Editorial

Selection of study endpoints and patients for clinical trials in primary Sjögren's syndrome

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ABSTRACT

In the last decade, many randomised controlled trials (RCTs) with biological DMARDs (bDMARDs) have been performed in patients with primary Sjögren's syndrome (pSS). Unfortunately, no bDMARD has yet been approved for systemic
treatment of pSS. The heterogeneity of disease manifestations raises two essential questions: 1) which outcome measure is valid, reliable and responsive to demonstrate treatment efficacy and should be used as primary study endpoint? and 2) which pSS patients should be included in clinical trials?
Both the selection of the primary study endpoint and the selection of patients are crucial and evolving issues in clinical trial design in pSS. This article summarises the history and comments the selection of primary study endpoints including the novel development of composite endpoints. Furthermore, this article gives an overview of inclusion criteria used for phase II and III trials, and illustrates by data-analysis based on two prospective observational cohorts that each additional selection criterion will (largely) decrease the number of eligible patients in daily clinical practice.

Introduction

Primary Sjögren's syndrome (pSS) is a systemic auto-immune disease characterised by lymphocytic infiltration of the salivary and tear glands, leading to symptoms of dry mouth (xerostomia) and dry eyes (keratoconjunctivitis sicca). Besides sicca complaints, patients often experience profound fatigue and diffuse pain. Systemic manifestations occur in roughly half of the pSS patients and can potentially affect almost every organ and tissue, such as joints, skin, lungs, kidneys as well as peripheral nerves (1-2). B-cell hyperactivity is a hallmark of the disease, reflected by serological abnormalities including elevated serum levels of total IgG, presence of autoantibodies (anti-Ro/SSA, anti-La/SSB, rheumatoid factor) and the increased risk of B cell lymphoma development, in particular lymphoma involving the mucosa-associated lymphoid tissue (MALT) (3-5).

Current treatment of pSS is mainly symptomatic. For systemic manifestations, immunosuppressants or conventional disease modifying antirheumatic drugs (cDMARDs) like hydroxychloroquine are used. In the last decade, multiple randomised controlled trials (RCTs) with biological DMARDs (bDMARDs) have been performed, but no bDMARD has yet been approved for the treatment of pSS (6). The heterogeneity of disease manifestations raises the essential question which aspect of the disease is clinically most relevant to determine efficacy of systemic treatment. This leads to two related important topics in clinical trial design in pSS: 1) which outcome measure is valid, reliable and responsive to demonstrate clinical treatment efficacy and should be used as primary study endpoint? and 2) which pSS patients should be included in clinical trials?

Selection of endpoints for clinical trials

Table I gives an overview of the primary endpoints used in the many completed phase II and III placebo-controlled trials in patients with pSS. As can be seen in this table, a wide variety of endpoints have been used. Initial trials used improvement in (multiple) visual analogue scores (VAS) of fatigue, pain and/or dryness, or change in stimulated whole

saliva (SWS) secretion rate. More recent trials used change from baseline in EULAR Sjögren's syndrome disease activity index (ESSDAI) or the minimal clinically important improvement (MCII) of ≥3 points in ESSDAI.

Several small, mostly open-label, phase II trials with bDMARDs showed promising results in patients with pSS, mostly based on ESSDAI and patient-reported outcomes (7). However, larger phase III RCTs failed to demonstrate significant superiority of the bDMARD compared to placebo treatment, which is necessary for official licensing of a new drug for the indication of pSS. These disappointing results opened the discussion about the selection of the most optimal primary study endpoint for clinical trials in pSS. When evaluating its quality, the endpoint should be 1) valid: the degree to which the instrument measures the construct it claims to measure and is considered clinically relevant, 2) reliable: the degree to which the instrument is free from measurement error, and 3) responsive to change: the ability of the instrument to detect changes over time in the construct to be measured. Single endpoints such as the ESSDAI for systemic disease activity and the EULAR Sjogren's Syndrome Patient Reported Index (ESSPRI) for patient-reported symptoms met all these three criteria (8). Unfortunately, RCTs using these outcome measures still failed. A detailed look at these trials revealed an important issue, namely large placebo response rates. For example, placebo response rates of >50% for the ESSDAI MCII of ≥3 points decrease were noted in trials which used ESSDAI ≥5 as inclusion criterion. This high placebo response makes it very difficult to demonstrate superiority of bDMARDs (7).

