Inhibition of Neovascularization but Not Fibrosis With the Fluocinolone Acetonide Implant in Autosomal Dominant Neovascular Inflammatory Vitreoretinopathy

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Objective: To review the effect of the fluocinolone acetonide implant in subjects with autosomal dominant neovascular inflammatory vitreoretinopathy (ADNIV), an inherited autoimmune uveitis.

Methods: A retrospective case series was assembled from patients with ADNIV who received fluocinolone acetonide implants. Visual acuity and features of ADNIV, including inflammatory cells, neovascularization, fibrosis, and cystoid macular edema, were reviewed.

Results: Nine eyes of 5 related patients with ADNIV with uncontrolled inflammation were reviewed. Follow-up ranged from 21.7 to 56.7 months. Visual acuity at implantation ranged from 20/40 to hand motion. Preoperatively, 8 eyes had vitreous cells (a ninth had diffuse vitreous hemorrhage). Eight eyes had cystoid macular edema, 7 had an epiretinal membrane, and 3 had retinal neovascularization. Following implantation, vitreous cells resolved in all eyes and neovascularization regressed or failed to develop. Central macular thickness improved in 4 eyes. During the postoperative course, however, visual acuity continued to deteriorate, with visual acuity at the most recent examination ranging from 20/60 to no light perception. There was also progressive intraocular fibrosis and phthisis in 1 case. Four eyes underwent cataract surgery. Six of the 7 eyes without previous glaucoma surgery had elevated intraocular pressure at some point, and 3 of these required glaucoma surgery.

Conclusions: The fluocinolone acetonide implant may inhibit specific features of ADNIV such as inflammatory cells and neovascularization but does not stabilize long-term vision, retinal thickening, or fibrosis. All eyes in this series required cataract extraction, and more than half required surgical intervention for glaucoma. Further studies may identify additional therapies and any benefit of earlier implantation.

ular infiltrates seem to involve only the eye, and it is not clear whether a local or systemic aberrant immune cell–mediated process triggers the ocular damage. Past treatments have included periocular or intraocular corticosteroid injections. In other types of posterior uveitis, local administration of steroid can reduce the need for systemic therapy, limit inflammatory activity, and reverse macular edema or macular hyperfluorescence on fluorescein angiography. There are also reports that suggest a potential benefit for intravitreal steroids in retinal neovascularization and proliferative vitreoretinopathy. The benefit of corticosteroid injections in ADNIV is limited, however, because the condition causes chronic active inflammation.

The fluocinolone acetonide (FA) implant (Retisert; Bausch & Lomb) provides continuous release of intraocular corticosteroid for approximately 2.5 years. It is surgically implanted through the pars plana into the vitreous and sutured to the sclera. Large multicentered clinical trials of noninfectious posterior uveitis demonstrated that this device was effective in controlling intraocular inflammation and reducing the need for systemic and local therapy. Although the original trials did not report the exact types of uveitis, we have had success using this implant in selected patients with specific types of severe uveitis such as sympathetic ophthalmitis. The FA implants were also recently shown to reverse features of diabetic retinopathy. Patients with ADNIV have responded poorly to conventional nonsteroidal oral immunosuppressive medications. Periocular and intravitreal steroids may be used but require injections at regular intervals to control inflammation and cystoid macular edema. In this study, we describe our experience using the FA implant in patients with ADNIV to try to delay or even halt the progression of this blinding disease.

