**Effect of rituximab on a salivary gland ultrasound score in primary Sjögren’s syndrome: results of the TRACTISS randomised double-blind multicentre sub-study**

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**ABSTRACT**

**Objectives:** To compare the effects of rituximab (RTX) versus placebo on salivary gland ultrasound (SGUS) in primary Sjögren’s syndrome (PSS), in a multicentre, multiobserver phase III trial substudy.

**Methods:** Subjects consenting to SGUS were randomised to RTX or placebo given at weeks 0, 2, 24 and 26, and scanned at baseline and weeks 16 and 48. Sonographers completed a 0-11 total ultrasound score (TUS) comprising domains of echogenicity, homogeneity, glandular definition, glands involved, and hypoechoic foci size. Baseline-adjusted TUS values were analysed over time, modelling change from baseline at each time point. For each TUS domain we fitted a repeated measures logistic regression model to model the odds of a response in the RTX arm (≥1 point improvement) as a function of the baseline score, age category, disease duration and time point.

**Results:** 66 patients consented and 52 (n=26 RTX and n=26 placebo) from 9 centres completed baseline and one or more one follow-up visits. Estimated between group differences (RTX-placebo) in baseline adjusted TUS were -1.2 (95% CI -2.1 to -0.3; p=0.0099) and -1.2 (95% CI -2.0 to –0.5; p=0.0023) at weeks 16 and 48. Glandular definition improved with an OR of 6.8 (95% CI 1.1-43.0; p=0.043) at week 16 and 10.3 (95% CI 1.0-105.9; p=0.050) at week 48. Improvement in TUS was not associated with improvement in salivary flow rates or symptoms of dryness.

**Conclusions:** TUS differed between study arms, favouring RTX. This encourages further research into both B cell depletion therapies in PSS and SGUS as an imaging biomarker.

**Key words**: Sjögren’s syndrome, rituximab, ultrasound, salivary gland, B cells

**Introduction**

Primary Sjögren’s syndrome (PSS) is characterised by focal lymphocytic infiltration of exocrine glands leading to profound dryness. It is often accompanied by systemic manifestations and high levels of fatigue. B cells are considered to have a central role in pathogenesis,[1] and two small randomised controlled trials (RCTs) of the anti-CD20 B cell depleting agent rituximab suggested benefits in PSS.[2, 3] Despite this, French (TEARS) and British (TRACTISS) phase III RCTs failed to demonstrate an effect on primary endpoints based on patient-reported visual analogue scales.[4, 5] Potential explanations for these disappointing findings include the lack of patient stratification, insufficient tissue depletion of B cellsand the choice and timing of primary outcome.

The requirement for new and validated outcome measures for PSS led to the development of the European Sjögren’s Syndrome Patient Reported Index (ESSPRI), and the physician assessed systemic disease activity index (ESSDAI).[6] These are a welcome advance but certain limitations suggest that additional objective outcome measures/biomarkers would be desirable. Utilisation of the ESSDAI, for example, requires a minimum threshold for trial entry that excludes a large proportion of patients. Other outcome measures include salivary flow rates, although these are subject to issues of standardisation and diurnal variation,[7] and histological examination of salivary gland biopsies, which may provide mechanistic information but is invasive.[8, 9] Salivary gland ultrasound (SGUS) is readily available, non-invasive and shows reasonable sensitivity and good specificity for the diagnosis of PSS.[10-12] In PSS, glandular echogenicity is altered and there is loss of homogeneity due to the presence of multiple hypoechoic or anechoic areas, as well as hyperechoic bands. Loss of definition of the glandular border may also be observed. A single site sub-study of SGUS in TEARS showed a greater number of patients had improvement in parotid gland echostructure at 24 weeks after rituximab compared with placebo.[13] Echostructure was assessed on a 0-4 scale that graded the presence of hypoechoic areas as well as hyperechoic bands. SGUS is, however, an operator-dependent technique and its utility in a multicentre study is uncertain. Here we report the results of a multiobserver, multicentre SGUS sub-study of TRACTISS over a longer therapeutic timeframe.

