PeriOcular and INTravitreal corticosteroids for uveitic macular edema (POINT) Trial

Protocol version 2.1
16 Feb 2017

Phase 4 study

Sponsor-investigator

Janet Holbrook, PhD, MPH
Director, MUST Coordinating Center
Associate Professor of Epidemiology
Johns Hopkins Bloomberg School of Public Health
415 N. Washington Street
Baltimore, MD 21231

Medical Safety Officer

Akrit Sodhi, M.D., Ph.D.
Assistant Professor of Ophthalmology
Retina Division
Smith 4039
Wilmer Eye Institute
Johns Hopkins Medical Institutions
400 North Broadway Street
Baltimore, MD 21231

ClinicalTrials.gov identifier: NCT02374060

Document distribution

Version	Version date	Distribution	Distribution date
1.0	20 Nov 2014	JHSPH IRB Office	25 Nov 2014
1.0	19 Dec 2014	JHSPH IRB Office	19 Dec 2014
1.0	16 Jan 2015	JHSPH IRB Office	16 Jan 2015
1.0	29 Jan 2015	Vanguard clinical centers	05 Feb 2015
		JHSPH IRB Office	06 Feb 2015
		META-MUST DSMC	13 Feb 2015
1.0	06 Apr 2015	JHSPH IRB Office Clinical Centers	14 Apr 2015 14 Apr 2015
1.0	03 Jun 2015	META-MUST DSMC JHSPH IRB Office Clinical Centers-PPM 4	04 Jun 2015 04 Jun 2015 08 Jun 2015
1.1	06 Aug 2015	New clinics: MUHC, MEEI, IOWA, OCB, SCRA All clinical centers JHSPH IRB	07 Aug 2015 11 Aug 2015 (PPM7) 24 Aug 2015
1.2	23 Feb 2016	WILL, MAYO UKIO CC IRB UPMC All clinical centers	23 Feb 2016 24 Feb 2016 11 Mar 2016 28 Mar 2016 07 Apr 2016 (PPM 14)
2.0	28 Jun 2016	JHSPH IRB Clinical centers	6 July 2016 6 July 2016 (PPM 18)
2.1	16 Feb 2017	JHSPH IRB Clinical Centers	21 Feb 2017 24 Mar 2017 (PPM 37)

Document revision history

19 Dec 2014

Throughout

- Added (Kenalog®) as specification for periocular triamcinolone acetonide
- Added clarification for intravitreal triamcinolone acetonide: Triesence is to be used at U.S. clinics and Triesence is preferred at non-U.S. clinics but Kenalog is allowed

1.5 Investigators and study centers

- Deleted clinical centers:
  - Massachusetts Eye Research and Surgery Institute, Cambridge, MA
  - University of California-SD, La Jolla, CA

3.1 Type of study

- Added second stratification variable: ≥ .5 disc areas of leakage on fluorescein angiography at baseline as assessed by study ophthalmologist

3.6 Eligibility criteria

- Clarified inclusion criterion 3 by adding italicized text: Macular edema (ME) defined as the presence of *central subfield* macular thickness greater than the normal range for the OCT machine being used, regardless of the presence of cysts, as assessed by study ophthalmologist
- Deleted: Evidence of leakage on fluorescein angiography at baseline as assessed by study ophthalmologist;

3.7 Randomization

- Added second stratification variable: ≥ .5 disc areas of leakage on fluorescein angiography at baseline as assessed by study ophthalmologist

3.8 Data collection

- Color fundus (disc) images changed to Color fundus/red reflex images
- Deleted: Slit lamp images

16 Jan 2015

3.8 Data collection

- Clarified that ophthalmic exam includes slit lamp exam and ophthalmoscopy

29 Jan 2015

Abstract

- Removed 'initial' in the sentence: The question of how to approach regional treatment of uveitic macular edema is a key question for ophthalmologists treating these patients.

2.1 Objective

- Removed 'initial' in the following: To evaluate the relative efficacy of three commonly utilized regional corticosteroids for the regional treatment of uveitic macular edema: periocular triamcinolone acetonide; intravitreal triamcinolone acetonide; intravitreal dexamethasone implant.

3.1 Type of study

- Deleted stratification variable ≥ .5 disc areas of leakage on fluorescein angiography at baseline as assessed by study ophthalmologist

3.6 Eligibility

- Added inclusion criterion: Baseline fluorescein angiogram that is gradable for degree of leakage in the central subfield

3.7 Randomization

- Deleted stratification variable ≥ .5 disc areas of leakage on fluorescein angiography at baseline as assessed by study ophthalmologist

3.8 Data collection schedule

- "Color fundus/red reflex images" changed to "Fundus reflex images"

6.2 Statistical methods

In fourth paragraph made the following changes to accommodate removal of leakage on fluorescein angiography as stratification variable: All analyses will be performed both unadjusted, except for the stratification variable, and adjusted for potential confounders. Effect modification due to factors such as disease location or uveitis activity, fluorescein leakage in the central subfield, systemic disease, gender and race also will be explored when appropriate.

16 Feb 2015

3.6 Eligibility

- Corrected misspelling of gradable

6 Apr 2015

Title page

- Medical Safety Officer changed from Douglas A. Jabs, MD, MBA to Akrit Sodhi, MD, PhD
- Added: ClinicalTrials.gov Identifier: NCT02374060

1.4 Financial sponsor

- Added: Allergan (Irvine CA) is donating Ozurdex for the NEI, UKIO, and RVEE clinical centers

3.3 Trial schema

- In footnote "§" changed timeframe of opening of MERIT enrollment from 6 months to 1 year after the initiation of POINT

3.6 Eligibility

- Participant-level exclusion criterion 1 (History of infectious uveitis, or of scleritis, keratitis, or endophthalmitis in either eye) was split into 2 to clarify that it history of **infectious** endophthalmitis is exclusionary:
    1. History of infectious endophthalmitis or infectious uveitis in either eye;
    2. History of scleritis or keratitis of any type in either eye;

3 Jun 2015

3.3 Trial schema

- In footnote "†" removed "best corrected visual acuity of 20/40 or worse" as condition for second injection

3.6 Eligibility

- Inclusion criterion 4 (an eye level criterion) best corrected visual acuity (BCVA) requirement changed from "BCVA of 20/40 to 5/200" to "BCVA worse than 20/32 and 5/200 or better"

4.2.2 Second injections of assigned treatment

- Deleted "Best corrected visual acuity of 20/40 or better" as repeat injection criterion

6 Aug 2015

1.5 Investigators and study centers

- Deleted: Texas Retina, Dallas, TX
- Added
    - Southeast Clinical Research Associates, Charlotte Eye Ear Nose &Throat Associates, Charlotte, NC
    - Massachusetts Eye and Ear Infirmary/Harvard Medical School, Boston, MA
    - McGill University and McGill University Health Center, Montreal, QC, Canada
    - Ophthalmic Consultants of Boston, Boston, MA
    - University of Iowa Hospitals and Clinics, Iowa City, IA
    - Vision Research/ROPARD Foundation of Associated Retinal Consultants, P.C., Royal Oak, MI
    - UW Medicine Eye Institute, University of Washington, Seattle, WA

4.4.3 Possible side effects and complications of treatments, Intravitreal dexamethasone – added "elevated intraocular pressure which may require surgery to control" under less frequently reported events

3.1 Design, type of study – updated number of clinical centers to 26

23 Feb 2016

1.5 Investigators and study centers

- Deleted
  - Southeast Clinical Research Associates, Charlotte Eye Ear Nose &Throat Associates, Charlotte, NC
  - Vision Research/ROPARD Foundation of Associated Retinal Consultants, P.C., Royal Oak, MI
- Added:
  - Mid Atlantic Retina, Wills Eye Hospital, Philadelphia, PA
  - Mayo Clinic, Rochester, MN

3.6 Eligibility

Added new exclusion criterion #11: (eye level exclusion) Torn or ruptured posterior lens capsule

4.3 Treatment administration guidelines

- Added the word "guidelines"
- Added note*: Ophthalmologist administering treatment may follow local of standard care guidelines for topical anesthesia and needle size if they have been reviewed by Study Clinic Director as appropriate for use in this trial.*

28 Jun 2016, version 2.0

1.4 Financial sponsor

Clarified that Allergan is donating a limited number of Ozurdex for study patients at U.S. clinical centers in special circumstances, e.g. patient's insurance denies coverage for Ozurdex rather than for use at non-U.S. clinical centers

1.5 Investigators and study centers

- Change of Principal Investigator at these clinical centers
  - University of Pennsylvania
  - University of Southern California
  - Washington University
- Added new clinical center University of Pittsburgh Medical Center

3.1 Type of study

- Changed number of clinical centers from 26 to 27

3.3 Trial schema

- Second injection IOP criterion changed from *≤21 mm Hg with ≤ 2 IOP lowering agents* to *≤21 mm Hg with ≤ 3 IOP lowering agents*

3.6 Eligibility

Inclusion criteria

- 3 - Clarified definition of macular edema for eligibility by adding specific eligibility thresholds for central subfield macular thickness for different types of OCT machines
- 4 - Removed upper limit of best corrected visual BCVA (i.e., worse than 20/32)
- 5 – Increased the number of IOP lowering medications permitted from 2 to 3 and added clarification that combination medications, i.e.,Cosopt, count as 2 IOP lowering medications

Exclusion criteria

- 3 - New patient-level exclusion added: History of central serous retinopathy in either eye
- 6 – Clarification added as italicized for exclusion for oral prednisone dose ≤ 10 mg per day *at baseline* that has not been stable for at least 4 weeks *(Note if patient is off of oral prednisone at baseline (P01 visit), dose stability requirement for past 4 weeks does not apply);*
- Deleted exclusion criterion: Topical NSAID use if dose has not been stable for at least 4 weeks.

