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Progress in the Use of Glucocorticoids and Biological Agents in Non-Infectious Uveitis

Yuxuan Liu, Xunyu Zou*, Shizhou Cheng*, Zuhai Zhang#

Department of Ophthalmology, The First Affiliated Hospital of Yangtze University, Jingzhou, China
Email: yuxuan_liua@sina.com, zzzxy9898@sina.com, shizhou_cheng@163.com, #zuhai_zhang@outlook.com

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Abstract

One of the main immune-mediated diseases that lead to avoidable blindness is non-infectious uveitis. Glucocorticoids are the first-line therapy choice for noninfectious uveitis; however, biologics are also showing promise in the management of this condition. The description of glucocorticoid and biologic usage in non-infectious uveitis is the main topic of this paper.

Keywords

Non-Infectious Uveitis, Glucocorticoids, Biological Agents

1. Introduction

Uveitis is a complex group of inflammatory diseases with a complicated etiology and pathogenesis that primarily affects young adults. Because of its recurrent nature, uveitis not only puts patients, society, and the economy at risk of financial hardship but also causes cumulative damage to the eye that results in ongoing visual impairment and even blindness [1] [2] [3]. In the United States and European countries, visual impairment due to uveitis accounts for approximately 5% - 20% of cases and 25% in developing countries [4]. Uveitis can be classified as anterior uveitis, intermediate uveitis, posterior uveitis, and total uveitis depending on the site of inflammation. It can be categorized into infectious and non-infectious uveitis (NIU) according to its etiology [2]. The main infectious causes of uveitis include bacteria, fungi, and viruses; The etiology and pathogenesis of NIU is complex and is now mainly thought to be related to autoimmune or autoinflammatory factors [5].

NIU is more common than infectious uveitis. Studies are showing that it has a

*Co-second authors.
#Corresponding author.

prevalence of 41% - 55% in China, 35% - 43% in Japan, and 25% - 45% in India [6]. An epidemiological study found that the prevalence of NIU in Australia was 80% [7]. Hsu *et al*. found that the percentage of NIU was 46.6% in Bangladesh, 10.8% in Myanmar, 24.8% in Korea, and 41.0% in Thailand [8]. Similarly, one study found that NIU accounts for 68% of uveitis in Greece [9]. Some studies have found that geographic factors may influence the prevalence of uveitis. A meta-analysis found that Europe and North America had similar prevalence rates, while Asia had a higher prevalence than both [10]. In the Joltikov *et al*. article, it was stated that anterior uveitis was the most common type of NIU, predominantly accounting for 47.5% - 93% of cases, posterior and intermediate uveitis accounted for a similar proportion, predominantly accounting for 20%, and intermediate uveitis was the least common, predominantly accounting for 10% - 15% of cases [11]. An epidemiologic study found that anterior uveitis was relatively more prevalent in developed countries, accounting for 90% of all uveitis cases in primary care settings in Western countries; posterior uveitis was more common in Africa; and total uveitis was particularly common in Japan [12]. For example, Vogt-Koyanagi-Harada disease is most common in individuals of East or South Asian ancestry but is also common in the Middle East. In the United States, the disease is most common in Hispanics or Indians [13]. With the risk of blindness associated with NIU, the treatment of NIU has also received a lot of attention from researchers. The main goal of current therapy is to control inflammation and prevent a recurrence. The main treatment regimens include glucocorticoids, biologics, and immunosuppressants. This review focuses on the use of glucocorticoids and biologics in NIU.

2. Glucocorticoids

Glucocorticoids are the first-line treatment option for NIU and are mainly used for rapid control of inflammation. Its main mechanism of action is that glucocorticoid molecules bind to soluble receptors in the cytoplasm, and the resulting complex induces or inhibits the transcription of certain mRNAs and down-regulates the expression of pro-inflammatory factors [6] [14], which in turn exerts an anti-inflammatory-action. The main treatment modalities include topical drop therapy, periocular therapy, intravitreal therapy, etc.

