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The Science Behind FcRn Antagonists: A Deep Dive Into Their Mechanism of Action

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCE curriculum.

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Dr. Silvestri:
This is CME on ReachMD, and I'm Dr. Nick Silvestri. Here with me today is Dr. Chip Howard.

Dr. Howard, what is the neonatal Fc receptor complex, and what are the normal physiologic functions of this complex?

Dr. Howard:
Thank you, Nick. The neonatal Fc receptor is not new, first described in the '50s by Sir Francis Bramwell as the mechanism by which maternal immunoglobulin was transferred across the placenta to the fetus. In the '90s, however, it was found to be fairly ubiquitous and present particularly in vascular endothelium. And we now know that it is a salvage pathway for immunoglobulin.

Immunoglobulin is endocytosed, internalized in acidic environment, bound very tightly to the Fc receptor, and then re-transported back to the cell surface membrane, released into circulation again, giving IgG its prolonged half-life, about 4 times what we see with IgD, IgM, IgA, etc.

Immunoglobulin that is not bound to the Fc receptor is shunted to the lysosome, where it undergoes destruction. It was found that it has a potential therapeutic effect. By developing antagonists of the neonatal Fc receptor, we could inhibit transport to the cell surface in recirculation and rather shunt it to the lysosome and rapidly clear, within hours, circulating IgG levels of all subclasses, IgG1, 2, 3, and 4.

Additionally, albumin works by a similar mechanism, but the two binding sites are different. And therefore, one has to be careful, in terms of therapeutics, that we don't obstruct its binding site as well. But it's a new first-in-class group of therapeutics that have the potential to be quite efficacious in IgG-mediated diseases.

Dr. Silvestri:
Thanks, Chip, for providing that overview. I mean, I think what's great about this class of medications, as well as, really, the future of therapy in MG, is the fact that they're more targeted therapies, and that benefits our patients not only in terms of potentially better efficacy but fewer off-target side effects, which we kind of talked about in previous episodes, that really affect our patients by the nonspecific and broad nature of the way that they act.

And so the hope is, is that we get more and more targeted in therapy such as using these classes of agents and others that we can really lead, again, to better disease control but not at the expense of what we've referred to as to the burden of treatment. And what I also think is interesting is this really potentially extends beyond myasthenia gravis, too, to other autoantibody-mediated disorders both within neurology and, frankly, without. So this is certainly an exciting time for our patients.

Dr. Howard:
Yeah. And right now, we're removing all IgG antibodies. And there is technology being developed to selectively pull a single antibody type and so that we could have very selective clearance, preserve all of the other immunoglobulin that we have as a patient, and thereby minimize other potential adverse events of the drug class.

Dr. Silvestri:
Yeah. So it seems we're getting more and more specific over time, which is great.

So this has been a brief but great discussion. I hope you found this information useful, and thanks again for tuning in.