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Ten years of the ESSDAI: is it fit for purpose?

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ABSTRACT

Primary Sjögren's syndrome (pSS) is a very heterogeneous disease with systemic manifestations such as arthritis, skin, lung and renal involvement. To be able to assess systemic disease activity, the EULAR Sjögren's syndrome disease activity index (ESSDAI) was developed for use in daily clinical practice and in clinical trials. Since its development it has been widely used in cohort studies and clinical trials. The ESSDAI gives a systematic overview of a patient's systemic disease activity, which is very useful in daily clinical practice. However, using the ESSDAI as outcome measure in trials has been more challenging. Several RCTs with the ESSDAI as primary endpoint failed and showed large 'response rates' in placebo-treated patients as well. In this review, we discuss what we learned from using the ESSDAI in cohorts and clinical trials. We recommend to use the ESSDAI only in combination with other important outcome measures, such as patient-reported symptoms and glandular function as part of a composite endpoint in clinical trials in pSS patients.

Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterised by lymphocytic infiltration of exocrine glands. Besides the exocrine glands the inflammatory process can potentially affect any organ, which leads to a wide variety of symptoms and a very heterogeneous disease. Symptoms often include dryness of eyes and mouth, fatigue and joint pain. Systemic manifestations such as arthritis, skin, lung and renal involvement and peripheral neuropathy occur in approximately 20–40% of patients (1-3).

The European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) was developed in 2009 to be used as measurement instrument for the evaluation of systemic disease activity of pSS in a standardised way, both in clinical trials and daily clinical practice (4). The ESSDAI consists of 12 organ-specific domains: cutaneous, pulmonary, renal, articular, muscular, peripheral nervous system, central nervous system, haematological, glandular, constitutional, lymphadenopathy and biological (5). Each domain is divided in 3 or 4 levels of activity (0: no activity; 1: low activity; 2: moderate activity; 3: high activity) and has a weight of 1 to 6. The domain score is obtained by multiplying the activity level by the weight of the domain (4). Validated cut-off values for the ESSDAI score have been developed to define low, moderate and high disease activity levels, which are respectively an ESSDAI score of <5, between 5 and 13 and ≥14. Minimal clinically important improvement (MCII) has been defined as a decrease of ≥3 points in ESSDAI score (6). Furthermore, the ClinESSDAI has been developed, which is the ESSDAI score excluding the biological domain, with adjustments in the weight of the remaining domains compared to the ESSDAI (7). The biological domain includes immunoglobulin G (IgG) serum levels, complement levels, cryoglobulinaemia and monoclonal gammopathy. The ClinESSDAI was developed to allow analysis of associations between biomarkers and true clinical activity, since the biological domain in itself could have strong associations with these new biomarkers. Furthermore, new biological drugs in clinical trials could influence only the biological domain and no other clinical domains, therefore showing improvement in ESSDAI which may not be a 'true' reflection of change in clinical disease activity.

Development of the ESSDAI

The ESSDAI has been developed by consensus of a large panel of experts.

Table I. Overview of the ESSDAI in cohort studies.

	SJÖGRENSER (n=437)	ASSESS (n=395)	GEAS-SS (n=921)	GRISS (n=825)	Sjögren Big Data Consortium (n=6331)
Patient characteristics					
Age (years)	59 (IQR 50-68)	58 (51-67)	55±15	52±14	52±14
Female	95	94	93	95	94
DD (years)	**10.4 (range 6-16)**	**5 (2-9)**	**0[a]**	**0[a]**	**0[a]**
Anti-SSA+	94	59	75	70	76
Salivary gland or lip biopsy+	30	88	80	Focus score 2 (range 0-12)	82
ESSDAI score	**2 (0-4)**	**2 (0-7)**	**5.8**	**6 (range 0-63)[b]**	**6 ± 7.5**
ESSDAI subdomain activity[c]					
Cutaneous	3	4	9	15	10
Pulmonary	6	14	6	7	12
Renal	5	3	2	3	5
Articular	**35**	**19**	**40**	**62**	**41**
Muscular	0.2	3	1	1	3
PNS	3	10	5	7	6
CNS	2	2	2	2	2
Glandular	**4**	**12**	**28**	**28**	**24**
Constitutional	8	4	9	14	10
Lymphadenopathic	**2**	**2**	**7**	**28**	**11**
Haematological	27	16	NA	28	22
Biological	**28**	**37**	**NA**	**54**	**47**

