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Pharmacological and surgical treatment of uveitic glaucoma with a focus on the latest operative techniques: a literature review

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ABSTRACT

The treatment of uveitic glaucoma (UG) is a very complex issue. The choice of an appropriate therapeutic approach depends primarily on determining the pathomechanisms responsible for the increase in intraocular pressure (IOP), but also on establishing the correct diagnosis of the underlying pathology. The first-line treatment of IOP elevation in patients with uveitis is pharmacotherapy based on the concomitant use of anti-inflammatory and IOP-lowering agents. The most commonly used topical treatment options include β-blockers and carbonic anhydrase inhibitors (CAIs). When choosing an active substance, care should always be taken to ensure that the treatment is tailored to the baseline IOP and to the patient's underlying disease and health status. The use of prostaglandin analogues in the treatment of patients with UG remains a controversial issue. Numerous studies are currently underway to evaluate the safety of new drug groups, including Rho kinase inhibitors. In approximately 30% of patients with UG pharmacological treatment is insufficient and surgical intervention is required. The current gold standard in the operative treatment of UG is trabeculectomy, but because of the unpredictability of outcomes and invasiveness of the technique, multiple attempts are made to use less invasive surgical modalities. In the most severe cases of UG, which are refractory to standard therapies, cyclodestructive procedures are employed. They achieve an IOP-lowering effect through damage to the ciliary body using a laser or low temperature. Despite being effective at reducing the IOP, cyclodestructive modalities may be associated with severe complications. The cornerstone of the management of narrow- and closed-angle uveitic glaucoma is laser iridotomy. However, it must be kept in mind that an active inflammation may shorten the duration of its patency. The management of patients with UG requires striking a balance between appropriate concomitant anti-inflammatory and IOP-lowering treatment to be able to stop progressive optic nerve damage.

KEY WORDS: uveitic glaucoma, ocular hypertension, uveitis, MIGS, trabeculectomy.

INTRODUCTION

Uveitic glaucoma (UG) is one of the most serious complications of uveitis. According to the current estimates, approximately 20% of patients diagnosed with uveitis in the United States develop glaucoma, regardless of their age, sex, and race [1]. A markedly higher probability of developing UG has been noted in patients with chronic uveitis, where the incidence is approximately 11% at five years after diagnosis, than in patients with acute uveitis, of whom approximately 7.6% develop glaucomatous optic nerve damage at 12 months [2, 3]. An increase in the IOP associated with uveitis may be intermittent or subacute, and it may initially resolve after the implementation of anti-inflammatory treatment with glucocorticoids (GCs) [4]. Correct selection of treatment modality for UG requires awareness of the variety of its associated pathomechanisms that may impact an increase in the IOP. In the mechanism of open-angle glaucoma, the following conditions should be considered: trabeculitis, especially in patients with herpetic uveitis [5]; scarring of Schlemm's canal, collector channels, and trabecular meshwork; and endothelial dysfunction, due to chronic inflammation [6]; as well as more specific mechanisms including the pro-proliferative effect of elevated levels of angiotensin-converting enzyme (ACE) on collagen in sarcoidosis [7]. A pronounced fibrotic response during active inflammation can lead to the formation of anterior and posterior synechiae [8], and peripheral retinal ischemia can result in the development of neovascular fibrous membranes

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potentially closing the filtration angle [9]. One should also bear in mind the possibility of IOP elevation caused by the chronic use of GCs, mainly topically, in some predisposed patient groups [10]. Before initiating the treatment of patients with UG, an attempt should be made to identify the primary pathomechanism underlying the increase in IOP and adjust the management modality accordingly. There are no specific guidelines for the treatment of glaucoma in patients with uveitis. Both conservative and invasive therapeutic strategies (laser-based and surgical) may be considered, including filtration procedures, glaucoma drainage devices (GDD), cyclodestructive procedures, and minimally invasive glaucoma surgery (MIGS). The literature reports on the efficacy of various UG treatment options depending on the type of uveitis are both scanty and often contradictory. This paper presents a review of published articles addressing the topic.

CONSERVATIVE TREATMENT

Because of the heterogeneous etiology and pathomechanism of ocular hypertension and glaucoma in patients with uveitis, there is no clearly defined therapeutic regimen. Each patient requires an individualized approach. Crucially, the treatment of ocular hypertension or UG must include the management of the underlying disease. The foundations of therapy include rapid and effective control of inflammation, with GCs being the drugs of choice for induction, and prevention of anterior and posterior synechiae. IOP-lowering therapies include both pharmacological and surgical methods. First-line treatment for elevated IOP is pharmacotherapy. If pharmacological treatment is unsuccessful, surgery is required. Of note, some specialists managing patients with uveitis argue that any increase in the IOP requires treatment, pointing to factors including diagnostic difficulties, rapid progression of changes, and far more frequent conversion of ocular hypertension to UG than in POAG [11, 12].

Active inflammation results in impaired absorption of antihypertensive drugs. Consequently, their therapeutic efficacy is lower than in non-inflamed eyes, averaging 70-80% [13]. In pharmacological treatment, the drugs of choice are agents inhibiting the production of aqueous humor: β-blockers and carbonic anhydrase inhibitors (CAIs).

