

Non-Conventional and Emerging Autoantibodies in Sjögren's Disease

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Abstract: Sjögren's disease (SjD) is a chronic autoimmune disease that is characterised by dryness symptoms, arthralgias, systemic disease and B-cell hyperactivity. Serum autoantibodies are key pathological features of this disease. Anti-Ro52, anti-Ro60 and anti-La immunoglobulin G autoantibodies (sometimes known as antinuclear antibodies) are perhaps the most well-known autoantibodies, are important in the formal classification criteria for SjD and exist in up to 70% of patients. Rheumatoid factors, which are present in approximately 50% of patients, can reveal important prognostic information regarding the development of B-cell lymphomas. Beyond these autoantibodies, there are several emerging and novel autoantibodies associated with SjD that hold promise in identifying clinical features of SjD and facilitating the diagnosis of patients who lack the classic SjD-associated autoantibodies. These include anti-fodrin antibodies, anti-muscarinic acetylcholine receptor 3 antibodies and those autoantibodies traditionally associated with systemic lupus erythematosus. This narrative review article provides an updated review of these autoantibodies, discussing their potential clinical utility and the current limitations. Although many clinical associations have been identified, the routine clinical use of these autoantibodies is hampered by issues such as poor diagnostic sensitivity, contradictory associations, heterogeneous studies and small single-cohort studies. Further research using harmonised testing and large, multicentre cohorts is required to explore and validate the utility of these autoantibodies.

Keywords: antibodies, autoantibodies, B cells, Sjögren's disease

Introduction

Sjögren's disease (SjD) is a systemic autoimmune disease that predominantly affects females, resulting in dryness (sicca) symptoms, arthralgias and fatigue, and involving various organs. It imparts a significant burden to patients' quality of life, particularly as there are currently no approved targeted therapies in existence. As a clinically heterogeneous disorder, the condition may be unified by the presence of B-cell hyperactivity and autoantibodies in a substantial proportion of patients.^{1,2} As such, there are several ongoing trials on SjD targeting B cells and plasma cells.³ SjD may exist in isolated or primary form, or be associated with other autoimmune diseases, including systemic lupus erythematosus (SLE).

Autoantibodies in SjD originate from self-reactive B cells and may target a number of nuclear, cellular and extracellular antigens, reflecting the B-cell hyperactivity of the disease.⁴ While autoantibodies also have a natural or physiological role in health, these autoantibodies in SjD may be directly pathogenic and induce apoptosis of salivary gland cells, leading to salivary gland dysfunction.⁵ Early studies have identified serum antibodies in SjD patients reacting with salivary gland antigens by indirect immunofluorescence microscopy. These may be of any isotype and are believed to bind keratin as one of their antigenic targets.^{6,7} Immunoglobulin G (IgG) autoantibodies towards ribonucleoprotein proteins, Ro52/tripartite motif-containing protein 21 (TRIM21), Ro60 and La, are particularly common in SjD patients and encompass the spectrum of antinuclear antibodies (ANA) commonly measured by fluorescence microscopy on HEp2 substrate. However, ANA screening may miss detection of these specific SjD-associated autoantibodies (ie, be negative), even with the sensitive HEp-2000 for detection of anti-Ro60 autoantibodies.⁸ In cohort studies, these autoantibodies are present in around 70–80% for Ro52/Ro60 IgG and 40% for La IgG;^{9,10} however, they are not specific for SjD and may be found in other systemic autoimmune diseases. Clinically, anti-Ro52/Ro60 IgG autoantibodies (also termed SS-A antibodies) are important in the identification of SjD, and

are an important disease feature in the American College of Rheumatology (ACR)/European Alliance of Associations of Rheumatology (EULAR) 2016 classification criteria.¹¹ Anti-La IgG are not included in these criteria since these antibodies have low clinical utility in the identification of SjD patients,¹² although they were included in the earlier 2012 Sjögren's International Collaborative Clinical Alliance (SICCA) criteria.¹³ Nevertheless, these autoantibodies may help to stratify patients into serological subsets, recognising patients at risk of serious systemic manifestations.^{10,14}