Data presented as median (IQR), mean ± SD or %, unless stated otherwise.
Main differences between cohort studies highlighted in bold text.
[a]ESSDAI at diagnosis.
[b]ESSDAI evaluated retrospectively.
[c]Percentage of patients showing activity (low, moderate or high) in ESSDAI subdomains.
ESSDAI: EULAR primary Sjögren's syndrome disease activity; SJÖGRENSER: Spanish Rheumatology Association's registry of patients with primary Sjögren's syndrome; ASSESS: Assessment of Systemic Signs and Evolution of Sjögren's Syndrome; GEAS-SS: SS Study Group and Autoimmune Disease Study Group; GRISS: Gruppo di Ricerca Italiano sulla Sindrome di Sjögren; EULAR: European League Against Rheumatism; DD: disease duration; SSA: Sjögren's-syndrome-related antigen A; NA: not available; PNS: peripheral nervous system; CNS: central nervous system.

First of all, domains of organ-specific involvement were selected by a steering committee and evaluated by a panel of experts who used an intention-to-treat approach to define the different activity levels ranging from no activity, requiring no treatment, to high activity, requiring high dose steroids or immunosuppressant. Second, experts scored the physician global disease activity (GDA) in real patient profiles and vignettes. The ESSDAI was also determined for these patient profiles and vignettes. In regression models, all domains were significantly associated with physician GDA. Weights of the different domains were derived from the regression coefficients of each domain (4).

It should be kept in mind that the ESSDAI was specifically developed to assess systemic disease activity. To assess symptoms of dryness, fatigue and pain a separate patient index was developed, the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) (8). Interestingly, the correlation between the ESSDAI and ESSPRI is very low (r=0.20), which indicates that these two indexes are complementary to each other and should both be used when assessing a patient's disease activity (9).

In other systemic auto-immune diseases like systemic lupus erythematosus (SLE), disease activity instruments are widely used to assess systemic disease activity. The ESSDAI is the first and only method available to assess systemic disease activity in pSS in a systematic way, which makes it an important tool for experts as well as for all treating physicians of pSS patients.

Performance of ESSDAI in patient cohorts

The ESSDAI has been implemented throughout the world in cohort studies to assess systemic disease activity. An overview of these studies including main patient characteristics is shown in Table I.

Two multi-centre, prospective cohort studies, in 437 pSS patients (SJÖGRENSER cohort) and in 395 pSS patients (ASSESS cohort) both showed median ESSDAI scores of 2 (IQR 0–5 and 0–7), respectively (10, 11). In the ASSESS cohort patients with early onset disease (age ≤35 years) were found to be at a higher risk of developing higher systemic disease activity in the following 5 years (12).

The GEAS-SS registry in 921 Spanish pSS patients showed a mean ESSDAI score of 5.8 at diagnosis and 82% of patients had some degree of systemic activity. After a follow-up period of 75 months mean ESSDAI score increased to 9.2 and 92% had some degree of systemic disease activity according to the ESSDAI (13, 14). A retrospective, multi-centre study in 825 pSS patients (GRISS group) showed a similar median ESSDAI score of 6 (range 0-63) at diagnosis (15). The Big Data Sjögren Project Consortium, an international, multi-centre registry in 6331 pSS patients reported a mean ESSDAI of 6.1 (SD±7.5) at diagnosis and 82% of pa-

tients had some degree of systemic activity according to the ESSDAI (1).

