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Correlation of hypogammaglobulinaemia with proteinuria, and the relationship between hypogammaglobulinaemia and infection in active lupus nephritis

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ABSTRACT
Objective To evaluate hypogammaglobulinaemia and risk of serious infectious adverse events in active lupus nephritis.
Methods The Abatacept and Cyclophosphamide Combination Efficacy and Safety Study (ACCESS) compared abatacept with placebo in participants with lupus nephritis undergoing treatment with Euro-Lupus Nephritis low-dose cyclophosphamide. Serum IgG levels were assessed prior to initiation of treatment and throughout the trial. Hypogammaglobulinaemia was defined as IgG <450 mg/dL.
Results Hypogammaglobulinaemia was observed in 16/102 (15.7%) participants prior to initiation of induction therapy for active lupus nephritis. Participants with nephrotic range proteinuria were more likely to have hypogammaglobulinaemia, and serum IgG levels were inversely correlated with urine protein to creatinine ratio (r=−0.42, p<0.0001). Following initiation of treatment for active lupus nephritis, additional participants developed hypogammaglobulinaemia by weeks 2–4. Serum IgG levels then increased, and all but one participant had serum IgG ≥450 mg/dL at 24 weeks. Hypogammaglobulinaemia was not associated with an increased risk of serious infectious adverse events.
Conclusions In active lupus nephritis in ACCESS, hypogammaglobulinaemia was common and inversely correlated with proteinuria. Serum IgG levels were lowest in the weeks immediately following initiation of induction therapy, and subsequently improved by 24 weeks. Hypogammaglobulinaemia was not associated with serious infectious adverse events.

INTRODUCTION
Reduced serum IgG has been reported in lupus nephritis (LN)1 2; however, levels are not routinely measured, and the prevalence of hypogammaglobulinaemia in active LN is not known. Persistent trough levels of IgG below 400 mg/dL in common variable immunodeficiency and X linked agammaglobulinaemia have been associated with increased risk of infection, pneumonia in particular,3 but there is little evidence that hypogammaglobulinaemia in active LN confers a similar risk. However, a phase II/III trial with atacicept in LN was halted after enrolment of six participants, when severe infections occurred in two participants with hypogammaglobulinaemia.4 Therefore, evaluation of serum IgG levels during treatment for active LN was undertaken in the Abatacept and Cyclophosphamide Combination Efficacy and Safety Study (ACCESS)5 to evaluate the relationship of serum IgG levels to serious infectious adverse events (SIAEs).

PATIENTS AND METHODS
Study treatment Details of ACCESS have been previously described.5 Briefly, ACCESS was a multicentre randomised controlled trial of abatacept compared with placebo in 134 participants with LN who underwent treatment with the Euro-Lupus Nephritis (ELN) low-dose cyclophosphamide regimen6 followed by azathioprine maintenance therapy. Participants also received prednisone. ACCESS, registered as NCT00774852, received institutional review or ethics board approval at each site, and was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki.

Assessments Quantitative serum IgG assessments were instituted after the initiation of ACCESS, and were assessed at the screening visit and at weeks 0, 2, 4, 12, 24 and 52. Hypogammaglobulinaemia was defined as serum IgG <450 mg/dL since serum IgG was expected to decline...
in the setting of LN treatment, and the risk for infection in immunodeficiency syndromes is associated with serum IgG <400 mg/dL. Nephrotic range proteinuria was defined as urinary protein ≥3.5 g in a 24-hour urine collection. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (NCI CTCAE v3.0).

Statistical methods
Comparisons of categorical variables were performed using a X² test or a Fisher exact test depending on the cell sizes. Comparisons of continuous variables were performed using a Wilcoxon rank-sum test. Pearson’s correlation coefficient was calculated to determine associations between IgG level and urine protein to creatinine ratio (UPCR). All statistical tests were two-sided.

RESULTS
Hypogammaglobulinaemia in active LN correlated with proteinuria
In ACCESS, 134 participants were treated for active LN with the ELN cyclophosphamide induction regimen and prednisone, in combination with abatacept or placebo. Serum IgG levels were examined beginning at the screening visit in 102 participants. Hypogammaglobulinaemia was observed in 16/102 (15.7%) participants prior to induction therapy. Four participants had serum IgG <300 mg/dL, and the lowest level of IgG observed prior to induction therapy was 170 mg/dL. Table 1 shows the characteristics of 16 participants with IgG <450 mg/dL prior to induction therapy, compared with 86 participants with IgG ≥450 mg/dL prior to induction therapy.