4.1 Treatment overview

4.2 Treatment schedule

- Pre-injection IOP criterion changed from *≤21 mm Hg with ≤ 2 IOP lowering agents* to *≤21 mm Hg with ≤ 3 IOP lowering agents*

8. Study timetable

- Removed this section because it is out of date.

16 Feb 2017, version 2.1

1.5 “Investigators and study centers” changed to “Resource and clinical centers”

- Replaced list of clinical centers and investigators with note that Clinical Centers and Clinic Directors are listed in the POINT Manual of Procedures in keeping with the convention that clinical centers are not listed in the protocol for multicenter trials with more than 3 clinical centers.

3.3 Trial schema

- Clarified that non-responders are eyes demonstrating less than a 20% reduction or worsening of ME as measured by central subfield macular thickness on OCT
- For dexamethasone arm, added that non-responders could be enrolled in MERIT at P06, if eligible
- Clarified that second injection time points on schema are the earliest time points for second injection but that second injections can be done at later time points
- Revised pre-injection IOP criteria for second injections – changed from ≤21 mm Hg to <25 mm Hg
- Updated last sentence in footnote explaining purpose of MERIT Trial regarding treatment of uveitic macular edema persistent after intravitreal corticosteroids; originally MERIT was to focus on uveitic macular edema persistent after intravitreal triamcinolone acetonide.

3.6 Eligibility criteria

Exclusion criteria

- Patient level exclusion criterion #2 changed

  From

  2. History of scleritis or keratitis of any type in either eye

  To

2. History of infectious scleritis of any type in either eye*. (Note: History of noninfectious scleritis that has been active in past 12 months is an eye-level exclusion –see #11 below.)*
3. History of keratitis (with the exception of keratitis due to dry eye)in either eye;

- Eye level exclusion criterion added

11. History of active noninfectious scleritis in past 12 months *(Note*: *History of noninfectious scleritis is acceptable if the last episode of active scleritis resolved at least 12 months prior to enrollment);*

4.1. Treatment overview

- Added to first bullet: Treatment administration instructions and pre-injection IOP criteria are included in sections 4.2 and 4.3.
- Added bullet: Treatment according to the best medical judgment of treating study ophthalmologist is permitted as deemed necessary. Repeat injections given before the protocol specified time points or other deviations from the treatment protocol (section 3.3.) should be reported expeditiously to CC on Unanticipated Event (UA) form, usually within a few days.
- Deleted last bullet: All injections of study treatments must be administered per protocol instructions and follow IOP injection criteria (IOP of ≤21 or mm Hg and treatment with ≤ 3 IOP-lowering agents).

4.2.1. Initial injections of assigned treatment

- Added explicit statement that IOP requirements for initial injection must be met on day injection administered.
- Added: *Note that IOP requirements for the initial injection are the same as for eye eligibility for the trial. If study treatment is initiated on the same day as eligibility is confirmed and treatment assigned, no additional IOP measurements are needed. If circumstances require patient to return to clinic for injection at a later date, IOP must be checked and IOP-lowering agents evaluated prior to injection. If the eligibility requirements are not met, the injection should not be given. If the treating ophthalmologist elects to proceed with assigned treatment per best medical judgment, the deviation from the protocol must be reported to CC on an Unanticipated Event (UA) form; the UA form should be submitted as soon as possible, usually within a few days.*

4.2.2. Second injections of assigned treatment

- Revised IOP requirements for second injection from "≤21 mm Hg and ≤3 IOP lowering agents" to "<25 mm Hg and ≤3 IOP lowering agents"

4.2.3. Treatment for non-responders (i.e., <20% reduction or worsening of ME)

- Clarified the study definition of non-responder: Eyes that demonstrate less than a 20% reduction no improvement or worsening of ME as measured by the central subfield thickness on OCT at specific time point in the trial

7.2.2 Confidentiality

- Added: CC will report serious adverse event data for participants randomized to Ozurdex to Allergan (Irvine, CA).

Global: minor edits in reference to changes above and formatting and spelling corrections

Abstract

Macular edema is the most common structural complication and leading cause of visual loss in patients with uveitis. Regional injections of corticosteroids are the most frequently used treatments specifically for uveitic macular edema but there is a lack of high quality evidence to guide choice of drug (e.g., triamcinolone acetonide, dexamethasone) and route of administration (e.g. periocular, intravitreal). The question of how to approach regional treatment of uveitic macular edema is a key question for ophthalmologists treating these patients. The Periocular and Intravitreal Corticosteroids for Uveitic Macular Edema (POINT) Trial is a randomized trial designed to compare the relative efficacy of three regional corticosteroids commonly utilized for the initial regional treatment of uveitic macular edema, periocular triamcinolone (Kenalog® , Bristol-Myers Squibb Company, Princeton, NJ), intravitreal triamcinolone (Triesence™, Alcon Pharmaceuticals, Fort Worth, TX), and the intravitreal dexamethasone implant (Ozurdex®, Allergan, Irvine CA). The design outcome is the percent change in central subfield macular thickness on OCT from baseline to the 8 week visit. Follow-up through 24 weeks will allow evaluation of the duration of response and the need for additional injections. Secondary outcomes include resolution of macular edema, IOP elevation, visual acuity, complications of treatment, and cost-effectiveness.

Contents

1. Introduction

1.1. Title

PeriOcular and INTravitreal corticosteroids for uveitic macular edema (POINT) Trial

1.2. IND exemption

IND exemption granted by FDA on 8 Sep 2013

1.3. Sponsor-investigator

Janet T. Holbrook, PHD, MPH, Director Coordinating Center
Johns Hopkins University Bloomberg School of Public Health
Baltimore, MD

1.4. Financial sponsor

U-10 grant, National Eye Institute

Allergan (Irvine CA) is donating a limited number of Ozurdex for study patients at U.S. clinical centers in special circumstances, e.g., patient's insurance denies coverage for Ozurdex. . Allergan will have no input into study design, management, data analyses, or interpretation of results.

1.5. Resource and clinical centers

Resource centers

Center	*Director*
Chairman's Office Icahn School of Medicine at Mount Sinai ,New York, NY	Douglas A. Jabs, MD, MBA
Coordinating Center Johns Hopkins Bloomberg School of Public Health, Baltimore, MD	Janet Holbrook, PhD, MPH
Reading Center University of Wisconsin at Madison, Madison, WI	Michael Altaweel, MD

Clinical Centers and Clinic Directors are listed in the POINT Manual of Procedures

1.6. Background and significance

Macular edema (ME) is the most common structural complication and cause of visual impairment and legal blindness in patients with uveitis.[1-3] In a retrospective study from two uveitis referral centers in the Netherlands in the early 1990s, 40% of patients with intermediate uveitis, posterior uveitis, or panuveitis had ME, and it was the most common cause of visual loss among all patients with uveitis, accounting for 41% of visual impairment.[3] In the Multicenter Uveitis Steroid Treatment (MUST) Trial, ME was present in approximately 40% of eyes with uveitis with a similar frequency for patients with intermediate uveitis, posterior uveitis, and panuveitis.[4-6] The presence of ME is the most common indication for treatment among patients with intermediate uveitis.[1, 2, 7-9] Furthermore, despite apparent control of inflammation with corticosteroids and immunosuppressive drugs such that no inflammatory white cells are present

in the anterior chamber or vitreous, many patients exhibit persistent ME requiring supplemental therapy, typically with periocular or intravitreal corticosteroid injections.[1, 2, 7-10]

The management of uveitic ME is principally directed toward treatment of the underlying inflammatory condition with appropriate medical therapy and less often, surgical intervention together with life-style modifications such as smoking cessation and stress reduction.[11-13] Current medical treatment modalities include nonsteroidal anti-inflammatory drugs, immunomodulatory therapies, acetazolamide, octreotide, oral, periocular, or intravitreal injections of various corticosteroid preparations, and most recently, intravitreal administration of anti-vascular endothelial growth factor (VEGF) inhibitors and methotrexate (MTX).[11, 14-17] While corticosteroid injections may reduce ME and improve vision, the effect is often variable with a limited duration.[18, 19] Pars plana vitrectomy (PPV) and PPV in combination with intravitreal corticosteroids have been investigated as treatment options for inflammatory ME unresponsive to medical therapy; however, the impact of this intervention is not yet clear.[20, 21] The frequently refractory nature of uveitic ME and its impact on visual function underscores the need to identify effective alternative medical therapeutic options.

The pathophysiology of ME associated with uveitis is thought to be a consequence of increased vascular permeability from mediators released by inflammatory cells which damage the function of the vascular endothelium, retina, and retinal pigment epithelial (RPE) cells with subsequent accumulation of fluid into the macula, characteristically distributed in the outer plexiform layer of the retina.[11] Exactly which mediators are critical in the pathogenesis of inflammatory ME is incompletely understood. Corticosteroids have been the first line of treatment for noninfectious uveitis in general and of inflammatory ME in particular. The mechanisms of action by which corticosteroids mediate their effect are likely their anti-inflammatory, anti-edema, and anti-angiogenic effects. Corticosteroids inhibit the phospholipase A2 pathway, interfere with the release of inflammatory mediators, and decrease VEGF secretion.[22, 23] Models of experimental autoimmune uveoretinitis in rats and studies in humans with uveitis and ME show an increased concentration of vascular endothelial growth factor (VEGF) in the aqueous humor.[24-27] VEGF is suspected to play a role in the loss of vascular integrity in the eye and is known to be induced by inflammatory cytokines, such as interleukin (IL)-1 and IL-6, which have been found to be elevated intraocularly in uveitis patients.[27, 28] Furthermore, aqueous VEGF concentrations are significantly higher in those uveitis patients with CME than those without CME. [25] The recent introduction of intravitreally administered nonsteroidal medications with anti-inflammatory activity for the treatment of inflammatory ME, such as methotrexate and those which inhibit inappropriate VEGF activity, offers potentially effective alternative treatment approaches to ME in this population which might obviate the well-known ocular side effects of corticosteroid based therapies.

