

## **Using local therapy to control non-infectious uveitis**

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Treating uveitis aims to prevent the development of ocular structural changes related to intraocular inflammation that could otherwise lead to vision loss. Inflammation control is achieved with immunosuppressive drugs, primarily corticosteroids, and for many years has relied on these, particularly in cases with concomitant systemic diseases or bilateral uveitis.<sup>1</sup> While they are effective in controlling the inflammation many patients do not have systemic involvement and are unkeen to take systemic treatment. Direct access to the intraocular space means the eye is an ideal organ for local therapy, achieving high drug concentration on target. Local therapeutic options for the management of sight threatening non-infectious uveitis (NIU) include corticosteroids, methotrexate, anti-vascular endothelial growth factor (anti-VEGF) and more recently intravitreal biologics. The increased ability of these agents to sustain inflammatory control, though requiring repeat drug administrations, can help reduce the dose of systemic immunosuppression while maintaining a no inflammation state and preserving vision in such vision threatening conditions.

The Multicentre Uveitis Steroid Treatment trial (MUST) is a multi-national trial, which was established as a prospective interventional study to compare local and systemic treatment for NIU. It examined the effect of systemic immunosuppression treatment on long term control of NIU with long acting local therapy in the form of a surgically inserted fluocinolone acetonide implant (Retisert®, Bausch and Lomb, Bridgewater, New Jersey), reported to maintain a constant intravitreal level of corticosteroids up to 30 months. The interventional trial ran for 24 months, with 255 patients (479 eyes with uveitis) randomized to either systemic immunosuppression or a fluocinolone implant and were further followed for an additional 5 years as part of an observational study. The primary results demonstrated that at 24 months the implant

resulted in comparable visual improvement to systemic immunosuppression with greater inflammatory control, and macular edema (ME) resolving in two thirds of eyes from both groups.<sup>2</sup> Interestingly, over 60% of eyes treated systemically still required at least one supplemental local steroid injection.<sup>3</sup> These trends remained stable throughout the next thirty months and were only lost at seven years follow-up, when eyes treated systemically showed a greater visual benefit of 7.2 letters.<sup>4</sup> Eyes receiving the implants had a greater likelihood of developing ocular side effects, with 90% of phakic eyes requiring cataract surgery and 45% underwent surgery to control raised IOP. However, the visual function remained comparable and many patients were disease free for many years without the need for additional treatment. The injectable fluocinolone inserts (Iluvien®, Alimera sciences, Aldershot, UK) avoid the need for surgery, provide long-term inflammatory control and possibly a smaller risk of raised IOP.<sup>5</sup>

Periocular corticosteroid injections and Intravitreal triamcinolone acetonide injections (IVTA) are widely used in the treatment of ocular inflammatory disorders, reducing macular edema (ME) and vitritis. These procedures are relatively easy and safe with an efficacy of up to 72.7% of the eyes achieving complete control of inflammation by six months and half gaining significant visual improvement.<sup>6, 7</sup> Their effect lasts up to 6 and 12 weeks for periocular and IVTA injections, respectively, at which point they can be repeated with similar effect. Cataract and glaucoma are the main complications associated with these approaches and the risk of developing visually significant cataract requiring surgery is reported to reach 100% of eyes receiving  $\geq 4$  repeated IVTA injections. This short duration of action and ocular side effect limits

their use as long term treatment options, but they remain a useful method of achieving rapid local control of uveitis.