In Table I, the prevalence rates of the different ESSDAI domains in these cohorts are stated. Overall, the most frequently affected domains were the articular (19–62%), biological (28-54%), haematological (16-–8%) and glandular (4–28%) domain. The lowest percentages were mostly reported by the SJÖGRENSER and ASSESS cohorts, which also had lower median ESSDAI scores than other cohorts with higher reported prevalence of activity in the ESSDAI domains (11, 16). These two studies included patients with median disease duration of 10 and 5 years, respectively, whereas the cohort studies with higher reported ESSDAI scores were scored at diagnosis (1, 12, 13). This might be an explanation for the difference in mean and median ESSDAI scores and might explain the difference in prevalence of activity in the ESSDAI domains. Moreover, geographical differences might influence ESSDAI scores since it has been shown that there is a north-south gradient in systemic disease activity at baseline, with higher reported ESSDAI scores in southern countries (17).

Interestingly, the Big Data Sjögren Project Consortium also assessed systemic manifestations outside of the ESSDAI. They showed that around a quarter of patients had such systemic manifestations, most frequently the Raynaud phenomenon, which was present in 15% of patients. Other systemic manifestations were present in less than 3% of patients. Comparing this with higher frequencies of most of the ESSDAI domains, this confirms the content validity of the ESSDAI (1).

A prospective international 6-month duration validation study of 395 pSS patients (EULAR study) conducted in 14 countries studied the responsiveness of the ESSDAI. The centres that participated were asked to include patients of which approximately half of the patients had systemic features. Median ESSDAI scores were 6 (IQR 2-12) at baseline. To evaluate sensitivity to change, physicians scored the disease activity of included patients as improved, stable or worsened after 6 months of follow-up. In these three subgroups sensitivity to change was assessed with the standardised response mean (SRM). The SRMs of the ESSDAI corresponded to the direction of reported change in disease activity. For patients with an improved/decreased disease activity the ESSDAI showed a large responsiveness (SRM -0.72), while for patients with worsened/increased disease activity the ESSDAI showed a smaller responsiveness (SRM +0.26). Most patients (57%) had stable disease activity, with SRM close to zero (-0.17), which indicates that the assessment of stability is accurate (9).

Interpretation of ESSDAI domains

A major advantage of the ESSDAI is being able to get an overview of the specific systemic disease activity of an individual patient in a systematic way. When looking at the different domains of the ESSDAI, some domains are easy to score, such as the biological and haematological domains which can be easily interpreted from laboratory values. Other domains are more difficult to score as they require a thorough physical examination or require additional testing. For example, a pulmonary function test or high-resolution CT scan may be needed to score the pulmonary domain.

To make scoring of the ESSDAI more accurate and reliable, in 2015 a new, more detailed glossary was developed (5). Even though this has given more clarity on how to rate several domains, there are still some domains that leave room for subjectivity and measurement errors since these are based on information reported by the patient and interpretation by the physician. For example, to score the constitutional domain, night sweats and fever have to be assessed. To properly score fever in an outpatient setting, the temperature has to be measured by the patient, which may not always be done correctly. The patient should be asked about the severity of the night sweats and whether the night clothes get wet, but in daily clinical practice this might not always be done thoroughly and patients answers may be biased.

Regarding the articular domain, a study in 43 pSS patients showed a good correlation between the ESSDAI articular domain and the DAS28, showing this is a representable domain compared to another validated and widely used instrument of articular activity in rheumatic musculoskeletal disorders (18). However, the evaluation of joint inflammation depends on the skill and interpretation of the physician. In contrast to rheumatoid arthritis, arthritis in pSS patients is often subtle, which makes it more difficult for the physician to evaluate articular activity. Furthermore, the definition of low activity in the articular domain is mainly subjective, since it is based on symptoms reported by the patient (arthralgia accompanied by morning stiffness of >30 minutes). There are similar difficulties scoring the glandular and lymphadenopathy domain.