The study was approved by the Institutional Review Board for Human Subjects Research at the University of Iowa, was compliant with the Health Insurance Portability and Accountability Act, and adhered to the tenets of the Declaration of Helsinki. A retrospective case series was assembled from the medical records of patients with ADNIV from the University of Iowa. All preoperative and postoperative clinical examinations were performed by vitreoretinal specialists (J.C.F. and V.B.M.). The diagnosis of ADNIV was made based on family history, pedigree review, and genetic mapping. All patients had inflammation in the vitreous; all patients had no other evidence of an infection; and all patients had negative tuberculosis skin test results. All visual acuities were best-corrected Snellen acuities. No standardized refractions or visual acuity measurements were used. A recurrence of inflammation after implantation was diagnosed by inflamm-
Measurements were compared with published data. In an effort to standardize OCT data from the alternate OCT equipment, central subfield macular thickness measurements were obtained using the Topcon TRC 50DX camera (Topcon). Images were viewed with OIS WinStation 5000 version 10.5.7 (Merge Healthcare). Over the course of the study period, optical coherence tomography (OCT) imaging was obtained from the spectral-domain Heidelberg HRA2 Spectralis, version 1.6.1 (Heidelberg Engineering Inc) and Cirrus (Carl Zeiss Meditec), as well as the time-domain Stratus (Carl Zeiss Meditec). In an effort to standardize OCT data from the alternate OCT equipment, central subfield macular thickness measurements were compared with published data.23,24

RESULTS

Implantation was performed in 9 eyes of 5 patients in 2 related families with ADNIV (Figure 1). Patient ages ranged from 24 years to 53 years. There were 4 women and 1 man, 4 right eyes, and 5 left eyes (Table 2). Observed intraocular features prior to surgery included vitreous cells (8 of 9; the ninth had diffuse vitreous hemorrhage), cystoid macular edema (8 of 9), retinal neovascularization (3 of 9), vitreous hemorrhage (2 of 9), epiretinal membrane as evident on OCT (7 of 9), tractional retinal detachment (1 of 9), opacified vitreous secondary to uveitis (6 of 9), and pigmentary retinal degeneration (9 of 9). Glaucoma was present in 3 of 9 eyes, which was managed by topical medications in 1 eye (patient 4, left eye), and 1 man, 4 right eyes, and 5 left eyes (Table 2). Observed intraocular features prior to surgery included vitreous cells (8 of 9; the ninth had diffuse vitreous hemorrhage), cystoid macular edema (8 of 9), retinal neovascularization (3 of 9), vitreous hemorrhage (2 of 9), epiretinal membrane as evident on OCT (7 of 9), tractional retinal detachment (1 of 9), opacified vitreous secondary to uveitis (6 of 9), and pigmentary retinal degeneration (9 of 9). Glaucoma was present in 3 of 9 eyes, which was managed by topical medications in 1 eye (patient 4, left eye),

### Table 2. Summary of Clinical Findings

| Patient No./Sex/Age, y | Eye | Examination | Preop | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 | 54 |
|------------------------|-----|-------------|-------|---|---|---|---|---|---|---|---|---|---|
| 1/M/24 OD | LogMAR VA; Snellen VA; OCT | 0.70; 20/100 | 0.90; 20/250 | 0.70; 20/200 | 0.70; 20/100 | 0.80; 20/200 | 0.70; 20/100 | 0.70; 20/100 | 0.70; 20/100 | 0.70; 20/100 | 0.70; 20/100 | 0.60; 20/100 |
| 2/F/44 OD | LogMAR VA; Snellen VA; OCT | 0.30; 20/40 | 0.40; 20/50 | 0.40; 20/50 | 0.40; 20/50 | 0.40; 20/50 | 0.40; 20/50 | 0.40; 20/50 | 0.40; 20/50 | 0.40; 20/50 | 0.40; 20/50 | 0.48; 20/50 |
| 3/F/36 OD | LogMAR VA; Snellen VA; OCT | 1.20; 20/30 | 1.00; 20/20 | 1.10; 20/20 | 1.10; 20/20 | 1.30; 20/20 | 1.30; 20/20 | 1.10; 20/20 | 1.10; 20/20 | 1.10; 20/20 | 1.10; 20/20 | 1.10; 20/20 |
| 4/F/38 OD | LogMAR VA; Snellen VA; OCT | 0.40; 20/50 | 0.40; 20/50 | 0.70; 20/50 | NA; 20/50 | 1.10; 20/50 | 1.10; 20/50 | 1.10; 20/50 | 1.10; 20/50 | 1.10; 20/50 | 1.10; 20/50 | 1.10; 20/50 |
| 5/F/53 OS | LogMAR VA; Snellen VA; OCT | 3.00; HM; 20/30 | 3.00; HM; 20/30 | 3.00; HM; 20/30 | 3.00; HM; 20/30 | 3.00; HM; 20/30 | 3.00; HM; 20/30 | 3.00; HM; 20/30 | 3.00; HM; 20/30 | 3.00; HM; 20/30 | 3.00; HM; 20/30 | 3.00; HM; 20/30 |

