Landmark Studies in Uveitis

Neil Onghanseng, MD[1,2], Franz Marie Cruz, MD[3,4,5]

[1] DOH Eye Center, East Avenue Medical Center, Quezon City
[2] Department of Ophthalmology, Makati Medical Center, Makati City
[3] College of Medicine, University of the Philippines-Philippine General Hospital, Manila
[4] International Eye Institute, St. Luke's Medical Center, Quezon City
[5] Peregrine Eye and Laser Institute, Makati City

Correspondence: Franz Marie Cruz, MD
Peregrine Eye and Laser Institute, 5/F Morning Star Center,
347 Sen. Gil Puyat Ave, Brgy Bel-Air, Makati City
e-mail: fmocruz@gmail.com

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ABSTRACT

This paper provides the summaries on nine (9) important and clinically relevant publications in the field of uveitis. The first is on the standardization of uveitis nomenclature, more popularly known by its acronym - SUN, which was a result of an international workshop participated by uveitis experts in 2004. Five (5) papers were large, multicenter, clinical trials that demonstrated safety and efficacy of two (2) corticosteroids delivery devices (dexamethasone implant [Ozurdex] and fluocinolone acetonide implant [Retisert™]) and one (1) immunomodulatory drug (adalimumab). The POINT trial compared various delivery approaches when using corticosteroids for the treatment of uveitic macular edema. The FAST trial compared two (2) durable and commonly-prescribed steroid-sparing immunosuppressants, methotrexate and mycophenolate mofetil, for the treatment of non-infectious uveitis. Lastly, the SITE study, which was a large retrospective cohort study, determined the risks of overall and malignancy-related deaths among patients with inflammatory eye diseases receiving systemic immunosuppressants. Findings of these studies provide basis and rationale for the care and management of patients with uveitis and lay the groundwork for future research.

Keywords: uveitis, clinical trial, review, inflammatory eye disease, corticosteroids

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The subspecialty field of uveitis is a relatively nascent addition to ophthalmology in general. Worldwide, there exist only a few uveitis fellowship training programs as few practitioners exist in general. One of the largest training programs in the United States has only around a hundred graduates in total to date.[1] Being the young field it is, there exists many debates regarding the ideal management of uveitis patients. From early disagreements regarding physical exam findings[2-4] to current mostly off-label use of various steroid-sparing agents in attempts to control disease,[5] the field has undergone and continues to undergo rapid growth and refinement aided by high-quality research. Given the ever-increasing number of studies being published, it may be difficult for ophthalmologists, especially those in training, to determine which studies are most crucial to know concerning uveitis. As such, we have summarized the following studies, which we believe have had tremendous impact in uveitis and guide future developments. It is our aim to provide the readers a concise summary of these studies that they may gain the valuable knowledge that these studies impart and may hopefully, be inspired to add to the high-quality researches discussed herein.

Standardization of Uveitis Nomenclature for Reporting Clinical Data

In 2004, an international workshop involving 45 uveitis specialists from 35 centers in 13 countries was held to standardize the methods of reporting clinical data in uveitis.[6] The group discussed 3 aspects, namely: (1) terminology; (2) grading of inflammation and documentation of complications; and (3) reporting outcomes and results. Their output was published in the *American Journal of Ophthalmology* in 2005 and has become known as the Standardization of Uveitis Nomenclature (SUN).

Recognizing the importance of correct anatomic classification of uveitis to serve as the basis for subsequent work on diagnostic criteria for various uveitic entities, the SUN Working Group first defined the 4 types of uveitis based on anatomic classification. This classification scheme was adapted from the International Uveitis Study Group, and included anterior, intermediate, posterior and panuveitis. Next, commonly-used terminologies to describe uveitis, in terms of its *onset* (sudden vs. insidious), *duration* (limited vs. persistent), and *course* (acute vs. recurrent vs. chronic), were also defined.

With regard to grading of inflammation, the group put forth separate standard methods for grading anterior chamber cells and flare. They, however, failed to reach consensus on a standard method for grading vitreous cells but endorsed the grading system for vitreous haze by The National Eye Institute with minor modification.

The group also enumerated the appropriate ancillary diagnostic tests to document structural complications in uveitis, such as fundus photography and fluorescein angiography for optic disc and retinal neovascularization, fluorescein angiography or optical coherence tomography for macular edema, and so on.

Lastly, the group defined terminologies pertaining to uveitis activity including *inactive, improved* or *worsened activity,* and *remission.*

COMMENT: Although not a clinical trial, the SUN workshop has become widely-accepted and applied in clinical practice worldwide. It was initially intended to standardize the nomenclature used in reporting research study outcomes in the field of uveitis, but has been adapted in most, if not all, ophthalmology residency training programs as well as has been cited in several ophthalmology and uveitis textbooks.[7,8] The original text, which was published as a "Perspectives" in the *American Journal of Ophthalmology* in 2005, is a worthwhile read with all the nitty-gritty detail often left out in textbooks. What is more exciting is that the group recently came out with 25 new publications in attempts to provide standardized classification criteria of 25 uveitic syndromes.[9]

Dexamethasone intravitreal implant for non-infectious intermediate or posterior uveitis