In the validation study, the total ESSDAI score showed good inter-rater reliability (intra-class correlation coefficient: ICC 0.96) (9). However, this study was conducted by experts in the pSS field. It is possible that in daily clinical practice, less experienced physicians score the ESSDAI based on available data and clinical interpretation, which may make the scoring less reliable.

Another important challenge when scoring the ESSDAI domains is to differentiate damage from disease activity, for example when scoring pulmonary and peripheral nervous system activity. Although there are now stricter guidelines on how to distinguish this, this can still be difficult. Also, it is unclear how often additional diagnostic testing, such as pulmonary function tests, should be performed to differentiate damage from disease activity (5).

Performance of ESSDAI in clinical trials

For a successful therapeutic trial, it is essential to use valid and reliable endpoints, which are sensitive to change and can discriminate between the effect of active treatment and placebo treatment. The ESSDAI has been specifically developed not only to be used in daily clinical practice, but also in clinical trials. Since its development, the ESSDAI has been used in several clinical trials as a primary or secondary outcome measure. In multiple open-label studies with rituximab and abatacept the ESSDAI showed significant im-

Table II. Overview of prospective open-label studies and registries using the ESSDAI as outcome measure.

	Treatment, number of patients	Study design	Patient characteristics					Baseline ESSDAI	Follow-up ESSDAI	Change in ESSDAI
			Age (years)	Gender (female)	DD (years)	Anti-SSA+	Salivary gland or lip biopsy+			
Meiners, (2012) (20)	Rituximab: n=28	Phase II, single-centre, open-label	43±14	96	7±4	100	100	8±5	Week 24: 3±3	-
Gottenberg, (2013) (19)	Rituximab: n=78	Multi-centre registry[a]	60 (29-83)	86	12 (3-32)	69	NA	11.0 (2-31)	Month 6: 7.5 (0-26)	-
Carubbi, (2013) (41)	Rituximab: n=19	Multi-centre, open-label	Mean 40 (range 27-53)	95	1 (0.5-2)	NA	Focus score 1.8 (1-3.3)	Mean 20.3 (range 6 to 41)	Week 24: Mean 9.8 SEM±2.0	-
	Traditional DMARD: n=22		Mean,43 (range 30-56)	100	1 (0.5-2)	NA	Focus score 1.8 (1-3.4)	Mean 19.8 (range 6 to 41)	Mean 14.2 SEM±3.0	-
Mariette, (2013) (42)	Belimumab: n=30	Phase II, bi-centric, open-label	50±17	100	6±6	97	83	8.8±7.4	Week 28 6.3±6.6	Mean -2.5 (95% CI -4.0 to -1.0)
Meiners, (2014) (21)	Abatacept: n=15	Phase II, single-centre, open-label	43 (IQR 32-51)	80	1 (IQR 0.5-3)	100	100	11±5	Week 24: 3±3	-
Machado, (2020) (22)	Abatacept: n=11	Phase II, single-centre, open-label	54±15	100	7±4	81.8	NA[b]	7.0 (0-30)	Month 24: 2.0 (0-27)	Median 3.0 (95% CI -0.5 to 8.0)

Data presented as median (range), mean ± SD or %, unless stated otherwise.
[a]ESSDAI assessed retrospectively.
[b]In 3 patients the biopsy was positive, of the remaining patients no biopsy was performed.
ESSDAI: EULAR primary Sjögren's syndrome disease activity; DD: disease duration; SSA: Sjögren's-syndrome-related antigen A; NA: not available; SEM: standard error of the mean; DMARD: disease-modifying anti-rheumatic drug; CI: confidence interval.

