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.[1] 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.[2] 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.[1] 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.[3] 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*,[4,5] 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 intact 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.

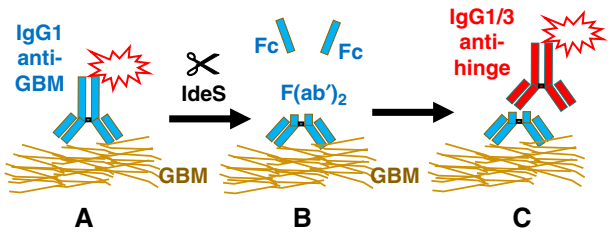

Figure 1. Proposed effects of anti-hinge antibodies in patients with anti-GBM disease who are treated with IdeS. (A) Anti-GBM IgG1 autoantibodies (blue) bound to the GBM (maroon) mediate inflammation (red starburst) *via* their Fc region. (B) Treatment with IdeS cleaves GBM-bound IgG1, removing the Fc 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.

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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Correspondence: Dr. Dorin-Bogdan Borza, Department of Microbiology, Immunology and Physiology, Meharry Medical College, 1005 Dr. D.B. Todd, Jr. Blvd., Nashville, TN 37208. Email: dborza@mmc.edu

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.

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See related reply, "Authors' Reply," on pages XXX–XXX, and original article "Endopeptidase Cleavage of Anti-Glomerular Basement Membrane Antibodies *in vivo* in Severe Kidney Disease: An Open-Label Phase 2a Study," in Vol. 33, Iss. 4, 829–838.

Dorin-Bogdan Borza[1] and Pallavi Manral[1]

Department of Microbiology, Immunology and Physiology, Meharry Medical College, Nashville, Tennessee

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