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7th Congress of the European Glaucoma Society

Comprehensive Management of Ocular Hypertension and Glaucoma

Introduction

Research conducted during the last decade has revolutionised the field of glaucoma medicine. Thanks to developments in molecular biology, imaging and epidemiology, there is now a much better understanding of the pathophysiology of glaucoma, as well as the risk factors associated with the disease. During the same period, new IOP-lowering medications have emerged that are both more effective and better tolerated than previous treatments. The convergence of these factors suggests a need to restage the disease, intervening earlier to slow progression and forestall visual disability.

An international faculty of glaucoma specialists co-chaired by Günther Krieglstein MD and Robert N. Weinreb MD gathered at a symposium in Florence, Italy during the 7th Congress of the European Glaucoma Society to provide the latest insights into translating the last decade's many important developments into clinical practice.

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The Glaucoma Continuum

Robert N Weinreb MD

Dr Robert Weinreb elucidated the concept of the glaucoma continuum and discussed the implications for practicing clinicians and their patients. He explained that glaucoma is a chronic, progressive optic neuropathy occurring along a continuum that begins with the normal healthy eye, progresses to undetectable disease, then to detectable asymptomatic disease, eventually leading to visual disability and finally blindness. [1,2]

The very earliest stages of the continuum occur at the molecular level as retinal ganglion cells begin to die through a process of apoptosis, or self-programmed cell death. Eventually, as more retinal ganglion cells are damaged or lost, characteristic signs of disease begin to appear in the retinal nerve fibre layer and the optic disc. Patients often remain asymptomatic at this stage.

The neuropathological changes occur in cells throughout the central visual pathway including neurons within the lateral geniculate nucleus. Indeed, different retinal ganglion cell types can be characterized by the layer of the lateral geniculate nucleus they target. For example, while magnocellular retinal ganglion cells target layers 1 and 2 of the lateral geniculate nucleus, the parvoceullar retinal ganglion cells target layers 3-6. The different layers have distinct functional properties corresponding to different functional tests. For example, the koniocellular sublayer mediates the blue-yellow response reflected by SWAP perimetry, while frequency doubling technology perimetry reflects the responses of cells targeting layers 1 and 2.

Dr Weinreb explained that the first indications of glaucoma in asymptomatic patients often correspond with demonstrable changes in the retinal nerve fibre layer. He described several case studies underscoring the long presymptomatic phase of the disease.

In the first case, Dr. Weinreb's patient was first seen in 1987. The patient had ocular hypertension, with a normal optic disc, normal standard visual fields and normal SWAP visual fields. That patient was considered a glaucoma suspect and not treated. Two years later an examination revealed a very small defect in the retinal nerve fibre layer, while the optic disc and visual fields remained normal. The patient was diagnosed with glaucoma and started on treatment. Another exam in 1992 showed that the retinal nerve fibre layer defect was still increasing in size. While the optic disc and standard visual fields were still normal, SWAP perimetry was now abnormal. Optic disc changes did not appear until September of 1995, at which time standard perimetry was still normal. Standard perimetry showed field changes only in 2003, 16 years after the first visit.

That case study supports an important development in glaucoma screening in recent years, retinal nerve fibre layer imaging. A growing number of published studies now conclude that changes seen in the RNFL precede the development of visual field loss by several years.

A second case of Dr. Weinreb's involved a patient with ocular hypertension first seen in 1989. The patient presented with a normal optic disc and visual fields. Examinations conducted every three to six months for the next 15 years demonstrated the glaucoma continuum in progress. Small changes in the RNFL along with a small optic disk hemorrhage appeared in 1993. Three years later, another optic disc hemorrhage was seen, and by 1999