Another common autoantibody, rheumatoid factor (RhF), is an autoantibody of any isotype directed against the Fc portion of circulating IgG. RhF is found in approximately half of SjD patients,⁹ and featured in earlier SjD classification criteria in combination with a positive ANA test by immunofluorescence microscopy.¹³ Like the classic Ro52/Ro60 and La IgG autoantibodies, RhF remains an important prognostic marker of disease and is associated with more severe disease¹⁵ and the future development of mucosa-associated lymphoid tissue (MALT) lymphomas.¹⁶ Occasionally, the RhF-producing B cells may acquire somatic and B-cell receptor mutations that may cause them to acquire cryoprecipitating properties and form cryoglobulins. These occur in approximately 9% of SjD patients, and may cause serious end-organ damage when they precipitate and deposit in tissue.¹⁷ These observations highlight the importance of accurate serological profiling of patients through autoantibodies.

There are several areas of unmet need for SjD and autoantibodies. Owing to the clinical heterogeneity and sometimes subtle clinical presentation, SjD continues to be poorly diagnosed and recognised, particularly when patients lack the classic SjD-related autoantibodies discussed above.¹⁸ This calls for the investigation for alternative autoantibody biomarkers that can help in diagnosing these cases. Furthermore, stratification of patients into those at risk of specific systemic manifestations would be highly desirable, particularly as patients remark about the unpredictability of their disease.² Therefore, biomarkers such as autoantibodies may be useful. Anti-Ro52, -Ro60, -La and RhF are commonly measured autoantibodies in SjD and either are currently or were previously part of the classification criteria.¹⁹ This narrative review examines less common and novel autoantibodies that have been or are being explored in the literature. Many of these have putative clinical associations; however, further studies to validate these findings in other cohorts are required.

Review Study Selection

A narrative review was undertaken to examine “non-conventional” and “emerging” autoantibodies in SjD. These were defined as any serum autoantibody that is novel and/or less well established in the diagnosis, monitoring, prediction or prognostication of SjD patients. Hence, these were autoantibodies other than anti-Ro52, -Ro60, -La IgG or RhF. The author focused on all isotypes and any assay for measurement. PubMed (MEDLINE) and Google Scholar databases were searched with the following combination of phrases: “Sjögren's”, “Sjögren's disease”, “Sjögren's syndrome”, “autoantibody”, “biomarker”, “novel” and “new”. Only publications published in English were considered and no restrictions on publication date were made. Results from the included publications were analysed and summarised for each autoantibody. Key diagnostic information, including prevalence, sensitivity and specificity, was extracted (where present) and pooled.

α -Fodrin Antibodies

α -Fodrin is a cytoskeletal protein, encoded by *SPTANI*, that provides cellular membrane support and has a role to play in the normal function of apoptosis.²⁰ Small interfering RNA (siRNA) silencing of α -fodrin in non-obese diabetic mice (a murine model for SjD) improved lymphocytic infiltration in lacrimal glands relative to controls, confirming that it is an important autoantigen in the pathogenesis of SjD.²¹

Research on antibodies targeting this protein (α -fodrin antibodies [AFA]) has historically been interested in the detection of SjD patients lacking the classic Ro/La autoantibodies.²² Therefore, the addition of AFA to the diagnostic algorithm may help to improve diagnostic sensitivity.²³ The IgG and IgA isotypes have predominantly been explored by enzyme-linked immunosorbent assay (ELISA), showing a prevalence of up to 55% for AFA IgG and 82% for AFA IgA in SjD; and 71% for AFA IgG and 59% for AFA IgA in SjD with other associated autoimmune diseases.^{24,25} They may be associated with various features of disease activity, including hypergammaglobulinaemia and neurological disease (Table 1).

A meta-analysis of studies revealed a pooled sensitivity of IgG/IgA AFA of 39% and specificity of 83% for the diagnosis of SjD.²⁶ However, the high prevalence of these autoantibodies in other autoimmune diseases and even healthy

Table 1 Overview of Novel and Non-Conventional Serum Autoantibodies in Sjögren's Disease (SjD)