Gender, age, race and ethnicity did not significantly differ between the two groups, nor did the proportion of participants with total lymphocyte counts <1000/µL. Mycophenolate mofetil and corticosteroid usage in the 30 days prior to enrolment was not significantly different. Participants did not receive cyclophosphamide or rituximab in the year prior to enrolment, or belimumab in the 6 months prior to enrolment.

In contrast, participants with low serum IgG level prior to induction therapy were significantly more likely to have nephrotic range proteinuria compared with participants without low serum IgG (p<0.01, table 1). Hypogammaglobulinaemia was observed in 13/44 (30%) participants with nephrotic range proteinuria ≥3.5 g prior to induction therapy, compared with 3/58 (5%) without nephrotic range proteinuria. Hypogammaglobulinaemia prior to induction therapy was observed most frequently in the setting of high levels of proteinuria, occurring in 5/12 (42%) participants with proteinuria >8.0 g and in 3/4 (75%) participants with proteinuria >14 g in a 24-hour collection. Pearson’s correlation analysis showed an inverse correlation between IgG level and UPCR in a 24-hour collection (r=−0.42, p<0.0001, figure 1A). Low serum IgG prior to induction therapy was also associated with LN duration ≥12 months (p=0.04, table 1).

Table 1 Characteristics of participants with hypogammaglobulinaemia prior to induction therapy for lupus nephritis

<table>
<thead>
<tr>
<th>IgG &lt;450 mg/dL</th>
<th>IgG ≥450 mg/dL</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=16</td>
<td>n=86</td>
<td></td>
</tr>
<tr>
<td>Age 29.8±7.2</td>
<td>32.3±11.0</td>
<td>0.61</td>
</tr>
<tr>
<td>Gender Female 16/16 (100%)</td>
<td>77/86 (90%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Race Asian 1/16 (6%)</td>
<td>2/86 (2%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Black 8/16 (50%)</td>
<td>36/86 (42%)</td>
<td></td>
</tr>
<tr>
<td>White 0/16 (0%)</td>
<td>6/86 (7%)</td>
<td></td>
</tr>
<tr>
<td>Other 7/16 (44%)</td>
<td>42/86 (49%)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity Hispanic or Latino 8/16 (50%)</td>
<td>53/86 (62%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Urinary protein ≥3.5 g* 13/16 (81%)</td>
<td>31/86 (36%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Lymphocyte count &lt;1000 8/16 (50%)</td>
<td>43/85 (51%)†</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Lupus nephritis ≥12 months 8/16 (50%)</td>
<td>20/86 (23%)</td>
<td>0.04</td>
</tr>
<tr>
<td>MMF within past 30 days 4/16 (25%)</td>
<td>9/86 (10%)</td>
<td>0.12</td>
</tr>
<tr>
<td>CS within past 30 days 12/16 (75%)</td>
<td>62/86 (72%)</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>

*In a 24-hour urine collection.
†1 missing.
CS, corticosteroids; MMF, mycophenolate mofetil/mycophenolic acid.

Serum IgG levels initially decreased following treatment for active LN, then increased by 24 weeks
Low serum IgG levels prior to induction therapy remained low during the initial few weeks of treatment. Furthermore, serum IgG levels decreased following induction therapy in participants without hypogammaglobulinaemia prior to treatment (figure 1B). Fifteen additional participants developed hypogammaglobulinaemia following initiation of induction therapy, including five who developed IgG <300 mg/dL. Thus, hypogammaglobulinaemia was observed in a total of 31/102 (30.4%) participants, either prior to treatment or in the weeks immediately following treatment initiation, while 71/102 (69.6%) never developed hypogammaglobulinaemia. Similar proportions of participants with hypogammaglobulinaemia were observed in the abatacept group and the placebo group (data not shown).

Serum IgG levels tended to be lowest at week 2 or week 4, and then increased by week 12, whether hypogammaglobulinaemia was present prior to treatment, developed after treatment or never occurred (figure 1B). At study week 24, hypogammaglobulinaemia resolved to IgG ≥450 mg/dL in nearly all participants remaining in the study, corresponding to overall improvement in UPCR in all groups.
Ten SIAEs occurred in nine participants during the 24 weeks of treatment (table 2).