provement during treatment compared to baseline values (Table II). For example, a registry of 78 pSS patients (Auto-Immune and Rituximab registry) treated with rituximab showed a decrease in median ESSDAI from 11 to 7.5 at 6 months following treatment (p<0.001) (19). A smaller open-label study in 28 pSS patients treated with rituximab showed a significant decrease in median ESSDAI from 8 to 3 at 36 weeks following treatment (p<0.001) (20). An open-label study in 15 pSS patients on abatacept (Active Sjögren Abatacept Pilot, ASAPII trial) showed that the median ESSDAI decreased from 11 at baseline to 2 after 24 weeks of treatment (p<0.001) (21). Another open-label study in 11 pSS patients treated with abatacept for 24 months showed a significant reduction in ESSDAI of 2.99 (95% CI -0.49; 7.99, p=0.013) (22). In these open-label trials, most improvement was found in the articular, constitutional, glandular, haematological and biological domains.

However, to be able to assess whether drugs are effective and the effects observed are not merely based on a placebo-effect, randomised, placebo-controlled trials (RCTs) should be performed. Several larger RCTs using the ESSDAI as endpoint have failed to show a significant difference between treatment groups (23-27). This may partly be explained by a large decrease in ESSDAI in placebo-treated patients, which was seen in several trials (Table III).

For example, a multi-centre RCT of rituximab treatment *versus* placebo treatment in 120 pSS patients (Tolerance and Efficacy of Rituximab in Primary Sjögren's Syndrome, TEARS trial) found no significant differences in ESSDAI as a secondary outcome (23). Mean baseline ESSDAI values for rituximab- and placebo-treated patients were 10.0 (SD±6.9) and 10.2 (SD±6.8) with change in ESSDAI after 24 weeks being -1.2 and -1.7, respectively (p=0.57). Of note, the ESSDAI was calculated retrospectively since the ESSDAI was in development during the study. Another multi-centre RCT of rituximab treatment in 133 pSS patients (Trial of Anti-B cell Therapy in Patients with Primary Sjögren's Syndrome, TRACTISS trial) also found no significant difference in ESSDAI as a secondary outcome. Mean baseline ESSDAI values were relatively low in this trial: 5.3 (SD±4.7) and 6.0 (SD±4.3) for rituximab- and placebo-treated patients. After 48 weeks mean ESSDAI was 3.4 (SEM±1.1) and 4.5 (SEM±1.1), respectively (p=0.072). At 36 weeks following treatment however, a small relative difference in ESSDAI was seen in favour of rituximab (mean 4.8, SEM±1.1 *vs*. mean 3.5, SEM±1.1, p=0.035) (24). A smaller RCT in 30 patients treated with rituximab (n=20) or placebo (n=10), in which the responsiveness of the ESSDAI was investigated, showed a significant decrease in median ESSDAI up to 36 weeks in rituximab-treated patients compared to placebo-treated patients with a large responsiveness at weeks 5-24 and moderate responsiveness at week 36 (SRM week 24 -1.04; SRM week 36 -0.44) (28).

Two RCTs in abatacept also failed to show significant differences in ESSDAI scores. The Abatacept Sjögren Active Patients (ASAP) III trial, a single-centre RCT in 80 pSS patients showed no significant difference in ESSDAI after week 24 of treatment between the abatacept- and placebo-treated group. A large decrease in ESSDAI was seen in patients treated with abatacept as well as patients treated with placebo (median ESSDAI baseline: 14.0 (IQR 9.0-–6.8) *vs*. 13.0 (8.0–18.0); median ESSDAI week 24: 8.0 (IQR 4.0–14.0) *vs*. 8.0 (5.0–14.5)) (25). Similar results

Table III. Overview of randomised, double-blind controlled trials using the ESSDAI as outcome measure.

