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Intravitreal Pegcetacoplan for Geographic Atrophy

By: Meaghan Rettele, Pharm.D.

Background: Geographic atrophy (GA) is an advanced form of age-related macular degeneration (AMD) which can lead to compromised visual function and irreversible blindness.[1] This disease state is associated with a gradual loss of central vision in one or both eyes. It is caused by atrophic lesions in the retina resulting from the loss of photoreceptors, retinal pigment epithelium, and underlying choriocapillaris.[2] Unlike neovascular AMD, which is associated with acute vision loss, GA is a progressive disease that can lead to irreversible blindness over time.[3] It is estimated that GA affects nearly one million people in the United States and accounts for one-quarter of the cases of legal blindness, significantly affecting the quality of life and posing a significant economic burden.[4] Historically, the approach to managing and slowing the progression of GA has been observation, reduction of modifiable risk factors such as smoking, and taking age-related eye disease vitamins.[5] The cause of GA is not fully known; however, dysregulation of the innate immune system, particularly the complement cascade, has been implicated in disease states like GA.[6] Consequently, intravitreal (IVT) pegcetacoplan (Syfovre™; Apellis Pharmaceutical), an agent that inhibits the complement system, was approved in February 2023 for the treatment of GA secondary to AMD.[7]

Mechanism of Action: Pegcetacoplan binds to complement protein C3 and its active fragment, C3b, to regulate the cleavage of C3.[7] It is hypothesized that accumulated C3 fragments on the retinal epithelium promote phagocytosis by macrophages, resulting in retinal degeneration. By inhibiting C3 activation, IVT pegcetacoplan prevents

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DaxibotulinumtoxinA for Treatment of Glabellar Lines

By: Carter Friedt Pharm.D., MBA

Background: The glabellar complex, specifically the corrugator and procerus muscles, are a group of facial muscles between the eyebrows that can cause different patterns of wrinkles called glabellar lines.[1] One way to prevent and slow the progression of wrinkles in the glabellar region is with botulinum toxin injections.[2] Currently, there are four types of botulinum toxins approved for the treatment of glabellar lines: onabotulinumtoxinA (Botox®), abobotulinumtoxinA (Dysport®), rimabotulinumtoxinB (Myobloc®), and incobotulinumtoxinA (Xeomin®). These agents have a duration of action of approximately 3 to 4 months often requiring frequent injections. DaxibotulinumtoxinA (Daxxify®;Revance Therapeutics, Inc) , which is also used to lessen glabellar lines, is the first botulinum toxin formulated with the proprietary stabilizing peptide RTP004.[3] This peptide has been shown to lengthen its duration of action to 6 months. The need

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further C3 deposition allowing cells to avoid phagocytosis and the growth of GA lesions.[4]