In patients with uveitis, in the absence of general contraindications, β-blockers are usually used in first-line treatment because of their more potent hypotensive effect compared to CAIs. In patients with arrhythmias or asthma, cardioselective β-blockers are recognized as a safer option. It must be borne in mind, though, that their IOP-lowering effect is less pronounced than that of the drugs acting on the and [14] receptors. Metipranolol is contraindicated in patients with uveitis, as there have been reports of granulomatous anterior uveitis associated with the use of the drug [15, 16].

Next to β-blockers, CAIs are the most commonly used drugs for the treatment of elevated IOP in patients with uveitis. Even though their antihypertensive effect is slightly weaker compared to β-blockers, their use is associated with a markedly lower incidence of systemic adverse effects. CAIs are the only group of anti-glaucoma medications that can be used both topically and systemically (orally or intravenously). Importantly, acetazolamide has a more potent IOP-lowering effect compared to topical drugs. In addition, it is characterized by a rapid onset of action, so it is widely used to control sudden high IOP spikes associated with uveitis, and to lower the IOP rapidly in patients with acute angle closure. An additional advantage of acetazolamide is that it reduces the incidence of cystoid macular edema (CME) and optic disc edema, both of which are known to coexist with specific types of uveitis [17]. There are reports highlighting the risk of CAI-related corneal decompensation in patients with pre-existing corneal endothelial abnormalities, such as Fuchs' dystrophy, endothelitis or recent history of posterior lamellar keratoplasty [18]. Consequently, caution must be exercised when prescribing CAIs for the treatment of herpetic uveitis coexisting with endothelitis.

Brimonidine, a selective α_2-adrenergic receptor agonist, is recommended as a second-line treatment for elevated IOP in patients with uveitis. The reduction in IOP observed after taking brimonidine arises from a decrease in the production of the aqueous humor and an increase in its outflow via the uveoscleral pathway. In patients with uveitis taking brimonidine who develop symptoms of drug allergy, treatment should be discontinued immediately. In the literature, there are case reports of granulomatous uveitis caused by brimonidine, which were always preceded by a significant decrease in drug tolerance [19]. Typical drug-induced anterior uveitis developed after long-term brimonidine therapy (> 1 year) and resolved rapidly upon treatment discontinuation [20, 21].

Because of their high therapeutic efficacy and a convenient dosing scheme (once daily), prostaglandin (PG) analogues are currently the most widely used drugs in glaucoma therapy. PG analogues lower the IOP by improving the aqueous humor outflow through the uveoscleral (unconventional) and the trabecular (conventional) pathways. The improvement in outflow via the uveoscleral route takes place through direct action on the prostaglandin F receptors (FP) located on the ciliary muscle, resulting in its relaxation. This is complemented by the secretion of matrix metalloproteinases (MMPs), leading to the remodeling of the extracellular matrix and loosening of cellular junctions. Improved outflow via the conventional pathway is attributed to the direct action of PGs on the FP receptor in the trabecular meshwork but also to an indirect mechanism involving the stimulation of endogenous PG production. Together, the two mechanisms contribute to increasing extracellular matrix degradation and lowering resistance to the outflow of the aqueous humor. Importantly, endogenous PGs are responsible for inducing the inflammatory process and disrupting the blood-retina barrier (BRB) and the blood-aqueous barrier (BAB) [22]. Due to concerns about the risk of exacerbating the inflammation and bringing about complications related to the disruption of natural barriers (mainly CME), until recently PGs were in-frequently used in the treatment of UG. However, the reports on the role of PGs in increasing the risk of inflammation are inconclusive [23]. In their study, Arcieri *et al*. failed to find evidence that the three most commonly used PG analogues (latanoprost, travoprost and bimatoprost) had any effect on BAB disruption (evaluated by flare meter) in patients without a history of ocular surgery [24]. In contrast, aphakic and pseudophakic patients showed an increase in flare meter values, with six out of 48 subjects developing CME that resolved upon the discontinuation of PGs [25]. A meta-analysis by Hu *et al*. demonstrates that the incidence of CME or recurrence of inflammation in patients treated with PGs (with no history of ocular surgery) is extremely low, amounting to 0.22% and 0.09%, respectively [26]. A study by Chang *et al*., conducted on a group of patients with uveitis, found no evidence for a higher incidence of CME or recurrence of inflammation associated with PG-based treatment regimens. PG analogues are currently considered to be an extremely important treatment option for elevated IOP in patients with uveitis [27]. Nonetheless, they should be used with caution in patients after recent ophthalmic procedures that further disrupt the BAB and BRB. In addition, relative contraindications to the use of PGs include an episode of CME (either currently active or in the past) and uveitis of herpetic origin.

Parasympathomimetics have been shown to exacerbate the inflammatory process in the uvea by compromising the integrity of the BAB and BRB. Furthermore, long-term parasympathomimetic drug therapy leads to the formation of posterior synechiae. In light of these findings, they are contraindicated in patients with uveitis [28].

