Primary open-angle glaucoma (POAG) is defined as a chronic and progressive disease. Date suggested that it is the second most common cause of the blindness in the world. Blindness, as a global problem, is partially consequences of poor health insurance, low medical education, etc. The only modifiable risk factor for glaucoma is intraocular pressure. Cost of the antiglaucomatous treatment increased by prescribing and using wide spectrum of antiglaucomatous drugs. If an ophthalmologist is not satisfied with glaucomatous disease control, need for the laser or surgical treatment is appeared. Disease stadium also determines the cost of the treatment. The social and economic burden of glaucoma can be changed by increased life expectancy, older population age and higher per capita GDP. Unique opinion about cost effectiveness cannot be reached, due to nonconforming findings of many studies. Treatment approach must be individualized to every patient, according to the disease's stadium, availability of therapeutic modalities and approaches, life expectancy and the level of GDP. Efficacy, compliance and potential side-effects of prescribed medication also determine the proper treatment choice.

**Key words:** primary open-angle glaucoma, therapy, pharmacoeconomics, social burden of glaucoma.

### INTRODUCTION

Primary open-angle glaucoma (POAG) is defined as a chronic and progressive disease. Also, it is a consequence of raised intraocular pressure (>21 mmHg) in at least one eye, with acquired loss of optic fibers, glaucomatous disc progression, visual field changes, and normal appearing anterior chamber angle with no underlying cause (1). It is a disease which requires life-long treatment (2). Without the adequate treatment, glaucomatous disease induces irreversible changes of the optic nerve head with consequential visual deterioration and loss. Burr et al. estimated that mild glaucomatous visual field impairment would progress to at least unilateral blindness in 23 years without the antiglaucomatous drugs (3). The minimum age limit for the occurrence of glaucoma becomes gradually decreased throughout the lifetime (38 years of age). However, glaucoma incidence raises and challenges our treatment fund (4).

Date suggested that it is the second most common cause of the blindness in the world. Quigley and Broman in their study established that in 2020, about 80 million of population will have glaucoma diagnosis in the world. Also, they calculated that 11 million of them will be blind bilaterally (5).

### THERAPEUTIC APPROACHES

The only modifiable risk factor for glaucoma is intraocular pressure (6). Visual field damages can be prevented by lowering the IOP using different therapeutically approaches: medications, laser and surgery (7).

### MEDICAL ANTIGLAUCOMATOUS THERAPY

There are five different groups of medications that can be used for IOP control: beta blockers, cholinergic, carbonic anhydrase inhibitors, alpha-2 agonists and prostaglandin analogs. Ophthalmologists, specialist for glaucoma, suggested antiglaucomatous medications as the first line drugs in treatment of glaucoma (8). Using different antiglaucomatous drugs decreased the antiglaucomatous surgeries number (9). On the other hand cost of the antiglaucomatous treatment increased by prescribing and using wide spectrum of antiglaucomatous drugs. Long term using antiglaucomatous drugs can
crease the noncompliance rate. If an ophthalmologist is not satisfied with glaucomatous disease control, the need for the laser or surgical treatment is option (7, 8, 9).

**LASER ANTIGLAUCOMATOUS THERAPY**

According to the ocular finding as well as the IOP value, different laser techniques can be used for controlling IOP (10). Trabeculoplasty done with argon or diode laser, gave similar results (50% with diode laser treated eyes and 58% with argon laser treated eyes were successful after 5 years) (11). Selective trabeculoplasty can be the first choice of glaucoma treatment in some cases. Data suggested that LTP as initial treatment in 50% of patients did not demand additional medical treatment for 1-2 years (12).