2.1. Topical Drop Therapy

Topical drop therapy is mainly applied to anterior uveitis [15], Eye drops including 1% prednisone acetate, 0.1% dexamethasone suspension, 0.1% fluticasone suspension, etc. The treatment regimen is every 2 hours, and the exact dosage to be used is based on the inflammation of the eyes. A data synthesis study analyzed data from two phase 3 clinics to evaluate the efficacy of 0.05% difluprednate and 1% prednisolone acetate in the treatment of endogenous anterior uveitis, It found that difluprednisolone had a higher rate of anterior chamber cell clearance than prednisolone acetate after 21 days of treatment. Meanwhile, the

study found that the most common adverse effect of the treatment was intraocular pressure (IOP) elevation [16]. Long-term use of glucocorticoid eye drops decreases patient compliance and also exacerbates the toxic effects of preservatives on the eye.

2.2. Periocular Therapy

Periocular therapy can be used to treat NIU combined with macular edema, retinal vasculitis, and vitritis [17]. Periocular triamcinolone acetonide (PTA) is 40 mg/ml of triamcinolone acetonide injected into Trans-Septal or posterior sub-Tenon's [18] to increase the drug delivery efficiency and intraocular drug concentration. The trans-septal method involves injecting the drug into the lower orbital space primarily through the skin of the lower eyelid. The posterior sub-Tenon's injection focuses on injecting the drug into the posterior sub-Tenon's area near the back of the globe. The duration of action of the drug is 3 months and the main adverse effect is higher IOP. Jung *et al.* [19] evaluated the efficacy of PTA in the treatment of NIU in a retrospective trial of non-infected uveitis patients aged ≤ 18 years. The study found that inflammation improved in 85.4% of eyes and macular edema (ME) resolved in 77.8% after 3 months postoperatively. In this study, it was shown that periocular injection therapy may be a better alternative treatment for uveitis in children.

2.3. Intravitreal Therapy

Intravitreal Glucocorticoid therapy is mainly used in conditions such as posterior uveitis when treatment is tolerant, or when there is ME and consequent loss of visual acuity [14], the advantage is that an effective concentration of the drug is injected immediately into the field of action and exerts a therapeutic effect. Currently, it includes mainly triamcinolone acetonide (TA), dexamethasone (DEX), and fluocinolone acetonide (FA). The most common adverse effects are higher IOP and cataracts. Some drugs require frequent injections for long-term benefits.

Intravitreal injections of preservative-free triamcinolone acetonide are most commonly used to treat unilateral refractory ME secondary to NIU [3]. It is commonly used at a dose of 4 mg/0.1ml and has a duration of action of 3 months. Park *et al.* [20] treated 49 patients with Behçet's disease (BD) combined with uveitis with intravitreal triamcinolone acetonide (IVTA) and conducted a follow-up study for up to 24 months. The study found that at 12 and 24 months the mean best corrected visual acuity (BCVA) in the affected eyes improved compared to baseline and that inflammation was controlled in 87% of the patients. This research shows that IVTA is an effective treatment option for patients with BD combined with uveitis who are unresponsive or intolerant to systemic medications. Ganapathy *et al.* [21] a retrospective cohort study that compared 2 mg and 4 mg of preservative-free intravitreal triamcinolone acetonide (PF-IVTA). This study indicates that the duration of treatment with 2 mg PF-IVTA is not significantly different

from the duration of treatment with 4 mg PF-IVTA and that the risk of receiving the treatment is less than doubled.