Rho kinase inhibitors are a new group of IOP-lowering drugs (not available on the Polish market). They produce their antihypertensive effect by improving the aqueous humor outflow through the trabecular meshwork. Their role in the treatment of ocular hypertension and glaucoma in patients with uveitis seems particularly promising. Studies on the animal model of uveitis have shown that Ripasudil, in addition to its ocular hypotensive effect, also produces anti-inflammatory reactions by reducing the number of pro-inflammatory cells and protein exudates in the anterior chamber, ciliary body, and retina. Following the administration of Ripasudil, there is a significant decrease in the level of mRNA for interleukin (IL), IL-1b, IL-6, tumor necrosis factor α (TNF-α) and monocyte chemotactic protein-1 (MCP-1) [29]. Elevated levels of these cytokines have long been known to underlie the development of uveitis. It has been argued that the observed increased Rho kinase gene polymorphism – and thus elevated levels of Rho kinase within the trabecular meshwork and Schlemm's canal in patients with Behçet's disease – may play a role in the development of inflammation and UG [30]. A study by Futakuchi *et al*. confirmed the efficacy and safety of this group of drugs in the treatment of UG. In addition, the authors found that administration of Ripasudil led to a significant decrease in the number of inflammatory cells in the anterior chamber in the study subjects [31].

INVASIVE TREATMENT

Failure or intolerance of pharmacotherapy requires surgical treatment. Studies estimate that approximately 30% patients with UG require surgery [32]. Anti-glaucoma procedures performed in uveitic eyes are associated with a higher risk of surgical failure and a higher incidence of complications than in non-uveitic eyes. Control of the inflammation prior to surgery vastly improves the efficacy of the procedure and reduces the incidence of complications [33]. The ideal time for surgical intervention is not less than three months after the resolution of inflammation. Unfortunately, patients with UG usually undergo surgery on an emergency rather than elective basis. Nevertheless, reducing inflammation is essential to ensure the safety of the procedure. This can be achieved through the preoperative use of GCs. Most authors recommend the administration of GCs at a dose equivalent to 0.5-1 mg/kg/BM of prednisone (or an equivalent dose of another glucocorticoid). The treatment should be maintained after surgery as well, and discontinued gradually by reducing the dose of the drug over a period of 1-3 months [34]. It has been shown that active inflammation persisting after surgery correlates inversely with postoperative success [35]. In view of the varied etiology and course of UG, there is no universally recognized therapeutic approach, so the best surgical procedure must be selected on a patient-by-patient basis.

Based on the available studies, a variety of surgical approaches including filtration surgery, GDD, cyclodestructive procedures, and MIGS have been successfully used to treat UG. However, it is important to note that even a minor interference in the eye with a history of uveitis disrupts the delicate homeostasis, which may reactivate the inflammation.

The most common first-line surgical procedure performed for the management of UG is trabeculectomy. The success of surgical treatment depends on a properly functioning filtering bleb. The major causes of bleb obliteration include excessive proliferation of conjunctival fibroblasts and increased collagen synthesis along with progressive subconjunctival fibrosis. It has been shown that the conjunctiva of patients with uveitis contains significantly more fibroblasts, lymphocytes, and macrophages compared to the conjunctiva of patients without uveitis, which increases the risk of faster obliteration of the filtration shunt [36]. Souissi *et al*., in their study evaluating five-year outcomes of trabeculectomy without the use of antimetabolites in patients with UG, showed that the procedure successfully reduced the IOP in the majority of patients with UG (45.5% achieved complete success, and 54.5% qualified success). However, the authors also highlighted that the outcomes of the procedure in the studied group were inferior to those reported in the literature for patients with POAG. [37]. Stavrou *et al*. demonstrated that surgery in previously unoperated eyes, combined with effective control of inflammation pre- and postoperatively, improved the surgery success rates in patients with UG. Once these criteria are satisfied, the therapeutic outcomes and complication rates are comparable in patients with UG and POAG: after five-year follow-up, the overall success rates for the IOP < 21 mmHg were 78% for UG and 82% for POAG, while the complete success rates were 53% and 67%, respectively, at $p = 0.87$) [38]. In most treatment centers, antimetabolites (mitomycin C (MMC) or 5-fluorouracil (5FUU) are administered during trabeculectomy in patients with UG to reduce bleb scarring and prolong the functionality of the filtration shunt. In addition to undeniable benefits, the use of antimetabolites during the procedure increases the risk of postoperative complications including wound leakage, infection, persistent hypotony, hypotonic maculopathy or choroidal detachment. Five years after trabeculectomy with antimetabolites in patients with UG, Kaburaki *et al.* achieved complete success (IOP < 15 mmHg without medication) in 57.1%, and qualified success (IOP < 15 mmHg with medication) in 64.7% of patients. When the IOP < 21 mmHg was adopted as the determinant of surgery success, the chance of complete success rose to 79.1% [39]. These results were not statistically significantly different from those obtained in patients with POAG, though there was a higher incidence of prolonged postoperative hypotony in the UG group ($p = 0.0063$). Kanaya *et al.* showed that trabeculectomy with MMC lowered the IOP to a comparable extent in UG and POAG patients over a 10-year follow-up (success rate for the IOP < 18 mmHg: 66.5% in the UG and 61.8% in the POAG group; for the IOP < 15 mmHg: 47.9% and 37.8% in the UG and POAG groups, respectively). Also, the authors found that surgery in the uveitic eye was not associated with a higher incidence of complications [40]. The available study findings show that the lack of postoperative control of uveitis worsens the success rate of the procedure. Some reports have shown that factors increasing the risk of surgery failure include male sex, non-granulomatous anterior uveitis or intermediate uveitis, Fuchs' heterochromia, age > 30 years, need for concurrent cataract extraction, and prior intraocular procedures [41].

