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REVIEW

Why do drug treatments fail in Sjögren's disease? Considerations for treatment, trial design and interpretation of clinical efficacy

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ABSTRACT

Introduction: Despite ongoing efforts to develop effective therapeutics, no disease-modifying drugs have been officially licensed for the indication of Sjögren's disease (SjD). This is partly due to heterogeneity in disease manifestations, which complicates drug target selection, trial design and interpretation of clinical efficacy in SjD.

Areas covered: Here, we summarize developments and comment on challenges in 1) identifying the right target for treatment, 2) selection of the primary study endpoint for trials and definition of clinically relevant response to treatment, 3) inclusion criteria and patient stratification, 4) distinguishing between disease activity and damage and 5) establishing the effect of treatment considering measurement error, natural variation, and placebo or nocebo responses.

Expert opinion: Targets that are involved in both the immune cell response and dysregulation of glandular epithelial cells (e.g. B-lymphocytes, type-I interferon) are of particular interest to treat both glandular and extra-glandular manifestations of SjD. The recent development of composite study endpoints (CRESS and STAR) may be a crucial step forward in the search for clinically effective systemic treatment of patients with SjD. Important additional areas for future research are symptom-based and/or molecular pathway-based patient stratification, prevention of irreversible damage, and establishing the effect of treatment.

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1. Introduction

Sjögren's disease (SjD) is a chronic, systemic auto-immune disease characterized by lymphocytic infiltration of the exocrine glands, e.g. salivary and tear glands. Current treatment of SjD consists of local symptom relief for sicca complaints of the mouth, eyes, vagina and skin. Treatment with conventional disease modifying antirheumatic drugs (DMARDs) can be considered in patients with extra-glandular organ involvement, e.g. central and/or peripheral nervous system, renal, pulmonary and/or skin involvement, and arthritis [1,2].

No DMARDs have been officially licensed for the indication of SjD to date. So far, the large majority of randomized placebo-controlled trials (RCTs) failed to demonstrate clinical efficacy based on their primary study endpoint, underscoring that drug development for SjD is challenging. Nonetheless, promising data have been published from small-scale phase II RCTs with hydroxychloroquine/leflunomide [3], ianalumab (anti-BAFF receptor) [4], iscalimab (anti-CD40) [5], and remibrutinib (BTK inhibitor) [6]. Confirmative results of larger trials with these and other DMARDs in the SjD drug pipeline are eagerly awaited.

For future trial design, it is important to understand why so many previous drug treatments have failed in SjD. This review provides an overview of considerations and challenges for treatment, trial design and interpretation of clinical efficacy in patients with SjD.

2. Which immunological pathway should we target in SjD?

The etiopathogenesis of SjD is still enigmatic, although it is known that genetic, environmental and sex-related factors are involved. The pathogenesis of SjD is characterized by defects in epithelial cells and their close interaction with immune cells in the target organs, e.g. salivary glands [7]. The initial steps that lead to glandular dysfunction remain, however, elusive and this dysfunction may even occur in the apparent absence of periductal infiltrates, i.e. in patients with a salivary gland focus score of zero [8]. Still, a higher focus score is associated with more severe disease features and a higher risk of developing lymphoma [9], suggesting that infiltrating immune cells do play an important role in disease progression.

The immune cell infiltrate in the salivary glands surrounds the striated and excretory ducts, and is typically dominated by *T*- and B-lymphocytes. Both *T*- and B-lymphocytes are attracted to the ducts by chemokines and cytokines secreted by activated epithelial cells, molecules which further induce

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Article highlights

- Promising targets for treatment of SjD include B-lymphocytes, co-stimulatory molecules (e.g. CD40/CD40L), and signaling pathways of key cytokines (i.e. BLyS/BAFF, type-I IFN).
- The development of composite endpoints (Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS) and the candidate Sjögren's Tool for Assessing Response (STAR)) capturing multiple clinically relevant aspects of disease activity is an important step forward in the evaluation of treatment response in clinicals trials.
- Recent trials have applied very strict inclusion criteria, e.g. combining systemic involvement, biological activity, residual salivary flow and high symptom burden, but this approach has major impact on the eligibility of patients to be included in a trial.
- The goal of SjD treatment is reducing disease activity to ultimately prevent irreversible tissue damage. Difficulty in distinguishing disease activity from damage is, however, still a major hurdle for the evaluation of treatment response.
- Establishing the effect of treatment in SjD is challenging because follow-up measurements can be influenced by measurement error, natural variation, regression to the mean and expectation bias related to the trial design (placebo or nocebo response).

