

Clinical and therapeutic profile of patients with glaucoma treated with latanoprost without macroglycerol-40 hydroxystearate (MGHS-40) – observational study



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ABSTRACT

Purpose: The aim of the study was to evaluate the clinical and therapeutic profile of patients with open-angle glaucoma (OAG) and intraocular hypertension (IHT) who were treated with latanoprost eye drops without macroglycerol-40 hydroxystearate (MGHS-40).

Methods: This was a multicenter, open-label, observational, non-interventional study evaluating the clinical and therapeutic profile of patients with glaucoma who received therapy with latanoprost eye drops, without MGHS-40. The study, conducted between April 2022 and July 2023, involved 7171 patients and 270 physician-investigators from across the country. The study included adult patients with OAG and IHT in whom the physician made an independent decision to change therapy or include a drug containing latanoprost without MGHS-40.

Results: The results of the study showed that the mean intraocular pressure in this group of patients was 22.6 mmHg. Most of the study participants had a diagnosis of comorbidities – the most common being high blood pressure. Risk factors for OAG were also noted in more than 70% of patients. Predominant among these were a positive family history and smoking.

Conclusion: Our study shows that the latanoprost therapy without MGHS-40 is effective in lowering intraocular pressure. The main factors determining a doctor's decision to use latanoprost without MGHS-40 were good topical tolerability and a simple formulation. The results suggest that this formulation has properties that could enhance patient compliance, possibly increasing long-term intraocular pressure-lowering effectiveness.

Key words: glaucoma, treating with latanoprost, latanoprost without macroglycerol-40 hydroxystearate, MGHS-40

HIGHLIGHTS

The latanoprost glaucoma open-angle glaucoma and intraocular hypertension therapy without MGHS-40 is effective in lowering intraocular pressure and presents good topical tolerability.

INTRODUCTION

In ophthalmology, the possibility of administering a drug directly into the ophthalmic tissues is commonly used, which allows the therapeutic substance to act at the target site. Ophthalmic medications, due to the high sensitivity of the ophthalmic tissues to external factors, must meet high requirements for their composition and properties. In order to achieve the expected physical and chemical characteristics, manufacturers use numerous additives. The most common excipients used in ophthalmic medications are preservatives that ensure the sterility of the drug during its use, isotonic substances, substances that increase the solubility of the active substance, as well as buffers (e.g. EDTA; *ethylenediaminetetraacetic acid*), stabilizers and antioxidants [1]. However, it should be kept in mind that additives used in ophthalmic medications are not inert to the tissues of the eye. This is particularly important in chronic glaucoma therapy, when prolonged use of drugs can cause adverse reactions. The reason for their occurrence may be the content and nature of additives, the way the patient uses the drops, or chronic contact of the ocular surface with the active substance. The example of additives with irritant potential are preservatives, which have antibacterial and antifungal effects, but can cause pain, discomfort, burning, and even superficial keratitis in patients [2]. In accordance with the guidelines of the Polish Society of Ophthalmology (PTO), therapy with preservative-free preparations should be considered in patients with baseline ocular surface disease (OSD) [3]. Another option is the use of substances in ophthalmic medications that increase the solubility of the active substance (detergents). One of these is the saturated fatty acid derivative macroglycerol-40 hydroxystearate (MGHS-40). In an *in vitro* study, the cytotoxic effect on corneal epithelial cell culture and the pro-inflammatory effect of MGHS-40 contained in the preparation of latanoprost without preservatives were demonstrated [4]. Macrogels should not be applied in eye preparations due to their high hygroscopicity and induction of soreness in the eye tissues [5].

Due to the paucity of studies on the use of ophthalmic medications without detergents, an observational study was conducted to verify what is the clinical and therapeutic profile of patients whose physician chose to use latanoprost therapy without MGHS-40.

MATERIALS AND METHODS

The aim of this multicenter, open-label, observational, non-interventional study was to evaluate the clinical and therapeutic profile of patients with open-angle glaucoma (OAG) and intraocular hypertension receiving latanoprost eye drop therapy without MGHS-40. The study, conducted between April 2022 and July 2023, involved 7171 patients and 270 physician-investigators from across the coun-

try. The study included adult patients with OAG and IHT in whom the physician made an independent decision to change therapy or include a drug containing latanoprost without MGHS-40. The study did not require any laboratory, diagnostic or therapeutic procedures other than those used as standard therapy. The study was based solely on observation and interview with the patient based on a prepared interview questionnaire.

Statistical analysis

Statistical analysis was performed using data obtained from all patients who met all inclusion criteria and no exclusion criteria and were included in the study. The use of a standardized research technique in the form of a questionnaire interview, which consisted of filling out the same questionnaire by all physician-researchers on the basis of an interview with patients, enabled counting the phenomena resulting from the collected data.

Analysis of the data obtained was based on the following statistics:

- spread – the difference between the maximum and minimum values
- mean (arithmetic) – the average calculated from the sum of all values by the number; sensitive to extreme values
- median – the mean, determined from a number that is exactly half of all values, not sensitive to extreme values
- standard deviation (SD) – the width of the spread of values around the mean; a plus/minus interval from the mean value; the larger the value of the deviation, the more scattered the values are from the mean value
- dominant – the value that occurred most frequently in the count
- quartile (Q) – division of the abundance into four equal parts of 25% each: the first quartile (Q1) up to 25%, the second (Q2) from 25% to 50%, the third (Q3) from 50% to 75%, the fourth quartile (Q4) from 75% to 100%.

