Different routes of steroidal administration for non-infectious uveitis: perspective

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Abstract

Uveitis is inflammation of the iris, ciliary body, and/or choroid and accounts for 10% to 15% of legal blindness cases in Europe and the United States, and particularly affects working-age people. Systemic steroids are the first-line treatment for intermediate and posterior non-infectious uveitis (NIU), whereas topical steroids are reserved for anterior uveitis. However, systemic steroids can lead to complications such as hypertension, diabetes, and secondary infection. Local use of steroids can suppress intraocular inflammation and cystic macular edema with fewer systemic risks. Intravitreal dexamethasone, fluocinolone acetonide, and/or triamcinolone acetonide implants can improve visual acuity and reduce central retinal thickness. Additionally, suprachoroidal injections of triamcinolone acetonide can reduce central subfield thickness in patients with uveitis. Subtenon injections of triamcinolone acetonide reduce central macular thickness more than periocular injections. Systemic intravenous methylprednisolone pulses can rapidly suppress uveal tract inflammation. Topical use of dexamethasone-cyclodextrin nanoparticles can penetrate the anterior segment to resolve vitritis and macular edema, but cataract progression, elevated intraocular pressure, and deterioration of glaucoma may still occur. During the COVID-19 pandemic, uveitis specialists preferred to use local corticosteroids rather than systemic immunosuppressants and biologics. They advocated dose tapering in patients taking high-dose corticosteroids to reduce their susceptibility to viral infection. NIU is increasingly managed with local steroids to reduce infection risk. This article highlights different routes for steroidal treatments of NIU, including intravitreal, suprachoroidal, periocular, systemic, and topical routes. It also discusses how NIU was managed during the COVID-19 pandemic, specifically addressing the use of immunosuppressants and biologics.

Key words: *Intravitreal injections; Steroids; Uveitis, intermediate; Uveitis, posterior*

Introduction

Uveitis refers to inflammation of the uveal tract, which includes the anterior ciliary body and iris (anterior uveitis), posterior ciliary body and vitreous humor (intermediate uveitis), and retina and choroid (posterior uveitis). Panuveitis refers to inflammation of all anterior, intermediate, and posterior structures involving the retina, sclera, and optic nerve. Non-infectious uveitis (NIU) can be associated with systemic diseases (such as juvenile idiopathic arthritis, sarcoidosis, and Behcet's disease) or can be an isolated ocular disease (such as birdshot chorioretinopathy). Uveitis causes 10% to 15% of legal blindness cases in Europe and the United States, with a prevalence of 121 per 100 000, and particularly affects working-age people.[1] It adversely affects patients' quality of life and can lead to cataracts, inflammatory vitreous haze, cystoid macular edema (CME), and blindness.[2]

Local corticosteroids are the first-line treatment for anterior uveitis but are contraindicated in patients with raised intraocular pressure (IOP) secondary to steroid use. Systemic corticosteroids are administered for first-episode intermediate and posterior NIU and panuveitis, bilateral NIU, NIU resistant to local therapy, and NIU associated with systemic disorders; oral prednisolone is the first-line treatment.[3] Systemic immunosuppressants (such as methotrexate, azathioprine, and mycophenolate mofetil) are used in patients with NIU refractory to steroids,[4] when steroids are poorly tolerated, or in young patients with anticipated long-term topical steroid use and risk of cataract progression. Biologics (such as adalimumab, infliximab, and tocilizumab) are increasingly used to treat NIU.[5] Subcutaneous adalimumab has a longer time to treatment failure than a placebo in treating intermediate or posterior uveitis.[6] Adalimumab injections lower the risk of uveitis flare or visual loss upon steroid withdrawal in patients with NIU.[6]

Posterior uveitis is sight threatening. Topical steroids have low bioavailability and do not effectively deliver the active ingredient to the posterior segment.[7] Different routes of steroid delivery have been developed to minimize the adverse effects of systemic steroid use, such as immunosuppression, hypertension, central obesity, and diabetes mellitus. This article highlights different routes for steroidal treatments of NIU, including intravitreal, suprachoroidal, periocular, systemic, and topical routes (**Figure 1**). It also discusses how NIU was managed during the COVID-19 pandemic, specifically addressing the use of immunosuppressants and biologics.

Intravitreal injection

The intravitreal route refers to administering drugs into the vitreous humor, usually at the superotemporal or inferotemporal sites. Intravitreal injection is contraindicated in patients with an active ocular infection. Caution should be taken in patients with prior trabeculectomy or a glaucoma drainage device to avoid injecting into the bleb or shunt. Injecting steroids locally, including through the intravitreal route, can minimize systemic side effects and are particularly suitable for patients with peptic ulcers or poor liver or renal function. Dexamethasone, fluocinolone acetonide, and triamcinolone acetonide all can improve visual outcomes and reduce the severity of uveitic macular edema (UME) [**Table 1**].

Dexamethasone

The corticosteroid dexamethasone blocks the cascading inflammatory mechanism and inhibits the release of cytokines or chemotactic proteins.[8] It is available in a liquid form (4 mg/mL) and is also used in a polymeric slow-release delivery system or as an intravitreal implant because of its low solubility. The intravitreal implant Ozurdex (dexamethasone 0.7 mg; Allergan, AbbVie, North Chicago [IL], USA) has been approved to treat retinal vein

