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Published in:
Clinical and Experimental Rheumatology

Publication date:
2021

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Received on July 14, 2021; accepted in revised form on September 29, 2021.

Clin Exp Rheumatol 2021; 39 (Suppl. 133): S100-S106.

Key words: primary Sjögren's syndrome, randomised controlled trial, outcome measures

Competing interests: M. Bombardieri has received unrestricted grants from Amgen/Medimmune and Janssen, consultancy fees from Amgen/Medimmune, Janssen, GSK, UCB. S. Bowman has consulted for Abbvie, Galapagos and Novartis in the past 12 months and part of his salary is funded by the Birmingham Biomedical Research Centre. H. Bootsma has received unrestricted grants from Bristol-Myers Squibb and Roche, consultant of Bristol-Myers Squibb, Roche, Novartis Medimmune, Union Chimique Belge, speaker for Bristol-Myers Squibb and Novartis. The other authors have declared no competing interests.

ABSTRACT

Objective. *To develop and evaluate the Clinical Trials EULAR Sjögren's Syndrome Disease Activity Index (ClinTrialsESSDAI), consisting of frequently active clinical domains of the ESSDAI, using two randomised controlled trials in primary Sjögren's syndrome (pSS).*

Methods. *The ASAP-III trial in abatacept (80 pSS patients) and TRACTISS trial in rituximab (133 pSS patients) were analysed. The most frequently active clinical domains were selected, and ClinTrialsESSDAI total score was calculated using existing weightings of the ClinESSDAI (which also excludes the biological domain). Performance of the ClinTrialsESSDAI was compared to ClinESSDAI and ESSDAI. Responsiveness was assessed using standardised response mean (SRM), and discrimination was assessed using adjusted mean difference.*

Results. *Besides the biological domain, the most frequently active domains were glandular, articular, haematological, constitutional, lymphadenopathy and cutaneous. These domains were selected for the ClinTrialsESSDAI. At primary endpoint visits, SRM values of ClinTrialsESSDAI, ClinESSDAI and ESSDAI were respectively -0.65/-0.59, -0.63/-0.59 and -0.64/-0.61 for abatacept/placebo and -0.33/-0.13, -0.34/-0.12 and -0.41/-0.16 for rituximab/placebo. Adjusted mean differences between active treatment and placebo groups were respectively -1.7, -1.4 and -1.1 for ASAP-III and -1.1, -1.1 and -1.2 for TRACTISS.*

Conclusion. *The ClinTrialsESSDAI, consisting of six frequently active clinical domains of the ESSDAI, shows closely similar responsiveness and discrimination between treatment groups compared to the ClinESSDAI and ESSDAI. Therefore, this ClinTrialsESSDAI is not preferable to ClinESSDAI and ESSDAI for use as primary endpoint. A composite endpoint combining response at multiple clinically relevant items seems more suitable as primary study endpoint in pSS.*

Introduction

Primary Sjögren's syndrome (pSS) is a systemic auto-immune disease, characterised by lymphocytic infiltration of exocrine glands. Due to impaired functioning of these glands, patients develop sicca symptoms primarily of the eyes and mouth. As well as sicca symptoms, pSS can lead to a wide variety of systemic symptoms since almost any organ can be affected. These extraglandular manifestations include, for example, arthritis, interstitial nephritis, interstitial lung disease or peripheral neuropathy (1). In order to assess this systemic disease activity, the European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) was developed in 2010 (2). The ESSDAI is a clinically relevant and validated index which consists of twelve domains each assessing a different component of systemic involvement in pSS. Furthermore, the ESSDAI is widely used in daily clinical practice by physicians and increasingly used in cohort studies and clinical trials (3). In 2016, the Clinical ESSDAI (ClinESSDAI), which leaves out the biological domain, was developed in order to measure a 'true' clinical effect. Biological drugs might induce a biological effect only, without showing an effect on clinical symptoms, whereas with the ClinESSDAI only the 'clinical effect' is measured.

