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REVIEW ARTICLE

Is it time for Precision Medicine in Glaucoma?

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Abstract

In the new era with ever-growing research and development of new concepts for patient care, it is important to interpret the information from the trials judiciously with the incorporation of patient targeted approach (precision medicine [PM]) along with evidence-based medicine to provide holistic care to the patient. As randomized controlled trials are usually conducted with strict criteria and a homogenous group of patients, the real-world situations are different, thus the individual-based approach has to be considered while managing patients, especially with chronic diseases which have a great impact on the patient's quality of life. This write-up highlights the importance of PM for glaucoma care and the factors which can help with decision making. A holistic and empathetic approach, with emphasis on lifestyle modifications including stress management, yoga therapy, and ocular motility exercises, can go a long way in improving both, the patient's coping skills, and the disease course. Newer empirical therapies, especially those without a demonstrable evidence base, may sometimes be considered for cases where all else fails, customized to the individual patient's requirements.

Introduction

Evidence-based medicine (EBM) is defined as a judicious use of treatment for the patients as per the results of clinical trials and research, whereas precision medicine (PM) is an individual based approach for patient's treatment with modifications in the standard treatment after taking into account the facts that every person has a different genetic makeup, environment, and lifestyle.[1]

In the context of glaucoma management, several authors have reported that despite standard care, many glaucoma patients progress, and some to blindness. The possible reasons for this have been variably quoted as non-intraocular pressure (IOP) related mechanisms, late diagnosis, improper treatment, inability to detect the rate of progression, or and a lack of compliance, etc.[1-3]

Therefore, it just might be the time for the dawn of a new era of personalized medicine. The concept is not novel; it was first discussed in 1999 and has become increasingly relevant today with advancements in drug development, surgical techniques, and more demands from patients. While it is the mainstay of treatment of breast cancer, it is yet to become a part of the management of other chronic diseases.[4]

This review aims to critically evaluate the relative merits of PM and EBM in current glaucoma management.

EBM versus PM

EBM has the inherent advantage of having gone through a rigorous scientific assessment. Its use, merits and demerits have been thoroughly tested in well-designed clinical trials and, therefore, give more confidence to the doctor as well as the patients about the predictability of results. That said, the results of clinical trials may not always be applicable to the individual patient as each clinical situation may be different in the real world, keeping in view the strict inclusion and exclusion criteria of the trials. Moreover, the results of clinical trials give a brief overview of the real-world experience of the individual patient. The focus is on the results of the intervention in the majority of the patients, with little mention of the rarer outcomes.

PM, on the other hand, is an individualized system of medicine, which involves a targeted treatment as per the patient's lifestyle, socio-economic status, genetics, and environment.[1] However, as it is not evidence based, the treatment might not work and one needs to be more cautious with frequent follow-up for the initial

period. In addition, more investigations and repeated changes in the treatment may also be required for the customization of the treatment protocol.

The Gaussian Curve

When analyzing an outcome, a normal (or Gaussian or Laplace–Gauss) distribution is of utmost importance and forms the mainstay of EBM. This continuous probability distribution for a real-valued random variable, along with the central distribution theorem guides clinicians in making choices that are applicable to most of their patients. The normal distribution represents data in which 68%, 95%, and 99.7% of the values fall within one, two, and three standard deviations (SDs) of the mean, respectively.[5,6] The majority of the population (95%), therefore, falls within 2 SDs of the mean, but a small percentage of people are statistical outliers.

Even though the Gaussian Curve is an important tool for the clinical acceptability of any intervention, it is important to remember that even though the results of various clinical trials may hold true for the majority of patients, it is impossible to ascertain which patients it will work for. That is, it is impossible to predict beforehand which patient is the statistical outlier. It is, therefore, important to highlight the need for PM at a time when EBM is the core of treatment planning.

PM for Glaucoma

Glaucoma, being a largely asymptomatic disease requiring lifelong therapy, requires a constant and equitable dialogue between the doctor and patient, regarding drug efficacy, dosing, their side effects, financial constraints, socio-economic barriers, etc. Thus, the very basis of patient participation implies individualized care, customized to the needs of the patient.