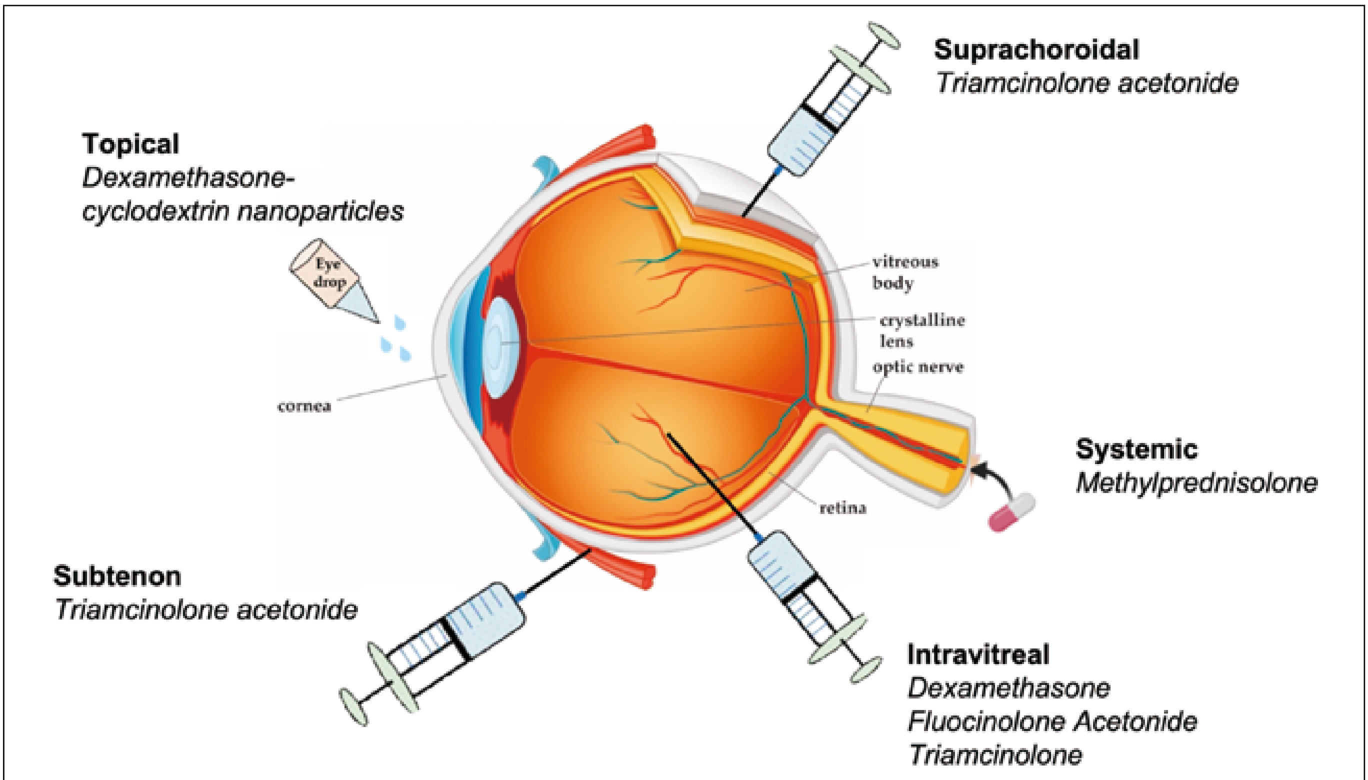


Figure 1. Schematic diagram showing the different routes of steroidal administration for non-infectious uveitis.

Table 1. Studies of intravitreal steroid injection for non-infectious uveitis

Study	Study type	Patient characteristics	Main results
Dexamethasone			
Bodaghi et al,[10] 2022	Prospective	245 patients with posterior NIU received 0.7 mg dexamethasone intravitreal implants were evaluated at months 2, 6, and 18.	20.5% and 25% of patients gained >15 letters at months 2 and 6, respectively. 50.0% of patients did not require alternative treatment or retreatment. CRT reduced by 27.4%, 18.5%, and 16.4% at months 2, 6, and 18, respectively.
Tsang et al,[12] 2017	Retrospective	15 patients with posterior NIU and CME received a single 0.7 mg dexamethasone intravitreal implant and were followed up for 12 months.	At month 3, 91.4% of patients had CRT reduction from 590 to 370 µm (p<0.001) and 80% of patients had visual acuity improvement from logMAR 0.614 to 0.35 (p=0.002).
Zeng et al,[13] 2022	Retrospective	77 patients with NIU received dexamethasone intravitreal implants and were assessed at week 1 and months 1, 3, and 6.	Respectively at week 1 and months 1, 3, and 6, the mean BCVA improved to logMAR 0.245, 0.437, 0.380, and 0.316, and the CRT decreased from 649.1 µm to 340.9, 287.9, 357.2, and 387.1 µm.
Hasanreisoglu et al,[11] 2019	Retrospective	44 patients with NIU with CME or vitreous haze and intraocular inflammation received intravitreal dexamethasone implants and were followed up for 20 months.	Respectively at months 1, 3, and 6, the mean BCVA improved from logMAR 0.55 to logMAR 0.38, 0.32, and 0.35, and the mean CRT decreased to 288, 311, and 302 µm. Vitreous haze decreased until month 6.
Nobre-Cardoso et al,[14] 2017	Retrospective	31 patients with NIU and persistent CME resistant to systemic immunosuppression received dexamethasone intravitreal implants.	The mean BCVA improved from 0.74 to 0.84 logMAR at month 1 but started to deteriorate at month 6 in 56.5% of eyes. CRT decreased at month 1 but increased at month 6 in almost all eyes.
Fluocinolone acetonide			
Tomkins-Netzer et al,[21] 2015	Randomized controlled trials	108 patients with uveitic macular edema were randomly assigned to receive systemic immunosuppression or an intravitreal FA 0.59 mg implant and were followed up for 2 years.	In the implant group, 71% of the eyes had improved macular edema and 60% had resolved edema. The decrease of macular thickness was more in the implant group than in the systemic therapy group (180 vs 109 µm, p=0.04). The mean BCVA improved by 10 letters in both groups.
Tomkins-Netzer et al,[23] 2021	Randomized controlled trials	177 patients with uveitic macular edema were randomly assigned to receive systemic immunosuppression or an intravitreal FA 0.59 mg implant and were followed up for 7 years.	Macular edema resolved in 94% of eyes after a median time of 1.09 years. 43% of eyes had relapsed macular edema by year 7, which was associated with central macular thickness (hazard ratio=2.02) and being Black (hazard ratio=1.80). Eyes with resolved macular edema gained 6.24 letters more than those with relapsed macular edema (p<0.001).
Kempen et al,[22] 2011	Randomized controlled parallel superiority trial	255 patients with bilateral NIU (intermediate, posterior, or panuveitis) were randomly assigned to receive systemic corticosteroids plus immunosuppression or an FA implant and were monitored for 24 months.	At month 24, the implant group improved better than the systemic therapy group in terms of letter gain (+6.0 vs +3.2, p=0.16) and vision-related quality of life improvement (11.4 vs 6.8 units, p=0.043). Only 12% of patients in the implant group had active uveitis (p=0.001). The two groups were comparable in terms of the proportion of patients with macular edema (p=0.071).
Kempen et al,[24] 2017	Randomized controlled trials	215 patients with NIU were randomly assigned to receive systemic corticosteroids and immunosuppression or an intravitreal FA 0.59 mg implant and were followed up for 7 years.	Over 7 years, the mean BCVA improved from 61.7 to 55.8 in the implant group and from 65.0 to 66.2 in the systemic therapy group. There was an overall -10 dB loss in visual field sensitivity. The two groups were comparable in terms of uveitic activity (p=0.69) and macular edema (p=0.30). The implant group had more incidences of elevated intraocular pressure and glaucoma requiring treatment.
Pavesio & Heinz,[16] 2022	Prospective, randomized, double-blinded	59 patients with bilateral NIU of the posterior segment and two previous recurrences received an FA implant 0.2 µg/day and were observed for 3 years.	The recurrence-free rate was higher in FA implant–treated eyes than fellow eyes (28.8% vs 5.1%, p=0.001). Over 3 years, BCVA improvement was greater in FA implant–treated eyes than fellow eyes (+9.6 vs -4.4 letters, p<0.0001). The FA implant group had rapid and consistent reduction in central foveal thickness and less frequent adjunctive intra/peri-ocular injection (p<0.0001) and topical corticosteroid use (p=0.0041).
Mahmud et al,[17] 2023	Retrospective	13 patients (19 eyes) with NIU received an FA implant and were followed up at months 2 and 6 month.	14 (74%) eyes achieved inflammatory control, with no additional therapy required, or had a 3-week tapered course of topical corticosteroids. Inflammatory control was inadequate in patients with CME.
Pockar et al,[18] 2023	Retrospective	9 patients (11 eyes) with chronic NIU and CME had an intravitreal FA implant 0.19 mg and were followed up for 52 weeks.	At 12 months, the mean CRT improved from 435.3 µm to 296.5 µm (p=0.01) and VA improved from logMAR 0.48 to 0.45 (p=0.59); only one eye gained >15 letters.
Hikal et al,[19] 2021	Retrospective	26 patients (34 eyes) with NIU and macular edema received an FA implant 0.19 mg and were followed up for 18 months.	70.6% of eyes had a completely dry macula, and 17.6% of eyes had decreased macular edema. 14.7% of eyes had relapsed macular edema requiring reinjection. VA improved in 12 eyes by 2±1.2 lines; nine eyes had stable VA and five eyes had deteriorating VA.
Studsgaard et al,[20] 2022	Retrospective	20 patients with chronic NIU associated with CME were treated with an FA implant 0.19 mg and were followed up for 2 years.	The mean BCVA improved at months 6, 12, and 18. CRT decreased by 45 µm at month 12 (p=0.006). Four patients had relapsed NIU within 18 months and were treated with corticosteroids.
Triamcinolone acetonide			
Thorne et al,[26] 2019	Randomized clinical trial	192 patients with uveitic macular edema were randomly assigned to receive periocular or intravitreal 40 mg triamcinolone acetonide implant or intravitreal 0.7 mg dexamethasone implant and were followed up for over 24 weeks.	All groups showed significant central subfield thickness reduction at week 8. At week 24, the two intravitreal groups were superior to the periocular group (p<0.0001) in terms of BCVA gain and proportion of eyes with resolved CME.