Recent randomised controlled trials (RCTs) have used the ESSDAI as a

primary endpoint, and several of these RCTs failed to meet their primary endpoint (4-6). In these trials, a large decrease in ESSDAI was observed, not only in the active treatment group, but also in the placebo group, which led to no difference in improvement at the primary endpoint visit (4-6).

Although the ESSDAI gives a comprehensive overview of a patient's systemic disease activity, there are some limitations to the ESSDAI (3). One of these limitations is that the ESSDAI consists of some domains which are sensitive to change and relatively easy to evaluate, such as the constitutional or glandular domain, but other domains which need to be evaluated using additional diagnostic tools. For example, the pulmonary domain needs to be evaluated by high-resolution computed tomography (CT) or a lung function test. Possibly, an adjusted ESSDAI which includes only the most frequently affected domains and domains that are most sensitive to change, would perform better in clinical trials by increasing responsiveness and would be more feasible to apply. Furthermore, since the ESSDAI showed large response rates in placebo arms, it is important to increase discrimination between treatment groups.

Therefore, the aim of this study was to develop the Clinical Trials ESSDAI (ClinTrialsESSDAI), consisting of frequently active clinical domains of the ESSDAI, using data from two RCTs in pSS. Secondly, the aim was to compare the performance of this ClinTrialsESSDAI to the existing ClinESSDAI and ESSDAI.

Methods

Patients and trial data

For this study, data from the Abatacept Sjögren Active Patients phase III (ASAP-III) RCT (4) and the Trial of Anti-B cell Therapy in Patients with Primary Sjögren's Syndrome (TRACTISS) (7) RCT were used. ASAP-III is a single-centre, randomised, double-blind, placebo-controlled phase III trial in 80 pSS patients which was conducted in the multidisciplinary tertiary referral expertise centre for pSS at the University Medical Center Groningen (UMCG, Groningen, Netherlands). The full trial protocol has been published previously (4). Patients were randomised 1:1 to abatacept or placebo and treated with weekly subcutaneous injections with either abatacept (125 mg) or placebo. The primary endpoint visit was at week 24 and earlier treatment effect was evaluated at week 12. TRACTISS is a multi-centre, randomised, double-blind, placebo-controlled phase III trial in 133 pSS patients. The full trial protocol has been published previously (7). Patients were randomised 1:1 to rituximab or placebo and received either intravenous rituximab (1000 mg) or placebo in two courses at weeks 0, 2, 24 and 26. All patients received methylprednisolone, acetaminophen and chlorpheniramine pre-infusion and oral prednisolone, which was tapered from 60 mg to 15 mg/day over seven days after the rituximab or placebo infusions. The primary endpoint visit was week 48 and earlier treatment effect was evaluated at week 24.

The ASAP-III trial included only patients with moderate or high disease activity according to the ESSDAI (score ≥5), whereas in the TRACTISS trial no inclusion criterion based on ESSDAI was applied, resulting in lower baseline ESSDAI values compared to the ASAP-III trial. Other in- and exclusion criteria of the two trials can be found in the original publications.

Development of the ClinTrialsESSDAI

As first step, activity in the ESSDAI domains was evaluated at baseline in both RCTs. The ESSDAI consists of twelve domains: a constitutional, lymphadenopathy, glandular, articular, cutaneous, pulmonary, renal, muscular, peripheral nervous system, central nervous system, haematological and biological domain. The most frequently active clinical domains were selected for inclusion in the ClinTrialsESSDAI. For this exploratory study, we did not calculate and validate new weightings for the domains included in the ClinTrialsESSDAI. Because the biological domain was not included in the ClinTrialsESSDAI, the ClinTrialsESSDAI was calculated based on existing weightings of the ClinESSDAI (Table I).

Table I. Domain activity levels, weightings and range of total score of the ClinTrialsESSDAI, ClinESSDAI and ESSDAI.

