Randomized controlled trial of rituximab and cost-effectiveness analysis in treating fatigue and oral dryness in primary Sjögren's Syndrome

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Short/Running Title: Rituximab for symptomatic fatigue and oral dryness in Primary Sjogrens Syndrome.

Title: Randomized Controlled Trial of Rituximab and cost-effectiveness analysis in treating fatigue and oral dryness in primary Sjogren's Syndrome

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Abstract:

Objective: We investigated whether rituximab, an anti-B-cell therapy, improved symptoms of fatigue and oral dryness in patients with Primary Sjögren's Syndrome (PSS).

Methods: Multicentre, randomised, double-blind, parallel-group placebo-controlled trial, including Health Economic Analysis. Anti-Ro positive patients with PSS, symptomatic fatigue and oral dryness were recruited from 25 UK rheumatology clinics from August 2011 to January 2014. Patients were centrally-randomised to either placebo IV or rituximab IV (1000mg in 250mL) at weeks 0, 2, 24 and 26, with pre-and post-infusion medication including corticosteroids. Primary endpoint was the proportion of patients achieving 30% reduction in either fatigue or oral dryness at 48 weeks, measured by Visual Analogue Scale. Other outcomes included salivary and lachrymal flow rates, quality of life, ESSDAI and ESSPRI, symptoms of ocular and overall dryness, pain, global disease assessment and cost-effectiveness. ISRCTN 65360827

Results: All patients (n=133) randomised to placebo (n=66) and to rituximab (n=67) were included in the primary analysis. Among complete cases, 21/56 placebo and 24/61 rituximab patients achieved primary endpoint. After multiple imputation of missing outcomes, placebo and rituximab response rates were 36·8% and 39·8%, respectively (adjusted odds ratio 1·13 95% CI 0·50-2·55). There were no significant improvements in any outcome measure, except unstimulated salivary flow. Mean (SD) costs for rituximab and placebo were £10,752 (SD 264·75) and £2,672 (SD 241·71). There were slightly more adverse events reported in total for rituximab, but no difference in serious adverse events (ten in each group).

Conclusions: Rituximab is neither clinically or cost-effective in this patient population.

Introduction

Primary Sjögren's Syndrome (PSS) is a common auto-immune rheumatic condition, second only in frequency to rheumatoid arthritis (RA) (1). PSS patients are typically female (9:1 female:male ratio) with prevalence estimated between 1 and 6 per 1,000 adult women. Typical symptoms of PSS are oral and ocular dryness, fatigue and pain. Fibromyalgia is also reported in 5% of PSS patients, comparable in frequency to its prevalence in Systemic Lupus Erythematosus. (2) Organ-specific systemic involvement is observed in 5-20% of patients and includes cutaneous involvement, peripheral neuropathy, non-erosive arthritis, interstitial cystitis, lung and renal disease. These patients almost always have evidence of B-cell hyper-reactivity with anti-Ro/La antibodies & hypergammaglobulinaemia.

Currently, PSS treatment focuses on relieving symptoms, rather than altering the course of the disease. For ocular dryness, artificial tears are reasonably effective. For oral dryness, however, symptomatic therapies (sprays, lozenges, pastilles) have limited efficacy. Pilocarpine has been shown to alleviate symptoms of dryness (3, 4). However, the utility of pilocarpine is generally considered to be limited, and its side effects reduce the risk-benefit profile. There is no effective therapy for fatigue.

In the absence of positive clinical trial data, treatment of systemic PSS is empirical. Hydroxychloroquine and/or low dose prednisolone are often used in mild disease (although recent findings from the JOQUER study suggest limited benefit (5)). For severe disease, such as progressive neuropathy, intravenous (IV) methylprednisolone, cyclophosphamide, azathioprine, ciclosporin, mycophenolate or chlorambucil may be used. In B-cell lymphoma, it is routine to treat with combination chemotherapy plus rituximab.

Rituximab is a monoclonal antibody against CD20, (a cell surface antigen expressed on B cells). Treatment with rituximab induces a rapid and sustained depletion of B cells. Rituximab is currently approved for the treatment of relapsed or refractory non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, and in combination with methotrexate for the treatment of RA patients.

Evidence from small prospective uncontrolled open-label studies of rituximab in PSS have shown improvements in patient-reported levels of dryness, pain, fatigue, global assessment, SF36 scores (6), stimulated salivary flow (7) and physician global assessment (8). A prospective study comparing symptom levels over ten years of follow-up between patients receiving rituximab in one hospital and disease modifying anti-rheumatic drugs (DMARD) in another found superior improvements for rituximab compared to DMARD therapy. (9)

Findings from small double-blind randomised placebo-controlled trials have also provided some cause for optimism in terms of reduced fatigue (10) and improvements in ocular dryness (11). More recently, however, in the TEARS study (12), there was no significant difference in the proportions of patients achieving the primary endpoint (absolute improvement of 30mm or more in 2 of 4 Visual Analogue Scales (VAS) measuring fatigue, dryness, pain and global assessment) at 24 weeks, although a greater response in terms of fatigue was demonstrated at earlier time-points.