In order to ensure the greatest possible accuracy of the research measurement, a sample of 7171 patients was examined, representing 9.6‰ of all glaucoma patients in Poland. This size of the study group takes into account its heterogeneity and allows for subgroup analysis of the data held in terms of all demographic and health variables, consistent with their distribution in the patient population. To ensure high standards for statistical inference, the confidence level was arbitrarily set at 99%, and the acceptable maximum error of estimation was set at 1%. The survey's sample of ophthalmologists participating in the study is 270.

RESULTS

In terms of socio-demographic structure, the majority of study participants were female (64.1%; n=4595), aged 61–70

years (29.9%; n=2143) and patients living in cities with a population of less than 50,000 (25.6%; n=1833). The mean age of patients was 64 years (± 12 years). The predominant subjects were 64 years old (dominant). The youngest participant in the study was 18 years old, and the oldest was 98 years old which was presented in table 1.

TABLE 1

Patients' age statistics.								
Mean	Standard deviation	Median	Dominant	Minimum	Maximum	Quartiles		
						25%	50%	75%
64	12	64	64	18	98	56	64	73

The table 2 were presented intraocular pressure (IOP) data. In nearly all patients, IOP was measured at the medical visit (98.6%; n=7074). The mean IOP was 22.6 mmHg.

TABLE 1

IOP at the time of the visit (mmHg).					
Mean	Standard deviation	Median	Dominant	Minimum	Maximum
22.6	4.2	23	24	5	50

The figure 1 shown the percentage of comorbidities. Comorbidities were reported in 88.5% (n=6347) of patients. Within this group, the highest percentage of patients also reported high blood pressure (39.8%; n=2523). 30% of patients (n=1903) reported dry eye syndrome, while 27.4% reported hyperlipidemia (n=1738).

Risk factors for open angle glaucoma were reported in 78.9% of patients (n=5655) which were presented on figure 2. The most commonly identified risk factors in the study sample were a positive family history and smoking, respectively: 35.6% (n=2015); 33.2% (n=1877).

The figure 3 presented the previously used topical drugs. In 59.8% (n=4286) of patients, no glaucoma therapy had been administered before. Among patients previously treated (40.2%; n=2885), topical medications predominated (93.6%; n=2713) – most commonly prostaglandin analogues (47.2%; n=1275). The other most commonly used drug types were carbonate dehydratase (anhydrase) inhibitors (37.9%; n=1025) and β -blockers (31.3%; n=847).

Among patients previously treated with a prostaglandin analogue, the majority used latanoprost (66.4%; n=846). Among those previously treated with a carbonate dehydratase (anhydrase) inhibitor, more than $\frac{3}{4}$ were using dorzolamide (77.2%; n=791). In contrast, in the group of patients using a β -blocker, the highest percentage were taking timolol (86.4%; n=732). 82.3% of patients in the study sample were prescribed latanoprost without MGHS-40 as monotherapy (n=5903). In contrast, 17.7% received combination therapy