sustained lymphocyte activation. In particular, B-lymphocytes are hyperactivated in SjD, most likely in a T-lymphocyte dependent fashion [10,11]. T-helper lymphocytes can activate B-lymphocytes at the site of inflammation via cognate interaction, provision of co-stimulatory signals (e.g. CD40L), and cytokine secretion (e.g. IL-21). Besides IL-21, other key cytokines involved in B-lymphocyte hyperactivity are type-I interferon (IFN) and B cell activating factor (BAFF/BLyS) [10]. Type-I IFN (IFN and IFN) seems to be an important driver of the pathogenic process [12], which might be suggestive for a role of viruses early in disease development. Overexpression of type-I IFN is responsible for the so-called IFN signature, defined by the elevated expression of IFN stimulated genes, which is characteristically seen in the peripheral blood and salivary gland tissue of SjD patients. The IFN signature is strongly linked to the presence of anti-SSA/Ro antibodies [12], suggesting that targeting the type-I IFN pathway is of particular interest for anti-SSA/Ro positive SjD patients.

Our expanding knowledge concerning pathophysiological mechanisms underpinning SjD is reflected in clinical trial development with DMARDs addressing these salient pathways and mechanisms. Several overviews of clinical trials in SjD have been recently published [13–15]. Most of the previous larger RCTs in SjD have failed to meet their primary endpoint, despite targeting promising pathways, e.g. RCTs with rituximab (anti-CD20), abatacept (inhibition of costimulation) and tocilizumab (anti-IL6). Small-scale phase II trials have shown promising results, e.g. trials with hydroxychloroquine/leflunomide, ianalumab (anti-BAFF receptor) and iscalimab (anti-CD40). Currently, there are many active clinical trials in SjD, targeting various pathways and/or cells, which we summarize in Figure 1. Ritter and colleagues postulated that direct B-lymphocyte targeting, inhibition of CD40/CD40L co-stimulation, inhibition of key cytokine activity (i.e. BLyS/BAFF, type-I IFN) and intracellular signaling pathways (in B-lymphocytes) are the most promising targets for biological