There is an abundance of data available from various clinical trials with different inclusion and exclusion criteria. How to choose a treatment and follow-up a patient is affected by many factors in the clinical setting, which may be different from the clinical trials, and therefore, evidence from the real-world experience becomes as important as the evidence base, in clinical decision-making.

Real-world Evidence (RWE) Studies

As there is a lot of difference in randomized controlled trials (RCT) and the real-world situations, real-world studies look at a disease or treatment as practiced in routine clinical practice either prospectively or retrospectively.[7] There have been RWE studies in context with age-related macular degeneration and the need of intravitreal injections. These studies have found that in the real world, the situations are very different in comparison to RCTs as in clinical practice, there are many constraints for the frequency of injections and follow-ups due to economic reasons; the outcome measures are also different in RWE studies as the clinical response is based more on the clinician's discretion and patient perceptions. In many of the RCTs, the data are gathered from the patients who are adherent to the treatment and does not include the dropouts. The dropout rate can be as high as 50% after 4 years of treatment with intravitreal injections.[8] In one analysis of multiple RWE studies, Mehta *et al.*[9] have shown that there is a risk of late reactivation of the disease probably due to decreased motivation and compliance and the eye being affected second may have better outcomes due to better vision at presentation.

There is a need for more of these studies in glaucoma care so as to bring up the factors such as quality of life (QoL), patient demands, socioeconomic status, and logistic reasons which change the type of treatment, follow-up durations, and frequency of structural or functional tests in clinical practice.

Some of the factors which can affect the decision-making in the care of glaucoma patients are listed as below:

QoL for each intervention for each patient

QoL is a very important factor to be taken into consideration while managing a chronic disease like glaucoma. The patient demands, expectations from treatment, financial constraints, distance from the hospital, etc., need to be considered for treatment planning. The first-line treatment for glaucoma is prostaglandins (PG). However, in the real world, many a times, patients cannot afford or are not willing for an expensive drug. Beta-blockers, being a cheaper drug may be a good option for patients with mild glaucoma, if not contraindicated, and similarly, generic drugs can be considered in such: patients so as to improve compliance.[10]

On the other hand chronic disease like glaucoma affects the patient's QoL very badly and many patients are not able to cope up with the disease or get frustrated with the treatment which can affect the compliance. Adherence to the medicines and follow-up can be improved by giving extra time to the patients so as to know their socio-economic status, to answer their queries, to check the drug instillation technique and compliance, difficulty with the use of drugs, etc., by a doctor or trained nurse.[11]

Stress has also been recognized as an important factor in diseases with vascular factors such as glaucoma, diabetic retinopathy, optic neuropathy, and stroke as stress leads to sympathetic system activity and vascular dysregulation.[12] Thus, an empathetic treatment can have a great role in the treatment of these diseases.

Target IOP level

Target IOP, by definition, is dynamic and individual, and conforms to the principles of PM, much more than EBM. Even though attempts have been made by various authors to define target OP as per the stage of glaucoma (mild, moderate, or advanced), corneal thickness, corneal hysteresis, ocular perfusion pressure, presence of pseudoexfoliation, comorbidities, the status of the other eye, initial IOP and the disk damage, and family history; customization to the individual patient is key.

This includes patient preference, affordability, ease of access and availability, the perceived QoL costs, side effects profile, as well as a risk-benefit analysis of the intervention for the individual patient. This target IOP, moreover, is not constant during the clinical course of the disease. It changes with time, depending on the change in any of the parameters described above.[13,14]

Drug non-responders, side effects

There are many patients who are non-responders to a particular group of drugs and the side effects may be different as with different genetic make-up, the pharmacodynamics of drugs change, and thus the treatment has to be modified accordingly. Drug non-response is mainly considered to be due to different genetic make-up with the absence of the enzymes responsible for conversion of prodrugs, or drug metabolism, or the absence of receptors, etc.

Drug non-response is better guided by uniocular drug trial with IOP measurement at least after 2 weeks of treatment.[15] A drug is considered inefficacious if there is a <15% IOP lowering.[16] Drug non-response is more common with beta-blockers compared to PG analogues. In a study, where a non-responder was defined as IOP reduction <15%, as many as 10% of the patients were found consistent non-responders to latanoprost and 26% to timolol after 6 weeks of treatment.[17] In another study with IOP criteria of <20% reduction, about 25% of the patients were found non-responder to latanoprost.[18] Among PG analogs, switching to another drug can be considered as few studies have reported better response with bimatoprost or travoprost if found non-responsive to latanoprost.[19] However, among beta-blockers or carbonic anhydrase inhibitors, if one drug of a group is found ineffective, all other drugs of the same group are usually not effective, thus need shifting to another class of drug rather than shifting to another drug of the same class.