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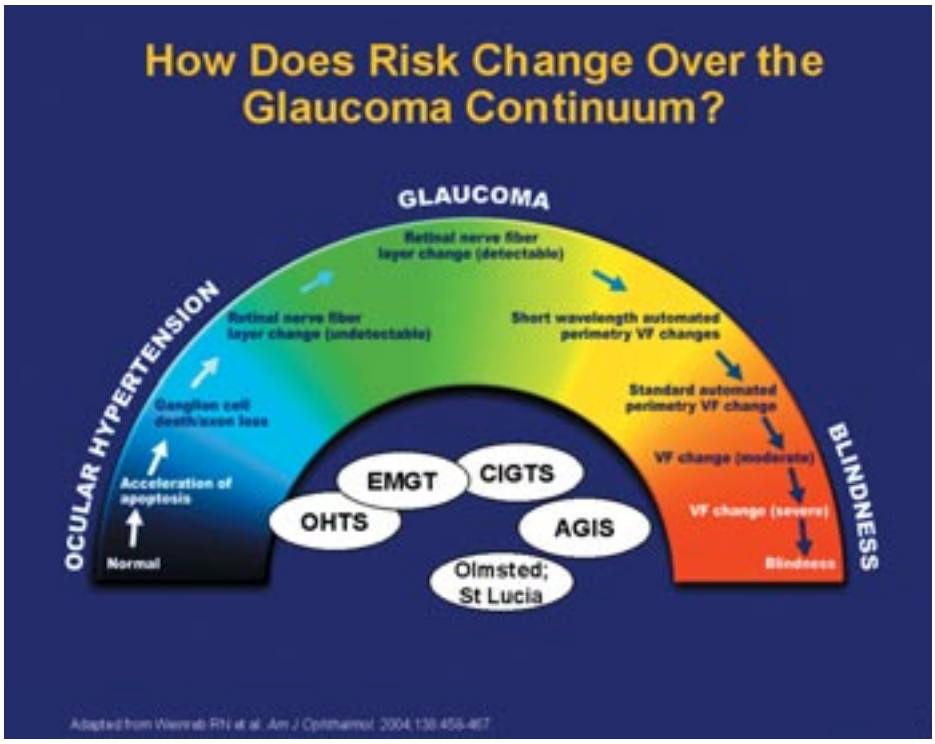

Courtesy of Robert Weinreb MD

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changes in the optic disc were apparent. SWAP perimetry showed a repeatable visual field defect in 1997 as did FDT perimetry later. Finally, an optic disc examination conducted in 2003 revealed a notch. In this case RNFL imaging, optic disc examination, SWAP and FDT perimetry all detected changes before standard visual field testing.

Standard automated perimetry remains the most widely used functional test for the diagnosis of glaucoma. As these case studies suggest, standard perimetry has several important limitations, including the long follow-up period spanning many years and the need for many repeat exams to detect meaningful changes. Standard automated perimetry is considered to be poorly sensitive and poorly reproducible, as demonstrated recently in the Ocular Hypertension Treatment Study (OHTS).[3,4]

These case studies also highlight the concept of restaging. By the time a visual field defect is detected with standard testing a patient may have lost half of his retinal ganglion cells. The implication is that patients once considered to have early disease may in fact have moderate to advanced glaucoma.

"I think we need to reconsider how we diagnose glaucoma. At the present time many textbooks of glaucoma still suggest that you need a visual field defect and corresponding change in the optic disc. An alternative definition that might be more sensitive and more specific would be a corresponding structural or functional abnormality such as a disc abnormality with a corresponding RNFL defect; or a disc or RNFL abnormality with a corresponding functional defect. Perhaps most specific of all would be a progressive structural or functional change like a progressive change in disc, RNFL, or visual field."

Earlier intervention to prevent vision loss would require earlier detection. Fortunately, several innovative imaging technologies are now available that can aid in earlier diagnosis. Scanning laser polarimetry and optical coherence tomography are useful for examining the RNFL[5]. Confocal scanning laser ophthalmology is useful for looking at early changes in the optic disc[6]. It is now also clear that more advanced methods for measuring visual fields including SWAP and FDT reveal functional changes earlier than standard white-on-white perimetry.[7]