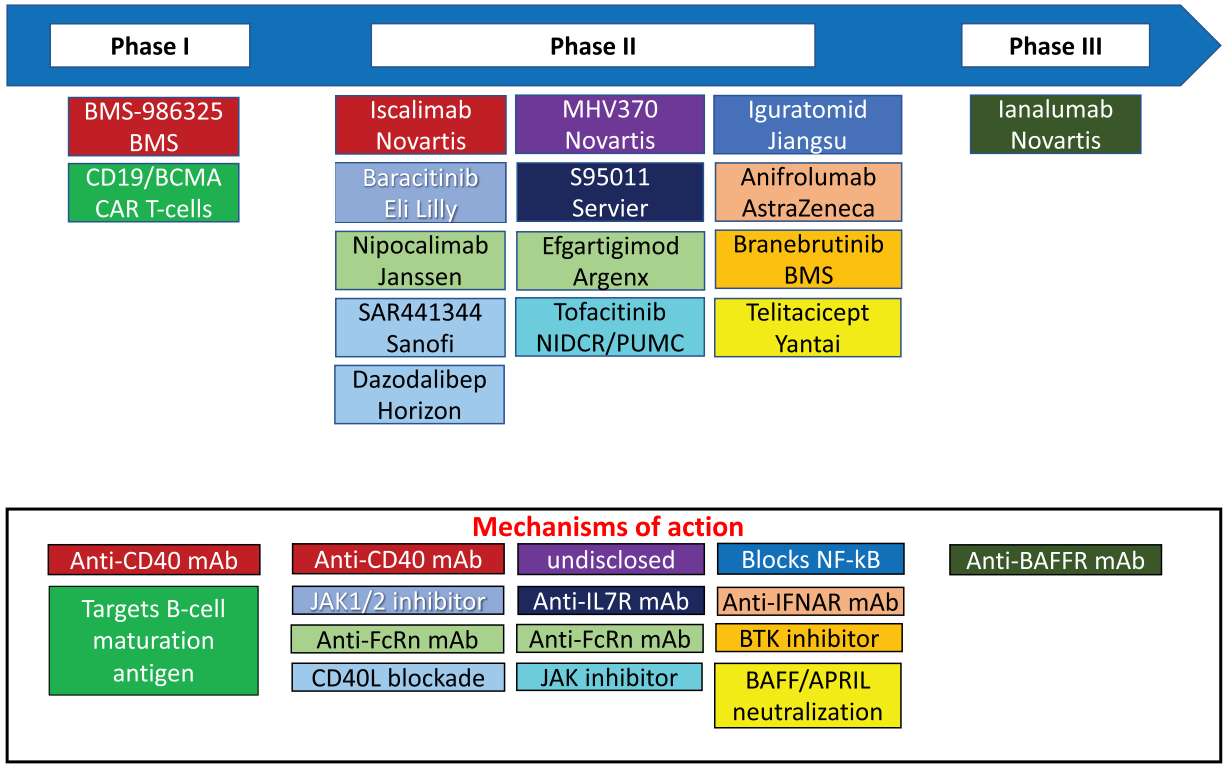

Figure 1. Overview of active clinical trials in patients with SjD (clinicaltrials.Gov) with results not published up to March 2023. BMS: Bristol-Myers Squibb, BCMA: B cell maturation antigen, CAR: Chimeric antigen receptor, NIDCR: National Institutes of Dental and Cranial Research, PUMC: Peking Union Medical Center, JAK: Janus kinase, FcRn: neonatal Fc receptor, mAb: monoclonal antibody, NF-Kb: nuclear factor kappa-light-chain-enhancer of activated B cells, IFNAR: interferon alpha receptor, BTK: Bruton's tyrosine kinase, BAFF: B cell activating factor, APRIL: a proliferation inducing ligand. Figure adapted from dr. A.N. Baer.

treatment of SjD [15]. Complementary to this, Felten and colleagues identified, using a drug repurposing transcriptomic approach, the IFN pathway as well as the PI3K/AKT/mTOR pathway as potential therapeutic targets [16]. Previous phase II trials with seletalisib, a small-molecule inhibitor of PI3Kδ, or filgotinib, a selective JAK1 inhibitor that downregulates IFN signaling, showed biological efficacy and potential clinical benefits. However, both studies did not meet their primary endpoint [17,18]. This phenomenon of biological efficacy (e.g. improvement of serological parameters, histological improvement) in the absence of significant clinical improvement is seen more frequently in clinical trials with SjD patients [19,20]. This may imply that treatment targets are identified in SjD patients at the group level, most often based on blood-derived data, not generally drive disease activity at individual patient level. The apparent heterogeneity in immunopathology argues for a more personalized approach, based on reliable biomarkers that reflect underlying disease mechanisms, to determine the choice of treatment at individual patient level or for subgroups of SjD patients with specific disease manifestations. The latter is, however, a challenge because of the variety of disease manifestations including patient signs and symptoms, glandular involvement, systemic organ involvement and serological abnormalities. Furthermore, this may also depend on the disease stage of the patient.

3. How should we measure clinical efficacy of treatment in SjD trials?

Most trials between 2004 and 2018 focused on non-validated primary endpoints including patient-reported outcome measures (PROMs) to assess improvement in symptoms of dryness, fatigue and pain, or used the change in saliva secretion to evaluate a more local effect of systemic treatment [14]. An important step forward was the development and validation of the European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) to assess systemic disease activity and the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) to assess patient-reported symptoms [21]. For the development of the ESSDAI, experts identified 12 organ-specific domains contributing to disease activity [22]. Together, these domains give a comprehensive overview of systemic disease activity. However, the individual domains reflect activity in different organs and the effect of treatment can be different per specific organ manifestation. Due to the heterogeneity of disease manifestations in SjD, trials have only limited power to evaluate which organ manifestations respond better to which drugs. In the ESSPRI, patients are asked to rate their symptoms of dryness, fatigue and pain on a numeric rating scale (NRS) of 0–10 [23]. These scores are averaged to calculate the ESSPRI total score, but it can also be useful to look at these symptoms separately. The ESSPRI is most often used in SjD, but there are also other questionnaires which measure SjD symptoms more specifically, such as the Sicca Symptoms Inventory (SSI), Xerostomia Index (XI), Profile of Fatigue and Discomfort (PROFAD) and the Primary Sjögren's Syndrome Quality of Life questionnaire (PSS-QoL). Correlations between PROMs, objective measurement of glandular function and systemic disease activity are low [24], indicating that these outcomes should be used complimentary to assess the complete clinical picture of SjD.

