SLE, Sjögren's and APS - treatment and SLE, Sjögren's and APS - clinical aspects (other than treatment)

OP0129

BELIMUMAB AFTER RITUXIMAB SIGNIFICANTLY REDUCED IGG ANTI-DSDNA ANTIBODY LEVELS AND PROLONGED TIME TO SEVERE FLARE IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: B cell depletion with rituximab, an anti-CD20 mAb, has shown efficacy for systemic lupus erythematosus (SLE) in open-label studies but failed to meet primary endpoints in two randomised, placebo controlled trials. Rituximab increases BAFF levels which has been associated with subsequent lupus flares. We hypothesised that high BAFF levels after rituximab limit its effectiveness in SLE and that the anti-BAFF monoclonal antibody belimumab given immediately after rituximab could be a valuable therapeutic strategy.

Objectives: To assess the safety and obtain preliminary evidence for efficacy of belimumab following rituximab therapy in patients with SLE.

Methods: BEAT-LUPUS (Belimumab after B cell depletion in SLE) is a 52-week phase IIb, randomised, double-blind, placebo-controlled clinical trial investigating the safety and efficacy of intravenous belimumab after B cell depletion therapy (rituximab). The maximum permissible prednisolone dose throughout the trial was 20mg/day with encouragement to reduce by 50% from baseline by 6 months. The primary outcome measure was log IgG anti-dsDNA antibody serum levels at 52 weeks measured by ELISA. A linear regression ANCOVA model was fitted to evaluate the difference in 52-week anti-dsDNA levels between treatment arms adjusting for anti-dsDNA value at screening (before rituximab) and randomisation (4-8 weeks after the 1st infusion of rituximab), CD19 > or < 0.01x10⁹/l at randomisation, and renal involvement at screen. Secondary outcomes included measures of disease activity and incidence of adverse events. B cell (CD19) counts were measured by flow cytometry. Intention to treat analysis was adopted. Full ethical and regulatory approval was obtained. A comprehensive description of the protocol and statistical analysis plan is available^(1,2).

Results: 52 patients with active SLE received rituximab (2 infusions, 2 weeks apart) and then randomised to receive either belimumab (n=26) or placebo (n=26) 4-8 weeks after their 1st dose of rituximab. 32 patients completed trial treatment protocol (belimumab or placebo) through to 52 weeks, withdrawals were equally split between belimumab and placebo. There was a significant reduction in IgG anti-dsDNA antibody levels in patients treated with belimumab compared to placebo at 52 weeks (p<0.001, Figure 1); 43 patients were included in the intention to treat analysis at 52 weeks.

Figure 1. Serum IgG anti-dsDNA antibody levels (geometric means with 95% confidence intervals) in patients treated with rituximab, then randomised to belimumab or placebo at 1st trial infusion. An intention to treat linear regression ANCOVA model was fitted to evaluate the difference in 52-week anti-dsDNA between belimumab or placebo adjusting for baseline values and stratification factors. N= patient numbers who provided serum samples at time indicated.

Kaplan-Meier curves demonstrated that belimumab reduced the risk of severe flare (BILAG A flare) compared to placebo (hazard ratio 0.27, 95% confidence

interval 0.07-0.97, unadjusted log-rank p=0.03). There were 10 and 3 severe flares in the placebo and belimumab group respectively. There was no difference in cumulative steroid dose over the course of the trial between belimumab and placebo.

Belimumab did not increase the incidence of infections, serious or total adverse events, nor withdrawals due to adverse events compared to placebo. Belimumab significantly suppressed B cell repopulation at 52 weeks compared to placebo (p=0.001), but not total serum IgG.

Conclusion: This placebo controlled double blind trial met its primary endpoint, a significant reduction in IgG anti-dsDNA antibody levels, and demonstrated that belimumab prolongs the time to severe flare compared to placebo. These results suggest that belimumab after rituximab is a safe and effective treatment for patients with SLE and supports further development of this combination as a novel therapeutic strategy.

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OP0130

COMPOSITE OF RELEVANT ENDPOINTS IN SJÖGREN'S SYNDROME (CRESS): A COMPREHENSIVE TOOL FOR CLINICAL TRIALS

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Background: Several large randomised controlled trials (RCTs) in primary Sjögren's syndrome (pSS) failed to demonstrate drug efficacy.¹⁻⁴ Many of these trials used ESSDAI as primary endpoint, showing large but similar response rates in active treatment and placebo groups.^{1,3,4} Given the heterogeneous nature of pSS, there is need for a composite endpoint including multiple clinically relevant parameters.

Objectives: To develop and validate the Composite of Relevant Endpoints in Sjögren's Syndrome (CRESS).

Methods: A multidisciplinary team of pSS experts selected clinically relevant items and measurements to include in the CRESS. Definition of response of CRESS items was based on clinical relevance, previously defined minimal clinically important improvement (MCII) and data of the single-centre ASAP-III (abatacept) trial.¹ CRESS was validated in three independent RCTs: TRACTISS (rituximab) trial²,

multi-centre abatacept trial³ and ETAP (tocilizumab) trial⁴. CRESS response rates were assessed at the primary endpoint visit of all four trials.

Results: Five complementary items were selected to form CRESS: systemic disease activity, patient-reported symptoms, tear gland, salivary gland and serological item. Definition of response per item is presented in Table 1. Total CRESS response was defined as response on ≥ 3 of 5 items. Since not all trials have ocular staining score or salivary gland ultrasonography (SGUS) available, the concise CRESS (cCRESS) was developed simultaneously, leaving Schirmer's test and unstimulated whole saliva flow for the tear and salivary gland items, respectively. In the ASAP-III trial, CRESS response rates were 24/40 (60%) for abatacept vs. 7/39 (18%) for placebo at week 24 ($p < 0.001$).

