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Literature Scan: Ophthalmic Anti-inflammatory Drugs

Month/Year of Review: May 2015

Date of Last Review: December 2009
Source Document: Provider Synergies

Current Status of PDL Class:
See **Appendix 1**.

Conclusions and Recommendations:
- There is high quality evidence that there is no difference in efficacy/effectiveness or in safety between ophthalmic corticosteroid agents.
- There is high quality evidence that there is no difference in efficacy/effectiveness or in safety between ophthalmic nonsteroidal anti-inflammatory drugs.
- No further review or research needed at this time. Review comparative drug costs in the executive session.

Previous Conclusions and Recommendations:
- There is high quality evidence that there is no difference in efficacy/effectiveness or in safety between agents.
- Consider at least one medication from each class (corticosteroids and NSAIDs).

Methods:
A Medline literature search for new randomized controlled trials (RCTs) assessing clinically relevant outcomes to placebo or active controls were conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this review is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drugs, indications, and safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
A Cochrane Review performed by Sivaprasad, et al.[1] investigated the effectiveness of non-steroidal anti-inflammatory inhibitors (NSAIDs) in cystoids macular edema following cataract surgery. Cystoid macular edema (CMO) is the accumulation of fluid in the central retina (the macula) due to leakage from dilated

capillaries. It is the most common cause of poor visual outcome following cataract surgery. Acute CMO, defined as edema of less than four months duration, often resolve spontaneously. CMO that persists for four months or more is termed chronic CMO. The primary outcome measures were: 1) an improvement of 2 or more lines in Snellen visual acuity or equivalent at end of treatment; and 2) persistence of improvement of vision one month after discontinuation of treatment. This review included seven randomized controlled trials with a total of 266 participants. Three trials studied the effects of topical NSAIDs in chronic CMO while the other three examined the effect of topical NSAIDs in acute CMO.[1] Two trials showed that topical 0.5% ketorolac tromethamine ophthalmic solution significantly improves 2 or more lines in Snellen visual acuity versus placebo on chronic CMO and a third trial assessing topical 1% fenoprofen was also supportive of this finding but did not find a statistically significantly difference versus placebo. Further work is needed for a more conclusive decision regarding use of ophthalmic NSAIDS in chronic CMO. A meta-analysis was performed for these drugs but 95% confidence intervals showed very imprecise estimates of their effect.[1] Similar results were also seen in Snellen visual acuity when either topical ketorolac or prednisolone was used in acute CMO, though both drugs used together were more effective than either agent alone. Persistent improvement of vision one month after discontinuing treatment was also noted for all 3 arms. In another study, 0.1% diclofenac sodium and 0.5% ketorolac tromethamine yielded similar results in Snellen visual acuity. A third cross-over study yielded less compelling results with ketorolac. All 3 studies were underpowered to show anything but major effects. Spontaneous resolution and drug effect in acute CMO are hard to distinguish in these very small studies. Because of the significant heterogeneity and small sample sizes of these studies, a meta-analysis was not performed and the effects of NSAIDs in acute CMO remain promising but unclear.[1]

A systematic review performed by Kessel, et al.[2] compared the efficacy of topical corticosteroids with topical NSAIDs in controlling inflammation and preventing pseudophakic cystoid macular edema (PCME, also termed “Irvine-Gass syndrome) after uncomplicated cataract surgery. The swelling of the fovea that results in occurs due to fluid accumulation occurring a few weeks to months after cataract surgery and is the most common cause of visual decline after cataract surgery. The primary outcome assessed was postoperative inflammation and PCME. Fifteen RCTs were identified.[2] The anti-inflammatory effect of these drugs was evaluated by examining signs of intraocular inflammation: cells and flare. Only studies used laser cell-flare photometry to identify inflammation were included in the meta-analysis because other methods did not use comparable grading systems. Inflammation measured as number of cells detected did not find a statistically significant difference between corticosteroids and NSAIDs; however, inflammation measured as amount of flare by laser flare photometry week 1 after surgery demonstrated superiority with NSAIDs relative to low potency corticosteroids but NSAIDs were equally effective to medium to high potency corticosteroids. The prevalence of PCME was significantly higher in the corticosteroid group (25.3%) than in the NSAID group (3.8%), a risk ratio of 5.35 (95% CI, 2.94 to 9.76). There was no significant difference in visual acuity after cataract surgery or adverse events between the two groups. Significant heterogeneity between the studies, as well as extensive exclusion criteria (i.e., history of uveitis, diabetes, diabetic retinopathy) limits the applicability of these results. The authors concluded there is low to moderate quality of evidence that topical NSAIDs are more effective in controlling postoperative inflammation after cataract surgery and high quality evidence that topical NSAIDs are more effective than topical corticosteroids in preventing PCME.[2]

A Cochrane Review performed by Herretes, et al.[3] assessed the effectiveness and safety of corticosteroids as adjunctive therapy for bacterial keratitis. Four eligible RCTs (n=612 eyes) that had evaluated adjunctive therapy with topical corticosteroids in people with bacterial keratitis who were being treated with antibiotics were included in the review. One of the three smaller trials was a pilot study of the largest study: the Steroids for Corneal Ulcers Trial.[4] All trials reported data on visual acuity ranging from three weeks to one year, and none of them found any important difference between the corticosteroid group and the control group. The pilot study of the SCUT reported that time to re-epithelialization in the steroid group was 53% slower than the placebo group after adjusting for baseline epithelial defect size (hazard ratio (HR) 0.47; 95% confidence interval (CI) 0.23 to 0.94). However, the SCUT did not find any important difference in time to re-epithelialization (HR 0.92; 95% CI 0.76 to 1.11). For adverse events, none of the three small trials found any important difference between the two treatment groups. The investigators of the largest trial reported that more patients in the control group developed intraocular pressure (IOP)

elevation (risk ratio (RR) 0.20; 95% CI 0.04 to 0.90). One trial reported quality of life and concluded that there was no difference between the two groups (data not available). Although the four trials were generally of good methodological design, all trials had considerable losses to follow-up (10% or more) in the final analyses. Three of the four trials were underpowered to detect treatment effect differences between groups. Heterogeneity between the outcomes studied prohibited a meta-analysis of the data. The authors concluded there is inadequate evidence as to the effectiveness and safety of adjunctive topical corticosteroids compared with no topical corticosteroids in improving visual acuity or adverse events.[3]

New Guidelines:
None identified.