FIGURE 1

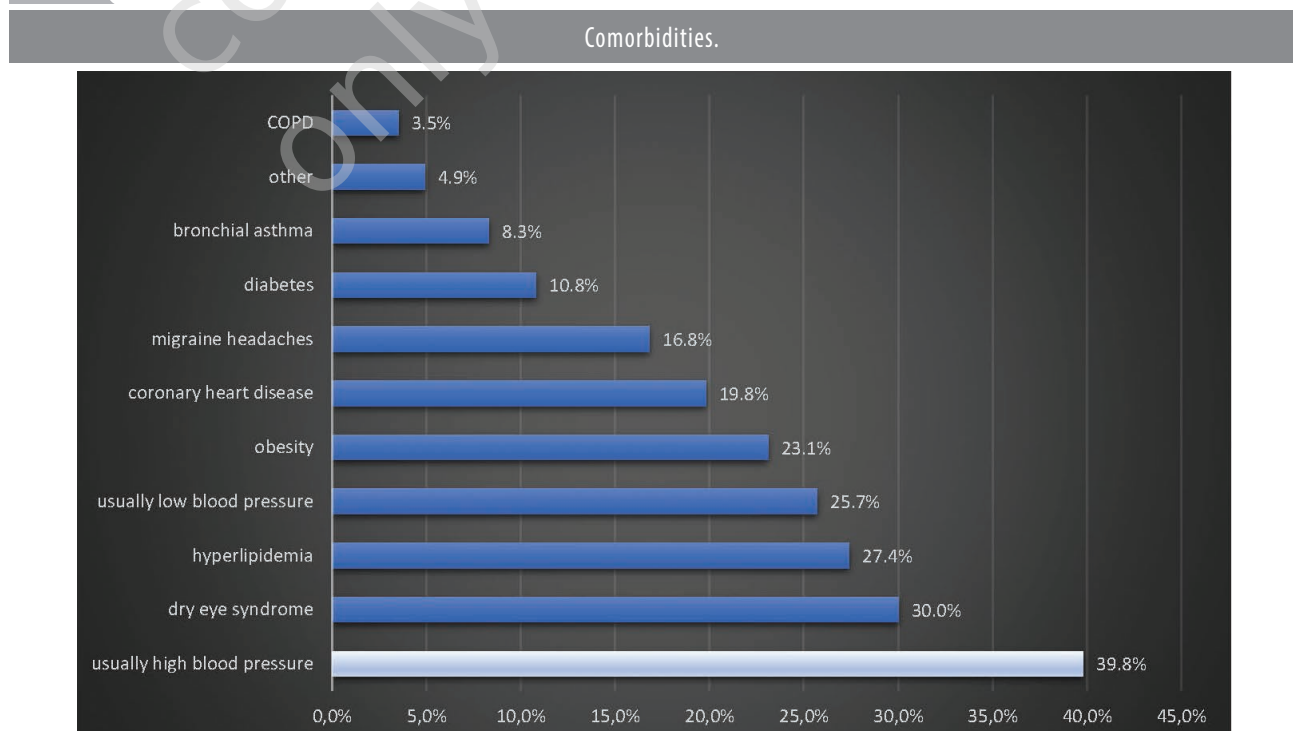


FIGURE 2

Risk factors for open angle glaucoma.

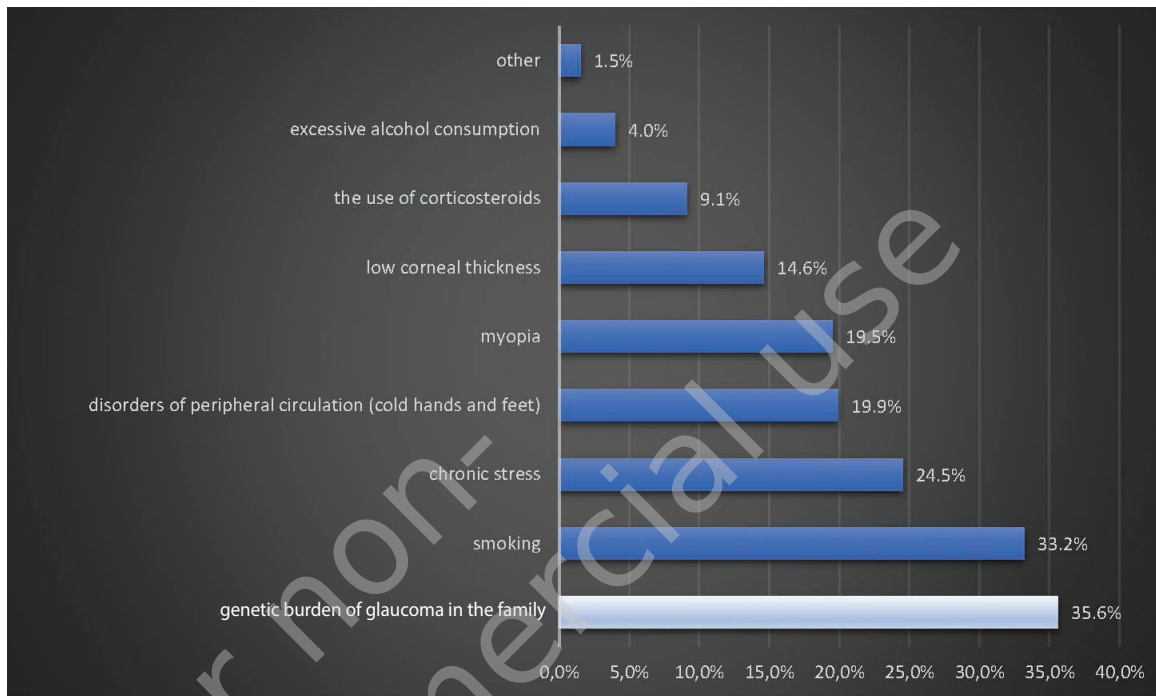
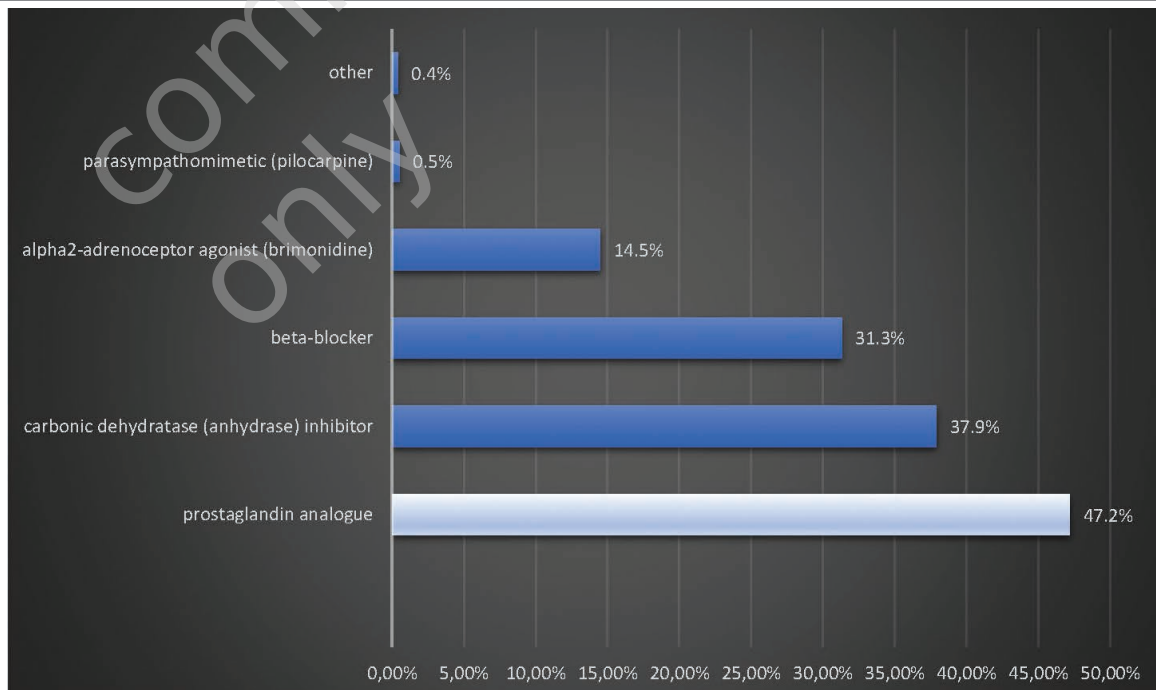