"The future is bright for being able to detect glaucoma at an early stage. Early glaucoma diagnosis and detection of progression clearly should be a goal of rational and high quality glaucoma management. There is a convergence of information from numerous clinical studies showing that treatment by lowering IOP has benefits across the glaucoma continuum.[3,8,9,10,11,12,13] This is true whether you are treating early in the continuum (as demonstrated in OHTS[4]), later (as in the Early Manifest Glaucoma Treatment study[11]), or even in advanced disease (as in the AIGS[9]). Each of these trials has demonstrated the benefit of IOP lowering"

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All of the available investigative tools can play a role in the management of glaucoma. The examination of optic disc and RNFL are essential for diagnosis and monitoring progression of the disease. Selective functional testing with SWAP and FDT perimetry also enables earlier diagnosis. Early diagnosis allows earlier treatment and enhances the opportunity to prevent vision loss across the glaucoma continuum.

Robert N Weinreb MD

Projecting progression rates in glaucoma

M. Roy Wilson MD

Clinicians have long known that the course of glaucoma disease progression varies significantly between individuals. Some patients are at risk for rapid progression sufficient to threaten vision, while others may live many years with no apparent symptoms. M. Roy Wilson MD discussed how the findings from recent clinical trials could help physicians to determine who to treat early and how aggressively to treat them.

Recent landmark clinical studies involving patients with ocular hypertension and different stages of glaucoma such as the Ocular Hypertension Treatment Study (OHTS)[4] and the Early Manifest Glaucoma Trial (EMGT)[13] have identified multiple baseline risk factors for conversion to glaucoma and progression of disease.

Dr Wilson noted that by combining the risk factors identified in these and other recent trials in a process of global risk assessment it may be possible to identify the individuals who are at greatest risk of visual disability, and who are thus most likely to benefit from early treatment.

"We now know a lot about the risk factors for glaucoma. Many risk factors have a large body of data [4,8-13] supporting them. These would include intraocular pressure, age, black race, and family history. In addition, it now appears that central corneal thickness and cup/disc ratio are risk factors, as the OHTS[4] indicated. So we can say that there will be patients with higher risk of progression. For example, older patients with elevated pressure, a large cup-disc ratio and thinner cornea would have a five year risk of developing glaucoma in the 30% range or higher. In contrast, a patient with none of those factors would only have a progression risk of two or three percent."

Newer structural tests notwithstanding, visual field changes are still the mainstay of monitoring glaucoma progression. What data there are on glaucoma progression are based mostly on visual field testing, and to a lesser extent, measurement of changes in the optic disc. The visual field data from recent studies are difficult to compare, since different perimetry systems are used, along with different methods of quantifying the visual field changes. Moreover, some of the visual field results come from cross-sectional studies while others come from longitudinal studies. Nonetheless, it is possible to glean a lot of useful information on what is happening with patients at that stage of the glaucoma continuum.

For example, in a four year longitudinal study[15] 25% of the cohort progressed, with visual fields declining about 1.39 dB per year. In a nine-year study[16], half of normal tension glaucoma patients progressed, as did one third of patients diagnosed with primary open-angle glaucoma. However, less than five percent of patients with ocular hypertension progressed in that study. In another study[17] 68% of patients had progressed during a 14-year period, with a mean annual rate of visual field loss of 2.1 dB.

Taken together, these studies suggest that four percent of patients will progress each year, at a rate of about 1.0 dB per year. Therefore, a hypothetical 60 year old with a diagnosis of early primary open-angle glaucoma would be considered to have a 40% chance of progression at ten years. In such a patient, progression to end stage disease could take anywhere from 33 to 47 years.

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"A more intuitive way to look at this is to consider the number needed to treat. In OHTS, we needed to treat 16 patients to prevent one patient from progressing to early stage glaucoma. In EMGT we needed to treat six patients with early glaucoma to prevent one patient from progressing to more advanced disease.

What remains to be clarified is what is the number needed to treat to prevent progression from early moderate glaucoma to functional vision loss to blindness. In a long-term study[17], 19% of treated patients in the study population had progressed to blindness after 20 years. Extrapolating the ten year results of the St Lucia Study[10], to 20 years suggests that 31% of the untreated patients would have become blind over a 20 year period. A rough calculation indicates that the number needed to treat would be eight in order to prevent one case of blindness.

