Update on the management of exfoliative glaucoma

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SHOULD treatment guidelines for exfoliative glaucoma be adjusted to take new treatment options into consideration? Should therapy follow the same stepwise pattern recommended for primary open-angle glaucoma? Experts addressed these controversies in a series of debates sponsored by the Lindberg Society at the 6th International Glaucoma Symposium.

In the first of the debates, W. William C. Stewart, MD, University of South Carolina Medical School, Columbia, South Carolina, US, took the position that exfoliative glaucoma should be treated in the same way as primary open-angle glaucoma because the diagnostic scenarios of the two conditions are similar and the goals of treatment are the same.

Dr Stewart noted that while exfoliative glaucoma is a secondary open-angle glaucoma arising from a different pathological mechanism than POAG, it nonetheless has the same characteristic of raised and fluctuating IOP. That is the aspect of both diseases that currently available therapies can modulate. However, XFG differs from POAG in that the IOPs are higher, visual field loss is greater and more treatment steps are needed to control the pressure.

Dr Stewart cited a study that compared the diurnal IOP curve of untreated eyes with XFG to that of untreated eyes with POAG (Konstas et al, Arch Ophthalmol, February 1997). In XFG eyes the mean maximum pressure was 38.2 mmHg, compared to 26.9 mmHg in patients with POAG, and the mean minimum pressures were 24.7 and 18.4 mmHg respectively.

"You can see that with exfoliation we are starting at a different place with higher pressures than we are with POAG," he said.

However, Dr Stewart noted that while the target pressures can vary between individual patients with either condition, prior studies have shown that maintaining a pressure below 18 mmHg can significantly lower the rate of visual field progression in eyes with either POAG or XFG.

Similarly, in another study (Konstas et al, Arch Ophthalmol: January 2004) a chart review of 167 XFG patients with at least five years of follow-up showed "There was more progression and there were higher pressures than we typically see with POAG, but the breakpoint that prevents progression was between 17-18 mmHg which is about what we see with POAG. So we start with higher pressures but our goal may well be the same," he added.

Fortunately, XFG patients respond to medicines in a similar or improved fashion as POAG patients. Unfortunately, no XFG specific treatment exists and we must use modalities also used to control POAG.

In summary, while XFG patients present with higher IOPs and visual field loss, treatment goals are the same as POAG. Furthermore, the response to therapy is the same or better with XFG than POAG.

Consequently, we may use the same therapies in XFG to achieve similar target IOP levels in the stepwise fashion that the physician believes is best for the individual patient, as in POAG. More research is needed to discover therapies that would specifically treat XFG.

More aggressive approach advocated

Countering Dr Stewart's argument, Miguel Teus MD, Madrid, Spain, said that although the same therapies are effective for both conditions, they must be administered in different, more aggressive ways.

"If treatment of both diseases is the same, then why do we tell residents to look for pseudoexfoliative material? Why do we tell residents to look for subtle signs of pseudoexfoliation pigmentation dispersion surrounding the pupillary area with loss of pigment in the pupillary border? Why do we teach them to look at the angle to look at the Sampaolussis line?" he asked.

Dr Teus pointed out that XFG has not only a different pathogenesis but also a different prognosis from POAG, with worsening of IOP over time and a closer correlation between IOP and damage to the optic nerve head and visual field loss.

He noted that the prevalence of glaucoma in patients with exfoliative syndrome is about 30 per cent, much higher than any other condition involving increased IOP, including ocular hypertension in patients without exfoliative glaucoma.

Moreover, exfoliative glaucoma patients with very high IOP are likely to have optic nerve head damage while those with normal IOP are not. In contrast, many POAG patients with a high IOP will have normal optic nerve heads, while others with a normal IOP will have glaucomatous damage.

The tendency for IOP to increase over time in exfoliative glaucoma patients further compounds the risk of progression, he pointed out.

"The more damage you have, the lower the target IOP should be and we have more damage with XFG. And the higher the risk of progression, whether it's related to the patient's age or the disease itself, the more you need to control IOP," he added.

What class of medication?

Most current guidelines recommend topical medication as the first step in treatment of both POAG and XFG, but the advent of prostaglandin analogues and the continued reliability and relative cheapness of beta-blockers has created a grey area around which medication should be used first.