Clinical Trials: The safety and efficacy of IVT pegcetacoplan were investigated in the FILLY trial, a multicenter, randomized, sham-controlled, Phase II study.[4] Patients ≥ 50 years of age, with best-corrected visual acuity of ≥ 24 letters using Early Treatment Diabetic Retinopathy Study charts (20/320 Snellen equivalent) and a diagnosis of GA secondary to AMD were included. Two hundred and forty-six eligible patients underwent 2:2:1:1 randomization to receive 15 mg IVT pegcetacoplan monthly (n=86), 15 mg IVT pegcetacoplan every other month (EOM) (n=79), sham injection monthly, or sham injection every EOM (pooled sham n=81). The primary efficacy outcome was the mean change in the square root of the GA lesion area from baseline to month 12. The majority of patients (88.6%) completed the first 12 months of the study. The modified intention-to-treat population consisted of patients with a mean age of 78 years, 60.5% were female, and 100% were white. The mean baseline square root GA lesion area was 2.8 mm (SD ± 0.72). The primary efficacy endpoint was significant in patients treated with monthly and EOM IVT pegcetacoplan, with the least square mean changes from baseline in GA area being 0.25 mm and 0.28 mm in the monthly and EOM groups, respectively, compared to 0.35 mm in the pooled sham group. Patients treated with monthly and EOM injections had smaller square root mean changes in GA lesion area growth compared to patients receiving sham, with 29% smaller increases in the monthly group (95% confidence interval [CI] 9%-49%, P=0.008) and 20% smaller increases in the EOM group (95% CI 0%-40%, P=0.067). The primary safety outcome was the number and severity of treatment-related adverse events. Treatment-related adverse events occurred in 25.6% and 13.9% of the monthly and EOM groups, respectively, and in none of the patients treated with sham. Patients treated with IVT pegcetacoplan had higher rates of new-onset exudative AMD than those in the sham group with 20.9% in the monthly group [95% CI 12.9%-31%] and 8.9% in the EOM group [95% CI 3.6%-17.4%] versus 1.2% in the sham group [95% CI 0%-6.7%]). Serious adverse effects in treated patients included endophthalmitis occurring in 2.3% of the monthly group and 1.3% in the EOM group, intraocular pressure (IOP) increases in 1.2% of the monthly group and 1.3% in the EOM group, and retinal detachment occurring in 1.2% of the monthly group and in none of patients in the EOM group. The authors concluded that IVT pegcetacophan was associated with significant reductions in GA lesion growth after 12 months of therapy and demonstrated an acceptable safety profile. These results were further investigated in the Oaks and Derby Phase III trials. The preliminary results of those studies are listed in the package insert.[7] A composite of 1258 patients included in the Oaks and Derby trials were randomized in a similar manner as the FILLY study with comparable interventions of 15 mg monthly IVT pegcetacoplan (n=202 in OAKS, n=201 in DERBY), 15 mg EOM IVT pegcetacoplan (n=205 in OAKS, n=201 in DERBY), and monthly or EOM sham (pooled sham n=207 in OAKS, n=195 in DERBY) for 24 months of treatment. Patients treated with IVT pegcetacoplan in the OAKS trial had a 21.9% and 18.1% decrease in the mean rate of change of GA lesion growth from baseline to 24 months with monthly and EOM injections, respectively; those in the DERBY trial had an 18.1% and 17.4% reduction in the mean rate of change of lesion growth from baseline to 24 months with monthly and EOM injections, respectively.

Safety: The most common side effects of IVT pegcetacoplan with an incidence of ≥ 5%, were ocular discomfort, neovascular AMD, vitreous floaters, and conjunctival hemorrhage.[7] It is recommended that females of childbearing potential use an effective form of contraception to prevent pregnancy during IVT pegcetacoplan treatment and 40 days after the last dose.

Dosing and Administration: Intravitreal pegcetacoplan is administered as a 15 mg (0.1 mL) intravitreal injection in each affected eye once every 25 to 60 days.[7] Following the injection, patients should be monitored for elevations in IOP and symptoms of endophthalmitis including eye pain, redness, and photophobia.

Cost and Availability: Syfovre™, NDC 73606-0020-01, is available as a clear, colorless to light yellow aqueous solution that requires refrigeration and protection from light.[7] Each glass vial contains an overfill to allow administration of a single 0.1 mL dose of a solution containing 15 mg of pegcetacoplan. The average wholesale price is $2,628 per vial and the estimated cost for 1 year of EOM or monthly injections is $15,768 and $31,536, respectively.[8]

Formulary Status: Intravitreal pegcetacoplan has been added to the CCHS Formulary and is restricted to the Department of Ophthalmology for outpatient use only.

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for a botulinum toxin with a prolonged clinical effect led to daxibotulinumtoxinA's approval by the Food and Drug Administration in September 2022 for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adults.[4,5]

Mechanism of Action: DaxibotulinumtoxinA is a neuromuscular blocker and an acetylcholine release inhibitor.[5,6] This neurotoxin cleaves SNAP-25, a protein responsible for successfully docking and releasing acetylcholine within nerve endings producing a dose-dependent decrease in muscle function. Recovery of neuromuscular activity is gradual. Following degradation of the drug, muscle reinnervation occurs leading to a slow reversal of neuromuscular blockade.

