Association Between Growth of Geographic Atrophy and the Complement Factor I Locus

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ABSTRACT: The association between the growth of geographic atrophy (GA) and a single nucleotide polymorphism (SNP) in the complement factor I (CFI) locus was investigated in the COMPLETE trial. Growth of GA at 52 weeks in eyes without the CFI at-risk allele was slightly faster than the growth in eyes with the CFI at-risk allele ($P \geq .72$). The authors of the current study found that in contrast to the faster growth rate reported in CFI-positive eyes from the MAHALO trial, the CFI positive eyes in the COMPLETE trial did not grow faster, and this analysis included 24 eyes that met the MAHALO eligibility criteria.

and by using spectral-domain optical coherence tomography (SD-OCT) imaging. OCT fundus images were derived from a slab beneath the retinal pigment epithelium (sub-RPE slab). All 30 COMPLETE study eyes were pooled and analyzed regardless of treatment assignment because no treatment effect was detected previously using eculizumab. Growth of GA was measured in all 30 eyes, as well as in a subset of 24 eyes meeting the MAHALO eligibility criteria, which included bilateral GA with adjacent banded or diffuse junctional fundus autofluorescence patterns and GA between one disc area and seven disc areas in size with multifocal lesions having one focal lesion at least one-half disc area in size. The growth rates were compared between those with and without the CFI at-risk allele using the two-sample t test.

RESULTS

The prevalence of at-risk alleles among the 30 patients in the COMPLETE study was as follows: CFI, 19 (63%); CFH, 28 (93%); C3, 11 (37%); C2/B, 30 (100%). At 52 weeks, growth of GA in eyes of patients without the CFI at-risk allele was slightly but not significantly faster than the growth of GA in eyes of those carrying the CFI at-risk allele ($P \geq .72$).

The Table presents the relationship between growth of GA in eyes from study participants with and without the at-risk CFI SNP. Both CSLO and SD-OCT measurements are available from baseline through week 26, and only SD-OCT measurements are available at 52 weeks. Among MAHALO-type eyes, GA growth based on the sub-RPE slab at 52 weeks was $2.05 \pm 1.13 \text{ mm}^2$ ($0.40 \pm 0.21 \text{ mm}$ using the difference in the square root of the areas) for nine patients with no CFI at-risk alleles and $1.83 \pm 1.41 \text{ mm}^2$ ($0.36 \pm 0.23 \text{ mm}$ using the difference in the square root of the areas) for 15 patients with at least one CFI at-risk allele ($P \geq .6$). The Figure provides a graphical depiction of the growth rates in each group. Analysis of fellow eye growth rates did not alter the results.

DISCUSSION

In contrast to the MAHALO trial, COMPLETE patients, who were carriers of the at-risk allele for CFI, were not found to have a faster growth rate of GA compared with those without the at-risk allele. Even
when we compared the 24 patients who met the strict inclusion criteria for the MAHALO study, no association was found. The major limitations of our study include its small sample size, the lack of autofluorescence imaging data beyond 26 weeks, and the lack of SD-OCT growth data beyond 52 weeks; however, we had the same number of patients included in the MAHALO analysis (29 patients), and GA measurements have been found to be equivalent with CSLO and OCT imaging.

While the MAHALO study measured GA growth over 18 months compared with our shorter period of 12 months, we saw no sign of separation between the two groups, which suggested that there was no trend toward faster growth in eyes carrying the CFI at-risk allele. Another limitation of the analysis is that we pooled both treated and untreated study eyes from the COMPLETE trial since no treatment effect was detected. Moreover, when we looked for a differential treatment effect of eculizumab in CFI-positive and CFI-negative patients, none was detected. Thus, the possibility that previous eculizumab therapy influenced our pooled results seems remote. We strongly advocate the need for additional larger studies in order to confirm or refute the association of CFI with GA progression.