New FDA Drug Approvals:
None identified.

New Formulations or Indications:
LOTEMAX® (loteprednol etabonate) 0.5% ophthalmic ointment is a corticosteroid approved by the FDA in April 2011 for the treatment of postoperative inflammation and pain following ocular surgery. Loteprednol was initially approved in the U.S. in 1998 as 0.2% and 0.5% ophthalmic suspensions.[5] Data submitted to the FDA provided evidence of effectiveness in adequate and well controlled studies that demonstrated the superiority of loteprednol etabonate 0.5% ophthalmic ointment to placebo vehicle in both the complete resolution of postoperative anterior chamber cell and flare and in complete resolution of postoperative pain following ocular surgery for up to 18 days.[5]

ILEVRO™ (nepafenac) 0.3% ophthalmic suspension is an NSAID approved by the FDA in 2012 for the treatment of pain and inflammation associated with cataract surgery. It was initially approved in the U.S. in 2005 as a 0.1% formulation given three times daily. The re-formulated suspension is 3-fold more potent but given only once daily. The suspension was shown to be effective and safe for the treatment of pain and inflammation associated with cataract surgery based on superiority to a placebo vehicle and non-inferiority to the previously approved formulation. No new adverse effects were identified in the two Phase 3 trials testing this formulation.[6]

LOTEMAX® (loteprednol etabonate) 0.5% ophthalmic gel is a corticosteroid approved by the FDA in September 2012 for the treatment of postoperative inflammation and pain following ocular surgery. Loteprednol was initially approved in the U.S. in 1998 as 0.2% and 0.5% ophthalmic suspensions.[7] The ointment, as noted previously, was approved in 2011. Data submitted to the FDA was contained in the results of two randomized, multicenter, double-blind, vehicle placebo-controlled Phase 3 trials in 813 patients randomized to one of the two arms: loteprednol etabonate four times daily for 14 days after cataract surgery (n=409) or vehicle control (n=404). Significantly more patients receiving loteprednol had complete resolution of anterior chamber cell inflammation versus placebo (30.5%-31.1% vs. 16.3%-13.9%, respectively; p<0.001). In addition, significantly more patients receiving loteprednol had complete resolution of pain versus placebo (72.9%-75.7% vs. 41.9%-45.8%, respectively; p<0.001).[7]

PROLENSA™ (bromfenac) 0.07% ophthalmic solution is an NSAID approved by the FDA in 2013 for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery. Bromfenac was initially approved in the U.S. as a 0.09% solution in 2005. The newer, less concentrated, suspension was shown to be effective and safe in two Phase 3 trials for the treatment of pain and inflammation associated with cataract surgery

based on superiority to a placebo vehicle. The primary efficacy endpoint was the proportion of patients with cleared inflammation by day 15, which was defined as the summed ocular inflammation score of Grade 0 (0 cells and absence of flare) at any post-surgery visit prior to and included day 15.[8]

New FDA Safety Alerts:
None identified.

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Appendix 1: Current Status on Preferred Drug List

Current Preferred Agents	Current Non-Preferred Agents
Ophthalmic Corticosteroids	
Dexamethasone (MAXIDEX) suspension Dexamethasone sodium phosphate suspension Fluorometholone (FML; FML S.O.P.; FLUOR-OP) suspension Loteprednol etabonate (LOTEMAX) suspension Prednisolone (OMNIPRED; PRED FORTE) suspension	Dexamethasone sodium phosphate (DECADRON) ointment Difluprednate (DUREZOL) emulsion Fluorometholone (FML FORTE) suspension Fluorometholone acetate (FLAREX) suspension Loteprednol etabonate (ALREX) suspension Loteprednol etabonate (LOTEMAX) gel and ointment Prednisolone acetate (PRED MILD) suspension Prednisolone sodium phosphate (INFLAMASE MILD; INFLAMASE FORTE) suspension Rimexolone (VEXOL) suspension
Ophthalmic Non-steroidal Anti-inflammatory Drugs (NSAIDs)	
Diclofenac sodium (VOLTAREN) solution Flurbiprofen (OCUFEN) solution Ketorolac tromethamine (ACULAR; ACULAR LS) solution	Bromfenac (PROLENSA) solution Ketorolac (ACUVAIL) solution Nepafenac (ILEVRO; NEVANAC) suspension

Appendix 2: New Clinical Trials

One hundred eight-six citations were scanned from the literature search. After further review, 103 articles were excluded because the study design did not meet our criteria. The remaining 13 RCTs are briefly described in the table below. Full abstracts are included in **Appendix 2**.

