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FDA approval of first complement C3 inhibitor flags up autoimmune and inflammatory opportunities

Asher Mullard

The FDA has approved Apellis Pharmaceuticals' complement protein C3 inhibitor pegcetacoplan for paroxysmal nocturnal haemoglobinuria (PNH). With this approval the pegylated cyclic peptide will now compete with Alexion/AstraZeneca's first-in-class blockbuster anti-C5 antibody eculizumab in this rare disease. But complement modulators could have activity in common diseases too.

"This is great news," says John Lambris, an immunologist at the University of Pennsylvania. Lambris discovered pegcetacoplan's parent molecule, and Apellis then licensed it. Despite speculation that sustained blockade of C3 might be unsafe because of C3's central role in innate immunity, this approval proves this is not the case, he adds.

PNH is a rare blood disorder in which uncontrolled complement activity kills red blood cells, causing life-threatening anaemia. The approval of pegcetacoplan was based on an 80-patient phase III trial of the drug versus eculizumab, in patients with low haemoglobin levels despite eculizumab treatment. Pegcetacoplan beat eculizumab on the primary end point, boosting haemoglobin levels by 3.84 g per deciliter compared with eculizumab at 16 weeks, investigators reported in the *New England Journal of Medicine*. With treatment in this trial, 85% of pegcetacoplan recipients no longer needed transfusions, up from 15% on eculizumab.

The most common serious adverse reaction on pegcetacoplan was infections. Like eculizumab, it carries a black box warning noting the risk of meningococcal infections.

Companies are working to expand the reach of complement-modulating agents. Apellis is developing pegcetacoplan for indications including rare kidney diseases called C3 glomerulopathies and amyotrophic lateral sclerosis. Amyndas Pharmaceuticals, founded by Lambris, is developing next-generation C3 inhibitors for periodontitis, ocular diseases and other diseases. Novartis and Roche/Ionis are in phase II trials with drugs that target complement factor B, a component of the alternative complement pathway. Sanofi is set to re-submit its anti-C1s antibody sutimlimab for approval in cold agglutinin disease.

"We're going to see a lot of activity here, especially if drug developers can succeed beyond the rare indications," says Lambris.

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