Due to the heterogeneous nature of pSS, the development of a composite endpoint was a logical next step as outcome measure. In total, five complimentary aspects were considered by experts as most relevant for the assessment of treatment response in pSS: systemic disease activity, patient-reported symptoms, tear gland function, salivary gland function and serological parameters. These domains are included in the newly developed Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS) as well as the candidate Sjögren's Tool for Assessing Response (STAR).(9, 10) Although these two endpoints are very similar to each other, an essential difference between CRESS and candidate STAR is the definition of response in the systemic disease activity domain. Response is defined as low disease activity at follow-up (ClinESSDAI<5) in CRESS and as decrease compared to baseline (ΔClinESSDAI ≥3 points) in STAR. Furthermore, in the CRESS the five domains are equally balanced; patients are classified as CRESS responders when they respond on ≥3 of these 5 domains. 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 points (Table II). *Post-hoc* re-analysis of previous RCTs with bDMARDs using these two composite endpoints showed promising results, *i.e.* a lower placebo response rate compared to the original single endpoint or even statistical superiority of the active treatment arm (9, 10). As a next step, these novel composite endpoints will require validation in a prospective RCT.

Use of composite endpoints in future phase II and phase III trials

There are important differences in design between phase II and phase III trials. In both designs, it is worthwhile to consider the use of a composite endpoint. In small-scale proof-of-mechanism studies, the primary aim is to explore both safety and clinical efficacy of a new drug on the full spectrum of disease activity in patients with pSS. A composite endpoint captures multiple clinically relevant aspects of pSS and therefore seems valuable as primary endpoint for explorative phase II trials. Importantly, total CRESS and STAR response are binary study endpoints (responder yes/no) and thus require a relatively large sample and/or effect size to detect a statistically significant difference between the active treatment and placebo treatment arms. For example, with a total sample size of 30 participants, allocation ratio of 1:1, power of 0.80, alpha of 0.05 (two-tailed), a response rate of ≈80% in the active treatment arm compared to ≈25% in the placebo treatment arm is needed to prove statistically significant superiority of the drug. Based on previous trials in pSS (Table I), it is unlikely that these response rates will be reached. However, the primary endpoint in a phase II trial should be interpreted for safety, proof-of-mechanism and clinical relevance, which is not the same as statistical significance.

The data of smaller phase II trials can provide a basis for larger RCTs with adequate statistical powering. Therefore, it is important to agree on a priori definition of clinical relevance based on the MCII for continuous endpoints or the proportion of responders for binary endpoints. For example, based on our expert opinion, a response rate of ≥40% in the active treatment arm of an open-label trial or ≥20% difference in response rate between the active treatment and placebo treatment arms may be considered as clinically relevant. In larger phase III RCTs, the primary aim is to demonstrate clinical efficacy. This type of trial should be adequately powered to demonstrate statistical superiority of the active treatment compared to placebo. In both phase II and III trials, it is also important to include all individual composite endpoint domains as secondary study endpoints to explore which particular domains are responding to systemic treatment. These items over time can be analysed as continuous variables using longitudinal data modelling.

In addition, analysis of serum, saliva, tears and repeated salivary gland biopsies can give valuable information as exploratory endpoints in phase II and III trials. Histopathological analysis of the area of infiltration (%$CD45^+$) or more specifically, numbers of T- and B-lymphocytes, will provide insight in the anti-inflammatory effect of the treatment at the tissue level. Other specific histopathologic parameters, such as the presence and severity of lymphoepithelial lesions or the number of follicular DC networks and ectopic

Table I. Primary endpoints and main inclusion criteria of placebo-controlled phase II and III RCTs in patients with pSS.