Most trials between 2019 and 2022 used the ESSDAI as the primary study endpoint. However, the many negative trials in combination with the heterogeneity of disease manifestations reopened the discussion regarding the most optimal primary study endpoint for RCTs in SjD [25]. Recently, the Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS) and the candidate Sjögren's Tool for Assessing Response (STAR) were developed as endpoints capturing multiple clinically relevant aspects of disease activity [26,27]. In both composite endpoints, patients are classified as responders or non-responders based on the combination of their response on five different items: systemic disease activity, patient-reported symptoms, tear gland involvement, salivary gland involvement and serological parameters (Figure 2). Multiple RCTs which were originally published as negative trials based on failure to demonstrate treatment efficacy with their primary endpoint showed positive results after reanalysis of trial outcomes using these composite endpoints [26,27].

4. Which patients should be included in clinical trials and is there a need for patient stratification?

Previously, we showed that the main inclusion criteria for recruitment into RCTs used to date can be summarized as: fulfilling the classification criteria for SjD, systemic involvement, biological activity, residual salivary flow and/or high symptom burden [14]. Selection of eligible patients can additionally be based on the specific target of the drug, e.g. including only anti-SSA/Ro positive SjD patients when targeting the type-I IFN pathway. It is not always necessary to exclude anti-SSA/Ro negative patients for SjD trials, as long as they meet the classification criteria. More recent trials applied very strict inclusion criteria. As a drawback, this approach has major impact on the eligibility of patients to be included in a particular trial. For example, combining three frequently used inclusion criteria (moderate to high systemic disease activity (ESSDAI ≥5), biological activity (presence of anti-SSA/Ro antibodies) and residual salivary flow (UWS of >0 ml/min)) resulted in eligibility of 76 (26.9%) of 283 patients from the Dutch REgistry of Sjögren Syndrome LongiTudinal (RESULT) cohort and 30 (17.4%) of 172 patients from the Belgian Sjögren's Syndrome Transition Trial (BeSSTT) cohort (Figure 3) [14]. Although it is possible to license a drug for a subgroup of patients with specific disease manifestations, our ultimate goal is to provide an effective treatment for preferably all SjD patients.

In the last years, three studies have been published on symptom-based stratification of patients with SjD. Firstly, Tarn and colleagues performed hierarchical cluster analysis based on the ESSPRI (dryness, fatigue and pain) and the Hospital Anxiety and Depression Scale (anxiety and depression) in 608 patients from the UK Primary Sjögren's Syndrome Registry (UKSJDR). They validated their findings in 334 patients from the French Assessment of Systemic Signs and Evolution of Sjögren's Syndrome (ASSESS) cohort and 62 patients from the Norwegian Stavanger cohort. Four distinct subgroups were identified with this Newcastle Sjögren's Stratification