Table 1. CRESS items and definition of response

Items	Measurements	Definition of response
Systemic disease activity	ClinESSDAI	Score < 5 (low disease activity)
Patient-reported symptoms	ESSPRI	Decrease of ≥ 1 point or $\geq 15\%$
Tear gland*	Schirmer/OSS**	-If abnormal Schirmer (≤ 5 mm) at baseline: increase of ≥ 5 mm in Schirmer -Or if abnormal OSS (≥ 3 points) at baseline: decrease ≥ 2 points in OSS -Or if both Schirmer/OSS normal scores at baseline: no change to abnormal in both
Salivary gland*	UWS/SGUS	Increase of $\geq 25\%$ in UWS (or if score is 0 at baseline, any increase) Or decrease of $\geq 25\%$ in total Hocevar score (SGUS)
Serological	RF/IgG	Decrease of $\geq 25\%$ in RF Or decrease of $\geq 10\%$ in IgG
CRESS responder	Responder on ≥ 3 of 5 items	

Ocular Staining Score (OSS), Unstimulated whole salivary flow (UWS), Salivary gland ultrasonography (SGUS), Rheumatoid factor (RF), Immunoglobulin G (IgG)***Concise CRESS (cCRESS):** CRESS without OSS and SGUS, leaving Schirmer and UWS for tear and salivary gland items, respectively**Mean of both eyes

Figure 1 A. CRESS and cCRESS (=CRESS without OSS and SGUS) response rates in ASAP-III trial at week 12 and 24. At week 12, only CRESS without SGUS was available. B. cCRESS response rates in TRACTISS (rituximab) trial at week 24 and 48. C. CRESS without SGUS response rates in multi-centre abatacept trial at week 12 and 24. D. cCRESS without rheumatoid factor response rates in ETAP (tocilizumab) trial at week 12 and 24. E. CRESS response rates vs. ESSDAI MCII response rates in ASAP-III trial at week 24. Median baseline ESSDAI scores for abatacept were 14.0 (IQR 9.0-16.8), for placebo 13.0 (IQR 8.0-18.0). F. cCRESS response rates vs. ESSDAI MCII response rates in TRACTISS trial at week 48. Mean baseline ESSDAI scores for rituximab were 5.3, SD=4.7, for placebo 6.0, SD=4.3. G. CRESS without SGUS response rates vs. ESSDAI MCII response rates in multi-centre abatacept trial at week 24. Mean baseline ESSDAI scores for abatacept were 8.7, SD=3.4, for placebo 10.1, SD=4.0. H. CRESS without RF response rates vs. ESSDAI MCII response rates in ETAP trial at week 24. Median baseline ESSDAI scores for tocilizumab were 11.0 (IQR 8.0-13.5), for placebo 10.0 (IQR 8.0-14.8). For all trials, ESSDAI response percentages were calculated imputing missing patients as non-responders.

In the external validation trials, cCRESS response rates for TRACTISS were: 33/67 (49%) rituximab vs. 20/66 (30%) placebo at week 48 ($p=0.026$). CRESS response rates (without SGUS) for the multi-centre abatacept trial were: 41/92 (45%) abatacept vs. 30/95 (32%) placebo at week 24 ($p=0.067$). cCRESS response rates (without rheumatoid factor) for ETAP were: 10/55 (18%) tocilizumab vs. 13/55 (24%) placebo at week 24 ($p=0.482$) (Figure 1A-D). Compared to ESSDAI MCII of ≥ 3 points decrease, CRESS was able to approximately halve placebo response rates in RCTs with high baseline ESSDAI scores (> 5) (Figures 1E-H).

Conclusion: CRESS shows lower placebo response rates compared to ESSDAI MCII, which is crucial for demonstrating treatment efficacy. With the CRESS, higher response rates in abatacept and rituximab treated patients compared to placebo were found in RCTs which previously showed negative primary endpoint results. CRESS confirmed that no differences were found for almost all outcome measures between tocilizumab and placebo,⁴ with low response rates. The CRESS is a well-balanced, feasible, composite endpoint for use in clinical trials in PSS patients.

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OP0131 ANIFROLUMAB EFFECTS ON RASH AND ARTHRITIS IN PATIENTS WITH SLE AND IMPACT OF INTERFERON SIGNAL IN POOLED DATA FROM PHASE 3 TRIALS

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Background: Treatment with the type I interferon (IFN) receptor antibody anifrolumab was associated with clinical improvements in mucocutaneous and musculoskeletal disease activity in patients with systemic lupus erythematosus (SLE) in the phase 2 MUSE trial (NCT01438489) and phase 3 TULIP trials.¹⁻⁴ Because rash and arthritis are the most common manifestations of SLE, the effect of anifrolumab on these symptoms can be examined in biomarker-defined subsets, as previously reported for the MUSE trial.²

Objectives: To evaluate the effect of anifrolumab on rash and arthritis in patients with SLE, and the impact of IFN gene signature (IFNGS) on treatment response, using disease measures of different stringency in pooled data from the phase 3 TULIP trials.

Methods: TULIP-1 (NCT02446912) and TULIP-2 (NCT02446899) were placebo-controlled, 52-week trials of intravenous anifrolumab administered every 4 weeks in patients with moderate to severe SLE.^{3,4} In this post hoc analysis, outcomes of rash and arthritis were evaluated using mucocutaneous and musculoskeletal domains of the SLE Disease Activity Index 2000 (SLEDAI-2K) and the