0.7 mg dexamethasone implant (Ozurdex, Allergan, Inc., Irvine, CA, USA) was approved by the FDA in 2010 for the treatment of NIU involving posterior segments [22]. It is effective for 6 months. In a multicenter, prospective study evaluated the efficacy and safety of the use of DEX implants for the treatment of non-infectious posterior uveitis (NIPU) in 241 patients. The study found that 20.5% of patients treated with DEX on day 0 had at least a 15-letter increase in visual acuity from baseline after 2 months. The study also found that central retinal thickness (CRT) was significantly reduced from baseline at 2, 6, and 18 months, with reductions of 27.4%, 18.5%, and 16.4%. This study indicates that Ozurdex is safe and effective in the treatment of NIPU [23]. Larossis *et al*. [24] assessed the efficacy of DEX and macular morphological changes by analyzing macular functional changes in children with NIU, The study found that children's visual acuity improved significantly from baseline values after 4 months of treatment; Over the entire course of treatment, the children's central macular thickness decreased from baseline and was statistically significantly difference. mfERG values were elevated and statistically different from baseline values at 1, 2, and 4 months after treatment. At the same time, it was found that mean central retinal thickness values were negatively correlated with mean visual acuity values ($R = 0.88$; $P = 0.04$), and mean mfERG amplitude was positively correlated with mean visual acuity values ($R = -0.97$; $P = 0.005$). This study showed that Ozurdex was effective and that there was a negative correlation between macular morphology and function.

0.59 mg FA implant (FAi) (Retisert®, Bausch & Lomb, Inc., Tampa, FL, USA) is the first FDA-approved implant for the treatment of non-infectious uveitis in the posterior segment of the cumulative [3]. It has a duration of action of 3 year. A multicenter Uveitis Steroid Treatment Trial (MUST) study found that patients treated with 0.59 mg FAi injections and systemic corticosteroids (supplemented with immunosuppressants when necessary) had a reduction in ME and improved vision, but the benefits of 0.59 mg FAi were more pronounced in terms of controlling inflammation over 54 months of the study [25]. Leinonen [26] reported the case history of eight patients with juvenile idiopathic arthritis-related uveitis, after treatment with FAi, the ME in the affected eye was more relieved and the vision was better than before. The case shows that 0.59 mg FAi is effective in the treatment of juvenile idiopathic arthritis-related uveitis with persistent ME.

0.18mg Fai (YUTIQ; EyePoint Pharmaceuticals, Watertown, MA, USA) was FDA-approved for the treatment of NIPU in 2018 [27], It has a duration of action of 3 years. Babel *et al*. [28] reported a case of recurrent bilateral NIPU, this patient has a history of localized corticosteroid use and intravitreal injections of TA and DEX, After bilateral injections of 0.18 mg FAi, the patient's BCVA improved from 20/60 to 20/50 in the right eye and from 20/70 to 20/40 in the left

eye, and ME and macular leakage were better than before. Similarly, Reddy *et al*. [29] studied 42 (64 eyes) patients with NIPU, the study found that among patients treated with 0.18 mg FAi, the probability of having no recurrence of disease was 68.8% after 6 months and 52.6% after 12 months. Meanwhile, the study found that only 15.6 percent of affected eyes required IOP-lowering eye drops, and 4.7 percent required surgery to lower IOP. This study demonstrates that YUTIQ is an effective option for the treatment of NIPU and that the incidence of higher IOP requiring intervention is relatively low.

0.19 mg ILUVIEN (fluocinolone acetonide [FAc] Alimera Sciences Inc., Alpharetta, GA, USA) was approved in 2019 for the prevention of NIPU recurrence [30], it has a duration of action of 3 years. Hikal *et al*. [31] evaluated the efficacy of ILUVIEN in the treatment of NIU combined with ME, the study found that after ILUVIEN treatment, 70.6% of affected eyes had better ME than before, 58.8% had better vision than before, and the study found that inflammation in the afflicted eyes was significantly less than before. This study demonstrated that 0.19 mg ILUVIEN is safe and effective in the treatment of NIU combined with ME. Similarly, Studsgaard *et al*. [32] undertook a 2-year follow-up study of 20 affected eyes treated with 0.19 mg ILUVIEN injections. The study found improved CRT and BCVA in the affected eyes compared to before. This study revealed that 0.19 mg ILUVIEN is effective in the treatment of NIU combined with ME.

