Travoprost Timing: Let Patients Choose

Though most once-daily prostaglandin analogues are prescribed for the evening, researchers in Canada report that when it comes to adherence and intraocular pressure (IOP) control, patients do just as well taking their medication in the morning.[1] In fact, patients prefer morning dosing.

The study involved 30 patients (16 men, 14 women, mean age 68 years) who were newly diagnosed with glaucoma or ocular hypertension and required IOP reduction. Patients were recruited from the authors' private practices and then randomized to morning (8 a.m. to noon) or evening (8 p.m. to midnight) administration of the prostaglandin travoprost. At the end of one month, patients crossed over to the opposite schedule for another month.

When the authors looked at the effect of timing of drug administration on IOP, they found a small but not significant difference favoring evening dosing: Pressures were 15.9 mmHg for dosing at night vs. 16.4 mmHg when used in the morning. (Pressures were measured during office hours.)

As for adherence—defined as the number of times a patient properly took medication over the prescribed time frame—the researchers wanted to know whether administration early or later in the day had an effect. They tracked adherence with an automated dosing aid that records the date and time the bottle is squeezed to dispense a drop.

MORNING OR EVENING? One study shows that patients prefer to take once-daily travoprost drops in the morning and that this regimen results in better adherence, though the latter finding is statistically significant only among men.

Overall, adherence was high—89.3 percent—said Bryce A. Ford, MD, FRCSC, clinical assistant professor of ophthalmology at the University of Calgary. But it did decline from 91.7 percent in the first month to 86.5 percent the next. Most studies show much lower numbers, he said, and he attributed the success rate to the patients being newly diagnosed with glaucoma.

Still, patients preferred morning dosing. Asked to rate the convenience of the dosing schedules on a 5-point scale, 80 percent gave a score of 4 or 5 to morning dosing. Only 40 percent rated evening dosing that high.

At the end of the study, patients who remained on travoprost were allowed to choose morning or evening dosing. One year later, 62 percent of patients still on travoprost monotherapy took drops in the morning, compared with 38 percent in the evening.

While there was a tendency overall toward better adherence in the morning (90.9 percent) than in the evening (87.3 percent), it just missed statistical significance, said Dr. Ford. In men, however, morning adherence was statistically significantly greater. Women were equally adherent day or night. There was no obvi-

ous reason for the gender difference, according to the authors.

In the past, Dr. Ford always suggested evening dosing because early studies on latanoprost showed greater effectiveness at that time of day. However, he said that medication works only if the patient takes it, so better adherence is more important than minimal differences in efficacy between dosing regimens. "Now I ask patients which time they think would be most convenient for them." —*Miriam Karmel*

1 Ford BA et al. *J Glaucoma.* 2013;22(1):1-4.

***Dr. Ford** is a consultant to Allergan and Alcon.*

Retina Report

Anti-VEGF Therapy Linked to RPE Atrophy

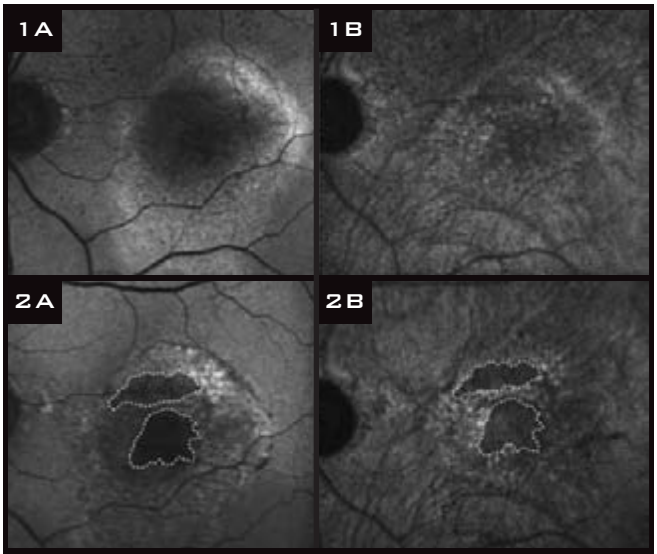
Retinal pigment epithelial (RPE) cell loss may occur in the wake of anti–vascular endothelial growth factor (VEGF) therapy for exudative age-related macular degeneration (AMD). When this happens, it's reasonable to conclude that a more aggressive disease has taken root. Researchers in Scotland, however, recently pursued another plausible theory: This deleterious effect might be linked to the treatment itself.[1]