Abbreviations: HM, hand motion; NA, not available; OCT, optical coherence tomography; Preop, preoperative; VA, visual acuity; VH, vitreous hemorrhage; Vit cells, vitreous cells.

a The age at which the fluocinolone acetonide implant was first placed.

b Data from the month prior to implantation.

c Uncomplicated cataract surgery was performed during the preceding interval, as well as intravitreal injections of bevacizumab and triamcinolone acetonide.

d Data are presented in micrometers (micrometers greater than normative published mean for the imaging equipment and software used).

e Uncomplicated cataract surgery performed during the preceding interval.

f Uncomplicated cataract surgery performed with (in the right eye) and without (in the left eye) intravitreal injection of triamcinolone acetonide during the preceding interval.

g Intravitreal bevacizumab administered during the preceding interval.
prior trabeculectomy in 1 eye (patient 3, right eye), and simultaneous trabeculectomy at the time of FA implant placement in 1 case (patient 3, left eye). Three eyes underwent removal and reimplantation of an exhausted FA implant with evidence of increased inflammatory activity (patient 3, right eye [29 months]; patient 3, left eye [26 months]; and patient 1, left eye [36 months]), whereas 1 required removal and reimplantation during wound revision 6 months after the primary implantation (patient 4, left eye), and another attempted removal and reimplantation failed because of poor intraoperative visualization with concern that the implant was beneath a traction detachment of the retina in the inferior periphery (patient 2, left eye [40 months]). In patient 1, the implant has been in place in the right eye for 53 months, and in patient 2, the implant has been in place in the right eye for 56.7 months, without need for replacement. Follow-up data for the primary implant of 21.7 months or greater were available in all patients (range, 21.7-56.7 months after insertion). The case of patient 1 is described in Figure 2.

Surgical objectives in placement of the primary FA implant were achieved in all eyes. Posterior segment complications such as retinal tear or dialysis, retinal detachment, suprachoroidal effusion or hemorrhage, or endophthalmitis were not observed during surgery or the immediate postoperative period. Late postoperative events included an intravitreal injection of vancomycin and ceftazidime 6 months after implantation in 1 eye (patient 3, left eye) that presented with sudden onset of pain, increased inflammation, and decreased vision. This eye had also previously undergone a trabeculectomy, but culture results were negative, and vision, inflammation, and OCT parameters returned to baseline shortly after the event, strongly suggesting a sterile inflammation. In another eye (patient 5, left eye), there was progressive posterior segment fibrosis that required surgery 4.2 months after primary implantation, during which extensive anterior intraocular scarring incorporating the implant was discovered. This implant was removed and the vitreous and membranes were peeled, resulting in 1 small hole in the superior retinal periphery. The eye developed a massive fibrin response that did not respond to 4 mg of intravitreal triamcinolone acetonide. The eye became hypotonous and subsequently phthisical. Another eye (patient 4, left eye) required multiple revisions of the wound and eventual exchange of the implant at 5 months because of exposure of the implant.

Preoperative visual acuity ranged from 20/40 to hand motion, and postoperative visual acuity at the most recent follow-up ranged from 20/60 to no light perception in the phthisical eye (patient 5, left eye). The 4 eyes that remained phakic after initial implantation subsequently underwent cataract surgery.