Ozurdex (Allergan, Inc, Irvine, CA, USA) is an intravitreal, bioerodible, sustained-release dexamethasone implant that was first approved by the United States Food and Drug Administration (US FDA) for the treatment of macular edema associated with retinal vein occlusion. The Dexamethasone Intravitreal Implant for Noninfectious Intermediate or Posterior Uveitis, published in 2011, was a prospective, multicenter, single-masked, randomized, sham-controlled clinical trial that determined the efficacy and safety of Ozurdex, or DEX implant, among eyes with noninfectious intermediate and posterior uveitis over a 26-week period.[10] The trial enrolled and randomized

229 patients from 46 study sites in 18 countries to 3 study groups: 77 patients received 0.7 mg DEX implant, 76 received 0.35 mg DEX implant, while the remaining 76 patients had sham injection. Majority (81%) of the patients enrolled had intermediate uveitis. In all study groups, patients were allowed to continue using their topical anti-inflammatory and/or systemic immunosuppressants under strict conditions that the doses remained stable from baseline to week 8. Primary outcome measures were the vitreous haze score and proportion of patients with vitreous haze score of 0 at week 8. Other outcome measures were time to reach a vitreous score of 0, proportion of patients with at least two-step improvement in vitreous haze score, mean change in vitreous haze score from baseline to week 26, best-corrected visual acuity (BCVA), and central macular thickness measured using optical coherence tomography (OCT). Safety parameters included adverse events, such as ocular hypertension, cataract, and proportion of eyes requiring rescue medications.

Study findings showed that the proportion of eyes with vitreous haze score of 0 at week 8 was significantly greater in both groups that received the DEX implant (47% in 0.7-mg DEX implant group vs 36% in 0.35-mg DEX implant group vs 12% in sham group). The proportion of eyes with vitreous haze score of 0 from weeks 6 through 26 was also significantly greater in the 0.7-mg DEX implant group than sham group. This proportion was also significantly higher in the 0.35-mg DEX implant group than the sham group at weeks 6 to 12 and at weeks 20 to 26. The proportion of eyes with at least a two-step improvement in vitreous haze score was also significantly higher in the 2 DEX implant groups compared to the sham group. In terms of BCVA, the mean improvement from baseline BCVA and the proportion of eyes that achieved at least 3 lines of improvement from baseline were greater in both DEX implant groups than the sham group. OCT studies showed there were significant reductions in the mean central macular thickness at weeks 8- and 26 compared to baseline in both DEX implant groups, whereas there was no statistically significant change in the central macular thickness in the sham group. The mean change in central macular thickness was similar between the DEX implant groups. Lastly, safety analysis revealed that the proportion of eyes requiring rescue medication at weeks 3- and 26 after the injection was significantly higher in the sham group than both DEX implant groups. Intraocular pressure (IOP) ≥35 mmHg was reported in less than 5% of eyes across all treatment groups and study visits, while less than 10% of eyes had IOP ≥25 mmHg. Less than a quarter of the patients in the 0.7-mg DEX implant group required IOP-lowering medications throughout the 26-week study period. Of these, majority required only 1 drug to achieve IOP control. Progression of cataract was higher in the 2 DEX implant groups compared to the sham group, but this failed to reach statistical significance. The rates of other ocular adverse events were also similar among the 3 groups.

The study concluded that a single dose of DEX implant was effective in controlling intraocular inflammation in eyes with non-infectious forms of posterior and intermediate uveitis. Furthermore, the 0.7-mg implant was more effective than the 0.35-mg implant with equal safety profile.

COMMENT: This multi-center clinical trial provided high-level of evidence on the effectiveness and safety of Ozurdex for the treatment of non-infectious intermediate and posterior uveitis. Since then, Ozurdex implant has been a valuable addition to the treatment armamentarium against non-infectious uveitis. It is most especially beneficial for patients who are intolerant or have contraindications to high-dose oral steroid therapy. Additional advantages include being an easy method of administration that can be done as an in-office procedure and effectiveness lasting up to 6 months, reducing the need for repeated localized steroid injections.

Systemic anti-inflammatory therapy versus fluocinolone acetonide implant for intermediate, posterior and panuveitis

The Multicenter Uveitis Steroid Treatment (MUST) Trial was a multicenter, randomized, controlled, clinical trial that determined whether an intravitreal fluocinolone acetonide implant (Retisert, Bausch & Lomb, Rochester, NY, USA) was more superior than systemic therapy of corticosteroids plus immunosuppressants in the treatment of noninfectious intermediate, posterior and panuveitis.[11] From December 2005 to December 2008, 255 patients aged 13 years and older with non-infectious intermediate, posterior or panuveitis in one or both eyes who required systemic corticosteroids to achieve uveitis control were enrolled in 23 centers in 3 countries. One-hundred twenty-nine (129) patients were randomized in the implant group, while 121 patients were enrolled in the systemic treatment group. Study participants

in the implant group received surgical fluocinolone acetonide 0.59 mg implant in one or both eyes, followed by tapering and discontinuation of systemic corticosteroids and immunosuppressants. While the majority of the participants in the systemic treatment group received oral prednisone at 1 mg/kg/day or 60 mg/day. A steroid-sparing immunosuppressive was allowed, when indicated. The primary outcome was change in visual acuity (VA) from baseline to 24 months. Other outcome measures included: visual field sensitivity, clinically-graded uveitis activity, ocular and systemic complications, and quality-of-life and health utility questionnaires.