However, the drugs from the same class may be different in terms of side effects. Thus, if a drug is found effective, but has side effects, for example, stinging and bitter taste with dorzolamide and can be shifted to brinzolamide; and cardioselective beta-blockers can be chosen over non-selective beta-blockers if there are contraindications such as cardiorespiratory disease.

Poor surgical candidates

Some patients are poor surgical candidates, for example, refractory childhood glaucoma, neovascular glaucoma, history of multiple eye surgeries, uveitic glaucoma, and Iridocorneal endothelial (ICE) syndrome. The choice of surgery in these patients is guided by many factors such as the status of the conjunctiva, predictability of success with a particular surgery, socioeconomic status, distance from the hospital, and compliance to follow-up. Considering an example of a patient with uncontrolled neovascular glaucoma, glaucoma drainage devices (GDD) are considered better options than trabeculectomy and in GDDs also, the choice differs depending on the patient's IOP level, economic status.[20] A cheaper, Baerveldt (Advanced Medical Optics, Santa Ana, California, USA) like non-valved drainage device like (Aurolab aqueous drainage implant; Aravind Eye Institute, Madurai, India) may be considered in patients who cannot afford the more well-known glaucoma shunts.[21,22]

In patients who prefer surgical options over medicines, minimally-invasive glaucoma surgery (MIGS) is a good option for early-moderate glaucoma as they are supposed to have lesser complications and are conjunctival sparing surgeries. An informed decision has to be made after discussing all the available therapeutic options, their costs, along with pros and cons, etc.

Stage of glaucoma

Ocular hypertension (OHT)

Patients with OHT need less aggressive follow-up and treatment, but in certain patients, if there is progression to primary open angle glaucoma (POAG) on structural presence of retinal nerve fiber layer (RNFL) defect on slit-lamp examination, fundus photograph or optical coherence tomography (OCT) or functional tests (visual filed defect on perimetry) despite the absence of risk factors (corneal thickness, vertical cup-disc ratio, absence of family history, etc.), the patients need to be treated. In the presence of risk factors of thin cornea, higher vertical cup-disk ratio or positive family history, the patient may still be observed after explaining about the possible disease course and regular follow-up and can be started on the treatment if signs of glaucoma are noted. This may be a more acceptable option for both clinicians and patients, since even if OHT progresses to early POAG, it is still manageable with medical treatment, and does not impact visual function related QoL, provided the patient is on regular follow-up and the clinician is vigilant.

In patients with steroid-induced OHT, if the patients need to be on steroids as in kidney transplant, post-penetrating keratoplasty, etc., antiglaucoma treatment may be continued until the steroids are stopped, keeping in mind the individual risk factors.

Glaucoma

In a diagnosed glaucoma case, it is important to monitor the patient on structural (fundus photography, RNFL thickness measurement) and functional tests (visual fields) to detect the progression at the earliest. The presence of disk hemorrhage, widening of RNFL defect or new RNFL defect, progression on visual field testing warrants a great concern to know the responsible factors such as narrowing of the angles in previously open angles, missed doses, thin cornea, hypertension, nocturnal hypotension, and sleep apnea. The target IOP has to be modified keeping all of these in mind at each follow-up, and not only once the rate of progression is determined.

Figure 1 shows the sequence of how to choose and modify the medical management in OHT or early POAG depending on the patient concerns and disease course.

Decision-making in surgery

Decision of a type of surgery depends on many factors such as the type of glaucoma, desired IOP level, age of the patient,

longevity, socioeconomic status, and patient demands. MIGS are newer conjunctiva sparing devices to control IOP, for early-moderate glaucoma, where they help decrease the dependence on AGMs. However, they are costly, not available worldwide and have a steeper learning curve than conventional glaucoma surgery. MIGS can be considered for young patients or elderly patients with comorbidities as they are considered to have lesser complications and spare the conjunctiva for future glaucoma surgery. Similarly, trabeculectomy and GDDs are better options for advanced glaucoma and secondary glaucoma, respectively.