As evidence from randomised trials has only assessed the efficacy of a single course of rituximab, there remains a gap in the clinical knowledge for a randomised, double-blind evaluation of a follow-up dose of rituximab in patients with PSS. The TRACTISS trial was designed to determine the effectiveness of rituximab in improving symptoms of fatigue or oral dryness in patients with PSS following two courses of therapy.

Patients and Methods:

Trial Design and Patients

TRACTISS (ISRCTN: 65360827, EudraCT Number: 2010-021430-64) is a randomised, 1:1, parallel-group, double-blind, multicentre, placebo-controlled trial, to determine the effectiveness of rituximab in alleviating patient-reported symptoms of fatigue and oral dryness, in patients with PSS. The trial was carried out in accordance with Good Clinical Practice, and the Declaration of Helsinki. Ethical and governance approval were obtained from the Leeds West Ethics Committee (ref 10/H1307/99) and the Leeds Teaching Hospitals NHS Trust respectively. An independent Data Monitoring and Ethics Committee (DMEC) had access to ongoing unblinded reports of safety and compliance, and a Trial Steering Committee (TSC) had overall oversight of the study.

The TRACTISS protocol has been published (13). Briefly, between August 2011 and January 2014, participants were recruited from 25 UK rheumatology clinics, and were eligible if they had PSS, were aged 18-80 years, positive for Anti-Ro autoantibodies, had some (greater than zero) unstimulated salivary flow, symptomatic fatigue and oral dryness worse than 5/10 on a patient-completed Likert scale, on a stable dose of corticosteroids, NSAIDS, DMARDS, pilocarpine and antidepressants for 4 weeks prior and throughout the study and provided written informed consent to participate. Exclusion criteria included Secondary Sjögren's Syndrome, Hepatitis B or C, tuberculosis, HIV or other immunodeficiency, prior rituximab or monoclonal antibody usage, malignancies within 5 years prior, recent organ transplant, major surgery planned or 3 months prior, pregnancy / lactation and unwillingness to use contraception throughout the study. Eligibility criteria were changed

after the 37th randomisation to reduce the required period of stable hydroxychloroquine use (where applicable) from 6 months to 4 weeks and to allow patients with benign ethnic neutropenia to take part, rather than being excluded due to neutropenia. There was no difference in characteristics between patients randomised before and after this change.

Intervention and Outcomes

Participants received either rituximab IV (1000mg in 250mL saline) or placebo IV (250mL saline) in 2 courses at weeks 0, 2, 24 and 26. To reduce risk of infusion reactions, patients received pre-infusion medication of methylprednisolone, acetaminophen and chlorphenamine, and post-infusion oral prednisolone, reducing from 60mg to 15mg over 7 days post infusion. (13)

At baseline and weeks 16, 24, 36 and 48, patients completed VAS Questionnaires recording Fatigue, Overall Dryness, Oral Dryness, Ocular Dryness, Pain and Global Assessment (average symptom level over previous 2 weeks: 0=None, 100mm=Severe) and the ESSPRI. PROFAD-SSI, SF36 and EQ5D-3L questionnaires were completed at baseline and weeks 24 and 48. Unstimulated and Stimulated (using 2% citric acid solution) Salivary Flow was measured at these visits, as was Lachrymal Flow using the Schirmers I Test. Physicians completed ESSDAI and Global Assessment of Disease Activity at all visits, and the SSDAI, SSDI, SSDDI, SCAI and the Global Assessment of Damage at Baseline and weeks 24 and 48. (13)

Randomisation and Blinding

Randomisation was by 24-hour central telephone service operated by the Clinical Trials Research Unit. Consenting participants were registered before undergoing further clinical

tests to ensure eligibility. Once eligibility was confirmed, participants were allocated by minimisation, which assigned a patient with 80% probability to the arm that reduced the between-group imbalance in randomising centre, age category, years since diagnosis, consent for ultrasound and for biopsy sub-studies.

Each site's dispensing pharmacy received details of the participant allocation, by fax, to facilitate infusion preparation. On the day of infusion, pharmacy provided either a pure saline bag (placebo) or a saline bag to which rituximab had been added. A small volume of saline was withdrawn from rituximab bags, to ensure no difference in bag volume was detected. Placebo and rituximab infusion bags were otherwise identical.