Traditional approaches to the treatment of uveitic ME have included the use of regional corticosteroid therapy, delivered periocularly, including posterior sub-Tenon's (PST) and orbital floor injections, or via the intravitreal route.[7, 10, 29-41] With respect to periocular delivery, available nonrandomized, but comparative, data suggest similar success rate with both approaches.[42-44] The most commonly used drug is triamcinolone acetonide (TA) even though both methylprednisolone and TA have been used for periocular injections. The estimated pharmacologic effect of a regional corticosteroid injection, whether given by the periocular or intravitreal route, appears to be approximately 3 months, although the duration of benefit in some patients with uveitis may be longer.

In a retrospective study of 159 eyes that underwent PST for ME from a variety of etiologies and were followed for a mean of 12 months, a single injection posed relatively little risk of IOP

complications and cataract progression whereas with repeated administration, these side effects increased.[45] A study from the Johns Hopkins Medical Institution of 126 patients (156 eyes) with uveitic ME who received a single periocular injection of corticosteroid reported clinical resolution of ME among 53% and 57% of eyes at 1 month and 3 months respectively. [46] Of the 83 eyes that had resolution of ME at 1 month, 50 (60%) had no recurrence of the ME at 3 months after the first periocular corticosteroid injection. Among those eyes that had recurrence of ME, the median time for recurrence was 20 weeks. Forty eyes were treated with more than one periocular injection due to persistence of ME one month following the first injection. Of the 21 eyes treated with a second periocular injection, 81% and 43% had no ME at one and 3 months, respectively, after the second injection. Overall, a 3-line improvement in visual acuity was observed in 52% at one month and in 57% at 3-months. Side effects attributed to periocular corticosteroid injections included IOP rise to >30 mm of Hg in 19% (rate = 0.14/eye-year [EY]), newly diagnosed cataract in 10% (rate = 0.13/EY), and ptosis in 14% (rate = 0.09/EY).

The largest study evaluating intravitreal triamcinolone acetonide in patients with uveitic ME was performed at Moorfields Eye Hospital.[33] This retrospective case series of 65 eyes in 54 patients found an improvement in ME and visual acuity in 83% of eyes and a mean 12-letter gain (2.4 lines) in BCVA with intravitreal triamcinolone acetonide with a mean follow-up of 8 months. The most important side effect was raised IOP with 43% experiencing IOP rise >10 mm of Hg. Although not strictly comparable, these data suggest that intravitreal triamcinolone acetonide may be superior to periocular TA for the treatment of uveitic ME, but that the frequency of ocular complications may be greater. Similarly, a study comparing the ocular side effects of PST to intravitreal triamcinolone acetonide in ME from a variety of causes demonstrated a significantly increased frequency of IOP> 30 mm Hg and the more frequent need for antiglaucoma medication among the intravitreal triamcinolone acetonide group with risk factor for the development of elevated IOP including; higher baseline IOP, younger age, and the presence of uveitis.[47]

Indeed, the major limitations of intravitreal triamcinolone acetonide are related to the relatively high rates of adverse ocular effects and to its limited duration of action. The rate of cataract development has been reported to range from 15-30% after a single injection[48-51] and increases with repeated injections.[52, 53] Steroid induced IOP elevations have been reported to arise in 25% and 45% of patients[33, 48-50, 54] are dose dependent[55, 56] and may be more frequent among children.[18] In most instances, elevated IOP is transient and may be controlled with antiglaucoma medications; however, surgical intervention may be required.[36, 57] While the long-term prognosis of uveitic ME treated with intravitreal triamcinolone acetonide is uncertain, a recent report demonstrated improved BCVA with no evidence of tachyphylaxis to repeated intravitreal triamcinolone acetonide injections or increased rates of IOP elevation, while cataract progression requiring surgery was seen in all phakic patients by the fifth injection.[58] In addition, intravitreal triamcinolone acetonide has been shown to be effective in the management of persistent ME despite adequate control of intraocular inflammation with response rates of up to 85%.[16, 52, 59, 60] There are currently two formulations of preservative free TA that have been approved by the Federal Drugs Administration (FDA) for intraocular use, Triesence™ (Alcon, Fort Worth, Texas, USA) and Trivaris™ (Allergan Inc., Irvine, California, USA).

In an effort to avert the limited duration of action of intravitreal triamcinolone acetonide and exposure to systemic medications, sustained release devices have been developed and approved by the FDA including the dexamethasone implant, a copolymer containing dexamethasone, lactic and glycolic acid, which degrades slowly into carbon dioxide and water over a period of 6 months following an office based injection into the vitreous cavity.[61-67] The safety and efficacy of a single intravitreal injection of two dexamethasone implant doses (0.7mg

and 0.35mg) has been recently reported from the HURON study, a large, 26 week, phase III, prospective, multicenter, masked, sham-controlled randomized clinical trial among 229 patients with noninfectious intermediate or posterior uveitis.[68] Patients were randomized 1:1:1 to receive either a high dose dexamethasone (0.7mg) implant, low dose dexamethasone (0.35mg) implant, or sham injections. While both implant doses were shown to be effective in controlling vitreous inflammation and in improving visual acuity, the higher dose implant proved to have a longer duration of action without a significant increase in untoward ocular side-effects and is the dose currently in clinical use. Vitreous haze scores of zero were achieved in 47% and 36% of the high and low dose implants respectively as compared with 12% among sham treated eyes at 8 weeks, a benefit which persisted among the high dose group to 26 weeks when compared to sham. At 8 weeks, 43% of treated eyes versus 7% in the sham group had at least a 15 letter improvement from baseline BCVA while the proportion of eyes achieving this level was 2- to 6-fold greater in the dexamethasone implant groups as compared to the sham group throughout the study period. The central macular thickness as measured by optical coherence tomography (OCT) was significantly lower at weeks 8 and 26 in both dexamethasone implant groups compared to baseline but not statistically different among the sham group. While the mean reduction in macular thickness from baseline was significantly greater in the dexamethasone implant treated eyes at week 8, this was not sustained at week 26. The percentage of eyes with IOP ≥25 mm Hg peaked at 7.1% for the high dose implant, 8.7% for the low dose implant, and 4.2% for the sham group with the ≤ 23% of eyes in the high dose group requiring antiglaucoma medication and none requiring surgical intervention. Likewise, at 26 weeks, there was no statistically significant increase in the rate of cataract between treatment groups (15% high dose, 12% low dose, 7% sham) with no patient requiring surgery.

Subsequent small, retrospective case series confirm the safety and efficacy of the dexamethasone implant in eyes with noninfectious posterior uveitis with an improved inflammatory activity, visual acuity and a reduction in mean central retinal thickness; however, the durability of the effect may be shorter (3-4 months) in clinical practice than that reported in the HURON trial and require repeated injections.[69-71] While the side effect profile of the dexamethasone implant may appear to be superior to intravitreal triamcinolone acetonide, it is important to note that steroid responders were excluded from the HURON trial and patients received a single injection, hence, the effect of multiple injections on cataract and IOP remains unknown. Finally, while preclinical data indicate that the vitreous and retinal concentrations of dexamethasone are similar in non-vitrectomized and vitrectomized eyes, it is of interest as to whether the dexamethasone implant will have an advantage in the latter situation in which clearance of intravitreal triamcinolone acetonide is known to be more rapid.[19, 64, 72]

Taken together these data suggest that intravitreal triamcinolone may be a more effective initial treatment than periocular triamcinolone although its side effects may be greater and that the intravitreal dexamethasone may have lower rates of side effects than those of intravitreal triamcinolone. However, differing methodologies and different enrollment criteria substantially hamper comparing the data from these different studies. One of the most substantial differences is the methodology used to evaluate macular edema. Clinical estimates of macular edema improvement are heavily influenced by visual acuity improvement and may overestimate the resolution rate and the apparent efficacy of interventions on macular edema. Fluorescein angiography and OCT measure somewhat different aspects of macular edema, vascular leakage and retinal thickness, respectively. Although the two methods correlate, the correlation is moderate, as compensated leakage may not result in thickening, and thickening may occur without evident leakage.[4] Of the three methods (OCT, fluorescein angiography, clinical examination), clinical examination is least likely to detect macular edema.[4] Visual acuity loss correlates better with retinal thickness than with the two-dimensional area of leakage.[73] Even

though vision is influenced by multiple factors, such as media opacity, change in macular thickness on OCT correlate with visual acuity improvement[74], suggesting that as a single measure of macular edema response for comparative studies, retinal thickness on OCT is a good one. Furthermore, a relatively short-term trial with macular thickness on OCT as a comparative measure may be adequate to evaluate relative efficacy. Somewhat longer-term follow-up (e.g. 6 months) will be needed to evaluate the duration of response and the need for additional injections. The POINT Trial was designed to compare the relative efficacy of periocular triamcinolone, intravitreal triamcinolone, and intravitreal dexamethasone as the initial regional approach to treatment of macular edema using central subfield macular thickness on OCT as the primary outcome measure with assessment of the relative efficacy at 8 weeks and evaluation of the duration of response and the need for additional injections over 24 weeks of follow-up.

2. Objective and study hypothesis

2.1. Objective

To evaluate the relative efficacy of three commonly utilized regional corticosteroids for the regional treatment of uveitic macular edema: periocular triamcinolone acetonide; intravitreal triamcinolone acetonide; intravitreal dexamethasone implant. The primary efficacy measure will be percent change in central subfield thickness as measured by OCT at 8 weeks. Participants will continue in the study for 24 weeks in order to evaluate relative effects of the 3 treatment strategies on the duration of treatment effects, requirement for additional injections, and adverse effects.