Figures 2 and 3 depict the sequence of surgical therapy to be followed in a patient with glaucoma with decision-making based on the patient characteristics, preferences, affordability, availability, surgeon training, etc.

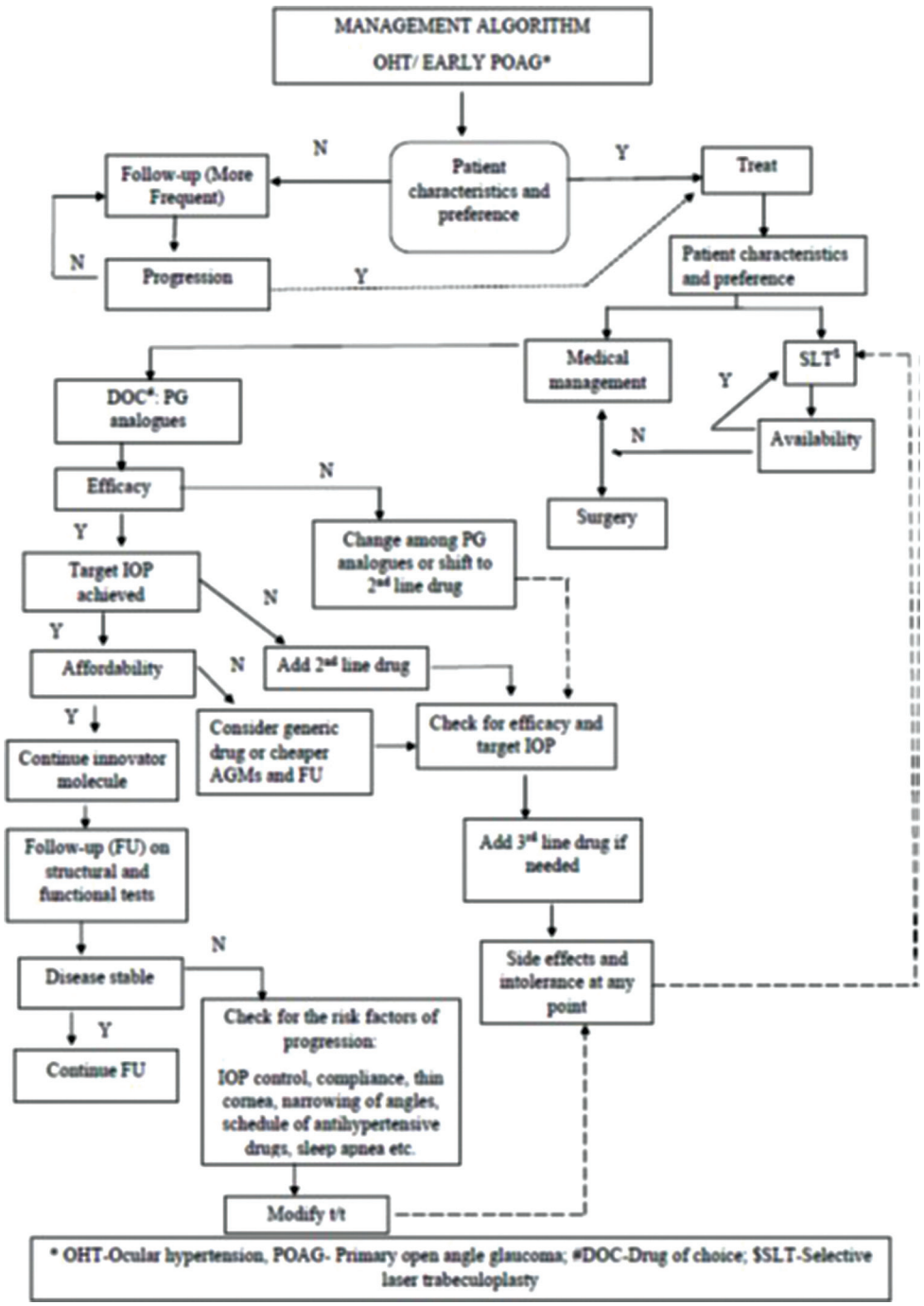

Figure 1: A flowchart of management in ocular hypertension or early primary open angle glaucoma with decision-making based on the patient demands, affordability, and tolerance to the treatment