**SURGICAL THERAPY**

Long-term use of antiglaucomatous drugs can lead to the fund insufficiency in the developing countries (13). Surgical treatment of glaucoma can help in solving this economic problem. Different surgical techniques can be used for IOP control. Basically, creating of alternative outflow of humour aqueous is the target of antiglaucomatous surgery. Trabeculectomy, as the main surgical technique, make the fistula through the sclera from anterior chamber to subconjunctival spaces. Wound healing can decrease the outcome of the surgery (14). The success rate can be improved using antimetabolites (mytomycin C, 5 fluorouracil) (15) or beta irradiation (16). If the antiglaucomatous surgery did not provide IOP control, glaucoma drainage devices are reserved (17). Also, some other surgical techniques were described for IOP control: trabecular aspiration, goniocurettage, laser trabecular ablation, angle shunting devices and translceral cyclophotocoagulation or cryoablation (17).

**NEW TREATMENT OPTION**

No matter how powerful the different antiglaucomatous drugs are, the glaucoma is still the second cause of blindness in the world (17). Also, despite the fact that IOP is normal, optic nerve damage progresses. This fact proves the statement that some improvements must be made in order to gain the better control of glaucoma disease. IOP control is not enough for controlling glaucoma disease, but neuro-protection or neuro-regeneration can improve control of optic nerves damages (17).

Ganglion cells apoptosis in glaucomatous eye can be explained by different mechanisms: deprivation of neurotrophic growth factors, mechanical compression with consequential ischemia, reactive astrocytosis, oxidative stress, etc (18). Lot of clinical trials was performed in order to prove the protective effect that different substances have on optic nerves. There has not been many benefits in examined groups compared to placebo groups in Phase III clinical trials (18). Recently published data suggested for new antiglaucomatous drug-Rho kinase inhibitor (RKI). It was proved that Rho kinase inhibitor inhibits Rho-associated protein kinase (ROCK)-signaling pathway. This pathway provokes cellular contraction and transdifferentiation of fibroblasts in myofibroblasts. Thus, Rho kinase inhibitor can relax trabecular meshwork, with consequently decrease resistance in outflow pathways. Also, it was documented that Rho kinase inhibitor decrease progression of glaucomatous optic disc damages acting on its blood vessel. After antiglaucomatous surgery, Rho kinase inhibitor improves its success by inhibiting myofibroblasts transdifferentiation (19).

**PHARMACOECONOMICS ASPECTS**

Blindness is reserved approximately about 90% in developing countries (20). Blindness, as the global problem, is partially consequences of poor health insurance, low medical education, etc. In ophthalmological world, lots of facts are known about POAG (pathogenesis, clinical signs, therapy), in developing countries knowledge about this insidious disease is very poor (21).

As glaucoma is asymptomatic when medical treatment is recommended, in developing countries surgery gives low improvement postoperatively, because of advanced stadium of glaucoma in the moment of establishing the diagnosis (21). Also, patients from developing countries showed poor acceptance of surgery suggestions (22). Developing countries reported some data which indicated that cost of surgical treatment in advanced stadium of glaucoma disease with postoperatively prescribed anti glaucomatous drugs is more expansive for the country, than medical therapy prescribed for medical treatment only (23). On the other hand, only successful surgical treatment, with postoperative IOP control, is cheaper than medical treatment (24). Non-drug costs (direct non-medical and indirect cost) accounted for 54%-66% of the overall treatment cost (25). Direct non-medical cost includes visit transportation fee, work hours off (3-8), as well as cost-time of accompanying person when visiting ophthalmologist (26, 27).

WHO Commission of Macroeconomics and health suggested that treatment which costs less than three times per capita GDP (gross domestic product) is cost effective (28).

In developing countries, data showed that default scenario for the glaucomatous patients is 4.4 up to 6 ti-
mes per capita GDP (medical treatment and eventual laser surgery) per year. Laser surgery fee in developing counties, is enough for the fee which WHO implies in cost-effectiveness definition (29).