Table 1: Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	Primary Outcome	Results	Quality*
Maca SM, et al.[9] 2010 RCT, PG, SB	Preservative-free diclofenac 0.1% (n=31), preserved diclofenac 0.1% (n=29) or preserved ketorolac tromethamine 0.5% (n=33) eyedrops	Patients who underwent small-incision phacoemulsification cataract surgery.	Not explicitly mentioned. Pre-specified outcomes were: anterior chamber flare and mean retinal (foveal) thickness and tolerability assessed by observer-based grading of conjunctival hyperemia and ocular discomfort as well as subjective ratings of ocular tolerability on a visual analog scale at 1-month follow-up	All 3 formulations had equal anti-inflammatory efficacy as measured by reduction of anterior chamber flare after surgery, mean foveal thickness and prevention of postoperative macular edema between week 1 and 1 month. Patients treated with preservative-free diclofenac eyedrops reported significantly better subjective tolerability values (p=0.001) and less ocular discomfort (p<0.001).	Poor
Foster CS, et al.[10] 2010 MC, RCT, DB	Difluprednate emulsion 0.05% (n=48) vs. Prednisolone acetate 1% (n=39).	Patients ≥2 years of age with endogenous anterior uveitis in at least one eye.	A noninferiority trial, assessing the change from baseline in mean AC cell grade on day 14, compared between difluprednate and prednisolone.	Difluprednate dosed 4-times daily was noninferior to prednisolone acetate dosed 8-times daily, with a mean AC cell grade improvement of 2.1, compared with 1.9 in the prednisolone group.	Good
Donnenfeld ED, et al.[11] 2011 MC, RCT, DB	Pulse-dosed difluprednate 0.05% (n=104 eyes) versus prednisolone acetate 1% (n=alternative 104 eyes)	Patients who underwent bilateral phacoemulsification cataract surgery.	Change from baseline in corneal thickness between the difluprednate- and prednisolone acetate-treated groups at day 1.	At day 1, the mean central corneal thickness of difluprednate-treated eyes increased by 28 microm (from 562 to 590 microm), roughly half the increase seen in the prednisolone-treated eyes, in which the increase was by 57 microm (from 562 to 619 microm), a difference of 33 microm which was statistically significant (p=0.026).	Fair

Miyake K, et al.[12] 2011 RCT, DM	Nepafenac 0.1% and flurometholone 0.1% (n=30) vs. flurometholone 0.1% alone (n=29)	Patients who underwent small-incision phacoemulsification cataract surgery.	Not explicitly mentioned. Outcomes included incidence of cystoid macular edema (CME) and blood-aqueous barrier (BAB) disruption after surgery.	Five weeks postoperatively, the incidence of fluorescein angiographic CME was significantly lower in the nepafenac group (14.3%) than in the fluorometholone group (81.5%) (P<.0001). CME classified as "severe" was 5 eyes in the fluorometholone group vs. no eyes in the nepafenac group; the difference in severity of CME was significant (p<0.0001).	Poor
Almeida D, et al.[13] 2012 SC, DB, PC, PG, RCT	Prophylactic ketorolac 0.5% (n=54) vs. nepafenac 0.1% (n=54) vs. placebo (n=54) in addition to routine topical antibiotic and prednisolone 1.0%	Patients with a cataract expected to have phacoemulsification with implantation of a posterior chamber intraocular lens.	Change in domain optical coherence tomography (OCT) macular cube central subfield thickness (CST), macular cube volume (VOL), and average macular tube thickness (AVG) at 1 month.	At 1 month, the VOL increased by 0.76 mm^3 in the placebo group (P<0.0001), by 0.43 mm^3 in the ketorolac group (P=0.0085), and by 0.48 mm^3 in the nepafenac group (P<0.0001). Similarly, the AVG increased by 21.2 microm (P<0.0001), 10.3 microm (P=0.0398), and 12.9 microm (P<0.0001) in the placebo, ketorolac, and nepafenac groups, respectively. For the CST at 1 month, there was an increase of 17.1 microm (P<0.0001) in the placebo group. In contrast, there was no significant increase in the CST in the ketorolac group (14.5 microm; P=0.0578) or the nepafenac group (10.2 microm; P=0.0578).	Good
Srinivasan M, et al.[4] 2012 MC, DB, PC, RCT	Prednisonlone sodium phosphate 1.0% (n=250) vs. placebo (n=250) as adjunctive therapy to topical moxifloxacin.	Culture-positive bacterial corneal ulcer (keratitis) receiving topical moxifloxacin for at least 48 hrs.	Best spectacle-corrected visual acuity (BSCVA) at 3 months from enrollment.	No significant difference was observed in the 3-month BSCVA between groups (95% CI, -0.085 to 0.068; p = 0.82)	Good
Wang, et al.[14] 2013 OL, RCT	Bromfenac 0.1% x1 month vs. bromfenac 0.1% x2 months vs. fluorometholone 0.1% x1 month vs. dexamethasone 0.1% x1 month.	Age-related cataract patients undergoing phacoemulsification with posterior chamber intra-ocular lens implantation	Not explicitly mentioned. Outcomes included Best corrected visual acuity, IOP, endothelial cell density, photon count value and retinal foveal thickness.	There were no significant differences in IOP among the groups at any time point duringthe follow-up period. There were also no significant differences in endothelial cell density among the groups at any time point. Flare, retinal foveal thickness and incidences of cystoid macular edema were significantly lower in the bromfenac groups than the other fluorometholone and dexamethasone groups.	Poor