Results of the study showed that both treatment groups had modest visual improvement of about 1-Snellen line from baseline to 24 months. There was, however, no statistically significant difference between the 2 treatment groups. In terms of uveitis control, significantly more eyes had controlled inflammation in the implant group than in the systemic treatment group at 24 months (88 vs 71%, respectively). In addition, eyes receiving the implant were 1.47x more likely to achieve a two-step improvement in vitreous haze at 24 months compared to the systemic treatment group.

In terms of ocular complication, the implant group had higher rates of IOP rise, glaucoma, cataract progression, and cataract surgery compared to the systemic treatment group. Transient vitreous hemorrhage was the most common procedure-related complication. On the other hand, the risk for systemic infection requiring treatment was higher in the systemic treatment group. However, the risk of hospitalization was similar in both groups. The rate of hypertension was also higher in the systemic treatment group but the rate of initiation of blood-pressure-lowering medications was the same in both groups. Other systemic complications of corticosteroids such as osteoporosis, fractures, diabetes mellitus, and hyperlipidemia were similar in both groups.

The authors concluded that the fluocinolone acetonide implant or systemic treatment was similarly effective in controlling intraocular inflammation. Neither was superior over the other. The choice for therapy for a patient with non-infectious uveitis should take the advantages and disadvantages of each approach into consideration. Lastly, long-term treatment with systemic immunosuppressants was safe and well-tolerated.

COMMENT: As of this writing, Retisert™ is still not available in the country. Nonetheless, two notable findings in the study include: (1) similar effectiveness of systemic therapy with aggressive use of steroid-sparing immunosuppressants and Retisert™; and (2) safety and tolerability of long-term treatment with systemic immunosuppressants which is a cornerstone for management of several inflammatory eye diseases. Furthermore, a 7-year follow-up of a cohort group of 180 patients from the original MUST study revealed that those who received systemic therapy had better visual outcomes compared to the implant group at final visit.[12] Indications for initiation of systemic immunosuppressants in the paper (i.e. refractory disease and certain high-risk uveitis syndromes) very much apply in the real-world clinical practice as well.

Adalimumab in Patients with Active Non-infectious Uveitis (VISUAL I)

The VISUAL I trial, entitled "Adalimumab in Patients with Active Non-infectious Uveitis" on its publication in September of 2016, was a multinational phase 3 trial involving 18 countries and was conducted between August of 2010 up until August of 2014.[13] Participants included individuals aged 18 year and older with a diagnosis of active noninfectious intermediate, posterior, or panuveitis involving at least one eye. Crucially, all patients included must have had uveitis that was persistent despite the use of prednisone (10 to 60 mg per day) or an equivalent glucocorticoid for 2 or more weeks before screening. Patients with contraindications to monoclonal antibodies or those receiving other forms of immunosuppression for systemic illness other than ocular were excluded. Patients with recent eye surgery or significant opacity precluding examination of the posterior pole were also excluded.

All patients were randomly assigned to receive either adalimumab, a fully humanized monoclonal antibody that functions as an inhibitor of tumor necrosis factor (TNF), or a placebo in a 1:1 ratio. Patients in the adalimumab group received the standard 80-mg drug loading dose, followed by 40 mg maintenance dosing every two weeks via subcutaneous route for the duration of the study. All patients were given 60 mg prednisone at the start of their trial, which was on a preset tapering schedule that persisted until week 15, wherein all patients were placed off steroids.

The main treatment end point was either physician-determined treatment failure or persistent control of uveitis past week 80, whichever came first. The trial was originally set to run until treatment failure in 138 patients, though it eventually concluded with 144 treatment failures as 6 additional patients were noted to have recurrence of disease by the last clinical exam. Nine ranked secondary endpoints were recorded on each visit (i.e., change in anterior chamber cell grade in each eye, change in vitreous haze grade in each eye via fundus photo, change in BCVA in each eye via ETDRS chart, time to OCT evidence of macular edema in at least one eye, percent change in central retinal thickness on OCT in each eye, change in NEI Visual Functioning Questionnaire-25 [VFQ-25] composite score, change in VFQ-25 distance vision subscore, change in VFQ-25 near vision subscore, and change in VFQ-25 ocular pain subscore). All patients who received adalimumab were monitored for adverse events until 70 days past their last given dose.

The trial included a total of 217 patients and found a significant median time to treatment failure of 24 weeks in the adalimumab group versus just 13 weeks in the placebo group (Hazard ratio [HR] 0.50; 95% CI 0.36-0.70; P<0.001) with early and sustained separation of the treatment-failure curves. Furthermore, hierarchical testing of the ranked secondary outcomes showed that worsening of anterior chamber cell grade, worsening of vitreous haze grade, and worsening of BCVA were significantly less common among patients who received adalimumab (P≤0.01 for all 3 end points). VFQ-25 overall and subscore analysis also showed that the results favored adalimumab for each outcome with the exception of the change in VFQ-25 distance vision subscore. However, the difference between the groups in the time to OCT evidence of macular edema was not significant. Regarding adverse events, there were no significant differences noted between adalimumab and placebo with most adverse events related to adalimumab being noted as mild, such as nausea, injection site pain, and body malaise. Though two cases of cancer (i.e., GI cancer and glioblastoma) were noted in the adalimumab group, these were deemed by the investigator not to be secondary to adalimumab use.