The need for iridectomy during trabeculectomy surgery is believed to increase the risk of reactivation of inflammation in UG eyes [42]. Advanced filtration procedures involve the implantation of a mini-drainage device from an ab-interno (XEN stent) or ab-externo (Ex-Press and PreserFlo shunts) approach, preserving the integrity of the iris. Another advantage of mini-drainage devices is that the diameter of the implant is standardized, which ensures a predictable outflow of the aqueous humor after the procedure and reduces the risk of persistent hypotony. Furthermore, XEN and PreserFlo implantation procedures have minimal impact on the conjunctival structure, which alleviates local inflammatory response and may lower the risk of scarring of the shunt. On the other hand, some researchers argue that the permanent presence of an implant may exert an irritant effect and trigger inflammation. However, given the relatively short time of these devices on the market, their application in the treatment of UG does not have a very solid basis [43]. Lee *et al.* implanted the Ex-Press device in five patients with UG. After six months of follow-up, the IOP < 21 mmHg without anti-glaucoma medication was achieved in four patients, while one patient required antihypertensive medication to achieve the target IOP. Complications observed during the follow-up period included wound leakage requiring additional suturing (two patients) and short-term postoperative hypotony (two patients) [44]. Dhanireddy *et al.* compared the outcomes of Ex-Press device implantation in patients with UG and POAG. One year after surgery, both the IOP value and the number of anti-glaucoma medications used by patients had decreased significantly in both groups. Surgical success was achieved in 90.9% of patients with POAG, while in the group of patients with UG, the success rate was slightly lower (75%) [45]. XEN Gel Stent is a biocompatible glaucoma drainage implant made of collagen. It is used in the only filtration procedure done via an ab-interno approach. Advantages of the device include shorter surgery time compared to conventional trabeculectomy, and no need for conjunctival incision and sclerectomy, which reduces the release of proinflammatory mediators. Twelve months after XEN implantation in 24 patients with uncontrolled UG, Sng *et al.* observed a 60.2% drop in the IOP and a reduced need for anti-glaucoma medication: from 3.3 ±0.8 preoperatively to 0.4 ±0.9 one year postoperatively. After a year, 62.5% of patients did not require any IOP-lowering agents. Kaplan-Meier curve analysis showed that qualified success was achieved in 79.2% of patients who had undergone the procedure. Only four patients in this group required traditional filtration surgery for IOP control. The most frequently observed complication was transient IOP elevation caused by occlusion of the implant lumen by the Tenon capsule or subconjunctival fibrosis. For this reason, 41.7% of patients required needling, and 20.8% needed wound revision with surgical excision of the Tenon capsule. Only one patient developed persistent hypotony (> 2 months) which required bleb revision [43]. Equally promising outcomes were reported by Qureshi *et al.*, who performed emergency XEN implantation in a total of 37 eyes with decompensated UG. One year after surgery, the mean decrease in the IOP was 65%, and the number of anti-glaucoma medications used by patients had been reduced by 83%. Overall, 13.5% of patients required other surgical procedures to achieve glaucoma control [46].