Lane SS, et al.[15] 2013 MC, SB, RCT	Loteprednol etabonate (Lotemax) 0.5% (n=48) vs. prednisolone acetate (Pred Forte) 1.0% (n=45).	Routine post-operative cataract surgery patients	Not explicitly mentioned. Likely level of anterior chamber cell and flare intensity in patients treated with loteprednol etabonate or prednisolone acetate.	No significant difference in mean IOP or control of inflammation (based on cell and flare grading) at 1, 3, 7 and 21 days postoperatively.	Poor
Ray KJ, et al.[16] 2014 Subgroup Analysis of Srinivasan[4]	Prednisonlone sodium phosphate 1.0% to placebo as adjunctive therapy to topical moxifloxacin.	Culture-positive bacterial corneal ulcer (keratitis) receiving topical moxifloxacin for at least 48 hrs.	Timing of administration of prednisolone (after 2-3 days vs. 4 or more days after starting topical moxifloxacin) on best spectacle-corrected visual acuity (BSCVA) at 3 months from enrollment.	Adjunctive prednisolone given within 2-3 days after starting topical moxifloxacin yielded 1-line better visual acuity at 3 months than did those given placebo. No significant difference was seen when prednisolone was administered 4 days or more after starting the antibiotic.	N/A – subgroup analysis
Srinivasan M, et al.[17] 2014 Extension of Srinivasan[4]	Prednisonlone sodium phosphate 1.0% to placebo as adjunctive therapy to topical moxifloxacin.	Culture-positive bacterial corneal ulcer (keratitis) receiving topical moxifloxacin for at least 48 hrs.	BSCVA and scar size at 12 months.	No significant difference seen in visual acuity (BSCVA -0.04 logMAR; 95% CI, -0.12 to 0.05; p=0.39) or scar size (0.03 mm; 95% CI, -0.12 to 0.18 mm; p=0.69). A significant advantage with prednisolone was only observed for these two outcomes when infections caused by *Nocardia sp*. were omitted.	N/A – extension study
Celik T, et al.[18] 2014 MC, PC, RCT	Fluoromethalone 0.1% and olopatadine 0.01% (n=52) vs. ketorolac 0.4% and olopatadine 0.01% in one eye (n=52) and placebo in contralateral eye.	Patients with acute seasonal allergic conjunctivitis	Not explicitly stated. Clinical signs (chemosis, mucus secretion, eyelid edema) and symptoms (itching, redness, burning and tearing) were evaluated using a 3-point scale (0 pt=absent; 1 pt=mild; 2 pts=moderate; 3 pts=severe)	All parameters improved; albeit very little by day 1; however, a significant reduction in the clinical signs and symptoms were seen by day 10 compared with those receiving placebo. There was a statistically significant greater response in redness, mucus secretion, chemosis, and eyelid edema with the olopatadine-fluoromethalone group vs. the olopatadine-ketorolac group.	Poor
Price MO, et al.[19] 2014 OL, RCT	Prednisolone 1% (n=164 eyes) vs. fluorometholone 0.1% (n=161 eyes)	Descemet membrane endothelial keratoplasty (DMEK) corneal transplant recipients	The proportion of eyes that exceeded a defined IOP elevation threshold and the proportion of eyes that experienced an immunologic graft rejection episode	The proportion of eyes that exceeded the defined IOP elevation threshold (≥24 mm Hg or ≥10 mm Hg increase over preoperative reading) was 21.9% in the prednisolone arm versus 6.1% in the fluorometholone arm (RR 3.5; 95% CI, 1.7 to 7.1; p=0.00012). Among the eyes that completed the study on the assigned intervention, none (0%) assigned to prednisolone and 2 (1.4%) assigned to fluorometholone experienced a possible or probable graft rejection episode.	Fair

Sheppard J, et al.[20] 2014 MC, DB, PG, RCT	Difluprednate 0.05% (n=46) vs. prednisolone acetate 1% (n=47).	Patients ≥2 years of age with endogenous anterior uveitis in at least 1 eye.	A noninferiority study, assessing change from baseline to day 14 in anterior chamber cell grade.	The mean (SD) changes in anterior chamber cell grade from baseline to day 14 were -2.2 (1.0) (a mean decrease of 2.2 grades) for the difluprednate group and -2.0 (1.0) (mean decrease, 2.0 grades) for the prednisolone acetate group (p=0.16; mean difference, -0.22). Given that the upper boundary of the 95% confidence interval (-0.53 to 0.09) was less than 0.5, the primary end point of difluprednate 0.05% being noninferior to prednisolone acetate 1% was met.	Fair

Abbreviations: DB = double blind; IOP = intra-ocular pressure; MC = multi-center; PC = placebo controlled; PG = parallel group; RCT = Randomized controlled trial; RR = relative risk; SB = single blind; SC = single-center.

*Quality of each study is ranked as “Good”, “Fair” or “Poor” based on DURM Standard Methods for Quality Assessment and Grading the Evidence.

Appendix 3: Abstracts of Clinical Trials

Maca SM, Amon M, Findl O, et al. Efficacy and tolerability of preservative-free and preserved diclofenac and preserved ketorolac eyedrops after cataract surgery. *Am J Ophthalmol*, 2010.

Purpose: To compare the anti-inflammatory efficacy and subjective tolerability of preservative-free and preserved diclofenac 0.1% and preserved ketorolac 0.5% eye drops for prophylaxis and management of inflammation after cataract surgery.
Design: Prospective, randomized, investigator-masked, parallel-group, comparative clinical trial.
Methods: One hundred two patients who underwent small-incision phacoemulsification cataract surgery in an institutional setting were assigned randomly to receive preservative-free diclofenac sodium 0.1% (Voltaren ophtha SDU; Novartis Pharma), preserved diclofenac sodium 0.1% (Voltaren ophtha; Novartis Pharma), or preserved ketorolac tromethamine 0.5% (Acular; Pharm Allergan) eye drops 4 times daily for 4 weeks after surgery. During the 1-month follow-up, anterior chamber flare and mean foveal thickness were evaluated for objective comparison of the anti-inflammatory effect. Ocular tolerability was assessed by observer-based grading of conjunctival hyperemia and ocular discomfort, as well as obtaining subjective ratings of ocular tolerability on a visual analog scale. Distance and near visual acuity and intraocular pressure served as safety measures.
Results: All 3 formulations demonstrated equal anti-inflammatory efficacy as measured by reduction of anterior chamber flare after surgery and prevention of postoperative macular edema. Patients treated with preservative-free diclofenac eye drops reported significantly better subjective tolerability values ($P = .001$), were classified as having less ocular discomfort ($P < .001$), and experienced earlier reduction of postoperative conjunctival hyperemia ($P = .029$).
Conclusions: Anti-inflammatory efficacy was comparable for all 3 agents. However, preservative-free diclofenac 0.1% eyedrops exhibited a significantly better postoperative subjective and objective tolerability when compared with preserved eye drops containing ketorolac or diclofenac.

Foster CS, DaVanzo R, Flynn T, et al. Durezol (Difluprednate Ophthalmic Emulsion 0.05%) compared with Pred Forte 1% ophthalmic suspension in the treatment of endogenous anterior uveitis. *Journal of Ocular Pharmacology and Therapeutics*, 2010.