Sample Size

The pre-defined minimum clinically important effect of rituximab was an increase in treatment response rate from 20% in the placebo arm to 50% in the rituximab arm. For a two-sided continuity-corrected Chi-Squared test, 50 patients with complete data in each arm were needed in order to have 80% power to detect this difference at a 5% significance level. To allow for non-completion, 110 patients (55 per arm) were required.

In July 2013, the DMEC recommended extending recruitment until the end of the planned recruitment period and, to reduce loss to follow-up, a protocol amendment allowed participants to complete the final primary endpoint questionnaire at home, rather than attending clinic.

Statistical Analysis

The primary endpoint was the achievement of a reduction of at least 30% relative to the baseline measurement in the patient-completed VAS assessments of either fatigue or oral

dryness at week 48. Secondary endpoints included the patient-completed and physician-completed assessments at other time-points and measurements of Salivary and Lachrymal Flow. The primary endpoint was modelled using mixed-effects logistic regression, adjusting for the minimisation factors (age category, disease duration category, consent for sub-studies as fixed effects and randomising centre as a random effect) and a fixed effect for the randomised treatment arm. All patients were included in this primary analysis, even if the patient had incomplete outcome data. For patients with incomplete primary endpoint questionnaire data (fatigue and oral dryness each at baseline and week 48), we used multiple imputation by chained equations (14) to impute plausible missing VAS values; the imputation function included fixed randomisation factors (for baseline values) and also the baseline values (for week 48 values). Missing values were imputed separately for each scale, both for placebo and for rituximab patients to produce one full dataset. This was repeated N times where N was the number of patients with incomplete data. Analysis was performed for each dataset, and the results combined to estimate treatment effects and appropriate confidence intervals using Rubin's rules (15). To assess sensitivity of results to alternative assumptions about missing data, we repeated the analysis using a Last Observation Carried Forward approach, a complete-case analysis and a per-protocol population analysis. In order to calculate adjusted absolute differences in response rates, we fitted a linear probability model (binary error structure with identity link function); we excluded the random centre effect from this model to ensure model convergence.

Secondary endpoints were analysed by fitting a random-coefficients mixed effects linear regression model, with fixed effects for baseline value, age, disease duration, the sub-study consent, time and time-by-treatment interaction, and random effects for patient and

patient-by-time interaction, taking the time to be the number of weeks since randomisation. Most endpoints were analysed on their original scale, though we logarithm-transformed the salivary and lachrymal flow rates and the ESSDAI (including an offset to avoid zero values) to better approximate normality. We repeated this longitudinal analysis using a covariance pattern type mixed model, treating assessments as discrete sequential observations (relaxing the assumption of a linear treatment effect) so as to provide graphical summaries of group means at each time-point using least-squares means.

Adverse Event data was reported throughout the trial duration, and returned after completion of follow up at 48 weeks.

Economic Analyses

An economic evaluation was conducted alongside the clinical trial to assess cost-effectiveness of rituximab compared to placebo over 48 weeks. Incremental cost-effectiveness ratios (ICERs) were calculated and assessed against a willingness to pay threshold of £20,000 per Quality-Adjusted-Life-Year (QALY) gain (16). QALYs were calculated using utility weights derived from the EQ-5D-3L collected at 16, 24, 36 and 48 weeks post-randomisation (17). Resource use was captured using bespoke patient-completed forms and nurse records of medications and hospital visits. Costs were attached to individuals employing NHS Reference costs, Personal Social Services Research Unit and British National Formulary databases (price year 2014) (18-20). Analyses were conducted from the perspective of the healthcare provider. The probability of cost-effectiveness was determined by bootstrapping and constructing cost-effectiveness acceptability curves using a range of willingness to pay thresholds for QALY gains (21). Multiple imputation was

employed to account for missing cost and EQ-5D data (22). No discounting was undertaken, due to the short follow-up duration of 48 weeks per patient.

Results

Recruitment

Between August 2011 and January 2014, 133 participants were randomised 1:1 to receive either rituximab or placebo (Figure 1). Final follow-up visit was completed by January 2015. Randomised patients were, on average, 54 years old (SD 11) with 23% (30/133) aged 65 or older, were 5·7 (SD 5·4) years post diagnosis (24/133, 18% with 10 or more years) and 124 (93.2%) were female. Baseline characteristics of patients are presented in Table 1.