Abbreviations: BCVA=best-corrected visual acuity; CME=cystoid macular edema; CRT=central retinal thickness; FA=fluocinolone acetamide; NIU=non-infectious uveitis; VA=visual acuity occlusion–related macular edema since 2009. Its action can last for up to 6 months. Since 2014, Ozurdex has been widely used to treat diabetic macular edema, particularly in pseudophakic patients who did not respond well to anti-vascular endothelial growth factor.[9]

In the LOUVRE2 study, Ozurdex was injected in 245 French patients with posterior segment inflammation secondary to NIU.[10] Two months after treatment, 20.5% of patients had gained ≥15 letters (the mean was 6.2 letters for all patients). 18 months after treatment, 25.0% of patients had gained ≥15 letters in best-corrected visual acuity (BCVA). Additionally, the mean central retinal thickness (CRT) reduced by 27.4%, 18.5%, and 16.4% at months 2, 6, and 18, respectively. The mean vitreous haze score reduced significantly by 0.19 and 0.18 at months 2 and 6, respectively. The mean quality-of-life score significantly increased 2 months after the injection. 50.0% of patients were not indicated to receive an alternative or repeat treatment at month 6 because inflammation had sufficiently subsided and was deemed stabilized or improved. Yet, ocular hypertension, cataract progression, and conjunctival hemorrhage occurred as treatment-related adverse effects.

Similarly, a study of Turkish patients with NIU (predominantly idiopathic posterior uveitis) also found Ozurdex effective.[11] Six months after treatment, BCVA had improved from 0.55 to 0.35 logMAR ($p<0.001$) and central foveal thickness had decreased from 386 to 302 μm ($p<0.001$). The decrease in vitreous haze persisted for 6 months. 35% of the patients required a second Ozurdex injection after a median interval of 4.5 months. Patients with chronic CME had limited responses to the first injection because of their long-term intraocular inflammation.

A study of Canadian patients with UME showed significant reductions in CRT ($p<0.001$) and improvements in BCVA ($p=0.002$) 3 months after treatment with Ozurdex.[12] Second implants were administrated if the CRT increased >10% and >50 μm; the median time to relapse was 6 months.

Ozurdex was reported to be safe and effective in a Chinese population with NIU (mainly idiopathic panuveitis).[13] After 1 week and 1, 3, and 6 months of treatment, BCVA improved by 0.245, 0.437, 0.380, and 0.316 logMAR, respectively ($p<0.001$), and CRT decreased from 649.1 μm at baseline to 340.9, 287.9, 357.2, and 387.0 μm, respectively ($p<0.05$). However, 14.29% of eyes required additional topical therapy for a transient rise in IOP (>21 mmHg).

However, Ozurdex was reported to have a limited and short-lived effect on BCVA in 31 patients with UME mainly caused by idiopathic panuveitis.[14] Three months after treatment, BCVA remained unchanged in 60% of patients and had deteriorated (a mean of 0.37 logMAR, $p<0.01$) in 40% of patients. Six months after treatment, BCVA had deteriorated (a mean of 0.39 logMAR) in 56.5% of the eyes. At 3 months, 31.3% of eyes had a macular edema relapse. The mean CRT increased from 308 μm at 1 month to 340 μm at 3 months to 442 μm at 6 months (3 vs 6 months, $p<0.001$). Reimplantation was performed based on the visual acuity reduction and/or CRT increase. 83.3% of patients relapsed within 12 months of reimplantation; the mean time to relapse was 5.0 months. Relapsed patients required a new intravitreal implant or systemic immunosuppressants. There were no significant differences in BCVA ($p=0.152$) and CRT ($p=0.427$) after reimplantation or after first implantation. The high relapse rate and worsening BCVA do not support the use of Ozurdex to treat uveitis. These findings may be due to recruitment bias; patients with advanced uveitis and CME resistant to other treatment regimens were recruited. In patients with chronic macular edema, the photoreceptors may be permanently damaged, so the potential for improving their visual acuity is limited.