Autoantibody	Prevalence	Clinical Utility	Sjögren's Disease Clinical Associations	References
α -Fodrin IgG	Isolated SjD: 20–55% (ELISA) 78% (IP) SjD + CTD: 5–71% (ELISA)	Pooled Sn 39%, Sp 83% for IgG or IgA isotype	<ul style="list-style-type: none"> • Seronegative SjD • Serological markers of disease including hypergammaglobulinaemia, rheumatoid factor (RhF) and anti-Ro52/Ro60 autoantibodies • Pernio, neurological disease • Age, duration of disease 	[22,24–29]
α -Fodrin IgA	Isolated SjD: 52–82% (ELISA) SjD + CTD: 57–59% (ELISA)		<ul style="list-style-type: none"> • Neurological disease 	[22,24,25,28]
Anti-salivary gland protein 1 IgG	Juvenile: 30% (ELISA) Adult: 55% (Western blot) 19–37% (ELISA)	Sn 26%; Sp 68%; AUC 0.69	<ul style="list-style-type: none"> • Seronegative SjD • Anaemia • Lacrimal gland dysfunction • Negative association with systemic involvement 	[30–34]
Anti-parotid secretory protein (any isotype)	19% (anti-Ro52/Ro60 ⁺) 18–48% (anti-Ro52/Ro60 ⁻) (ELISA/CLIA)	Sn 10%; Sp 98%; AUC 0.78 (IgG); AUC 0.68 (IgA)	<ul style="list-style-type: none"> • ESR, IgG • Anaemia • Lacrimal gland dysfunction (IgG) • Higher focus scores 	[33–35]
Anti-carbonic anhydrase (any isotype, isoform)	21–37% (ELISA) Juvenile: 52% (ELISA)	–	<ul style="list-style-type: none"> • Associated with anti-fodrin antibodies and IgA levels • Long-standing seropositive SjD • Corneal and conjunctival scores 	[32, 34–38]
Anti-carbonic anhydrase 6 IgG	55% (Western blot)	Sn 20%; Sp 98%; AUC 0.80	<ul style="list-style-type: none"> • IgG levels and ESR • Higher focus scores • Negative correlation with dry eye pain intensity score 	[30,33,37]
Anti-carbonic anhydrase 2 IgG	20–62% (ELISA)	–	<ul style="list-style-type: none"> • Distal renal tubular acidosis 	[39–41]
Anti-muscarinic acetylcholine M3 receptor IgG	55–90% (ELISA) 75% (in-cell Western assay)	Sn 43%, Sp 95% (pooled studies)	<ul style="list-style-type: none"> • Disease activity, extraglandular manifestations • Ro52, Ro60 and La autoantibodies, IgG • Focus score • Ocular staining score • Leukopenia • Shorter disease duration 	[42–46]
Anti-cofilin-1 and anti-rho GDP-dissociation inhibitor 2 (RGI2)		<u>Anti-cofilin</u> Sn 70%; Sp 86%; AUC 0.80 <u>Anti-RGI2</u> Sn 50%; Sp 92%; AUC 0.74	<ul style="list-style-type: none"> • Mucosa-associated lymphoid tissue (MALT) lymphoma 	[47]
α -Enolase I	92–98% (IgG) 68–82% (IgA) (ELISA)	Sn 75%; Sp 84%; AUC 0.78	<ul style="list-style-type: none"> • MALT lymphoma (IgG) • Decreased salivary flow rate (IgG) • Ro52/Ro60 IgG autoantibodies (IgA) • Arthritis 	[47–50]
Aquaporin 5 IgG	14% (ELISA)	Sn 95%, Sp 70% (CTD cohort)	<ul style="list-style-type: none"> • High disease activity • Objective measures of xerophthalmia 	[51–53]

(Continued)

Table 1 (Continued).

Autoantibody	Prevalence	Clinical Utility	Sjögren's Disease Clinical Associations	References
Anti-centromere IgG	6–13% (IIF) 8–11% (ELISA)	–	<ul style="list-style-type: none"> ● Raynaud's, sicca symptoms/glandular dysfunction ● Lower rates of hypergammaglobulinaemia and Ro/52/Ro60 autoantibodies 	[54–57]
Anti-dsDNA (IgG/any isotype)	14–24% (Farr, Crithidia)	–	<ul style="list-style-type: none"> ● Higher disease activity and systemic involvement ● Serological activity with autoantibodies and hypergammaglobulinaemia 	[58,59]
Anti-ribonucleoprotein IgG	4–9% (Bioplex, immunodot)	–	<ul style="list-style-type: none"> ● Hypergammaglobulinaemia, younger age of onset and more systemic disease 	[60,61]
Anti-histone IgG	22% (ELISA)	–	<ul style="list-style-type: none"> ● Older age of onset of SjD 	[62]
Anti-cyclic citrullinated peptide IgG	7–10% (ELISA)	–	<ul style="list-style-type: none"> ● Possible synovitis association 	[63,64]
Anti-vimentin IgG	24% (ELISA)	–	<ul style="list-style-type: none"> ● Objective measures of dryness, eg, ocular staining score 	[65]
Anti-N-methyl-D-aspartate receptor 2 (any isotype)	–	–	<ul style="list-style-type: none"> ● Cognitive impairment 	[66]