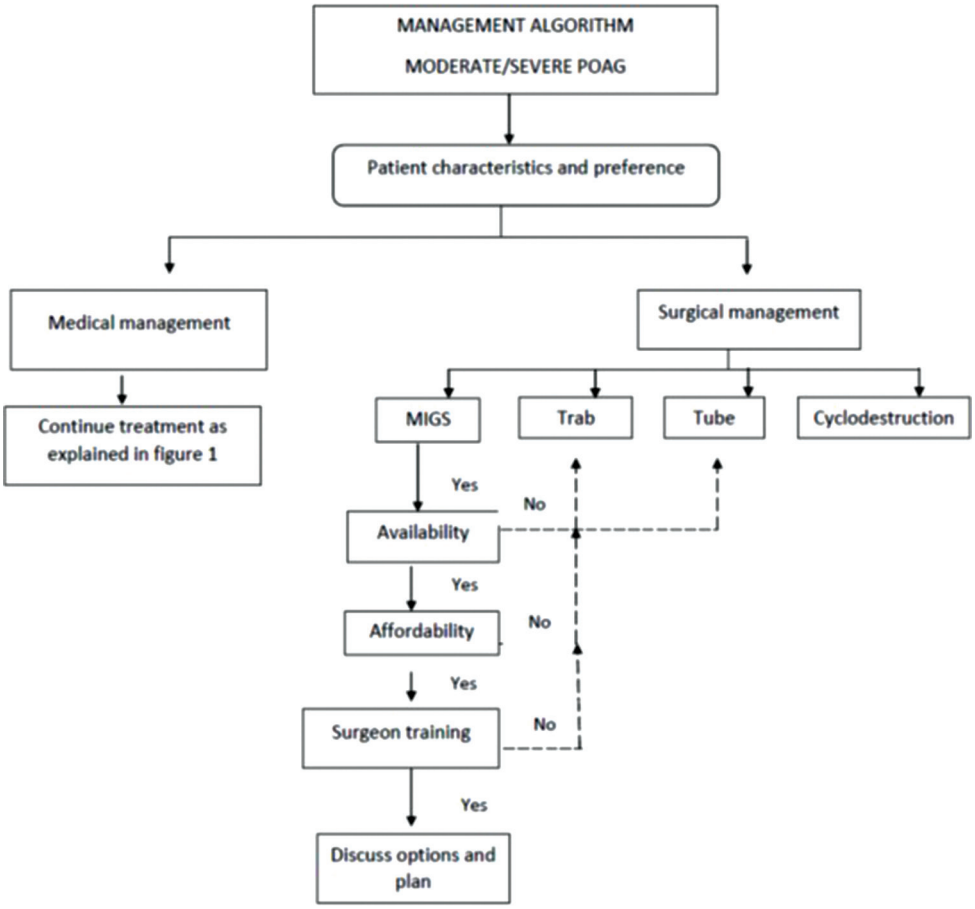

Figure 2: A flowchart of management in a case of moderate-severe primary open angle glaucoma

Newer Concepts and Therapy

N-of-1 trial or single subject trial includes a single patient for trial in view of the high need for PM as each individual has different genetic make-up. It is a study of any intervention on a single subject to see the effect of treatment.[23] The n-of-1 trials have the potential to change the treatment protocol for larger groups, since they may collect data for risk factors or surrogate endpoints that previously have not been evaluated in RCTs. N-of-1 trials do not only provide a direct benefit to the patient but they also assist the clinician in further decision-making. In fact, with continued practice, several patient characteristics that can be the differentiating factors for those that benefit more from a particular therapeutic modality of glaucoma may be identified, allowing for logical and evidence-based risk stratification of patient groups. If found beneficial, the same trial can be conducted on a large scale (n-of-1, pilot, or RCT) so as to bring out the new facts of response to a particular modality in a given patient group. Given that they cost significantly less than large population-based studies, n-of-1 trials may bring in an era of PM, backed by an evidence base.