Purpose: The aim of this study was to evaluate the efficacy and safety of difluprednate ophthalmic solution 0.05% (Durezol; Alcon Laboratories, Fort Worth, TX) compared with prednisolone acetate ophthalmic suspension 1% (Pred Forte; Allergan, Inc., Irvine, CA) for endogenous anterior uveitis.
Methods: In this phase 3, multicenter, randomized, noninferiority trial, 90 patients with endogenous anterior uveitis [>10 anterior chamber (AC) cells and an AC flare score of ≥2 in at least 1 eye] received either difluprednate 4x/day (QID) (n=50) or prednisolone 8x/day (n=40) for 14 days, followed by a 2-week tapering regimen. The main outcome measure was change from baseline in AC cell grade on day 14.
Results: At day 14, mean AC cell grade improvement for difluprednate-treated patients was similar to prednisolone-treated patients (2.1 vs. 1.9, respectively), proving noninferiority. At day 14, 68.8% of difluprednate patients had AC cell clearing (grade 0: ≤1 cell) compared with 61.5% of prednisolone patients. In the prednisolone-treated group, 12.5% of patients were withdrawn because of investigator-determined lack of efficacy; no difluprednate-treated patients were withdrawn for this reason (P¼0.01). Clinically significant intraocular pressure elevation occurred in 3 difluprednate-treated patients (6.0%) and 2 prednisolone-treated patients (5.0%).
Conclusions: Difluprednate administered QID is at least as effective as prednisolone administered 8x/day in resolving the inflammation and pain associated with endogenous anterior uveitis. Difluprednate provides effective treatment for anterior uveitis and requires less frequent dosing than prednisolone acetate.

Donnenfeld ED, Holland EJ, Solomon KD, et al. A multicenter randomized controlled fellow eye trial of pulse-dosed difluprednate 0.05% versus prednisolone acetate 1% in cataract surgery. *Am J Ophthalmol*, 2011.

Purpose: To compare the effects of 2 corticosteroids on corneal thickness and visual acuity after cataract surgery.
Design: Multicenter, randomized, contralateral-eye, double-masked trial.
Methods: Fifty-two patients (104 eyes) underwent bilateral phacoemulsification. The first eye randomly received difluprednate 0.05% or prednisolone acetate 1%; the fellow eye received the alternative. Before surgery, 7 doses were administered over 2 hours; 3 additional doses were given after surgery, before discharge. For the remainder of the day, corticosteroids were administered every 2 hours, then 4 times daily during week 1 and twice daily during week 2. Corneal pachymetry, visual acuity, and corneal edema were evaluated before surgery and at days 1, 15, and 30 after surgery. Endothelial cell counts were evaluated before surgery and at 30 days after surgery. Retinal thickness was evaluated before surgery and at 15 and 30 days after surgery.
Results: Corneal thickness at day 1 was 33 µm less in difluprednate-treated eyes (P = .026). More eyes were without corneal edema in the difluprednate group than in the prednisolone group at day 1 (62% vs 38%, respectively; P = 0.019). Uncorrected and best-corrected visual acuity at day 1 were significantly better with difluprednate than prednisolone by 0.093 logMAR lines (P = .041) and 0.134 logMAR lines (P < .001), respectively. Endothelial cell density was 195.52 cells/mm(2) higher in difluprednate-treated eyes at day 30 (P < .001). Retinal thickness at day 15 was 7.74 µm less in difluprednate-treated eyes (P =0.011).
Conclusions: In this high-dose pulsed-therapy regimen, difluprednate reduced inflammation more effectively than prednisolone acetate, resulting in more rapid return of vision. Difluprednate was superior at protecting the cornea and reducing macular thickening after cataract surgery.

Miyake K, Ota I, Miyake G, et al. Nepafenac 0.1% versus fluorometholone 0.1% for preventing cystoid macular edema after cataract surgery. *J Cataract Refract Surg*, 2011.

Purpose: To compare a topical nonsteroidal antiinflammatory drug (nepafenac 0.1%) and a topical steroidal antiinflammatory drug (fluorometholone 0.1%) in preventing cystoid macular edema (CME) and blood-aqueous barrier (BAB) disruption after small-incision cataract extraction with foldable intraocular lens (IOL) implantation.
Setting: Shohzankai Medical Foundation, Miyake Eye Hospital, Nagoya, Japan.
Design: Randomized double-masked single-center clinical trial.
Methods: Patients were randomized to receive nepafenac 0.1% eyedrops or fluorometholone 0.1% eyedrops for 5 weeks after phacoemulsification with foldable IOL implantation. The incidence and severity of CME were evaluated by fluorescein angiography, retinal foveal thickness on optical coherence tomography, and BAB disruption on laser flare-cell photometry.
Results: Thirty patients received nepafenac and 29 patients, fluorometholone. Five weeks postoperatively, the incidence of fluorescein angiographic CME was significantly lower in the nepafenac group (14.3%) than in the fluorometholone group (81.5%) (P<.0001). The fovea was thinner in the nepafenac group than in the fluorometholone group at 2 weeks (P=.0266) and 5 weeks (P=.0055). At 1, 2, and 5 weeks, anterior chamber flare was significantly less in the nepafenac group than in the fluorometholone group (P<.0001, P<.0001, and P=.0304, respectively). The visual acuity recovery from baseline was significantly greater in the nepafenac group (80.0%) than in the fluorometholone group (55.2%) (P=.0395). There were no serious side effects in either group.
Conclusion: Nepafenac was more effective than fluorometholone in preventing angiographic CME and BAB disruption, and results indicate nepafenac leads to more rapid visual recovery.

Almeida D, Khan Z, Xing L, et al. Prophylactic nepafenac and ketorolac versus placebo in preventing postoperative macular edema after uneventful phacoemulsification. *J Cataract Refract Surg*, 2012.