Primary Endpoint Analysis

All 66 placebo (PLC) and 67 rituximab (RTX) patients were included in the primary endpoint analysis. Sixteen participants (12.0%) had incomplete fatigue or oral dryness measurements at baseline (1PLC, 1RTX) or at week 48 (9PLC, 5RTX). The primary endpoint response rates among complete cases were 21/56 (37·5%) for placebo patients and 24/61 (39·3%) for rituximab patients. After multiple imputation of missing responses, the mean response rates were 36·8% and 39·8% for placebo and rituximab arms (unadjusted absolute difference RTX-PLC 3·0% 95%CI: -14·5 to 20·5%). In the primary analysis, rituximab patients were not significantly more likely to achieve 30% reduction in fatigue or oral dryness than placebo patients (odds ratio 1·1; 95% CI 0·5 to 2·5; P=0·76). The baseline-adjusted absolute difference in response rates (RTX-PLC) was 1·7% (95% CI -16·5 to 19·1%; P=0·84). The lack of significant treatment effect remained even when using different endpoint imputation

strategies, or a complete case analysis. A per-protocol population analysis (excluding patients found to be ineligible, those not receiving all 4 doses within a reasonable timeframe and those with incomplete primary endpoint data) was also not significant (odds ratio 0·9; 95% CI 0·1 to 6·5; P=0·95).

Secondary Endpoints

Longitudinal analyses of patient VAS scales did not reveal significant differences in change over time between randomised arms for any of the six VAS scores. Figure 2 (A and B) illustrates the levels of symptomatic fatigue and oral dryness reported over time; there were no significant differences between the groups at any time-point for these, or any of the other symptom scales (Online Supplement Figure D1).

Composite disease activity scores, and patient-reported outcome measures showed no benefit for rituximab. There was no significant difference between the two groups over time in the average ESSPRI or the ESSDAI scales (except for a small relative difference in ESSDAI scores at week 36 in favour of rituximab) (Table 2). There was no improvement in any domain of the SF-36 for rituximab over placebo, or in the SF-36 component scores. There was also no improvement in the PROFAD-SSI domains at any time-point for rituximab compared to placebo.

We did observe a difference between the arms in unstimulated salivary flow. Over the duration of follow-up, we found that the log-transformed USF values seemed to hold constant for rituximab patients, and to deteriorate for placebo patients. Although the treatment-by-time interaction effect was not statistically significant at traditional thresholds (estimate: 0·013, 95% CI (-0·001 to 0·028), P=0·066) the between-group differences

between the mean values of USF at weeks 36 and 48 were statistically significant (Table 2, Figure 2C). No similar benefit was seen in stimulated salivary flow or in mean lachrymal flow (Figure 2D).

We performed four post-hoc subgroup analyses to investigate treatment modification effect due to baseline ESSDAI scores (using two different thresholds), baseline ESSPRI scores and the disease duration since diagnosis (Table 3). No significant treatment modification effect was observed in any of these subgroup analyses.

Cost effectiveness

The mean costs and QALY estimates by trial arm at 48 weeks are included in Appendix Table B1. When excluding the rituximab infusion no significant difference in resource use between treatment arms was observed. However inclusion of the rituximab infusion conferred significant differences in costs between arms. The mean cost per patient in the rituximab arm was £10,752 (SD 264·75) compared to £2,672 (SD 241·71) for the placebo arm. Mean QALYs were 0·55 (SD 0·003) and 0·56 (SD 0·004) for rituximab and placebo groups respectively. The higher mean costs, and lower QALYs mean that placebo dominates rituximab (Appendix figure B1). Bootstrapping the mean costs and QALYs suggested that rituximab had a 0% probability of being cost-effective at any threshold from £0 to £200,000.

Safety

Rituximab was well-tolerated among patients. There were no deaths in either arm, ten serious adverse events (SAE) among nine patients in each arm - of which three events in three patients were serious adverse reactions (Table 4). One participant randomised to rituximab did not receive any rituximab prior to having a SAE. One serious infusion reaction

was reported in one patient receiving rituximab, and one serious Anaphylaxis event was reported in one patient receiving placebo. For non-serious adverse events, 275 were reported in 55 placebo patients (of which 61 events (22.2%) were suspected to be related to intervention, 24 (8.7%) resulted in delayed or modified treatment administration, and 5 (1.8%) resulted in cessation of treatment); 325 events were reported in 61 rituximab patients (82 (25.2%)of events suspected to be related to treatment, 33 (10.2%) resulted in delayed or modified administration and 10 (3.1%) resulted in cessation of treatment).

Discussion

TRACTISS is the largest, randomised, placebo-controlled, trial of rituximab in patients with primary Sjögren's Syndrome to date. After two courses, each comprising 2 doses of 1000mg of rituximab, patients were not significantly more likely to report a response to treatment at the 48 week time-point (in terms of a reduction of 30% of baseline measurement in either Oral Dryness or Fatigue VAS) than those randomised to receive placebo. These and other patient-reported outcomes of Ocular and Overall Dryness, Joint Pain and Global Assessment of disease activity were not significantly improved by rituximab at any time-point. We also did not observe a significant benefit in terms of lachrymal flow, or in any of the composite patient-reported outcomes, or disease activity indices, except for a one-off significant difference between groups in the ESSDAI score at week 36. We did observe significant differences between the groups in average Unstimulated Salivary Flow rates; rituximab patients maintained their baseline flow rate, while placebo patients decreased. However, given the many statistical tests performed in these secondary outcome analyses, this may well be a Type I error and should not be over-interpreted. No difference in the safety profile for the two arms was observed.