2.4. Suprachoroidal Therapy

Suprachoroidal therapy is primarily used for ME associated with uveitis [33]. This treatment modality focuses on injecting CLS-TA into the suprachoroidal space to achieve a more targeted treatment and reduce the exposure of the anterior segment of the eye [34]. In a Phase III Randomized Trial evaluating the safety and efficacy of suprachoroidal injections of CLS-TA for the treatment of NIU combined with ME, the study found that BCVA improved from baseline in 47% of patients in the CLS-TA group compared with the control group; patients had a decline in central subfield thickness (CST) from baseline that was statistically significant ($P < 0.001$). Similarly, the study found that the most common ocular adverse effects were cystoid ME, eye pain at the time of surgery, and elevated IOP. This study showed that suprachoroidal injection of CLS-TA is effective in the treatment of NIU combined with ME [35]. In the same way, Ryan Henry *et al*. [36] found that suprachoroidal CLS-TA was safe and effective in the treatment of NIU with or without ME. Concurrently, this study found that after suprachoroidal CLS-TA treatment, TA plasma concentrations were <1 ng/mL in all quantifiable samples and were well tolerated over 24 weeks.

2.5. Systemic Therapy

Systemic glucocorticoid therapy consists mainly of oral prednisone or intravenous methylprednisolone, which is characterized by a fast-acting effect and is

used for rapid control of inflammation. The initial dose of oral prednisone is 1 - 1.5 mg/kg/day, which is then tapered according to the degree of inflammation to achieve disease quiescence at a dose of ≤7.5 mg/day. Intravenous methylprednisolone dose 500 mg - 1 g pulses/day over 60 min in 100 mL normal saline × 3 days followed by the oral steroid [37]. This treatment is mainly used for severe binocular uveitis, systemic diseases, or topical treatments that do not control the inflammation [38]. Although systemic glucocorticoids play an important role in the treatment of NIU, their long-term use can cause serious adverse effects such as Cushing syndrome, hypercholesterolemia, osteoporosis, and impairment of the cardiovascular system [39], If the patient needs to use systemic glucocorticoids, during the use of patients need to monitor the patient's glucose, cholesterol, hypertension, etc., and at the same time to limit the use of long-term high-dose.

3. Biologics

While conventional anti-inflammatory treatments are effective in most cases of uveitis, researchers have begun to explore alternative treatments due to factors such as toxicity, resistance, and patient compliance. Biologics mainly refer to monoclonal antibodies, cytokines, cytokine antagonists, etc. which are prepared through genetic engineering [40]. These drugs target specific components of the inflammatory pathway, allowing for more precise control of uveitis and systemic inflammation. These drugs can be used as alternatives to more traditional therapies or in combination as adjunctive therapies to traditional therapies. The biologics currently used for the treatment of NIU include anti-tumor necrosis factor-α (TNF-α) inhibitors, selective B-cell antagonists, and interleukin (IL) receptor antagonists.

3.1. Anti-TNF-α Inhibitors

TNF-α, a cytokine with pleiotropic effects on multiple cell types, is a major regulator of the inflammatory response and is involved in the pathogenesis of autoimmune diseases [41]. TNF-α inhibitors mainly act as antagonists by blocking the interaction of TNF-α with TNFR1/2 [42]. The following agents are currently approved for clinical use: infliximab (IFX), Adalimumab (ADA), Etanercept (ETN), golimumab (GLM/GOL), and Certolizumab pegol (CZP).

3.1.1. Infliximab (IFX)

Infliximab (Remicade®, Janssen Biotech, Inc. Horsham, PA, USA), a murine-human chimeric monoclonal antibody, was approved by the FDA in 1998 for the treatment of Crohn's disease, and was later used in the treatment of rheumatoid arthritis (RA) and ankylosing spondylitis (AS), among others [43], and was the first anti-TNF-α agent to be used in the treatment of uveitis. The drug works by binding to TNF-α and TNF-α receptors to reduce inflammation and thus provide a therapeutic effect [44]. The current recommended treatment