2.2. Hypothesis

Primary hypotheses:

(1) Intravitreal triamcinolone injections will have greater efficacy than periocular triamcinolone as a treatment for uveitic macular edema.

(2) Intravitreal injections of the dexamethasone pellet will have greater efficacy than periocular triamcinolone injections as a treatment for uveitic macular edema.

(3) Intravitreal injections of the dexamethasone pellet will be non-inferior to intravitreal triamcinolone as a treatment for uveitic macular edema.

Secondary hypothesis:

(1) Intravitreal injections of the dexamethasone pellet will have a lower rate of IOP elevation than intravitreal triamcinolone injections over the 24 weeks of follow-up.

3. Design

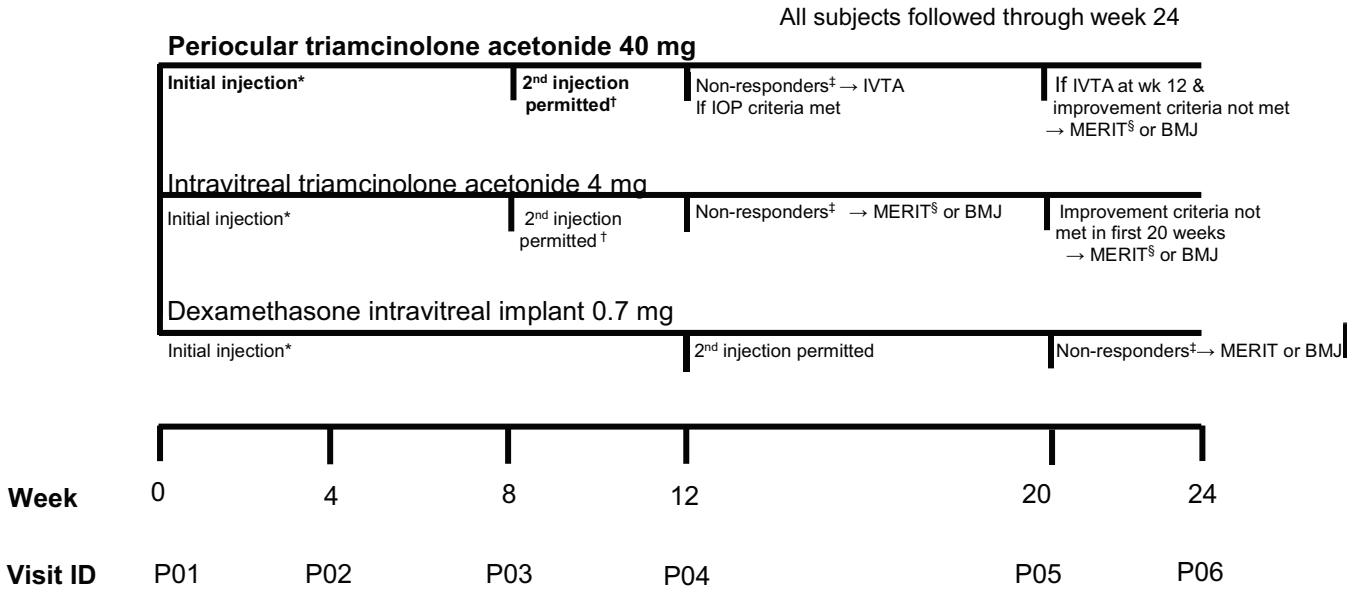
3.1. Type of study

- Three-armed, parallel design randomized comparative trial
- Allocation ratio 1:1:1
- Randomization stratified by the presence or absence of concomitant systemic therapy for uveitis (e.g., oral corticosteroids and/or immunosuppressive drugs)
- Unit of randomization is patient, not eye; if both eyes meet eligibility criteria, both receive the assigned treatment
- Multicenter
- Fixed sample size, 267 (89 per treatment group)
- Anniversary close-out at the 24 week clinic visit
- Reading center graders assessing primary outcome and visual acuity examiners masked to treatment
- Open-label; treating physicians and patients unmasked to treatment (the therapies are different in appearance and have potentially different injection schedules)

3.2. Treatment Arms

- Periocular triamcinolone acetonide (Kenalog) (40 mg)
- Intravitreal triamcinolone acetonide (preservative-free preparation, Triescence at U.S. clinics; Triesence preferred at non-U.S. clinics but Kenalog allowed) (4 mg)
- Dexamethasone intravitreal implant (Ozurdex) (0.7 mg)

3.3. Trial schema



* Eye(s) meeting trial eligibility criteria receive initial injection of assigned treatment at P01 visit.

† Second injection of assigned treatment permitted at 8 week visit or later for periocular and intravitreal triamcinolone acetonide and at 12 week visit or later for intravitreal dexamethasone when following conditions are met:

- Eye does not meet the improvement definition (a 20% decrease in central subfield thickness of the macula) OR eye has a normal central subfield thickness but has cystoid spaces in the 1 mm central subfield OR ME is worse after initial improvement;
- IOP of <25 mm Hg and treatment with ≤3 IOP-lowering agents;

‡ Eyes demonstrating < 20% reduction or worsening of ME as measured by the central subfield macular thickness on OCT are considered primary treatment non-responders at these time points

§ Macular Edema Ranibizumab v. Intravitreal Anti-inflammatory Therapy (MERIT) Trial is a companion study to POINT (funded by the same grant) for treatment of macular edema persisting after intravitreal triamcinolone therapy. MERIT will begin enrollment approximately 1 year after the initiation of POINT and continue concurrently. POINT participants who meet MERIT eligibility criteria at indicated time points may enroll in MERIT while concurrently completing follow-up in POINT. MERIT will evaluate the relative effectiveness among two regionally-administered alternatives to regional corticosteroid injections, a) intravitreal ranibizumab (Lucentis®, Genentech Inc., San Francisco, CA), and b) intravitreal methotrexate (MTX), with c) the intravitreal dexamethasone (Ozurdex) for the treatment of uveitic macular edema persistent after intravitreal corticosteroids.

3.4. Primary outcome

The primary outcome is the percent change in central subfield thickness from the baseline OCT measurement at the 8-week visit. The time point of 8 weeks was chosen for assessment of the primary outcome because it encompasses the window for maximum benefit for all three treatment strategies. The results will be transformed to represent relative change. Assessment of OCT outcomes will be performed by masked readers.

3.5. Secondary outcomes

- Rate of IOP elevation of >21 mm Hg or ≥ 10 mm Hg from baseline during the 24 weeks of follow-up
- Percent change in macular thickness as measured by OCT over the 24 weeks of follow-up
- Proportion of eyes with macular edema events over the 24 weeks of follow-up
  - ≥20% reduction in macular thickness (or normalization of macular thickness even if there is <20% reduction)
  - ”Resolution”, defined as normalization of the macular thickness to within $\pm$2 standard deviations of the normative mean for the OCT machine used
  - Worsening defined as a 20% increase in macular thickness from the lowest value after an injection
  - “Recurrence” defined as >20% increase in the central subfield measurement on OCT to an abnormal value in an eye that previously had resolution of ME
- Mean change in BCVA over the 24 weeks of follow-up.
  Best-corrected visual acuity score will be measured at every study visit under standardized lighting conditions by certified study examiners masked to study treatment using logarithmic (ETDRS) visual acuity charts, according to the method described by Ferris, et al.[75]
- Inflammation as graded using the semi quantitative scales used in the MUST Trial i.e., clinician grading of the presence and extent of anterior chamber cells, anterior vitreous cells, and vitreous haze based on previously published standard ordinal scales (0, trace, 1+, 2+, 3+, 4+)[76-78] using the scales endorsed by the Standardization of Uveitis Nomenclature Working Group when applicable[79]
- Safety outcomes including elevated IOP (>30 mm Hg thresholds); new onset posterior subcapsular (PSC) cataract or progression of pre-existing PSC (using the Age-Related Eye Disease Study [AREDS] scheme[80]; vitreous hemorrhage; retinal tear/detachment; endophthalmitis; severe vision loss (≥15 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) during the 24 weeks of follow-up.
- Cost-effectiveness of treatments for uveitic macular edema during the 24 weeks of follow-up will be assessed by enumerating costs of treatments and procedures for uveitis during the 24 week follow-up; participants’ utilities will be measure with the EuroQol questionnaire.
- Visual function related quality of life as measured by the NEI Visual Function Questionnaire (25 item version).

3.6. Eligibility criteria

Inclusion criteria:

Patient level inclusion criterion:

1. 18 years of age or older;

Eye level inclusion criteria - at least one eye must meet all of the following conditions

2. Non-infectious anterior, intermediate, posterior or panuveitis; either active or inactive uveitis is acceptable;
3. Macular edema (ME) defined as the presence of central subfield macular thickness greater than the normal range for the OCT machine being used *(>300 µm for Zeiss Cirrus/Topcon 3DOCT or >320 µm for Heidelberg Spectralis)*, regardless of the presence of cysts, as assessed by study ophthalmologist;
4. Best corrected visual acuity (BCVA) 5/200 or better;
5. Baseline intraocular pressure > 5 mm Hg and ≤ 21 mm Hg (current use of 3 or fewer intraocular pressure-lowering medications and/or prior glaucoma surgery are acceptable – *note that combination medications, i.e., Cosopt, count as 2 IOP lowering medications)*;
6. Baseline fluorescein angiogram that is gradable for degree of leakage in the central subfield
7. Pupillary dilation sufficient to allow OCT testing.