Abbreviations: IgG, immunoglobulin G; IgA, immunoglobulin A; dsDNA, double-stranded DNA; ELISA, enzyme-linked immunosorbent assay; IP, immunoprecipitation; CTD, connective tissue disease; CLIA, chemiluminescence assay; IIF, indirect immunofluorescence; Sn, sensitivity; Sp, specificity; AUC, area under the curve; ESR, erythrocyte sedimentation rate; MALT, mucosa-associated lymphoid tissue.

donors made some researchers question the diagnostic utility of AFA. Therefore, AFA did not adequately discriminate between SjD patients and these controls on receiver operating characteristics (ROC) curve analysis.^{25,27}

Salivary Gland Protein 1 and Parotid Secretory Protein Antibodies

These autoantibodies have often been studied together (as “tissue-specific” antibodies) in SjD and, therefore, will be considered together in this section. Similarly to AFA, interest in these autoantibodies lies in identifying patients who lack Ro/La autoantibodies, stemming from a murine model of SjD (interleukin 14 α transgenic mice [IL14 α TG]) that demonstrates autoantibodies to salivary gland protein 1 (SP1) and parotid secretory protein (PSP), with minimal antibodies to Ro/La autoantigens.³⁰ In patients with long-standing seropositive (anti-Ro60⁺) SjD, these autoantibodies of the IgG and IgM isotype are rare, being found in approximately 10% of patients.³⁶ In addition, anti-PSP and anti-SP1 IgA were found in 10–50% of SjD associated with autoimmune diseases; in contrast, the IgG and IgM isotypes were rarer, and anti-Ro IgG was found less commonly, suggesting that the IgA isotype may be helpful in identifying patients with connective tissue disease (CTD) with associated SjD and who lack Ro52/Ro60 antibodies.³⁶

Autoantibodies (IgG, IgA and IgM) towards these autoantigens may be found in patients with objective evidence of dry eye disease in the absence of Ro52/Ro60/La autoantibodies and SjD. However, it is possible that in these cross-sectional studies, some of these patients would eventually develop SjD or other diseases.^{30,67} In one study, 19% of SjD sera contained anti-SP1 antibodies (by immunoblot), and these patients also lacked autoantibodies to Ro52/Ro60/La autoantigens.³¹ Anti-SP1 IgG and IgM – but not anti-PSP isotypes – correlate with tear break-up time.³⁷

In juvenile SjD, the detection of these autoantibodies (of any isotype) generally has low sensitivity for the diagnosis; however, combining them with traditional SjD-related autoantibodies, such as ANA, increases sensitivity at the expense of diagnostic specificity.³² Clinically, these autoantibodies have not demonstrated clinical utility in this group of patients, with no correlations having been found with salivary gland focus score, anti-Ro52/Ro60 autoantibodies or unstimulated salivary flow rate.³²

Carbonic Anhydrase Antibodies

Carbonic anhydrase (CA) is an important enzyme in acid–base regulation, found in the exocrine glands, skin and kidney.³⁸ It catalyses the conversion of carbon dioxide to bicarbonate ions and carbonic acid, and is therefore important in normal physiological roles. CA isoforms may be found in cells or secreted in bodily fluids, including saliva.⁶⁸ CA-I

protein is up-regulated in the salivary gland tissue of SjD patients compared to healthy controls.⁴⁷ Antibodies to CA and specific isoforms have been studied in SjD. CA isoform antibodies also correlate with disease activity,⁶⁹ implicating these autoantibodies in the pathology of the disease.