regimen is 5 mg/kg intravenous at weeks 0, 2, and 6, then every 6 - 8 weeks. The drawback may be that frequent injections are required to obtain long-term benefits. Takeuchi *et al*. [45] evaluated the efficacy of IFX in a multicenter retrospective trial in 140 patients treated with IFX for BD combined with uveitis over a 10-year follow-up period. The study found that among the 140 patients, 75.7% continued treatment for more than 10 years after receiving IFX, and 24.3% stopped treatment within 10 years. Patients who underwent IFX and continued treatment for more than 10 years showed gradual improvement in logMAR VA after IFX and reached statistical significance after 2 years of treatment; At the same time, logMAR VA showed a trend of continuous improvement over the 10 years compared to baseline; The number of patients who had recurrence of uveitis after IFX treatment (recurrence group) was 50; the number of patients who did not have recurrence of uveitis after IFX treatment (non-recurrence group) was 56. The percentage of recurrences of uveitis within 1 year of treatment was 58% and 74% within 2 years. Meanwhile, the study found that 30.7% of the 140 patients treated with IFX experienced adverse reactions, and the percentage who continued treatment for up to 10 years or more was 13.6%. This study showed that IFX was effective in treating BD combined with uveitis, with 75% of patients treated for more than 10 years, and during those 10 years, patients showed significant improvement in their vision. Although the most common form of treatment for IFX is an intravenous drip, researchers are also exploring the safety and efficacy of intravitreal injections, considering the potential side effects that may be present. It has been shown that 3 sequential intravitreal injections of IFX 6 weeks apart are safe and effective in the treatment of uveitis in combination with BD. The study by Reffa *et al*. [46] is different. One of their prospective trials studied the safety of nine consecutive intravitreal IFX injections (1 mg/0.05 ml) at 4-week intervals in patients with BD combined with active posterior uveitis; The trial found that treatment was in 22 eyes, but only 7 (35%) were successful and inflammation was controlled. During the treatment period, patients showed an improvement in BCVA compared to baseline (postoperative month 3 $P = 0.02$, postoperative month 9 $P = 0.005$), and significant improvement in vitreous clouding compared to the previous period; thirteen eyes (65%) failed treatment, with the main reason for failure being uncontrolled inflammation or further progression of the disease; This study revealed that monthly intravitreal injections of IFX for the treatment of BD combined with active posterior uveitis have a relatively high complication and failure rate and should not be used as an alternative to systemic therapy.

3.1.2. Adalimumab (ADA)

Adalimumab (Humira® AbbVie Inc. North Chicago, IL, USA) is a recombinant human immunoglobulin monoclonal antibody [47] that received FDA approval for the treatment of NIU in 2016. The main mechanism of action of ADA is to reduce plasma vascular endothelial growth factor (VEGF) production by com-

bining specifically with TNF-*α*, thus providing a therapeutic effect [48]. The current recommended treatment schedule is an initial dose of 80 mg followed by 40 mg subcutaneously every 2 weeks. The VISUALI and VISUAII trials were randomized, double-blind, controlled studies that focused on the assessment of the safety and efficacy of ADA for the treatment of NIU. The VISUALI trial, which focused on dividing patients with active NIU into an experimental group and a placebo group, found that the risk of treatment failure reduced by 44% in the ADA group compared with the placebo group (HR = 0.56; 95% CI, 0.40 - 0.76; $p < 0.001$), and that both had comparable rates of adverse events (placebo group: 960 E/100 PY, PY, experimental group: 1063 E/100 PY); The VISUAII trial, in which patients with quiescent NIU were divided into an experimental group and a placebo group, found a 48% reduction in the risk of treatment failure in the ADA group compared to the placebo group (HR = 0.52; 95% CI, 0.37 - 0.74; $p < 0.001$), and both had comparable rates of adverse events (placebo group: 884 E/100 PY, experimental group: 854 E/100 PY) [49]. This study revealed that ADA is safe and effective in the treatment of NIU. Similarly, Namba *et al*. [50] evaluated the safety and efficacy of ADA for the treatment of NIU; the study discovered that during the 52-week monitoring period, 27.9% of patients reported at least one adverse event, and 5.6% reported at least one serious adverse drug reaction, the most serious of which was infection. The study also found that patients had improved visual acuity, CRT, and anterior chamber cell grading compared to before treatment.