**Methods**

The TRACTISS study has been previously described.[4] Briefly, 133 patients with PSS were randomised 1:1 to 1000mg rituximab or placebo given at weeks 0, 2, 24 and 26. Patients and clinicians were blind to the randomised allocation. The primary outcome (30% reduction in either oral dryness or fatigue VAS) was assessed at week 48. 100mg of methylprednisolone was given prior to each infusion of rituximab or placebo. Subjects could consent to an optional SGUS substudy, with assessments at baseline and weeks 16 and 48. The substudy primary outcome was total ultrasound score (TUS, range 0-11; Table 1). Imaging followed a standard sequence with data recorded by the sonographer on a study proforma. Additional information was collected for each of the four major salivary glands on vascularity, gland echogenicity (normal, heterogenous or hypoechoic), gland margins (well or ill-defined), approximate hypoechoic foci number (0, 1-5, 5-9 and >10), hypoechoic foci size (<3, 3-7 and >8 mm), as well as domains capturing lymph node abnormalities.

ESSPRI score was calculated as the mean of 0-10 scales for dryness, fatigue and limb pain. The ESSDAI score was scored by the local investigator. Unstimulated whole salivary flow was collected over 15 mins, and stimulated whole salivary flow over 10mins following application of citric acid with a cotton swab to the lateral borders of the tongue every 60 seconds.

TUS was modelled using mixed effects linear regression, including baseline score, patient age, disease duration and time-point. Odds of domain improvement were modelled by repeated measures logistic regression, including baseline score, age, disease duration and time-point. Descriptive summary statistics, scatterplots and boxplots were produced to explore and summarise the data.

**Results**

66 patients (49.6%) from the total study population consented to SGUS, and 52 (39.1%; n=26 RTX and n=26 placebo) patients from 9 centres completed the baseline and at least one follow-up visit. There were no apparent differences in relevant characteristics between those consenting and not consenting to the sub-study (supplementary Table 1). The two arms of the sub-study were also similar (Table 2), although TUS in the rituximab arm was on average one point greater.

Figure 1 illustrates the baseline-adjusted values of TUS over time, modelling the change from baseline at each time point. Estimated baseline-adjusted TUS at week 16 was 6.2 (95% CI 5.4-7.0) for placebo and 5.0 (95% CI 4.4-5.6) for rituximab, and at week 48, 6.1 (95% CI 5.5-6.6) and 4.8 (95% CI 4.2-5.4) respectively. Estimated between group differences (Rituximab-placebo) in baseline adjusted TUS was -1.2 (95% CI -2.1 to -0.3; p=0.0099) and -1.2 (95% CI -2.0 to –0.5; p=0.0023) at weeks 16 and 48 respectively.

For each TUS domain we fitted a repeated measures logistic regression to model the odds of a response in the rituximab arm (defined as ≥1 point improvement) as a function of the baseline score, age category, disease duration and time point. Glandular definition was the only domain to show statistically significant improvement with an OR of 6.8 (95% CI 1.1-43.0; p=0.043) at week 16 and 10.3 (95% CI 1.0-105.9; p=0.050) at week 48. No difference between rituximab and placebo was observed in any of the additional ultrasound parameters collected, with the exception of gland margin scores which showed deterioration in the placebo group [mean sum of scores over all glands increasing from 1.8 (SD 1.95) at baseline to 2.4 (SD 1.89) at 48 weeks compared with 2.3 (SD 1.83) to 2.4 (SD 1.97) in the rituximab group].

Improvement of ≥1 point in TUS, compared with no improvement or worsening, was not associated with improvement in unstimulated or stimulated salivary flow rates, ESSPRI score or dryness domain VAS at weeks 16 or 48, in the whole population or when analysing the rituximab arm alone. No associations were observed with ≥1 point improvement in either the glandular definition or hypoechoic foci size domains. TUS did not correlate with ESSDAI score or salivary flow rates at any time point, in the whole population or the rituximab arm. Baseline TUS was not correlated with improvement in salivary flow rates, ESSPRI, or oral dryness VAS at either weeks 16 or 48 in the rituximab arm (data not shown).