The investigators concluded that adalimumab was both safe and effective for use in non-infectious intermediate, posterior, or panuveitis.

COMMENT: Though prior to this trial, TNF inhibitors were already being used in the treatment of non-infectious uveitis, particularly those that were steroid resistant. Most evidence for this was either based on case reports[14-16] or open label trials.[17-19] The VISUAL I trial clearly demonstrated that adalimumab was not only superior to placebo, but also provided a safe and prolonged period of treatment success for these patients. This paved the way for US FDA approval of adalimumab for the treatment of non-infectious uveitis. This was a clinical milestone as adalimumab was the first drug in its class to be granted FDA approval for uveitis treatment.[20] Follow-up studies to the VISUAL I trial would later further increase indications and are discussed later on in this review.

Adalimumab for prevention of uveitic flare in patients with inactive non-infectious uveitis controlled by corticosteroids (VISUAL II)

The VISUAL II trial, entitled "Adalimumab for prevention of uveitic flare in patients with inactive non-infectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial", was the follow up to the VISUAL I trial published in August 2016 and involved many of the same collaborators as its predecessor.[21] It expanded involvement to 21 countries, 3 more than in VISUAL I. In contrast to its predecessor, which evaluated active non-infectious uveitis patients, VISUAL II investigated inactive, non-infectious intermediate, posterior, or panuveitic uveitis. Inactive uveitis was defined as clinical inactivity for at least 28 days before the baseline visit wherein use of oral prednisone 10–35 mg daily to maintain inactive disease was permitted. Exclusion criteria were identical to VISUAL I.

All patients were randomized to either receive adalimumab or placebo injection in a 1:1 allocation ratio. Adalimumab dosing was identical to the VISUAL I protocol. As included patients were clinically inactive, prednisone boost was not given at the start of trial and all patients were gradually tapered off existing doses when applicable, with no patient being on steroids by week 16. Both primary and secondary endpoints were identical to those in the VISUAL I study.

The trial included an end total of 229 patients (114 in the placebo group and 115 in the adalimumab

group) and found that there was an early and sustained separation of the treatment failure curves between the adalimumab and placebo groups. Treatment failure occurred in 61 (55%) of 111 patients in the placebo group compared with 45 (39%) of 115 patients in the adalimumab group. Furthermore, the time to treatment failure was significantly improved in the adalimumab group compared with the placebo group (43% risk reduction) and more than half the adalimumab-treated patients did not have treatment failure vs. 8.3 months with placebo (HR 0.57, 95% CI 0.39–0.84; p=0.004). The secondary endpoint results, however, were numerically, but non-significantly, in favor of adalimumab for all ranked secondary variables except for change from baseline in VFQ-25 near vision subscore. There were no significant differences regarding adverse events with one malignancy (non-serious squamous cell carcinoma) noted and deemed related to adalimumab use by the investigators.

The investigators concluded that, in addition to their previous finding supporting adalimumab use in active uveitis disease, use of adalimumab could also effectively allow for safe withdrawal of maintenance steroids in clinically inactive cases without increasing the risk of disease flare-up or increasing risk of adverse events.

COMMENT: The results of the VISUAL II trial gave rationale for the eventual US FDA approval of adalimumab to cover inactive non-infectious uveitis as well. This landmark trial proved that not only was adalimumab superior to placebo in regards to controlling active disease, but that it was also a safe and effective alternative to steroids as a maintenance medication. This is of particular importance as long term use of corticosteroids above a dose of 10 mg/day carries several notable side-effects from weight gain up to loss of bone density.[22] Ophthalmologic side-effects exist with chronic steroid use as well, such as cataract formation and increased IOP.[23] Despite these side effects, a subset of uveitis patients become dependent on immunosuppressive medications, such as steroids, in order to prevent reactivation or flare-up of their disease. As such, the ophthalmologist is often forced to balance using the lowest dose of immunosuppressive agent needed to control the eye disease while causing the least amount of side-effect. Though other steroid-sparing agents exist, such as methotrexate, mycophenolate, and azathioprine among others, these carry their own individual side-effect profiles, notably liver damage with long-term use, and may not be suitable for every patient.[24] Thus, the approval of a new drug class in adalimumab, which has excellent long-term safety profile in use by other specialties, such as rheumatology and dermatology,[25,26] legitimized this option and made the use of TNF inhibitors more accessible to the general population.

Long-Term Safety and Efficacy of Adalimumab in Patients with Non-infectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis (VISUAL III)

Entitled "Long-Term Safety and Efficacy of Adalimumab in Patients with Non-infectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis" and published only last year, the VISUAL III study was an open-label extension study of the preceding VISUAL II and involved nearly all of the same collaborators as the latter, comprising a total of 85 centers from 21 countries.[27] Any patient with non-infectious uveitis qualifying for adalimumab therapy were included. Exclusion criteria were identical to that of the preceeding VISUAL I and II trials.