Vitreous cells resolved in all eyes except the one with a fibrin response (patient 5, left eye). Although there was no clear trend for improvement or worsening of cystoid macular edema, 6 of the 9 eyes progressively worsened in visual acuity over their postoperative period. The 3 eyes demonstrating an improvement of visual acuity at their last postoperative visit improved from 20/100 to 20/80 (patient 1, right eye), 20/230 to 20/200 (patient 2, left eye), and 20/320 to 20/250 (patient 3, right eye) (Table 2). One of these eyes (patient 3, right eye) also received multiple intravitreal injections of bevacizumab (Avastin; Genentech), while patient 1 received a single intravitreal injection in the right eye of both bevacizumab and triamcinolone acetonide, 4 mg (Kenalog-40; Bristol-Myers Squibb). The degree of thickening on OCT did not reliably correspond to visual acuity measurements (Table 2). None of the eyes achieved a central macular thickness equal to or less than the published normative means at any time during the study period.22,24

We have carefully examined more than 90 patients with ADNIV. All but 1 patient developed proliferative neovascularization (stage III disease). Stage III disease usually develops during the third or fourth decades but can start earlier in some cases. Panretinal laser photocoagulation with careful treatment to the ora does not cause resolution of the neovascularization.6 In this series, 3 eyes demonstrated evidence of retinal neovascularization at the time of implantation (patient 5, left eye; patient 1, right eye; and patient 1, left eye). The neovascularization regressed in 2 of the eyes after device implantation and panretinal laser photocoagulation, although 1 eye (patient 1, right eye) had also received 1 dose of intravitreal bevacizumab. The third eye (patient 5, left eye) developed progressive posterior segment fibrosis and eventual phthisis. Neovascularization has not developed in the 6 eyes without evidence of new vessels at the time of initial implantation.

Each of the 6 eyes with visual potential and no previous glaucoma surgery demonstrated elevated intraocular pressure following implantation. Three underwent glaucoma surgery (patient 4, left eye; patient 1, right eye; and patient 1, left eye), 1 was prescribed long-term topical intraocular pressure–lowering medication (patient 4, right eye), and 2 required topical therapy for a limited time (patient 2, right eye and patient 2, left eye).

Treatment with systemic immunomodulatory agents was attempted in 4 patients but appeared to have no effect, so only 2 patients continued therapy at the time of implantation. At the time of implantation, patient 5 was treated with 200 mg of azathioprine and 5 mg of prednisone daily. The azathioprine was discontinued soon after surgery, and the prednisone was discontinued after the eye proceeded toward phthisis. Patient 1 was initially taking 60 mg of oral prednisone, but this was tapered and discontinued soon after implantation (patient 1, left eye). This patient was treated briefly with oral prednisone for all subsequent intraocular procedures (both eyes) and for a brief time while exhibiting evidence of a mild central retinal vein occlusion (right eye). Patients 2, 3, and 4 were not treated with further systemic immunomodulation at any time.

**COMMENT**

Although the number of eyes described in this report is limited, they all share an identical genetic defect and provide a unique insight into uveitis therapy. Autosomal dominant neovascular inflammatory vitreoretinopathy is a difficult condition to treat because the inflammation is often severe and chronic, neovascularization devel-
ops leading to hemorrhage, fibrosis causes traction retinal detachments, and there is an ongoing retinal degeneration. Immunohistopathological findings support the concept that an underlying ocular immune dysfunction is present in these eyes. Profound vision loss results from photoreceptor degeneration, cataract, cystoid macular edema, vitreous hemorrhage, dense membrane formation leading to tractional retinal detachment, and neovascular glaucoma. Patients universally undergo early cataract surgery and many require glaucoma surgery. By stage III disease, however, retinal neovascularization develops at the disc and retinal periphery, and patients seem to pass a point of no return with complications leading to complete blindness and phthisis bulbi. There is only

