

manifestations of systemic LE (SLE). The typical histopathologic pattern in CLE/SLE is interface dermatitis, which can also be observed in dermatomyositis (DM). While LE may affect any organ system, DM most commonly affect muscles and skin.

The aim of this study was to investigate the whole proteome of skin inflammatory foci in the cohort of CLE and DM patients in a comparative, hypothesis-free manner and identify disease-unique molecular mechanisms.

Methods CLE (n=6), DM (n=5) patients and controls (n=6) were recruited at diagnosis or disease exacerbation. Skin biopsies were acquired, examined by a pathologist and selected inflammatory foci were laser micro-dissected. The total protein content was analyzed by mass-spectrometry, further analysis was performed by string-db.org platform. Certain proteomic findings were confirmed by immunohistochemistry (IHC).

Results CLE infiltrates were more protein rich in comparison to DM lesions. There ratio of 5x upregulated proteins in LE/DM was 60, while ratio for DM/LE was 13. Our results confirmed high abundance of (IFN)-regulated proteins both in CLE and DM, including: IFIT1, IFIT2, IFIT3, MX1, MX2, OAS2, OAS3, STAT1, STAT2, DDX58, DDX60 and EIF2AK2. Proteins expressed differentially in CLE covered complement proteins (C1b), including membrane attack complex (MAC) (C5, C6, C7, C8A and B) and complement regulators (CFHR1, CFHR2, CFHR5), as well as regulators of coagulation: thrombospondin 2 (THBS2), thrombin (F2), fibrinogen (F12) and annexin A3 (ANXA3). Importantly, we identified interleukin (IL) -16 as the only detectable and highly abundant cytokine in the CLE lesions and confirmed this finding by IHC.

Conclusions Our data confirm evidence on IFN-regulated processes in CLE/SLE. Importantly, we identified IL-16 as a novel cytokine most strongly upregulated locally in the skin lesions. Moreover, we identified activation of MAC, complement regulating proteins as well as involvement of coagulation/fibrinolysis system. The study brings information on novel pathways involved in the inflammatory foci of the skin lesions in CLE patients. Our findings are of interest in further search of new therapeutic targets.

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PER-PROTOCOL REPEAT KIDNEY BIOPSY PORTENDS RELAPSE AND LONG-TERM OUTCOME IN INCIDENT CASES OF PROLIFERATIVE LUPUS NEPHRITIS

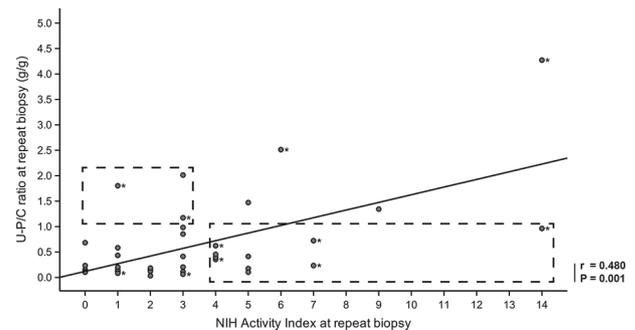
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Background In patients with Lupus Nephritis (LN), clinical response to treatment and renal histopathology have been shown to be discordant. We investigated whether per-protocol repeat renal biopsies are predictive of LN relapses and long-term impairment of renal function.

Methods Forty-two patients with an incident biopsy-proven active proliferative (class III/IV ± V) LN from the LN database of the Université catholique de Louvain were included in the present retrospective study. Per-protocol repeat kidney biopsies were performed in all patients after a median time of 24.3 (IQR: 21.3–26.2) months. The NIH activity index (AI) and chronicity index (CI) scores were assessed in both baseline and repeat biopsies.

Results Despite a moderate correlation between urinary protein/creatinine (U-P/C) ratios and AI scores at repeat biopsy ($r=0.48$; $P=0.001$), ten patients (23.8%) with U-P/C ratios <1.0 g/g still had a high degree of histological activity (AI score >3 ; figure 1). High AI scores in repeat biopsies were associated with an increased probability and/or shorter time to renal relapse (N=11) following the repeat biopsy (HR: 1.2; 95% CI: 1.1–1.3; $P=0.007$), independently of proteinuria levels. High NIH CI scores in repeat biopsies were associated with a sustained increase in serum creatinine levels corresponding to $\geq 120\%$ of the baseline value (HR: 1.8; 95% CI: 1.1–2.9; $P=0.016$) through a median follow-up time of 131.5 (IQR: 73.8–178.2) months. Baseline AI/CI scores were not predictive of these outcomes.