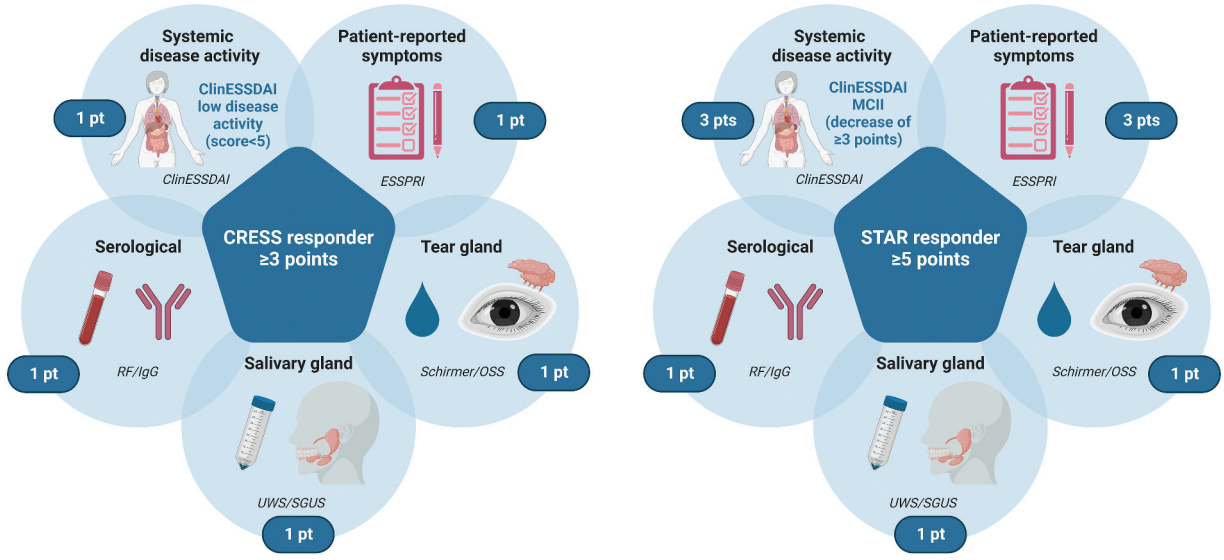

Figure 2. Overview of composite endpoints: Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS) and candidate Sjögren's Tool for Assessing Response (STAR). Figure adapted from [26]. The CRESS and candidate STAR include the same 5 domains: systemic disease activity, patient-reported symptoms, tear gland function, salivary gland function and serological parameters. Response in the systemic disease activity domain is defined as low disease activity at follow-up (ClinEssdai <5) in CRESS and as decrease compared to baseline (ΔClinESSDAI ≥3 points) in STAR. In the CRESS, all domains are equally balanced (1 point per item). Patients are classified as CRESS responders when they reach ≥ 3 of 5 points. In the candidate STAR, systemic disease activity and patient-reported symptoms are considered as major items (3 points per item) and tear gland function, salivary gland function and serology as minor items (1 point per item). Patients are classified as STAR responders when they reach ≥ 5 of 9 points.

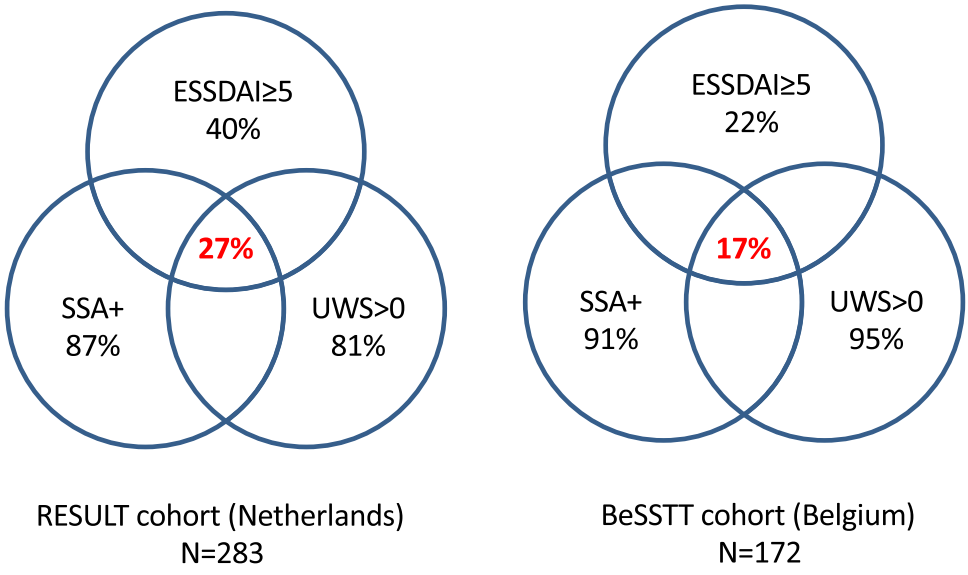

Figure 3. The proportion of SjD patients fulfilling frequently used inclusion criteria for clinical trials in the Dutch REgistry of Sjögren Syndrome LongiTudinal (RESULT) and Belgian Sjögren's Syndrome Transition Trial (BeSSTT) cohort studies from daily clinical practice. Figure adapted from [14].