"We now know more about the relative strength of risk factors, but we are well behind the field of cardiology in this regard. In cardiology one can pinpoint with some precision what will happen with some risk factors if a patient goes untreated. We are getting to that stage with glaucoma, but treatment is still more of an art than a science. We are starting to utilize the concept of the glaucoma continuum. With all the data coming in I expect we will catch up with cardiology in five to ten years."

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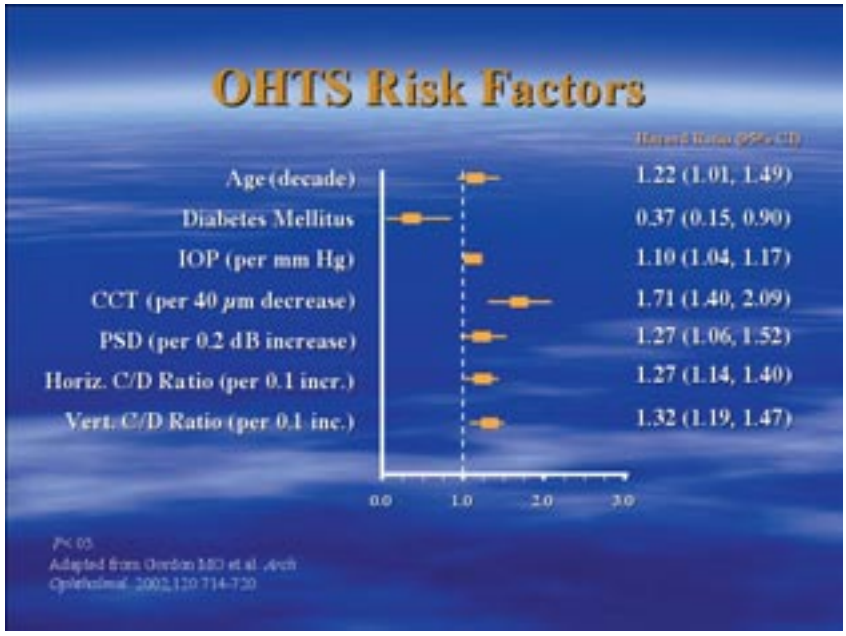
As clinicians begin to treat patients with identifiable risk factors earlier in the glaucoma continuum, demographic and economic issues will come into play. Physicians and their patients will have to consider the costs of treatment. Older patients on fixed incomes often have to ration resources to treat multiple chronic diseases. Other factors to consider include quality of life, life expectancy and side effects.

M. Roy Wilson MD



Courtesy of M. Roy Wilson MD

Restaging Glaucoma

Anne Coleman MD

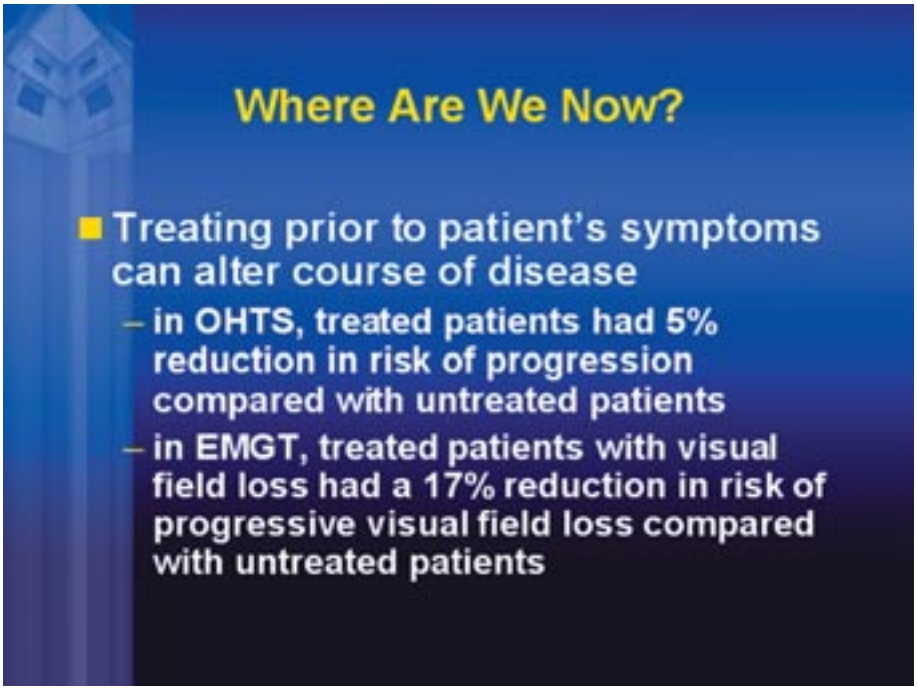
Restaging glaucoma based on earlier diagnosis and risk stratification has implications that go well beyond the individual patient. Dr Anne Coleman discussed how the changing definition of glaucoma in recent years has set the stage for restaging, and the likely impact of glaucoma restaging on society.