	Treatment, number of patients	Study design	Patient characteristics					Baseline ESSDAI	Follow-up ESSDAI	Change in ESSDAI or mean difference between treatment groups
			Age (years)	Gender (female)	DD (years)	Anti-SSA+	Salivary gland or lip biopsy+			
Devauchelle, (2014) (23)	Rituximab: n=63	Phase III, multi-centre RCT[a]	53±13	91	5±5	81	89	10.0±6.9	-	Week 24: -1.2
	Placebo: n=57		56±14	97	6±7	81	86	10.2±6.8	-	-1.7
Gottenberg, (2014) (43)	Hydroxychloroquine: n=56	Phase III, multi-centre RCT	56±12	89	1 (IQR 1-3)[c]	56	90	2.0 (IQR 0-5.5)	Week 24: 2.0 (IQR 0-3.0)	0 (-2.0-0)
	Placebo: n=64		56±14	94	1 (IQR 0-5)[c]	54;	91	2.5 (IQR 2.0-6.0)	2.0 (IQR 0-5.3)	0 (-2.0-0)
Bowman, (2017) (24)	Rituximab: n=67	Phase III, Multi-centre RCT	54±12	94	5±5	99	NA	5.3±4.7	Week 48: Mean 3.4 (SEM±1.1)	0.75 (95% CI 0.55, 1.03)
	Placebo: n=66		54±12	92	6±6	100	NA	6.0±4.3	Mean 4.5 (SEM±1.1)	
St. Clair, (2018) (44)	Baminercept: n=33	Phase II, multi-centre RCT	50±11	94	NA	88 (or SSB+)	27	2.7±2.8	-	Week 24: Mean -1.23 (95% CI -2.03, -0,43)
	Placebo: n=19		50±11	95	NA	79	37	3.8±4.2	-	Mean -0.15 (95% CI -1.18, 0,87)
Baer, (2019) [abstract] (26)	Abatacept: n=92	Phase III, multi-centre RCT	52±13 (n=187)	95 (n=187)	NA	NA	NA	8.7±3.4	-	Week 24: Mean -3.2 (SE 0.7)
	Placebo: n=95							10.1±5.0	-	Mean -3.7 (SE 0.7)
Felten, (2019) [abstract] (27)	Tocilizumab: n=55	Phase II, Multi-centre RCT	51 (26-76)	98	NA	85	NA	Mean 11.5 (range 5-25)	Week 24: Mean 6.6 (range 4.7-9.0)	-
	Placebo: n=55		55 (30-80)	90	NA	88	NA	Mean 12.4 (range 5-39)	Mean 5.4 (range 3.7-7.6)	-
Van Nimwegen, (2020) (25)	Abatacept: n=40	Phase III, single-centre RCT	48±15	93	2 (IQR 0-4)	85	100	14.0 (IQR 9.0-16.8)	Week 24: 8.0 (IQR 4.0-14.0)	AD -1.3 (95% CI -4.1 to 1.6)
	Placebo: n=40		49±16	93	2 (IQR 1-4)	85	100	13.0 (IQR 8.0-18.0)	8.0 (IQR 5.0-14.5)	
Van der Heijden, (2020) (31)	Leflunomide/ Hydroxychloroquine: n=21	Phase IIA, single-centre RCT	55±12	95	8±10	86	100	10.4±3.9	Week 24: 6.6±3.9	AD -4.35 (95% CI -7.45 to -1.25)
	Placebo: n=8		54±15	100	9±7	88	100	9.1±3.4	10.4±4.4	
Fisher, (2020) (32)	Cohort 1: Iscalimab 3 mg/kg s.c.: n=8	Phase IIA, multi-centre RCT	56±12	100	NA	88	NA	12.0±3.8	Week 12: Adjusted mean 9.5	-
	Cohort 1: Placebo: n=4		49±3	100	NA	100	NA	11.8±3.9	Adjusted mean 9.9	-
	Cohort 2: Iscalimab 10 mg/kg i.v.: n=21		52±14	90	NA	100	NA	10.6±4.4	Adjusted mean 4.3	-
	Cohort 2: Placebo: n=11		51±12	100	NA	100	NA	11.0±5.2	Adjusted mean 9.5	-

Data presented as median (range), mean ± SD or %, unless stated otherwise.
[a]ESSDAI assessed retrospectively.
ESSDAI: EULAR primary Sjögren's syndrome disease activity; RCT: randomised controlled trial; DD: disease duration; SSA: Sjögren's-syndrome-related antigen A; SSB: Sjögren's-syndrome-related antigen B; NA: not available; SEM: standard error of the mean; DMARD: disease-modifying anti-rheumatic drug; CI: confidence interval; AD: adjusted difference.

were found in a larger, multi-centre RCT in abatacept (26).