In a retrospective review of 63 patients (72 eyes) treated with ranibizumab for wet AMD, lead author Noemi Lois, MD, PhD, and colleagues followed up on their previous observation that certain patients developed RPE atrophy despite control of the exudative process.

In the study, patients received monthly injections of anti-VEGF therapy until there was no further improvement in visual acuity and control of the exudative process was achieved for two consecutive visits. Follow-up continued monthly for a median of 16 months, with retreatment only upon occurrence of active choroidal neovascular membranes. Patients received a median of six injections.

On follow-up, 62 percent of patients developed de novo atrophy or enlargement of atrophic areas, said Dr. Lois, consultant ophthalmologist, Grampian University Hospital in Aberdeen, Scotland. "Notably, the number of anti-VEGF injections used was associated with progression of atrophy at follow-up," she said. Each additional anti-VEGF injection appeared to increase the odds of developing atrophy by a factor of 1.35.

Patients received a variety of tests. But autofluorescence (AF) and near-infrared autofluorescence (NIA) at baseline and at follow-up proved to be an effective combination for spotting areas of RPE atrophy. Here's why: If a low signal was present when using both the shorter wavelength of AF and the longer wavelength of NIA, it was possible to confidently attribute the low signal to a lack of RPE cells at that site, said Dr. Lois. When used alone, however, each mode of imaging may produce a low signal that may not relate to an absence of RPE. "Interestingly, a reduced NIA signal in the context of a normal distribution of AF seemed to presage the development of RPE atrophy," she said.



BEFORE AND AFTER. (1A, 1B) Fundus autofluorescence (AF, left) and near-infrared autofluorescence (NIA, right) in a patient with a classic choroidal neovascularization at presentation. **(2A, 2B)** At follow-up three years later, after ranibizumab treatment. The dotted lines outline areas of reduced AF (left) and NIA (right) signals, indicating RPE atrophy.

The novel findings seem to be supported by the recent two-year results of the Comparison of AMD Treatments Trial, said Dr. Lois. "It showed that patients receiving monthly intravitreal anti-VEGF injections developed statistically significantly higher rates of atrophy than those on PRN regimens, suggesting that the development of atrophy may have a direct relationship with the VEGF blockade."

Dr. Lois noted that it is important to judge carefully the need for each injection offered. "Baseline autofluorescence prior to anti-VEGF therapy and at regular intervals is of great help in monitoring progression of atrophy. Areas of low reflectivity on OCT may not necessarily indicate active neovascular AMD; AF, NIA, and fluorescein angiography are very helpful in deciding the need to continue treatment," she said. —*Annie Stuart*

1 Lois N et al. *Retina.* 2013;33(1):13-22.

***Dr. Lois** reports no related financial interests.*

Lois N et al. Retina. 2013;33(1):13-22.

Cornea News

Rx for Fungal Ulcer: Stick With Natamycin

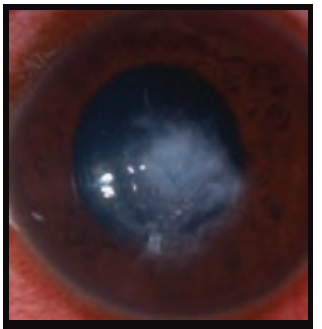
When cornea specialists were surveyed several years ago, a substantial majority said that if topical voriconazole were available, they would choose it over natamycin to treat filamentous fungal keratitis.[1] But now, new findings from the Mycotic Ulcer Treatment Trial (MUTT) show that doctors should stick with the tried-and-true natamycin—at least for *Fusarium* infections.[2]

Thomas M. Lietman, MD, professor of ophthalmology, University of California, San Francisco, who analyzed the MUTT data, called the findings a surprise. "Our earlier, therapeutic exploratory study with Dr. Prajna [N. Venkatesh Prajna, MD] and colleagues at Aravind [Eye Care System, India][3] had not prepared us for the striking results in this larger, therapeutic confirmatory trial."