Drug (target)	Number of patients (enrolled or aim)	Primary endpoint	Main inclusion criteria	Reference (when already published), ClinicalTrials.gov number
Etanercept (TNF-α)	28	≥20% improvement in ≥2 of 3 domains (subjective and/or objective measures for oral and ocular dryness, and ESR and IgG) at week 12	AECG criteria, symptoms of oral and ocular dryness, elevated ESR or IgG	(16), NCT00001954
Infliximab (TNF-α)	103	≥30% improvement in ≥2 of 3 VAS (joint pain, fatigue, dryness) at week 10	AECG criteria, >50 mm on ≥2 of 3 VAS (joint pain, fatigue, dryness)	(17), N/A
Rituximab (CD20)	17	≥20% improvement in fatigue VAS at week 24	AECG criteria, anti-SSA or –SSB+, >50 mm on fatigue VAS	(18), N/A
Rituximab (CD20)	30	Change in SWS	AECG criteria, SWS ≥0.15 ml/min, RF+ and anti-SSA or –SSB+	(19), NCT00363350
HCQ (TLR signalling)	120	≥30% improvement in ≥2 of 3 NRS scales (dryness, fatigue, pain) at week 24	AECG criteria	(20), NCT00632866
Anakinra (IL1)	26	Difference between groups in fatigue scores adjusted for baseline values at week 4	AECG criteria	(21), NCT00683345
Rituximab (CD20)	120	≥30 mm improvement on 2 of 4 VAS (global disease activity, pain, fatigue, dryness) at week 24	AECG criteria, ≥50 mm on 2 of 4 VAS (global disease activity, pain, fatigue, dryness), onset of symptoms in past 10 years, biological activity or ≥1 extraglandular manifestation	(22), NCT00740948
Rituximab (CD20)	133	≥30% improvement in fatigue or oral dryness VAS at week 48	AECG criteria, anti-SSA positivity, UWS>0 ml/min, symptomatic fatigue, oral dryness >5/10	(23), N/A
Baminercept (LTβR)	52	Change in SWS at week 24	AECG criteria, SWS≥0.1 ml/min, severe parotid swelling or one of the following: >50mm on fatigue or joint pain VAS or extraglandular manifestations causing organ dysfunction	(24), NCT01552681
HCQ/LEF (T-cells and TLR signalling)	29	Change in ESSDAI at week 24	AECG criteria, ESSDAI≥5, labial salivary gland biopsy+	(25), N/A
Tocilizumab (IL6)	110	≥3 points improvement in ESSDAI, no occurrence of moderate or high activity in a new ESSDAI domain and no worsening in physician GDA (≥1/10) at week 24	AECG criteria, ESSDAI≥5, SSA+	(26), NCT01782235
Abatacept (CTLA4)	80	Change in ESSDAI at week 24	AECG criteria, ESSDAI≥5, disease duration ≤7 years, parotid gland biopsy+	(27), NCT02067910
Ianalumab (BAFF receptor)	27	Change in ESSDAI at week 12	AECG criteria, ESSDAI≥6, ANA≥1:160 and RF+ or SSA+, SWS>0 ml/min	(28), NCT02149420
Iscalimab (CD40)	44 (two cohorts)	Safety and change in ESSDAI at week 12	AECG criteria, ESSDAI≥6, SSA+ or ANA≥1:160 and RF+, SWS>0 ml/min	(29), NCT02291029
MEDI5872 (ICOSL)	32	Change in ESSDAI at week 14	AECG criteria, ESSDAI≥6, SSA+ or SSB+, and IgG>13 or RF+ or cryo+	(30), NCT02334306
Seletalisib (PI3K)	27	Change in ESSDAI at week 12	AECG criteria, ESSDAI≥5, SSA or SSB+, UWS>0 ml/min	(31), NCT02610543
Belimumab/rituximab (BAFF/CD20)	86	Number of participants with (S)AEs at week 68	AECG criteria, ESSDAI≥5, SSA+ or SSB+, UWS>0 or SWS>0.05 ml/min, oral dryness ≥5 on NRS	(32), NCT02631538
RO5459072 (cathepsine-S inhibitor)	75	≥3 points improvement in ESSDAI at week 12	AECG criteria, ESSDAI≥5, ESSPRI≥5, SSA+ or SSB+	N/A, NCT02701985
CDZ173 (leniolisib) (PI3K-delta)	30	Safety and change in ESSPRI at week 12	ESSDAI≥6, ESSPRI≥5, seropositive pSS, SWS>0	(33), NCT02775916
Abatacept (CTLA4)	187	Change in ESSDAI at week 24	ACR-EULAR criteria, ESSDAI≥5, SSA+	(34), NCT02915159
Ianalumab (BAFF receptor)	190	Change in ESSDAI at week 24	AECG criteria, ESSDAI≥6 (within domains: constitutional, lymphadenopathy, glandular, articular, cutaneous, haematological, biological), ESSPRI≥5, SSA+, SWS>0.1 ml/min	(35), NCT02962895
Filgotinib (JAK), laraplenib (SYK), tirabrutinib (BTK)	150	Composite endpoint of CRP and patient-reported VAS scores (global disease, pain, oral, ocular dryness, fatigue) at week 12	AECG criteria (primary or secondary SS), ESSDAI≥5, SSA+ or SSB+	(36), NCT03100942
RSLV-132 (RNAse)	28	Interferon gene expression at day 99	AECG criteria, SSA+, interferon signature+	(37), NCT03247686
Iscalimab (CD40)	260 (two cohorts)	Cohort 1: Change in ESSDAI at week 24. Cohort 2: Change in ESSPRI score at week 24	Both cohorts: ACR-EULAR criteria, SSA+, SWS≥0.1 ml/min Cohort 1: ESSDAI≥5 (within 8 domains), ESSPRI≥5 Cohort 2: ESSPRI≥5 (fatigue or dryness), ESSDAI<5 (within 8 domains scored for cohort 1), increased IgG or lymphocytopenia or low C3/C4	N/A, NCT03905525