Murat Irycèk MD, Department of Ophthalmology, Hacettepe University, Ankara, Turkey, presented his arguments in favour of the beta-blocker timolol as the first line choice for treatment of exfoliative glaucoma.

An important factor in timolol's popularity is that it costs only a fourth as much as prostaglandin analogues, he acknowledged. But price can be of a very real, sight-saving benefit to patients from economically deprived areas of the world.

Moreover, prostaglandin analogues provide a relatively modest additional benefit over timolol, he added. He cited a meta-analysis of randomised controlled trials comparing latanoprost with timolol in the treatment of patients with open-angle glaucoma or ocular hypertension (Zhang et al, Br J Ophthalmol, August 2001). It showed that there was only a five per cent reduction from baseline IOP with latanoprost compared to timolol.

Studies of timolol's efficacy in exfoliative glaucoma patients have yielded contradictory results, with some suggesting greater benefit than those in POAG, and others suggesting equal or worse results.

Timolol is generally well tolerated. It does have a few important contraindications, such as obstructive airways disease, heart failure, second and third degree atrioventricular block. Moreover, prostaglandin analogues are more likely to cause subconjunctival inflammation and fibrosis, which can adversely affect the outcome of trabeculectomy.

"Except in cases with XFG where IOP must be reduced from the 30s and 40s to around 12 mmHg timolol actually controls the IOP very well. It's a very affordable medication with a very convenient regimen, it has lifelong efficacy and it is superior in its safety profile. Therefore beta-blockers should be the first treatment of choice in exfoliative glaucoma," he added.

Taking the opposing view, Gabor Holló MD, Semmelweis University, Budapest, Hungary, emphasised that prostaglandin analogues are more effective at lowering IOP than beta-blockers. In addition, beta-blockers do not control IOP as effectively in XFG patients as they do in POAG patients. Moreover, XFG patients may be particularly susceptible to the cardiovascular side effects of beta-blockers, he said.

In a study comparing the response to timolol in patients with XFG or POAG (Konstas et al, Arch Ophthalmol, August 1997), although IOP reduction was more pronounced in those with XFG, a higher proportion of patients with POAG achieved their target IOP and good IOP control throughout the day.

The treatment reduced the range of diurnal IOP fluctuation by 40 per cent in those with XFG, compared to only 26 per cent in patients with POAG. However, the range of IOP fluctuation was still higher in those with XFG than in those with POAG (7.0mm Hg vs 5.6mm Hg) and only five (13 per cent) of the patients with XFG had an IOP of 18.0 mmHg or less at all time points compared to 12 (32 per cent) of the patients with POAG.

Prostaglandin analogues, in contrast, appear to provide a more adequate control of IOP in exfoliative glaucoma patients. In a recent study that compared the efficacy of different prostaglandin analogues in the treatment of XFG patients (Konstas et al, the British Journal of Ophthalmology, April 2007), IOP after eight weeks of treatment was 17.8 mmHg with latanoprost, and 17.3 mmHg on travoprost.

A recent study (Visontai et al, Br J Ophthalmol. 2006) produced evidence that patients with XFG characteristically have increased carotid artery stiffness and decreased baroreflex sensitivity, which could make them more likely to experience cardiovascular side effects when treated with beta-blockers.

"As we all know, the goal of our treatment is to preserve vision until the end of patients' lives. Saying in an extreme and funny way, as it fits to this debate, there are two ways to achieve that, one is to treat them properly with prostaglandins and the other is to shorten their life expectancy with beta-blockers," Dr Hollo added.

Fixed combinations as first line therapy?

Current guidelines recommend a strategy of gradually increasing intervention in all forms of open-angle glaucoma, with first one
medication and then a second if the first is not effective, or a combination of two or three partially effective medications either fixed or unfixed.

However, since exfoliative glaucoma patients generally present with much higher more unstable IOP, the more aggressive approach of going directly to a fixed combination might be advisable in some cases, argued Vital P. Costa MD, Departments of Ophthalmology, State University of Campinas, Campinas, Brazil. He noted that in the OTHS study, where patients had a very modest IOP P reduction target of about 20 per cent, 40 per cent nonetheless required two or more medications. Furthermore, in the CIGTS study, where IOP was targeted individually, 75 per cent required two or more medications to achieve their target IOP.