In the consideration of surgery cost, lots of different facts are included. Wound healing is one of them. Postoperatively, scar wound healing is not rare complication (30). It is the consequence of the great prevalence of capsular glaucoma (31). So, antimetabolites must be included in the treatment. This drug raised the cost of the treatment (30, 31, 32). On the other hand, some glaucoma surgeons preferred to use radiation postoperatively (16). It is well known that â-radiation induces cataract, bleb’s leakage, postoperatively endophthalmitis, advanced and poor prognosis hypotony. All those complications, which are not so rare, need additional follow up care and expansive treatment (additional surgery, expansive antibiotics and other drugs) (30). Despite the all used tools to prevent blindness and to control glaucoma disease, blindness has an upward trend. Patients, who need more follow up care, surgeries and drugs increase their treatment cost. In the case, of earlier bad surgical antiglaucomatous experience, they do not accept suggested new surgeries (30). This situation can decrease their work abilities.

The situation is completely different in developed countries. The medical education of the patients is on higher level. Ophthalmologist and medical scientist should give more attention whether something works, to evaluating which works better, and whether it is worth the expenditure. Researchers have more resources for the evaluating the cost-effectiveness ratio and cost of the treatment alone. It makes it difficult to compare the cost of glaucoma and the costs or cost-effectiveness between studies (31, 32).

Direct cost in ocular hypertension, normal tension glaucoma and POAG, based on drug (19 different drugs) and non-drug (inpatient/outpatient, surgical or medical procedures, and diagnostic testing) costs was analyzed in Glasgow study. Its results suggested that average yearly and life time cost of glaucoma treatment is approximately similar as surgical treatment for 8-year period (33). Today, situation is different. Lots of drugs (prostaglandin analogues) become generic, which decreases the cost and increase medical treatment rate. Economic situation is also changeable, based on normal inflationary pattern, or changeable monetary trend (26).

Disease stadium also determines the cost of the treatment. Progressive stadium of the disease is more expensive for the fund than initial. European studies indicated that US$ 613 per person in 0 stadium of the disease was used for the treatment; but 1335 US$ was used in advanced stadium of the glaucoma (34). So, it implies for the improving the prevention of glaucoma progression. Non-compliant patients also increase the treatment cost (34).

By not using the prescribed therapy, expected life quality was decreased, and the cost was increased (35). These data was mentioned in the Stein et al study (36). They compared the cost of the treatment and life lasting of the three groups: no treated, PG and LTP. The results of their study showed that the cost PG group was higher than other, but the life quality and lasting was the highest in LTP group. But, it must be added that LTP treatment effect lasts for seven years (37), and additional medical or laser treatment is indicated (38).

The best and the most useful way for the glaucoma treatment is drug treatment in developed countries. We must think of its tolerating and side effects. The main reason for not using the prescribed drugs is their costs and life-long application. The glaucomatologists suggested minimal therapy switches as the initial. This state can be compromised by surgery and low vision support. Overall medical therapies accounted for around 8%–42% of the total cost of glaucoma (38). The cost of the glaucoma treatment also increases if the outdoor patients with unsuccessfully treatment referred back to the hospital (39, 40).

Glaucoma reduces quality of life (QoL) despite the fact that there is no one gold standard. QoL is a subjective category and individual approach. The relationship between disease progression and QoL are inversely proportional. QoL labeling is an important outcome in understanding disease progression and evaluating the effectiveness of health care interventions (40). Clinical signs (IOP level, visual acuity, visual field finding, side-effects of the antiglaucomatous drugs) were used for the glaucoma medication efficacy (41). Decrease visual acuity and visual filed defects have impact on vision related of life (VRQoL). These parameters make clinicians for better understanding of patients’ life quality (42).

