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Glaucoma treatment: by the highest level of evidence.

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Glaucoma treatment - finally the highest level of evidence

Glaucoma is a disease in which optic nerve axons are damaged, leading to gradual loss of vision and, too frequently, to blindness. 50 years ago, ophthalmologists considered glaucoma and elevated intraocular pressure (IOP) to be more or less synonymous.¹ In the 1950 Leydhecker defined normal limits for IOP,¹ and as a result patients with elevated IOP (≥ 21 mmHg) received a diagnosis of glaucoma, regardless of whether there were any signs of glaucomatous damage. They were given pressure-lowering eye drops, and were told to use these drops 3 to 4 times a day or they would go blind. On the other hand, patients having pressures of 20 mmHg or lower did not have glaucoma.

The problem was that it simply is not true that elevated IOP and glaucoma are synonymous. The first epidemiological study of glaucoma, in Wales in the 1960s, found that a considerable proportion of glaucoma patients had IOP values within Leydhecker's normal range, and these patients were said to have normal tension glaucoma.² These findings have been confirmed in dozens of other epidemiological studies, and it is now well accepted that about half of all glaucoma patients have normal tension glaucoma – and in Japan as much as 90%.³ The other side of the coin was equally confusing: patients having pressures ≥ 21 mmHg without glaucomatous damage were in fact found to be very numerous, and if followed without treatment for up to 20 years, most of them developed no signs of glaucomatous damage.⁴

Thus, ophthalmologists realized that the relation between elevated IOP and glaucoma was not all that clear, which led to doubts regarding the efficacy of IOP-lowering therapy. Because this uncertainty was an obstacle to clinical decision-making and to allocation of sufficient resources to glaucoma care, clinical studies were needed. The problem was first addressed in four randomized clinical trials in the 1980s to investigate whether reducing IOP in patients having elevated pressure in the absence of glaucomatous damage – ocular hypertension – could reduce the incidence of glaucoma damage. Results were inconclusive,⁵⁻⁸ and in 1989 a report ordered by the US Congress concluded that there was no proof that lowering pressure reduced glaucomatous damage. Soon two randomized studies with untreated control arms involving patients with manifest glaucoma were started. The Collaborative Normal Tension Glaucoma Study (CNTGS) enrolled only glaucoma with normal tension glaucoma, whereas the Early Manifest Glaucoma Trial (EMGT) studied glaucoma patients both with normal and elevated pressures. In 1998 the intent-to-treat analysis in CNTGS was negative, but after correction for the increased incidence of cataract in the treated arm, positive treatment effects were seen.⁹ In 2002 EMGT results showed that pressure lowering had clearly positive effects, regardless of patients' initial IOP.⁹

The United Kingdom Glaucoma Treatment Study (UKGTS) by Garway-Heath and co-workers¹² is the second randomized clinical trial to investigate the effects of IOP-lowering therapy in glaucoma patients having elevated or normal pressures. In some ways, the UKGTS was modelled after the EMGT, e.g. the primary outcome criteria but the two studies also differ in a number of respects. First the UKGTS was placebo-controlled, while the EMGT was not. Second, the UKGTS used mono-therapy in the treatment arm, prostaglandin analog eye drops (latanoprost 0.005%), the most

commonly used anti-glaucoma therapy today. The authors also sought a study design from which conclusions could be drawn in a relatively short amount of time, patients were followed for only 2 years. To achieve this, 11 visual field tests were obtained during this period, since it is well known that identifying visual field progression or measuring rate of progression requires multiple field tests, and that the time needed to identify progression strongly depends upon the frequency of testing. Also, UKGTS, was a multi-centre study involving ten centres in the UK in which a large number of subjects – 516 – were randomized.

This study is important in many ways, perhaps most significantly, because it is the 2nd study to demonstrate the positive treatment effects of IOP reduction in manifest glaucoma. For the highest level of medical evidence, more than one study is usually required and this has been lacking until now. Since modern glaucoma treatment is based upon IOP reduction, and since glaucoma management uses about 25% of all ophthalmology resources, this is a fundamental issue in ophthalmic care. That the study was placebo controlled is a further strength.

The magnitude of treatment effects also is important. The IOP difference between the treated and the placebo arms after 24 months was a modest 2.9 mmHg – due to the fact that untreated pressure levels at study entry were quite low. IOP-reducing agents produce much smaller pressure reductions in eyes that start out with low pressures than in eyes where pressure is high. Still the risk of progression was 40% lower in the treated group than in eyes receiving placebo drops. This is a risk reduction of 13% per mmHg, confirming EMGT and Canadian Glaucoma Study results, demonstrating that IOP reduction is highly effective, and that “every mm of pressure counts”.^{12,13} These results motivate careful clinical follow-up and monitoring of disease progression in glaucoma patients, and should also serve as a stimulus to the pharmaceutical industry to continue development of new and even more potent drugs.

It is also important that very significant treatment effects could be seen after only 24 months; in fact, the first differences were seen already after 12 months. Certainly, the UKGTS took a lot longer than 2 years to complete, but only because recruitment took several years. Measuring glaucomatous progression by following visual field status is the gold standard, and visual field sensitivity also is important to patients. Nevertheless, in recent years it has often been stated that studies using visual field endpoints take too long, and that it, therefore, is too difficult to assess the effects of new drugs or other treatment modalities. The authors clearly demonstrate that this view is too pessimistic, and that with frequent testing using widely available clinical tools, important studies can be completed within a very reasonable time.

This is just the first of what I expect will be a series of papers reporting UKGTS results; I am convinced that additional intriguing findings will be reported in the future, notably comparing the results obtained with visual field testing with those of ophthalmic image analysis.

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