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FcRn Inhibitors: A Potential New Targeted Therapy Option

Announcer:

You're listening to *NeuroFrontiers* on ReachMD. On this episode, we'll discuss the role of FcRn inhibitors in treating generalized myasthenia gravis, or gMG, with Dr. Nick Silvestri. He's a Professor of Neurology at the University at Buffalo Jacobs School of Medicine and Biomedical Sciences and a recipient of the 2023 A.B. Baker Teacher Recognition Award from the American Academy of Neurology. Let's hear from Dr. Silvestri now.

Dr. Silvestri:

The pathophysiology of generalized myasthenia gravis involves the creation of antibodies—in most cases, acetylcholine receptor antibodies—that target the acetylcholine receptors on the postsynaptic portion of the neuromuscular junction. To a lesser extent, there are antibodies against MuSK and Lrp4. And these antibodies also attack different components of the postsynaptic membrane. And because this is an antibody-driven disease, FcRn inhibitors play a role by reducing antibody levels. So FcRns are present in many tissues of our body, including endothelial cells, and what FcRns do is allow for recycling of IgG antibodies. So every once in a while, IgG antibodies, including pathogenic antibodies like those in myasthenia gravis, are brought into the endothelial cells, and when they bind to the Fc receptor, they are recycled back into the circulation. And in the case of pathogenic antibodies, they're then allowed to affect the neuromuscular junction, leading to symptoms in our patients.

If antibodies aren't bound to FcRn in the endosome into the endothelial cell, they're shunted to the lysosome where they're destroyed. And so by inhibiting FcRn with several of the medications that have been approved recently, it reduces the amount of IgG—including pathogenic antibodies—to be released into the circulation and puts more of those antibodies into the lysosome where they're destroyed. So again, it's effectively reducing antibody levels. And in the case of an antibody-mediated disorder, like generalized myasthenia gravis, it's reducing pathogenic antibody levels, almost like we would do with plasma exchange, but in a slightly different way.

Some of the key benefits that FcRn inhibitors offer compared to traditional therapies— immunosuppressive therapies, such as corticosteroids—is they have fewer off-target side effects. Another way to say it is they're more targeted therapies. So with traditional treatment of generalized myasthenia gravis, we would more broadly suppress the immune system with things like corticosteroids or oral immunosuppressants. And unfortunately, in doing so, we'd put people at risk for off-target side effects such as increased risk of infection over time increased risk of malignancy. Corticosteroids have myriad side effects that would put people at risk for other health problems—frankly, as do other immunosuppressant therapies—so by using more targeted treatments like FcRn inhibitors, we're able to control the disease very well in most cases. But we're also not putting patients at risk for side effects of the medications we've traditionally used to treat generalized myasthenia gravis.

So the potential risks or side effects associated with FcRn inhibitors tends to be an increased risk of infection. If you look at the clinical trials that were done of these agents, the most common side effects were upper respiratory tract infection and urinary tract infection. They were also associated with other side effects, like headache and myalgias. However, generally speaking, with the data that we have—now, keep in mind these agents have only been available for a few years—the risk of infection seems to be fairly low compared to more broad immunosuppression that we've been using for years. And there doesn't appear to be many off-target side effects or any off-target side effects that have really been seen. So again, it does put people at a slightly higher risk for infection. That's true really whenever you're manipulating the immune system to treat an autoimmune disease. But generally speaking, these newer agents seem to be safer when it comes to things like risk of infection.

To close, I think that it's important when we treat patients with generalized myasthenia gravis that we take into account different attributes of medications, because if you think about it there's really two burdens that patients have. It's the burden of their disease—

and by treating patients with these and other agents, we're really trying to minimize or perhaps eliminate these symptoms of myasthenia gravis—but we're really also dealing with, in many cases, the burden of therapy, and that tends to come in the things like side effects and tolerability. And with newer, targeted agents like FcRn inhibitors, we're really reducing the side effect profile; we're really trying to make this more tolerable and convenient for patients so that we can control their disease, but not at the expense of side effects or tolerability issues.

Announcer:

That was Dr. Nick Silvestri talking about how FcRn inhibitors can treat generalized myasthenia gravis. To access this and other episodes in our series, visit *NeuroFrontiers* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!