A multi-centre RCT of tocilizumab treatment in 110 pSS patients found mean ESSDAI scores at baseline for tocilizumab- and placebo-treated patients of 11.5 (range 5–25) and 12.4 (range 5–39), respectively. After 24 weeks of treatment ESSDAI scores decreased to 6.6 (4.7–9.0) and 5.4 (3.7–7.6), respectively, which was not significantly different (27). A smaller RCT which investigated the efficacy of ianalumab, a B-cell activating factor (BAFF) receptor-blocking monoclonal antibody, in 27 pSS patients, found no significant differences in ESSDAI scores at week 24 between patients treated with placebo and ianalumab (29). The larger, follow-up RCT of ianalumab treatment in 190 pSS patients did find a dose-dependent reduction in ESSDAI and a significantly larger number of ESSDAI responders in patients treated with ianalumab compared to placebo (ianalumab 300 mg 89.4% *vs*. placebo 61.2%). However, the largest mean difference in ESSDAI between groups was only 1.9 points which is below the minimal clinically important improvement of 3 points (30).

In contrast, two recent, small RCTs did show a significant difference in ESSDAI between patients with active treatment and placebo treatment. A small single-centre, phase IIA RCT in 29 pSS

patients treated with leflunomide/hydroxychloroquine combination therapy (n=21) or placebo (n=8) showed a significant decrease in ESSDAI in favour to the leflunomide/hydroxychloroquine group (31). Mean baseline ESSDAI values were 10.4 (SD±3.9) in the leflunomide/hydroxychloroquine group and 9.1 (SD±3.4) in the placebo group. After 24 weeks mean ESSDAI scores were 6.6 (SD±3.9) and 10.4 (SD±4.4), respectively. It should be noted that in this study IgG levels were significantly higher in the leflunomide/hydroxychloroquine group compared to the placebo group, which may have biased the results. An RCT of iscalimab treatment in 44 pSS patients showed a significant improvement in ESSDAI in iscalimab-treated patients compared to placebo (mean ESSDAI baseline: 10.6 (SD±4.4) *vs*. 11.0 (SD±5.2); week 12: adjusted mean 4.3 *vs*. 9.5) (32). However, both studies are small trials and results should therefore be confirmed in larger RCTs.

As mentioned, several RCTs have shown a large decrease in ESSDAI in the active treatment group as well as in the placebo group. A possible explanation for this might be regression to the mean, since several of these studies used ESSDAI ≥5 or ≥6 as an inclusion criterion and the natural course of disease activity will vary over time. Furthermore, it has been shown that different stimuli such as rituals of the therapeutic act or participation in a trial may change chemistry and circuitry of the patient's brain, which can lead to a response in placebo-treated patients (33, 34). This might influence ESSDAI domains which are (partly) based on patients information, such as the constitutional domain or the articular domain. Domains which are largely interpreted based on the physical examination of the treating physician, such as the articular, lymphadenopathy and glandular domain, could also be influenced. Interestingly, looking at the aforementioned RCTs, studies reported most improvement in the articular, glandular and constitutional domains (25, 29, 32). In most trials in pSS patients, drugs were administered subcutaneously or as intravenous infusions, which is a strong therapeutic ritual, and may have led to a strong placebo-effect. Since an effective systemic treatment is not yet available for pSS patients, the expectation of improvement might be very large in pSS patients treated with novel medication, which may also lead to a relatively large placebo-effect. Not only in pSS high placebo response rates are seen, but also several RCTs in SLE, using endpoints largely based on systemic disease activity, show high placebo response rates, which are associated with primary endpoint failure (35).