With increasing leveraging of medical records systems and artificial intelligence (AI), the benefit of n-of-1 trials may be far more, compared with the effort involved. This may dramatically change the practice of glaucoma, as both data collection and visualization will be easier, by the integration of data capture with electronic medical records across the globe.

As in glaucoma, there are many rare diseases such as aniridia, ICE syndrome, and Fuchs cyclitic crisis where the knowledge is scanty and every patient has different clinical findings apart from glaucoma, for example, difference in lens status (subluxation in aniridia and phakia/pseudophakia), corneal status (corneal clarity, corneal graft, etc.). In these cases, a patient-centric approach is required and n-of-1 trial may provide answers.

There are many newer therapies which are still in the experimental phase or initial clinical phase which need a mention as they can be used in desperate cases. Some of these therapies are as follows:

Neuroprotection

Neuroprotection holds great importance in cases where there is a disproportionate progression of glaucoma despite controlled IOP, and also in very advanced cases. Various drugs/therapies presumed to have neuroprotective properties have still not found widespread clinical use. These include the ciliary neurotrophic factor, Memantine (NMDA receptor antagonist),

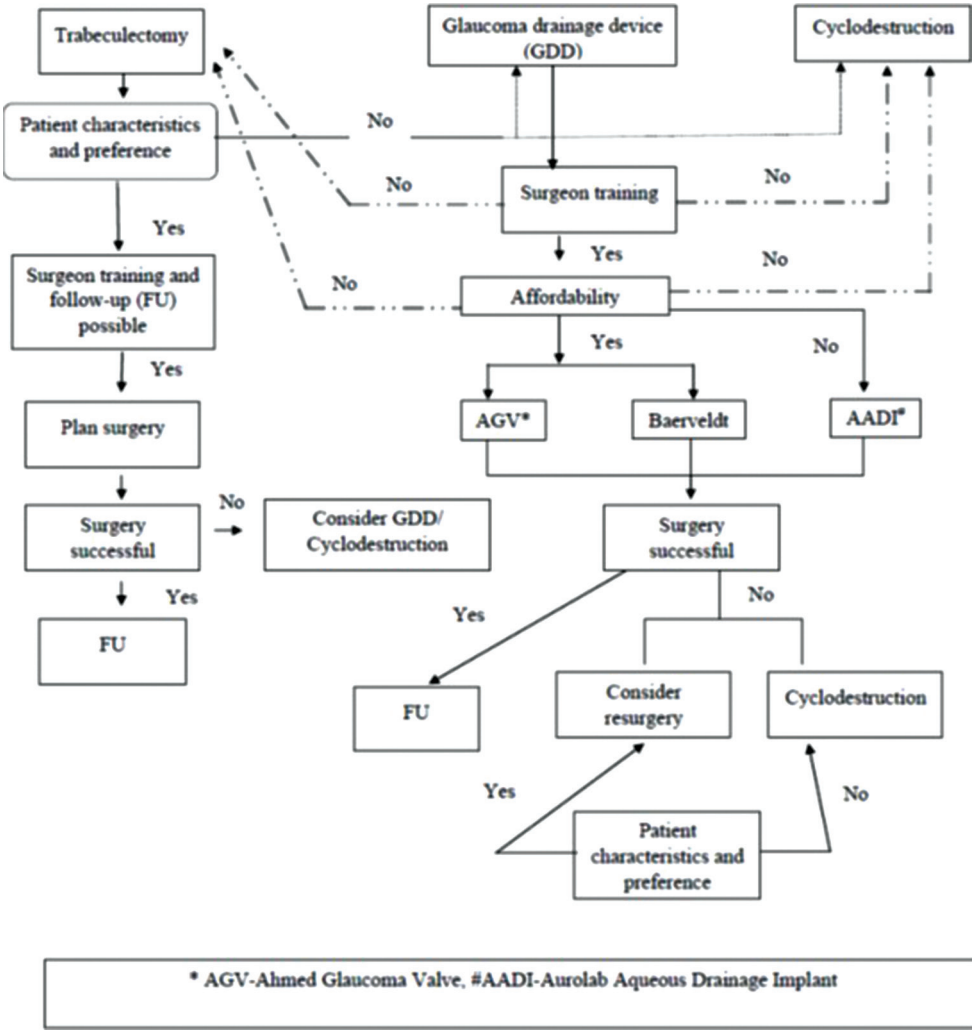

Figure 3: A flowchart of decision-making while choosing the surgical options for glaucoma (Trabeculectomy, Glaucoma drainage device, and Cyclodestruction) depending on the patient characteristics, preferences and affordability

brimonidine, nicotinamide, Ginkgo biloba extract, cell therapy, gene therapy, etc.

