

# The Next-Generation Steroid

Durezol is proving to be a major innovation in the treatment of inflammation after ocular surgery.

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For more than 6 decades, topical corticosteroids have been the cornerstone of therapy for the treatment of various forms of ocular inflammation, both surgical and autoimmune in nature.<sup>1</sup> By inhibiting the release of phospholipase A2 early in the inflammatory cascade, steroids provide a broad range of anti-inflammatory activity, because they attenuate the effects of inflammatory mediators and prevent their release. Despite steroids' ubiquity in the treatment of inflammation, little innovation in this class of drug has occurred in terms of therapy for moderate-to-severe inflammation. In late 2008, however, Durezol (difluprednate ophthalmic emulsion 0.5%; Sirion Therapeutics) was approved for the treatment of inflammation and pain associated with ocular surgery.

Although we were initially skeptical that Durezol was any different from prednisolone acetate, we soon realized that the former performs in ways that the latter cannot. One of our initial experiences with Durezol involved a 30-year-old woman who had received bilateral corneal transplants for pellucid marginal degeneration. After doing well for 9 months with excellent visual acuity, she developed chronic, bilateral endothelial and stromal rejection. Despite several courses of oral prednisone combined with subconjunctival and intracameral corticosteroids and frequent dosing with a topical steroid, the patient's inflammation and visual loss continued to progress. Her condition finally stabilized with oral mycophenolate (CellCept; Genentech, Inc.) and topical prednisolone acetate dosed every 2 hours. She continued, however, to have a low-grade anterior chamber reaction and progressive stromal neovascularization.

When Durezol was approved by the FDA, this patient was the first to whom we prescribed it. She administered the drug every 2 hours and discontinued the prednisolone acetate. Over the next few weeks, her stromal neovascularization regressed, and her anterior chamber reaction cleared. During the next 2 months, her CellCept

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was tapered and then discontinued. By the fourth month, the patient's use of Durezol was tapered to four times a day. By 6 months, she used the drug twice a day and was free of inflammation.

This article provides an overview on this next-generation steroid.

## THE MOLECULE

Durezol's active ingredient, difluprednate, is a glucocorticoid, a derivative of prednisolone that has been modified in three ways for increased potency, anti-inflammatory activity, and penetration. Difluprednate is fluorinated at both the C-6 and C-9 positions. Fluorination of corticosteroids greatly increases their specificity for the glucocorticoid receptor,<sup>2,3</sup> and many of the more powerful glucocorticoids are fluorinated at the C-6 or C-9 position (eg, betamethasone, clobetasol) or at both (eg, fluticasone).

The second modification is the addition of a butyrate ester at the C-17 position. This not only increases the potency of difluoroprednisolone (the active metabolite), but it is also the key to the activity of difluprednate. In the absence of the C-17 butyrate ester, difluprednate is inactive.

The third modification of difluprednate increases the drug's ability to reach the relevant ocular glucocorticoid receptors. The corneal penetration of glucocorticoids is enhanced by the addition of an acetate group to the molecule.<sup>4</sup> In difluprednate, the addition of the acetate

ester at position C-21 enhances tissue penetration, enabling more active drug to reach the uvea. In fact, glucocorticoids with 17,21-double esters, such as difluprednate, generally penetrate tissue better than monoester derivatives.<sup>5</sup>

### THE FORMULATION

Most topical ophthalmic medications are preserved with benzalkonium chloride, which can be toxic to ocular tissues.<sup>6-8</sup> To avoid these adverse events, difluprednate was formulated with sorbic acid. This preservative has been shown to cause little damage to ocular tissue or irritation, and it is recommended for sensitive eyes.<sup>9</sup> Because Durezol is typically used when ocular tissues are compromised, minimizing any additional insult from preservative-related toxicity is an important consideration.

Of all the ophthalmic glucocorticoids, only Durezol is formulated as an emulsion. Difluprednate is very hydrophobic, but it dissolves readily in the oil droplets of an emulsion. Thus, delivery by emulsion greatly increases the bioavailability of difluprednate compared with a suspension formulation. A comparison of the amount of drug substance delivered to the aqueous humor of rabbits showed that a 42% higher concentration of difluprednate ( $C_{max}$ ) was delivered from an emulsion formulation than from a suspension.<sup>10</sup> The very small droplet size of the Durezol emulsion (110 nm) combined with the high solubility of difluprednate in the droplet results in a uniform blanketing of the ocular surface with a high dose of steroid. The result is rapid corneal penetration. This improved bioavailability gives Durezol a level of clinical effectiveness that is greater than predicted from receptor binding alone.