Tool (NSST): low symptom burden, high symptom burden, dryness dominant with fatigue and pain dominant with fatigue. Re-analysis of data from the JOQUER and TRACTISS trials using this NSST suggested positive effect of treatment with hydroxychloroquine in the high symptom burden subgroup and with rituximab in the dryness dominant with fatigue subgroup [28]. Secondly, Lee and colleagues performed latent class analysis for clustering based on ESSPRI (dryness, fatigue, pain) and EQ-5D (anxiety, depression) in a prospective SjD cohort of 341 patients in Korea. Their analysis identified three classes: low symptom burden, dryness dominant and high symptom burden. Latent transition analysis revealed temporal stability of class membership up to 5 years of follow-up [29]. Finally, McCoy and colleagues performed hierarchical clustering based on (non-validated) questions of dryness, fatigue and pain in 1454 patients from the Sjögren's International Collaborative Clinical Alliance (SICCA) Registry and based on the ESSPRI (symptoms of dryness, fatigue, pain) in 2920 participants from the Sjögren's Foundation survey. They identified four clusters: low symptom burden, dry with low pain and low fatigue, dry with high pain and low to moderate fatigue, and high symptom burden. There was a discordance between experienced symptoms, disease severity and treatment. For example, patients in the high symptom burden cluster

received immunomodulatory treatment most often, despite having milder disease as measured by laboratory tests and organ involvement [30]. These data combined provide a rationale to perform explorative analyses regarding clinical efficacy according to symptom-based stratification in larger RCTs.

5. Is it possible to distinguish disease activity from damage in SjD?

The goal of SjD treatment is to decrease disease activity to ultimately prevent irreversible tissue damage. However, it can be very difficult to distinguish disease activity from damage in the evaluation of treatment response.

For systemic manifestations, ESSDAI is currently the preferred measurement instrument to assess activity. Multiple studies have demonstrated that the ESSDAI is valid, reliable and sensitive to change to assess systemic disease activity. The minimal clinically important improvement (MCII) is defined as ≥3 points improvement in ESSDAI compared to baseline [31]. However, for some domains e.g. the pulmonary and peripheral nervous system domains, differentiating disease activity from damage, can be challenging. For each single domain, long-lasting fixed manifestations (stable for at least 12 months) are considered as damage and are not anymore scored in the ESSDAI [32]. This can 'artificially' result in a decrease in ESSDAI score during long-term follow-up.

If it is preferred to evaluate disease activity independent of serological activity, e.g. in the case of B-lymphocyte targeted treatment, the ClinESSDAI can be used. The ClinESSDAI is based on the ESSDAI but does not include biological domain and uses different domain weights [33]. Recently, we evaluated the performance of the ClinTrialsESSDAI, which is based on the six most active domains (constitutional, lymph nodes, glandular, articular, cutaneous, hematological) of the ClinESSDAI. This new adapted measure did not show superior performance in responsiveness and discrimination compared to the ClinESSDAI and original ESSDAI, in two RCTs with abatacept and rituximab [34].

For patient-reported symptoms, the ESSPRI is the preferred measurement instrument to assess activity. The MCII is defined as ≥1 point or 15% improvement in ESSPRI compared to baseline [31]. The origin of persistent pain and fatigue may not be attributed to inflammation only, but also to other pain mechanisms such as central sensitization, disease perceptions, coping strategies and physical fitness, all contributing to the hyper-responsiveness of the central nervous system [35]. Overall, distinguishing between the influence of inflammatory disease activity, altered pain mechanisms and chronicity/damage is challenging when interpreting patient-reported symptoms of dryness, fatigue and pain.

For the salivary gland, the unstimulated whole saliva (UWS) can be used to measure glandular function or the stimulated whole saliva (SWS) to assess functional potential. Furthermore, salivary gland ultrasonography (SGUS) can be assessed with the Hocevar score, which includes the following five components: parenchymal echogenicity, homogeneity, presence of hypoechogenic areas, hyperechogenic reflections and clarity of the salivary gland border [36]. Poor correlations were found between salivary flow and SGUS, indicating that these are complementary measurements [37]. Although salivary flow rate and SGUS score may improve after immunomodulatory treatment [20,38], irreversible damage to the glands likely reduces the efficacy of such treatment. Irreversible damage is likely underpinned by the fact that salivary gland stem cells, critical for restoration of the glandular epithelium, are significantly reduced in numbers and potency in SjD [39]. The last years, a sub-taskforce of the Outcome Measures in Rheumatology Clinical Trials (OMERACT) working group developed a semi-quantitative scoring system for the ultrasonographic assessment of the parotid and submandibular salivary glands [40]. This scoring system is reliable and valuable for the classification of SjD, but a more detailed scoring system may be needed for the evaluation of treatment effects.