Nicotinamide, brimonidine, and Ginkgo biloba extract are cheaper drugs with some demonstrable neuroprotection. Nicotinamide has been found in Phase 3 studies to be effective as a mitochondrial protective by fulfilling the energy demand and reducing the retinal ganglion cells (RGCs) death.[24,25] Brimonidine has been found to have neuroprotective action as well apart from IOP reduction which is believed to be due to the upregulation of brain-derived neurotrophic factor, basic fibroblast growth factor with improvement in cell survival mechanisms and reduction in apoptotic pathways.[26-29] Few studies have reported Ginkgo biloba extract to be useful in slowing the rate of visual field progression (some of these studies report non-significant effect) in patients with normal-tension glaucoma, by its antioxidant effects and improving the blood flow with recommended doses of 40 mg thrice a day or 80 mg twice a day.[30-33] It has to be avoided in patients on anticoagulants or having bleeding disorders. Being a cheaper drug, it may be considered as a treatment option in patients with progressive glaucoma despite controlled IOP.

Yoga

Recently, yoga therapy and mindful meditation have been shown to be effective in reducing stress and IOP levels.[34] Ocular motility exercises and Tratak Kriya (staring at an object) have been hypothesized to relieve the stress and improving the trabecular meshwork outflow during accommodation and uveoscleral outflow when accommodation is relaxed. Mindful meditation has been shown to reduce the stress biomarkers, lower IOP, improve gene expression, and improved QoL.[35]

Mesenchymal stem cells (Msc) transplantation as an intravitreal injection is in the experimental phase in patients with advanced glaucoma and bilateral low vision with the treatment of the worse affected eye first as they prevent apoptosis of RGCs, but can also induce reactive gliosis in retinal astrocytes and Muller

cells with side effects of worsening of the visual acuity.[36,37] MScs can be obtained from bone marrow/adipose tissue.

Gene therapy and individualized drug for each genetic profile

The targeted therapy as per the genetic markers has been used for a long time for the treatment of breast cancer.[4] As of now, there is no gene therapy for glaucoma treatment and many studies are still underway and there is a long way to go. The glaucoma types with a single gene defect as in myocilin in juvenile open-angle glaucoma have more potential for treatment by gene therapy. In a mouse model study by Jain *et al.*,[38] where Clustered Regularly Interspaced Short Palindromic Repeats-associated systems technology has been used to modify the mutant myocilin gene has shown improvement in IOP control. The authors also studied it on human explants and have reported a decrease in myocilin-dependent RNA in trabecular meshwork cells.

Bionic eye

There has been tremendous interest in the development of visual prostheses to improve the vision of blind patients. These include retinal prostheses, visual cortical prostheses with implantation of microelectrodes in the eye (epiretinal, retinal, or subretinal) to stimulate the optic nerve or in the brain, respectively.[39,40] Argus II retinal prosthesis was found to have severe adverse effects mainly in the 1st year of implantation and the device worked in 80% of the cases.[41] Retinal prostheses are able to function only if there are few functioning retinal cells present. The image formed is of low resolution because of the non-specific stimulation of retinal cells by the electrodes and the images formed by the retinal prostheses are mainly the flashes with which the patient has to adapt to improve navigation.[42]

There is a concept of non-invasive stimulation of retina (transcorneal, transorbital, or transcranial) as well to prevent surgical complications using direct or alternating current. It has been hypothesized to stimulate as well as synchronize the firing of neurons, has neuroprotective actions with improvement in brain plasticity.[43]

Newer treatments for desperate cases

Savir (Sabel Vision Restoration) therapy therapy has been described where transorbital alternating current therapy is given by electrodes applied over the forehead and current pulses are given for 30–50 minutes for 10 days.[12,44] The treatment has been shown to improve the visual fields and the hypothesis for the same is the co-ordinated stimulation of retinal cells through which signals go to the brain and also improves the blood flow. The treatment has been found to have a persistent effect over 6–12 months and for years in some of the patients and is considered safe with minimal side effects of tingling or temporal headache during treatment.[44] The treatment however, has not found resonance or replicability elsewhere.