Exclusion criteria:

Patient level exclusion criteria:

1. History of infectious endophthalmitis or infectious uveitis in either eye;
2. History of infectious scleritis of any type in either eye*. (Note: History of noninfectious scleritis that has been active in past 12 months is an eye-level exclusion –see #11 below.)*
3. History of keratitis (with the exception of keratitis due to dry eye)in either eye;
4. History of central serous retinopathy in either eye;
5. For women of childbearing potential: pregnancy, breastfeeding, or a positive pregnancy test; unwilling to practice an adequate birth control method (abstinence, combination barrier and spermicide, or hormonal) for duration of trial;
6. Use of oral acetazolamide or other systemic carbonic anhydrase inhibitor at baseline;
7. Oral prednisone dose > 10 mg per day (or of an alternative corticosteroid at a dose higher than that equipotent to prednisone 10 mg per day) OR oral prednisone dose ≤ 10 mg per day at baseline that has not been stable for at least 4 weeks *(note that if patient is off of oral prednisone at baseline (P01 visit), dose stability requirement for past 4 weeks does not apply)*;

8. Systemic immunosuppressive drug therapy that has not been stable for at least 4 weeks;
9. Known allergy or hypersensitivity to any component of the study drugs;

Eye level exclusion criteria - at least one eye that meets all inclusion criteria cannot have any of the following conditions:

10. History of severe glaucoma as defined by optic nerve damage (cup/disc ratio of ≥ 0.9 or any notching of optic nerve to the rim);
11. History of active noninfectious scleritis in past 12 months *(Note*: *History of noninfectious scleritis is acceptable if the last episode of active scleritis resolved at least 12 months prior to enrollment);*
12. Media opacity causing inability to assess fundus or perform OCT;
13. Presence of an epiretinal membrane noted clinically or by OCT that per the judgment of study ophthalmologist may be significant enough to limit improvement of ME (i.e., causing substantial wrinkling of the retinal surface)[81];
14. Torn or ruptured posterior lens capsule
15. Presence of silicone oil;
16. Periocular or intravitreal corticosteroid injection in past 8 weeks;
17. Injection of dexamethasone intravitreal implant in past 12 weeks;
18. Placement of fluocinolone acetonide implant (Retisert) in past 3 years;

3.7. Randomization

After the patient has given written informed consent, eligibility has been confirmed and baseline data have been keyed and passed an electronic eligibility review, the patient will be randomly assigned to one of the three treatment groups, via a web-based system, returning the treatment assignment result in real time. Receipt of treatment assignment will be confirmed by user re-entry of the treatment assignment. Beginning at this point, the patient's data will be included for primary analyses, regardless of subsequent actual treatment and/or extent of adherence to therapy. Randomization will be accomplished using an auditable, documented scheme generating a reproducible order of assignment. Randomization schedules will be developed by the Coordinating Center (CC), using permuted blocks of varying lengths, designed to yield expected assignment ratio of 1:1:1. Randomization will be stratified by the presence or absence of concomitant systemic therapy for uveitis (e.g., oral corticosteroids and/or immunosuppressive drugs).

3.8. Data collection schedule

Visit ID	P01	P02	P03	P04	P05	P06
Time	**Baseline**	**4-wk**	**8-wk**	**12-wk**	**20-wk**	**24-wk**
Medical/ophthalmic history	X	X	X	X	X	X
Treatment history	X	X	X	X	X	X
Best-corrected visual acuity	X	X	X	X	X	X
Tonometry	X	X	X	X	X	X
Ophthalmic exam (slit lamp exam and ophthalmoscopy)	X	X	X	X	X	X
Gonioscopy	X					
OCT	X	X	X	X	X	X
Fundus reflex images	X					X
Fluorescein angiogram	X					
EuroQol Questionnaire	X	X	X	X	X	X
Visual Functioning Questionnaire - 25	X	X	X	X	X	X
Adverse event monitoring	X	X	X	X	X	X
Pregnancy testing†	X					

† Required for women of childbearing potential

4. Study treatment schedule and administration

4.1. Treatment overview

- The timing and administration of initial injections and earliest permissible second injections of assigned treatment are specified by the protocol. Treatment administration instructions and pre-injection IOP criteria are included in sections 4.2 and 4.3.
- Additional guidance is provided for treatment of non-responders and simultaneous enrollment of eligible patients in the MERIT Trial at certain time points.
- The protocol does not prescribe treatment options for every situation
- Treatment according to the best medical judgment of treating study ophthalmologist is permitted as deemed necessary. Repeat injections given before the protocol specified time points (section 3.3.) or other deviations from the treatment protocol should be reported expeditiously to CC on Unanticipated Event (UA) form, usually within a few days.

4.2. Treatment schedule

4.2.1. Initial injections of assigned treatment

- Patients will be randomized to receive an injection of one of three treatments; doses and routes of administration are those standardly used in clinical care:
  - Triamcinolone acetonide 40 mg given by the periocular route
  - Triamcinolone acetonide 4 mg given by intravitreal route
  - Intravitreal placement injection of the 0.7 mg dexamethasone implant
- Injection of assigned treatment should be given on the day of randomization or as soon after randomization as possible
- IOP requirements for injection of initial study treatment must be met on the day the treatment is administered:
  - ≤21 or mm Hg and treatment
  - ≤ 3 IOP-lowering agents (combination meds, e.g., Cosopt, count as 2 agents)

Note that the IOP requirements for the initial injection are the same as for eye eligibility for the trial. If study treatment is initiated on the same day as eligibility is confirmed and treatment assigned, no additional IOP measurements are needed. If circumstances require patient to return to clinic for injection at a later date, IOP must be checked and IOP-lowering agents evaluated prior to injection. If the eligibility requirements are not met, the injection should not be given. If the treating ophthalmologist elects to proceed with assigned treatment per best medical judgment, the deviation from the protocol must be reported to CC on an Unanticipated Event (UA) form; the UA form should be submitted as soon as possible usually within a few days.

4.2.2. Second injections of assigned treatment

Second injections of assigned treatment are permitted at or after specified time points if macular edema has not improved and re-treatment criteria are met. The time points and IOP limitations for second injections of periocular triamcinolone and intravitreal triamcinolone are consistent with typical clinical care approaches.

- Time points for second injection:
  - Periocular triamcinolone acetonide : 8 weeks *after OCT* (i.e., after ascertainment of primary outcome data)

  - Intravitreal triamcinolone acetonide: 8 weeks *after OCT*
  - Intravitreal dexamethasone: 12 weeks *after OCT*

- Reasons to give second injection:
  - Eye does not meet the improvement definition (a 20% decrease in central subfield thickness of the macula)
  - ME is worse after initial improvement
  - Eye has a normal central subfield thickness but has cystoid spaces in the 1 mm central subfield

- Re-treatment IOP requirements:
  - <25 mm Hg
  - ≤ 3 IOP-lowering agents (combination meds, e.g., Cosopt, count as 2 agents)

4.2.3. Treatment for non-responders (i.e., <20% reduction or worsening of ME)

Eyes that demonstrate less than a 20% reduction or worsening of ME as measured by the central subfield thickness on OCT at time points specified below will be considered primary treatment failures and will be handled in the following manner:

- Eyes in periocular triamcinolone arm at 12 weeks
  - Intravitreal triamcinolone acetonide 4mg if following conditions met:
    - IOP of <25 mm Hg and treatment with ≤3 IOP-lowering agents
  - Follow to close-out visit (week 24)

- Eyes in intravitreal triamcinolone acetonide arm at 12 weeks
  - Offer enrollment in the MERIT Trial if eligible OR treat according to best medical judgment
  - Follow to close-out visit (week 24)

- Eyes in the intravitreal dexamethasone arm at 20 weeks
  - Treat according to best medical judgment
  - Follow to the close-out visit (week 24)

4.3. Treatment administration guidelines

Note: Ophthalmologist administering treatment may follow local of standard care guidelines for topical anesthesia and needle size if they have been reviewed by Study Clinic Director as appropriate for use in this trial.

4.3.1. Administration of periocular triamcinolone acetonide

The injection may be given either by posterior sub-Tenon's approach or by the orbital floor approach, as both appear to have similar efficacy; the approach to the periocular injection will be recorded for analysis if needed.

4.3.1.1. Posterior sub-Tenon injection

- Saturate a cotton-tipped applicator with topical anesthetic (e.g., in 1 or 2% lidocaine) and place under the upper lid for posterior sub-Tenon's approach
- Instruct patient to look inferonasally with eye to receive injection
- Retract upper lid

- Introduce needle (e.g., 16-mm 25 gauge needle) into the sub-Tenon space, bevel side down
- Advance needle with a lateral to and fro motion to ensure the tip does not engage sclera
- When needle is judged to be behind the macula, deliver 40-mg (1-mL) bolus of triamcinolone acetonide[43]

4.3.1.2. Orbital floor injection

- Saturate a cotton-tipped applicator with topical anesthetic (e.g., 1 or 2% lidocaine) and place in inferior fornix where needle will be directed
- Introduce needle (e.g., 25-mm 25 gauge) at the lateral third of the inferior orbital rim
- Pass needle posteriorly parallel to the orbital floor periosteum to approximately 25 mm depth
- Slowly deliver 40-mg (1-mL volume) bolus of triamcinolone acetonide43

4.3.2. Standard preparation for all intravitreal injections

Intravitreal injection procedures should be carried out under controlled aseptic conditions which include the use of sterile gloves and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide such as betadine, applied to the periocular skin, eyelid and ocular surface are required prior to an intravitreal injection.