Figure 2. Autosomal dominant neovascular inflammatory vitreoretinopathy (ADNIV) case report. A, An electroretinogram showing a diminished b-wave helped diagnose patient 1 with ADNIV at age 17 years. B and C, Composite fundus drawings show vitreoretinal pathology overlaid with treatment that took place over several years beginning at age 21 years when the patient’s visual acuity (VA) was 20/100 OU. He developed aggressive ADNIV with cystoid macular edema (CME), epiretinal membrane, and small punctate areas of peripheral neovascularization and vitreous hemorrhage in the right eye. There was a central vitreous hemorrhage secondary to neovascularization of the disc with a VA of counting fingers OS. Traction was noted in the periphery in the left eye. Both eyes showed characteristic peripheral pigmentary changes. Oral steroids and panretinal scatter photocoagulation (PRP) initially stabilized the patient to 20/30 OD and 20/50 OS. He subsequently lost vision because of continuous inflammation, CME, and recurrent vitreous hemorrhage while taking steroid-sparing agents over the next 2 years, including methotrexate and infliximab, and moderate doses of prednisone. At age 24 years, fluocinolone acetonide implants were placed in each eye. NVD indicates neovascularization of the disc; NVE, neovascularization elsewhere; OD, right eye; and OS, left eye. D, Preoperative fundus image of the right eye shows an epiretinal membrane and CME (VA 20/100). E, Cystoid macular edema was confirmed by fluorescein angiography. F, Postoperative fundus image shows worsening membrane in the right eye. G and H, Preoperative and postoperative optical coherence tomography (OCT) shows CME that resolved soon after device implantation. Within 1 month after surgery, a mild central retinal vein occlusion developed, and the patient was treated with oral steroids. A small area of retinal neovascularization was noted at that time, precipitating a dose of intravitreal bevacizumab and further laser photocoagulation. All vascular changes regressed in 6 months. Cataract surgery and trabeculectomy were performed in the right eye 1 and 2 years after implant placement, respectively. The right eye also required a laser peripheral iridotomy for pupillary block, but inflammation was controlled nearly 4 years after device implantation without need for replacement. I, Preoperative fundus image of the left eye shows regressed NVD, preretinal fibrosis, and an epiretinal membrane. J, Findings consistent with recurrent CME are apparent on preoperative fluorescein angiography. K, Postoperative fundus image shows progressive fibrosis in the left eye. L, The immediate postoperative OCT shows early tractional membranes superiorly (right side of OCT), without traction on the fovea or significant CME. M, Postoperative OCT shows increased tractional membranes. Implantation in the left eye was followed nearly immediately by elevated intraocular pressure that was controlled initially with topical glaucoma medication. Initially, the VA stabilized to 20/60 OS without recurrent CME, neovascularization, or hemorrhage. One year later, cataract surgery was performed, and 2 years later the implant was replaced and a trabeculectomy was performed. The only systemic immunomodulatory medications this patient received at any time after initial implant surgeries were short courses of prednisone for a mild central retinal vein occlusion in the right eye and any subsequent intraocular surgeries. Despite control of neovascularization and vitreous cells, there was worsening of preretinal fibrosis and tractional membranes and deterioration of VA to 20/80 OD and 20/200 OS.
a partial response to laser photocoagulation of the peripheral retina to neovascularization of the retina and iris. Although vitrectomy surgery repaired several detachments in the original report, long-term results have been disappointing, with recurrent membranes and detachments. Implantation with the FA device can reduce the need for systemic therapy, but systemic medication, including oral steroids, methotrexate, and anti-tumor necrosis factor agents and other nonsteroids, has shown either limited or no benefit in patients with ADNIV (J.C.F. and V.B.M., unpublished data, 2001-2011). The observation that the FA implant causes resolution of neovascularization is important, however. Only 1 patient from among the more than 90 we have examined never developed neovascularization even into her ninth decade; she had severely restricted visual fields and 20/400 visual acuity in both eyes. She is the only patient, however, who did not develop no light perception visual acuity in both eyes by the eighth decade. Thus, the FA implant may limit the neovascular changes and alter the course of ADNIV into that of other more common retinal degenerations that develop constricted visual fields but retain limited vision in the center.