In a natural extension to the preceding VISUAL studies, VISUAL III investigated the ability of adalimumab to maintain long-term quiescence, defined as no new active inflammatory chorioretinal vascular lesions, inflammatory retinal vascular lesions, or both, and anterior chamber cell grade and vitreous haze grade of 0.5. or less in both eyes relative to baseline. As this was an open-label trial based on clinical practice, all patients were permitted to continue, taper, or discontinue concomitant corticosteroid therapy, immunosuppressive therapy, or both at the investigator's discretion. Patients were also allowed up to two or fewer PTA injections per eye per year so long as quiescence was maintained. Secondary objectives were identical to the previous VISUAL trials.

All patients were given subcutaneous adalimumab with 80 mg as loading dose, then 40 mg every two weeks starting one week after. Patients were then evaluated at weeks 0-, 2-, 4-, 8-, 12-, and 18, then every 12 weeks thereafter until the final visit. Data were collected for up to 7 years per patient, but data analysis was standardized at up to 150 weeks in order to confer uniformity to the study. AE monitoring was continued for up to 70 days after last treatment with adalimumab.

A total of 424 patients were included in the final analysis. At study entry, 67% of patients had active uveitis and 33% had inactive uveitis. Quiescence was

maintained beyond week 78 in both active and inactive groups, with 80% of patients in the active group and 96% in the inactive group showing quiescence at week 150. Furthermore, at week 150, 54% of patients with active uveitis at study entry and 89% of patients with inactive uveitis achieved corticosteroid-free quiescence. Finally, for patients with active uveitis at study entry who were in quiescence at week 150 and receiving systemic corticosteroids, most were receiving 7.5 mg/day or less. On subset analysis, it was noted that out of 141 patients receiving corticosteroids to control active uveitis at study entry, 68 remained in the study at week 150, with 44% of those showing corticosteroid-free quiescence at week 150. Regarding patients with active uveitis at study entry, 68% experienced one or more episodes of uveitis recurrence between week 8 and their final visit and 9% discontinued adalimumab because of recurrence. Regarding patients with inactive uveitis at study entry, 39% experienced one or more episode of uveitis recurrence between week 0 and their final visit, with 0.8% discontinuing adalimumab because of recurrence. Overall, the trends observed for quiescence were similar for other efficacy variables, including AC inflammation, vitreous haze, CST, and BCVA. The mean daily dose of systemic corticosteroids was reduced from 9.4 - 17.1 mg/day at week 0 to 1.5 - 3.9 mg/day at week 150 for all patients.

Adverse event (AE) profile was likewise acceptable. While 226 patients (53% or 80 events/100 person-years [PY]) experienced one or more AEs that were considered by the investigator to be possibly or probably related to the study drug, no AEs resulted in permanent blindness. The most frequently reported AEs were infections, with 275 instances recorded (65% or 79 events/100 PY). Thirteen (13) patients (3% or 1.3 events/100 PY) reported treatment-emergent malignancies, but only 4 cases of nonmelanoma skin cancers were deemed possibly related to adalimumab use by the investigators. Six (6) patients (1.4% or 0.5 event/100 PY) reported treatment-emergent demyelinating events, comprising demyelination (n=2), multiple sclerosis (n=2), and optic neuritis (n=2). Five (5) of these patients discontinued adalimumab as a result. Four (4) patients (0.9% or 0.4 event/100 PY), all with a medical history of sarcoidosis, reported treatment- emergent sarcoidosis. Four (4) deaths (0.4 event/100 PY) were reported during the entire study period, caused by B-cell lymphoma, metastatic pancreatic carcinoma, trauma, and brain abscess. Of these, only the brain abscess was considered by the investigator to be possibly related to study drug.

The authors concluded that adalimumab proved efficacious for inducing and maintaining long-term quiescence in non-infectious uveitis patients. Further, they noted that the AE profile was similar to that seen in the previous VISUAL studies and ruled that this profile was within acceptable risk levels.

COMMENT: With the completion of VISUAL III, a full exploration of the usage of adalimumab for non-infectious uveitis was completed. Ophthalmologists had been prior informed that this TNF inhibitor was effective for both active uveitis in terms of controlling disease[28] and for inactive uveitis in terms of enabling steroid-tapering.[29] This study examined the use of adalimumab in a real-world setting and found excellent integration into the existing uveitis armamentarium. As of this writing, the effects of this study have yet to be seen as it is the most recent study to be included in this list of uveitis landmark studies. It is hopeful that, given the stellar overall performance of adalimumab in this three-part investigation, the door would be open for future approval of other drugs in this class. Current monoclonal antibody drugs under trial for uveitis include: baricitinib, a janus kinase inhibitor (NCT04088409); efalizumab, a lymphocyte inactivator (NCT00280826) and; golimumab, a TNF inhibitor similar to adalimumab (NCT04218565). Other drugs are also being investigated. Recently, the STOP uveitis trial, which investigated the efficacy of tocilizumab, an anti-IL-6 antibody medication, in the management of active non-infectious uveitis, was completed with favorable reports in international conventions.[30] With the ever-increasing adoption and testing of new and existing medications, the practice of uveitis continues to evolve at a rapid rate.

