FRI0310

ACHIEVEMENT OF LOW DISEASE ACTIVITY IN LUPUS PATIENTS TREATED WITH BELIMUMAB IS INDEPENDENT OF SEROLOGIC STATUS AT BASELINE: A REAL-LIFE OBSERVATIONAL STUDY

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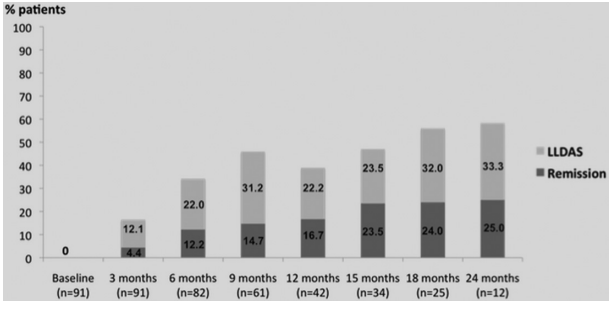
Background: Low disease activity is a validated target of systemic lupus erythematosus (SLE) therapy.

Objectives: To assess the ability of belimumab to induce low disease activity states in real-life setting.

Methods: Multicentre prospective observational study of SLE patients receiving belimumab due to active disease, refractory to at least one conventional immunosuppressant. Disease activity, including attainment of lupus low disease activity state (LLDAS) and remission-on-glucocorticoids (GC) (clinical SLEDAI-2K=0 with prednisone ≤5 mg/day), accrual of organ damage, flares and side effects were documented.

Results: Ninety-one patients were included [94.5% women, mean (SD) age 45.9 (12.5) years]. Most frequent manifestations were arthritis (76.7%), rash (72.5%), serologic activity (low C3/C4 and/or high anti-dsDNA; 54.9%), hair loss (47.2%) and mucosal ulcers (27.5%). Median (range) duration of treatment was 10.5 (3.0–42.1) months. Belimumab decreased average SLEDAI-2K, physician global assessment and daily prednisone dose over time, as early as 3 months after initiation. Complete withdrawal of GC was achieved in 17.8%, 22.5%, 31.7% and 23.3% at 3, 6, 9 and 12 months, respectively. The number of flares and severe flares was reduced by 62% and 50%, respectively, during the first year of treatment. Although reduction in clinical SLEDAI-2K was more pronounced in patients who were serologically active (from 8 to 1.5 at 12 months) compared to serologically inactive (from 6 to 4) at baseline, attainment of low disease activity states (LLDAS or remission) did not differ between groups and was reached by more than 40% of completers after 9–12 months (figure 1). Twenty patients (22.0%) discontinued treatment due to inadequate response and two due to side effects potentially related to the drug.



Conclusions: Belimumab is efficacious in achieving low disease activity in over 40% of active SLE patients, accompanied by complete GC discontinuation in more than 20%. Serologically active and inactive patients respond equally to the drug.

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FRI0311

THE EFFECT OF B CELL TARGETED THERAPIES ON AUTOANTIBODIES AND EXCESSIVE NEUTROPHIL EXTRACELLULAR TRAP FORMATION IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS

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Background: Systemic lupus erythematosus (SLE) is a severe systemic autoimmune disease characterised by immune-complexes which cause systemic inflammation and damage. Neutrophil extracellular traps (NETs) are an important source of autoantigens in SLE patients leading to the production of autoantibodies. Functionally, SLE-specific autoantibodies as immune-complexes are important triggers of excessive NET formation. As such, effective targeting of pathogenic autoantibodies in SLE is subject to several promising experimental treatment strategies. Recently, the combination of Rituximab (RTX) and Belimumab (BLM) in patients with severe SLE led to a strong decrease of autoantibodies and diminished excessive NET formation as well as improvement of clinical disease. A consortium was formed to study different experimental treatment strategies that target the humoral autoimmune system, including RTX, Bortezomib (BTZ) or combination treatment with RTX and BLM.

Objectives: The present study aimed to investigate the effects of B cell targeted therapies on relevant autoantibody levels and excessive NET formation in severe SLE.

Methods: This study involved three cohorts of anti-dsDNA positive, severe SLE patients that were eligible to experimental treatment with RTX (n=16), BTZ (n=6) or RTX +BLM (n=16). A cross-sectional cohort of 35 anti-dsDNA positive SLE patients served as a control cohort. A panel of SLE relevant autoantibodies against dsDNA, histones, nucleosomes and C1q were measured by ELISA. As a functional result of autoantibody levels, NET formation was quantified by our novel highly-sensitive NET quantification assay using 3D confocal microscopy[1].

Results: Comparing three regimens, RTX +BLM resulted in the strongest reduction of anti-dsDNA (median ratio of baseline; 0.32 vs 0.78 vs 0.65; p=0.08), anti-histone (0.36 vs 0.51 vs 0.53; p=0.45), anti-nucleosome (0.38 vs 0.61 vs 0.58; p=0.15), and significantly the strongest reduction of anti-C1q antibodies (0.55 vs 0.91 vs 1.00; p=0.016) compared to RTX and BTZ. Excessive NET formation diminished significantly with a ratio of 0.66 [0.49–0.93] after RTX (p=0.005) and 0.25 [0.15–0.47] after RTX +BLM (p=0.0002), however it was not reduced after BTZ with 1.37 [0.90–1.61]. As such, excessive NET formation correlated with disease activity (p=0.004), except for the BTZ cohort. Importantly, regression of excessive NET formation was associated with reduction of anti-C1q antibodies. In an independent cohort of SLE patients, we confirmed that the presence of anti-C1q antibodies correlated with excessive NET formation (p=0.03). We further observed that the presence of three or more autoantibody specificities associated with excessive NET formation (p=0.02).

Conclusions: This study demonstrates a synergetic effect of RTX +BLM compared to RTX or BTZ on the reduction of relevant autoantibodies in SLE patients which associated with significant regression of NET formation. The reducing effects of RTX +BLM, RTX and BTZ on anti-C1q antibodies underpinned the observed, immunological effects on humoral autoimmunity.

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