Some thirty years ago, the definition of glaucoma was based on intraocular pressure elevation alone. The guideline of 21 mmHg originated in studies of IOP in the general public, which determined the average IOP in a healthy individual to be 15.5 mmHg, with 21 mmHg as the upper confidence limit.

It has since become clear that using IOP as a sole criterion for identifying glaucoma is not very sensitive or specific. For example, it misses cases of normal tension glaucoma. Another problem is that it appears that many patients with ocular hypertension may never develop glaucoma, as demonstrated in OHTS[3], where 90% of untreated ocular hypertension patients did not develop glaucoma in a five-year period. Moreover, it has also become clear that Goldmann tonometry, the current standard of IOP measurement, is not reliable when measuring very thick or very thin corneas[19].

Visual field measurements have been another mainstay of glaucoma diagnosis for decades. Perimetric evaluation of visual fields does offer a level of specificity and has proven useful for following patients in the long term. However, it is not an ideal screening tool since it recognises disease only rather late in the glaucoma continuum.

Recent consensus glaucoma guidelines take the shortcomings of IOP and visual field measurements into consideration- by leaving them out of the definition. In 2000, the American Academy of Ophthalmology[20] defined



Courtesy of Anne Coleman MD

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glaucoma as a multifactorial optic neuropathy with characteristic loss of retinal ganglion cells and atrophy of the optic nerve. The European Glaucoma Society guidelines released in 2003[21] define glaucoma as a chronic progressive optic neuropathy, having characteristic morphological changes of the optic nerve head and retinal nerve fibre layer, in the absence of other ocular disease or congenital anomalies.

"You really want to know, when does the disease start? This is a question with which epidemiologists struggle. In some diseases, treatment starts with the appearance of noticeable symptoms. In other diseases you want to treat them as soon as markers are detected, because delaying initial treatment would be associated with significant impacts on patients and/or society. Examples of the latter include heart disease, hypertension, diabetes, and possibly glaucoma."

The consensus emerging from recent clinical studies is that it is possible to alter the course of disease by initiating treatment before symptoms appear, as in OHTS[3], or to slow progression to visual loss, as in EMGT[13]. One implication of those findings is that early glaucoma treatment, by reducing visual disability and blindness, would save money in the long run.

Acknowledging that supportive health resource studies are currently sparse, Dr Coleman buttressed this argument by referring to US Medicare database[22] of patients 65 years or older. The average medical costs for ophthalmology-related visits and hospital reimbursements were $707 per year for blind patients, compared with $463 for sighted patients. While the figures did not include indirect costs such as medication or lost wages, they did provide a crude indication of the increased costs associated with blindness to society.

Dr Coleman emphasized that long before it leads to blindness, glaucoma can have significant negative effects on quality of life. Even with mild visual field loss patients experience decreased mobility and increased rates of accidents.

