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Novel Mechanisms of Action: FcRn Inhibitors

### 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. Joining me today is Dr. Jeff Allen.

Jeff, let's focus on the FcRn inhibitors. What can you tell us about their novel mechanism of action?

### Dr. Allen:

Yeah. So the FcRn inhibitors are a new class of medication that's used for a couple of different autoimmune disorders. And now we have some evidence that they can potentially be an effect in CIDP as well. So the FcRn receptor is kind of a recycling mechanism where it's a little receptor that sits in endothelial cells, and that receptor is kind of a gateway to determine what sort of antibodies or proteins should be destroyed and which one should be returned to circulation. So these antibodies, IgG antibodies, are in circulation. They get taken up by these endothelial cells, and then once they're in the cell, they're going to try to bind to the FcRn receptor, at least the IgG antibodies and proteins. And if they're bound to that, then they get kicked back out into circulation. And if they're unbound, then they get destroyed by the lysosome.

So IgG antibodies, by doing this, can kind of increase their circulation and increase their recycling into the circulation. If it's a pathogenic antibody, that can potentially continue to cause mischief in the circulation.

So what an FcRn receptor antagonist does is basically block that receptor. So if you block that receptor in a very targeted sort of way, then any IgG antibody that's being taken up by the endosome can't bind to the receptor. Well, if it can't bind to the receptor, then instead of being returned to circulation, it all gets destroyed by the lysosome.

So it's a very slick mechanism in order to try to decrease IgG levels, but also to try to decrease antibodies that are IgG antibodies that are presumably pathogenic.

The FcRn is a receptor that lives in the endosome of an endothelial cell. And essentially, what this receptor does is it's very important to kind of determine what antibodies and proteins should be recycled and returned to circulation and which ones should be destroyed. So if you have antibodies, IgG antibodies that are floating through the circulation, they get taken up by this endothelial cell, and then once in the endothelial cell, they try to bind to the FcRn receptor. Once those are bound, if they are lucky enough to get bound, then those bound proteins are going to be returned to the circulation. And anything that's unbound is going to be destroyed by the lysosome.

So this allows IgG proteins to have a relatively long half-life because they can bind to the receptor and return in the circulation. Now, if you've got something like a pathogenic antibody, the same principle is also true where these, if they can bind to that receptor, get returned to the circulation and continue to cause whatever mischief they're causing.

So what an FcRn antagonist does is basically targets that FcRn receptor and blocks it. And if you block the receptor by a medication or a drug, like FcRn antagonist, then any protein that gets taken up by that cell can't also bind it. And if they can't bind it, then instead of being kicked back out into the circulation, it gets destroyed by the lysosome. So we think by using these FcRn receptors, we can cause all pathogenic IgG autoantibodies to be destroyed by a lysosome, and that could potentially improve a disease state.

So we think that if we can block that receptor by a drug like an FcRn antagonist, we can potentially remove a lot of these pathogenic antibodies and perhaps improve a disease state.

**Dr. Silvestri:**

Well, thanks, Jeff. That's a great answer. I really don't think I could have explained it better myself. And certainly, I think that there's a lot of potential for these agents in antibody-mediated disorders like CIDP. So the future is bright.

So thanks for a great discussion, and I really thank our audience for tuning in.

**Announcer:**

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