CA-6 is secreted in saliva and plays a role in the production of saliva from acinar and ductal cells.⁶⁸ As such, it has received special attention as an autoantigen in SjD, particularly as these autoantibodies are found in mouse models of SjD that lack the traditional Ro52/Ro60/La autoantibodies.³⁰ Higher levels of serum anti-CA6 IgG and IgM have been noted in SjD patients compared with healthy donors and disease controls,³³ and the IgA isotype is relatively prevalent (38%) in patients with long-standing SjD.³⁶ Anti-CA-6 IgG is present in up to half of SjD patients, and is correlated with serum IgG levels and higher minor salivary gland biopsy focus scores.³³

Furthermore, given the enzyme's role in the modulation of acid–base balance, others have studied the autoantibody's putative links with acid–base disorders in SjD. Anti-CA-6 IgG is associated with lower serum sodium and potassium, higher urinary pH and higher urinary bicarbonate, suggesting associations with a urinary acidification defect.^{70,71} Anti-CA-2 IgG was detected in 20–61% of SjD patients, and higher levels were found in SjD patients with distal renal tubular acidosis (RTA).^{39,40} Experimental data seem to support the role of CA autoantibodies in the pathogenesis of RTA. PL/J mice immunised with human CA-2 induced autoantibodies to this antigen and salivary gland focal lymphocytic sialadenitis.⁷² These mice had defects in urinary acidification, suggesting that the autoantibodies are likely to be pathogenic in the pathogenesis of RTA.⁷³

Muscarinic Acetylcholine M3 Receptor Antibodies

Muscarinic acetylcholine M3 receptor (M3R) is a G protein-coupled receptor found in major salivary glands and is involved in mediating salivation. Mice deficient in this receptor have deficiencies in salivation.⁷⁴ Anti-M3R may be directed against several components of the M3R, but most commonly targets the second extracellular domain.⁷⁵ In *in vitro* experiments, sera derived from SjD patients positive for anti-M3R differentially modulated intracellular calcium influx from cevimeline-treated salivary gland cell lines. Antibodies to the second extracellular loop of this receptor loop inhibited this calcium influx, whereas those directed to the N-terminus and first extracellular loop potentiated the calcium influx.⁴² In addition, SjD anti-M3R IgG was found to cause the internalisation of M3R and major histocompatibility class-I on human submandibular gland cell lines, which may present a novel mechanism for the targeting of these cells for destruction by natural killer (NK) cells.⁷⁶ In contrast, in BALB/c mice immunised with peptides of the second extracellular loop, the induction of anti-M3R IgG led to antibody deposition in salivary glands. However, this did not result in the reduction of salivary or tear flow up to 20 weeks post-induction. Furthermore, the transfer of IgG from immunised mice into recipient mice did not elicit evidence for exocrine gland dysfunction. These data indicate that anti-M3R modulate receptor activity but are unlikely to be pathogenic.⁷⁷

Similarly, the clinical utility of anti-M3R has been somewhat disappointing. Anti-M3R IgG (to specific extracellular loops) is present in approximately 50% of SjD patients,⁴² and is elevated compared to disease controls (rheumatoid arthritis [RA] and SLE) and non-SjD sicca patients.⁴³ However, on ROC curve analysis, the autoantibodies could not adequately distinguish between SjD and SLE patients,^{43,78} and showed poor sensitivity in diagnosing SjD from healthy controls.⁴⁴ In contrast to the data in the previous paragraph, there is no demonstration of any correlation between these autoantibodies and objective salivary flow rate.^{42,45} The autoantibodies, however, identified younger SjD patients and patients with greater disease manifestations, including IgG levels and focus scores.^{43,78}

Cofilin-1, α -Enolase and Rho GDP-Dissociation Inhibitor 2 Antibodies

Using mass spectrometry, cofilin-1, α -enolase, annexin A2 and rho GDP-dissociation inhibitor 2 (RGI2) were found to be overexpressed in the parotid salivary gland tissue of SjD patients compared to non-SjD controls.^{47,48} Therefore, researchers tested the clinical utility of autoantibodies to these autoantigens. IgG to cofilin-1, α -enolase and RGI2 was able to discriminate between SjD patients with MALT lymphomas and those without, with an area under the curve (AUC) of at least 0.74.⁴⁷

Given that α -enolase is overexpressed in the salivary gland tissue of SjD patients, their role in SjD salivary gland pathology has been studied. Mass spectrometry of a submandibular gland cell line (SMG-C6) that overexpresses α -enolase revealed an up-regulation of proteins related to immunodulation, metabolism and salivary secretion.⁴⁸ As such, anti- α -enolase IgG levels were also associated with decreased salivary flow rate in SjD patients.⁴⁸ However, anti- α -enolase IgG and IgA antibodies have limited association with other clinical manifestations, apart from, possibly, arthritis and high urine pH.^{49,50}