Drug (target)	Number of patients (enrolled or aim)	Primary endpoint	Main inclusion criteria	Reference (when already published), ClinicalTrials.gov number
LOU064 (BTK)	252	Change in ESSDAI at week 24	ACR-EULAR criteria, ESSDAI≥5 (within 8 domains), ESSPRI≥5, SSA+, UWS>0 ml/min	N/A, NCT04035668
RC18 (TACI)	42	Change in ESSDAI at week 24	ACR-EULAR criteria, ESSDAI≥5, SSA+	N/A, NCT04078386
VIB4920 (CD40L)	174 (two cohorts)	Cohort 1: Change in ESSDAI at week 24 Cohort 2: Change in ESSPRI at week 24	Both cohorts: ACR-EULAR criteria, SSA+. Cohort 1: ESSDAI≥5 (within domains: constitutional, lymphadenopathy, glandular, articular, cutaneous, renal, muscular, haematological, biological) Cohort 2: ESSDAI<5, ESSPRI≥5, SWS>0.1 ml/min	N/A, NCT04129164
Branebrutinib (BTK)	RA: 80, pSS: 45 and SLE: 60	Composite endpoint of ESSPRI, ESSDAI, ocular staining, salivary flow and serological marker at week 24	ACR-EULAR criteria, ESSDAI ≥6 (with activity in at least one of these domains: lymphadenopathy, glandular, articular, haematological, biological), disease duration ≤7 years, SSA+ and one of the following: low C3/C4, RF+, cryo+ or increased IgG, SWS>0.05 or UWS>0.01 ml/min	N/A, NCT04186871
Tofacitinib (JAK1 and JAK3)	30	Safety and tolerability	AECG criteria, ESSDAI ≤13, SWS>0	N/A, NCT04496960
SAR441344 (CD40 ligand)	88	Change in ESSDAI at week 12	ACR-EULAR criteria, ESSDAI≥5 (within domains: constitutional, lymphadenopathy, glandular, articular, muscular, haematological, biological), disease duration ≤15 years, SSA+, SWS≥0.1 ml/min, RF+ or increased IgG	N/A, NCT04572841
S95011 (CD127r)	45	Change in ESSDAI at week 13	ACR-EULAR criteria, ESSDAI≥6 (within domains: constitutional, lymphadenopathy, glandular, articular, cutaneous, hematologic, biologic), SSA+ or ANA≥1:1320 or RF>20, SWS>0 ml/min	N/A, NCT04605978
Iguratimod (B- and T-cells)	144	Change in ESSDAI at week 12	ACR-EULAR criteria, ESSDAI≥6, ncreased IgG, SSA+	N/A, NCT04830644
Nipocalimab (neonatal Fc receptor, FcRN, blocks binding of IgG on FcRn)	150	Change in ClinESSDAI at week 24	ACR-EULAR criteria, ClinESSDAI≥6, at least one abnormal laboratory marker for pSS, SSA+	N/A, NCT04968912
MHV370 (TLR signalling)	pSS: 48, MCTD: 12	Change in ESSDAI at week 24	ACR-EULAR criteria, ESSDAI≥5 (within domains: constitutional, lymphadenopathy, glandular, articular, cutaneous, renal, hematologic, biologic), UWS>0 ml/min	N/A, NCT04988087
HCQ/MMF, HCQ/LEF (T-cells and TLR signalling)	300 (two cohorts)	Cohort 1 and cohort 2: preliminary STAR response at week 24	Both cohorts : ACR-EULAR criteria Cohort 1: ESSPRI≥5, ESSDAI<5 Cohort 2: ESSDAI≥5	N/A, NCT05113004
Ianalumab (BAFF receptor)	489	Change in ESSDAI at week 48	ACR-EULAR criteria, ESSDAI≥5 (within domains: constitutional, lymphadenopathy, glandular, articular, cutaneous, renal, hematologic, biologic), disease duration ≤7.5 years, SSA+ (SSA- negative allowed if salivary gland biopsy positive confirmed by central external laboratory, no more than 10% negative), SWS≥0.05 ml/min	N/A, NCT05349214
Ianalumab (BAFF receptor)	268	Change in ESSDAI at week 48	ACR-EULAR criteria, ESSDAI≥5 (within domains: constitutional, lymphadenopathy, glandular, articular, cutaneous, renal, hematologic, biologic), disease duration ≤7.5 years, SSA+ (SSA- allowed if salivary gland biopsy positive confirmed by central external laboratory, no more than 10% negative), SWS≥0.05 ml/min	N/A, NCT05350072
Anifrolumab (type-1 IFN signalling)	30	CRESS response at week 24	ACR-EULAR criteria, disease duration ≤10 years, ESSDAI≥5 and/or ESSPRI≥5 (at least 50% ESSDAI≥5)	N/A, NCT05383677