Methodological considerations about the performance of ESSDAI in clinical trials

Besides the mentioned possible explanations for a relatively large decrease in ESSDAI score in placebo-treated patients, failure to show difference in response between treatment groups might also be due to limitations of the ESSDAI when it is used in clinical trials. As the activity of domains is evaluated categorically, using cut-off values, changes in absolute values do not always lead to a change in the domain score if the cut-off value is not reached. For example, an improvement of high IgG levels does not result in improvement in the ESSDAI score of the biological domain, if the cut-off of 20 g/L is not reached.

Although pSS is a very heterogeneous disease with many different systemic manifestations, one of the hallmarks of the disease is loss of tear and salivary gland function. Glandular function is not taken into account in the glandular domain of the ESSDAI, since this is no measure for systemic disease activity. Treatment goals may differ between patients with different characteristics. In patients with early disease, the primary aim may be to improve glandular function and prevent further glandular damage. However, in patients with irreversible glandular damage, the main goal may be to improve extra-glandular manifestations or fatigue. Moreover, for quality of life, the patient-reported symptoms are more important than the ESSDAI (36). Since glandular function and patient-reported symptoms are both important factors in pSS, these measures are also important to evaluate in clinical trials. Also, although there is a biological domain in the ESSDAI, there are additional serological markers which are used to monitor disease activity in pSS, such as rheumatoid factor, which are not included in the biological domain. Although the ESSDAI might not be adequate on its own to use as a primary endpoint in clinical trials, it is an important measurement of systemic disease activity and important to assess in trials for eventual registration of drugs. Therefore, a composite endpoint which combines not only systemic disease activity, but also patient-reported symptoms, glandular function and serological measures might be more suitable to show efficacy in this heterogeneous patient population in different phases of the disease.

The SSRI is a composite endpoint, which defines response as a 30% improvement or more in at least two of the five domains (VAS oral dryness, VAS ocular dryness, VAS fatigue, unstimulated whole saliva (UWS) and erythrocyte sedimentation rate) (37). However, the SSRI does not include systemic disease activity or tear gland function, which are also considered important outcomes in pSS.

An interesting project, the innovative medicines initiative (IMI) project 'NECESSITY', has been set up to identify and validate a new sensitive composite clinical endpoint: the Sjögren's Syndrome Tool for Assessing Response (STAR) (38). Moreover, a new composite endpoint has been developed based on expert opinion in combination with analysis of data from the ASAPIII trial (25), trials in rituximab (20, 39) and the REgistry of Sjögren syndrome in Umcg LongiTudinal (RESULT) cohort (40) for use in future clinical trials in pSS: the Composite of Relevant Endpoints in Sjögren's Syndrome (CRESS, manuscript in preparation). The CRESS includes 5 items, consisting of several measurements: systemic disease activity (ClinESSDAI), patient-reported symptoms (ESSPRI), tear gland function (Schirmer's test and Ocular Staining Score), salivary gland function (UWS and salivary gland ultrasonography) and a serological item

(RF and IgG). The CRESS shows good discrimination between abatacept- and placebo-treated patients in the ASAP-III trial (25) and needs to be validated in different clinical trials.

Conclusion

The ESSDAI has been used in several cohort studies and seems to be fit for assessing systemic disease activity of Sjögren's syndrome in a systematic way. The ESSDAI has also been used to monitor systemic disease activity over time in some patient cohorts and has shown to be sensitive to change. However, there are some limitations to the ESSDAI and several RCTs using the ESSDAI as primary endpoint have failed. In future clinical trials, we recommend to combine the ESSDAI with other important outcome measures for pSS patients such as patient-reported symptoms and glandular function.

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