	ClinTrialsESSDAI	ClinESSDAI	ESSDAI
Constitutional (0-2)	4	4	3
Lymphadenopathy (0-3)	4	4	4
Glandular (0-2)	2	2	2
Articular (0-3)	3	3	2
Cutaneous (0-3)	3	3	3
Pulmonary (0-3)	N/A	6	5
Renal (0-3)	N/A	6	5
Muscular (0-3)	N/A	7	6
Peripheral nervous system (0-3)	N/A	5	5
Central nervous system (0-3)	N/A	5	5
Haematological (0-3)	2	2	2
Biological (0-2)	N/A	N/A	1
Score total	0-48	0-135	0-123

ClinTrialsESSDAI: Clinical Trials European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI); ClinESSDAI: Clinical ESSDAI; N/A: not applicable.

Evaluation of the ClinTrialsESSDAI

The performance of the ClinTrialsESSDAI was compared to the ClinESSDAI and ESSDAI in both RCTs. Responsiveness and discrimination between treatment groups was analysed for all three scores at week 12 and week 24 (primary endpoint) for ASAP-III and at week 24 and week 48 (primary endpoint) for TRACTISS.

Statistical analyses

For statistical analyses, IBM SPSS version 23.0 was used. Number and percentage of patients with low, moderate or high activity in the separate ESSDAI domains were analysed in both trials for patients on active treatment (abatacept or rituximab) and placebo. Total scores of the ClinTrialsESSDAI, ClinESSDAI and ESSDAI were calculated at base-