3.1.3. Etanercept (ETN)

Etanercept (Enbrel; Amgen, Inc. Thousand Oaks, CA, USA) is a soluble recombinant TNF receptor fusion protein, mainly composed of TNF-*α* receptor and IgG1 Fc [51], which was approved by the FDA in 1998 for the treatment of RA, AS, psoriatic arthritis(PsA) and so on. The main mechanism of action of this drug is to act as an anti-inflammatory by combining with TNF1 and TNF2 receptors thereby preventing the binding to TNF-*α* and thus providing an anti-inflammatory effect [43]. The current recommended dose is 25 mg twice a week. A retrospective trial evaluated the long-term efficacy of anti-TNF-*α* drug therapy in 142 patients with HLA-B27-positive AS combined with uveitis, this study found that IFX, ADA, and ETN could relieve ocular inflammation and reduce the number of uveitis recurrences, but the overall efficacy of ETN was inferior to that of ADA and IFX [52].

3.1.4. Golimumab (GLM/GOL)

Golimumab (Simponi® and Simponi Aria®, Janssen Biotech, Inc. Horsham, PA, USA) is a fully human monoclonal antibody that was approved by the FDA in 2009 for the treatment of RA, PsA, and AS. The main mechanism of action of this drug is to reduce the level of TNF-*α* protein and prevent TNF-*α* from combining with its receptor by binding to soluble and transmembrane TNF-*α* proteins [41]. The current recommended treatment regimen is 50 mg subcuta-

neously weekly. A multicenter prospective study found that the incidence of acute uveitis decreased from 11.1/100 patient-years to 2.2/100 patient-years after GLM treatment in patients with AS (rate ratio 0.20, 95% CI 0.04 - 0.91); It also found that disease activity indicators were significantly improved from the earlier period. This study concluded that GLM is safe and effective in the treatment of AS combined with uveitis [53]. Lanz *et al*. [54] evaluated the efficacy of GLM in the treatment of juvenile idiopathic arthritis (JIA) in combination with uveitis, this study revealed that out of 10 (17 eyes) patients with JIA combined with uveitis after failed ADA treatment, the treatment was effective after GLM treatment in 6 patients, with 2 patients experiencing complete remission of ocular inflammation and 4 patients showing improvement from the previous situation; After 3 months, the treatment was effective in 8 patients, with 4 patients experiencing complete relief of ocular inflammation and 4 patients showing improvement over the previous level. The study also found that after treatment with GLM, the dose of topical corticosteroids was reduced compared to baseline. This study demonstrated that treatment with GLM is effective in patients who are not responding to treatment with ADA. A recent animal model study found that a single intravitreal injection of GLM reduced adeno-associated virus (AAV)-mediated TNF-α-induced uveitis and retinal thickening [55]. However, due to the relatively small sample size of the above clinical trials, further trials may be required to prove its safety and efficacy.

3.1.5. Certolizumab Pegol (CZP)

Certolizumab pegol (Cimzia®, USB Pharma Inc Smyrna, GA, USA) is an Fc-free, pegylated monoclonal antibody that has received FDA approval for use in adult uveitis [55]. The mechanism of action of the drug is to combine with soluble and transmembrane TNF-α proteins thereby blocking their association with their receptors and thus having an anti-inflammatory effect. The current treatment regimen is to give a standard dose of 40 mg at weeks 0, 2, and 4, followed by monthly injections of 400 mg or 200 mg every other week. Sharon *et al*. [56] reported three cases of intractable NIU patients treated with CZP. Of the three NIU medical histories, three patients had failed previous treatment with immunomodulatory therapy or intolerance to anti-TNF inhibitors, and all three patients showed improvement in ocular inflammation after CZP treatment. A multicenter clinical trial studied its safety and efficacy in 80 patients with uveitis due to immune-mediated inflammatory diseases after CZP treatment, this study found that CZP is effective in improving visual acuity, ocular inflammation, and macular thickness; it also found that the median dose of glucocorticoids decreased after CZP use compared to before. This study revealed that CZP is safe and effective in the treatment of uveitis caused by different immune-mediated inflammatory diseases [57].