Purpose: To evaluate the efficacy of prophylactic ketorolac 0.5% versus nepafenac 0.1% versus placebo on macular volume 1 month after uneventful phacoemulsification and evaluate the healthrelated quality-of-life (HRQOL) of topical nonsteroidal anti-inflammatory drugs (NSAIDs) in the context of cataract surgery.
Setting: Hotel Dieu Hospital, Kingston, Ontario, Canada.
Design: Prospective placebo-controlled parallel-assignment double-masked randomized clinical trial.
Methods: In this study, patients 18 years or older scheduled for routine phacoemulsification were randomized to a placebo, ketorolac 0.5%, or nepafenac 0.1% and dosed 4 times a day starting 1 day before surgery and continuing for 4 weeks. Spectral-domain macular cube ocular coherence tomography scans measuring central subfield thickness, macular cube volume, and average macular cube thickness were performed at baseline and 1 month postoperatively. The HRQOL metrics were determined with the Comparison of Ophthalmic Medications for Tolerability (COMTOL) questionnaire.
Results: Each study group comprised 54 patients. One month postoperatively, although a trend toward significance occurred for nepafenac and ketorolac, analysis of the means of differences showed no statistically significant differences between the 3 study groups (PZ.2901). The COMTOL analysis found no difference in tolerability, compliance, side-effect frequency and bother, and effects on HRQOL between ketorolac and nepafenac compared with the placebo.
Conclusions: One month after uneventful phacoemulsification, there was no difference in macular volume between the placebo, ketorolac, and nepafenac. Ketorolac and nepafenac were well tolerated with minimal side-effect profiles. Thus, for patients without risk factors having routine surgery, prophylactic topical NSAIDs are not recommended.

Srinivasan M, Mascarenhas J, Rajaraman R, et al. Corticosteroids for bacterial keratitis: the steroids for corneal ulcers trial (SCUT). *Arch Ophthalmol*, 2012.

Objective: To determine whether there is a benefit in clinical outcomes with the use of topical corticosteroids as adjunctive therapy in the treatment of bacterial corneal ulcers.
Methods: Randomized, placebo-controlled, double-masked, multicenter clinical trial comparing prednisolone sodium phosphate, 1.0%, to placebo as adjunctive therapy for the treatment of bacterial corneal ulcers. Eligible patients had a culture-positive bacterial corneal ulcer and received topical moxifloxacin for at least 48 hours before randomization.
Main outcome measures: The primary outcome was best spectacle-corrected visual acuity (BSCVA) at 3 months from enrollment. Secondary outcomes included infiltrate/scar size, reepithelialization, and corneal perforation.
Results: Between September 1, 2006, and February 22, 2010, 1769 patients were screened for the trial and 500 patients were enrolled. No significant difference was observed in the 3-month BSCVA (-0.009 logarithm of the minimum angle of resolution [logMAR]; 95% CI, -0.085 to 0.068; P = .82), infiltrate/scar size (P = .40), time to reepithelialization (P = .44), or corneal perforation (P > .99). A significant effect of corticosteroids was observed in subgroups of baseline BSCVA (P = .03) and ulcer location (P = .04). At 3 months, patients with vision of counting fingers or worse at baseline had 0.17 logMAR better visual acuity with corticosteroids (95% CI, -0.31 to -0.02; P = .03) compared with placebo, and patients with ulcers that were completely central at baseline had 0.20 logMAR better visual acuity with corticosteroids (-0.37 to -0.04; P = .02).
Conclusions: We found no overall difference in 3-month BSCVA and no safety concerns with adjunctive corticosteroid therapy for bacterial corneal ulcers.

Wang Q, Yao K, Xu W, et al. Bromfenac sodium 0.1%, fluorometholone 0.1% and dexamethasone 0.1% for control of ocular inflammation and prevention of cystoid macular edema after phacoemulsification. *Ophthalmologica*. 2013;229:187-194.

Purpose: To compare bromfenac sodium 0.1%, fluorometholone 0.1% and dexamethasone 0.1% for the control of postoperative inflammation and prevention of cystoid macular edema (CME) after phacoemulsification.
Methods: Patients were randomized to receive bromfenac sodium 0.1% for 1 month (OBS1) or 2 months (OBS2), or fluorometholone 0.1% for 1 month (OFM) or dexamethasone 0.1% for 1 month (ODM). Best-corrected visual acuity, intraocular pressure, endothelial cell density, photon count value and retinal foveal thickness were measured.
Results: Mean photon count values were lower in the OBS1 and OBS2 groups compared with the ODM group during the first week. Bromfenac sodium cleared the ocular inflammation more rapidly than fluorometholone and dexamethasone. The foveal thickness was thinner in the second month and the incidence of CME was lower in the OBS1 and OBS2 groups compared with the OFM and ODM groups.
Conclusion: Bromfenac sodium was more effective and safer than fluorometholone and dexamethasone as an anti-inflammatory, decreasing macular thickness and preventing CME in age-related cataract patients after cataract surgery.

Lane SS, Holland EJ. Loteprednol etabonate 0.5% versus prednisolone acetate 1.0% for the treatment of inflammation after cataract surgery. *J Cataract Refract Surg*, 2013.

Purpose: To evaluate the efficacy of loteprednol etabonate 0.5% versus prednisolone acetate 1.0% for the control of postoperative inflammation in patients having routine cataract surgery.
Methods: Patients were at least 18 years of age and scheduled for routine cataract surgery. Patients were excluded from the study if they had preexisting medical conditions (ie, elevated intraocular pressure [IOP], retinopathy, maculopathy, uveitis) or required medications the investigator believed would put the patient at risk or confound the study. Patients were randomized to receive loteprednol etabonate or prednisolone acetate 4 times daily in addition to bromfenac 0.09% and besifloxacin 0.6% after surgery. Visual acuity, IOP, and anterior chamber cell and flare intensity were assessed over 3 weeks after cataract surgery. The primary endpoint was the level of anterior chamber cell and flare intensity in patients treated with loteprednol etabonate or prednisolone acetate.
Results: The study enrolled 88 patients (46 loteprednol etabonate, 42 prednisolone acetate). Equivalency was achieved between the 2 treatment groups with no significant differences throughout the 3-week follow-up. There was less fluctuation in IOP assessments in patients treated with loteprednol etabonate than in patients treated with prednisolone acetate, in particular 1 day and 3 days postoperatively.
Conclusions: The results indicate that equivalent control of inflammation can be obtained through treatment with loteprednol etabonate or prednisolone acetate after cataract surgery. In addition, treatment with loteprednol etabonate may result in less IOP fluctuation.

