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## A Scientific Look at FcRn Antagonists: Mechanisms of Action Explained

### Announcer:

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### Dr. Brill:

This is CME on ReachMD, and I'm Dr. Vera Brill. Here with me today is Dr. Nicholas Silvestri.

The neonatal Fc receptor, or FcRn, and antagonists of FcRn function have burst onto the scene as a fascinating potential way to decrease circulating pathogenic IgGs associated with gMG. I will start off the discussion with an overview of the FcRn, its normal physiologic function, and how these antagonists modulate that function.

So the normal physiologic functions associated with the FcRn molecule are recycling in nature at the level of immunoglobulins. So IgGs are taken up by the cell and combined with the FcRn molecule and are delivered back to the cell surface and back into the circulation. This helps prolong the half-life of IgG molecules, both normal and pathogenic IgG molecules.

If you use an FcRn antagonist, it will combine with the FcRn molecule and prevent combination of IgGs with the FcRn molecule. Therefore, the IgGs are delivered to the lysosomes where they are destroyed instead of being delivered back to the cell surface membrane. What this does is lower the levels of IgG, both normal and pathogenic IgG molecules, in the circulation. And this is the mechanism of action in generalized MG.

Now there are different structures to the FcRn antagonists. There's therapeutic monoclonal antibody that binds or blockades the FcRn. There's an Fc fragment, or Fc multimer, that binds with the FcRn. There are bivalent antibody mimetics, and other formats may be in development. They all generally produce the same drop in IgG levels and have similar effects on generalized MG.

These agents are unique compared to traditional treatment approaches in that they act quickly, within 1 to 2 weeks, and they are replicable with repeated administrations and are more focused than treatments such as plasma exchange or intravenous immunoglobulin, which both act fairly quickly but have many diffuse actions on the immune systems.

### Dr. Silvestri:

Thanks for that overview, Dr. Brill, that was brilliant. I don't know that I could have done much better myself. I mean, I think just to add my 2 cents on this mechanism of action, it's very interesting. I mean, this mechanism has been known now for decades. I think it was initially described as a way of maternal transfer of antibodies to fetus. But it's very cool how we've been able to harness this mechanism in order to reduce antibody levels in an autoimmune disease like myasthenia gravis.

I think one of the potential benefits of agents like these being more targeted is that it leaves the remainder of the immune system intact, which allows patients to fight off infections. Now we could argue that perhaps that also helps drive the disease a little bit, but I do think that with targeted therapy such as these, using this novel approach, this normal physiologic approach, and really harnessing it, will do wonders for our patients going forward.

And with that, our time is up. Thank you for listening. We hope you found our perspectives useful.

**Announcer:**

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