4.3.3. Administration of intravitreal triamcinolone acetonide (Triesence)

- Standard preparation as described for intravitreal injections in section 4.3.2.
- Saturate a sterile cotton-tipped applicator with 0.5% proparacaine hydrochloride drops and hold the swab against the planned intravitreal injection site for 10 seconds in preparation for the subconjunctival injection of 1% lidocaine hydrochloride ophthalmic solution for injection (without epinephrine). Alternatively, an injection may be given with just topical anesthesia.
- Use a sterile 4×4 pad in a single wipe to absorb excess liquid and to dry the periocular skin.
- Instruct subject to direct gaze away from syringe prior to intravitreal injection.
- An intravitreal injection using a 30-gauge needle is given 4 mm posterior to the limbus after marking that distance on the ocular surface. Inject medication slowly aiming inferiorly to minimize the dispersal of medication in the visual axis that could affect the patient's vision.
- Place a cotton swab on the site as the needle is injected to help prevent extrusion of medication
- Following the intravitreal injection, patients should be monitored for elevation in IOP
  - Monitoring may consist of a gross assessment of visual acuity
  - Check for perfusion of the optic nerve head immediately after the injection and/or tonometry within 30 minutes following the injection

4.3.4. Administration of dexamethasone implant (Ozurdex)

- Standard preparation as described for intravitreal injections in section 4.3.3 above
- Saturate a sterile cotton-tipped applicator with 0.5% proparacaine hydrochloride drops and hold the swab against the planned intravitreal injection site for 10 seconds in preparation for the subconjunctival injection of 1% lidocaine hydrochloride ophthalmic

solution for injection (without epinephrine). Alternatively, an injection may be given with just topical anesthesia.
- Open the foil pouch over a sterile field and gently drop the applicator on a sterile tray
- Carefully remove the cap from the applicator
- Hold the applicator in one hand and pull the safety tab straight off the applicator; do not twist or flex the tab
- Hold long axis of the applicator parallel to the limbus and engage the sclera at an oblique angle with the bevel of the needle up (away from the sclera) to create a shelved scleral path
- Advance tip of the needle within the sclera for about 1 mm (parallel to the limbus), then re-direct toward the center of the eye and advance until penetration of the sclera is completed and the vitreous cavity is entered; do not advance the needle past the point where the sleeve touches the conjunctiva.
- Slowly depress the actuator button until an audible click is noted. Before withdrawing the applicator from the eye, make sure that the actuator button is fully depressed and has locked flush with the applicator surface.
- Remove the needle in the same direction as used to enter the vitreous
- Following the intravitreal injection, patients should be monitored for elevation in IOP
  - Monitoring may consist of a gross assessment of visual acuity
  - Check for perfusion of the optic nerve head immediately after the injection and/or tonometry within 30 minutes following the injection.[82]

4.4. Possible side effects and complications of treatments

4.4.1. Periocular triamcinolone acetonide

Possible side effects and complications associated with periocular triamcinolone acetonide injections are similar to those associated with intravitreal injections of triamcinolone acetonide, but rates are lower because the drug is not injected directly into the eye.

- Commonly reported events
  - Elevated intraocular pressure
  - Cataract development
- Less frequently reported events
  - Ocular discomfort
  - Transient visual blurring
  - Subconjunctival hemorrhage
  - Ptosis with posterior sub-Tenon's injections (risk increases with multiple injections)
- Rare and serious events
  - Glaucoma or severe IOP elevation requiring surgical therapy
  - Breach of sclera
  - Endophthalmitis (occurs with inadvertent breach of sclera and injection of drug into the eye (less than 1 in 1000 cases)
  - Subretinal deposition of drug
  - Retinal tear with or without retinal detachment
  - Vitreous hemorrhage

4.4.2. Intravitreal triamcinolone acetonide

- Commonly reported events (≥ 20% of patients)
  - Elevated intraocular pressure in up to 40% of cases
  - Cataract development or progression of existing cataract
  - Subconjunctival hemorrhage
- Less frequently reported events
  - Mild short-term ocular discomfort
  - Short-term visual disturbances
  - Severe increase in eye pressure (~10% of patients), some of whom may require glaucoma surgery[83]
- Rare and serious events
  - Endophthalmitis (infectious and non-infectious)
  - Perforation of the globe where there is thinning of the outer covering of the eye
  - Vitreous hemorrhage
  - Retinal detachment
  - Retinal tear

4.4.3. Intravitreal dexamethasone

- Commonly reported events (≥ 20% of patients)
  - Elevated intraocular pressure which may require medication to lower
  - Subconjunctival hemorrhage
- Less frequently reported events
  - Mild short-term ocular discomfort
  - Short-term visual disturbances
  - Vitreous detachment
  - Headache
  - Cataract development
  - Elevated intraocular pressure which may require surgery to control
  - In eyes with non-intact posterior capsule implant migration to anterior chamber
- Rare and serious events
  - Endophthalmitis
  - Perforation of the globe where there is thinning of the outer covering of the eye
  - Vitreous hemorrhage
  - Retinal detachment
  - Retinal tear
  -

4.4.4. Intravitreal injection

Risks of an intravitreal injection that may be associated with the injection procedure itself have been included along with each type of drug injection above.

5. Adverse event reporting

5.1. Adverse events

Adverse events (AEs) and complications of study treatment will be recorded on study data forms and submitted to the CC. The CC Safety Officer and the DSMC Safety Officer will review all adverse events and make recommendations to the DSMC as to any actions that may be needed.

5.2. Serious adverse events

A serious adverse event (SAE) is an adverse event that results in one of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or congenital anomaly/birth defect. Also, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention (treatment) to prevent any of the outcomes previously listed in this definition.

Clinical centers will report all SAEs to the Coordinating Center expeditiously regardless of the relationship to study treatment. When an investigator or clinical center staff member becomes aware of an SAE, it will be reported to the Coordinating Center (CC) within 72 hours with follow up reporting until the event is terminated. The SAE report will include an assessment by the clinical investigator at the managing clinical center as to whether the event is related to treatment. Upon receipt at the CC, the SAE report will be sent to the CC Safety Officer for immediate review and determination as to whether the event meets the criteria for a safety report and whether expedited review by the DSMC Safety Officer is warranted.

All serious and unexpected events possibly related to study treatment will be reported as safety reports to the NEI project officer, the FDA, the pharmaceutical supplier (where appropriate), and all clinical centers in accordance with FDA regulations. The CC and clinical centers will submit all safety reports as expedited reports to their IRBs. Reports of SAEs not deemed to be unexpected will be submitted to the CC's IRB, to the IRB of the clinical center in which the event was reported, as well as to any other study center IRBs which require such reports.

6. Sample size and statistical methods

The primary outcome measurement for the POINT Trial is percent change from baseline in retinal thickness at 8 weeks. The primary analysis will be based on the assigned treatment and all randomized individuals will be included in the analysis (intention-to-treat) with additional sensitivity analyses based on treatment received. Individuals will be randomized to treatment groups, i.e., all eligible eyes from an individual will receive the same treatment.

6.1. Sample size, power and detectable differences

The units of analysis for the primary outcome for POINT are eyes as opposed to individuals. Since we expect approximately 25% of individuals to have bilateral disease, our sample size calculations take advantage of the information from both eyes by incorporating the effect of correlated, multiple measurements from the same individual. To arrive at the target sample sizes, we first calculated the number of independent eyes needed to power a specific aim (i.e. act as though each participant had only one study eye) and then used the following adjustment to calculate the required number of individuals:

$$NS = NIE * [(1 + r)/ (2*p + (1+r)(1-p))]$$

where NS denotes the required number of individuals, N_{IE} denotes the number of independent eyes, p denotes the percentage of individuals with bilateral disease (and so two study eyes), and r denotes the correlation between eyes[86]. Estimates for the correlation (r) between outcome measurements for an individual are based upon preliminary data from the MUST Trial and FS.

Power calculations for the primary hypotheses are based upon pair-wise comparisons of the three treatment arms: intravitreal injection of triamcinolone, dexamethasone pellet, and periocular injection of triamcinolone. A Bonferroni correction will be used to adjust for multiple comparisons, i.e. a two-sided type I error rate of 0.05/3 = 0.01667 will be used to determine statistical significance. The sample sizes needed to provide 90% power for the superiority hypotheses (intravitreal injection or dexamethasone pellet versus periocular injection) and 80% power for the non-inferiority hypothesis (intravitreal injection versus dexamethasone pellet) were computed separately for each comparison and then the maximum sample size was selected. The primary outcome is the change in retinal thickness at the central subfield at 8 weeks. Given the skewness in the distribution of retinal thickness, a log-transformation will be used to analyze the primary outcome[74, 87]; hence, the comparisons will be represented on a relative scale (i.e. percent of baseline) and transformed to obtain the percent change from baseline. A 20% change in retinal thickness is associated with clinically meaningful changes in visual acuity.[74] In the MUST Trial, approximately 25% of individuals had bilateral macular edema and the correlation between-eyes was 0.40 for log retinal thickness.[4, 6] The standard deviation for change in log retinal thickness was approximately 0.33 in the MUST Trial; a conservative estimate since the treatment of macular edema was not standardized and the timing of the assessment, at 6 months after randomization, was not linked to the implementation of treatment for macular edema. Based upon the 6-month OCT evaluation in the MUST Trial, we allowed for a 10% loss to follow-up.

For the first two superiority hypotheses, we evaluated the power to show that each of the treatment methods for intravitreal corticosteroids (triamcinolone injections and dexamethasone pellets) is superior to periocular triamcinolone injections at 8 weeks. In previous studies, treatment with the dexamethasone pellet has resulted in a decrease in retinal thickness of 30%-

50%, so a 40% decrease or log change in retinal thickness of log (0.60) = -0.5108 was selected. Intravitreal triamcinolone is expected to have a similar level of improvement; whereas periocular triamcinolone is expected to have a smaller but clinically meaningful change, i.e. a 25% reduction or log change of log(0.75) = -0.2877. Based upon a standard deviation of log-retinal thickness of 0.33, a sample size of 89 independent eyes per treatment group, i.e. 89 individuals with one eye for each individual, provides 98% power to detect a 40% reduction in retinal thickness for an intravitreal corticosteroid treatment as compared to a 25% reduction for periocular triamcinolone at 8 weeks with a two-sided type I error rate of 0.01667 (i.e. 0.05/3). This number increases to 99 individuals after inflating it for a 10% loss to follow-up. By including outcomes from both eyes for participants with bilateral macular edema (assuming a between eye correlation of 0.4 and 25% bilateral disease), we can reduce our sample size to 89 individuals enrolled in each arm (267 total). That is, 10 fewer participants per arm after accounting for losses to follow-up than are required if we only include a single eye per participant.