**Discussion**

We demonstrated a statistically significant improvement in TUS after rituximab compared with placebo. Whilst this observation is similar to that in the TEARS substudy there are a number of key differences. Firstly, in TRACTISS rituximab was given at baseline and then again at 6 months, with a longer follow-up to 48 weeks. Secondly, the TRACTISS substudy was larger, multicentre and multiobserver. The ability of ultrasound to detect changes in this setting is important in encouraging further development of this tool. Thirdly, TRACTISS used a composite SGUS score. Fourthly and related to the last point, the number and size of hypoechogenic foci showed no change in TRACTISS, in contrast to the TEARS study.

The pathological correlate of the hypoechogenic areas observed on ultrasound in PSS is uncertain. In TEARS there was a correlation between histological focus score and SGUS score, suggesting that hypoechogenic areas represent areas of inflammatory cell infiltrate.[14] Furthermore, both high baseline SGUS score and high numbers of infiltrating B cells were both predictive of non-response.[15, 16] However, opposite findings on B cell infiltration and rituximab responsiveness have been reported by Delli et al,[17] and in a cohort of patients with suspected PSS there was only a modest agreement between the same SGUS score and biopsy.[11] Therefore it remains possible that the highest grades of hypoechoic lesions might reflect damage as well as inflammation in a subset of patients, explaining why we observed no change in their size or number.

Our results suggest that glandular definition was an important domain driving change in TUS. Whilst there is a pragmatic attractiveness in simplified scores focusing on hypoechogenic areas for diagnosis,[18] our data encourage the collection of a wider range of features/domains in clinical trials, as there is yet much to learn about the responsiveness of US to effective treatments in PSS.

The clinical significance of our findings is uncertain. TRACTISS did not meet its primary endpoint,[4] and no association with between TUS improvement and salivary flow was found. Furthermore the improvement in the glandular definition domain was only of marginal statistical significance. Other limitations include the utilisation of a novel composite score, although the domains themselves are commonly assessed in other scores, and the small number of subjects, as well as the multiplicity of statistical comparisons, for which we did not adjust our nominal significance levels. Although the sonographers in this study were experienced in salivary gland ultrasound, interobserver concordance between the domains was not studied and could have impacted our findings; further standardisation of SGUS in PSS is urgently required.

There is good reason to believe that rituximab monotherapy may stimulate new autoimmune B cells through elevation in BLyS levels,[19] and may be inefficient at depleting tissue B cells.[20] The fact that we observed a difference in TUS between study arms despite these limitations, strongly encourages further research on B cell depletion therapy in PSS, including use of combination therapies,[21] and on salivary gland ultrasound as an imaging biomarker.

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**Conflict of Interest**

B Fisher paid instructor/consultant for: Novartis, Roche, Virtualscopics. W.-F. Ng Consultant for: Pfizer, UCB, MedImmune, Takeda and Sanofi. M. Bombardieri Consultant for: GSK, Amgen/MedImmune and UCB. S. Bowman Consultant for: Cellgene, Glenmark, GSK, Eli Lilly, Novartis, Roche, Takeda, UCB

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Table 1. Domains of the total ultrasound score (TUS)

|  |  |  |
| --- | --- | --- |
| **Domain** | **Description** | **Score** |
| Echogenicity | Normal | 0 |
| Hypo-echoic | 1 |
| Consistency | Normal | 0 |
| Mild heterogeneity | 1 |
| Evident honeycombed | 2 |
| Gross multifocal | 3 |
| Definition | Normal | 0 |
| Moderately defined | 1 |
| Ill-defined | 2 |
| Glands involved | None | 0 |
| Parotids or submandibular glands | 1 |
| All glands | 2 |
| Hypoechoic foci size | None | 0 |
| Small 2-5 mm | 1 |
| Large 5-8 mm non-vascular | 2 |
| Over 8 mm +/- vascular | 3 |
| **Total** |  | **0-11** |