FIGURE 3

Previously used topical drugs.



(n=1268). Combination therapy with another topical drug was given to 84.2% (n=1068) of patients, while combination therapy with an oral drug/preparation was given to 22.8%

(n=289) of patients. The most frequently chosen drug combinations for topical therapy were latanoprost with dorzolamide and latanoprost with timolol (3.1% of the total study

population; n=221 and 2.6% of the total study population; n=190, respectively) which were presented on figure 4. The main factors determining the doctors' decision to use latanoprost without MGHS-40 were presented on figure 5 and were good topical tolerability (81.4%; n=5840) and sim-

ple formulation (74.1%; n=5316). The "other" category was dominated by the answer: "convenient dosage/dosing once a day". It accounted for 55.1% (n=109) of the "other" category. Analyzing the data for the entire study sample, the investigators most often indicated that they expected a reduction in

FIGURE 4

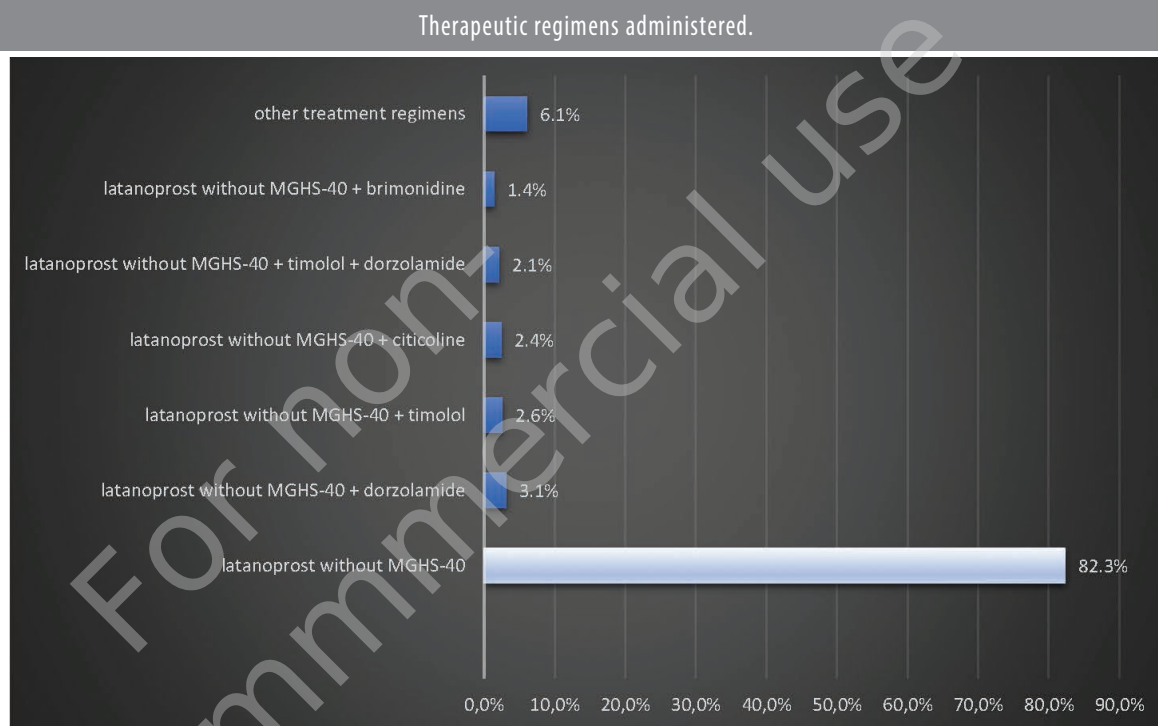


FIGURE 5

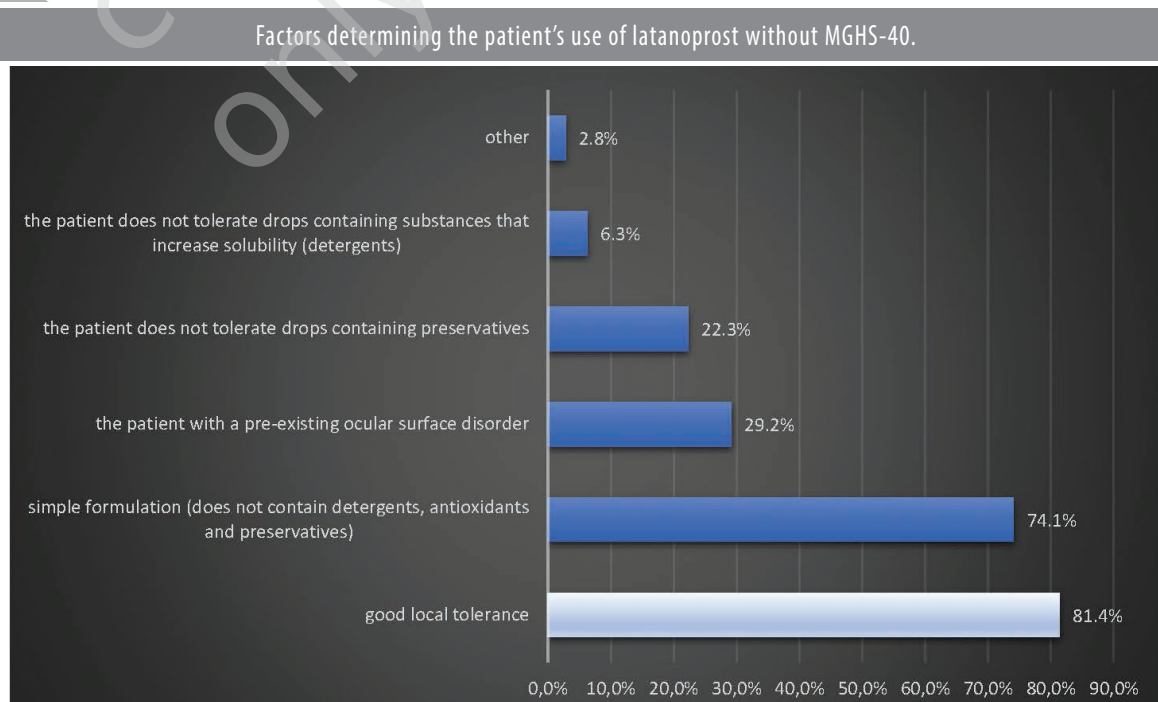
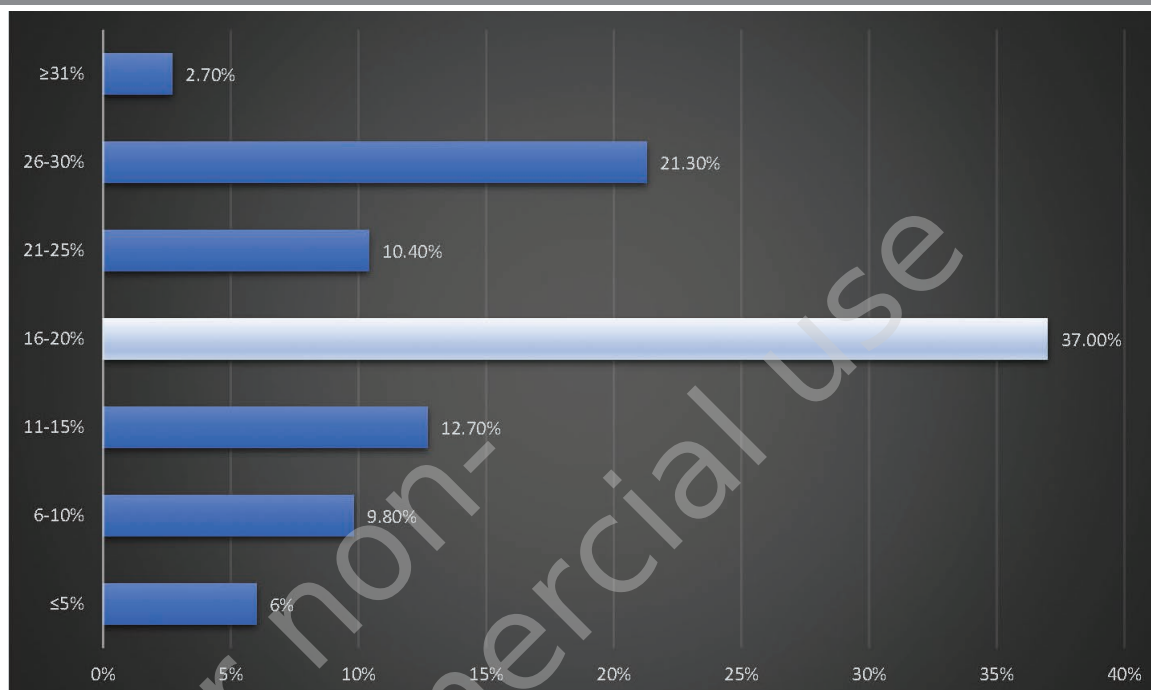


FIGURE 6

Expected reduction in IOP.



IOP (fig. 6) in the range of 16–20%. This was true for 37% of patients participating in the study (n=2656). Slightly less frequently, investigators expected an IOP reduction of 26–30% (21.3% of patients; n=1531).