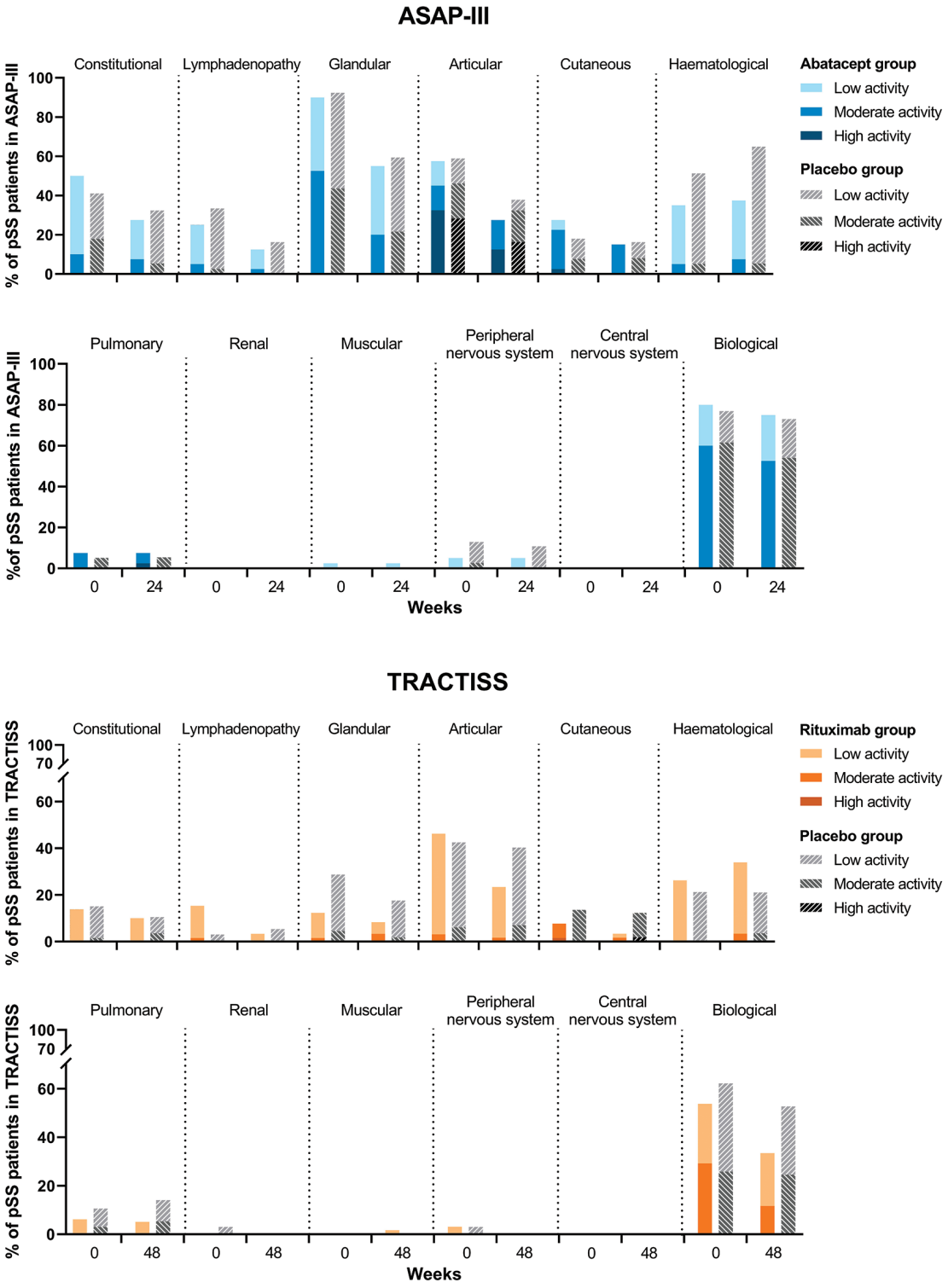

Fig. 1. Activity in ESSDAI domains in ASAP-III and TRACTISS trial.

line, presented as median with interquartile range (IQR). Responsiveness of ClinTrialsESSDAI, ClinESSDAI and ESSDAI total scores was assessed using the standardised response mean (SRM). SRM <0.5 was interpreted as small, 0.5-0.8 as moderate and >0.8 as large. The difference between active treatment and placebo groups for change in these three scores was evaluated using linear generalised estimating equations (GEE). For both trials, the GEE model included baseline values of the dependent variable, treatment, visits, and interactions of treatment by visits. For the ASAP-III trial, the randomisation factor of previous DMARD use was also included. For the TRACTISS trial, the randomisation factors of randomisation centre, age, diagnosis duration, consent for biopsy and ultrasound were also

Table II. Responsiveness measured with SRM of ClinTrialsESSDAI (weighting of ClinESSDAI), ClinESSDAI and ESSDAI in ASAP-III and TRACTISS trial.

ASAP-III	**Week 12**		**Week 24**	
	Abatacept	*Placebo*	*Abatacept*	*Placebo*
ClinTrialsESSDAI	-0.78	-0.30	-0.65	-0.59
ClinESSDAI	-0.74	-0.30	-0.63	-0.59
ESSDAI	-0.76	-0.34	-0.64	-0.61
TRACTISS	**Week 24**		**Week 48**	
	Rituximab	*Placebo*	*Rituximab*	*Placebo*
ClinTrialsESSDAI	-0.10	-0.27	-0.33	-0.13
ClinESSDAI	-0.12	-0.30	-0.34	-0.12
ESSDAI	-0.23	-0.32	-0.41	-0.16

SRM: standardised response mean; ClinTrialsESSDAI: Clinical Trials European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI); ClinESSDAI: Clinical ESSDAI; ASAP-III: Abatacept Sjögren Active Patients phase III; TRACTISS: Trial of Anti-B cell Therapy in Patients with Primary Sjögren's Syndrome.

included. Residuals of the three scores were normally distributed. Different correlation structures (exchangeable, M-dependent, unstructured) were tested and the model with the lowest information criterion was used, which was the exchangeable correlation structure for all variables. *p*-values <0.05 were considered statistically significant. Number and percentage of responders on the minimal clinically important improvement (MCII) and low disease activity (LDA) for the ClinTrialsESSDAI, ClinESSDAI and ESSDAI were calculated. MCII has previously been defined and validated as decrease of ≥3 points for the ClinESSDAI and ESSDAI (8, 9). The low disease activity (LDA) was defined and validated for ClinESSDAI and ESSDAI as score <5 (8, 9). For the ClinTrialsESSDAI, these existing definitions were used.