For the third hypothesis, we evaluated the power to show that the dexamethasone pellet is non-inferior to injected triamcinolone. Previous research has indicated that the threshold for reproducibility is 10% and that a 20% change is associated with changes in visual acuity.[74, 88] Therefore, we chose a non-inferiority margin of 10%, i.e. we would consider the dexamethasone pellet to be non-inferior if the percent reduction in retinal thickness was 30% or more (log [0.7]) as opposed to a 40% (log [0.60]) in the intravitreal injection group, i.e. the difference in the log retinal change was at most 0.15 (log[0.7] – log[0.6]). A sample size of 89 independent eyes per treatment group will provide 80% power to demonstrate non-inferiority with a one-sided type I error rate of 0.01667. We would reject the null hypothesis of inferiority if the upper bound of the 96.7% confidence interval of the difference in log retinal change from baseline at 8 weeks was less than 0.15 (log[0.7] – log[0.6]) or equivalently if the ratio of the percent of baseline for the two groups was less than 1.16 (0.7/0.6). Assuming a between-eye correlation of 0.4, 25% bilateral disease, and a 10% loss to follow-up, we will need to enroll 89 individuals in each treatment arm to attain 80% power, i.e. the inclusion of both eyes for bilateral disease off-sets the sample size inflation necessary to account for losses to follow-up.

An important secondary outcome for the comparison of intravitreal triamcinolone injection versus the dexamethasone pellet will be change in IOP. In prior studies, treatment with intravitreal triamcinolone resulted in IOP elevation for 40% of study eyes.[33, 51] In contrast, reports of IOP elevation with dexamethasone pellet have been more variable but consistently lower, ranging from 5% to 17%.[62, 68] A sample size of 89 independent eyes per treatment group, which is equivalent to 89 individuals per arm allowing for bilateral disease and losses to follow-up, will provide 99% power to detect an increase in the percent of eyes with an IOP elevation from 12% in the dexamethasone pellet arm to 40% in the intravitreal triamcinolone injection arm with a 2-sided, type I error rate of 0.05.

Clinical resolution is one of the standard outcomes in macular edema trials. Based upon the MUST Trial and other research, this improvement likely represents a measureable reduction in OCT measurement rather than complete resolution.[4, 6, 74, 89] A single PST triamcinolone injection resulted in clinical improvement for 50-55% of eyes between one and three months.[30, 46] Intravitreal triamcinolone and the dexamethasone pellet are expected to result in improvements of 35% and 25%, respectively. Based upon the assumptions outlined above, the sample size of 89 independent eyes per treatment group, which is equivalent to 89 individuals per arm allowing for bilateral disease and losses to follow-up, would allow us to detect an increase from 50% to 85% or 75% with 99.9% or 93% power, respectively, assuming a 2-sided type I error rate of 0.05 for this important secondary outcome.

6.2. Statistical methods

The primary analysis will adhere to the intention to treat principle regardless of treatment deviations made either in error or per the best medical judgment of the treating ophthalmologist. Evaluation of continuous outcomes over time (such as log change in retinal thickness or best corrected visual acuity) and binary outcomes over time (such as normal/abnormal IOP) will use a repeated measures analysis with Gaussian or logit links that account for the nested correlations between observations over time and between eyes of the same patient.[90] A saturated mean model, including visit and visit by treatment interaction terms, will be used. An unstructured covariance matrix will be used to model the within-eye repeated measurements augmented by random effects to induce cross-sectional between-eye associations. Alternatives, including a first-order, auto-regressive process (an AR(1) model) along with a random intercept, will be considered if the unstructured covariance model is unstable. This structure allows for correlation to decrease with increasing time-separation down to a level set by the random intercept.

Significance for superiority hypotheses in POINT will be determined by comparing the p-value of the interaction term for the week 8 visit with 0.01667 (i.e. 0.05/3). Significance for the non-inferiority hypothesis in POINT will be assessed by comparing the upper bound of the 96.7% confidence intervals for estimate of the difference in change in log retinal thickness at 8 weeks, which is estimated by the 8-week interaction term, with the defined non-inferiority boundary of 0.15 on the log scale, which is equivalent to a 10% difference in percent reduction (40% vs 30% reduction) for the two groups.

Evaluation of risk factors for time-to-event outcomes such as incidence of cataracts, as well as time to remission will be performed using Cox proportional hazards regression as well as parametric time-to-failure models, such as gamma models[91]. Implementation of these models that allows for clustering (within patients and within eyes), assessment of recurrent events, and incorporation of time-dependent covariates will be used. When the relevant follow-up time in the analysis reflects the clinical time scale (e.g. time since diagnosis of uveitis), it is necessary to incorporate the prevalent cases (longstanding diagnosis of uveitis) into the analysis. To accommodate the prevalent cases we will use the staggered entry technique[92], which is one method of adjusting for potential survival bias. The analysis compares the event rates among patients with similar duration of disease and then combines over these comparisons. Event rates for multiple recurring events, e.g. the number of adverse events, will be modeled using Poisson regression or Negative Binomial regression[93], including a random effects term to account for the between eye correlation.

All analyses will be performed both unadjusted, except for the stratification variable, and adjusted for potential confounders. Effect modification due to factors such as disease location or uveitis activity, fluorescein leakage in the centeral subfield, systemic disease, gender and race also will be explored when appropriate. Robust standard errors will be computed using statistical program-based approaches when available and a bootstrap with the individual as the sampling unit, when a pre-programmed approach is not available.

POINT has a focused set of primary research questions and related analyses. Bonferonni corrections will be applied to control the type I error rates for the primary hypotheses within each study. However, a large number of comparisons are planned for secondary outcomes and caution is needed in the reporting of interpretation of the results. Our primary focus for analyses of these outcomes will be on the parameter estimates and confidence intervals as opposed to p-values as recommended by Wang et al[94]. Several methods of adjusting P-values for multiple comparisons exist, however no clear consensus as to the most appropriate method is available and it is difficult if not impossible to quantify ahead of time the number of comparisons that will be performed. In general, issuing cautions is sufficient, but for identifiable and related sets of

estimates we will do adjustments. We expect that related sets of estimates will have a high positive correlation, making a Bonferroni correction extremely conservative. Therefore, we will estimate the covariance matrix for these related sets using a bootstrap approach and also estimate the null distribution of the minimum P-values for the multivariate distribution of Z-scores using a global null hypothesis permutation distribution.

The best protection against bias caused by missing data is to prevent it. We will work with coordinators and participants, as we have done in previous trials, to ensure that missing data are infrequent. Regardless, we will perform a variety of sensitivity analyses to determine the potential for bias due missing data. For a crude estimate of the range of potential impact, 'best' and 'worst' case single imputation techniques will be implement. In addition, more sophisticated approaches (e.g. multiple imputation and pattern mixture) will also be used to assess the impact of missing data[95, 96]. For the principal sensitivity analysis, we will retain all features of the primary analysis other than how missing values for visits beyond the last one with a measured value are handled. As is implicit in the primary analysis where missing data indicators are used (e.g. "." in SAS, "NA" in R), we will treat all missing values as Missing at Random (MAR). We will impute other missing values to generate 10 pseudo-complete records for each such individual by sampling from a joint predictive distribution for the missing data given the observed data. We will use a covariance matrix equal to the estimated covariance matrix from the primary analysis, but will "take control" of the prediction mean. Varying the mean of the predictive distribution allows us to assess the sensitivity of our results to a variety of missing data scenarios. The pattern mixture model approach stratifies participants on their pattern of missing data, estimates stratum-specific parameters and then combines estimates over strata using inverse variance weights. The approach is similar to stratified analysis to adjust for potential confounders and allows for comparison of stratum-specific estimates. We stratify by three patterns: complete data, at least one internal measurement missing, and closeout weight missing (along with any other missingness).

7. Regulatory and ethical issues

7.1. Recruitment and informed consent procedures

Eligible patients will be recruited from the patient populations seen at and referred to the MUST Research Group clinical centers, the majority of which are in the US and one each is in London, England, UK, Melbourne, Australia, and Montreal, Canada. Typically, patients will be identified in the course of usual clinical practice by the study physicians. When a potentially eligible patient is identified, the study physician and study coordinator will describe the study to and discuss the study with the patient. Patients considering enrollment will be given the consent statement and IRB-approved informational materials and allowed time to decide about joining the study. After patients have time to review materials and discuss enrollment with family members when appropriate, the clinic coordinator or study physician will obtain written informed consent, using a written, local IRB-approved consent document based on a prototype prepared by the CC and approved by the CC's IRB, the JHSPH IRB Office. The trial is registered on www.ClinicalTrials.gov (NCT02374060). Recruitment efforts and eligibility criteria for POINT are subject to review and approval by IRBs and the DSMC.

7.2. IRB/Protection of human subjects

7.2.1. Potential risks and procedures to minimize risks to participants

The injection procedures, dosage of medication and treatment algorithm within the study will be consistent with standard clinical treatment, e.g., sterile technique. To minimize risks associated with increased ocular pressure post-injection, patients with uncontrolled ocular hypertension or glaucomatous changes will be excluded from the trial. Patients in the trial will not be exposed to risk beyond what they would be exposed to with standard clinical care for their condition. Adverse events encountered will be managed by the best medical judgment of the treating physician.

