of relying on a single commercial kit. This example illustrates how false conclusions were drawn based on results from an assay that was not satisfactorily validated for the purpose for which it was used. Thus, our data document that eculizumab efficiently inhibited C5a generation both in vitro and in vivo, in contrast to the wrong conclusion drawn in the paper by Burwick et al.1

This study was approved by the regional ethical committees and was performed in accordance with the appropriate version of the Declaration of Helsinki. Informed consent of the patients was obtained before analysis.

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Response

Maternal and cord C5a in response to eculizumab

We appreciate the interest of Volokhina et al1 in our recent letter to the editor in Blood.2 Their data on measurement of C5a in human plasma in response to eculizumab adds to the scant literature on this topic. They raise 2 criticisms that we did not address in our original letter: (1) plasma C5a levels may be spuriously elevated due to cross-reactivity with other epitopes specific to the BD C5a enzyme-linked immunosorbent assay (ELISA) (BD Bioscience, San Jose, CA), and (2) eculizumab-C5 (E-C5) complexes may be the source of cross-reactivity.3 These are both important considerations.

Although the data were not included in our initial report, we also measured umbilical cord plasma levels of C5a in our patient with preeclampsia and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome using the BD C5a ELISA. Umbilical cord plasma C5a levels were measured at 94.1 ng/mL (56% of maternal plasma levels). The umbilical cord plasma levels of C5a in 10 randomly selected severe preeclampsia cases not on eculizumab measured 19.3 ± 8.2 ng/mL (median, 58.8% of maternal levels). Similar cord C5a measurements were noted in 3 HELLP cases not on eculizumab (26.7 ± 9.5 ng/mL; median, 61.0% of maternal levels). In light of the findings of Volokhina et al, the higher levels of cord C5a detected in our preeclampsia/HELLP patient treated with eculizumab may reflect increased levels of E-C5 complex. The detection of E-C5 complex is an important consideration, because E-C5 complexes are capable of crossing the placenta4 and may also be deposited in the kidney.5 Hallstensen et al estimate that newborns carry 6% to 7% of the E-C5 detected in their eculizumab-treated mothers with paroxysmal nocturnal hemoglobinuria.6 Nonetheless, it is also noted that the ratio of umbilical cord C5a to maternal C5a was similar between our preeclampsia/HELLP patient treated with eculizumab and our preeclampsia/HELLP cases not exposed to eculizumab. In addition, as we previously reported, baseline (pretreated) plasma C5a levels (measured by the BD C5a ELISA) in our case study were high compared with healthy pregnant controls and subjects with severe preeclampsia.2,5 Together, these data suggest that E-C5 complexes may not be the sole factor contributing to elevated maternal and cord C5a readings in the BD assay.

Although we have successfully used eculizumab to treat severe preeclampsia/HELLP syndrome6 and believe that it is a promising treatment of this condition, we feel that plasma C5a levels may be less helpful than other markers of complement activation.5,7,8 Cofell et al suggested that urinary C5a and sC5b-9 levels may be more useful in guiding response to eculizumab,6 and our published data...
support such use in preeclampsia. Regarding the enigmatic C5a, further in vivo studies in humans are necessary.

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