Results

Baseline systemic disease activity and selection of ClinTrialsESSDAI domains

Baseline characteristics of the included patients in the ASAP-III and TRACTISS trial can be found in the original publications (4, 7). At baseline, median ClinTrialsESSDAI, ClinESSDAI and ESSDAI total score in the ASAP-III trial were respectively 11.5 (IQR 9.0–17.0), 14.0 (9.0–18.8) and 14.0 (9.0–16.8) in the abatacept group and 11.0 (7.0–16.0), 12.0 (8.0–19.0) and 13.0 (8.0–18.0) in the placebo group. In the TRACTISS trial this was respectively 3.0 (IQR 0.0–5.5), 3.0 (0.0–6.5) and 4.0 (2.0–6.5) in the rituximab group and 3.0 (0.0–6.3), 4.0 (2.0–8.0) and 4.0 (2.0–7.3) in the placebo group.

The six most frequently active clinical ESSDAI domains at baseline in the ASAP-III trial were: glandular (any activity: 91%), articular (58%), constitutional (46%), haematological (43%), lymphadenopathy (29%) and cutaneous (23%) domain. In the TRACTISS trial they were: articular (44%), haematological (24%), glandular (21%), constitutional (15%), cutaneous (11%) and lymphadenopathy (9%) (Fig. 1). These domains were selected to include in the ClinTrialsESSDAI.

Responsiveness and discrimination between treatment groups

Responsiveness measured with SRM showed closely similar responsiveness when using ClinTrialsESSDAI, ClinESSDAI or ESSDAI in both the ASAP-III and TRACTISS trial. At the primary endpoint visits, SRM values of ClinTrialsESSDAI, ClinESSDAI and ESSDAI were respectively -0.65/-0.59, -0.63/-0.59 and -0.64/-0.61 for abatacept/placebo and -0.33/-0.13, -0.34/-0.12 and -0.41/-0.16 for rituxi-

Table III. Baseline values and differences between groups at week 12 and week 24, using ClinTrialsESSDAI, ClinESSDAI and ESSDAI.

ASAP-III	**Baseline**		**Week 12**		**Week 24**	
	Abatacept (n=40)	*Placebo (n=39)*	*Adjusted difference (95% CI)*	*p-value*	*Adjusted difference (95% CI)*	*p-value*
ClinTrialsESSDAI	11.5 (9.0-17.0)	11.0 (7.0-16.0)	-3.2 (-6.0 to -0.5)	0.022	-1.7 (-5.1 to 1.5)	0.297
ClinESSDAI	14.0 (9.0-18.8)	12.0 (8.0-19.0)	-3.0 (-5.7 to -0.2)	0.036	-1.4 (-4.8 to 2.1)	0.435
ESSDAI	14.0 (9.0-16.8)	13.0 (8.0-18.0)	-2.3 (-4.5 to -0.01)	0.049	-1.1 (-4.0 to 1.7)	0.428
TRACTISS	**Baseline**		**Week 24**		**Week 48**	
	Rituximab (n=65)	*Placebo (n=66)*	*Adjusted difference (95% CI)*	*p-value*	*Adjusted difference (95% CI)*	*p-value*
ClinTrialsESSDAI	3.0 (0.0-5.5)	3.0 (0.0-6.3)	0.6 (-0.8 to 2.0)	0.408	-1.1 (-2.8 to 0.6)	0.216
ClinESSDAI	3.0 (0.0-6.5)	4.0 (2.0-8.0)	0.8 (-0.9 to 2.5)	0.349	-1.1 (-3.1 to 0.9)	0.265
ESSDAI	4.0 (2.0-6.5)	4.0 (2.0-7.3)	0.3 (-1.2 to 1.8)	0.672	-1.2 (-3.0 to 0.5)	0.171

Baseline scores are presented as median (IQR). All scores are non-transformed and analysed with exchangeable structure in generalised estimating equations (GEE).
ClinTrialsESSDAI: Clinical Trials European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI); ClinESSDAI: Clinical ESSDAI; ASAP-III: Abatacept Sjögren Active Patients phase III; TRACTISS: Trial of Anti-B cell Therapy in Patients with Primary Sjögren's Syndrome; CI: confidence interval.

