6.
27. Tsampoulas, C.G., et al., *Hand radiographic changes in patients with primary and secondary Sjogren's syndrome*. Scand J Rheumatol, 1986. **15**(3): p. 333-9.
28. Brown, L.E., et al., *Clinical characteristics of RA patients with secondary SS and association with joint damage*. Rheumatology (Oxford), 2015. **54**(5): p. 816-20.
29. Birnbaum, J., et al., *Relationship Between Neuromyelitis Optica Spectrum Disorder and Sjogren's Syndrome: Central Nervous System Extraglandular Disease or Unrelated, Co-Occurring Autoimmunity?* Arthritis Care Res (Hoboken), 2017. **69**(7): p. 1069-1075.
30. Sofat, N. and P.J. Venables, *Is Sjogren myelopathy Devic disease?* Ann Rheum Dis, 2008. **67**(5): p. 730-1.
31. Lendrem, D., et al., *Health-related utility values of patients with primary Sjogren's syndrome and its predictors*. Ann Rheum Dis, 2014. **73**(7): p. 1362-8.
32. Miyamoto, S.T., V. Valim, and B.A. Fisher, *Health-related quality of life and costs in Sjogren's syndrome*. Rheumatology (Oxford), 2019.
33. Gottenberg, J.E., et al., *Efficacy of Epratuzumab, an Anti-CD22 Monoclonal IgG Antibody, in Systemic Lupus Erythematosus Patients with Associated Sjogren's Syndrome: Post-hoc Analyses from the EMBODY Trials*. Arthritis Rheumatol, 2018.
34. Tishler, M., et al., *Anti-Ro (SSA) antibodies in rheumatoid arthritis patients with gold-induced side effects*. Rheumatol Int, 1997. **17**(4): p. 133-5.
35. Tishler, M., et al., *Anti-Ro(SSA) antibodies in patients with rheumatoid arthritis--a possible marker for gold induced side effects*. J Rheumatol, 1994. **21**(6): p. 1040-2.
36. Matsudaira, R., et al., *Anti-Ro/SSA antibodies are an independent factor associated with an insufficient response to tumor necrosis factor inhibitors in patients with rheumatoid arthritis*. J Rheumatol, 2011. **38**(11): p. 2346-54.
37. Mariette, X., 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**(4): p. 1270-6.
38. Sankar, V., et al., *Etanercept in Sjogren's syndrome: a twelve-week randomized, double-blind, placebo-controlled pilot clinical trial*. Arthritis Rheum, 2004. **50**(7): p. 2240-5.
39. Mavragani, C.P., et al., *Augmented interferon-alpha pathway activation in patients with Sjogren's syndrome treated with etanercept*. Arthritis Rheum, 2007. **56**(12): p. 3995-4004.
40. Batten, M., et al., *TNF deficiency fails to protect BAFF transgenic mice against autoimmunity and reveals a predisposition to B cell lymphoma*. J Immunol, 2004. **172**(2): p. 812-22.
41. Palucka, A.K., et al., *Cross-regulation of TNF and IFN-alpha in autoimmune diseases*. Proc Natl Acad Sci U S A, 2005. **102**(9): p. 3372-7.
42. Tsuboi, H., et al., *Efficacy and safety of abatacept for patients with Sjogren's syndrome associated with rheumatoid arthritis: rheumatoid arthritis with orencia trial toward Sjogren's syndrome Endocrinopathy (ROSE) trial-an open-label, one-year, prospective study-Interim analysis of 32 patients for 24 weeks*. Mod Rheumatol, 2015. **25**(2): p. 187-93.

43. Bodewes, I.L.A., et al., *Hydroxychloroquine treatment downregulates systemic interferon activation in primary Sjogren's syndrome in the JOQUER randomized trial.* Rheumatology (Oxford), 2019.