Abstract O33 Figure 1

Conclusions Our results highlight the usefulness of per-protocol repeat biopsies as an integral part of the treatment evaluation, also in patients who have shown adequate clinical response.

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VARIANTS IN BANK1 ARE ASSOCIATED WITH LUPUS NEPHRITIS

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Background Lupus Nephritis (LN) is a cause of significant morbidity in SLE. While the genetic background to SLE has been well characterized, less is known about genes predisposing to LN.

Methods The study consisted of 2886 SLE patients, including 947 (33%) with LN. The discovery cohort (Sweden, n=1091) and replication cohort 1 (US, n=962) were genotyped on the ImmunoChip and replication cohort 2 (Norway/Denmark, n=833) on a custom array chip. Allele frequencies were compared between patients with LN and LN-negative patients. SNPs with a p-value <0.001 in the LN vs LN-negative analysis in the discovery cohort ($n_{\text{SNPs}}=139$) were analyzed in replication cohort 1. Ten SNPs associated to LN ($p<0.0002$) in the discovery cohort were genotyped in replication cohort 2. A Bonferroni-corrected p-value of $<1.0\times 10^{-6}$ correcting for 48,000 independent SNPs was considered significant.

Results In the discovery cohort, strong association to LN was found with several highly linked SNPs in *BANK1*, with the top signal in the intronic SNP rs4699261 ($p=9.9\times 10^{-5}$, OR 0.66). The association was also present in replication cohort 1 ($p=9.5\times 10^{-4}$). In a meta-analysis of the discovery and replication cohort 1, a total of 20 SNPs in *BANK1* were associated to LN with the highest signal in rs4699261 ($p=3.3\times 10^{-7}$). There was a tendency towards association in replication cohort 2 ($p=0.05$) and in a meta-analysis of all cohorts, the association with *BANK1* was strengthened ($p=1.7\times 10^{-7}$).

Conclusion *BANK1* variations are associated with LN in patients with SLE. Upregulated *BANK1* expression in renal biopsies from LN patients has previously been shown, however the exact role of *BANK1* in LN pathogenesis remains to be elucidated.

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B-CELL DEPLETION AND RESPONSE IN A RANDOMIZED, CONTROLLED TRIAL OF OBINUTUZUMAB FOR PROLIFERATIVE LUPUS NEPHRITIS

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Background Previous analyses identified associations between the degree of B-cell depletion and response in lupus nephritis (LN). NOBILITY tested whether enhanced B-cell depletion with the type II anti-CD20 mAb obinutuzumab could improve responses in LN.

Methods 126 patients with active Class III/IV LN were randomized to obinutuzumab or placebo infusions in combination with mycophenolate and corticosteroids. Peripheral B-cells were measured using a flow cytometry method with a lower limit of 0.441 cells/ μL . Sustained depletion was assessed by flow cytometry measurements at weeks 24 and 52.

Results Obinutuzumab was associated with increased CRR (40% vs. 18%, $P=0.007$) and ORR (51% vs. 29%, $P=0.015$) at week 76. Obinutuzumab resulted in rapid and

Abstract 035 Table 1 Renal responses at week 76 by depletion status

	Obinutuzumab sustained depletion (N=32)	Obinutuzumab detectable B-cells (N=20)	Placebo group (N=62)
CRR	50%**	35%*	18%
Modified CRR	72%**	50%	37%
ORR	66%***	45%*	29%

Eleven patients in the obinutuzumab group with insufficient data to determine depletion status are excluded.

* $P < 0.2$ vs. placebo group

** $P < 0.05$ vs. placebo group

*** $P < 0.001$ vs. placebo group

CRR = complete renal response, which required UPCr <0.5 with serum creatinine \leq the upper limit of normal and not increased >15% from baseline with <10 RBCs/HPF and no RBC casts.

Modified CRR = UPCr < 0.5 with normal serum creatinine.

ORR = overall renal response, which required either CRR or partial renal response: $\geq 50\%$ reduction in UPCr from baseline to <1 (<3 if baseline UPCr ≥ 3) with serum creatinine not increased >15% from baseline and $\leq 50\%$ increase in urinary RBCs (or <10 RBCs/HPF).