For the tear gland, the Schirmer's test can be used to measure tear production and the ocular staining score (OSS) can be used to measure ocular surface disease, taking into account corneal and conjunctival staining scores, the presence of filaments, staining in the pupillary area, and patches of confluent staining [41]. UWS, SGUS, Schirmer's test and OSS, measuring glandular function and structural glandular changes, were included in the CRESS and candidate STAR to be able to detect changes in activity in glandular disease, but it should be kept in mind that they all can be affected by damage.

One of the measurements for assessing disease damage is the Sjögren's Syndrome Disease Damage Index (SSDDI) [42]. This measure includes damage of the salivary glands, by assessing salivary flow impairment and loss of teeth, damage of the tear glands, by assessing tear flow impairment and structural damage to the eyes, and also systemic disease damage. The SSDDI includes items regarding neurological, pleuropulmonary and renal damage and an item for lymphoproliferative disease. Although the SSDDI is not useful as outcome measure in clinical trials, it could be helpful to assess damage already present at baseline.

6. What can be considered as treatment effect?

Capturing the effect of active treatment in SjD can be challenging because of several reasons. Firstly, follow-up measurements can be influenced by measurement error related to the reliability of a test or the observer. This is especially challenging for international multicenter trials, in which it is more difficult to calibrate the tests and observers. Secondly, natural variation in activity can occur within patients over time and regression to the mean is likely when selecting only patients with active disease at baseline. Background medication should be avoided or at least kept at a stable dose, especially corticosteroid use, during the trial to minimize its influence on the study endpoints [14].

Thirdly, response rates in RCTs can also be affected by expectation bias related to trial design. This can be based on positive or negative expectations, leading to placebo response, nocebo response or both [43]. Multiple RCTs with ESSDAI as primary study endpoint showed response rates >50% in the placebo treatment arm. A large placebo response

rate makes it difficult to statistically demonstrate superiority of the active treatment arm, considering that an extremely high clinical efficacy of the drug is needed under these circumstances. Due to the heterogenic and systemic nature of the disease, a composite endpoint which combines the response on different items seems more feasible to define responders in SjD. During development and validation studies, the CRESS reduced the response rate in the placebo treatment arm and enabled discrimination in terms of responders between the active treatment and placebo treatment arms for trials with abatacept and rituximab [26].

Based on the large placebo response rates in PROMs, Wratten and colleagues recently developed and tested an alternative responder definition for ESSPRI. They concluded that completing a trial with ESSPRI score of ≤3 and with improvement of ≥1.5 points compared with baseline, is a relevant responder definition for clinical trials. This strict definition ensures that patients achieve low/minimal symptom severity and exceed minimally important change. In their phase IIb trial, the between group difference in response rate increased from 5% to 15%. However, the drastically reduced proportion of responders in both the active treatment (VAY 300 mg) and placebo treatment arms (21% vs. 6%) questions the clinical usefulness of such a strict ESSPRI responder definition [44].

Besides placebo effects, nocebo effects can also occur in placebo-controlled trials, which is created by the knowledge of participants that they may have received placebo, whilst actually being allocated to the active treatment arm. On the other hand, an active comparator, e.g. already licensed effective treatment as gold standard, may result in improvement in both treatment arms, owing to patients certainty that they receive treatment whichever arms they are allocated to, complicating the establishment of the 'true' effect of the tested drug. A recent systematic analysis of RCTs in patients with rheumatoid arthritis demonstrated that the American College of Rheumatology (ACR) 20, ARC50 and ACR70 response rates in the active treatment arm are systematically higher in so-called head-to-head comparisons with an active comparator compared to placebo-controlled trials [43], providing solid data confirming the existence of this phenomenon in RCT in the rheumatology world.

Overall, it is important to agree on *a priori* definition of a clinically relevant response to interpret clinical efficacy results in trials. For the CRESS, based on our expert opinion, we proposed a response rate of ≥40% in the active treatment arm of an open-label trial or ≥20% difference in the proportion of responders between the active treatment and placebo treatment arms may be considered as clinically relevant [14].