**Table 1.** Classification criteria for ‘primary’ and ‘secondary’ Sjögren’s syndrome

	<b>SjS criteria</b>	<b>Specific ‘secondary’ SjS criteria</b>
<b>Bloch et al., 1965</b>	(i) keratoconjunctivitis sicca (ii) xerostomia (iii) rheumatoid arthritis, or other connective tissue disease  ≥ 2 criteria  <b>autoantibodies or histopathology not mandatory</b>	None
<b>Vitali et al., 2002, AECG</b>	(i) ocular symptoms (ii) oral symptoms (iii) ocular signs (iv) positive histopathology (v) objective salivary gland involvement (salivary flow, sialography, scintigraphy) (vi) autoantibodies (Ro/SSA or La/SSB) ≥ 4 criteria as long as either (iv) or (vi) are positive  <b>autoantibodies and/or histopathology mandatory</b>	‘In patients with a potentially associated disease (for instance, another well defined connective tissue disease), the presence of item (i) or item (ii) plus any 2 from among items (iii), (iv), and (v) may be considered as indicative of secondary SS’  <b>autoantibodies or histopathology not mandatory</b>
<b>Shiboski et al., 2012, ACR (provisional)</b>	(i) autoantibodies ([Ro/SSA and/or La/SSB] or [RF and ANA ≥ 1:320]) (ii) histopathology (iii) ocular staining score ≥ 3  ≥ 2 criteria  <b>autoantibodies and/or histopathology mandatory</b>	‘... the diagnosis of SS should be given <b>to all who fulfill these criteria</b> , while also diagnosing any concurrent organ specific or multi-organ autoimmune diseases, without distinguishing primary or secondary.’
<b>Shiboski et al., 2016, EULAR/ACR</b>	(i) histopathology (3 points) (ii) Ro/SSA+ (3 points) (iii) ocular staining score ≥ 5 (1 point) (iv) Schirmer’s test ≤ 5mm/5min (1 point) (v) unstimulated whole saliva flow rate ≤0.1ml/min (1 point)  ≥ 4 points  <b>autoantibodies and/or histopathology mandatory</b>	‘Consistent with our goal of producing criteria to aid in recruitment for clinical trials, <b>we focused on primary rather than secondary SS</b> . Patients with the latter would typically not be eligible for experimental treatments for SS.’



**Table 2.** Clinical characteristics of patients with Sjögren`s syndrome and associated autoimmune disease

	Publication	Numbers	Classification criteria used	SjS with and without other autoimmune disease	Other autoimmune disease with and without SjS
<b>SjS/RA</b>	Moutsopoulos et al., 1979, Am J Med [3]	22 SjS versus 21 SjS/RA	not specified	<i>SjS versus SjS/RA</i> Frequency of parotitis ↑ Raynaud phenomenon ↑ Purpura ↑ Lymphadenopathy ↑ Myositis ↑ Renal involvement ↑	
<b>SjS/RA</b>	He et al., 2013, Rheumatology [17]	187 SjS versus 74 SjS/RA	Vitali et al., 2002, AECG	<i>SjS versus SjS/RA</i> Rash ↑ Parotid enlargement ↑ Interstitial lung disease ↓ Arthritis ↓ Anemia ↓ ESSDAI ↓ Morning stiffness ↓ Fever ↓ Cytopenia ↑	<i>RA/SjS versus RA</i> DAS28 ↑ Interstitial lung disease ↑ Fever ↑ Rash ↑ Cytopenia ↑ Autoimmune liver disease ↑ Renal involvement ↑ Nervous system involvement ↑
<b>SjS/RA</b>	Brown et al., 2014, Rheumatology [15]	744 RA versus 85 SjS/RA	Rheumatologist diagnosis (medical record review)		<i>RA/SjS versus RA</i> Disease duration ↑ Female gender ↑ DAS28 ↑ Sharp score ↑
<b>SjS/SSc</b>	Salliot et al., 2007, Rheumatology [31]	202 SjS versus 27 SjS/SSc	Vitali et al., 2002, AECG	<i>SjS versus SjS/SSc</i> Peripheral neuropathy ↑	<i>SSc/SjS versus SSc</i> Pulmonary fibrosis ↓ Renal crisis (trend, not significant) ↓ Pulmonary arterial hypertension (trend, not significant) ↓ High proportion of limited SSc when associated to SS
<b>SjS/SLE</b>	Manoussakis et al., 2004, Arthritis & Rheumatism [18]	86 SjS versus 26 SjS/SLE	Vitali et al., 2002, AECG	<i>SjS versus SjS/SLE</i> Raynaud phenomenon ↓ Arthritis ↓ Central nervous system involvement ↓ Lymphadenopathy ↑	<i>SLE/SjS versus SLE</i> Raynaud phenomenon ↑ Kidney involvement ↓ Lymphadenopathy ↓ Thrombocytopenia ↓