"I'm sure we'll be seeing further changes in the definition and staging of glaucoma as we learn even more about the disease and develop even better diagnostic techniques. The ultimate goal of restaging is not only to prevent blindness but also to preserve vision. We want to preserve vision quality so our patients can continue to live their lives to the fullest potential."

"I'm sure we'll be seeing further changes in the definition and staging of glaucoma as we learn even more about the disease and develop even better diagnostic techniques. The ultimate goal of restaging is not only to prevent blindness but also to preserve vision."

Anne Coleman MD

Implications of restaging: comprehensive IOP lowering

Mitch Menage FRCS, FRCOphth

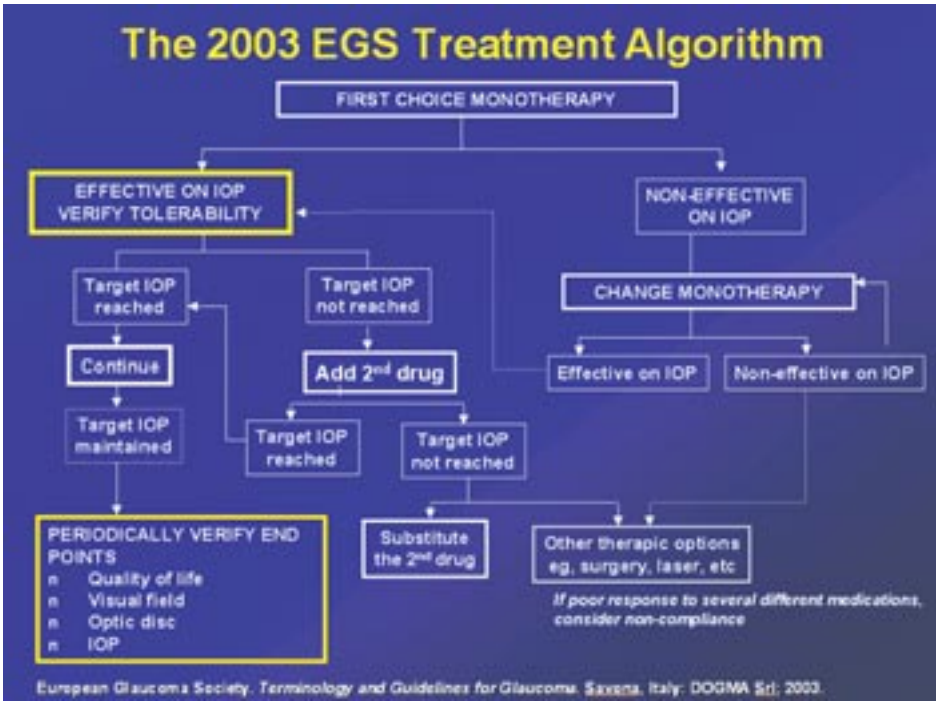
Although IOP measurement may be assuming a secondary role in the diagnosis of glaucoma, lowering intraocular pressure with medication remains a primary goal of glaucoma treatment. Dr Mitch Menage discussed the best way to reach that goal in the short term and to maintain effective treatment over the long term.

Earlier diagnosis provides the impetus to restage glaucoma. This means patients will begin treatment earlier, will remain asymptomatic longer, and will need to remain on medical therapy longer. This requires a more comprehensive appreciation of IOP lowering treatment that supersedes the narrow view focused exclusively on the magnitude of a given agent's ocular hypotensive effect.

The emphasis on quality of life is a central theme in the 2003 EGS guidelines[21]. This implies a complicated interaction of factors including not only effective pressure control but also long-term efficacy with minimal side effects, reasonable cost and maximum convenience.

How low should the clinician go with IOP reduction? Clinical trials such as AGIS[23] typically set a target, which was 18 mm Hg in that study. But practicing clinicians are more likely to aim for a percentage reduction, for example, a 30% reduction of IOP in mild to moderate glaucoma, while aiming for an absolute pressure number of 18 mmHg or even lower in cases of advanced disease[21].