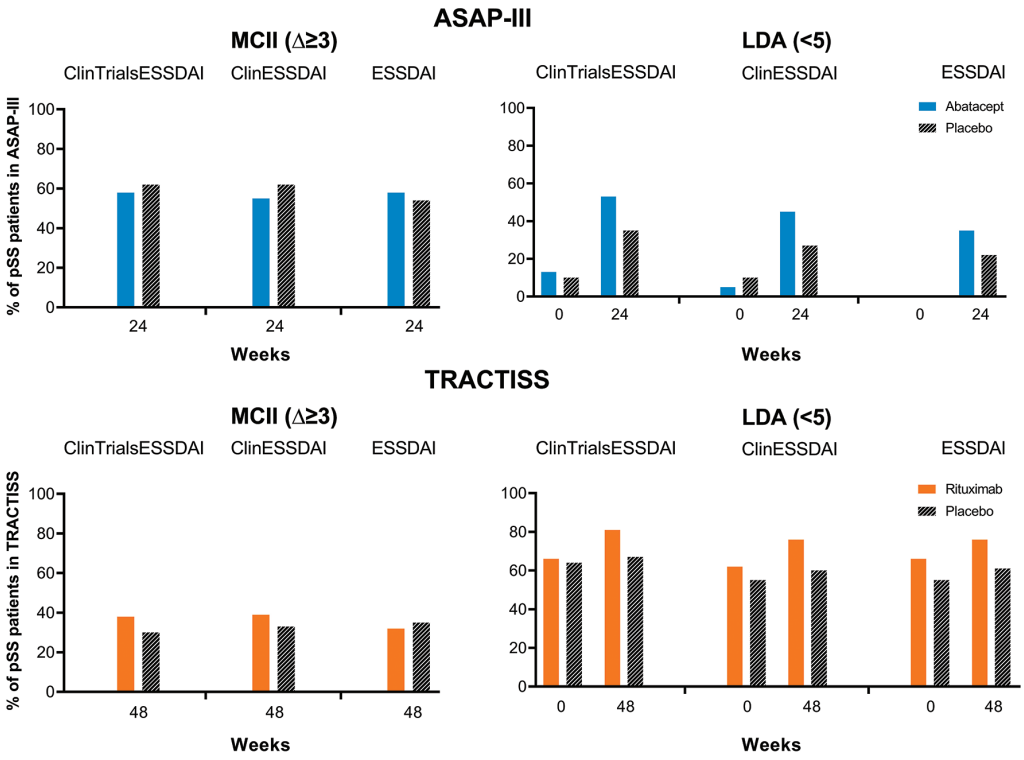

Fig. 2. ClinTrialsESSDAI, ClinESSDAI and ESSDAI minimal clinically important improvement (MCII) and low disease activity (LDA) responders in ASAP-III and TRACTISS trial.

mab/placebo (Table II). In the ASAP-III trial, the adjusted mean difference was somewhat higher using ClinTrialsESSDAI compared to ClinESSDAI and ESSDAI (respectively -1.7, -1.4 and -1.1 at week 24). At week 12, the adjusted difference between treatment groups was significant using any of the three scores, whereas this remained not significant using the ClinTrialsESSDAI at week 24 (primary endpoint). In the TRACTISS trial, the adjusted mean difference was similar using ClinTrialsESSDAI compared to ClinESSDAI and ESSDAI (respectively -1.1, -1.1 and -1.2 at week 48) and was not significant at both time points (Table III).