RCT: randomised controlled trial; pSS: primary Sjögren's syndrome; TNF: tumor necrosis factor; ESR: erythrocyte sedimentation rate; IgG: immunoglobulin G; AECG: American-European Consensus Group; VAS: visual analogue scale; SWS: stimulated whole saliva secretion; RF: rheumatoid factor; HCQ: hydroxychloroquine; TLR: toll-like receptor; NRS: numeric rating scale; IL: interleukin; LTβR: lymphotoxin β receptor; LEF: leflunomide; ESSDAI: European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index; GDA: global disease activity; CTLA: cytotoxic T-lymphocyte-associated protein 4; BAFF: B-cell activating factor; ICOSL: inducible T-cell costimulatory ligand; cryo: cryoglobulin; PI3K: phosphoinositide 3-kinase; UWS: unstimulated whole saliva secretion; SAE: serious adverse event; ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index; JAK: Janus kinase; SYK: spleen tyrosine kinase; BTK: Bruton's tyrosine kinase; CRP: C-reactive protein; TACI: transmembrane activator and calcium modulatory and cyclophyline ligand interactor; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; FcRN: neonatal Fc receptor; MCTD: mixed connective tissue disease; MMF: mycophenolate mofetil; STAR: Sjögren's Tool for Assessing Response; IFN: interferon; CRESS: Composite of Relevant Endpoints for Sjögren's Syndrome; N/A: not applicable.

Table II. Composite endpoints: CRESS and candidate STAR items and definition of response.