For the economic analyses a small non-significant difference in QALYs was observed between the arms in favour of the placebo. The main driver of costs was the rituximab infusion which attracted a cost of £1,746 per 1000mg and a significantly higher overall cost compared with placebo. There was no significant difference in costs when rituximab was excluded. Further analysis revealed that even at a willingness-to-pay threshold ten times higher than the current NICE recommendation (16) rituximab was not cost effective; even with a relatively large reduction in price the use of rituximab is unlikely to be cost effective.

TRACTISS is the fourth, double-blind, placebo-controlled, randomised trial of rituximab reported to date, bringing the total number of patients included in such studies to 302. The first study, a pilot RCT in 17 patients (10) reported a greater reduction in fatigue among patients randomised to rituximab compared to those receiving placebo, but no significant difference in proportions of patients achieving either 20% or 30% reduction from baseline in fatigue at 6 months. A later RCT in 30 patients (11) reported significant changes from baseline for most variables (including salivary flow rates and patient-reported measures of fatigue, oral and ocular dryness) in both arms, but the 20 rituximab patients only reported significant differences compared to the 10 placebo patients in Stimulated Salivary Flow at 12 weeks, and in ocular dryness at 36 and 48 weeks.

Most recently, the TEARS study (12) analysed 120 patients randomised to either rituximab or placebo in a multicentre trial and did not detect a significant difference in numbers of patients achieving the primary endpoint (reductions of 30mm in at least 2 VAS for Dryness, Pain, Fatigue and Global Assessment). Although a significant response was detected at 6 weeks, particularly in fatigue, this was not sustained by the 24 week time-point. Signs of efficacy were evident in fatigue and dryness when these outcome data were analysed

longitudinally, but symptoms of Pain and Global assessment were not significantly improved. As in previous studies, TEARS found no significant difference in the safety profiles of the arms.

TRACTISS differed from these randomised trials in that patients were randomised to two doses of the trial drug, to be received in a double-blind manner. It was hoped that signals of efficacy observed in earlier studies would be seen at the same time-points in TRACTISS, and that a second dose would demonstrate long-term efficacy of rituximab. However, early efficacy measured by fatigue at 16 weeks (TEARS) and late efficacy in terms of ocular dryness (Meijer et al) were not observed in TRACTISS. Similarly, although we observed significant deterioration in unstimulated salivary flow for placebo compared to rituximab, at later time-points, no such effect was reported in other RCTs.

Early evidence from non-randomised trials and uncontrolled studies was more promising. In an open-label prospective study (9), 19 patients at one centre received rituximab, and 22 patients at another received DMARD therapy over a 10 year period. Patients in this study had higher disease activity (mean baseline ESSDAI score was 20). Significant differences between the two arms was demonstrated in Fatigue and Dryness VAS scores (week 120 mean (SEM) fatigue DMARD 51·8 (4·5) vs RTX 41·1 (4·2); week 120 mean (SEM) Dryness DMARD 51·8 (11·1) RTX 25·1 (7·7)), as well as ESSDAI (week 120 mean (SEM) DMARD 8·8 (1·7) vs RTX 5·2 (0·9)), Unstimulated Salivary Flow (DMARD 0·1 (0·08) vs RTX 0·4 (0·04)) and Lachrymal flow (DMARD 5·5 (0·8) vs RTX 7·3 (0·8)). However, bias due to potential differences between centres' practices, the open label nature of the study, and the differing additional study medications (DMARD & prednisone vs RTX & chlorphenamine, paracetamol and methylprednisolone) cannot be ruled out. Sixteen patients who received rituximab in an

uncontrolled study (23) reported significant improvements from baseline in SF-36 component scores (Mean Physical and Mental Component Summary improvements of 16·9 and 31·2, respectively), but no such improvement was found in either our study (Table 2) or in the TEARS study.

Researchers have previously suggested (5, 12) that outcome measures used in studies of these patients are not sufficiently sensitive to changes in the patient condition after successful treatment. To that end, composite outcome measures to be completed by the physician (24) and by the patient (25) were developed by the European League Against Rheumatism (EULAR). These outcome measures were developed in patient populations of a similar age to those in TEARS and TRACTISS, but the development population profiles for both tools involved patients with slightly longer disease durations (approximately 8·5 years) than seen here. Moerman *et al* computed ESSDAI scores for all patients in one RCT (26) to conclude that the ESSDAI was sensitive enough to detect a treatment effect of rituximab, despite low average ESSDAI scores. In both TEARS and TRACTISS, patients had low ESSDAI scores at baseline (relative to the maximum score of 123) and mean improvement in ESSDAI was not different between the two arms. The ESSPRI did not suffer the same problem as the ESSDAI in TRACTISS, but no significant difference was detected overall, nor did it define a subgroup that demonstrated a benefit. A recent re-analysis of data from TEARS (27) proposed a data-driven composite outcome measure, the Sjögren's Syndrome Responder Index (SSRI), rooted in the assumption that rituximab is effective. Data from TRACTISS may assist in the external validation of the SSRI.