Online Supplementary Table 1. Selected baseline characteristics of subjects consenting and not-consenting to the salivary gland ultrasound (SGUS) substudy.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | | Did not consent (n=67) | Consented to SGUS substudy (n=66) | All (n=133) |
| Age (Years) | | 52.8 (11.24) | 56.0 (11.66) | 54.4 (11.5) |
| Years since diagnosis | | 6.1 (5.82) | 5.4 (4.92) | 5.7 (5.4) |
| 10 or more years since diagnosis: n (%) | | 14 (20.9) | 10 (15.2) | 24 (18.0) |
| Female Sex: n (%) | | 62 (92.5%) | 62 (93.9%) | 124 (93.2) |
| Current Medications (prior to randomisation) | |  |  |  |
|  | Pilocarpine: n (%) | 5 (7.6%) | 9 (13.4%) | 14 (10.5) |
|  | Hydroxychloroquine: n (%) | 34 (51.5%) | 40 (59.7%) | 74 (55.6) |
|  | Corticosteroids: n (%) | 8 (12.1%) | 11 (16.4%) | 19 (14.3) |
|  | NSAIDS: n (%) | 15 (22.7) | 20 (29.9) | 35 (26.4) |
| Unstimulated Salivary Flow (mL/15min) | | 1.1 (1.25) | 1.2 (1.77) | 1.2 (1.52) |
| Stimulated salivary flow (mL/10min) | | 3.4 (4.10) | 3.5 (4.43) | 3.4 (4.26) |
| IgG (g/L) | | 18.8 (8.19) | 17.2 (6.8) | 18.0 (7.5) |
| IgA (g/L) | | 3.2 (1.33) | 3.2 (1.98) | 3.2 (1.7) |
| IgM (g/L) | | 1.1 (0.52) | 1.3 (0.71) | 1.2 (0.6) |
| Anti-Ro autoantibody positive | | 67 (100.0) | 65 (98.5) | 132 (99.2) |
| Reduced C4 | | 9 (13.4%) | 10 (15.2%) | 19 (4.3) |
| Visual Analogue Scales (Average over last 2 weeks, mm. 100=Severe, except Global) | |  |  |  |
|  | Fatigue | 71.7 (16.37) | 74.0 (15.87) | 72.8 (16.1) |
|  | Oral Dryness | 74.0 (14.61) | 78.6 (17.43) | 76.3 (16.2) |
|  | Ocular Dryness | 65.0 (20.20) | 76.4 (18.68) | 70.7 (20.2) |
|  | Overall Dryness | 72.2 (14.07) | 78.3 (17.00) | 75.2 (15.8) |
|  | Joint Pain | 50.7 (28.32) | 58.8 (27.26) | 54.7 (28.0) |
|  | Global Assessment (100=PSS very active) | 68.1 (17.27) | 71.2 (18.47) | 69.7 (17.9) |
| ESSPRI (10=Maximal Symptom Severity) | | 6.7 (1.71) | 6.5 (1.57) | 6.6 (1.6) |
| ESSDAI (123=Maximal Disease Activity) | | 5.6 (5.10) | 5.7 (3.91) | 5.7 (4.52) |