3.1.6. Licaminlimab

Licaminlimab (Oculis SA, Lausanne, Switzerland) is a novel anti-TNF-α anti-

body fragment combining a single-chain antibody fragment of TNF-α [58]. Currently, it is utilized for partial applications. A multicenter clinical study evaluates the efficacy of Licaminlimab in the treatment of non-infectious acute anterior uveitis, the study found a 56% relief rate on day 15 of Licaminlima. This study reveals that Licaminlima is effective in the treatment of acute anterior uveitis [59]. The use of this drug in uveitis is still being explored.

3.2. Selective B-Cell Antagonists

Rituximab (RTX) (Rituxan®, Genentech, South San Francisco, CA, USA) is a fully humanized anti-CD20 antibody that is approved by the FDA for the treatment of non-Hodgkin's lymphoma, chronic granulocytic leukemia, rheumatoid arthritis and other [60]. The mechanism of action of the drug may be therapeutic by eliminating the antibody-independent function of B cells and promoting T cell responses [61]. The recommended treatment regimen is 1000 mg intravenously at weeks 0 and 2 and 500 - 1000 mg every 6 months thereafter. More and more research is now focusing on its use in refractory NIU. A retrospective study by Bolletta *et al*. [62] evaluated the efficacy of Vogt-Koyanagi-Harada (VKH)) patient who were poorly controlled by conventional immunosuppressive therapy after RTX treatment, this study found that following RTX treatment, patients' mean BCVA significantly improved from 20/32 Snellen equivalents to 20/28 Snellen equivalents ($p < 0.08$); mean subfoveal choroidal thickness (SFCT) decreased from 564.4 ± 176.2 μm to 280.0 ± 140.4 μm ($p = .015$); The study also found that systemic corticosteroid accumulation decreased to 2.26 ± 0.99 g in patients 1 year after RTX treatment and no side effects were seen during the follow-up period.

3.3. Selective T-Cell Antagonists

Abatacept (ABA) (Orencia®) is a T-cell co-stimulatory modulator that consists mainly of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and IgG1Fc and is approved for the treatment of moderate-to-severe RA [63]. The main mechanism of action of this drug is to prevent the combination of CD28 and CD80/CD86, thereby interfering with T-cell activation and leading to a decrease in pro-inflammatory cell secretion [64]. There have been some case reports indicating that ABA may be effective in the treatment of refractory uveitis. A multicenter clinical trial by Birolo *et al*. [65] evaluated the safety and efficacy of ABA after treatment in 35 patients with JIA combined with uveitis, there were 14 of the 31 patients in the trial were treated with ABA as first-line therapy (ABA-1), and 17 were treated with ABA as second-line therapy; The study found that after 12 months of follow-up, 17 (54.8%) patients attained clinical remission of the drug; the mean frequency of uveitis episodes decreased from 4.1 to 1.2 in the ABA-1 group ($p < 0.01$); the mean frequency of uveitis episodes decreased from 3.7 to 1.2 in the ABA-2 group ($p < 0.01$); In addition, all but five patients with ocular complications that were present at baseline improved or remained stable.

This study revealed that ABA is effective as first-line therapy in the treatment of JIA combined with uveitis.