A post-hoc analysis of data from the TEARS study (28) to estimate the required sample size to detect a significant difference in response rates suggested that the most sensitive

endpoint by which response to treatment can be assessed would be change in ultrasound grading. However, the observed ultrasonography improvement in TEARS (29) did not translate into patient-reported symptomatic improvement. Findings of the TRACTISS ultrasound sub-study will be presented at a later date, as will results of the labial gland biopsy sub-study.

Despite the requirement for a minimum level of symptomatic fatigue and oral dryness in order to take part in TRACTISS, the patients were mostly of recent onset and had mild systemic disease activity as measured by the ESSDAI. Although the two courses of rituximab given constituted a different treatment regimen to the single course in other RCTs, it remains a possibility that a benefit to patients would be seen if rituximab is administered over longer periods of time, such as those seen in longer open-label comparative studies. Further, although TRACTISS is the largest trial of rituximab in PSS to date, a sample size of 133 patients is small by the standards of Phase III randomised trials, and confidence intervals around our estimates were wide. The low population prevalence of PSS poses challenges to recruitment, and emphasises the importance of patient retention, to ensure that studies are adequately powered.

Despite ambitions towards meta-analysis with data from the TEARS study, our study omitted a 6 week assessment visit, which was the time-point at which the greatest fatigue response was observed in TEARS. We omitted this visit to reduce the patient burden. Although our study had low levels of patient withdrawal (and used multiple imputation to account for uncertainty due to incomplete data) it was necessary to offer mailed questionnaires to some participants to capture primary endpoint data at 48 weeks.

Like the TEARS trial, TRACTISS was designed to have power to detect a large difference in response rates between the arms: the possible side-effects due to rituximab, as well as the underlying inconvenience and costs of rituximab administration mean that a large benefit would need to be demonstrated for rituximab to be worthwhile. The existence of a smaller long-term effect cannot be ruled out – and may be identified in a possible meta-analysis – but it remains to be seen if a smaller effect would be worthwhile or cost-effective. Moreover, in common with other studies in this context many outcome measurements were compared at several time points and we did not adjust our secondary endpoint analyses for multiple comparisons; it is possible that the relative deterioration in unstimulated salivary flow for placebo patients was a false positive finding.

Although there did not appear to be any excess risk due to rituximab, the results of the TRACTISS trial do not support the general use of rituximab in treating PSS, particularly in patients with recent disease onset and / or low disease activity. Meta-analysis with the TEARS study may improve overall precision of findings, but it seems unlikely that the combined results will identify a worthwhile treatment benefit. The need for further large randomised trials to demonstrate longer-term benefit appears questionable, since the lack of effect of 2 courses of rituximab seems in line with the lack of benefit of one course in randomised trials. Rituximab may still have a role in treating PSS patients with high levels of systemic disease activity who have failed to improve following conventional immunosuppressive therapy.

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Tables

Table 1: Selected Baseline Characteristics

	Placebo (N=66)	Rituximab (N=67)	All (N=133)
Age (Years)	54·4 (11·6)	54·3 (11·5)	54·4 (11·5)
Aged 65 years or older: n (%)	15 (22·7)	15 (22·4)	30 (22·6)
Years since diagnosis	6·2 (5·8)	5·3 (4·9)	5·7 (5·4)
10 or more years since diagnosis: n (%)	13 (19·7)	11 (16·4)	24 (18·0)
Female Sex: n (%)	61 (92·4)	63 (94·0)	124 (93·2)
Current Medications (prior to randomisation)			
Pilocarpine: n (%)	3 (4·5%)	11 (16·4%)	14 (10·5%)
Hydroxychloroquine: n (%)	35 (53·0%)	39 (58·2%)	74 (55·6%)
Corticosteroids: n (%)	12 (18·2%)	7 (10·4%)	19 (14·3%)
NSAIDS: n (%)	16 (24·2%)	19 (28·4%)	35 (26·3%)
Unstimulated Salivary Flow (mL/15min)	1·2 (1·8)	1·2 (1·2)	1·2 (1·5)
Mean Lachrymal Flow (Schirmers I) (mm/5min)	8·2 (11·3)	6·6 (8·8)	7·4 (10·2)
IgG (g/L)	17·7 (7·9)	18·4 (7·3)	18·0 (7·5)
IgA (g/L)	3·4 (2·2)	3·0 (0·9)	3·2 (1·7)
IgM (g/L)	1·2 (0·6)	1·3 (0·6)	1·2 (0·6)
Anti-Ro autoantibody positive	66 (100·0%)	66 (98·5%)	132 (99·2%)
Reduced C4	9 (13·6%)	10 (14·9%)	19 (14·3%)
Current Smoker: n (%)	8 (12·1)	3 (4·5)	11 (8·3)
Visual Analogue Scales (Average over last 2 weeks, mm. 100=Severe, except Global)			
Fatigue	74·6 (15·3)	71·2 (16·8)	72·8 (16·1)
Oral Dryness	77·3 (17·0)	75·3 (15·3)	76·3 (16·2)
Ocular Dryness	72·0 (19·6)	69·4 (20·9)	70·7 (20·2)