DISCUSSION

Glaucoma is known as the leading cause of irreversible blindness worldwide which has an increasing prevalence with age [6–9]. It should be kept in mind that glaucoma has been diagnosed in about 80 million people worldwide, a number expected to exceed 111 million by 2040 due to the rapid aging of the population [6–9].

The incidence of glaucoma in Poland is rising due to an aging population and could rise to 1.2 million by 2035 [10]. Epidemiological estimates show that in Poland most likely about 800,000 people have glaucoma and the number could be higher [10]. Only half of them are diagnosed and treated. The distribution of glaucoma patients in Poland vs the survey is consistent in that the disease most often affects patients over 65 years of age (the dominant age in the study is 64), while the distribution of associated diseases is consistent when compared to the general population of people of that age in Poland. The epidemiology of diseases affecting patients over 65 years of age in Poland notes the following most often: myopia, diabetes and cardiovascular diseases, which is reflected in the present study.

According to World Health Organization (WHO) data, primary open angle glaucoma (POAG) is the second most common cause of blindness in highly civilized countries and about 68 million people worldwide suffer from glaucoma, and 7 million are blind due to it. Therefore, the WHO has declared glaucoma a disease of civilization. One cause of glaucoma may be elevated IOP, which causes ischemia of the optic disc and disruption of its nutrition. But in some patients with glaucoma, IOP is normal or even low. Other factors that can affect the development of glaucoma, include myopia, age after 35 years, thin corneas of the eye, low overall blood pressure, over-treated hypertension, body fat disorders, vascular disorders, and stress.

According to treatment regimens, PTO [3] as well as European Glaucoma Society (EGS) [11] recommends to start treatment with a single drug. Each patient's eye should be treated individually, choosing the best topical therapy. Prostaglandins/prostamides are recommended as a first-line drugs. Other first-line medications include β -blockers, α_2 -agonists, carbonic anhydrase inhibitors. Choosing the appropriate drug for a patient requires consideration of the degree of IOP lowering, the patient's chronic general and ophthalmic diseases, drug characteristics, drug tolerability, quality of life and cost of therapy.

Latanoprost (0.005%) was launched in 1996 and was the first of the currently available topical PGF₂ α analogues for the treatment of glaucoma. Later launches included

travoprost (0.004%), bimatoprost (0.03%), and tafluprost (0.0015%). Latanoprost still represents about 65% of prescriptions for prostaglandin analogues [12]. Prostaglandin analogues have good pressure-lowering effects, are generally well tolerated, and should be used as first-line drugs [13]. For the majority of patients included in this study latanoprost was first prescribed without MGHS-40. 82% of patients received latanoprost in monotherapy, and in the case of this study, 59,8% had no previous glaucoma therapy, so 82,3% of patients prescribed monotherapy is the standard from which practitioners start respecting the general management principles [13]. Beta-blockers have nearly equally good pressure-lowering properties, but more systemic adverse effects, and are a possible first choice as well. The treatment should be changed to another monotherapy in the first place when the prescribed drug does not work or works poorly. If the effect of the drug is good but insufficient, an additional substance is added. Such substance should belong to a different class of drugs and preferably with a different mechanism of action. To ensure good compliance, a fixed combination is usually chosen. If the pressure reduction is still inadequate, a third substance from a third group of preparations is added [13]. Latanoprost has been very well studied, with numerous published data. Preliminary studies have shown that topical once-daily latanoprost (0.005%) is both safe and effective in the short- and long-term treatment of glaucoma or ocular hypertension [12]. Alm et al. observed that 6-month treatment with latanoprost lowered IOP by 35% when given in the evening and by 31% when given in the morning [14]. Specialists assume that it is best to apply substances with as many studies as possible, which is why latanoprost is used on such a large scale and has not lost its popularity throughout the years. It is worth remembering that preservative-containing glaucoma drops are related to reduced patient adherence, which could impact on therapeutic effectiveness over time and cause an excessive public health burden [15]. Therefore, it is important to monitor the content and tolerability of all additives, not only preservatives, in eye drops administered into the conjunctival sac. Moreover, it should be emphasized that determining factors for choosing MGHS-40-free therapy is good topical tolerance and simple formulation which should not only be understood as without preservatives but also without antioxidants, detergents. To date, everyone has focused on these preservatives – this study moves the emphasis to yet the absence of other auxiliary ingredients. Nowadays, doctors' awareness in terms of topical tolerance of the formulation and the choice of a simple formulation is increasing, which is confirmed by the related studies [6, 7, 15, 16]. Patients with baseline OSD should be considered for chronic glaucoma therapy with preservative-free preparations and substitution of preservative-free lubricating drops. Using the above regimen reduces the