Examples of exfoliative glaucoma patients who might benefit from fixed combinations as first line therapy include those with high pressures around 30 mmHg or higher, and marked damage to the optic nerve head. While it is important to achieve a low target IOP in many cases with exfoliative glaucoma, the efficacy of fixed combinations do not exceed that of monotherapy with its stronger constituent in any clinically significant way. Stefano Miglior MD, Universita' di Milano Bicocca, Milan, Italy. He noted for example, that in most trials comparing latanoprost and timolol lowered IOP by only an additional 1-1.5 mmHg compared to latanoprost alone. As for Ganfort (Allergan), with their inconvenience and side effects. It is a better quality of life while trabeculectomy has a greater risk of progression. So we need to be quite aggressive, and whatever more IOP lowering we can get will be of great benefit to our patients,” Dr Carassa added.

He pointed out that while one of SLT’s advantages over ALT is that it can be repeated if it begins to lose its effect, there are no long term studies to show how effective the re-treatments will be.

Trabeculectomy vs non-penetrating surgery

The final debate addressed the question of whether trabeculoplasty or penetrating is the best surgical option.

Robert G. Carassa, San Raffaele Hospital, Milan, Italy championed trabeculectomy as the best choice of surgery in exfoliative glaucoma patients because it is actually more effective in XFG than it is in POAG and has a proven track record.

He pointed out that XFG follows a more rapid course than POAG. In the EMGT study, the rate of progression was twice as high among patients with XFG as it was among patients with POAG. Even among the treated exfoliative glaucoma patients who achieved the target 25 per cent IOP reduction, the proportion that progressed was far greater than it was among the untreated POAG patients.

“It is quite clear that this disease is quite aggressive and needs to be treated aggressively. And the EMGT study also showed that, overall for each 1.0 mmHg of IOP reduction there was a 10 per cent lower risk of progression. So we need to be quite aggressive, and whatever more IOP lowering we can get will be of great benefit to our patients,” Dr Carassa added.

He pointed out that exfoliative glaucoma patients who underwent non-penetrating surgery showed that 67.8 per cent of patients maintained a pressure 21 mmHg at 12 months’ follow-up (Cheng et al, Chin Med J (Engl), 2004 Jul).

“The result that we have at a year is quite similar to the result we are still getting with XFG at 48-50 months, so penetrating surgery is performing far better,” he added.

The advantage of non-penetrating surgery is that they have fewer complications and long term sequelae and can therefore be performed earlier, enhancing long term outcomes, responded Prof Vassilios Kozobolis, Chairman of the Department of Ophthalmology and of the Eye Institute of Thrace (EJIT), Democritus University of Thrace, Alexandroupolis, Greece. “It is crucial to avoid the intra- and postoperative complications and their consequences, as well as the cataract progression and cataract extraction, which can lead to worsening of IOP and visual fields. With non-penetrating glaucoma surgery we have a safer profile and better quality of life,” he added.

He pointed out that, as with trabeculectomy, non-penetrating surgery also yields a higher success rate in XFG than it does in POAG. He cited a recent study by Liv Drolshus MD (Drolshus et al, Acta Ophthalmologica Scandinavica, August 2006) in which 27 patients with POAG and 28 with XFG underwent deep sclerectomy. At a follow-up of 45-50 months the proportion with an IOP lower than 19 mmHg without medication was 50 per cent in the XFG group compared to 33 per cent in the POAG group.

The advantages of non-penetrating surgery over trabeculectomy are numerous, he noted. For example, they are less likely to damage the already compromised blood-aqueous barrier and cause bleb failure. Such procedures are also less likely to induce hyphaema through rupture of undetected iris neovascularisations. They are also less likely to cause damage to the fragile zonules of XFG patients, and finally they are less likely to induce cataract.

“The fact that medical therapy is less effective in the long term leads us to the decision for early surgical treatment. The sooner the operation the better the result.

Deep sclerectomy has a good success rate for this type of glaucoma and provides a better quality of life while trabeculectomy has a higher complication rate,” Prof Kozobolis added.