MCII and LDA responders

In both trials, response rates of the MCII of ≥3 points decrease were similar in both the active treatment and placebo group when using any of the three scores (Fig. 2). In the ASAP-III trial, response rates for the MCII ranged from 55–58% in the abatacept group and 54–62% in the placebo group at week 24. In the TRACTISS trial this was 32–39% in the rituximab group and 30–35% in the placebo group at week 48. Using ClinTrialsESSDAI, LDA (score <5) was reached somewhat more often when compared to ClinESSDAI or ESSDAI LDA. In the ASAP-III trial, LDA for ClinTrialsESSDAI, ClinESSDAI and ESSDAI was reached in respectively 53%/35%, 45%/27% and 35%/22% of abatacept/placebo patients. In the TRACTISS trial this was reached in respectively 81%/67%, 76%/60% and 76%/61% of rituximab/placebo patients. Since the slight increase in LDA responders using the ClinTrialsESSDAI occurred in both the active treatment and placebo groups, discrimination between treatment groups remained the same when using ClinTrialsESSDAI, ClinESSDAI or ESSDAI LDA (Fig. 2).

Discussion

In this exploratory study, we developed and evaluated the ClinTrialsESSDAI, consisting of six frequently active clinical ESSDAI domains, in the ASAP-III and TRACTISS trial. There was no major difference in responsiveness of ClinTrialsESSDAI, ClinESSDAI or ESSDAI scores in both RCTs. Somewhat higher discrimination between treatment groups was found when using the ClinTrialsESSDAI in the ASAP-III trial, which did not lead to a significant difference between treatment groups at the primary endpoint visit. Furthermore, discrimination between active treatment and placebo groups remained similar when using the MCII or LDA in any of the three scores in both RCTs.

Although baseline ESSDAI values were higher in the ASAP-III trial than in the TRACTISS trial, similar domains were most frequently active in these trials. Besides the biological domain, the most frequently active clinical domains in both trials combined were (from most frequently to less active) glandular, articular, haematological, constitutional, lymphadenopathy and cutaneous. Comparable domains were found to be most frequently active in several cohort studies. For example, a large cohort study in 6331 patients, the Big Data Sjögren Project Consortium, found that the most frequently active domains were the biological, articular, haematological, glandular and pulmonary domain (10). This was also seen in other cohort studies and, overall, the most frequently active domains were articular (any activity 19–62%), biological (28–54%), haematological (16–28%) and glandular (4–28%) (3, 11-14). Somewhat less activity was found in the constitutional (4–14%) and cutaneous domains (3–15%) in these cohort studies (3, 11-14). Some clinical trials have also

reported on the baseline activity of the ESSDAI domains. For example, in a different multi-centre RCT of abatacept treatment in 187 pSS patients, most frequently affected domains at baseline were articular, biological, glandular and lymphadenopathy (5). Another multicentre RCT of rituximab treatment in 120 pSS patients, showed that most frequently affected domains at baseline were biological, haematological, articular and glandular (15). These results confirm for the most part the findings from our study.

Responsiveness was closely similar using any of the three scores, which was the case in both the ASAP-III and TRACTISS trial. This implies that response measured with these scores is mostly determined by the six domains that we have included in the ClinTrialsESSDAI, and less by the other domains. This is not an unexpected finding, since these six domains showed the highest activity at baseline (besides the biological domain) and are therefore more likely to respond than domains which rarely show activity. The lower baseline ESSDAI values in TRACTISS probably explain the small responsiveness of all three scores in this trial.

Since several recent RCTs showed a large placebo response using ESSDAI (4-6), it is also important to evaluate if an outcome measure can discriminate between active treatment and placebo groups. We found a moderately higher adjusted mean difference using the ClinTrialsESSDAI in the ASAP-III trial compared to the other scores. However, this did not lead to a significant difference at the primary endpoint visit, raising the question of whether this is a relevant finding. Furthermore, for the TRACTISS trial the adjusted difference remained similar when using any of the three scores. Response rates of the MCII (decrease ≥3 points) were similar using the three scoring methods, in both treatment groups of both trials. Response rates of the LDA (score <5) were moderately higher using the ClinTrialsESSDAI compared to the (Clin)ESSDAI in both active treatment and placebo groups, which is to be expected since the ClinTrialsESSDAI leaves out some domains of the (Clin)ESSDAI, leading to a lower total score and a higher chance of reaching a score <5.