The PeriOcular vs. INTravitreal corticosteroids for uveitic macular edema (POINT) Trial

The POINT trial, entitled "Periocular Triamcinolone vs. Intravitreal Triamcinolone vs. Intravitreal Dexamethasone Implant for the Treatment of Uveitic Macular Edema: The PeriOcular vs. INTravitreal corticosteroids for uveitic macular edema (POINT) Trial", was published in 2018 and was a randomized multicenter trial involving three countries (USA, UK, and Australia).[31] The trial enrolled patients with active or inactive, non-infectious anterior, intermediate, posterior, or panuveitis, with a focus on all enrolled

patients having macular edema (ME) on OCT deemed to be secondary to their uveitis. Furthermore, all patients investigated needed to have persistence and stability of their ME findings, such that if receiving systemic medications for the treatment of uveitis, patients needed to be on stable doses of oral corticosteroids and immunosuppressive drugs as applicable for at least four weeks.

The aim of the POINT trial was to compare treatment efficacy of the different routes of steroid administration, whether (periocular injection, intravitreal injection, or intravitreal implant, on ME. To that end, its primary objective was the change in central subfield thickness (CST) on OCT at week 8 relative to the findings at baseline. Absolute numerical changes could not be investigated as use of different OCT machines were allowed in order to potentially include a larger number of institutions and subsequently, a larger number of patients. Secondary endpoints included: change in CST at other time points and mean change in BCVA over the entire 24 weeks follow-up. The proportion of eyes with either improvement, defined as 20% reduction in macular thickness or normalization of macular thickness even if there is <20% reduction, or resolution, defined as normalization of the macular thickness to less than 2 standard deviations above normative mean, were also calculated over the follow-up period. Adverse events monitored for included: need for rescue treatment, IOP changes, and the proportion of patients requiring glaucoma and/or cataract surgery during the observation period.

The investigated patients were randomized at a 1:1:1 allocation ratio, though those with bilateral disease were given the same treatment for both eyes as standard ethics dictates. Periocular steroids (PTA) were administered as 40 mg triamcinolone acetonide given via periorbital floor or posterior sub-Tenon's approach, depending on the preference of the administering physician. All intravitreal injections (ITA) utilized 4 mg triamcinolone acetonide with the injection site being up to the decision of the injecting doctor. All intravitreal implants (IDI) utilized the same 0.7 mg dexamethasone implant (Ozurdex, Allergan, Dublin, Ireland). Patients were evaluated at baseline and at 4, 8, 12, 20, and 24 weeks of follow-up. Images were taken on all visits except on week 20. Re-treatment was allowed at the 8-week visit for the periocular and intravitreal triamcinolone treatment arms and at the 12-week visit for implants.

The trial investigated a total of 192 patients (235 eyes) and found that overall, CST improved compared with baseline at all follow-up visits for all treatment groups (P <0.0001) with percent reductions of 23%, 39%, and 46%, for PTA, ITA, and IDI, respectively. However, comparative analysis revealed that both ITA (ITA/PTA, HR, 0.79; 99.87% CI, 0.65-0.96) and IDI (IDI/PTA, HR, 0.69; 99.87% CI, 0.56-0.86) were superior to PTA (P <0.0001) and that this superiority was evident as early as week 4 with early separation of the treatment curves that eventually became attenuated by week 24. Further, IDI was superior to ITA, but not in a clinically significant level (P=0.035). On longitudinal comparison, it was noted that both ITA and the IDI were superior to PTA for improvement of the uveitic ME at all follow-up time points, except at the 24-week visit, upon which it was deemed by the investigators that no further medical benefits were likely to be gained from the initial intervention. Both intravitreal treatment groups were then compared and were found to have had higher proportions of eyes with resolution of uveitic ME when compared with PTA at each follow-up visit through the 8-week visit primary endpoint. Both intravitreal treatment groups also had statistically significantly greater improvements (4-7 letters better) in BCVA from baseline relative to PTA during the initial treatment period (4 and 8 weeks) and at the end of the follow-up period, with a mean of 5 letters improvement at 24 weeks. Finally, no significant differences were found between the intravitreal groups at any time. Safety analysis also favored the intravitreal groups as there were no significant differences regarding risk for IOP rise among groups at any point in the study, though the proportion of eyes treated with IOP medications increased steadily throughout the follow-up period, from 22% at randomization, to 32% at 8 weeks, then to 39% at 24 weeks. No glaucoma or cataract surgeries were encountered during the 24-week study period. The investigators concluded that intravitreal treatments, both ITA and IDI, performed superiorly versus periocular steroids for the management of uveitic macular edema. Though there was a recognized effect on IOP from the intravitreal approach, this effect was ruled as moderate and was not statistically significant. The authors further concluded that either intravitreal approach (ITA or IDI) were acceptable and did not differ from each other regarding both efficacy and safety.