Fluocinolone acetonide

Fluocinolone acetonide is a selective glucocorticoid receptor agonist with high lipophilicity and potency. It is 5 times stronger than triamcinolone acetonide in anti-inflammation. Two fluocinolone acetonide intravitreal implants: RETISERT 0.59 mg (Bausch & Lomb, Rochester [NY], USA) and YUTIQ 0.18 mg (EyePoint Pharmaceuticals, Watertown [MA], USA) have been approved by the United States Food and Drug Administration to treat NIU, whereas a third, ILUVIEN 0.19 mg (Alimera Sciences, Alpharetta [GA], USA), has been approved to treat diabetic macular edema only.[15] All three implants are designed to slowly release fluocinolone acetonide over 30 to 36 months. YUTIQ is injected with a 25-gauge needle, whereas RETISERT requires scleral fixation of the implant by a vitreoretinal surgeon. Various studies, notably the multicenter uveitis steroid treatment (MUST) trial, have illustrated the effect of intravitreal fluocinolone acetonide implants on improving BCVA, reducing CRT, and drying macular edema.[16-20]

In the MUST trial, 117 patients with UME (intermediate, posterior, or panuveitis) were randomly assigned to either RETISERT 0.59 mg or systemic immunosuppression.[21] Re-implantation was performed for patients with initial failure to control inflammation, systemic disorders requiring systemic therapy, or treatment-limiting toxicity. After 2 years of treatment, 71% of the eyes with RETISERT had improved UME (≥20% reduction in or normalization of macular thickness) and 60% had resolved edema (decrease in macular thickness to <240 μm). The mean macular thickness reduced by 180 μm in the RETISERT group and by 109 μm in the systemic immunosuppression group ($p=0.04$). The mean BCVA improved by +10 letters in both groups, with resolved and improved UME. Eyes with leakage on fluorescein angiography had 20% more improvement in UME compared with those without leakage ($p=0.03$), but the two groups were comparable in terms of resolution of UME ($p=0.49$). Baseline macular leakage was associated with better visual acuity (by 7 letters) 2 years after treatment. After 2 years of treatment, the two groups were comparable in terms of BCVA improvement ($p=0.16$) and EuroQol-EQ5D health utility ($p=0.060$).[22] Compared with systemic immunosuppression, RETISERT resulted in higher improvement in vision-related quality of life (+11.4 vs +6.8 units, p=0.043) and lower percentage of active uveitis (12% vs 29%, p=0.001), and lower (but not significantly) percentage of macular edema (22% vs 30%, p=0.071).[22] However, eyes with RETISERT had higher risks of cataract surgery (80%, hazard ratio [HR]=3.3, p<0.0001), raised IOP requiring treatment (61%, HR=4.2, p<0.0001), and glaucoma progression (17%, HR=4.2, p=0.0008).[22]

The MUST follow-up study evaluated the 7-year outcomes of RETISERT for UME.[23] Macular edema resolved in 94% of eyes after a median treatment time of 1.09 years. However, 43% of the eyes with macular edema relapsed by year 7; the relapse was associated with a thicker central macular thickness (HR=2.02, p=0.007) and being Black (HR=1.80, p=0.039). The presence of an epiretinal membrane was associated with lower probability of macular edema resolution (HR=0.74, p=0.05). Eyes with macular edema resolution gained a mean of 6.24 letters, whereas eyes with macular edema lost a mean of 8.65 letters (p<0.001). RETISERT could effectively control UME, but relapse was common.

In another MUST 7-year follow-up study, the mean BCVA decreased from 61.7 to 55.8 Early Treatment Diabetic Retinopathy Study (ETDRS) letters in the RETISERT group but improved from 65.0 to 66.2 letters in the systemic immunosuppression group.[24] There were no significant differences in uveitic activity (p=0.69) and macular edema (p=0.30) between groups. The RETISERT group had a higher incidence of elevated IOP necessitating treatment, whereas the systemic immunosuppression group had higher incidences of hyperlipidemia, hypertension, osteopenia, and fractures. Irreversible chorioretinal lesions were found in the RETISERT group, owing to multiple inflammatory recurrence. Hence, RETISERT may only control inflammation and CME in the short term, with risks of relapse in the long run, whereas systemic therapy may be more effective in improving BCVA.

Triamcinolone acetonide

Triamcinolone acetonide is a strong synthetic glucocorticoid with immunosuppressive and anti-inflammatory effects. It is commonly used to treat various ocular conditions, such as branch or central retinal vein occlusion, diabetic macular edema, and pseudophakic CME. It reduces vessel proliferation in choroid neovascularization, neovascular glaucoma, or proliferative ischemic retinopathies.[25] It is available commercially as Kenalog (40 mg/mL, Bristol-Myers Squibb, Princeton [NJ], USA) but is not yet licensed for periocular or intraocular injection; its effects last for at least 3 months. It is also available commercially as a preservative-free injectable suspension for uveitis known as Triesence (40 mg/mL, Alcon Laboratories, Geneva, Switzerland); its effects last for 3 months. Triesence has a lower risk of pseudo-endophthalmitis than Kenalog.

In the POINT randomized controlled trial, 192 patients with UME (mainly intermediate or panuveitis) were randomly assigned to receive periocular triamcinolone acetonide 40 mg/mL injection (Kenalog), intravitreal triamcinolone acetonide 40 mg/mL injection (Triesence), or intravitreal dexamethasone 0.7 mg implant (Ozurdex).[26] All three groups showed significant central subfield thickness (CST) reduction at weeks 4, 8, 12, and 24 (p<0.0001). Triesence and Ozurdex were superior to Kenalog in resolving macular edema at week 4 (p<0.0001). Ozurdex was non-inferior to Triesence at week 8. At week 24, both Triesence and Ozurdex demonstrated significantly higher BCVA gains (+4 to +7 letters) and a higher proportion of eyes with resolved macular edema than Kenalog. Triesence and Ozurdex achieved similar BCVA at any time point. Complications reported were elevated IOP requiring anterior chamber paracentesis, vitreous hemorrhage, and hypotony. Both Triesence and Ozurdex were effective for the treatment of UME, but Ozurdex quickly became less effective over time and warrants earlier retreatment.