Domain	Definition	CRESS	Candidate STAR
Systemic disease activity	ClinESSDAI: score <5 (CRESS) ClinESSDAI: decrease of ≥3 points from baseline (STAR)	1	3
Patient-reported symptoms	ESSPRI: decrease of ≥1 point or ≥15% from baseline	1	3
Tear gland function*	Schirmer's test: if abnormal score (≤5 mm) at baseline: increase ≥5 mm from baseline. Or OSS: if abnormal score (≥3 points) at baseline: decrease of ≥2 points from baseline. Or If both Schirmer and OSS normal score at baseline: no change to abnormal.	1	1
Salivary gland function	UWS: if score is >0 at baseline: increase of ≥25% from baseline. If score is 0 at baseline: any increase from baseline. Or SGUS: decrease of ≥25% in total Hocevar score from baseline.	1	1
Serological	Serum RF level†: decrease of ≥25% from baseline. Or Serum IgG level: decrease of ≥10% from baseline.	1	1
Responder		≥3 points	≥5 points

CRESS: Composite of Relevant Endpoints for Sjögren's Syndrome; STAR: Sjögren's Tool for Assessing Response; ClinESSDAI: Clinical EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index; OSS: ocular staining score; UWS: unstimulated whole saliva secretion; SGUS: salivary gland ultransonography; RF: rheumatoid factor.
*Mean of both eyes. †Total RF or RF-IgM (IU/mL).

germinal centres may also provide valuable information on the mode of action of the treatment (11).

Selection of patients for clinical trials

Table I gives an overview of the wide variety of inclusion criteria used in placebo-controlled RCTs in patients with pSS. As shown in this table, the main inclusion criteria can be summarized as fulfilling the classification criteria for pSS, systemic involvement, biological activity, residual salivary flow and/or high symptom burden. With respect to fulfilling the classification criteria, there was a change from the American-European Consensus Group (AECG) criteria in 2002 to the ACR-EULAR criteria in 2016. The ACR-EULAR criteria give more weight (3 points) to salivary gland biopsy (focus score ≥1 foci/4mm^2) and anti-Ro/SSA compared to ocular staining score (OSS), Schirmer's test and unstimulated whole saliva (UWS) flow rate (1 point) (12).

Exclusion criteria are mainly based on contra-indications of the specific bDMARD, presence of any other connective tissue disease, previous systemic medication use with its corresponding wash-out period and current medication use. If background medication including corticosteroids is allowed (although no systemic drugs are approved for pSS), a stable dose is often recommended during the trial to minimise its influence on the study endpoints.

An important question in trial design is which subgroup of pSS patients should be included to be able to show clinical efficacy. Selection can be based on characteristics for which the specific drug is targeted. For new drugs, there is only limited possibility to show its clinical efficacy, since in case of clearly negative results in a phase II trial this drug or even this mode of action will be abandoned for the indication of pSS. Therefore, the intuitive choice is to include the most active group of patients, as systemic treatment will improve disease activity and tissue damage is irreversible. The choice for a short disease duration can also be based on glandular involvement. Loss of salivary gland function is already prominent in early onset pSS and progression of salivary gland dysfunction will lead to very low levels of salivary flow in approximately 4–7 years of diagnosis (13). Early disease can be interpreted as active disease, which is referring to rheumatic arthritis and systemic lupus erythematosus, but the course of the disease can be different in pSS, with moderate to severe phases years after diagnosis.

Since its development in 2010, the ESSDAI has been used frequently in trials as inclusion criterion to include patients with moderate to high systemic disease activity. A drawback of inclusion of only highly active patients is that this may lead to regression to the mean due to natural variation, which will increase response rates in both active treatment and placebo treatment arms. Recent trials with ESSDAI as inclusion criterion also specified that there should be activity in the ESSDAI domains which are more sensitive to change, such as the articular or constitutional domain. However, a recent reanalysis of trial data of two RCTs (one with rituximab, one with abatacept) using the Clinical Trials ESSDAI (ClinTrialsESSDAI) found no major difference in responsiveness of the ESSDAI (consisting of all 12 domains), ClinESSDAI (*i.e.* the ESSDAI excluding the biological domain) and ClinTrialsESSDAI (consisting of the 6 most frequently active clinical domains: glandular, articular, haematological, constitutional, lymphadenopathy and cutaneous domain) (14). This study argues against the recent trend of inclusion based on specific ESSDAI domains. Furthermore, a consequence could be that patients for example with lung or nerve involvement, but without involvement of these more sensitive to change domains, will not be included in trials. Despite their lower prevalence (around 20%), lung and nerve involvement are clinically relevant manifestations of pSS for which effective treatment is highly needed, advocating for inclusion of patients with activity in these domains in trials as well.