Footnote: Values are Mean and standard deviation unless otherwise stated

Table 2. Selected baseline characteristics of subjects with both baseline and follow-up data in salivary gland ultrasound (SGUS) substudy.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | | Placebo (n=26) | Rituximab (n=26) | All (n=52) |
| Age (Years) | | 57.4 (11.1) | 56.7 (10.92) | 57.1 (10.91) |
| Years since diagnosis | | 6.6 (5.67) | 5.38 (4.82) | 6.0 (5.25) |
| 10 or more years since diagnosis: n (%) | | 6 (23.1) | 4 (15.4) | 10 (19.2) |
| Female Sex: n (%) | | 23 (88.5) | 25 (96.2) | 48 (92.3) |
| Current Medications (prior to randomisation) | |  |  |  |
|  | Pilocarpine: n (%) | 1 (3.8) | 4 (15.4) | 5 (9.6) |
|  | Hydroxychloroquine: n (%) | 13 (50.0%) | 15 (57.7%) | 28 (53.8%) |
|  | Corticosteroids: n (%) | 6 (23.1%) | 2 (7.7%) | 8 (15.4%) |
|  | NSAIDS: n (%) | 7 (26.9%) | 5 (19.2%) | 12 (23.1%) |
| Unstimulated Salivary Flow (mL/15min) | | 1.4 (2.34) | 0.8 (0.71) | 1.1 (1.72) |
| Stimulated salivary flow (mL/10min) | | 3.8 (4.08) | 3.7 (5.51) | 3.7 (4.82) |
| IgG (g/L) | | 17.2 (7.67) | 17.8 (6.02) | 17.5 (6.82) |
| IgA (g/L) | | 3.7 (2.87) | 3.0 (1.0) | 3.3 (2.14) |
| IgM (g/L) | | 1.2 (0.64) | 1.4 (0.65) | 1.28 (0.64) |
| Anti-Ro autoantibody positive: n (%) | | 26 (100) | 25 (96.2) | 51 (98.1) |
| Reduced C4: n (%) | | 4 (15.4%) | 4 (15.4%) | 8 (15.4%) |
| Visual Analogue Scales (Average over last 2 weeks, mm. 100=Severe, except Global) | |  |  |  |
|  | Fatigue | 74.5 (13.46) | 67.0 (18.22) | 70.8 (16.30) |
|  | Oral Dryness | 75.6 (15.13) | 73.8 (13.30) | 74.7 (14.14) |
|  | Ocular Dryness | 64.7 (23.25) | 65.7 (19.25) | 65.2 (21.09) |
|  | Overall Dryness | 73.4 (15.64) | 71.3 (13.17) | 72.4 (14.36) |
|  | Joint Pain | 56.4 (28.40) | 47.2 (27.21) | 51.8 (27.93) |
|  | Global Assessment (100=PSS very active) | 73.4 (14.08) | 62.2 (18.90) | 67.8 (17.45) |
| ESSPRI (10=Maximal Symptom Severity) | | 6.7 (1.63) | 6.4 (1.64) | 6.6 (1.64) |
| ESSDAI (123=Maximal Disease Activity) | | 6.8 (3.82) | 5.1 (4.55) | 6.0 (4.24) |
| ESSDAI Glandular domain: n (%) | |  |  |  |
| No activity | | 17 (65.4%) | 22 (84.6%) | 39 (75.0%) |
| Low activity | | 8 (30.8%) | 3 (11.5%) | 11 (21.2%) |
| Moderate activity | | 1 (3.8%) | 1 (3.8%) | 2 (3.8%) |
| Total ultrasound score (TUS) | | 5.02 (3.06) | 6.5 (2.04) | 5.9 (2.65) |
| TUS domains | |  |  |  |
| Echogenicity | | 0.5 (0.51) | 0.8 (0.43) | 0.7 (0.48) |
| Consistency | | 1.3 (1.00) | 1.5 (0.91) | 1.4 (0.95) |
| Definition | | 0.8 (0.83) | 1.3 (0.74) | 1.0 (0.82) |
| Glands involved | | 1.5 (0.81) | 1.9 (0.43) | 1.7 (0.67) |
| Hypoechoic foci size | | 1.0 (0.68) | 1.1 (0.48) | 1.1 (0.58) |

Footnote: Values are Mean and standard deviation unless otherwise stated

Figure 1. Baseline-adjusted total ultrasound score (TUS) at follow-up. Mean baseline-adjusted TUS, and between group differences at Week 16 and 48.

Footnote/Caption: data modelled using a covariance pattern mixed model, with the baseline value fitted as a fixed effect. Values presented are least-squares means and 95% confidence intervals for the two groups, and the differences between the groups.