IgG levels dropped following induction therapy with low-dose cyclophosphamide and prednisone, and then gradually rose, such that hypogammaglobulinaemia resolved in nearly all participants by 24 weeks. A similar result was observed in another study of IgG levels in LN, in participants treated with methylprednisolone and mycophenolate mofetil in the prior 30 days was not associated with hypogammaglobulinaemia at study entry. However, serum IgG levels dropped following induction therapy with low-dose cyclophosphamide and prednisone, and then gradually rose, such that hypogammaglobulinaemia resolved in nearly all participants by 24 weeks. A similar result was observed in another study of IgG levels in LN, in participants treated with methylprednisolone and mycophenolate mofetil.2

**Persistent hypogammaglobulinaemia in common variable immunodeficiency and X-linked agammaglobulinaemia is associated with risk for serious infections.3**

Sustained very low levels of IgG <100 mg/dL are associated with the highest risk, while transient or less
severe hypogammaglobulinaemia is tolerated in most subjects. A retrospective study of rituximab-associated hypogammaglobulinaemia in multisystem autoimmune disease showed that hypogammaglobulinaemia occurred in 56% of 243 subjects treated with rituximab, and IgG replacement was undertaken in only 4.2% of subjects due to recurrent infection. In contrast, recurrent infections have been associated with hypogammaglobulinaemia in smaller vasculitis series, and a phase II/III trial with atacicept in LN was halted when severe infections occurred in the setting of hypogammaglobulinaemia.4

The ACCESS results demonstrate that hypogammaglobulinaemia in active LN is common, transient and well-tolerated. Most participants with hypogammaglobulinaemia in ACCESS did not develop serious infections, although a small increased risk of infection might not have been detected. The results are consistent with intact production of IgG despite urinary loss, and the adequate humoral response to vaccination observed in SLE.4

A number of factors can contribute to hypogammaglobulinaemia in LN, including proteinuria, corticosteroids and other immunosuppressive medications. Comorbid common variable immunodeficiency can also occur.4 Although these other factors should be considered, treatment of LN with induction therapy should not be delayed due to hypogammaglobulinaemia alone, and in ACCESS induction therapy for LN was followed by resolution of hypogammaglobulinaemia in nearly all participants. The ACCESS results do not support routine prophylactic treatment with replacement immunoglobulin for transient asymptomatic hypogammaglobulinaemia that occurs in LN, nor do they support exclusion of participants with hypogammaglobulinaemia from LN clinical trials. Nevertheless, vigilance is required for serious or recurrent infections in LN, and for comorbid common variable immunodeficiency.

**Table 2** Serious infectious adverse events during the first 24 weeks of the ACCESS trial

<table>
<thead>
<tr>
<th>Participant</th>
<th>Adverse event term</th>
<th>Bacterial</th>
<th>Start Day</th>
<th>Stop Day</th>
<th>Screening IgG mg/dL</th>
<th>Nadir IgG mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tubo-ovarian abscess</td>
<td>Yes</td>
<td>45</td>
<td>57</td>
<td>1470</td>
<td>1140</td>
</tr>
<tr>
<td>2</td>
<td>Cellulitis</td>
<td>Yes</td>
<td>1</td>
<td>6</td>
<td>630</td>
<td>431</td>
</tr>
<tr>
<td>3</td>
<td>Urinary tract infection</td>
<td>Yes</td>
<td>0</td>
<td>5</td>
<td>493</td>
<td>493</td>
</tr>
<tr>
<td>4</td>
<td>Gastroenteritis</td>
<td>No</td>
<td>88</td>
<td>94</td>
<td>1554</td>
<td>1025</td>
</tr>
<tr>
<td>5</td>
<td>Pneumonia</td>
<td>Yes</td>
<td>56</td>
<td>59</td>
<td>1268</td>
<td>1268</td>
</tr>
<tr>
<td>6</td>
<td>Viral infection</td>
<td>No</td>
<td>59</td>
<td>63</td>
<td>1143</td>
<td>797</td>
</tr>
<tr>
<td>7</td>
<td>Pneumonia</td>
<td>Yes</td>
<td>7</td>
<td>11</td>
<td>852</td>
<td>690</td>
</tr>
<tr>
<td>8</td>
<td>Gastroenteritis viral</td>
<td>No</td>
<td>95</td>
<td>110</td>
<td>577</td>
<td>347</td>
</tr>
<tr>
<td>9</td>
<td>Viral infection</td>
<td>No</td>
<td>38</td>
<td>41</td>
<td>688</td>
<td>327</td>
</tr>
</tbody>
</table>

ACCESS, Abatacept and Cyclophosphamide Combination Efficacy and Safety Study.
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REFERENCES