Ray KJ, Srinivasan M, Mascarenhas J, et al. Early addition of topical corticosteroids in the treatment of bacterial keratitis. *JAMA Ophthalmol*, 2014.

Purpose: To determine whether topical corticosteroids are beneficial as an adjunctive therapy for bacterial keratitis if given early in the course of infection.
Design, Setting, and Participants: The Steroids for Corneal Ulcers Trial (SCUT) was a randomized, double-masked, placebo-controlled trial that overall found no effect of adding topical corticosteroids to topical moxifloxacin hydrochloride in bacterial keratitis. Here, we assess the timing of administration of corticosteroids in a subgroup analysis of the SCUT. We define earlier administration of corticosteroids (vs placebo) as addition after 2 to 3 days of topical antibiotics and later as addition after 4 or more days of topical antibiotics.

Main Outcomes and Measures: We assess the effect of topical corticosteroids (vs placebo) on 3-month best spectacle-corrected visual acuity in patients who received corticosteroids or placebo earlier vs later. Further analyses were performed for subgroups of patients with non-*Nocardia* keratitis and those with no topical antibiotic use before enrollment.
Results: Patients treated with topical corticosteroids as adjunctive therapy within 2 to 3 days of antibiotic therapy had approximately 1-line better visual acuity at 3 months than did those given placebo (–0.11 logMAR; 95%CI, –0.20 to –0.02 logMAR; P = .01). In patients who had 4 or more days of antibiotic therapy before corticosteroid treatment, the effect was not significant; patients given corticosteroids had 1-line worse visual acuity at 3 months compared with those in the placebo group (0.10 logMAR; 95%CI, –0.02 to 0.23 logMAR; p=0.14). Patients with non-*Nocardia* keratitis and those having no topical antibiotic use before the SCUT enrollment showed significant improvement in best spectacle-corrected visual acuity at 3 months if corticosteroids were administered earlier rather than later.
Conclusions and Relevance: There may be a benefit with adjunctive topical corticosteroids if application occurs earlier in the course of bacterial corneal ulcers.

Srinivasan M, Mascarenhas J, Rajaraman R, et al. The Steroids for Corneal Ulcers Trial (SCUT): secondary 12-month clinical outcomes of a randomized controlled trial. *Am J Ophthalmol*, 2014.

Purpose: To determine whether topical corticosteroids as adjunctive therapy for bacterial keratitis improves long-term clinical outcomes.
Methods: This multicenter trial compared 1.0% prednisolone sodium phosphate to placebo in the treatment of bacterial keratitis among 500 patients with culture positive ulcers receiving 48 hours of moxifloxacin before randomization. The primary endpoint was 3 months from enrollment, and 399 patients were evaluated at 12 months. The outcomes examined were best spectacle corrected visual acuity (BSCVA) and scar size at 12 months. Based on previous results, regression models with adjustments for baseline status and/or causative organism were used for analysis.
Results: No significant differences in clinical outcomes by treatment group were seen with the prespecified regression models (BSCVA: -0.04 logMAR, 95% CI, -0.12 to 0.05, P=0.39; scar size: 0.03 mm, 95% CI, -0.12 to 0.18, P=0.69). A regression model including a *Nocardia*-treatment arm interaction found corticosteroid use associated with a mean 1-line improvement in BSCVA at 12 months among patients with non-*Nocardia* ulcers (-0.10 logMAR, 95% CI, -0.19 to -0.02, P=0.02). No significant difference was observed in 12-month BSCVA for *Nocardia* ulcers (0.18 logMAR, 95% CI, -0.04 to 0.41, P=0.16). Corticosteroids were associated with larger mean scar size at 12 months among *Nocardia* ulcers (0.47 mm, 95% CI, 0.06-0.88, P=0.02) and no significant difference was identified by treatment for scar size for non-*Nocardia* ulcers (-0.06 mm, 95% CI, -0.21 to 0.10, P=0.46).
Conclusions: Adjunctive topical corticosteroid therapy may be associated with improved long-term clinical outcomes in bacterial corneal ulcers not caused by *Nocardia* species.

Celik T, Turkoglu EB. Comparative evaluation of olopatadine 0.01% combined with fluorometholone 0.1% treatment versus olopatadine 0.01% combined with ketorolac 0.4% treatment in patients with acute seasonal allergic conjunctivitis. *Current Eye Research*, 2014.

Purpose: To evaluate the therapeutic effects of low-effective steroid fluorometholone 0.1% and non-steroidal anti-inflammatory ketorolac 0.4% when concomitantly used with olopatadine 0.01% in relieving clinical signs and symptoms of acute seasonal allergic conjunctivitis (SAC).
Methods: In this randomized, placebo-controlled, multi-center study, 104 eyes of 52 patients with the diagnosis of SAC were conducted. The patients were assigned into two groups to receive either olopatadine and fluorometholone one eye and placebo in the contralateral eye or olopatadine and ketorolac one eye and placebo in the contralateral. The clinical signs (chemosis, mucus secretion, eyelid edema) and symptoms (itching, redness, tearing, burning) of the patients

were evaluated by summing up the scores using a 3-point scale. Results were analyzed by Mann-Whitney U test, p values less than 0.05 were defined as significant.
Results: All parameters were improved less amount on the first day of the treatment in both groups, however, significant reduction in clinical signs and symptoms were seen on the 10th day compared with those receiving placebo. Fluorometholone was found superior to ketorolac in reducing redness, mucus secretion, chemosis and eyelid edema ($p = 0.032$ for redness, $p = 0.028$ for mucus secretion, $p = 0.030$ for chemosis, $p = 0.042$ for eyelid edema) and both drugs were similar in alleviating the symptoms itching, burning and tearing ($p = 0.074$ for itching, $p = 0.064$ for burning, $p = 0.072$ for tearing).
Conclusions: Fluorometholone was better than ketorolac in relieving redness, chemosis, mucus secretion and eyelid edema when concomitantly used with olopatadine, however, these two drugs were found equal in attenuating the symptoms itching, burning and tearing.