Overall Dryness	76·3 (16·3)	74·2 (15·4)	75·2 (15·8)
Joint Pain	57·5 (28·7)	52·0 (27·2)	54·7 (28·0)
Global Assessment (100=SS very active)	70·7 (17·8)	68·6 (18·0)	69·7 (17·9)
ESSPRI (10=Maximal Symptom Severity)	6·7 (1·6)	6·4 (1·6)	6·6 (1·6)
ESSDAI (123=Maximal Disease Activity)	6·0 (4·3)	5·3 (4·7)	5·7 (4·5)
SF-36 Physical Component Score	35·6 (10·9)	36·6 (9·8)	36·1 (10·3)
SF-36 Mental Component Score	40·7 (12·3)	39·2 (11·6)	40·0 (11·9)

Footnote: Values are Mean and standard deviation unless otherwise stated

Table 2: Summaries of secondary outcomes adjusted for baseline measurement.

	Time-point in weeks	Placebo (SEM)	Rituximab (SEM)	Difference (RTX – PLC, adjusting for baseline values) (95% Confidence Interval)	Wald P-Value
Fatigue Visual Analogue Scale					
	16	65·2 (3·4)	65·4 (3·2)	0·16 (-7·79, 8·10)	0·9693
	24	64·9 (3·4)	69·5 (3·0)	4·67 (-2·87, 12·22)	0·2241
	36	68·2 (3·3)	65·7 (3·7)	-2·54 (-11·19, 6·11)	0·5639
	48	65·8 (3·3)	67·9 (3·3)	2·10 (-5·89, 10·09)	0·6053
Oral Dryness Visual Analogue Scale					
	16	69·0 (3·1)	65·7 (3·2)	-3·28 (-10·50, 3·94)	0·3725
	24	70·1 (3·2)	70·2 (3·3)	0·09 (-7·46, 7·64)	0·9821
	36	65·7 (3·4)	58·3 (4·0)	-7·33 (-16·35, 1·69)	0·1110
	48	70·5 (3·0)	66·4 (3·7)	-4·06 (-12·01, 3·89)	0·3157
ESSDAI (Log-transformed [a])					
	16	4·1 (1·1)	3·4 (1·1)	0·85 (0·64, 1·11)	0·2234
	24	4·4 (1·1)	4·1 (1·1)	0·94 (0·73, 1·22)	0·6549
	36	4·8 (1·1)	3·5 (1·1)	0·74 (0·55, 0·98)	0·0352
	48	4·5 (1·1)	3·4 (1·1)	0·75 (0·55, 1·03)	0·0721
ESSPRI					
	16	6·3 (0·3)	6·5 (0·3)	0·19 (-0·45, 0·82)	0·5682
	24	5·8 (0·2)	6·3 (0·2)	0·55 (0·01, 1·09)	0·0458
	36	6·4 (0·3)	6·2 (0·3)	-0·21 (-0·90, 0·49)	0·5622
	48	5·7 (0·2)	6·3 (0·3)	0·54 (-0·12, 1·20)	0·1087
Unstimulated Salivary Flow (mL/15min) (Log-transformed [a])					
	16	0·6 (1·1)	0·9 (1·1)	1·36 (0·99, 1·88)	0·0583
	24	0·7 (1·1)	0·8 (1·1)	1·25 (0·91, 1·72)	0·1742
	36	0·6 (1·2)	1·0 (1·1)	1·56 (1·11, 2·18)	0·0103
	48	0·6 (1·1)	1·0 (1·1)	1·71 (1·23, 2·37)	0·0015
Mean Lachrymal Flow (Schirmers I) (mm/5min) (Log-transformed [a])					
	16	2·0 (0·2)	2·2 (0·2)	1·19 (0·88, 1·61)	0·2624

