Published in final edited form as:
Br J Haematol. 2013 August ; 162(4): 558–559. doi:10.1111/bjh.12387.

Use of eculizumab in the treatment of a case of refractory, ADAMTS13-deficient thrombotic thrombocytopenic purpura: additional data and clinical follow-up

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Keywords

thrombotic thrombocytopenic purpura; atypical haemolytic uraemic syndrome; complement factor H; antibodies

We reported last year, in this Journal, a case of thrombotic microangiopathy, defined as thrombotic thrombocytopenic purpura (TTP) by virtue of a severe deficiency in ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity with high titre anti-ADAMTS13 autoantibodies, complicated by severe haematological, neurological and renal dysfunction, which was recalcitrant to multiple therapeutic modalities for TTP (Chapin *et al.*, 2012). These treatments included twice-daily plasma exchange, high dose glucocorticoids, rituximab, and vincristine. Prompt haematological and organ system responses to the anti-C5 humanized monoclonal antibody eculizumab were observed, and the patient has been on continuous treatment with this agent, given as maintenance every 11–12 days, for over 18 months. Several attempts to broaden the treatment interval to the 14 days recommended by the Federal Drug Administration as part of its approval of eculizumab in the therapy of atypical haemolytic-uraemic syndrome (aHUS) result in thrombocytopenia and increases in lactate dehydrogenase (LDH) and creatinine. We also reported that a screen for complement regulatory factor mutations, using a platform offered commercially by University of Iowa researchers, failed to uncover an abnormality (Chapin *et al.,* 2012). New data now further inform our pathophysiological

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Conflict of interest disclosure

Drs. H-M Tsai and J. Laurence serve on the Advisory Board and Speaker's Bureau of Alexion Pharmaceuticals.

Author contributions

Dr. E. Tsai designed and performed the experiments and revised the manuscript. Drs. Chapin and Laurence provided clinical data and patient samples and revised the manuscript. Dr. H. Tsai supervised the design and performance of the experiments and drafted the manuscript.

understanding of the disease processes involved in this patient, and the response to treatment.

First, utilizing a different assay system for ADAMTS13 activity, which was reported to completely segregate cases of acquired and hereditary TTP during periods of thrombocytopenia or decreasing platelet counts (ADAMTS13 less than 10% of normal) from individuals with other types of thrombotic microangiopathy (mean 86%, standard deviation 22%) and normal subjects (mean 103%, standard deviation 12%) (Tsai & Lian, 1998; Levy *et al*, 2001), we found that although the patient did have inhibitors of ADAMTS13, the ADAMTS13 level was not sufficiently decreased (14%) to account for his thrombocytopenia on day 85. Furthermore, his ADAMTS13 was 103% of normal on day 120, when he continued to exhibit a propensity to recurrent thrombocytopenia that was responsive to the sole treatment of eculizumab.

Second, a more comprehensive genetic sequence analysis was performed in the laboratory of Dr. Richard Smith (Maga *et al*, 2010). An E936D polymorphism in the complement factor H gene (*CFH*) was documented, although the functional significance of this mutation is unclear.

Third, an enzyme-linked immunosorbant assay (ELISA), similar to one previously described by Dragon-Durey *et al.* (2005), was used to search for anti-CFH antibodies. Such antibodies have been found in 5–10% of aHUS patients, often in association with *CFHR1* genomic deletion (Dragon-Durie *et al*, 2010). In this assay we used a stringent definition of positive result for difference of the optical densities between the test wells coated with recombinant CFH and control wells coated only with buffer above the mean +3 standard deviations of healthy donor controls. Plasma samples obtained at three time points in the patient's course were assessed, in triplicate, and compared to those of 35 healthy blood donors. The patient's samples were negative for CFH antibodies on day 54 of his hospital course, which was characterized by resolution of thrombocytopenia with daily or twice daily plasma exchanges as well as treatment with rituximab and eculizumab (see Figure 1 in Chapin *et al.,* 2012), but positive for these antibodies on days 85 and 120 when, as an outpatient, he required eculizumab to treat and prevent recurrence of thrombocytopenia and elevated LDH. We speculate that the CFH antibodies were undetectable on day 54 because plasma exchange replenished CFH and decreased the antibodies.

Taken together, these results suggest that, despite the presence of ADAMTS13 inhibitors, in terms of pathophysiology, illustrated by deposition of terminal complement components in the patient's skin (see Chapin *et al.,* 2012) and his response to anti-C5 but not plasma therapy, our patient has a coexistent disease process involving both TTP and aHUS. We propose that similar disease processes may also explain the poor response of at least a subset of TTP patients to plasma exchange therapy.

Acknowledgments

Funding support

The work was supported in part by a grant (R01 HL62136 to H.M. Tsai) from the Heart Lung and Blood Institute of the National Institutes of Health, USA.

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