Table III. Patients from the observational RESULT or BeSSTT cohort who fulfil the ACR-EULAR criteria for pSS: overview of patient characteristics and the proportion of patients meeting single inclusion criteria used in clinical trials.

	RESULT cohort, patients fulfilling ACR-EULAR criteria for pSS (n=302)	BeSSTT cohort, patients fulfilling ACR-EULAR criteria for pSS (n=180)
Age	55 (43-65)	54 (43-66)
Female gender	269 (89.1%)	159 (88.3%)
Disease duration	5.0 (2.0-11.0)	1.1 (0.0-6.3)
Current systemic treatment		
HCQ	50 (16.6%)	72 (40.0%)
Methotrexate	4 (1.3%)	10 (5.6%)
Corticosteroids	19 (6.3%)	17 (9.4%)
Other immunosuppressives	25 (8.3%)	8 (4.4%)
ESSDAI	4 (2-7)	2 (0-4)
ESSPRI	6.0 (4.3-7.3)	5.8 (4.1-7.3)
Short disease duration		
≤4 years	127/302 (42.1%)	118/180 (65.6%)
≤7 years	189/302 (62.6%)	139/180 (77.2%)
≤10 years	225/302 (74.5%)	149/180 (82.8%)
Systemic involvement		
ESSDAI ≥5	115/296 (38.9%)	39/180 (21.7%)
ClinESSDAI ≥5	103/296 (34.8%)	30/180 (16.7%)
ClinTrialsESSDAI ≥5	93/296 (31.4%)	22/180 (12.2%)
Patient-reported symptoms		
ESSPRI ≥5	196/283 (69.3%)	109/172 (63.4%)
Positive salivary gland biopsy		
Parotid gland (FS ≥1)	136/171 (79.5%)	4/8 (50.0%)
Labial gland (FS ≥1)	84/99 (84.8%)	52/74 (70.3%)
Parotid or labial	195/223 (87.4%)	56/81 (69.1%)
Biological activity		
Anti-SSA positive	255/294 (86.7%)	163/180 (90.6%)
RF positive	185/291 (63.6%)	N/A
Increased IgG (>16 g/L)	128/292 (43.8%)	61/180 (33.9%)
Residual salivary flow		
UWS >0	236/292 (80.8%)	172/180 (95.6%)
SWS >0	242/285 (84.9%)	N/A
SWS >0.1 ml/min	227/285 (79.6%)	N/A
SGUS Hocevar score ≥15	211/294 (71.8%)	130 (72.2%)

RESULT: REgistry of Sjögren Syndrome LongiTudinal; BeSSTT: Belgian Sjögren's Syndrome Transition Trial; pSS: primary Sjögren's syndrome; ACR-EULAR: American College of Rheumatology/European League Against Rheumatism; HCQ: hydroxychloroquine; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index; ClinTrialsESSDAI: Clinical Trials ESSDAI; ESSPRI: EULAR Sjögren's Syndrome Patient-Reported Index; FS: focus score; RF: rheumatoid factor; IgG: immunoglobulin G; UWS: unstimulated whole salivary secretion; SWS: stimulated whole salivary secretion; SGUS: salivary gland ultransonography; N/A: not applicable.

Another recent development is the use of patient-reported symptoms as inclusion criterion. This criterion can either be used as single criterion or together with an inclusion criterion for systemic disease activity. The combination can also be implemented by inclusion of two cohorts of patients: one cohort of patients with high systemic disease activity, and one cohort of patients with low systemic disease activity but high symptom burden (often based on ESSPRI ≥5). This allows inclusion of a broader patient population with the whole spectrum of the disease, not only focusing on systemic manifestations, especially in larger phase III trials. Furthermore, this gives the opportunity to assess whether the particular drug will have more effect in a certain pSS phenotype.