3.4. Interleukin Receptor Antagonists

Tocilizumab (TCZ) (Actemra; Genentech, South San Francisco, California, USA）is a humanized monoclonal antibody against IL6R that is approved for the treatment of polyarthritis [66]. The main mechanism of action of this drug is to inhibit the pro-inflammatory effects of cytokines by conjugating with IL6R, thus providing a therapeutic effect [67]. The recommended treatment regimen is 4 - 8 mg/kg intravenously every 4 weeks. Some studies support the effectiveness of TCZ in the treatment of NIU. Wennink *et al*. [68] evaluated the efficacy of TCZ in the treatment of refractory intermediate and total uveitis in children, in these seven patients, who were treated with TCZ after ineffective use of corticosteroids or conventional biologics or anti-TNF-α inhibitors, this study found a significant decrease in FA score from baseline 14 to 8 ($p = 0.018$) based on angiographic scores from the Uveitis Working Group after 6 months of treatment, and to 5 ($p = 0.018$) after 12 months; The patients' central macular thickness was significantly reduced after treatment compared to baseline. Systemic corticosteroids are discontinued in three-fifths of patients after 12 months of treatment. During the entire course of the study, no systemic or ocular complications were reported. This study demonstrated that TCZ is effective in the treatment of refractory non-anterior uveitis in children. Similarly, a single-center retrospective study by Maccora *et al*. [69] evaluating the efficacy of Tocilizumab for the treatment of chronic noninfectious uveitis in children. A total of 18 patients were enrolled in the study, 10 patients were treated with ABA and 8 patients were treated with Tocilizumab, which was found to resolve symptoms in 13 out of 18 patients, with a higher rate of resolution with Tocilizumab compared to ABA; At the same time, the study found a significant difference between the two groups in the percentage of disease recurrence after treatment cessation, which was higher in the ABA group than in the Tocilizumab group. The adverse events of using Tocilizumab for the patient in this trial included mild neutropenia, elevated aminotransferases, upper respiratory tract infections, and skin rashes. This study revealed that Tocilizumab is superior to ABA in the treatment of chronic NIU in children.

Secukinumab (Cosentyx®; Novartis International AG, Basel, Switzerland) is a fully human monoclonal antibody against IL-17a, which has been approved for the treatment of PsA, psoriasis, and AS [70]. The main mechanism of action of this drug is the induction of inhibition of IL-17 leading to the reduction of pro-inflammatory factors and thus therapeutic effects. The current treatment program is 150 mg subcutaneously once a week or 10 mg/kg intravenously every 2 weeks. The actual dosage is determined by the condition. In a recent study synthesizing and analyzing data from three phase 3 clinical trials, the study discovered that treatment with Secukinumab in patients with AS combined with

uveitis resulted in a reduction in the incidence of uveitis in the patients [71]. Lu *et al*. [72] reported a case of successful treatment of NIU with Secukinumab, this patient had erythrodermic psoriasis and PsA, and a history of TNF-α inhibitor and DEX implant use after developing NIU in both eyes. After the Secukinumab injection, the visual acuity in the patient's left eye was restored from 0.01 to 0.02, and the 28 Joint Disease Activity Score was reduced from 7.07 to 3.22; Meanwhile, after 12 weeks of treatment, the patient's psoriatic lesions were eliminated. Although long-term side effects are not known at this point, Secukinumab treatment is effective for the moment.

4. Conclusion

Non-infectious uveitis is a vision-threatening inflammatory disease that is currently thought to be related to autoimmunity or autoinflammation. The target of treating the disease is to control active inflammation and prevent disease recurrence. Glucocorticoids are the main treatment option for NIU, but due to side effects, drug resistance, patient demand, and compliance, researchers are exploring new treatment methods and new drugs. Intravitreal implants and biologics show good therapeutic promise, but some drugs have relatively small sample sizes and further clinical trials are still needed to determine their safety and efficacy. In general, glucocorticoids and biologics showed good therapeutic effect in treating NIU. This review focuses on the use of glucocorticoids and biologics to provide therapeutic ideas for clinicians' treatment.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations for Technical Terms

non-infectious uveitis (NIU)
Periocular triamcinolone acetonide (PTA)
macular edema (ME)
triamcinolone acetonide (TA),
dexamethasone (DEX)
fluocinolone acetonide (FA).
best corrected visual acuity (BCVA)
intraocular pressure (IOP)
Behçet's disease (BD)
intravitreal triamcinolone acetonide (IVTA)
preservative-free intravitreal triamcinolone acetonide (PF-IVTA)
non-infectious posterior uveitis (NIPU)
FA implant (FAi)
central retinal thickness (CRT)
tumor necrosis factor-α (TNF-α)
interleukin (IL)
infliximab (IFX)
Adalimumab (ADA)
Etanercept (ETN),
golimumab (GLM/GOL)
Certolizumab pegol (CZP)
rheumatoid arthritis (RA)
ankylosing spondylitis (AS)
psoriatic arthritis (PsA)
Juvenile idiopathic arthritis (JIA)
Rituximab (RTX)
Abatacept (ABA)
Tocilizumab (TCZ)