Although the inflammatory uveitis response of the patients with ADNIV may be similar to cases of severe idiopathic posterior uveitis, the visual outcome of patients with ADNIV is worse than published reports of other posterior uveitides treated with the FA implant. Patel and colleagues, in their report examining the treatment of pediatric uveitis, reported that inflammation was well controlled in all eyes, while Pavesio et al demonstrated a delayed onset of uveitis recurrence and lower onset of recurrence compared with standard therapy (18.2% vs 63.5%). Callanan et al demonstrated that recurrence of inflammation during the year prior to implantation with a 0.59-mg FA device was 62% vs 4%, 10%, and 20% at 1, 2, and 3 years postimplantation, respectively. Pavesio and colleagues demonstrated that mean visual acuity decreased transiently relative to the patient’s baseline immediately after surgery and from 15 to 21 months but was otherwise at baseline by 24 months after surgery.

Patel et al found that 3 of 6 eyes improved at least 3 lines while being followed up to 39 months. Callanan et al found that FA implants improved, or at least stabilized, eyes with posterior uveitis. One of the 9 eyes with ADNIV that were given the FA implant developed visual acuity of no light perception and only 2 had vision at 24 months that was equal to or better than the immediate preimplantation vision (patient 1, right eye and patient 2, left eye). Therefore, ADNIV eyes did worse than eyes with other types of uveitis. Our study does not address whether implantation during earlier stages of ADNIV might show improved visual acuity benefit.

Previous reports have shown FA implants to be efficacious in controlling inflammation, but the implant almost universally causes cataracts and many eyes develop elevated intraocular pressure. Two studies reported that 45% and 40% of eyes with FA implants needed glaucoma surgery. Other studies reported that 21.2% and 26.2% required glaucoma surgery. Five of 9 eyes in this study required glaucoma surgery. Two of the 9 eyes had received glaucoma surgery prior to implantation and 3 additional eyes required glaucoma surgery after implantation. Another eye in this study has required long-term topical pressure-lowering drops. Previous reports stated that 80.4% to 93% of patients with phakic eyes will require cataract surgery after implantation. All 4 eyes with ADNIV in this report that remained phakic after the initial implantation required cataract surgery. One eye that underwent FA implant placement subsequently required vitrectomy surgery for severe preretinal membranes and a tractional retinal detachment. This eye developed a severe fibrin response and became phthisical (patient 5, left eye). There is a report of the formation of visually significant vitreous bands after FA implant placement requiring further surgery.

One possible explanation for understanding the pathological processes in ADNIV is that the constellation of findings is all a consequence of ocular inflammation. The observations herein suggest otherwise. Implantation of the FA device reversed vitreous cells and neovascularization and prevented future neovascularization, which did not develop in any previous unaffected eyes. However, cystoid macular edema on OCT did not change consistently over the long-term, and visual acuity results, while better than the previously described course of vision in ADNIV eyes, did not stabilize as had been hoped, indicating the possibility that photoreceptors continue degenerating even when cystoid macular edema is under control. Electroretinography demonstrates early retinal and photoreceptor dysfunction. Interestingly, the fibrotic response progressed despite inflammatory control with the development of proliferative vitreoretinopathy, which even required explantation in the most severe case. If, however, the FA implant prevents neovascularization and alters the course of ADNIV toward that seen in more common pigmented retinal degeneration, this would be of benefit. Older patients with ADNIV may then retain at least some vision instead of losing light perception progressing to phthisis in both eyes. Although the rate of later fibrotic complications after FA device implantation may be higher in patients with ADNIV than in other types of posterior uveitis, the benefits of FA device implantation still outweigh its accompanying risks.

Prolonged inflammatory suppression with the FA implant only partially controls the disease progression in ADNIV. Although the exact mechanisms of immune suppression are not known, steroid-based transcriptional regulation within the eye may be sufficient to inhibit cytokine signals that activate the cell-mediated immune responses and neovascularization, but not photoreceptor death or intraocular fibrosis. Effectively targeting each pathway may require different therapeutic modalities, and the study of patients with ADNIV may reveal the molecular signals involved in vitreous inflammation, retinal neovascularization, photoreceptor degeneration, and proliferative vitreoretinopathy.

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