COMMENT: The POINT trial is quite interesting as it appears to show clear superiority with intravitreal

approaches for targeted steroid therapy in cases of uveitic ME. Careful scrutiny of the data, however, shows that while there was a clear early separation of the treatment curves at week 4, PTA patients maintained a slow, but steady decrease in the ME until becoming equivalent to both intravitreal approaches near week 24. This finding holds true regarding both the primary and secondary endpoint measured showing that targeted steroid therapy by any approach is still an effective management for uveitic ME. Further, though the trial did not note any significant AE profile with intravitreal steroid use, it only utilized a total follow up period of 24 weeks. Trials investigating the use of intravitreal steroids for longer periods of time, such as the 0.59 mg fluocinolone acetonide intravitreal implant (Retisert, Bausch & Lomb, Quebec, Canada), found that by 12 months, 100% of implanted phakic patients developed visually significant cataracts and 44% developed glaucoma or ocular hypertension requiring surgical management.[32] Though these findings did not hold true with the use of shorter-acting IDI devices, prescribing ophthalmologists must remain aware of these potential complications should they attempt long-term therapy using IDI devices in general. As this trial is relatively new as of the time of writing, its effects on therapeutic trends have yet to be seen. Though this study demonstrates the capacity for faster and sustained recovery of uveitic ME when utilizing intravitreal approaches, long term safety and efficacy data regarding these 3 approaches remains lacking and any targeted approach may still be viable so long as the physician is aware of the benefits and possible detriments of each approach, deciding the approach based on available data and informed discussions in partnership with the affected patient.

Effect of Corticosteroid-sparing Treatment with Mycophenolate Mofetil vs. Methotrexate on Inflammation in Patients with Uveitis (FAST)

The FAST trial, entitled "Effect of Corticosteroid-Sparing Treatment With Mycophenolate Mofetil vs. Methotrexate on Inflammation in Patients With Uveitis: A Randomized Clinical Trial" on its publication in 2019, was a randomized clinical trial involving multiple centers from 5 countries (USA, India, Australia, Saudi Arabia, and Mexico).[33] It included patients with non-infectious intermediate, posterior, or panuveitis affecting at least one eye and requiring, but had not yet started corticosteroid-sparing immunosuppressive therapy, who were aged 16 years or older.

The trial aim was to compare the treatment efficacy of two commonly used steroid-sparing immunomodulatory agents in the management of uveitis: methotrexate (MTX) and mycophenolate mofetil (MMF). Its primary aim was corticosteriod-sparing control of ocular inflammation at month 6, with multiple secondary objectives including: treatment success at 6 months by anatomical subtype of the uveitis, treatment success at 12 months in patients who continued their randomized antimetabolite, number of patients who needing switching to the other antimetabolite, BCVA at 6 months, and CST at 6 months on OCT. Treatment success was defined as adequate control of uveitis with no flare-ups, based on SUN definitions[6] with allowance for minimal use of steroids, defined as 7.5 mg or less daily equivalent prednisone dose for oral steroids or two drops or less daily equivalent prednisolone acetate dose for topical steroids. The frequency and proportion of patients experiencing AEs from their prescribed medication were also recorded.

Patients were randomized at a 1:1 allocation ratio, with one group receiving 25 mg weekly oral MTX after a 15 mg weekly 2-week trial dose to screen for drug tolerance, and the other group receiving 1.5 g BID MMF after a 500 mg BID 2-week trial dose also to screen for drug tolerance. All patients were evaluated at baseline, 2 weeks, then at every 4 weeks up to 6 months in total. Patients with treatment success at this point then continued taking their randomized medication for another 6 months. If treatment was deemed a failure, patients switched to the other antimetabolite with a subsequent 6-month follow-up.

The trial investigated a total of 216 patients: 107 patients in the MTX group and 109 patients in the MMF group. The main study finding was that treatment success was achieved in 66.7% in the MTX group vs. 57.1% in the MMF group (P = 0.20), with the main reason for treatment failure being inefficacy of treatment for majority of failure cases in both groups. In regards to overall efficacy, neither drug proved significantly superior to the other. Further, there was no significant difference regarding change in visual acuity between treatment groups. There was also no significant difference regarding the CST changes between treatment groups at six months. However, MTX was superior regarding treatment success in patients with posterior uveitis and panuveitis (74.4 vs 55.3%; difference, 19.1% [95%CI, 3.6%to30.6%]; OR, 2.35 [95%CI, 1.16 to4.90]; P = 0.02), but not significantly different for patients with intermediate

uveitis. For both drugs though, if maintained successful at six months, 80% of MTX patients in the methotrexate group and 74.1% of MMF patients remained a treatment success at 12 months, with the majority (50.0% for MTX and 55.0% for MMF) discontinuing prednisone, indicating a high rate of treatment success regardless of the chosen drug. There was however, greater treatment success at 12 months on MTX (69.0%) in the 29 patients for whom MMF had previously failed vs. patients in the MMF group (35.0%) in the 20 patients in whom MTX had failed (difference, 34.2% [95% CI, 6.6% to 52.6%]; OR, 4.2 [95%CI, 1.3 to 13.2]; P = 0.02).