risk of toxic damage to the ocular surface. In order to reduce damage to the ocular surface, earlier laser and surgical procedures should also be considered for glaucoma therapy. Analogous rationale leads us to recommend the use of combination drugs when a patient requires a minimum of two drugs to inhibit disease progression (lower rate of side effects due to damage to the ocular surface, better patient cooperation, synergism of action of some preparations) [3]. Worth noting is the fact that as many as 30% of patients with glaucoma according to our study had dry eye syndrome. It should be kept in mind that in this indication it is particularly important to prescribe to the patient preparations with the simplest possible composition – not only without preservatives, but pay attention to other additives (macrogels, MGHS-40, EDTA). The data from this study are different from the general data on the prevalence of dry eye syndrome in patients in general (in Poland, the range is from 5% to 34%) [17]. Studies suggest that 40–50% of patients with glaucoma have dry eye syndrome, and women are more likely to have it than men. The relationship between glaucoma and dry eye syndrome may be due in part to glaucoma treatment. Increased use of anti-glaucoma medications and more daily dropping of anti-glaucoma eye drops are associated with OSD in patients with glaucoma [18]. Several studies suggest that more frequent use of anti-glaucoma drugs is associated with an increased risk of dry eye syndrome. Chen et al. in their study of patients with glaucoma (n=10,325) found that the odds of dry eye syndrome have increase with the number of medications used (OR=1.23 with 2 medications; OR=1.63 with 3 medications; OR=2.60 with 4 medications) [19]. Likewise, Baudouin et al. reported an increase in the incidence of OSD with the number of anti-glaucoma medications administered, the number of drops instilled daily, and a history of treatment changes due to ocular intolerance [20]. It should be emphasized that the distribution of comorbidities is consistent with the general population of people of this age in Poland. Comorbidities, such as low blood pressure is associated with lower blood flow velocity in the nailfold capillaries of glaucoma patients which was described in several studies by Gasser et al. [21–23]. Moreover, there is a link between migraines headaches and glaucoma. Migraine is associated with endothelial dysfunction and is considered a systemic vasculopathy. Curiously, systemic vascular disease also affects patients with glaucoma and is considered a vascular risk factor [24]. Migraine headaches can direct a patient to get tested for glaucoma, but such testing should be ordered by a specialist. A headache (according to the study) may be a signal for a broader diagnosis.

To sum up, drug excipients play many vital roles in medications. Ophthalmic medications, due to their characteristics, often also require the addition of excipients. Among their roles are to ensure the sterility of the drug, to maintain

isoosmoticity to avoid irritation of the eyeball, to ensure the proper pH of the drug solution, to increase the solubility of the active substance or to reduce the oxidation of medicinal substances [1]. Despite the importance of their properties, the use of excipients must be thoughtful, rational and justified. This applies both to the choice of substances and their quantity in the medicinal product. This is because it should be remembered that a matter of great importance is the tolerance of the drug. This is an individual characteristic, depending, among other things, on comorbidities, but it can also be strongly influenced by the content of excipients [2]. The development of biotechnology, as well as packaging technology, allows the use of innovative solutions to reduce the use of additives. As a result, a growing number of medicinal products are available on the market without preservatives, for instance. A detergent-free ophthalmic drug is also available on the market containing latanoprost for topical application to the conjunctival sac. The formulation does not use the detergent MGHS-40, which may contribute to the formulation's tolerability of the drug. The product uses single-dose packaging and is also free of preservatives and EDTA. With the potential to enhance the effects of antioxidants and preservatives. EDTA can increase the toxicity of eye drops and cause eye surface disease [25]. The study showed that it was the simple formulation and good topical tolerability that determined the use of the detergent-free latanoprost drug MGHS-40 in the enrolled patients who participated in the study.

CONCLUSIONS

The aim of the study was to evaluate the clinical and therapeutic profile of patients with OAG and IHT who were treated with latanoprost eye drops without MGHS-40. The results of the study showed that the mean IOP in this group of patients was 22.6 mmHg. Most of the study participants had a diagnosis of comorbidities – the most common being high blood pressure. Risk factors for OAG were also noted in more than 70% of patients. Predominant among these were a positive family history and smoking. The main factors determining the doctor's decision to use latanoprost without MGHS-40 were good topical tolerability and simple formulation.

ABBREVIATIONS

EDTA	– Ethylenediaminetetraacetic acid
EGS	– European Glaucoma Society
IHT	– Intraocular hypertension
IOP	– Intraocular pressure
MGHS-40	– Macroglycerol-40 hydroxystearate
OAG	– Open-angle glaucoma
OSD	– Ocular surface disease
OR	– Odds ratio
PTO	– Polish Society of Ophthalmology
SD	– Standard deviation
WHO	– World Health Organization
Q	– Quartile

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References

1. Kluk A, Sznitowska M, Substancje pomocnicze w lekach do oczu. *Farm Pol.* 2010; 66(8): 567-72.
2. Misiuk-Hojło M, Mulak M. Leki bez konserwantów – czy już standard w terapii jaskry? *Przeegl Okul.* 2018; 15(4): 1-2.
3. Polskie Towarzystwo Okulistyczne 2022. Wytyczne diagnostyki i leczenia jaskry (aktualizacja 2022).
4. Smedowski A, Paterno JJ, Toropainen E. Excipients of preservative-free latanoprost induced inflammatory response and cytotoxicity in immortalized human HCE-2 corneal epithelial cells. *J Biochem Pharmacol Res.* 2014; 2(4): 175-84.
5. Janicki S, Fiebig A, Sznitowska M. *Farmacja Stosowana. Podręcznik dla Studentów Farmacji.* Wydanie IV uzupełnione. Warszawa 2013.
6. Bacharach J, Ahmed IIK, Sharpe ED et al. Preservative-Free versus Benzalkonium Chloride-Preserved Latanoprost Ophthalmic Solution in Patients with Primary Open-Angle Glaucoma or Ocular Hypertension: A Phase 3 US Clinical Trial. *Clin Ophthalmol.* 2023; 17: 2575-88. <http://doi.org/10.2147/OPHT.S414015>.