MUTT, a phase 3, multicenter, double-masked trial, randomized 323 patients to one or the other topical treatment at three medical centers in South India.

Voriconazole, FDA approved for invasive aspergillosis, is used in the eye on a compassionate basis. It was the first azole with good in vitro activity against *Fusarium*, and ophthalmologists liked its relatively low toxicity, Dr. Lietman said.

But in MUTT, natamycin was associated with significantly better clinical and microbiological outcomes, especially in *Fusarium* species cases, which accounted for 40 percent of isolated organisms. At six days after initiation of treatment, 48 percent of voriconazole patients tested culture positive, compared with 15 percent in the natamycin group. The effect on *Fusarium* cases was even more pronounced: 60 percent treated with voriconazole had positive cultures at six days, compared with 8 percent of the natamycin group.



MYCOTIC ULCER. The Mycotic Ulcer Treatment Trial showed that *Fusarium* infections are best treated with natamycin.

Overall, natamycin-treated patients had about two more lines of visual acuity at three months than those treated with voriconazole. But in the *Fusarium* subgroup, the natamycin-treated cases improved 4.1 lines more than the voriconazole group. Both agents were equally effective against non-*Fusarium* species.

A big lesson from MUTT, said Dr. Lietman, "is that while we should be trying new and better therapies, we shouldn't be too quick to discard the old tried-and-true medications."

—Miriam Karmel

1 Loh AR et al. *Cornea*. 2009; 28(8):856-859.
2 Prajna NV et al. *Arch Ophthalmol*. 2012 Dec 10. [Epub ahead of print].
3 Pranja NV et al. *Arch Ophthalmol*. 2010;128(6):672-678.

***Dr. Lietman** reports no related financial interests. Pfizer and Alcon donated medications but did not provide financial support for the trial. Neither company had a say in the design of the trial or publication of results.*

IOP Update

OHT, POAG Eyes Similar

Until recently, little has been known about the daylong intraocular pressure (IOP) variation in patients with ocular hypertension (OHT). Now a team of researchers at the Hamilton Glaucoma Center at University of California, San Diego, and the Yale Eye Center has filled in some of the blanks.[1]

They found that, compared with healthy controls, OHT patients and those with primary open-angle glaucoma (POAG) share similar characteristics in their baseline, untreated 24-hour IOP patterns.

The findings are based on seated and supine IOP measures taken every two hours for 24 hours in 15 patients with untreated OHT in both eyes. Researchers compared the 24-hour IOP profile with previously reported but contemporaneously obtained IOP patterns in age-matched healthy eyes and eyes with early POAG.

Furthermore, the study separately compared the baseline 24-hour IOP characteristics of those who prospectively converted to POAG and those who did not with the healthy controls and POAG patients. The biggest surprise, said Tomas M. Grippo, MD, assistant professor of ophthalmology and visual science at Yale University: "In contrast to nonconverters, OHT patients who converted to glaucoma show significant differences from healthy controls and share similarities with the glaucoma group."

Though research with a larger sample population is needed, he said this preliminary study suggests the possibility that the 24-hour IOP pattern may help identify OHT patients at higher risk for glaucoma conversion.

—Miriam Karmel

1 Grippo TM et al. *Invest Ophthalmol Vis Sci*. 2013;54(1):512-517.

***Dr. Grippo** reports no related financial interests.*

THOMAS M. LIETMAN, MD