In patients at high risk of trabeculectomy failure (i.e. with a history of anti-glaucoma surgery, presenting with extensive conjunctival scarring, young, with a thick Tenon capsule), the treatment of choice is seton surgery (glaucoma drainage device, GDD). The procedure involves establishing an additional pathway for the outflow of the aqueous humor from the anterior chamber into a fibrous reservoir located behind the equator around the implant. Both valved (Ahmed) and non-valved (Baerveldt, Molteno) glaucoma drainage devices have been successfully used in the treatment of UG. In their metaanalysis, Ramdas *et al.* found that the outcomes of GDD surgery (Ahmed valve and Baerveldt implant) were similarly favorable in patients with UG and POAG [47]. Compared to the POAG group, patients with UG had a slightly higher incidence of complications including CME (6.6% POAG; 12.2% UG) and postoperative hypotony (8.2% POAG; 15.8% UG), but the differences were statistically insignificant. Ahmed valve implantation is an effective method of lowering the IOP in patients with UG, but IOP control deteriorates significantly a year after the procedure. Papadaki *et al*. observed that the probability of surgical success after implantation of the Ahmed valve (defined as the IOP value between 5 and 21 mmHg + min. 25% reduction) declined from 77% (at 12 months) to 50% (four years after surgery). Qualified success, defined as the above-mentioned IOP control, but with no significant complications, was achieved in 39% of patients. At one year of follow-up, 50% of patients required anti-glaucoma medications, but the percentage rose to 74% in the fourth year of the study. Complications occurred in 17% of patients, with corneal decompensation being the most common cause of impaired visual acuity. Overall 28% of patients needed another glaucoma procedure to stabilize the IOP [48]. Nilforushan *et al*. reported that in patients with Fuchs' heterochromia, trabeculectomy resulted in better IOP control than Ahmed valve implantation [49]. Twenty-two months after the procedure, the IOP value decreased from 26.81 ±6.69 mmHg to 11.61 ±4.15 mmHg in patients after trabeculectomy. In patients after Ahmed valve implantation, the reduction was significantly less prominent (from 31.41 ±6.76 mmHg to 22.41 ±5.09 mmHg). Postoperative success at six months was comparable in both patient groups (100% trabeculectomy, 91% Ahmed valve implantation), but at 36-month follow-up, effective IOP control was seen in 76% of patients after trabeculectomy and only in 9% of patients after Ahmed valve implantation. The findings of studies comparing the efficacy of trabeculectomy and non-valved Baerveldt glaucoma implant are radically different. In the study conducted by Iverson *et al*., the cumulative probability of treatment failure five years postoperatively was 62% in the trabeculectomy group and 25% in the Baerveldt valve group ($p = 0.006$) [50]. The efficacy of the Baerveldt implant in the treatment of UG was also confirmed by Ceballos *et al*. In their study, 91.7% of patients had stable IOP two years after surgery, and 58.3% did not use anti-glaucoma drugs. The complication rate was similar to that reported in the literature for patients undergoing Baerveldt glaucoma implant surgery in other types of glaucoma [51]. Molteno non-valved implants were shown to be similarly successful to Baerveldt implants in UG therapy. According to the available studies, 10 years after implantation, the probability of maintaining the IOP < 21 mmHg is approximately 77% [52]. Chow *et al*. compared the efficacy of trabeculectomy, Ahmed valve and Baerveldt implant surgery in the treatment of UG. All methods significantly reduced the IOP and decreased the number of anti-glaucoma medications used by patients. After one year of follow-up, the surgery failure rate was 23% after Ahmed valve implantation, 18% after trabeculectomy, and only 3% after Baerveldt implant surgery ($p = 0.0015$). The majority of complications occurred at a similar rate across all groups, with the exception of early postoperative hypotony (< 4 months after surgery), which was observed in 47% of patients after trabeculectomy, 18.5% of patients after Baerveldt implant surgery, and 18% after Ahmed valve implantation. However, the incidence rates of late hypotony were comparable in all groups [53].

In recent years, non-penetrating anti-glaucoma procedures such as deep sclerectomy and viscocanalostomy have become increasingly widespread in the treatment of UG. The assumption underlying non-penetrating procedures is reducing resistance to the outflow of the aqueous humor at the filtration angle. This is done by removing the trabecular meshwork in the pericanalicular region and the endothelium of the inner wall of Schlemm's canal (so-called 'unroofing'). Both these structures have been shown to account for approximately 70-75% of the aqueous outflow resistance, so their excision results in an IOP reduction. Based on the available evidence, one of the mechanisms leading to chronic IOP elevation in patients with uveitis is an increase in the amount of the extracellular matrix within the trabecular meshwork resulting in a loss of elasticity and narrowing of intertrabecular spaces. Similar changes in the trabecular meshwork are induced by GCs. Non-penetrating procedures restore the physiological mechanisms of the outflow of the aqueous humor by removing the pathologically altered structures. Furthermore, the procedure does not involve the opening of the anterior chamber or the incision of the iris, which alleviates surgery-induced inflammation, thus reducing the risk of uveitis reactivation. This is especially relevant in patients with UG, as it significantly reduces the risk of reactivation of the underlying disease. The Descemet's window is a natural barrier against excessive filtration, so post-surgery hypotony and associated complications (such as maculopathy or choroidal detachment) are very rare. A disadvantage of non-penetrating procedures is that they are slightly less effective compared to the conventional filtration surgery. The use of anti-metabolites and anti-scarring implants during the procedure contributes to improving patient outcomes. Non-penetrating procedures are contraindicated in patients with extensive anterior synechiae. A study by Mercieca *et al*. showed that the probability of achieving the IOP < 22 mmHg was 60%, and the IOP < 19 mmHg – 51%, in patients with UG five years after deep sclerectomy. In 60% of patients, laser goniopuncture was required. The number of anti-glaucoma drugs used by patients also decreased from 3.0 ±1.2 preoperatively to 0.8 ±1.2 at the end of the follow-up period. In 16.3% of patients, other interventions were required to stabilize the IOP. The complication rate was low, with only two patients (4.6%) developing hypotony. Over a five-year period, reactivation of uveitis was noted in 37% of patients, but it was probably unrelated to the procedure [54]. Dupas *et al*. compared the efficacy and safety of deep sclerectomy and trabeculectomy in patients with UG. One year after surgery, the IOP level was comparable in both patient groups. The cumulative probability of success was 89% for trabeculectomy and 88% for deep sclerectomy. Evaluation of the degree of postoperative inflammatory response in the anterior chamber by laser flare meter revealed that a week after the procedure it was significantly greater in the eyes that underwent trabeculectomy (245.8