Suprachoroidal injection

The suprachoroidal injection route refers to administering drugs into the space between the sclera and choroid, targeting the choroid, retinal pigmental epithelium, and retina. The advantages of this route over the intravitreal route are that a higher drug concentration can be delivered to the posterior segment, and a lower drug concentration to the anterior segment and lens.[27] This reduces the risk of steroid-induced cataracts or glaucoma progression. Suprachoroidal injection is contraindicated in patients with active ocular or periocular infection. During the injection, the beveled end of the proprietary needle at 1 mm should avoid covering the outer sheath to reduce the risk of drug leaking out. In a porcine model, suprachoroidal injectable suspension of triamcinolone acetonide (CLS-TA) reduced ocular inflammation and vitreous cellular infiltration more effectively than intravitreal administration.[28] Commercially, Xipere (40 mg/mL, Clearside Biomedical, Alpharetta [GA], USA) is a CLS-TA available for the treatment of UME; it requires repeat injections every 12 weeks.

Studies have evaluated the effectiveness of CLS-TA in patients with uveitis (**Table 2**). In the AZALEA prospective trial, 37 patients with NIU (mainly chronic and idiopathic intermediate uveitis, with or without macular edema) were treated with two CLS-TA 4 mg via a proprietary microinjector at day 0 and week 12.[29] The mean BCVA improved from 68.9 at baseline to 75.0 at week 8 and 75.9 at week 24. The mean CST decreased by 15% from 335.9 μm at baseline to 284.0 μm at week 24. The proportion of patients with no vitreous haze improved from 44.7% at baseline to 89.5% at week 24. Four patients developed cataracts but did not require surgery. Six patients had elevated IOP from a mean of 13.3 mmHg at baseline to 15.2 mmHg at week 24. Four patients required an additional IOP-lowering eye drop, while three patients required two additional medications. Suprachoroidal CLS-TA was safe and effective in improving BCVA and macular edema.

Table 2. Studies of suprachoroidal steroid injection for non-infectious uveitis

Study	Study type	Patient characteristics	Main results
Henry et al,[29] 2022	Prospective	37 patients with NIU with or without CME received two CLS-TA 4 mg 12 weeks apart and were followed up for 24 weeks.	At week 24, the mean BCVA improved from 68.9 at baseline to 75.9, and the mean CST improved from 335.9 to 284.0 µm (a 15% decrease). The proportion of patients with a vitreous haze grade of 0 improved from 44.7% to 89.5%.
Khurana et al,[33] 2022	Non-interventional extension study	28 patients with NIU-associated macular edema received two CLS-TA at baseline and week 12 and were followed up for 48 weeks and compared with five controls.	Over 48 weeks, the median rescue time was more in the treatment than control group (257.0 vs 55.5 days, p<0.001). The treatment group gained a mean of 12.1 letters by week 48 (p=0.004) and had CST reduction from 292.5 to 174.5 µm (p=0.001).
Singer et al,[32] 2022	Post-hoc analysis	129 patients with NIU complicated by CME received two CLS-TA 4 mg 12 weeks apart and were compared with sham-controls.	At week 24, outcomes were better in the treatment than control group in terms of letter gain (15.7 vs 10.9 letters) and CST reduction (174.0 vs 148.5 µm, p=0.040).
Merrill et al,[31] 2023	Post-hoc analysis	117 uveitic macular edema patients received CLS-TA with or without systemic corticosteroids or steroid-sparing therapy and were followed up for 24 weeks.	In patients without steroid-sparing therapy, outcome was better in the CLS-TA than control group in terms of the mean BCVA gain (15.6 vs 4.9 letters, p<0.001) and mean CST reduction (169.8 vs 10.3 µm). In patients with steroid-sparing therapy, the two groups were comparable in BCVA and CST.
Yeh et al,[30] 2020	Masked, randomized trial	160 patients with CME secondary to NIU were randomly assigned to receive CLS-TA or sham injection at weeks 0 and 12 and were monitored for 24 weeks.	Outcome was better in the CLS-TA than control group in terms of the proportion of patients with improvement of ≥15 ETDRS letters (46.9% vs 15.6%, p<0.001) and CST reduction (153 vs 18 µm, p<0.001).

Abbreviations: BCVA=best-corrected visual acuity; CLS-TA = injectable suspension of triamcinolone acetonide; CME=cystoid macular edema; CST = central subfield thickness; ETDRS = Early Treatment of Diabetic Retinopathy Study; NIU=non-infectious uveitis

The PEACHTREE was a phase III randomized trial assessing the efficacy of suprachoroidal CLS-TA in patients with CME secondary to NIU.[30] A total of 160 patients (most with intermediate uveitis and panuveitis) were randomly assigned in a 3:2 ratio to receive CLS-TA 4 mg or sham injection at day 0 and week 12. Patients were allowed systemic corticosteroids, including oral prednisolone ≤20 mg/day. The patients had intraretinal or subretinal fluid with a CST ≥300 µm. At week 24, more patients in the CLS-TA group than in the placebo group achieved an improvement of ≥15 ETDRS letters (46.9% vs 15.6%, p<0.001). Early BCVA improvement at week 8 was observed in the CLS-TA group, with more proportion of patients attaining >70 ETDRS letters (49% vs 15%, p<0.001). At week 24, the CLS-TA group had greater reduction in CST (153 vs 18 µm, p<0.001). At week 4, more patients in the CLS-TA group achieved CME resolution (53% vs 2%, p<0.001). A smaller proportion of patients in the CLS-TA group required rescue therapy (13.5% vs 72%, p<0.001).

A post-hoc analysis of the PEACHTREE study demonstrated the benefits of CLS-TA in patients with UME who received sham controls or suprachoroidal CLS-TA with or without systemic corticosteroids and/or steroid-sparing therapy.[31] At week 24, among those without systemic corticosteroids and steroid-sparing therapy, the CLS-TA group achieved better outcome than controls in terms of BCVA gain (15.6 vs 4.9 letters, p<0.001) and CST reduction (169.8 vs 10.3 µm, 95% confidence interval [CI] for difference= -219.1 to -99.9 µm, p<0.001). Likewise, among those with systemic corticosteroids and/or steroid-sparing therapy, the CLS-TA group achieved better outcome than the systemic therapy alone group in terms of BCVA improvement (+9.4 vs -3.2 letters, p=0.019) and CST reduction (-108.3 vs -43.5 µm, 95% CI difference= -163.2 to 33.6 µm, p=0.190), but the difference in CST reduction was not significant.

In another post-hoc analysis of the PEACHTREE study, patients were randomly assigned to receive CLS-TA with or without rescue therapy.[32] The median time to the first rescue therapy (mainly topical or intravitreal corticosteroids) was 84 days. At week 24, the CLS-TA alone group had better BCVA gain (15.7 vs 10.9 letters, p=0.080) and CST reduction (174.0 µm vs 148.5 µm, p=0.040).