Ocular surface disease deteriorates patient’s quality of life and work’s ability (42). Frequently use of antiglaucomatous drug during long term has influence on the ocular surface disease signs. Pisella et al. reported that 50% of all examined patients had at least one symptom after the using prescribed antiglaucomatous medications (43). OSD symptoms are more frequent in patients using preservative containing eye drops compared with patients using preservative-free eye drops (43). Converting the prescribed eye drops with preservative to preservative-free eye drops increase the quality of life of glaucomatous patients, or even the decreasing the number of application (44, 45). All those facts must be in mind of ophthalmologists when prescribing antiglaucomatous drugs.
Glaucoma diagnosis has the impact on the quality of life of glaucomatous patients in different ways (45). The cognition that glaucoma is presented changes patients’ conscience, by producing the depressive episodes and anxiety without presented any other symptoms. Also, progression of the glaucoma, decreased vision acuity, fear of blindness aggravates the life quality. Long-term follow up decreases their mental condition as well (46).

Non-compliance of glaucomatous patients, as mentioned in Mansberg et al study, is linked with fear of blindness, forgetfulness, health literacy, difficulty with drop application, and age (47). All those facts are described in Glaucoma Treatment Compliance assessment tool, authored Mansberg. Personalized information and guidance improve the compliance. In developing countries, surgery increases the compliance if medical treatment has no positive effect on the disease progression (48).

Information about the disease, potential risks, side effects of the prescribed drugs, potential blindness and inconvenience of eye drops have the impact on the compliance as well as on the quality of glaucomatous patients (49, 50).

CONCLUSION

The social and economic burden of glaucoma can be changed in order to increase the life expectancy and higher per capita GDP. Unique opinion about cost effectiveness cannot be reached because of conflict of different findings in many studies. The level of country’s development impacts on the final finding of those studies. In the developing nation, individual patient availability and affordability to treatment may vary the treatment choice. Treatment approached must be individualized to each patient according to disease’s stadium, availability of therapeutic modalities, life expectancy and level of GDP. Efficacy, compliance and potential side-effects of prescribed medication also determine the proper treatment choice.

Conflict of interest

Authors confirmed that no actual or potential conflict of interest exists in relation to this article.

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There were no external funding source for this study.

Abbreviations

POAG — Primary-Open Angle Glaucoma
GDP — Global personal
IOP — intraocular pressure
LTP — laser-trabeculoplasty
RKI — Rho kinase inhibitor
ROCK — Rho-associated protein kinase
QoL — quality of life
VRQoL — vision related quality of life

Sažetak

PRIMARNI GLAUKOM OTVORENOG UGLA I FARMAKOEKONOMIJA

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Primarni glaukom otvorenog uga (POAG) se definiše kao hronična i progresivna bolest. Glaukom predstavlja drugi najčešći uzrok sleplila u svetu. Slepilo, kao globalni problem, je delimično posledica lošeg zdravstvenog osiguranja, loše medicinske edukacije, itd. Faktor rizika na koji može da se utiče je visina intraokularnog pritiska. Troškovi antiglaukomskog tretmana povećani su zbog propisivanja i korišćenja širokog spektra antiglaukomskih lekova. Ako oftalmolog nije zadovoljan kontrolom glaukomske bolesti, ukazuje se potreba za laserom i/ili hirurškim tretmanom. Razvojni stadiumi bolesti takođe određuju troškove lećenja. Socijalni i ekonomski teret glaukoma može da se promeni zbog povećanja životnog standarda, starije dobi stanovništva i većeg bruto ličnog dohotka (GDP) po glavi stanovnika. Jedinstven stav o troškovima efektivnosti ne može da se postavi zbog sukoba različitih nalaza u mnogim studijama. Terapija glaukoma ima individualni pristup za svakog pacijenta u zavisnosti od stadijuma bolesti, dostupnih terapijskih modaliteta, očekivane dužine života i nivoa BDP. Eftikasnost, pridržavanje tretmana i potencijalnih sporednih efekata propisanog leka određuje potencijalnu terapiju glaukomne bolesti.

Ključne reči: primarni glaukom otvorenog uga, terapija, farmakoekonomija, socioekonomski aspekt.
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