In Intravitreal Pegetectacoplan 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) pegetectacoplan (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: Pegetectacoplan 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 pegetectacolan prevents

(Continued on page 2)

DaxibotulinumtoxinA for Treatment of Glabellar Lines

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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

(Continued on page 3)
further C3 deposition allowing cells to avoid phagocytosis and the growth of GA lesions.⁴

**Clinical Trials:** The safety and efficacy of IVT pegdecatocoplan 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 pegdecatocoplan monthly (n=86), 15 mg IVT pegdecatocoplan 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 2.88 mm (SD ± 0.72). The primary efficacy endpoint was significant in patients treated with monthly and EOM IVT pegdecatocoplan, 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 pegdecatocoplan 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 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 pegdecatocoplan 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 pegdecatocoplan (n=202 in OAKS, n=201 in DERBY), 15 mg EOM IVT pegdecatocoplan (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 pegdecatocoplan 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 pegdecatocoplan 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 pegdecatocoplan treatment and 40 days after the last dose.

**Dosing and Administration:** Intravitreal pegdecatocoplan 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 pegdecatocoplan. 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 pegdecatocoplan has been added to the CCHS Formulary and is restricted to the Department of Ophthalmology for outpatient use only.

**References**

for a botulinum toxin with a prolonged clinical effect led to
daxibotulinumtoxinA's approval by the Food and Drug Ad-
ministration in September 2022 for the temporary im-
provement in the appearance of moderate to severe gla-
bellar lines associated with corrugator and/or procerus muscle activity in adults.\(^4\)\(^5\)

**Mechanism of Action:** DaxibotulinumtoxinA is a neuro-
muscular 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 rein-
nervation occurs leading to a slow reversal of neuromus-
cular blockade.

**Clinical Trials:** The SAKURA 1 and 2 trials were two mul-
ticenter, 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 de-
termined by the validated, 4-point, Investigator Global As-
sessment-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 as-
sess 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 ran-
domized to DAXI (n=204) or placebo (n=102). Patients
and investigators were trained to rate glabellar line sev-
verity using the IGA-FWS and the PFWS scales to assess effi-
cacy. 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 treat-
ment 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 improve-
ment in glabellar line severity as determined by both in-
vestigator and patient ratings at maximum frown at
4 weeks (P<0.0001 for both; difference, 74.2% (95% con-
didence interval [CI] 68.2%-80.2%) and 72.9% (95% CI
66.6%-79.1%), respectively. The secondary endpoints in-
cluded the duration of response for patients who main-
tained 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 se-
vere glabellar lines, DAXI proved to be a safe and effective
therapy with an extended duration of action.

**Safety:** The most common treatment-related adverse ef-
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 in-
jection site and the potential for life-threatening swallow-
ing and breathing difficulties. It is important to note that
daxibotulinumtoxinA is not approved for conditions other
than glabellar lines.

**Dosing and Administration:** Daxify® 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. Daxify®
should not be administered more frequently than every
3 months. The units of biological activity of daxibotuli-
numtoxinA are not interchangeable with other botulinum
toxin preparations.

**Cost and Availability:** Daxify®, 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 re-
quire reconstitution with 1.2 mL of preservative-free
0.9% sodium chloride. Reconstituted vials may be refrig-
erated 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.

**References:**

3. Carruthers JD, Fagien S, Joseph IH, Humphrey SD, Biesman BS, Gallagher CJ, et al. Daxi-
4. U.S. Food and Drug Administration [Internet]. Silver Spring, MD: Food and Drug Ad-