The MAGNOLIA extension study evaluated 33 patients with UME from the PEACHTREE trial who were followed up for 48 weeks without rescue therapy.[33] Most patients had chronic and idiopathic posterior uveitis of insidious onset. The median time to rescue therapy was longer in the CLS-TA group than in controls (257.0 vs 55.5 days, p<0.001). At week 48, the CLS-TA group had BCVA gain of 12.1 letters (p=0.004) and CST reduction from 292.5 µm at baseline to 174.5 µm (p=0.001). The percentage of patients with no vitreous haze increased from 25.0% at baseline to 85.7% at week 48. Regarding adverse events, seven patients developed cataracts and four developed elevated IOP. Overall, the clinical trials PEACHTREE, MAGNOLIA, and AZALEA support the use of suprachoroidal CLS-TA for patients with UME.

Suprachoroidal injection enables more targeted delivery of steroids to chorioretinal structures than intravitreal injection, while reducing drug exposure in the anterior segment.[34]

Treatments via the suprachoroidal route effectively improve visual acuity, reduce CST, and resolve vitreous haze. Nonetheless, suprachoroidal injection was associated with the risk of vitreous detachment, which occurred in 5.2% of patients.[30] Additionally, suprachoroidal hemorrhage and retinal detachment can occur, although none did in the AZALEA study.

Periocular injections

Subtenon injection refers to drug administration into the potential space between the Tenon's capsule and sclera, usually at the superotemporal quadrant. After going through the conjunctiva and Tenon's capsule, a half-inch 27-gauge needle is then advanced posteriorly along the outside of the globe. This route is contraindicated in patients with previous extensive vitreoretinal surgery, strabismus surgery, or eye trauma. Orbital floor injection, a localized deposition of steroids into the orbital floor, can lead to cataract progression and increased IOP, although the risks are lower than those of intravitreal injection.[35] Subtenon triamcinolone acetonide injections, which last for 2 to 3 months, improve visual acuity and decrease central macular thickness (**Table 3**).

Pediatric patients with uveitis have a worse prognosis owing to sight-threatening complications such as secondary cataracts and glaucoma. In a retrospective review, 30 pediatric patients (48 eyes) with NIU (63% being pars planitis) received subtenon triamcinolone acetonide 20 mg injection with topical anesthesia.[36] At 3 months after treatment, inflammation had improved in 41 of the 48 eyes, with the number of vitreous cells reduced and macular edema/optic nerve edema resolved. Of 18 eyes with baseline central macular thickness of ≥300 μm or the presence of cystic intraretinal fluid, 14 (77.8%) had resolved in 3 months. Oral corticosteroids and systemic immunomodulatory therapy were tapered and eventually stopped in all patients. Visual acuity improved in both the right eyes (p=0.0002) and left eyes (p=0.007). However, 15% of the eyes developed cataracts after 1 year, and the percentage increased to 33.3% after 2 years. Moreover, 12.5% of the eyes developed ocular hypertension and required IOP-lowering medication.

A retrospective review analyzed 115 adults with NIU (mainly idiopathic posterior or panuveitis) who received in a 1:2 ratio either modified posterior subtenon injection or trans-septal injection of triamcinolone acetonide 40 mg/mL.[37] At 6 months, the proportion of patients with visual acuity of 20/40 or better was higher in the posterior subtenon injection group than in the trans-septal injection group (72.2% vs 51.9%, p=0.02). In the former group, logMAR visual acuity improved from 0.35 at baseline to 0.22 at 6 months (p=0.002), and the mean central macular thickness decreased from 455 μm to 359 μm (p=0.048); 85.7% of patients had vitritis quiescence at 6 months. In another study,[38] seven patients had steroid-induced elevated IOP, and four required cataract surgery. This highlights the efficacy of subtenon delivery of triamcinolone acetonide in improving visual acuity and macular edema, despite its side effects of cataracts and glaucoma progression.

Intravenous administration of methylprednisolone

High-dose intravenous methylprednisolone pulse (IVMP) is widely used for systemic juvenile idiopathic arthritis, systemic lupus erythematosus, and optic neuritis (**Table 4**). Methylprednisolone is injected into the bloodstream so that the steroid can take effect within 6 to 8 hours. Delayed control of ocular inflammation correlates to poor visual outcomes.[39] IVMP rapidly suppress inflammation and the recurrence of immune-mediated disorders. It is used in severe cases of NIU with unfavorable visual prognostic factors including dense vitreous haze or macular edema.

In a retrospective study of 56 children with active idiopathic NIU who received high-dose IVMP of 10 to 30 mg/kg/day for 3 days and were followed up for a median of 2.7 years.[40] Of them, 30 had additional methotrexate and 13 had additional biologic disease-modifying anti-rheumatic drugs because of failure to develop a sustained response. Visual acuity improved from 0.52 ETDRS letters at baseline to 0.69 ETDRS letters at 3 months (p<0.001) to 0.78 ETDRS letters (p<0.001) at 6 months. Optic disc edema decreased from 30% to 13% (p<0.001) and macular edema from 15% to 4% (p=0.01). Compared with patients with one IVMP, patients with ≥3 IVMP had fewer relapse events and required fewer eye surgeries for intraocular complications or fewer biologic disease-modifying anti-rheumatic drugs. However, patients

Table 3. Studies of periocular steroid injection for non-infectious uveitis (NIU)

Study	Study type	Patient characteristics	Main results
Jung et al,[38] 2022	Retrospective	30 pediatric patients with NIU received subtenon triamcinolone acetonide 20 mg injection with topical anesthesia and were followed up for 6 months.	The level of inflammation – defined by the number of vitreous cells or the presence of macular edema/optic nerve edema – improved in 41 out of 48 eyes. Of the 18 eyes with cystoid macular edema, 14 resolved in 3 months. Visual acuity improved in both right eyes (p=0.0002) and left eyes (p=0.007).
McKay et al,[37] 2021	Retrospective	115 patients with NIU received modified posterior subtenon or trans-septal triamcinolone injection 40 mg/ mL and were followed up for 6 months.	At 6 months, the proportion of patients with visual acuity of 20/40 or better was higher in the posterior subtenon injection group than in the trans-septal injection group (72.2% vs 51.9%, p=0.02). In the former group, logMAR visual acuity improved from 0.35 to 0.22 (p=0.002), and the mean central macular thickness decreased from 455 μm to 359 μm (p=0.048); 85.7% of patients had vitritis quiescence at 6 months.

