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DOI: 10.1136/annrheumdis-2017-eular.1127

OP0235 A NOVEL B CELL SPECIFIC IFN-I BIOMARKER IS ASSOCIATED WITH PLASMABLAST NUMBERS FOLLOWING B CELL DEPLETION THERAPY IN SLE

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Background: SLE is a Type I interferon (IFN-I) mediated disease with autoreactive B cells. Plasmablasts, the immediate progeny of B cells, are expanded in SLE and correlate with disease activity. We showed that their rate of regeneration after therapeutic B cell depletion with rituximab is variable and predicts relapse[1]. IFN-I has been shown *in vitro* to induce the differentiation of B cells into plasmablasts. We previously showed that therapeutic B cell depletion with anti-CD20 mAb leads to a transient reduction in CD20-negative plasmablasts, following which plasmablasts repopulate and their numbers predict clinical relapse. We developed tetherin as a flow cytometric, cell-specific marker for IFN-I response.
Objectives: To test the hypothesis that memory B cell tetherin determines the rate of plasmablast repopulation after rituximab.
Methods: 117 rituximab-treated SLE patients were studied prosectively using BILAG-2004 and flow cytometry. In 97 responders we tested plasmablasts at 6 months as a predictor of clinical relapse before 12 months to validate our previous finding. In 50 patients pre-rituximab and 28 patients post-rituximab we performed additional flow cytometry to measure tetherin on each cell subset. Expression of 18 ISGs was measured using Taqman on PBMCs and an ISG score calculated.
Results: We divided clinical responders to rituximab into earlier relapse (12 months) or later relapse (>12 months). As in our published discovery cohort, plasmablasts were strongly predictive of clinical relapse. ROC analysis indicated that a plasmablast count of >0.0008 x 10^9/L at 6 months yielded 73% (95% CI 45–92%) sensitivity and 90% (95% CI 56–99%) specificity in predicting earlier relapse; area under the curve of 0.86.
Plasmablast numbers after rituximab were associated with Memory B cell tetherin (R=0.38, p=0.047) but not ISG score (R=0.24, p=0.219) (Table 1).
In Pre-rituximab there was no relationship between any IFN assay and plasmablast count. After rituximab treatment there was no correlation between plasmablast count and ISG expression, nor with monocyte or NK cell surface tetherin. However, memory B cell tetherin MFI was positively correlated with plasmablast count (Table 1).

Table 1

Interferon assay	Plasmablast Count (cells x10^9/L)	
	Pre-rituximab (*n* =50)	Post-rituximab (*n* =28)
ISG expression Score:	-0.11, *P*=0.448	0.24, *P*=0.219
Tetherin protein level: Monocytes	-0.08, *P*=0.592	0.20, *P*=0.296
T-cells	-0.16, *P*=0.269	0.32, *P*=0.096
NK cells	-0.14, *P*=0.324	0.05, *P*=0.795
Naïve B-cells	-0.04, *P*=0.801	0.30, *P*=0.121
Memory B-cells	0.07, *P*=0.618	0.38, *P*=0.047

Values are Spearman's Rank Correlation Coefficient and *P* values.

Conclusions: Although interferon stimulated gene expression is commonly used to measure IFN-I activity, tetherin provides a cell-specific assay. We demonstrate that by measuring IFN-I response in B cells specifically, we could explain plasmablast differentiation, and thereby clinical outcome. Memory B cell tetherin is valuable to immunophetype SLE.
References:
[1] Vital et al. Arthritis Rheum. 2011 Oct;63(10):3038–47.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.6423