Because Durezol is a stable emulsion, the active drug does not settle. The dose that is delivered therefore does not change with time, as can occur with suspensions. Research presented at ARVO last year compared Durezol, Pred Forte (Allergan, Inc.), and generic prednisolone acetate 1%. The data showed that, in various different scenarios (ie, bottles that were inverted, upright, shaken, and not shaken), the amount of Durezol delivered remained constant. In contrast, when the branded and generic prednisolone acetate formulations were stored inverted and not shaken, the amount of drug delivered (despite the claim on the label) varied many hundredfold over the course of therapy. More surprisingly, even when both prednisolone suspensions were stored upright and shaken before use (the optimum dosing scenario), the amount of drug substance actually delivered (as opposed to the claim on the label) varied fourfold or more. There was a tendency for more drug to be dispensed toward the end

of the dosing period (possibly during tapering) than at the beginning.<sup>11</sup>

### CLINICAL STUDIES

Two phase 3, randomized, placebo-controlled trials were conducted in 438 patients with inflammation and pain. The goal was to assess the efficacy and safety of Durezol dosed b.i.d. and q.i.d., beginning 1 day after intraocular surgery, in eyes with more than 10 anterior chamber cells. The main outcome measures (including anterior chamber cell scores and counts, anterior chamber flare, and pain scores) demonstrated that both dosages of Durezol cleared inflammation and reduced pain rapidly and effectively after ocular surgery when compared with placebo.

Significant differences were noted in the proportion of patients achieving a clinical response (defined as five cells or fewer in the anterior chamber and no flare) as early as day 8: 46.4% and 42.1% ( $P < .0001$ ) in the b.i.d. and q.i.d. groups, respectively, compared with 18.9% in the placebo group. The percentage of patients achieving a clinical response continued to increase at day 15, a trend that was sustained through day 29, with 79.1% and 82.2% of patients in the b.i.d. and q.i.d. groups achieving a clinical response, respectively, versus 39.4% in the placebo group ( $P < .0001$ ). In addition, postoperative corneal edema decreased significantly in the eyes receiving Durezol b.i.d. ( $P = .0003$ ) and q.i.d. ( $P < .0001$ ) compared with the control group.<sup>12</sup>

An additional study compared Durezol q.i.d. and prednisolone acetate dosed eight times a day in 90 patients with endogenous anterior uveitis. Difluprednate demonstrated comparable and numerically greater results than prednisolone acetate, the standard for the topical treatment of uveitis in the United States,<sup>13</sup> even though Durezol was dosed at half the frequency. Drugs were administered for 14 days, followed by 2 weeks of tapering at half the dose and 2 weeks of follow-up. On day 14, the mean reduction in cell grade in the Durezol group was 2.1 versus 1.9 in the Pred Forte group. In addition, 69% of Durezol patients had an anterior chamber cell grade of 0 (one cell or fewer) by day 14, compared with 62% of prednisolone acetate patients. Interestingly, in this study, 12.5% of prednisolone acetate patients were withdrawn from the trial for a lack of efficacy, whereas no Durezol patients were withdrawn for this reason. Finally, visual acuity returned more rapidly in the uveitic patients treated with Durezol, with a notably greater improvement in BCVA compared with prednisolone acetate at day 3 ( $P = .02$ ), day 21 ( $P = .03$ ), day 28 ( $P = .03$ ), and day 35 ( $P = .04$ ).<sup>14</sup>

## POTENTIAL INDICATIONS

### Treatment of Inflammation

At present, Durezol is our steroid of choice for the treatment of significant inflammation. Patients with uveitis, corneal graft rejection, stromal keratitis, and scleritis and some individuals with conjunctivitis are good candidates for Durezol. Significant inflammation should be treated at its onset with the most potent steroid, with therapy then possibly tapered to a weaker steroid.

### Prevention of Inflammation

More often than not, ophthalmologists must suppress inflammation resulting from ocular surgery. For example, glaucoma operations, like trabeculectomy and tube shunt surgery, are associated with significant postoperative inflammation. Moreover, the preservation of a bleb after trabeculectomy is important, and increased inflammation (even moderate levels) can lead to scarring that may cause the bleb to fail. The success of several types of corneal transplant surgeries (eg, Descemet's stripping endothelial keratoplasty, deep lamellar anterior keratoplasty, penetrating keratoplasty) may depend in part on the postoperative control of inflammation. In addition, the main cause of failure in conjunctival surgery such as pterygium excision is inflammation. Even in routine cataract surgery, it is becoming more important to identify patients who may be at risk of increased inflammation because of the associated complications. These individuals include patients with benign prostatic hypertrophy who are using Flomax (Boehringer Ingelheim Pharmaceuticals, Inc.), those who have a history of maculopathy, and patients with dense cataracts who may require more phaco time. Preventing a surgical inflammatory reaction can improve the outcomes of all these procedures.

The use of anti-inflammatory medications is common in many of these cases. Sometimes, these agents are dosed every hour, which is not optimal for patients' health. Because a potent steroid will likely facilitate a rapid resolution of inflammation, Durezol has the potential to be very beneficial for patients after the aforementioned surgical procedures. Not only should its use increase compliance due to its less frequent dosing, but the agent may also clear inflammation faster and decrease steroid exposure, all of which improves surgical outcomes.

Finally, with an incidence of 6% to 43%,<sup>15,16</sup> postoperative cystoid macular edema can complicate many forms of ocular surgery. It is the standard of care to employ topical ophthalmic steroids in this setting,<sup>17</sup> but more data are needed regarding the use of stronger steroids with and without nonsteroidal anti-inflammatory drugs before the best regimen can be determined.

As ophthalmologists' knowledge about conditions that increase inflammation grows, so, too, should their efforts to reduce the effects that this reaction may have long after the surgery is complete. ■

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