Eligible patients for clinical trials

An important issue to consider is that each additional selection criterion will (largely) decrease the number of eligible patients in daily clinical practice. Previously, this notion was demonstrated in a cross-sectional analysis of patients fulfilling the main inclusion criteria used in published RCTs between 2001 and 2014 in the Assessment of Systemic Signs and Evolution in Sjögren's Syndrome (ASSESS) cohort. The combination of symptom onset within the last 4 years, systemic manifestations (ESSDAI ≥2), at least two of three VAS scores (dryness, pain, fatigue) ≥50, and biological activity leads to inclusion of only 30 (9%) of the 342 screened patients with pSS (15).

To further explore the proportion of eligible pSS patients in daily clinical practice fulfilling frequently used inclusion criteria of recent trials, we analysed data from the REgistry of Sjögren Syndrome LongiTudinal (RESULT) cohort and Belgian Sjögren's Syndrome Transition Trial (BeSSTT) cohort. RESULT is a prospective observational longitudinal cohort study including consecutive patients with probable or confirmed pSS who visit the outpatient clinic of the Department of Rheumatology and Clinical Immunology at the UMCG, a tertiary referral expertise centre. BeSSTT is a prospective observational longitudinal cohort study including consecutive patients fulfilling at least one of the ACR-EULAR criteria (objective sicca and/or immunological criterion) who visit the outpatient clinic of the Department of Rheumatology at the Ghent University Hospital. The cohorts have been approved by the Medical Ethics Committee of the UMCG (RESULT: METC 2014/491) and of the Ghent University Hospital (BeSSTT: EC 2019/04542), respectively. All patients provided written informed consent.

The present cross-sectional analysis included the baseline visit of patients fulfilling the ACR-EULAR criteria for pSS, who were included in the RESULT cohort between January 2016 and August 2021 (n=302) or in the BeSSTT cohort between October 2019 and March 2022 (n=180). Table III gives an overview of the proportion of patients who meet a single inclusion criterion used in clinical trials. Systemic activity is the most frequently used inclusion criterion in previous trials (Table I). When ana-

lysing 283 patients with complete data in the RESULT cohort, ESSDAI ≥5 was present in 112 (39.6%) patients, biological activity (anti-SSA+) was present in 247 (87.3%) patients and residual salivary flow (UWS of >0 ml/min) was present in 229 (80.9%) patients. Combining these 3 inclusion criteria resulted in a total of 76 (26.9%) eligible patients from Groningen in daily clinical practice. When analysing 172 patients with complete data in the BeSST cohort, ESSDAI ≥5 was present in 37 (21.5%) patients, biological activity (anti-SSA+) in 156 (90.7%) patients and residual salivary flow (UWS of >0 ml/min) in 164 (95.3%) patients. Combining these 3 inclusion criteria resulted in a total of 30 (17.4%) eligible patients from Ghent in daily clinical practice.

As another example, combining the inclusion criteria of systemic activity (ESSDAI ≥5) and high symptom burden (ESSPRI ≥5) resulted in 79 of 279 (28.3%) and 25 of 172 (14.5%) eligible patients in the RESULT and BeSSTT cohort, respectively. When at least one of these features should be present, so ESSDAI ≥5 and/or ESSPRI ≥5, respectively 232 of 300 (77.3%) and 123 of 172 (71.5%) patients fulfil in both cohorts.

Finally, in case of very strict inclusion criteria for larger RCTs, generalisability of the trial population to the total population of pSS patients may be questioned. The use of a composite endpoint, consisting of multiple clinically relevant items on which patients can respond, may facilitate a broader inclusion of pSS patients, especially in phase III trials. This corresponds to daily clinical practice, where physicians do not only want to treat patients with active organ involvement, but also patients with a wide variety of disabling symptoms with large impact on quality of life.

To conclude, both the selection of the primary study endpoint and the selection of patients are crucial for clinical trial design in pSS. Hopefully, the recent development of composite endpoints will help us to demonstrate superiority of the active treatment versus placebo (9, 10). We should realise that the use of very strict inclusion criteria will largely decrease the number of eligible patients and may question the external validity and generalisability to patients in daily clinical practice. Our ultimate goal is to have access to officially licensed systemic treatment for all pSS patients in different phases of their disease with different manifestations.

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Competing interests

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