The authors concluded that both drugs were equally found to be effective as corticosteroid-sparing agents for use in the treatment of non-infectious uveitis. They further stated that both agents were non-inferior to each other from a clinical standpoint.

COMMENT: Discussions regarding the superiority of MTX versus MMF as initial drug of choice for steroid-sparing in uveitis have been long and ongoing, given the ready availability and relative ease of use of both agents in multiple countries.[34, 35] Though clinical evidence exists supporting efficacy of either drug and both have well-documented use in the management of uveitis patients, comparisons have mostly been conducted through either retrospective or open-label studies. The FAST study shows clinical equivalence of both drugs and, crucially, non-inferiority of either in a randomized study. Although study findings leaned slightly in favor of MTX on subset analysis, the authors conceded that further studies are still required for verification. As of this writing, the FAST trial is still a relatively new one and its effects on prescribing practice, if any, are still yet to be known. Doubtless to say however, that the non-inferiority of either drug lends credence to current prescribing patterns and uveitis practitioners are still well within their rights to opt for either MTX or MMF as their initial steroid-sparing drug of choice following informed discussion with their uveitis patients.

Overall and malignancy-related mortalities among patients with inflammatory eye disease treated with systemic immunosuppressive therapy

The Systemic Immunosuppressive Therapy for Eye Disease (SITE) Study was a large retrospective cohort study performed at 5 academic institutions in the United States to determine whether use of specific systemic immunosuppressant agents was associated with increased overall and cancer-related mortalities.[36] Medical charts of patients with non-infectious ocular inflammatory disease examined from 1979 to 2005 were reviewed. These included patients diagnosed with uveitis, scleritis, cicatrizing conjunctivitis of mucous membrane pemphigoid, corneal, optic nerve, and orbital inflammatory diseases. Persons with pre-existing cancer before the start of the cohort were excluded. Mortality incidence from 1979 to 2005 were checked against the US national death registry using the patients' identifiers. A death was counted when an exact match was found and the cause of death was obtained.

The study included 7,957 patients seen over 68,751 visits over 14,910 person years. There were 936 deaths; of which, 230 (25%) were due to cancer. Out of 936 deaths, 323 had received systemic immunosuppressants while 613 were unexposed. Statistical analyses showed that the cohort's overall mortality and cancer-mortality risks were similar to the US population. With regard to the class of immunosuppressive drugs, the study results revealed that antimetabolites, including azathioprine, methotrexate and mycophenolate mofetil, were not associated with significant increase in overall and cancer-related mortalities. Similar findings were also observed with T-cell inhibitors (i.e. cyclosporin). Interestingly, TNF-inhibitors, as an aggregate, were associated with significant increases in overall mortality (HR: 1.99, 95%, CI 1.00-3.98, p=0.050) and cancer-related mortality (HR: 3.83, 95%, CI 1.13-13.01, p=0.031). However, estimated risk ratios for the two TNF-inhibitors, etarnecept and infliximab, were similar in magnitude but insignificant. There was little information on adalimumab as it was only introduced in 2005. Lastly, systemic corticosteroids and dapsone, individually, were not associated with increased risks of overall and cancer-related mortalities.

The authors concluded that patients with ocular inflammatory disease receiving azathioprine, methotrexate, cyclosporine, dapsone or systemic corticosteroids most likely do not have increased risks of overall and cancer-related mortalities compared to the general population. Meanwhile, the use of TNF-inhibitors may be associated with small to moderate increased risks in overall and cancer-related mortalities. This finding should be interpreted with caution in light of the methodological limitations and confirmed in future studies.

COMMENT: Several non-infectious ocular

inflammatory diseases including uveitis require prolonged systemic immunosuppression to prevent flare-ups and preserve vision. Systemic corticosteroids have limited use due to its constellation of side-effects. Oftentimes, immunosuppressants are needed. One major concern is the risk of increased malignancy and malignancy-related deaths from use of these drugs. In fact, the association of immunosuppressants and cancer-related deaths is well-established among organ-transplant patients.[37] There are, however, differences in the subsets of population; patients with ocular inflammatory diseases receive far lower doses of immunosuppressants than transplant patients. Hence, a few studies, mostly retrospective in nature, have been performed to check for association between immunosuppressants and cancer among patients with ocular inflammatory disease. While, the study by Yates *et al*. showed that patients receiving immunosuppressants for inflammatory eye disease have increased risk for malignancy, it was not powered to allow stratification according to the classes of immunosuppressants.[38] No cancer-related death was observed in that study as well. The SITE Study above is, by far, the largest retrospective cohort study on this subject matter and provides additional evidence on the safety profile of several immunosuppressive agents, such as azathioprine, methotrexate, and cyclosporine, in the doses used to control inflammatory eye diseases. Results for the 3 immunosuppressants plus dapsone and corticosteroids show that they do not pose risk for malignancy-related deaths. However, the study was inconclusive with respect to the TNF-inhibitors, including adalimumab, and alkylating agents.

CONCLUSION

The above-mentioned studies have all greatly added to the subspecialty field of uveitis. From standardizing clinical nomenclature, to supporting the safe and effective use of medical therapy, these studies provide a handy basic rationale for clinical decision-making when managing the uveitis patient.

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