Clinical Trials: The SAKURA 1 and 2 trials were two multicenter, randomized, double-blind, placebo-controlled, Phase III studies that assessed the efficacy and safety of daxibotulinumtoxinA (DAXI) for the treatment of glabellar lines.[3] Subjects were enrolled between December 5, 2016 through November 14, 2017 for SAKURA 1 and November 22, 2016 through November 3, 2017 for SAKURA 2. Eligible patients had to be in good general health and have moderate to severe glabellar lines at maximum frown determined by the validated, 4-point, Investigator Global Assessment-Frown Wrinkle Severity (IGA-FWS) scale and the Patient Frown Wrinkle Severity (PFWS) scale. Patients were randomized in a 2:1 ratio to receive either DAXI 40 units or placebo and were followed for 36 weeks to assess efficacy, safety, and duration. In SAKURA 1, patients (N=303) were randomized to DAXI (n=201) or placebo (n=102), and in SAKURA 2, patients (N=306) were randomized to DAXI (n=204) or placebo (n=102). Patients and investigators were trained to rate glabellar line severity using the IGA-FWS and the PFWS scales to assess efficacy. Both scales rate wrinkle severity as none (0), mild (1), moderate (2), and severe (3). The primary outcome was the percentage of patients who achieved at least a 2-point improvement from baseline to week 4 using both wrinkle severity scales. In SAKURA 1, 73.6% in the active treatment group versus 0% in the placebo group and in SAKURA 2, 74% in the active treatment group versus 1% in the placebo group achieved at least a 2-point improvement in glabellar line severity as determined by both investigator and patient ratings at maximum frown at 4 weeks (P<0.0001 for both; difference, 74.2% (95% confidence interval [CI] 68.2%-80.2%) and 72.9% (95% CI 66.6%-79.1%), respectively. The secondary endpoints included the duration of response for patients who maintained a severity score of none or mild and the time until glabellar line severity returned to baseline. The median duration of response that subjects maintained a wrinkle severity score of none or mild was 24 weeks in SAKURA 1 and 23.9 weeks in SAKURA 2. The median time until glabellar line severity returned to baseline was 27.7 weeks in SAKURA 1 and 26 weeks in SAKURA 2. The authors concluded that in patients with moderate to severe glabellar lines, DAXI proved to be a safe and effective therapy with an extended duration of action.

Safety: The most common treatment-related adverse effects of daxibotulinumtoxinA were headache (6%), eyelid ptosis (2%), and facial paresis (1%).[5] There is a black box warning regarding the spread of the drug beyond the injection site and the potential for life-threatening swallowing and breathing difficulties. It is important to note that daxibotulinumtoxinA is not approved for conditions other than glabellar lines.

Dosing and Administration: Daxxify® is administered as an intramuscular injection into five glabellar sites.[5,6] Two injections are given in each corrugator muscle and one in the procerus muscle. Each injection site should contain 8 units (0.1mL) of drug for a total of 40 units. Daxxify® should not be administered more frequently than every 3 months. The units of biological activity of daxibotulinumtoxinA are not interchangeable with other botulinum toxin preparations.

Cost and Availability: Daxxify®, NDC 72960-0111-01, is available as a 100 unit single-dose vial for reconstitution.[5] Unopened vials can be stored at room temperature 20°C to 25°C (68°F to 77°F) or refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton protected from light. Vials require reconstitution with 1.2 mL of preservative-free 0.9% sodium chloride. Reconstituted vials may be refrigerated for 72 hours. The suggested wholesale price is $504 a vial.[6] The annual cost per patient is approximately $1,000 and would not be covered by insurance due to its cosmetic indication.

Formulary Status: DaxibotulinumtoxinA was added to the CCHS Formulary restricted to outpatient use only.

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