ph/ms) compared to the eyes treated with deep sclerectomy (38.5 ph/ms). Despite this, the incidence of complications was similar in both groups. The authors highlighted that patients who had undergone deep sclerectomy required more frequent follow-up and close monitoring, with as many as 85% needing additional procedures, mainly laser goniopuncture, to achieve the desired IOP. For comparison, the percentage of patients requiring additional procedures in the post-trabeculectomy group was significantly lower (9.5%) [55]. The advantage of viscocanlostomy over deep sclerectomy is additional widening of collapsed Schlemm's canal. Based on a follow-up of 16 patients with UG who were treated with viscocanalostomy, Salloukh *et al*. determined the total success rate of the procedure (IOP < 21 mmHg without the need for using anti-glaucoma medications and performing goniopuncture) in half of the patients three years after surgery and in only 19% five years after the procedure. The outcomes of the procedure were significantly better if the IOP < 21 mmHg with the need for anti-glaucoma medication and/or goniopuncture was defined as treatment success. Qualified success was then noted in 86% and 75% of patients at three and five years after surgery, respectively. Previous intraocular surgery was found to be a predictor of unsuccessful outcome of viscocanalostomy [42]. During viscocanalostomy, dilatation of Schlemm's canal occurs only in the immediate vicinity of the two ostia surgically created in the canal during the procedure. Studies have shown that Schlemm's canal dilated in this manner recollapses easily, which compromises the outcomes of the intervention. Placing a tension suture in Schlemm's canal and its viscodilatation at 360°, as is done during canaloplasty, helps to prevent recollapse of Schlemm's canal and thus improves surgical outcomes [56]. The therapeutic efficacy of canaloplasty in patients with POAG and secondary glaucoma (pigmentary type or pseudoexfoliation syndrome – PEX) is similar to trabeculectomy, but the procedure has a superior safety profile. The procedure involves no opening of the anterior chamber, so post-surgery inflammatory response is mild. The scleral flap in canaloplasty is tightly sutured, lowering the risk of postoperative hypotony. Moreover, there is no bleb formation, which prevents the associated complications [57]. Initial concerns about the irritating effect of the prolene suture left in Schlemm's canal have not been validated in numerous studies. No increased incidence of uveitis was observed after surgery [58]. Based on the characteristics of the procedure listed above, canaloplasty appears to be a highly promising potential treatment option for UG. At present, there are only isolated published reports on the application of canaloplasty in patients with UG. Kalin-Hajdu *et al*. found that 2.5 years after canaloplasty performed in patients with UG, effective IOP control defined as the IOP > 6 mmHg and < 21 mmHg, with a simultaneous minimum 20% reduction from baseline values, was achieved in 84.2% of patients, 73.7% of whom did not require any anti-glaucoma medication for IOP control. Furthermore, the authors noted no sight-threatening complications, nor a tendency for reactivation of uveitis after the procedure [59].

Over the past decade, the spectrum of modalities available for the treatment of UG has been extended through the introduction of minimally invasive glaucoma surgery (MIGS). MIGS procedures are characterized by a very favourable safety profile, short surgery time, and rapid visual recovery. Because of these features, they cause only minor disruption to the homeostasis of the anterior chamber, which is expected to reduce the risk of uveitis reactivation. According to the definition of the European Glaucoma Society, MIGS refers to a group of surgical procedures that are done exclusively by an ab-interno approach, preserving the integrity of the conjunctiva and sclera, which makes it possible to perform filtration surgery safely in the future. MIGS techniques can be divided into two main categories: with and without implantation of a mini-drainage device. Most MIGS procedures are contraindicated in patients with narrow filtration angle, angle abnormalities, and anterior synechiae. The IOP achieved after MIGS procedures is higher compared to filtration procedures, so the best candidates for MIGS are patients with moderate to mild glaucomatous damage [60]. One group of MIGS procedures consists of surgical techniques in which IOP reduction is achieved through implantation a mini-drainage device either into Schlemm's canal (istent, Hydrus – to improve the outflow via the conventional pathway) or into the suprachoroidal space (CyPass, iStent Supra, Gold Shunt, STARflo – to improve the uveoscleral outflow route). The other of the groups includes ab-interno trabeculotomy, which does not require a drainage implant and a decrease in the IOP is due to the excision of tissue (a strip of trabecular meshwork and the inner wall of Schlemm's canal) providing the greatest resistance to the outflow of the aqueous humor. The latter modalities have been the most widely used options in UG treatment to date. Anton *et al*. presented evidence for the therapeutic efficacy of trabeculotomy in the treatment of UG, reporting an average 40% decrease in the IOP and a reduction in the need for anti-glaucoma eye drops from 2 to 0.67 [61]. In turn, Swamy *et al*. reported the success rate of 91% in 45 eyes with UG after one year of follow-up [62]. The IOP drop was 71%, and the number of anti-glaucoma medications used by the patients had decreased from 4.0 ±1.0 to 2.5 ±1.6. The authors reported no serious complications during the follow-up period. In another study, Shimizu *et al*. compared the success rates of two surgical modalities, trabeculotomy and trabeculectomy, in patients with UG [63]. At the end of the follow-up period (mean: 40.32 ±32.53 months), the surgical success rate was higher in the trabeculectomy group (82.86%), compared to 75% in the trabeculotomy group.

