Endopeptidase Therapy for Anti-Glomerular Basement Membrane Disease: Beware of Anti-Hinge Antibodies!

We read with great interest the recent publication reporting an open-label phase 2a study of imlifidase (IdeS endopeptidase) in severe anti–glomerular basement membrane (anti-GBM) disease. IdeS specifically cleaves human IgG in the lower hinge region, producing an F(ab′)2 fragment and two half-Fc fragments. Prior studies in experimental anti-GBM disease showed that IdeS can cleave GBM-bound IgG in vivo, removing the Fc portion that harbors the effector functions; as a result, IdeS-treated mice had significantly lower complement C1q and C3 deposition and reduced influx of leukocytes in glomeruli. Although the fate of the F(ab′)2 fragments has not been studied, they likely remain attached to the GBM due to their bivalent binding.

In this trial, 67% of patients with anti-GBM disease who were treated with imlifidase achieved kidney survival at 6 months, and half of patients who were dialysis dependent regained independent kidney function. Although these results are encouraging, not all patients showed clinical improvement after endopeptidase therapy. We posit that less-favorable outcomes are partly due to high levels of anti-hinge autoantibodies, which specifically recognize IgG neoepitopes created by IdeS cleavage and occur naturally in 68% of healthy individuals. Anti-hinge antibodies bound to F(ab′)2 have been shown to restore the effector function to proteolytically inactivated IgG in vitro and in vivo, thereby negating the benefits of endopeptidase treatment.

In preliminary studies, we found that serum levels of anti-hinge antibodies recognizing IdeS-generated neoepitopes in the IgG1 hinge (the predominant subclass of anti-GBM antibodies) are significantly higher in those with anti-GBM disease than in healthy controls (median levels 32.5 versus 11.5 AU; P=0.0031 by Mann–Whitney test). Although preexisting anti-hinge antibodies would be cleaved upon IdeS administration, the ongoing production of intact anti-hinge antibodies would eventually lead to their fixation onto GBM-bound F(ab′)2 fragments within 2–3 weeks after the therapy, potentially restoring the effector functions of proteolytically inactivated anti-GBM antibodies (Figure 1).

Our observation raises several questions. Are high levels of anti-hinge antibodies correlated with nonresponsiveness to endopeptidase therapy? Do pretreatment levels predict post-treatment levels of anti-hinge antibodies? Are IdeS-generated neoepitopes antigenic, inducing de novo production of anti-hinge IgG in some patients treated with IdeS? Follow-up studies addressing these questions are important to clarify how anti-hinge antibodies affect clinical outcomes after IdeS endopeptidase therapy. We propose assaying anti-hinge antibodies before and after endopeptidase treatment may help prospectively identify patients with anti-GBM disease who are more likely to respond to therapy and predict outcomes. In closing, we congratulate the authors for their progress in developing a much-needed novel therapy for anti-GBM disease.

DISCLOSURES

D.-B. Borza reports serving on the editorial board of BMC Nephrology (as associate editor). The remaining author has nothing to disclose.

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AUTHOR CONTRIBUTIONS

D.-B. Borza conceptualized the study, provided supervision, and wrote the original draft; D.-B. Borza and P. Manral reviewed and edited the manuscript; and P. Manral was responsible for investigation.

REFERENCES


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