A notable difference is seen in responsiveness and response rates of the ESSDAI MCII versus the LDA in the ASAP-III and TRACTISS trial, which is due to the difference in baseline ESSDAI scores. The ASAP-III trial reports high baseline ESSDAI values. Large response rates are seen in the MCII in both the abatacept (58%) and placebo group (54%) at week 24, leading to no discrimination between treatment groups. Response rates on LDA are lower in the abatacept group (35%) and placebo group (22%), showing more discrimination compared to the MCII. In the TRACTISS trial, low response rates are seen in the MCII in both the rituximab (32%) and placebo group (35%) at week 48, showing no discrimination, whereas high response rates are seen with the LDA (76% and 61%, respectively). This shows that in a trial with a high baseline ESSDAI, the LDA might be preferred to the MCII to assess treatment response, since this prevents a large placebo response. In a trial with a low baseline ESSDAI, it is impossible for a large part of the patients to reach the MCII (decrease of ≥3 points), which is therefore not ideal. Support for using a 'target state' such as low disease activity as response criterion instead of a change measure also comes from the Lupus Low Disease Activity State (LLDAS), which has been developed and validated in systemic lupus erythematosus[16], and was found to be associated with less damage accrual and higher health-related quality of life (17, 18). A possible disadvantage of using the LDA in trials with low baseline ESSDAI is that a large proportion of the patients who already have a low systemic disease activity according to the ESSDAI might remain in this state, leading to a high number of responders. Although this can also be clinically relevant, it seems worthwhile to combine LDA with other outcome measures.

In this exploratory study, ClinESSDAI weightings were used for calculation of the total ClinTrialsESSDAI score. It could be methodologically desirable to develop different weightings for the included domains. These six domains are more easily scored, and do not require additional diagnostic measurements. However, if the ClinTrialsESSDAI is adapted using different weightings, the issue of a large placebo response might still remain, especially since it seems that response is mostly determined by the six domains included in the ClinTrialsESSDAI. Some of these domains might be domains more prone to a placebo effect. For example, the constitutional and articular domains are partly subjective and based on information the patient gives, and this may also influence other domains. Another limitation of the ClinTrialsESSDAI might be that when this score is adopted as a primary endpoint in clinical trials, responsiveness of less frequent, but severe manifestations of pSS will not be taken into account in the primary efficacy analyses. Still, since the ClinTrialsESSDAI is more feasible and gives an overview of systemic disease activity in the most frequently active domains, it might be suitable to use as a secondary endpoint. Validation in other prospective studies of the ClinTrialsESSDAI to further evaluate the added value of this outcome measure would be warranted.

Another proposition has been made as possible solution to the negative findings in RCTs in pSS, which is the use of a composite endpoint. Since pSS is a very heterogeneous disease, it might be more suitable to combine multiple clinically relevant features of pSS in a primary endpoint, instead of evaluating only systemic disease activity. The Composite of Relevant Endpoints in Sjögren's Syndrome (CRESS) has been developed (19), which consists of five complementary items: a systemic disease activity item, measured with ClinESSDAI, patient-reported symptoms, measured with EULAR Sjögren's Syndrome Patient Reported Index, tear gland item, measured with Schirmer's test and ocular staining score, salivary gland item, measured with unstimulated whole salivary flow and salivary gland ultrasonography and a serological item, measured with rheumatoid factor and IgG. Using the CRESS, it was possible to show a higher efficacy

of active treatment compared to placebo in multiple RCTs which previously showed negative results. Furthermore, CRESS was able to lower placebo response compared to ESSDAI, which is essential to demonstrate treatment efficacy, and CRESS was able to confirm a negative trial with low response rates in both treatment groups (19).

In this study, the ClinTrialsESSDAI, consisting of six frequently active clinical domains of the ESSDAI, did not show a superior performance in responsiveness and discrimination compared to ClinESSDAI and ESSDAI in two large RCTs. Therefore, this ClinTrialsESSDAI is not preferable to the ClinESSDAI or ESSDAI for use as primary endpoint. A composite endpoint combining response at multiple clinically relevant items may be more suitable as primary study endpoint in pSS.

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