7. Davuluru SS, Jess AT, Kim JSB et al. Identifying, understanding, and addressing disparities in glaucoma care in the United States. *Transl Vis Sci Technol.* 2023; 12(10): 18. <http://doi.org/10.1167/tvst.12.10.18>.
8. Tham Y-C, Li X, Wong TY, Quigley HA, Aung T, Cheng C-Y. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology.* 2014; 121(11): 2081-90. <http://doi.org/10.1016/j.ophtha.2014.05.013>.
9. Allison K, Patel D, Alabi O. Epidemiology of glaucoma: the past, present, and predictions for the future. *Cureus.* 2020; 12(11): e11686. <http://doi.org/10.7759/cureus.11686>.
10. Osial N, Kaczyńska A, Gorecka A et al. Glaucoma – the significant challenge for the healthcare system in Poland. *Journal of Education, Health and Sport.* 2022; 12(7): 30-39. <http://doi.org/10.12775/jehs.2022.12.07.004>.
11. European Glaucoma Society Terminology and Guidelines for Glaucoma, 5th ed. *Br J Ophthalmol.* 2021; 105(Suppl 1): 1-169.
12. Alm A. Latanoprost in the treatment of glaucoma. *Clin Ophthalmol.* 2014; 8: 1967-85. <http://doi.org/10.2147/OPTH.S59162>.
13. Jóhannesson G, Stille U, Taube AB et al. Guidelines for the management of open-angle glaucoma: National Program Area Eye Diseases, National Working Group Glaucoma. *Acta Ophthalmol.* 2024; 102(2): 135-50. <http://doi.org/10.1111/aos.16599>.
14. Alm A, Camras CB, Watson PG. Phase III latanoprost studies in Scandinavia, the United Kingdom and the United States. *Surv Ophthalmol.* 1997; 41(Suppl. 2): S105-10.
15. Harasymowycz P, Hutnik C, Rouland JF et al. Preserved Versus Preservative-Free Latanoprost for the Treatment of Glaucoma and Ocular Hypertension: A Post Hoc Pooled Analysis. *Adv Ther.* 2021; 38(6): 3019-31. <http://doi.org/10.1007/s12325-021-01731-9>.
16. Lee JW, Ahn HS, Chang J, Kang HY et al. Comparison of Netarsudil/Latanoprost Therapy with Latanoprost Monotherapy for Lowering Intraocular Pressure: A Systematic Review and Meta-analysis. *Korean J Ophthalmol.* 2022; 36(5): 423-34. <http://doi.org/10.3341/kjo.2022.0061>.
17. Reisner P, Malukiewicz G. Diagnostics, classification and treatment of dry eye syndrome in the era of COVID-19. *Klinika Oczna / Acta Ophthalmologica Polonica.* 2021; 123(1): 8-13. doi:10.5114/ko.2021.104746.
18. Nijm LM, Schweitzer J, Gould Blackmore J. Glaucoma and Dry Eye Disease: Opportunity to Assess and Treat. *Clin Ophthalmol.* 2023; 17: 3063-76. <http://doi.org/10.2147/OPTH.S420932>.
19. Chen HY, Lin CL, Tsai YY et al. Association between glaucoma medication usage and dry eye in Taiwan. *Optom Vis Sci.* 2015; 92(9): e227-32. <http://doi.org/10.1097/OPX.0000000000000667>.
20. Baudouin C, Renard JP, Nordmann JP et al. Prevalence and risk factors for ocular surface disease among patients treated over the long term for glaucoma or ocular hypertension. *Eur J Ophthalmol.* 2013; 23(1): 47-54. <http://doi.org/10.5301/ejo.5000181>.
21. Gasser P, Flammer J. Blood-cell velocity in the nailfold capillaries of patients with normal-tension and high-tension glaucoma. *Am J Ophthalmol.* 1991; 111: 585-8. [http://doi.org/10.1016/S0002-9394\(14\)73703-1](http://doi.org/10.1016/S0002-9394(14)73703-1).
22. Gasser P, Flammer J, Guthauser U et al. Do vasospasms provoke ocular diseases? *Angiology.* 1990; 41: 213-20. <http://doi.org/10.1177/000331979004100306>.
23. Gasser P. Ocular vasospasm: a risk factor in the pathogenesis of low-tension glaucoma. *Int Ophthalmol.* 1989; 13: 281-90. <http://doi.org/10.1007/BF02280088>.
24. Huang JY, Su CC, Wang TH et al. Migraine and increased risk of developing open angle glaucoma: a population-based cohort study. *BMC Ophthalmol.* 2019; 19: 50. <https://doi.org/10.1186/s12886-019-1062-9>.
25. Epstein SP, Ahdoot M, Marcus E et al. Comparative toxicity of preservatives on immortalized corneal and conjunctival epithelial cells. *J Ocul Pharmacol Ther.* 2009; 25(2): 113-9.

Conflict of interest:

None.

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Ethics:

The content presented in the article complies with the principles of the Helsinki Declaration, EU directives and harmonized requirements for biomedical journals.