REFERENCES


<table>
<thead>
<tr>
<th>Risk Status</th>
<th>ER CSLOA 26 wk (mm²)</th>
<th>ER OCT 26 wk (mm²)</th>
<th>ER sqrt CSLOA 26 wk (mm)</th>
<th>ER sqrt OCT 26 wk (mm)</th>
<th>ER OCT 52 wk (mm²)</th>
<th>ER sqrt OCT 52 wk (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CFI G alleles (n = 11)</td>
<td>0.97 ± 0.78</td>
<td>0.99 ± 0.87</td>
<td>0.22 ± 0.19</td>
<td>0.20 ± 0.13</td>
<td>2.03 ± 1.09</td>
<td>0.38 ± 0.19</td>
</tr>
<tr>
<td>≥ 1 CFI G allele (n = 19)</td>
<td>0.82 ± 0.74</td>
<td>0.87 ± 0.76</td>
<td>0.20 ± 0.16</td>
<td>0.17 ± 0.13</td>
<td>1.85 ± 1.32</td>
<td>0.36 ± 0.22</td>
</tr>
<tr>
<td>P value</td>
<td>.59</td>
<td>.65</td>
<td>.77</td>
<td>.55</td>
<td>.72</td>
<td>.81</td>
</tr>
<tr>
<td>Difference in growth (95% confidence interval)</td>
<td>-0.16 (−0.74, 0.43)</td>
<td>-0.12 (−0.68, 0.43)</td>
<td>-0.19 (−0.15, 0.12)</td>
<td>-0.03 (−0.13, 0.07)</td>
<td>-0.17 (−1.14, 0.79)</td>
<td>-0.02 (−0.18, 0.14)</td>
</tr>
<tr>
<td>No CFI G alleles, MAHALO-type eyes (n = 9)</td>
<td>0.98 ± 0.86</td>
<td>1.03 ± 0.65</td>
<td>0.23 ± 0.21</td>
<td>0.22 ± 0.14</td>
<td>2.05 ± 1.13</td>
<td>0.40 ± 0.21</td>
</tr>
<tr>
<td>≥ 1 CFI G allele, MAHALO-type eyes (n = 15)</td>
<td>0.80 ± 0.75</td>
<td>0.89 ± 0.81</td>
<td>0.20 ± 0.15</td>
<td>0.17 ± 0.12</td>
<td>1.83 ± 1.41</td>
<td>0.36 ± 0.23</td>
</tr>
<tr>
<td>P value, Mahalo-type eyes</td>
<td>.60</td>
<td>.66</td>
<td>.72</td>
<td>.45</td>
<td>.70</td>
<td>.68</td>
</tr>
<tr>
<td>Difference in growth, MAHALO-type eyes (95% confidence interval)</td>
<td>-0.18 (−0.87, 0.52)</td>
<td>-0.14 (−0.80, 0.52)</td>
<td>-0.03 (−0.18, 0.13)</td>
<td>-0.05 (−0.15, 0.07)</td>
<td>-0.22 (−1.37, 0.93)</td>
<td>-0.04 (−0.23, 0.15)</td>
</tr>
</tbody>
</table>

Values represent the mean ± standard deviation.

ER = enlargement rate; CSLOA = confocal scanning laser ophthalmoscopic autofluorescence; OCT = optical coherence tomography; sqrt = square root;

ER CSLOA 26wk: Enlargement rate measured as the difference in the area of GA measured at baseline and week 26 using CSLOA imaging.
ER OCT 26wk: Enlargement rate measured as the difference in the area of GA measured at baseline and week 26 using OCT en face imaging.
ER sqrt CSLOA 26 wk: Enlargement rate measured as the difference in the square root of the area measurements at baseline and week 26 using CSLOA imaging.
ER sqrt OCT 26wk: Enlargement rate measured as the difference in the square root of the area measurements at baseline and week 26 using OCT en face imaging.
ER OCT 52wk: Enlargement rate measured as the difference in the area of GA measured at baseline and week 52 using OCT en face imaging.
ER sqrt OCT 52wk: Enlargement rate measured as the difference in the square root of the area measurements at baseline and week 52 using OCT en face imaging.