Aquaporin Antibodies

Aquaporins (AQP) are cellular membrane water channels found in various organs, including the kidneys and exocrine glands.⁷⁹ Autoantibodies to these channels have received interest from researchers in various autoimmune diseases. Serum and cerebrospinal fluid AQP4 IgG are characteristic of neuromyelitis optica, and may coexist in up to 20% of SjD patients.⁸⁰ AQP proteins may be expressed on human salivary glands,⁵¹ and AQP5 expression is down-regulated in SjD salivary glands.^{81,82}

Using ELISA, serum anti-AQP1 and AQP5 IgG were higher in SjD patients than in healthy controls, but only anti-AQP5 levels were higher than in other patients with CTD.⁵² At a cut-off of 18.79 ng/mL, anti-AQP5 antibodies had an AUC of 0.86, with a sensitivity of 95% and specificity of 70%, compared to the CTD cohort.⁵² The clinical value of anti-AQP5 is mixed. One study did not find any correlation with disease activity or serological parameters,⁵² however, when using a EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) cut-off of 14, anti-AQP5 was independently associated with high ESSDAI SjD patients.⁵³ In another study, the presence of IgG towards AQP proteins was associated with more severe xerophthalmia using the van Bijsterveld scoring assessment.⁵¹ Differences in these associations between studies probably reflect differences in assays and collected clinical parameters.

Centromere Antibodies

While centromere IgG antibodies (ACA) are regarded as a sensitive marker for scleroderma, and they may signify SjD associating with this disease,⁸³ ACA may also exist in SjD patients with no scleroderma features. Using immunoprecipitation methods, the majority of ACA in SjD targets centromere protein C (CENP-C) alone, and rarely targets both CENP-C and centromere protein B (CENP-B).⁸⁴

ACA has a prevalence of approximately 6–13% in SjD,^{54–57} and 3% of SjD patients negative for Ro52/Ro60/La autoantibodies have ACA,⁸⁵ indicating that this may be a helpful biomarker in a small fraction of cases. ACA⁺ SjD patients tend to be older, to have Raynaud's phenomenon, sclerodactyly and left ventricular diastolic dysfunction, and to be seronegative for Ro52, Ro60 and La autoantibodies.^{54,56,86} ACA⁺ patients also tend to have higher disease activity (ESSDAI) than ACA⁻ patients.⁵⁴

An area of interest in ACA⁺ patients lies in the salivary gland pathology. Studies are conflicting over whether ACA⁺ patients have higher salivary gland focus scores than ACA⁻ patients, with some studies finding lower focus scores,⁵⁷ others finding no difference,^{54,87} and another finding slightly higher focus scores⁵⁵ in ACA⁺ patients. Nevertheless, the salivary glands of ACA⁺ patients tend to have a higher degree of fibrosis histologically.⁵⁷ Indeed, using single-cell interrogation from minor salivary gland biopsies from ACA⁺ and ACA⁻ patients, ACA⁺ patient biopsies demonstrated an enrichment of memory B cells and age-associated B cells, and gene signatures of fibrosis and transforming growth factor (TGF)- β signalling.⁸⁸

Systemic Lupus Erythematosus-Associated Autoantibodies

Anti-double-stranded DNA (dsDNA) may be found in SjD, particularly when associated with SLE.⁸⁹ Occasionally, patients with primary SjD and no features of SLE may develop new anti-dsDNA and clinical features of SLE,⁹⁰ highlighting the importance of monitoring SjD patients and retesting autoantibodies, particularly when new clinical features emerge. In primary SjD, these autoantibodies may exist in around 14–24% of individuals with no features of SLE, and identify patients who have hypergammaglobulinaemia, greater systemic involvement and disease activity.^{58,59}

Anti-ribonucleoprotein (RNP) may be found in both SLE and mixed connective tissue disease (MCTD).⁸³ However, similarly to anti-dsDNA, its presence in SjD without SLE/MCTD signifies SjD patients with an earlier onset of disease,

higher systemic burden and higher levels of IgG. Complications include interstitial lung disease, myositis and Raynaud's phenomenon.^{60,61}