7. Conclusion

No DMARDs have been officially licensed for the indication of SjD to date. In the last 20 years, many RCTs have been performed, but unfortunately most drugs failed to demonstrate clinical efficacy in SjD in phase II and/or III trials. Evolving challenges in treatment, trial design and interpretation of clinical efficacy in this multifaceted disease include 1) identifying the right target/immunological pathway for treatment, 2) selection of the primary study endpoint for trials and definition of clinically relevant response to treatment, 3) patient inclusion and stratification: including a specific study population vs. broad indication for SjD, 4) distinguishing between disease activity and damage and 5) establishing the effect of treatment considering measurement error, natural variation and expectation bias (placebo or nocebo response).

8. Expert opinion

The main question is why do (most) drug treatments fail in SjD? This is a complex question to answer, since we face multiple challenges in this heterogeneous systemic autoimmune disease. There are several concerns that need to be addressed. Which immunological pathway should we target in SjD? How should we measure clinical efficacy of treatment in SjD trials? Which patients should be included in clinical trials and is there a need for patient stratification? Is it possible to distinguish disease activity from damage in SjD? What can be considered as treatment effect?

In this expert review, we summarized available literature and shared our personal view to (partially) answer these questions. In light of the first challenge, targets that are involved in both the immune cell response and dysregulation of glandular epithelial cells (e.g. B-lymphocytes, type-I interferon) are of particular interest to treat both glandular and extra-glandular manifestations of SjD. With regard to the other challenges, the recent development of composite study endpoints (CRESS, STAR) can be a crucial step forward in the evaluation of treatment efficacy in clinical trials. Recent trials have applied very strict inclusion criteria, but we should keep in mind that this has major impact on the eligibility of patients to be included in a particular trial. Recently, symptom-based stratification in multiple large cohorts revealed distinct clinical phenotypes or pathobiological endotypes with potentially different responses to immunomodulatory treatments, which is interesting to investigate further in larger RCTs or using pooled data. For the evaluation of treatment response, the difficulty to distinguish disease activity from damage is still a major hurdle. In addition, follow-up measurements can be influenced by measurement error, natural variation, regression to the mean and expectation bias related to the trial design.

In addition, there are several remaining inquiries for daily clinical practice and research in the field of SjD. What are the most important clinical indications to start systemic treatment? Which patients are most likely to respond to which targeted treatment? What is the treatment goal; should we aim for patient acceptable symptom state (PASS), clinically relevant improvement, low disease activity or remission? Can we benefit from a consensus-based definition of flare and remission in patients with SjD?

At this moment, we cannot answer all these questions, but we have interesting data and initiatives to consider. The 2019 EULAR recommendations for the management of SjD with topical and systemic therapies have been developed by a large multidisciplinary team and are mostly based on experience rather than evidence-based medicine [1]. In daily clinical practice, DMARDs are mainly used in SjD patients with severe systemic involvement such as nervous system, renal, pulmonary or cutaneous involvement and arthritis, in line with

treatment of closely related systemic autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis. So far, we have definitions for high, moderate or low disease activity and MCII based on the ESSDAI and ESSPRI as well as responder definitions based on the recently developed composite endpoints. A recent analysis in our observational RESULT cohort showed discordance between the proportion of patients reported being in an acceptable symptom state according to the PASS question versus patients with an acceptable symptom state according to the predefined ESSPRI cut-off point of score <5. Of the 278 included SjD patients, 72% answered positive to the PASS question 'Considering all the different ways your disease is affecting you, if you were to stay in this state for the next few months, do you consider your current state satisfactory?,' whereas 31% had a score <5 on the ESSPRI total score (NRS 0–10) considering 'How severe has your dryness, fatigue and pain been during the last two weeks?' [45]. Within the innovative medicines initiative (IMI) project 'NECESSITY,' consensus of patients and researchers, together with data-analysis in many RCTs, will be used for the development of the Sjögren's Tool for Assessing Flare (STAF) to define a flare in patients living with SjD. The future research agenda should also focus on further defining the target to treat including the definition of clinically relevant improvement, low disease activity or remission in SjD.

Hopefully, all combined efforts will eventually lead to finding effective treatment for SjD and the official licensing of drugs for the indication of SjD, for the total group and/or for a targeted group. This will be an important step forward in the treatment of SjD patients in daily clinical practice.

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