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


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Background: Obinutuzumab is a humanized monoclonal antibody that depletes B cells by targeting the B-cell receptor (BCR). It has been approved for the treatment of chronic lymphocytic leukemia and has shown activity in autoimmune diseases. In this randomized, placebo-controlled, double-blind phase 2b study, we evaluated the efficacy and safety of obinutuzumab in patients with proliferative lupus nephritis.

Methods: This was a multicenter trial that enrolled patients with proliferative lupus nephritis. Patients were randomized to receive obinutuzumab or placebo every 4 weeks for 24 weeks. The primary endpoint was the change in the mean weekly proteinuria from baseline to week 24. Secondary endpoints included changes in other renal parameters and safety assessments.

Results: A total of 115 patients were randomized, 57 to obinutuzumab and 58 to placebo. At week 24, there was a significant decrease in the mean proteinuria in the obinutuzumab group compared to the placebo group (-25.6% vs -5.1%, p=0.03). Additionally, there was a significant decrease in the estimated glomerular filtration rate (5.6% vs -2.9%, p=0.04) and a trend towards a decrease in the serum creatinine level (-8.9% vs -3.7%, p=0.07). No serious adverse events were reported in the obinutuzumab group, while one patient in the placebo group withdrew due to adverse events.

Conclusion: Obinutuzumab showed significant improvement in proteinuria and other renal parameters in patients with proliferative lupus nephritis. Further studies are needed to confirm these results and explore the potential role of obinutuzumab in the management of this disease.

References:
Background: Incomplete B-cell and plasmablast depletion, as measured using highly sensitive flow cytometry (HSFC), is associated with lower response rates following rituximab in SLE [1]. Enhanced B-cell depletion with the type II anti-CD20 mAb obinutuzumab resulted in increased renal responses in proliferative lupus nephritis (LN) in the NOBILITY trial (NCT02550585) and will be further evaluated in the Phase 3 REGENCY trial (NCT04221477).

Objectives: To measure peripheral B-cells, B-cell subsets (naïve, memory and plasmablast) and B-cell activating factor (BAFF) levels and to assess associations between B-cell depletion and renal response in LN patients in a clinical trial of obinutuzumab.

Methods: 128 patients with active Class III/IV LN were randomized to obinutuzumab or placebo infusions in combination with mycophenolate and glucocorticoids. Peripheral B-cells were measured using a HSFC method with a lower limit of quantitation of 0.441 cells/μL. Serum levels of BAFF were evaluated using ELISA. Sustained depletion was defined by total B-cells below the limit of detection at both weeks 24 and 52. Renal response definitions from Phase 2 NOBILITY and Phase 3 REGENCY trials were used.

Results: Obinutuzumab resulted in rapid and complete depletion of total B-cells, memory and naïve B-cells, and plasmablasts from peripheral blood, with 88% of obinutuzumab patients depleted to < 0.441 total B-cells/μL at week 2 (Figure). Mean serum BAFF increased from 4,585 pg/mL at baseline to 14,601 pg/mL at week 52 in the obinutuzumab group. Sustained B-cell depletion was achieved in 32/52 (62%) of patients with complete data and was associated with higher renal response rate at week 76 (Table), although patients who achieved sustained depletion also had lower baseline proteinuria and serum creatinine.

Conclusion: Obinutuzumab, a type II anti-CD20 mAb, mediated rapid, complete and sustained depletion of peripheral B-cells and plasmablasts and large increases in serum BAFF. Similar to previous reports, sustained B-cell depletion was associated with increased renal response though there may be confounding factors. REGENCY is being conducted to further evaluate the therapeutic hypothesis with obinutuzumab in LN.

References:

Figure. Mean levels of selected biomarkers over time by treatment group

Table. Data from NOBILITY at week 76 by depletion status at weeks 24 and 52

<table>
<thead>
<tr>
<th>Definition of response</th>
<th>Obinutuzumab sustained depletion (N = 32)*</th>
<th>Obinutuzumab detectable B-cells (N = 20)**</th>
<th>Placebo group detectable B-cells (N = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOBILITY complete response</td>
<td>50%**</td>
<td>35%*</td>
<td>18%</td>
</tr>
<tr>
<td>UP CR &lt; 0.5, SCr ≤ ULN and not increased &gt; 15% from baseline SCr, and &lt; 10 RBC/hpf without casts</td>
<td>66%***</td>
<td>45%*</td>
<td>29%</td>
</tr>
<tr>
<td>NOBILITY overall response</td>
<td>CRR or ≥ 50% reduction in UPCRb with SCr not increased &gt; 15% from baseline and urinary RBCs not increased &gt; 50% from baseline</td>
<td>69%**</td>
<td>45%</td>
</tr>
<tr>
<td>REGENCY complete response</td>
<td>UP CR &lt; 0.5, SCr ≤ ULN and not increased &gt; 25% from baseline SCr</td>
<td>84%***</td>
<td>55%</td>
</tr>
</tbody>
</table>

* P < 0.2 vs. placebo group.
** P < 0.05 vs. placebo group.
*** P < 0.001 vs. placebo group.

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RACIAL DIFFERENCES IN THE IMPACT OF HYDROXYCHLOROQUINE ON IMMUNOLOGIC MARKERS IN SLE PATIENTS

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Background: In patients with Systemic Lupus Erythematosus (SLE), Hydroxychloroquine (HCQ) treatment has been associated with reduced disease activity, lower rates of certain forms of organ damage, and improved survival1. Objectives: To gain insight into the mechanisms involved, we examined the impact of HCQ treatment on immunologic biomarkers that have been associated with higher rates of organ damage. These include lupus anticoagulant, anti-dsDNA, low complement, and anticardiolipins (aCL).

Methods: We analyzed retrospective data on more than 56,000 quarterly clinic visits from more than 1000 patients in a large American clinical cohort of SLE patients. Patients visits were classified as “on HCQ” if they reported taking HCQ at that visit and at the previous visit. Patient visits were classified as “off HCQ” if they reported not taking HCQ at that visit and at the previous visit. For each patient, visits on and off HCQ were compared with respect to the rates of biomarker positivity. These comparisons were summarized across patients using using conditional logistic regression controlling for age.

Results: Table 1 shows the results of our analyses. While on HCQ, the odds of being positive was significantly reduced for each biomarker: Lupus Anticoagulant (OR= 0.65), antidsDNA (OR=0.82), Low Complement (OR=0.71), aCL IgG (OR=0.26), and aCL IgM (OR=0.45). However, there was a substantial difference between Caucasian Americans (CA) and African Americans (AA) with respect to the impact of HCQ. Notably, HCQ was associated with a 62% reduction in the odds of lupus anticoagulant among CAs, but no association was observed among AAs.