The dexamethasone implant (Ozurdex®, Allergan, Irvine CA) has been licensed for the treatment of uveitis, offering a sustain release treatment option that may have a reduced risk of ocular complications compared to other local corticosteroids.<sup>7,8</sup> The HURON trial demonstrated that following a single implantation, treated eyes were more likely to achieve inflammatory control and improved vision than untreated eyes.<sup>9</sup> In both adults and children the effect lasts for several months and can then be repeated as needed.<sup>8</sup> The risk of developing cataract and glaucoma is relatively low, with the majority of patients not requiring surgical intervention. The addition of local treatment as an adjunctive to systemic immunosuppression in young patients can help reduce their risk of developing systemic side effects related to systemic corticosteroids or long term use of steroid sparing agents.<sup>10</sup> With an extended duration these patients could have long periods with good inflammatory control and no additional treatment. To clarify the place of each of these agents as treatment options for NIU the PeriOcular and INTravitreal corticosteroids for uveitic macular edema (POINT) Trial is an ongoing multicenter, randomized trial designed to compare the relative efficacy of periocular triamcinolone (Kenalog®, Bristol-Myers Squibb Company, Princeton, NJ), IVTA and the intravitreal dexamethasone implant. The trial will include 267 patients with uveitic ME randomized to one of the three treatment arms and will compare the percent change in central retinal thickness from baseline to the 8 week visit, duration of effect, change in visual acuity and the need for additional injections by 24 weeks for each of these treatment options.

Intravitreal methotrexate injections (400µg/0.1 mL) may be considered an alternative in refractory cases. Though there are few studies that examined this treatment option it seems to offer a duration of effect of up to four months and a reduced risk of ocular hypertension.<sup>11-13</sup> It has been reported that some of the treated eyes might even achieve a longer remission suggesting it may be a suitable option for glaucomatous patients or those with a history of steroid-induced ocular hypertension.

The rationale for using intravitreal anti-VEGF drugs for treating NIU relates to blocking VEGF, restricting the induction of pro-inflammatory cytokines and reversing increased vascular permeability. Anti-VEGF is considered as treatment option mainly for refractory inflammatory ME, neovascularization and choroidal neovascular membrane. Small series studies suggest that using anti-VEGFs in eyes with uveitic ME can lead to a reduction in ME and improved vision, however the current level of evidence is regarded as low quality, lacking a conclusive comparison to other options, such as intravitreal corticosteroids. The mechanism of action of these drugs limits their effect as anti-inflammatory agents and possibly restricts their use only to selective cases of refractory ME in otherwise non-active uveitis. The multicenter, Mcular Edema Ranibizumab v. Intravitreal anti-inflammatory Therapy (MERIT) Trial is an ongoing randomized prospective study to compare the relative efficacy and safety over six months of intravitreal methotrexate, ranibizumab, and the dexamethasone implant for persistent uveitic ME. The trial includes 240 patients randomized to the three treatment arms and will compare the percent change in CRT from the baseline to the 12 week visit, improvement in vision and adverse events.

Anti tumor necrosis factor drugs are taking on a prominent role in controlling uveitis, with adalimumab recently approved in the USA and Europe for treatment of NIU not responding to corticosteroids and at least one additional immunosuppression agent. The intravitreal use of these drugs has been the focus of several studies with conflicting results. While small prospective studies have demonstrated improved visual acuity and inflammatory control for both intravitreal infliximab<sup>14</sup> and adalimumab,<sup>15</sup> there is a reported increased risk of persistent ME and an intra-retinal immunogenic reaction.<sup>16</sup> The efficacy of intravitreal sirolimus was examined in the Sirolimus study Assessing double-masked Uveitis tReAtment (SAKURA) Study,<sup>17</sup> and found that those receiving an intravitreal dose of 440µg demonstrated a significant reduction in vitreous haze and ocular inflammation, maintained good visual outcome and in 77% of cases were able to taper off systemic corticosteroids.

Local therapy, while not without significant ocular complications, primarily cataract progression and raised intraocular pressure related to use of corticosteroids, can nevertheless provide lasting good control of intraocular inflammation and stabilize vision. The need to repeat these invasive procedures remains a limiting factor, particularly among young patients. However, long-lasting agents, office-based injection procedures and improved patient response make these an important tool to long-term control of and a disease free state in such young patients with a chronic disease.

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