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 endoprotease) 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 anti-GBM F(ab′)_2 fragments. Prior studies in experimental anti-GBM disease showed that IdeS can cleave GBM-bound IgG in vivo, removing the Fc fragments which carry out effector functions. (C) Anti-hinge antibodies (red) recognize neoepitopes generated when IgG1 is cleaved by IdeS, restoring the effector functions of the proteolytically inactivated anti-GBM F(ab′)_2 fragments.

Figure 1. Proposed effects of anti-hinge antibodies in patients with anti-GBM disease who are treated with IdeS. (A) Anti-GBM IgG1 autoantibodies (blue) bound to the GBM (maroon) mediate inflammation (red starburst) via their Fc region. (B) Treatment with IdeS cleaves GBM-bound IgG1, removing the Fc fragments which carry out effector functions. (C) Anti-hinge antibodies (red) recognize neoepitopes generated when IgG1 is cleaved by IdeS, restoring the effector functions of the proteolytically inactivated anti-GBM F(ab′)_2 fragments.

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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