Table 4. Studies of systemic steroid for non-infectious uveitis

Study	Study type	Patient characteristics	Main results
Schnabel et al,[40] 2020	Retrospective	56 patients with juvenile NIU received IVMP 10-30 mg/kg/day for 3 days. Most had additional biologic disease-modifying anti-rheumatic drugs.	At month 6, visual acuity improved from 0.52 to 0.78, and papillary edema ($p<0.001$) and macular edema ($p=0.01$) reduced significantly. Visual acuity of <0.3 were more likely to occur in patients with three to five IVMP than in patients with one IVMP (44% vs 11%, $p=0.023$).
Vegas-Revenga et al,[39] 2022	Retrospective	112 patients with severe NIU refractory to oral corticosteroids or biologics received IVMP 80-1000 mg every 24 hours for 2-5 days and were followed up for 30 days.	At 1 month, the mean best-corrected visual acuity improved from 0.46 to 0.74 ($p<0.05$), and macular thickness reduced from 409.7 to 275 µm ($p<0.05$). The mean basal Tyndall for vitritis reduced from 0.87 to 0.08 ($p< 0.05$); only 5% of patients had residual vitritis.
Namba et al,[42] 2022	Retrospective	157 patients with relapsed NIU secondary to Vogt-Koyanagi-Harada disease or sarcoidosis received systemic corticosteroids for 12 months.	The mean total steroid dose over 12 months for all patients was 3874±2775 mg. A higher total steroid dose was associated with immunosuppressant use ($p=0.0196$). The mean treatment time was 318.7±89.3 days. 39.5% of patients had a subsequent relapse.

Abbreviations: IVMP=intravenous methylprednisolone pulse; NIU=non-infectious uveitis

with visual acuity of <0.3 were more likely to receive more IVMP (44% had three to five IVMP vs 11% had one IVMP, $p=0.023$).

In a multicenter retrospective study of 112 NIU patients (68 of them had panuveitis that was idiopathic or secondary to Vogt-Koyanagi-Harada disease) who received IVMP 80 to 1000 mg every 24 hours for 2 to 5 days.[39] At 1 month, the mean BCVA improved from 0.46 to 0.74 ($p<0.05$), and macular thickness reduced from 409.7 µm to 275 µm ($p<0.05$). Of 50 patients with CME, 38 had resolution of macular edema. The mean basal vitreous haze score for vitritis reduced from 0.87 to 0.08 ($p<0.05$); only 5% of patients had residual vitritis; no patient had grade 3 or 4 vitritis. 69.3% of patients with retinitis and 69.9% of patients with choroiditis had significant BCVA improvement ($p<0.05$). Regarding adverse events, three patients had respiratory infections and one had uncontrolled hyperglycemia and oral candidiasis.

Long-term systemic corticosteroid use is associated with diabetes, hypertension, and glaucoma, so the maximum recommended dose is ≤7.5 mg/day.[41] Accurate dosage of systemic corticosteroids prevents relapse. In a retrospective observational study of systemic steroids for relapsed NIU secondary to Vogt-Koyanagi-Harada disease or sarcoidosis, 157 patients with relapsed non-infectious intermediate or posterior or panuveitis received systemic corticosteroids (initial dose, 8.5±7.1 mg/day) for 12 months.[42] The mean total steroid dose for all patients was 3874.0±2775.0 mg. The total dose was highest at 1 month and decreased every 3 months until 12 months. The mean duration of treatment was 318.7 days; the mean days of high dosage (≥10 mg/day) was 178.5. A higher total steroid dose was associated with immunosuppressant use ($p=0.0196$). 39.5% of patients had a subsequent relapse. Steroid-related adverse events included cataracts, worsening diabetes, femoral head necrosis, and central serous chorioretinopathy. Therefore, patients who receive high-dose corticosteroids for a long time require additional immunosuppressants to prevent NIU relapses.

Topical administration of dexamethasone-cyclodextrin nanoparticles

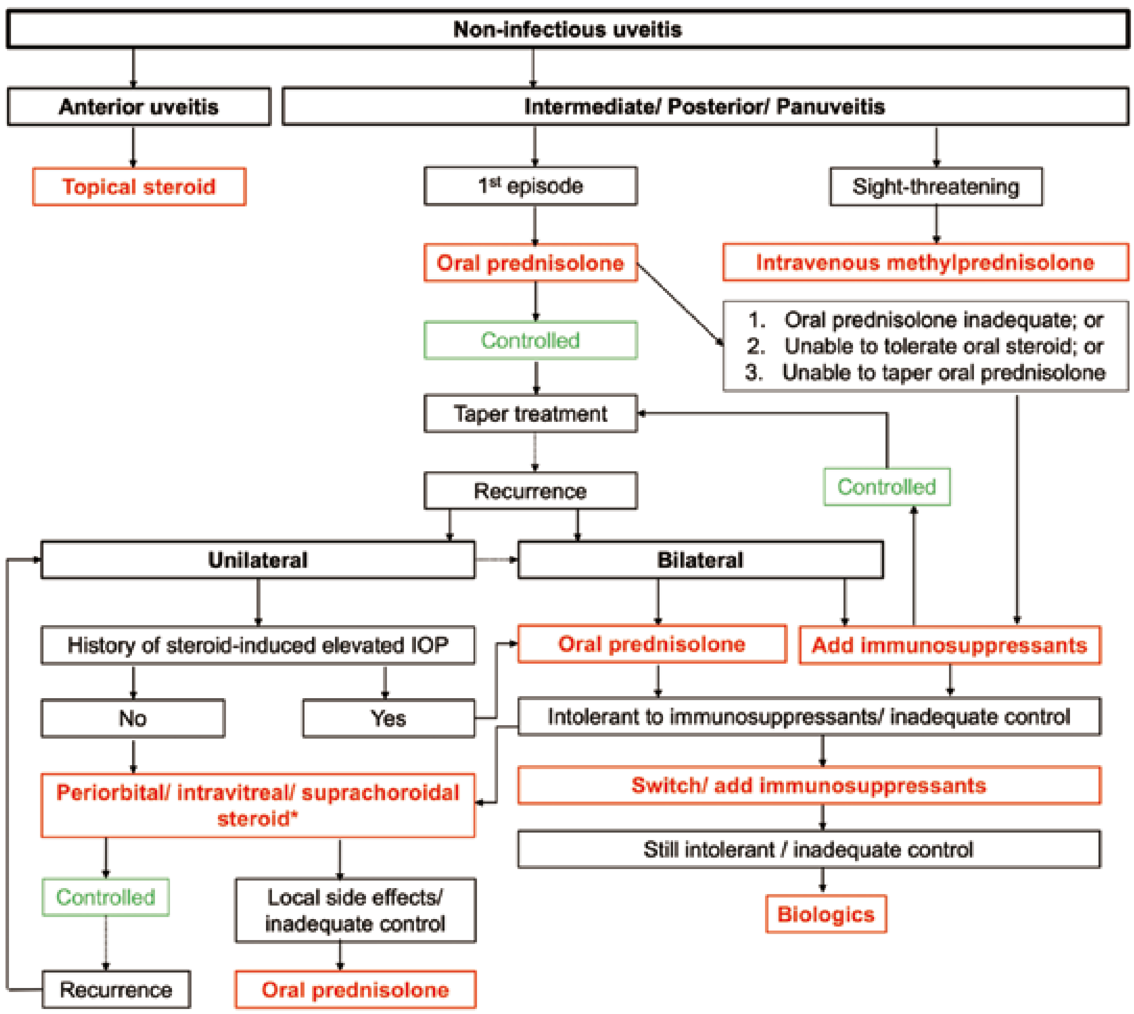
The topical steroid route refers to the administration of drugs into the ocular system via the cornea or conjunctival epithelium. It is mainly reserved for anterior uveitis because of its limited penetration to the cornea and sclera. Topical therapy reduces the risk of complications arising from intraocular injections such as retinal detachment, vitreous hemorrhage, and endophthalmitis.[43] Cyclodextrin, an oligosaccharide, promotes ocular drug delivery by dissolving the lipophilic drug molecule in the aqueous tear film.[44] The cyclodextrin is left in the tear film and flows into the nasolacrimal ducts. However, topical therapy for NIU is not yet approved for clinical use.