	24	2·2 (0·2)	2·2 (0·2)	1·01 (0·75, 1·35)	0·9642
	36	2·1 (0·2)	2·3 (0·2)	1·09 (0·79, 1·51)	0·5926
	48	2·0 (0·2)	2·2 (0·2)	1·16 (0·84, 1·61)	0·3698
SF-36 – Physical Component Summary Score					
	24	38·2 (1·0)	36·3 (1·1)	-1·86 (-4·15, 0·43)	0·1107
	48	37·9 (1·0)	37·1 (1·1)	-0·79 (-3·25, 1·67)	0·5246
SF-36 – Mental Component Summary Score					
	24	41·7 (1·4)	41·0 (1·4)	-0·64 (-3·81, 2·54)	0·6924
	48	41·0 (1·6)	41·1 (1·5)	0·12 (-3·58, 3·82)	0·9495

Footnotes:

Values are Mean (Standard Error of Mean) and Mean Difference (95% Confidence Interval) from covariance pattern model

a – Salivary flow rates, mean lachrymal flow rates and ESSDAI scores were highly positively-skewed, and so raw values were logarithm-transformed prior to analysis, and results back-transformed for presentation. Treatment effects presented for these comparisons are ratios on the original scale, rather than differences on the logarithm scale.

Table 3: Odds ratios for the effect of rituximab relative to placebo on the primary outcome, and the interaction between subgroup and treatment effect, for selected post-hoc subgroups.

Categorisation	Adjusted Odds Ratio of Primary Endpoint response Rituximab vs Placebo (95% CI)	Wald P-Value (For interaction)
Baseline ESSDAI 5+	0·55 (0·18, 1·73)	
Baseline ESSDAI 0-4	2·16 (0·65, 7·16)	
Interaction Effect (Relative OR)	0·26 (0·05, 1·33)	0·1044
Baseline ESSDAI 14+	1·27 (0·06, 26·44)	
Baseline ESSDAI 0-13	1·13 (0·49, 2·63)	
Interaction Effect (Relative OR)	1·12 (0·05, 26·01)	0·9441
Years Since Diagnosis: 5+	1·10 (0·31, 3·90)	
Years Since Diagnosis: 0-4	1·11 (0·38, 3·23)	
Interaction Effect (Relative OR)	1·00 (0·19, 5·35)	0·9969
Baseline ESSPRI 5-10	1·16 (0·48, 2·80)	
Baseline ESSPRI 0-4	1·02 (0·14, 7·62)	
Interaction Effect (Relative OR)	1·14 (0·13, 10·07)	0·9086

Table 4: Summary of numbers of Serious Adverse Events and Reactions observed

System Organ Class	Event	Placebo	Rituximab
TOTAL		10	10
Serious Adverse Events			
Cardiac disorders	Myocardial Infarction	1	-
Endocrine disorders	Hydatid Disease	1	-
Gastrointestinal disorders	Diarrhoea and Abdominal Pain	1	
	Diarrhoea	-	1
	Abdominal Pain	-	1
Infections and infestations	Pneumonia	1	-
Metabolism & nutrition disorders	Episode of Hypotensiveness	-	1
Musculoskeletal & connective tissue disorders	Fractured bone	-	1*
	Swollen ankle	-	1
	Chest Pain	1	-
Neoplasms	Pancreatic Tumor	-	1
Renal and Urinary disorders	EUA Cystoscopy and TVT Release	1	-
Respiratory, thoracic and mediastinal disorders	Pulmonary Embolus	1	-
Skin and Subcutaneous tissue disorders	Malignant Melanoma	-	1
Serious Adverse Reactions			
Infections and Infestations	Chest Infection	1	-
	Sepsis	-	1
	Urinary Tract Infection	-	1
Injury, poisoning and procedural complications	Anaphylaxis	1	-
	Serious Infusion Reaction	-	1
Respiratory, thoracic and mediastinal	Epiglotitis	1	-

disorders

*-A patient randomised to receive rituximab withdrew prior to the first infusion. Subsequently, the patient reported a fall leading to a bone fracture.

Note: one patient in the placebo arm, and one patient in the rituximab arm each reported two serious adverse Events

Figures:

Figure 1: Participant flow diagram

Figure 2: Mean (95% Confidence Intervals) values of (A) Fatigue VAS (mm), (B) Oral Dryness VAS (mm), (C) Unstimulated Salivary Flow (mL/15min), (D) Lachrymal Flow (mm/5min). Least-squares means adjusted for baseline values, age, disease duration and substudy consent (left axes) and between group differences (right axes) at each visit (weeks). Salivary and Lachrymal flow plotted on Log_2-scale. Higher VAS values (A,B) indicate worse symptom severity, higher log-flow rates indicate greater salivary or lachrymal flow. The region in which a difference favours rituximab (RTX) is annotated.