Other ab-interno trabeculotomy methods are also used in the treatment of UG. A preliminary study by Miller *et al*. found that using the Kahook blade for the procedure led to a 62.5% reduction in the IOP and significantly decreased the use of anti-glaucoma medications at the end of the five-month follow-up period [64]. A slightly longer follow-up was reported by Parikh *et al*., who performed GATT (Gonioscopy-Assisted Transluminal Trabeculotomy) in a total of 16

UG eyes. After one year, the authors achieved a therapeutic success in 81% of patients, with no vision-threatening complications [65]. However, they observed transient hyphema in the anterior chamber in as many as 44% of patients in the first days after surgery. In 2020, reports were published on the successful application of GATT in the treatment of UG in children with JIA [66].

Implantation of Hydrus and iStent glaucoma surgery devices is associated with favorable outcomes in the treatment of POAG [67]. Operative success in combination with short duration of the procedure and low complication rate make these implants a frequently selected option in first-line treatment. However, there are as yet no reports of their application in the therapy of UG.

At present, MIGS procedures reducing the IOP in the mechanism of connecting the anterior chamber with the suprachoroidal space are no longer performed because of numerous complications, including the loss of endothelial cells and uveitis [68]. In view of the considerations outlined above, these modalities do not have applications in the treatment of UG.

Traditionally, cyclodestructive procedures are restricted to the most severe cases of UG, which are refractory to other therapies. Cyclodestructive surgery lowers the IOP by reducing the production of the aqueous humor through destruction of the ciliary body with low temperature or laser. Cyclodestruction triggers an inflammatory response not only in the ciliary body, but also within the surrounding structures, which may provoke the recurrence of uveitis. Cakir *et al.* demonstrated that the inflammatory response in the anterior chamber, as measured by flare meter, increased significantly on the first day after transscleral diode laser cyclophotocoagulation (TDLC) and did not return to baseline values for up to 30 days after the procedure. The severity of the inflammatory response in the anterior chamber has been shown to be closely correlated with the amount of energy delivered to the site and the number of audible crackles, or 'pop sounds', heard during the procedure [69]. High power of the energy delivered, together with large treatment site, increases the risk of 'freezing' of the ciliary body, resulting in persistent hypotony, which can even lead to ocular atrophy [70]. In patients with uveitis, the risk of the complications mentioned above is far higher than in patients with other types of glaucoma, as damage to the ciliary body induced by the procedure is compounded by reduced secretion of the aqueous humor caused by the chronic inflammatory process. Sympathetic inflammation is a rare complication associated with cyclodestructive procedures. The risk of developing the complication after transscleral surgery is estimated at approximately 0.01-0.07% [71]. Effective advanced anti-inflammatory therapy (based on GCs and immunomodulatory agents) has contributed to improving the therapeutic effects of cyclodestruction. Schlote *et al.* reported on the outcomes of TDLC in patients with refractory UG. One year after the procedure, an effective IOP reduction was observed in 77.3% of patients; 63.6% required more than one anti-glaucoma procedure to achieve this outcome. In more than half of followed-up patients, there was a transient increase in inflammatory response in the anterior chamber on the first postoperative day. Only one patient developed a severe inflammatory response with a massive fibrotic reaction. During the entire follow-up period, no patient experienced reactivation of the underlying disease [72]. TDLC is known to be less effective in the pediatric population. Heinz *et al.* achieved therapeutic success in only 32% of children with UG secondary to JIA [73]. Novel cycloablative techniques (endoscopic cyclophotocoagulation – ECP, micropulses) cause less damage to surrounding tissues than conventional procedures, which is why they are also employed in the treatment of patients with less advanced glaucoma [74]. Because of lower severity of postoperative inflammatory response, new cyclodestructive modalities are a promising option for the treatment of UG, but there are, as yet, no studies demonstrating their success in this indication.