The human brain has a great ability to adapt as we see in a stroke patient; there is a gradual improvement in motility with time because of rearrangement of the existing neural networks. There is great hope of improving the patient's existing vision or field by different rehabilitative techniques, eye exercises, relaxation therapy, vision training, etc.[12]

How AI May Help?

Electronic medical record (EMR) systems mean that the saved data can be retrieved in a single click. EMRs also offer summary sheets which are very important in glaucoma care to document the progression and aid communication with the patient, which can help improve adherence to the treatment. Most of the glaucoma diagnostic tests including OCT, visual fields also have network interfaces with direct transfer of the information to EMR and provide an overall picture of the patient.

The incorporation of deep learning algorithms can help interpret the data, aid disease diagnosis and monitoring of progression. Data sharing can enable real time interpretation of clinical results of other surgeons, helping in clinical benchmarking. N-of-1 trials can also be conducted by a cloud system with sharing of the information and can help in improvement in the disease diagnostics and therapy for rarer diseases.

AI can help in the diagnosis of patients and predicting the disease course as it takes into account the data of so many patients with different disease severity, clinical characteristics, risk factors, and disease course.[45] The role of AI is continuously increasing for ophthalmic care for early detection of a common yet underdiagnosed disease with vision-threatening consequences including diabetic retinopathy, age-related macular degeneration, and glaucoma.[46] Models for ocular blood flow can help in the prediction of disease onset or progression as there is a complex interaction between BP, IOP, ocular perfusion pressure, retrobulbar blood flow, and cerebrospinal fluid pressure.

Genetic database and use of AI

Newer biomarkers have been developed to predict the disease onset, progression, response or side effects of drugs or surgery, many of which are still in the experimental phase, but have a great potential to improve the outcomes.[47]

Transmembrane and coiled-coil domains 1 variant has been shown to predict progression of OHT to POAG and TGFBR3-CDC7 (TGF beta-receptor type 3) locus has been found to be associated with about 6 times more progression in visual fields in POAG.[48,49]

Genome-wide association studies look at the small nucleotide polymorphisms in the whole genome to diagnose complex genetic diseases. A genetic database can be used with AI to know the possibility of a disease.

Other patient factors other than those we look at can impact glaucoma, for example, smoking, diet, yoga, and lifestyle which can be used to create an AI platform which can help with the prediction of the risk of disease onset and progression using different permutations and combinations using a large database.

AI algorithms can also incorporate modifiable patient factors like smoking, diet, exercise, and lifestyle, in risk modelling for onset as well as progression of glaucoma.

Translating Evidence from Trials into Clinical Practice

EBM is central to acceptable treatment protocols, and promises predictable results with medicolegal safety for the treating physician. It also inspires patient confidence, especially since large scale clinical trials have results that may be considered universally applicable.

Clinical trials look at a homogenous group of the patients, whereas in the real-world scenario, a treating physician has to see a heterogenous group of the patients. Furthermore, there are many trials and studies which report variable results of similar interventions and many studies may have many limitations in the study design or follow-up and there is ever-growing research with the change in concepts over time.[50,51] The individual patient characteristics often ignored in these analyses, may be the confounding factors that impact clinical outcomes dramatically.

Thus, in clinical practice, along with EBM, one must keep in mind the additional factors which can impact the treatment, including the patient's QoL concerns, comorbidities, and socioeconomic status, and modify the treatment protocol to the individual's needs.

At this point, it is also critical to remember that one should also try to modify the patient's perspective regarding the disease and use a holistic approach to modify the disease progression by giving extra time for counseling, stress management, yoga, and rehabilitation techniques for better coping ability.

In fact, more and more of real-world studies would be of a great advantage in providing guidelines for treating a variety of patients with different genetic, lifestyle, and environmental factors.

Conclusion

While EBM is the mainstay of patient treatment protocols in glaucoma, as in every other disease, glaucoma practitioners have been customizing care plans to the individual's needs since its inception. PM further refines this customization, bringing in patient centricity, patient values, and the caregivers personal experience into the treatment paradigm.

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