The prostaglandin analogue class of IOP-reducing agents, including latanoprost, has 'in the hands of many ophthalmologists superceded B-blockers as their first choice medical



Courtesy of European Glaucoma Society, IInd Edition, Chart 8

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therapy' for glaucoma in part because those agents have shown an ability to reduce pressure by 25% to 35%, significantly more than either the beta blocker or carbonic anhydrase inhibitor drug classes.[21]

"Compliance is a very important factor in the management of glaucoma. You want to ensure daily constant pressure control. Poor compliance is associated with vision loss. Successful compliance depends on the patient using the right medication correctly. You need to make sure that your patients understand the importance of compliance and know how to instill their drops properly."

"If we really want to help prevent or delay visual disability in our patients, then we have to do everything we can to minimise the side-effects, inconvenience and cost of treatment"

Yet compliance is notoriously poor among glaucoma patients.[21] Patients may be put off by inconvenient dosing regimens, side effects, or the costs of the medications. Taken together, these factors inhibit persistency, and thus the benefits that accrue by remaining on therapy in the long term.

"We've been reassured in recent years that IOP lowering is an evidence based approach. We also now know that pressure reduction is a benefit at various stages of disease. But if we really want to help prevent or delay visual disability in our patients, then we have to do everything we can to minim ise the side-effects, inconvenience and cost of treatment."

Mitch Menage FRCS, FRCOphth

Implications of restaging: the importance of persistency

Roberto Carassa MD

Randomised clinical trials, the basis for evidence-based treatment strategies, of necessity rely on the use of carefully selected groups of patients in carefully controlled clinical settings. These trials provide essential information on the safety and efficacy and tolerability of drugs. Nonetheless, they do not provide clinicians with much information on prescribing these drugs in the real world as they treat a variety of patients over periods of many years. Dr Roberto Carassa discussed some of the real-world implications of long-term treatment of glaucoma.

Dr Carassa noted that health outcomes studies can often provide the kind of real world information on the therapeutic value of a specific treatment approach in a way that randomised controlled clinical trials cannot. These are population based observational studies derived from chart reviews, insurance databases, pharmacy records, and other sources.

Health outcomes studies are used to determine the economic drivers of disease management. This is important because they identify differences in real world health outcomes with different treatment strategies. This helps researchers to identify differences in costs, which helps move the process of health policy decision making.

"Patient persistence is a key measure in these studies. Persistence is a measure of the time the patient remains on continuous therapy. It can be a good measure of real world clinical effectiveness. It incorporates the physician's perception of the value of therapeutic choice, and the patient's perception of the need for therapy[24]. Factors associated with persistence include tolerability, efficacy, convenience, and value.[25]"

These studies measure persistence by looking at the rates at which patients either discontinue therapy or change to a different therapy. Persistence is easier to measure than compliance, since there is less bias from the physician or the patient. From the clinical point of view, persistence is a surrogate marker of compliance, tolerability, and ultimately, efficacy.

In one observational chart review study[26] researchers compared the time on initial therapy with latanoprost or beta-blocker in 260 patients with primary open angle glaucoma or ocular hypertension. Patients in the latanoprost group stayed on therapy twice as long as those who received a beta-blocker, a statistically significant difference. Patients receiving a beta-blocker were also more than three times more likely to change therapy than those initially treated with latanoprost. The latanoprost group also experienced greater mean decreases in IOP during the two-year period.

Another larger study[27] used managed care administrative claims data to compare persistency among 2850 glaucoma patients taking either betaxolol, brimonidine, dorzolamide, latanoprost, or timolol monotherapy over a 21 month period. Patients treated with latanoprost were significantly less likely to discontinue or change treatments than those taking any of the other agents.

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Results like these tend to indicate better tolerability and patient acceptance of one drug over another. Nonetheless, there is a long way to go to improve patient compliance and persistency with glaucoma therapy.

"We see problems with compliance and persistency with most chronic disease including glaucoma.[28,29,30] We need to improve persistency if we are going to improve outcomes. This has major implications for our health care systems. While the search for new, effective therapies must continue, a focus on issues like persistence may have a greater overall impact on health than the discovery of any new agent."

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Footnotes

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