Laser therapy is used chiefly in the treatment of narrow-angle uveitic glaucoma. The primary indication for peripheral iridotomy is acute angle closure due to pupillary block. Pupillary block in patients with uveitis is most commonly caused by a fibrotic reaction in the anterior chamber leading to the formation of posterior synechiae. Occasionally, severe inflammatory process leads to what is referred to as 'pupillary seclusion', i.e. occlusion of the pupil over 360°. Gao *et al.* noted that peripheral iridotomy led to partial disruption of the BAB, persisting for up to two weeks [75]. In uveitic eyes, laser iridotomy may, therefore, exacerbate the existing inflammation. A rare complication of peripheral iridotomy, reported by Ali *et al.*, is the induction of anterior uveitis [76]. Another difficulty relating to patients with UG is maintaining the patency of iridotomy. In a study conducted by Spencer *et al.* in a group of patients with uvetis, 60.7% of peripheral iridotomies failed. By contrast, all peripheral iridotomies retained their patency in patients with a narrow angle but no uveitis. The loss of patency occurred on average in the first 85 days after surgery [77]. Therefore, in patients with uveitis the recommended treatment regimen involves several peripheral iridotomies in conjunction with aggressive anti-inflammatory therapy. Contraindications to peripheral iridotomies include very severe inflammatory response in the anterior chamber, iridocorneal contact, and corneal haze and edema. Consequently, some authors argue that the treatment of choice for acute angle closure due to uveitis should be surgical iridectomy (SI). Betts *et al.* highlighted that the risk of failure was significantly higher for peripheral iridotomy compared to SI. Peripheral iridotomy remained patent for an average of 70 days after surgery (compared to 11 years after SI). Factors identified as predictors of failed patency of peripheral iridotomy included young age (HR 0.933, $p < 0.001$) and iris bombé (HR 2.180, $p = 0.046$) [78].

Laser trabeculoplasty induces a hypotensive effect by improving the outflow of the aqueous humor via the conventional pathway. The therapeutic mechanism underlying the procedure has not been fully elucidated. According to the mechanical theory, laser energy induces scarring and 'shrinks' part of the trabecular meshwork, which leads to the stretching of intertrabecular spaces adjacent to the treatment site. The biochemical/cellular theory postulates that laser energy stimulates the recruitment and activation of macrophages in the trabecular meshwork. In addition, laser energy stimulates the release of pro-inflammatory mediators including IL-1 and TNF-α, which increase the expression of MMP, resulting in the remodeling of the trabecular structure [79]. The procedure relies on the argon and Nd:YAG lasers, and micropulses. Argon laser trabeculoplasty (ALT) causes thermal damage also to the tissues adjacent to the surgical site, triggering an inflammatory reaction in the anterior chamber which, if severe, can lead to the formation of peripheral anterior synechiae. Because of these effects, ALT is not a recommended procedure in patients with UG. In contrast to ALT, in selective laser trabeculoplasty (SLT), the energy of the laser is selectively absorbed by the pigment-containing trabecular cells, which significantly reduces damage to tissues surrounding the surgical site [78, 79]. Ayala *et al.* showed that SLT performed in 90° of the trabecular meshwork did not exacerbate the inflammatory response in the anterior chamber [80]. The risk of post-SLT inflammatory response rises in patients with a history of uveitis. Swan *et al.* demonstrated an increase in flare meter values in 10% of eyes after SLT. In addition, the authors noted that the severity of the inflammatory response was inversely proportional to the duration of remission of uveitis [81]. One year after surgery, the efficacy of SLT in patients with steroidal glaucoma who were in remission from uveitis was 65% in the study by Xiao *et al.* [82] and 72% in the study by AlObaida *et al.* [83]. In both studies, there were neither serious sight-threatening complications in the follow-up period, nor an increased incidence of reactivation of uveitis. According to preliminary reports, micropulse laser trabeculoplasty (MLT) is even less invasive and safer than SLT, however it has not been used in the treatment of UG to date [84].

CONCLUSIONS

There is no universally recognized treatment regimen for uveitic glaucoma. The majority of published studies are based on isolated clinical reports. There is a scarcity of large randomized trials with extensive control groups that could provide more comprehensive data on different therapeutic options. An integral element of UG treatment must be the management of the underlying disease. Concomitant treatment with anti-inflammatory, immunosuppressive, and IOP-lowering drugs is indicated. The pathomechanisms underlying the IOP increase should be considered in each individual patient with uveitis, as their establishment helps to select the most appropriate treatment. In first-line pharmacological therapy, the choice of active substance should be based on the treatment target, the underlying disease, and the contraindications present in the patient, if any exist. In patients who fail to achieve an improvement or are intolerant of pharmacological therapy, the treatment of choice is surgery. By controlling inflammation for a minimum of three months before the scheduled anti-glaucoma procedure, the risk of postoperative complications can be markedly reduced. Often, however, surgery is performed without full anti-inflammatory preparation because of a sudden IOP spike in uveitis patients.

The most common type of anti-glaucoma surgery in UG is trabeculectomy, but it is associated with a number of complications and a high failure rate. A review of the literature shows that there is a strong demand for other surgical methods that are safer and less invasive. It is important to stress that uveitic glaucoma affects young people, often professionally active, with a very life expectancy with the disease. Consequently, MIGS procedures are being increasingly used in the treatment of UG on account of their comparable efficacy and lower risk of vision-threatening complications. Furthermore, it is a major benefit that advanced surgical techniques can be applied at an earlier stage of the disease, with more invasive procedures reserved for further treatment.

DISCLOSURE

The authors declare no conflict of interest.

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