Phase III studies:

Trial: Difluprednate potent efficacy confirmed

Corticosteroid found significantly superior to placebo in reducing postop pain, inflammation

By Cheryl Guttman
Reviewed by Steven M. Silverstein, MD

Kansas City, MO—Results from a series of multicenter, randomized, double-masked, placebo-controlled clinical trials are consistent in demonstrating that difluprednate 0.05% ophthalmic emulsion (Durezol, Sirion Therapeutics) provides safe, potent, and reliable control of ocular inflammation and pain, said Steven M. Silverstein, MD.

In June, 2008, Sirion Therapeutics gained FDA approval to market its new corticosteroid for the treatment of inflammation and pain associated with ocular surgery. The regulatory agency’s decision considered data from two pivotal phase III studies involving 438 patients who qualified for participation based on the presence of significant postoperative inflammation (more than 10 anterior chamber cells).

In this study, where treatment was initiated after surgery, the results showed statistically significant efficacy of difluprednate compared with placebo whether the corticosteroid was dosed b.i.d. or q.i.d.

More recently, results reported from two phase IIb studies showed that when treatment started on the day before surgery, both b.i.d. and q.i.d. difluprednate regimens were significantly superior to placebo in reducing postoperative pain and inflammation. In addition, in a trial enrolling 90 patients, difluprednate initiated with q.i.d. dosing was found to be comparable to prednisolone acetate 1% (Pred Forte, Allergan) dosed 8 times a day for reducing inflammation, pain, and other signs and symptoms of noninfectious anterior uveitis.

“Reducing the dosing frequency of any medication enhances compliance, and it also decreases opportunities for a dilution effect that can occur in patients using multiple medications,” Dr. Silverstein said. “With twice-daily dosing of difluprednate, these benefits are achieved while providing patients with efficacy equal to or better than that associated with previous standard ophthalmic corticosteroid regimens.”

The phase IIIb surgery clinical trial program enrolled 124 patients in the study comparing difluprednate or placebo administered q.i.d. and 121 patients in the b.i.d. dosing trial. In both studies, patients were randomly assigned 2:1 to difluprednate or placebo. Treatment began on the day before surgery, and patients using multiple medications, the NMD for these effects was 3.5 mg/kg/day.

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The differences comparing di flu pred nate with placebo were statistically significant in both studies, but data from earlier follow-up visits showed statistically significant differences favoring di flu pred nate versus placebo were seen in both the b.i.d. (64.6% versus 30%) and q.i.d. studies (72.5% versus 40%). However, by the day 3 or 4 visit, more than 60% of patients using di flu pred nate b.i.d. or q.i.d. were already free from ocular pain/discomfort compared with just more than one-third of the controls, and this early difference favoring di flu pred nate was also statistically significant.

Clinical practice perspective

Dr. Silverstein’s medication regimen for patients undergoing cataract surgery includes di flu pred nate, a fourth-generation fluoroquinolone, and a non-steroidal anti-inflammatory drug (NSAID), and based on review of postoperative OCT images, my impression is that there is a definite benefit for the combination in preventing macular edema, diabetic macular thickening and reducing the incidence of CME,” Dr. Silverstein said.

“Even though di flu pred nate is a superpotent corticosteroid, I have not found it to be associated with any increased incidence of corticosteroid-related adverse events relative to the previously available corticosteroids, and I am not overly concerned if a treatment-related IOP elevation occurs since the treatment duration is short in most patients and the IOP increase resolves after the停药 period,” said Dr. Silverstein.

Patients undergoing cataract surgery who receive q.i.d. di flu pred nate are those with any of the following findings in their history: diabetic macular edema, diabetic retinopathy, vitreoretinal surgery, significant epiretinal membrane, macular pucker, uveitis, autoimmune disease, or rheumatologic disease. Patients whose case involved a significant intraoperative complication, such as vitreous prolapse, are treated with di flu pred nate every 2 hours on the day of surgery and then q.i.d. beginning on the first postoperative day.

“In any of these high-risk patients, the di flu pred nate and NSAID are generally continued for 2 to 3 months, with the exact duration determined by the findings from their postoperative exams,” Dr. Silverstein said.

Di flu pred nate has demonstrated a favorable safety profile in clinical trials, and that too is consistent with Dr. Silverstein’s clinical experience. In the phase IIb study, a criterion increase in IOP (≥21 mm Hg and a change from baseline ≥10 mm Hg at the same visit) occurred in 6% of patients using di flu pred nate q.i.d., 3.7% of patients instilling the corticosteroid twice daily, and in none of the placebo-treated controls. In the anterior uveitis study, there was no difference between the di flu pred nate and prednisolone acetate groups in rates of clinically significant increases in IOP.

“I am not surprised that patients who receive di flu pred nate and NSAID are those with any of the following findings in their history: diabetic macular edema, diabetic retinopathy, vitreoretinal surgery, significant epiretinal membrane, macular pucker, uveitis, autoimmune disease, or rheumatologic disease. Patients whose case involved a significant intraoperative complication, such as vitreous prolapse, are treated with di flu pred nate every 2 hours on the day of surgery and then q.i.d.

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