Price M, Price F, Kruse F, et al. Randomized comparison of topical prednisolone acetate 1% versus fluorometholone 0.1% in the first year after Descemet membrane endothelial keratoplasty. *Cornea*, 2014.

Purpose: The aim of this study was to compare the efficacy and side effects of prednisolone acetate 1% versus fluorometholone 0.1% after Descemet membrane endothelial keratoplasty (DMEK).
Methods: DMEK recipients used prednisolone acetate 1% for 1 month, and they were randomized to either prednisolone or fluorometholone for months 2 through 12. Dosing was 4 times daily in months 1 to 3, thrice daily in month 4, twice daily in month 5, and once daily in months 6 to 12. The main outcomes were immunologic rejection episodes and intraocular pressure (IOP) elevation (defined as ≥24 mm Hg or ≥10 mm Hg increase over the preoperative baseline level), assessed by the Kaplan–Meier survival analysis.
Results: The study included 325 eyes (99% were white, 96% had Fuchs dystrophy, and 9% had a previous glaucoma diagnosis). No eyes (0%) assigned to prednisolone versus 2 eyes (1.4%) assigned to fluorometholone experienced a possible (n = 1) or probable (n = 1) rejection episode (P = 0.17). Both rejection episodes resolved successfully with increased topical steroids. In the prednisolone arm, a significantly higher proportion exceeded the defined IOP elevation threshold (22% vs. 6%, P = 0.0005), and glaucoma medications were initiated or increased more often (17% vs. 5%, P = 0.0003). The most frequent reasons for discontinuing the assigned intervention were IOP management (n = 13 eyes assigned to prednisolone) or inflammation management (n = 3 eyes assigned to fluorometholone). One-year endothelial cell loss was comparable in both arms (30% vs. 31%, P = 0.50).
Conclusions: DMEK has a remarkably low rejection episode rate (<1% through 1 year), as confirmed in this prospective randomized study. This provides a unique opportunity to reduce postoperative topical corticosteroid strength and thereby reduce the risk of steroid-associated complications.

Sheppard JD, Toyos MM, Kempen JH, et al. Defluprednate 0.05% versus prednisolone acetate 1% for endogenous anterior uveitis: a phase III, multicenter, randomized study. *Investigative Ophthalmology & Visual Science*, 2014.

Purpose: Endogenous anterior uveitis (AU), when untreated, may lead to vision loss. This study compared the safety and efficacy of difluprednate versus prednisolone acetate for the treatment of this condition.
Methods: This phase III, double-masked, noninferiority study randomized patients with mild to moderate endogenous AU to receive difluprednate 0.05% (n=56) four times daily, alternating with vehicle four times daily, or prednisolone acetate 1% (n=54) eight times daily. The 14-day treatment period was followed by a 14-day dose-tapering period and a 14-day observation period. The primary efficacy end point was change in anterior chamber cell grade (range, 0 for 1 cell to 4 for >50 cells) from baseline to day 14.

Results: At day 14, the mean change in anterior chamber cell grade with difluprednate was noninferior to that with prednisolone acetate -2.2 vs. -2.0, p=0.16). The proportions of difluprednate-treated patients versus prednisolone acetate–treated patients demonstrating complete clearing of anterior chamber cells at day 3 were 13.0% vs. 2.1% (p=0.046) and at day 21 were 73.9% vs. 63.8% (p=0.013). A significant between-group difference in the mean IOP increase was seen at day 3 (2.5 mm Hg for difluprednate-treated patients and 0.1 mm Hg for prednisolone acetate–treated patients, p=0.0013) but not at other time points. The mean IOP values in both groups remained less than 21 mm Hg throughout the study.
Conclusions: Difluprednate 0.05% four times daily is well tolerated and is noninferior to prednisolone acetate 1% eight times daily for the treatment of endogenous AU.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to February Week 2 2015

1 exp Dexamethasone/ 21442
2 exp Fluorometholone/ 152
3 loteprednol.mp. 93
4 exp Prednisolone/ 21144
5 difluprednate.mp. 26
6 exp Fluocinolone Acetonide/ 378
7 rimexolone.mp. 35
8 exp Anti-Inflammatory Agents/ or exp Glucocorticoids/ 218574
9 1 or 2 or 3 or 4 or 5 or 6 or 7 42422
10 exp Diclofenac/ 4525
11 exp Flurbiprofen/ 831
12 exp Ketorolac Tromethamine/ or exp Ketorolac/ 1222
13 bromfenac.mp. 112
14 nepafenac.mp. 70
15 exp Triamcinolone/ 3763
16 exp Anti-Inflammatory Agents, Non-Steroidal/ 87571
17 10 or 11 or 12 or 14 or 15 10240
18 9 or 17 52120
19 exp Ophthalmic Solutions/ or exp Administration, Ophthalmic/ or ophthalmic.mp. 19650
20 exp Uveitis, Anterior/ or exp Uveitis, Suppurative/ or exp Uveitis/ or exp Uveitis, Posterior/ or exp Uveitis, Intermediate/ 12485
21 exp Conjunctivitis/ or exp Conjunctivitis, Allergic/ 6337
22 exp Cataract Extraction/ or exp Cataract/ 21829
23 19 or 20 or 21 or 22 56520
24 18 and 23 2237
25 limit 24 to (yr="2010 -Current" and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or randomized controlled trial)) 186