OP0236 BENEFIT AND SAFETY OF ANTITHROMBOTIC TREATMENT IN 264 PREGNANCIES IN PATIENTS WITH ANTIPHOSPHOLIPID SYNDROME

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Background: The management of pregnancy in patients with antiphospholipid syndrome (APS) with aspirin and heparin is based on empiric recommendations.
Objectives: Our study aimed to evaluate the outcomes of treated patients with thrombotic and obstetric APS and the safety of antithrombotic treatments prescribed during pregnancy.
Methods: Inclusion criteria were (1) APS (Sydney criteria), (2) live pregnancy at 12 weeks of gestation (WG) with (3) follow up data until 6 weeks post-partum. Data were collected prospectively (PROMISSE study) and retrospectively (four French centers). Adverse pregnancy outcomes (APOs) were defined by fetal death or neonatal death; pre-term delivery before 36 WG due to preeclampsia or placental insufficiency; or small for gestational-age (SGA; <5th percentile). Major bleeding was defined as blood loss greater than 500mL and/or requiring surgery or transfusion.
Results: 264 pregnancies (87 collected prospectively) in 204 patients were included (46% with a history of thrombosis, and 23% with associated systemic lupus erythematosus). During pregnancy, treatment included heparin (n=253; 96%) and low-dose aspirin (n=223; 84%).
The live birth rate was 86%. APOs occurred in 32%, mostly during the 2nd trimester: fetal deaths 11%, SGA 11%, pre-term delivery before 36 WG due to preeclampsia or placental insufficiency 17%. Thirteen maternal thrombotic events occurred in 12 (4.5%) pregnancies. Forty-six maternal hemorrhagic events occurred in 40 (15%) pregnancies (30 events in the post-partum period). Major bleeding was reported in only 6 pregnancies (2.3%) and occurred only after delivery. Except for two events, post-partum hemorrhage occurred in the early post-partum before hospital discharge. No maternal death was observed.
Aspirin therapy during pregnancy was the only independent factor associated with a lower risk of APOs (odds ratio: 0.34; 95% CI: 0.15 – 0.78; p=0.01) in multivariate analysis.
Neither heparin or aspirin alone, nor combined therapy increased the risk of hemorrhage. In the retrospective cohort, emergency caesarian section was the only factor associated with hemorrhagic events during the study period (53% hemorrhages in patients who underwent emergency caesarian compared to 18%, p=0.005). Independent risk factors for APOs were elevated body mass index and the presence of lupus anticoagulant.
Conclusions: We report a high level of obstetrical complications in conventionally-treated APS pregnancies, and a beneficial effect of addition of aspirin to prevent obstetrical morbidity. Moreover, heparin and aspirin were well tolerated and did not increase risk of hemorrhage.
Disclosure of Interest: None declared
DOI: 10.1136/annrheumdis-2017-eular.1926

OP0237 LIFITEGRAST OPHTHALMIC SOLUTION 5.0% FOR TREATMENT OF DRY EYE DISEASE: COMBINED EVIDENCE FROM 5 RANDOMIZED CONTROLLED TRIALS

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Background: Dry eye disease (DED) is a multifactorial disease of the tear film and ocular surface, characterized by ocular discomfort and visual disturbance.[1] DED is associated with a number of systemic autoimmune diseases, particularly rheumatoid arthritis and Sjögren's syndrome.[2,3] Lifitegrast is a lymphocyte function-associated antigen-1 (LFA-1) antagonist that inhibits T-cell–mediated inflammation (an underlying factor in DED) and is approved in the US for the treatment of signs and symptoms of DED (lifitegrast ophthalmic solution 5.0%, Xiidra®).
Objectives: To evaluate the combined evidence from 5 clinical trials of lifitegrast ophthalmic solution 5.0% (LIF) in subjects with dry eye disease (DED).
Methods: Adults with DED were randomized to LIF or placebo (PBO) in 5 randomized, double-masked, placebo-controlled trials: 4 12-week efficacy/safety studies (phase 2, LIF n=58, PBO n=58; phase 3 trials: OPUS-1, LIF n=293, PBO n=295; OPUS-2, LIF n=358, PBO n=360; OPUS-3, LIF n=355, PBO n=356), and a 1-year safety study (SONATA, LIF n=220, PBO n=111). Individuals with secondary Sjögren's syndrome associated with autoimmune disease (eg, rheumatoid arthritis, systemic lupus erythematosus) were eligible to participate if they were not immunodeficient/immunosuppressed, not taking steroids, and met all other inclusion and exclusion criteria. Change from baseline to day 84 in DED signs and symptoms was evaluated across the 12-week studies. Key measures were inferior corneal staining score (ICSS; 0–4 scale), eye dryness score (EDS; visual analogue scale [VAS], 0–100 scale), and visual-related function subscale of a symptom scale (0–4 scale). Pooled safety data (LIF n=1287, PBO n=1177) from all 5 trials were also analyzed.
Results: LIF improved ICSS versus PBO in the phase 2 study (secondary endpoint; treatment effect 0.35, nominal *P*=0.0209), OPUS-1 (co-primary; 0.24,