Histone antibodies are commonly detected in SLE, and may be found in drug-induced lupus erythematosus and other autoimmune rheumatic disorders. Directed against histones – structures that chromatin can be wrapped around – antibodies towards these structures commonly make their appearance in SLE and drug-induced lupus erythematosus.⁹¹ In SjD, serum histone IgG was present in 22% of patients and a subset of patients with late-onset disease was identified. No other clinical features were associated with this autoantibody and there was no evidence of SLE overlap syndrome in any of these patients.⁶²

Other Autoantibodies

The presence of other autoantibodies in SjD may signify another associated autoimmune disorder. For example, anti-mitochondrial-M2 IgG may be found in SjD patients with concomitant primary biliary cirrhosis.⁹² However, a range of single-cohort or smaller studies have explored other autoantibodies in SjD patients in the absence of their associated autoimmune disorder. Anti-cyclic citrullinated peptide IgG autoantibodies have been regarded as a specific marker for RA; yet, in the absence of RA, they can be present in up to 10% of SjD patients. Although they are not associated with any SjD clinical features or RhF, one study found an association with synovitis,⁶³ whereas a later study did not.⁶⁴ These studies examined patients with isolated SjD and excluded those with associated RA from their analyses.

Vimentin is a filament protein that forms the structural cytoskeleton of a cell. Anti-vimentin IgG can be found in various autoimmune diseases. One cohort study found these autoantibodies in 24% of SjD patients, and the levels positively correlated with dryness measures, including ocular surface staining score and unstimulated whole salivary flow rate.⁶⁵ In SjD associated with other autoimmune diseases, including RA, this prevalence may be increased to approximately 66%.⁹³

Finally, in a single cohort of SjD patients, anti-*N*-methyl-D-aspartate (NMDA) receptor subtype 2 IgG/A/M in the serum and cerebrospinal fluid was associated with poor memory and learning scores.⁶⁶ These are of particular interest since anti-NMDA antibodies may be seen in patients with NMDA receptor autoimmune encephalitis. Further work in other cohorts is required to replicate these findings.

Discussion and Concluding Remarks

Since autoantibodies have become important diagnostic and prognostic biomarkers in autoimmune diseases, attention has turned to more accurately phenotyping SjD patients, particularly when they lack the classic SjD-associated autoantibodies such as anti-Ro60. However, the generally low prevalence of these novel serum autoantibodies in the seronegative SjD population, and their limited ability to discriminate these patients from controls, limits their clinical utility.³¹ Moreover, and particularly with respect to earlier studies, it is unclear whether anti-Ro52 was tested, which may affect the classification of “seronegative” patients, since “SS-A” and “anti-Ro” are now somewhat ambiguous terms.⁹⁴

A tremendous number of studies have been dedicated to lesser known and non-conventional serum autoantibodies in SjD in an attempt to improve diagnoses and define clinical subsets (Table 1). However, as of now, these studies have largely been restricted to either small numbers of SjD patients or homogeneous single cohorts. Moreover, some early studies used differing classification criteria to define SjD patients and most studies did not report what treatments, if any, these patients were receiving. This introduces a significant selection bias. The controls for these studies have also been variable. For example, some used SLE as their disease controls,²⁸ whereas others used hospital staff as their healthy donors.⁷⁸ These controls and their ages would vastly affect the immunoassay cut-off that defines positivity and, hence, the diagnostic performance of the autoantibody under investigation.

Furthermore, a major challenge in autoantibody diagnostics is standardisation of testing, as heterogeneity exists in the preanalytical handling of samples, testing methodology and the definitions of a positive result, among other things. For instance, immunoprecipitation assays, as used in a few studies,²⁵ offer reduced analytical sensitivity but better specificity than immunoblot assays.⁹⁵ For analytical validity, a few studies utilised more than one assay to measure and report their autoantibody results (eg, Refs^{25,31}), but the majority of studies used one assay (ELISA), and for in-house assays, no details were provided about the validation of the assay, including its accuracy and precision. All these sources of

variation may account for the vast differences in prevalence of these autoantibodies reported across the studies, and may explain differences in clinical associations and apparently conflicting utility (Table 1). Therefore, future research in well-defined SjD and control cohorts, using validated assays, is required to improve the validity and generalisability of these findings. Ideally, studies should also test autoantibodies using more than one assay and should describe assay validation procedures.