A study reported five patients (8 eyes) with idiopathic intermediate uveitis, macular edema, and vitritis received 1.5% dexamethasone-cyclodextrin nanoparticle drops four times a day for 4 weeks, followed by 4 weeks of tapering doses (**Table 5**).[45] The median BCVA improved from 0.2 logMAR at baseline to 0.15 logMAR at week 4 ($p=0.034$) but returned to 0.2 logMAR at week 12. Central macular thickness improved from 435 µm at baseline to 350 µm at week 12 ($p<0.05$). Four eyes had resolution of CME at week 8 and maintained at week 12. Of the three eyes with vitritis, two resolved at week 12. No adverse event was reported. Topical steroids have good penetration and minimal adverse effects, making it a promising non-invasive therapy for intermediate uveitis.

Clinical guidelines for steroid use in intermediate and posterior uveitis

Figure 2 illustrates the flowchart of treatment options for uveitis. Systemic or periocular steroids are the first-line treatment for non-infectious intermediate, posterior, or panuveitis. Subtenon or orbital floor injections of triamcinolone acetonide are recommended for unilateral uveitis with or without CME. Systemic steroids, oral prednisolone, and IVMP are recommended for bilateral

Table 5. Study of topical steroid for non-infectious uveitis (NIU)			
Study	**Study type**	**Patient characteristics**	**Main results**
Shulman et al,[45] 2015	Prospective	Five patients (eight eyes) with NIU with cystoid macular edema and/or vitritis received 1.5% dexamethasone-cyclodextrin nanoparticles drops 4 times a day for 4 weeks, followed by tapering to one drop every 10 days. Patients were monitored for 4 weeks without treatment and then further for 12 weeks.	At week 12, the median best-corrected visual acuity remained unchanged at 0.2 logMAR, and the central macular thickness improved from 435 to 350 μm ($p<0.05$). All eyes showed complete resolution of cystoid macular edema at week 8. Two of the three eyes with vitritis resolved by week 12.



Route	Advantages
Intravitreal	Minimal systemic adverse effects Longer action than topical drops Can target the posterior segment Used in patients with vitritis or macular edema who are unlikely to respond or have failed to respond to periocular injection
Suprachoroidal	Minimal systemic adverse effects Targets posterior pathology without elevating intraocular pressure or causing cataracts
Periorbital	Minimal systemic adverse effects Longer action than topical drops Can reach the posterior segment

Figure 2. Flowchart of steroidal administration options for non-infectious intermediate, posterior, or panuveitis. Copyright: College of Ophthalmologists of Hong Kong.

and/or severe uveitis and those not responding to periocular steroid injections. Steroid-sparing agents (including methotrexate, mycophenolate mofetil, and azathioprine) are second-line treatments, whereas biologic disease-modifying anti-rheumatic drugs (such as adalimumab and infliximab) are third-line options. If medical therapy fails to control the vitreous haze, retinal detachment, or CME, vitrectomy should be considered, with laser therapy as an adjuvant treatment to peripheral retinal neovascularization.[46] There is no guideline on the use of suprachoroidal /intravitreal/ periocular steroid injections; route selection is based on clinician preference.

Management of NIU during the COVID-19 pandemic

Patients with COVID-19 are at risk of cytokine storm involving interleukin-6 and interleukin-10 and reactivation of uveitis. The World Health Organization recommended avoiding the use of systemic corticosteroids in patients with severe COVID-19.[47]

In the COPE study, 91.5% of patients with NIU received systemic immunosuppressants (azathioprine, methotrexate, mycophenolate mofetil) and 14.5% of patients with NIU received biologics.[48] In 18% of patients without COVID-19, the dosage of systemic immunosuppressants was reduced to decrease the risk of infection. Of 163 patients, 53 had a relapse. 25 of the 53 patients had dosage reduced by uveitis experts or stopped medication by self. Uveitis experts preferred oral over intravenous steroids and tapering dosage despite active inflammation. Immunosuppressants and/or biologics should not be used when COVID-19 is suspected or confirmed. Local corticosteroid therapy is preferred (over systemic therapy). Multidisciplinary care is essential to manage NIU during the COVID-19 pandemic; for example, rheumatologists can help monitor drug effectiveness and safety.[49]

Retina microvasculature and perfusion can be adversely affected by COVID-19. Retinal hemorrhage, cotton wool spots, and drusen can occur in acute patients with COVID-19. The mean vein diameter is higher in infected patients, which positively correlates with disease severity.[50]

In the long term, post-COVID patients can develop retinal vessel changes, namely, narrower arteries and veins on fundus examination.[51] The macular and peripapillary retinal nerve fiber is thinner in patients who had recovered from COVID. This could be due to neurodegeneration of the retinal vascular system or central nervous system after infection. These irreversible changes can affect retinal tissue perfusion and function in the long run.

Conclusion

Corticosteroids including dexamethasone, fluocinolone acetonide, triamcinolone acetonide, and methylprednisolone are effective for the management of NIU. They can be administered via the intravitreal, suprachoroidal, periocular, and systemic routes and even via topical nanoparticles. Corticosteroids significantly improve visual acuity and macular edema and should be the first-line treatment for NIU.

Contributors

All authors designed the study, acquired the data, analyzed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data availability

All data generated or analyzed during the present study are available from the corresponding author on reasonable request.

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