Study design is an important consideration in the assessment of evidence strength. Most studies have been observational, cross-sectional studies of SjD cohorts. While these make for quick and convenient recruitment, cross-sectional studies generally offer a weak study design and cannot readily offer insights into the longitudinal benefits of biomarker assessment.⁹⁶ This limits the clinical translatability of these studies, since no study has yet demonstrated the potential to alter usual clinical practice for SjD.

From a practical and clinical point of view, the autoantibodies reviewed may be broadly classified as 1) those for diagnosing SjD patients apart from other CTD, such as SLE, and/or healthy donors; 2) those potentially identifying seronegative SjD patients; or 3) those identifying/predicting specific disease manifestations of SjD. The diagnostic antibodies, such as AFA, generally offer good diagnostic specificity for SjD and have reasonable discriminatory power (AUC around 0.70–0.80), but have poorer sensitivity. Therefore, their potential use may be for ruling in disease rather than screening for SjD. These statistics are dependent on the prevalence of SjD and the controls, and the ideal situation is differentiating SjD from non-SjD sicca, which may lack the classic anti-Ro52/Ro60/La autoantibodies. Since most studies have not examined this control cohort of patients, further evaluation is required before these antibodies may be considered for routine clinical use. In addition, given that anti-Ro52/Ro60 (SS-A) already demonstrates favourable specificity,⁹⁷ it remains to be determined how these newer autoantibodies may fit into the routine clinical work-up of a patient with SjD. In the latest Outcome Measures in Rheumatology (OMERACT) Working Party for the development of SjD guidelines,⁹⁸ novel autoantibodies were considered but ultimately not recommended for routine measurement in clinical trials.

Interest in some of these autoantibodies (eg, SP1 antibodies) in identifying seronegative SjD patients – or patients who lack the classic SjD-associated autoantibodies – is a particular focus.³¹ However, a limited number of studies has been performed in this area and, as these were cross-sectional studies, it is possible that these patients will go on to develop autoantibodies as their disease evolves.⁹⁹ Seronegative SjD patients may also be a product of insensitive assays, as one study found that line immunoassays, which are commonly used to detect Ro52/Ro60/La autoantibodies, may not detect anti-Ro60 if its expression is too low.¹⁰⁰ Salivary autoantibody testing for anti-Ro60 is a promising strategy to identify a subset of possible SjD patients who have demonstrable objective sicca, yet lack serum anti-Ro60.¹⁰¹

A final concern is about the translatability of many of the studies, in that many of the identified clinical associations (Table 1) can already be readily determined using standard and accessible clinical tests, with the possible exception of the assessments for cognitive impairment and MALT lymphoma (Table 1). For instance, anti-M3R antibodies are associated with disease activity and leukopaenia, which are already assessed using pre-existing tests and tools. Thus, these autoantibodies offer pathogenic insight but are yet to demonstrate clinical utility. These studies also highlight the difference between statistical significance and clinical significance. Many studies have analysed a large number of disease parameters (eg, Ref³²) and statistically significant associations would arise by chance. Future studies are required to assess the clinical effect size and relevance, particularly regarding the potential to change clinical practice.

Newer studies are now taking a “shotgun” approach to identifying novel autoantibodies in SjD by probing protein and peptide arrays with patient and control sera.^{102,103} Although there are some promising candidates in identifying seronegative cohorts,¹⁰³ validation in other and larger cohorts is required. Furthermore, some of these autoantibodies have limited clinical utility,¹⁰⁴ and for these to be helpful in a practical sense, they would need to demonstrate equal or superior utility to the current conventional autoantibodies and biomarkers. This highlights the need for ongoing research and validation in patient cohorts. In summary, this review highlights several novel and non-conventional serum autoantibodies in SjD, and explores areas for future research. As markers of immune dysregulation, their identification not only aids with understanding the pathology of SjD, but also identifies potential therapeutic targets. While none of the autoantibodies explored so far has been validated for routine clinical use, upcoming studies are likely to clarify their potential utility.

Data Sharing Statement

Data sharing is not applicable as no new data were generated.

Author Contributions

The author has made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; has agreed on the journal to which the article has been submitted; and agrees to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

AL received a speaker honorarium and consultancy fees from Novartis. The author reports no other conflicts of interest in this work.

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