7.2.2. Confidentiality

Confidentiality of patient data will be maintained in accordance with legal regulations. This includes the storage of protected health information (PHI) in locked cabinets or rooms and limited access to secure data areas by certified study personnel. Name, social security number, address, and other such personal data will be kept solely at the clinical center where the patient receives her/his clinical care. All transmission of data to the Coordinating Center for analysis is done by study ID codes alone. A dataset limited so as to contain a minimal amount of protected health information–that required to make the data useful for accomplishing the purposes of the POINT Trial–may be disclosed, as needed, to collaborating study sites, the NEI, and the FDA. Rarely, for reasons of good clinical practice or legal reasons, data with personal information may need to be reviewed by regulatory bodies such as the IRB, FDA, or DSMB. If such an audit occurs, care will be taken to protect confidentiality of participants. Clinically relevant information from the study may be placed in the patient's medical record. The CC will report serious adverse event data for participants randomized to Ozurdex to Allergan (Irvine CA). Release of protected health information to any other persons or organizations will require additional written consent of the patient affected, except as required by law.

A privacy acknowledgment designed to conform to the specifications of HIPAA regulations and approved by the local governing authorities invested with oversight of HIPAA regulations at each participating site, will be signed by the participant before his/her enrollment in the study. This acknowledgement will be included in the consent form or as a stand-alone document per local institutional requirements.

7.2.3. Inclusion of children

Patients under 18 years of age will not be included; the intravitreal dexamethasone pellet is not approved for use in pediatric patients.

7.2.4. Data and safety monitoring

Treatment effects and safety monitoring will be conducted by a study Data and Safety Monitoring Committee (DSMC). The DSMC will consist mostly of members of the standing DSMC, which monitored the Multicenter Uveitis Steroid Treatment (MUST) Trial and now is monitoring the MUST Follow-up Study. However, the Chair of the MUST DSMC, who is a biostatistician, is unable to serve because of potential conflicts of interest. Hence a new biostatistician has been appointed and the Chair of the DSMC for this protocol will be one of the clinical experts. The committee consists of voting members with expertise in biostatistics, clinical trial design, ophthalmology, and medical ethics who were appointed by NEI and non-voting members (i.e., Study Officers). Initially, the DSMC will meet at least twice a year, once in-person and once by conference call. For each DSMC meeting, data will be summarized in a report prepared by the CC. These reports will include information related to monitoring the safety and effectiveness of the study treatments and will include tables and graphs that summarize baseline, outcome, and adverse event data by treatment assignment, and if indicated, within specific subgroups. Analyses will be included as requested by the DSMC. Pertinent information from outside sources such as a reprint of a recent publication reporting on results of other, related studies will also be included as available. The DSMC report will also include an overall study performance report, designed for monitoring the effectiveness of the participating centers.

The DSMC Safety Officer will be appointed from among the physician voting members of the DSMC, who periodically will review summaries of serious adverse event data prepared by the CC between DSMC meetings to make a determination as to whether the event is unexpected and possibly related to treatment.

8. References

Bibliography

1. Okhravi N, Lightman S. Cystoid macular edema in uveitis. Ocul Immunol Inflamm. 2003;11(1):29-38. Epub 2003/07/11. PubMed PMID: 12854025.
2. Lardenoye CW, van Kooij B, Rothova A. Impact of macular edema on visual acuity in uveitis. Ophthalmology. 2006;113(8):1446-9. Epub 2006/08/01. doi: 10.1016/j.ophtha.2006.03.027. PubMed PMID: 16877081.
3. Rothova A, Suttorp-van Schulten MS, Frits Treffers W, Kijlstra A. Causes and frequency of blindness in patients with intraocular inflammatory disease. Br J Ophthalmol. 1996;80(4):332-6. Epub 1996/04/01. PubMed PMID: 8703885; PubMed Central PMCID: PMC505460.
4. Kempen JH, Altaweel MM, Holbrook JT, Jabs DA, Sugar EA. The multicenter uveitis steroid treatment trial: rationale, design, and baseline characteristics. Am J Ophthalmol. 2010;149(4):550-61.e10. Epub 2010/01/26. doi: 10.1016/j.ajo.2009.11.019. PubMed PMID: 20097325; PubMed Central PMCID: PMCPmc2975449.
5. Kempen JH, Sugar EA, Jaffe GJ, Acharya NR, Dunn JP, Elner SG, et al. Fluorescein Angiography versus Optical Coherence Tomography for Diagnosis of Uveitic Macular Edema. Ophthalmology. 2013. Epub 2013/05/28. doi: 10.1016/j.ophtha.2013.01.069. PubMed PMID: 23706700; PubMed Central PMCID: PMCPmc3758459.
6. Kempen JH, Altaweel MM, Holbrook JT, Jabs DA, Louis TA, Sugar EA, et al. Randomized comparison of systemic anti-inflammatory therapy versus fluocinolone acetonide implant for intermediate, posterior, and panuveitis: the multicenter uveitis steroid treatment trial. Ophthalmology. 2011;118(10):1916-26. Epub 2011/08/16. doi: 10.1016/j.ophtha.2011.07.027. PubMed PMID: 21840602; PubMed Central PMCID: PMCPmc3191365.
7. Dong Z, Namba K, Kitaichi N, Goda C, Kitamura M, Ohno S. Efficacy and complications of intravitreal injection of triamcinolone acetonide for refractory cystoid macular edema associated with intraocular inflammation. Jpn J Ophthalmol. 2008;52(5):374-9. Epub 2008/11/11. doi: 10.1007/s10384-008-0574-2. PubMed PMID: 18991038.
8. Estafanous MF, Lowder CY, Kaiser PK. Patterns of macular edema in uveitis patients. Ophthalmology. 2005;112(2):360; author reply -1. Epub 2005/02/05. doi: 10.1016/j.ophtha.2004.11.011. PubMed PMID: 15691581.
9. Markomichelakis NN, Halkiadakis I, Pantelia E, Peponis V, Patelis A, Theodossiadis P, et al. Patterns of macular edema in patients with uveitis: qualitative and quantitative assessment using optical coherence tomography. Ophthalmology. 2004;111(5):946-53. Epub 2004/05/04. doi: 10.1016/j.ophtha.2003.08.037. PubMed PMID: 15121373.
10. Martidis A, Duker JS, Puliafito CA. Intravitreal triamcinolone for refractory cystoid macular edema secondary to birdshot retinochoroidopathy. Archives of ophthalmology. 2001;119(9):1380-3. Epub 2001/09/27. PubMed PMID: 11545651.
11. Ossewaarde-van Norel A, Rothova A. Clinical review: Update on treatment of inflammatory macular edema. Ocul Immunol Inflamm. 2011;19(1):75-83. Epub 2010/11/03. doi: 10.3109/09273948.2010.509530. PubMed PMID: 21034302.
12. Thorne JE, Daniel E, Jabs DA, Kedhar SR, Peters GB, Dunn JP. Smoking as a risk factor for cystoid macular edema complicating intermediate uveitis. Am J Ophthalmol. 2008;145(5):841-6. Epub 2008/03/07. doi: 10.1016/j.ajo.2007.12.032 S0002-9394(08)00011-1 [pii]. PubMed PMID: 18321467; PubMed Central PMCID: PMC2574684.

13. Lin P, Loh AR, Margolis TP, Acharya NR. Cigarette smoking as a risk factor for uveitis. Ophthalmology. 2010;117(3):585-90. Epub 2009/12/29. doi: 10.1016/j.ophtha.2009.08.011 S0161-6420(09)00900-2 [pii]. PubMed PMID: 20036011; PubMed Central PMCID: PMC2830339.
14. Hazirolan D, Pleyer U. Think global--act local: intravitreal drug delivery systems in chronic noninfectious uveitis. Ophthalmic Res. 2013;49(2):59-65. Epub 2012/12/22. doi: 10.1159/000345477 000345477 [pii]. PubMed PMID: 23258374.
15. Modorati G, Miserocchi E. Intravitreal injection therapy in the treatment of noninfectious uveitis. Dev Ophthalmol. 2012;51:110-21. Epub 2012/04/21. doi: 10.1159/000336471 000336471 [pii]. PubMed PMID: 22517209.
16. Sallam A, Taylor SR, Lightman S. Review and update of intraocular therapy in noninfectious uveitis. Curr Opin Ophthalmol. 2011;22(6):517-22. Epub 2011/09/08. doi: 10.1097/ICU.0b013e32834bbd68. PubMed PMID: 21897242.
17. Lobo AM, Sobrin L, Papaliodis GN. Drug delivery options for the treatment of ocular inflammation. Semin Ophthalmol. 2010;25(5-6):283-8. Epub 2010/11/26. doi: 10.3109/08820538.2010.518522. PubMed PMID: 21091013.
18. Sallam A, Comer RM, Chang JH, Grigg JR, Andrews R, McCluskey PJ, et al. Short-term safety and efficacy of intravitreal triamcinolone acetonide for uveitic macular edema in children. Arch Ophthalmol. 2008;126(2):200-5. Epub 2008/02/13. doi: 10.1001/archophthalmol.2007.59 126/2/200 [pii]. PubMed PMID: 18268210.
19. Beer PM, Bakri SJ, Singh RJ, Liu W, Peters GB, 3rd, Miller M. Intraocular concentration and pharmacokinetics of triamcinolone acetonide after a single intravitreal injection. Ophthalmology. 2003;110(4):681-6. Epub 2003/04/12. doi: S0161-6420(02)01969-3 [pii] 10.1016/S0161-6420(02)01969-3. PubMed PMID: 12689886.
20. Tranos P, Scott R, Zambarakji H, Zambarajki H, Ayliffe W, Pavesio C, et al. The effect of pars plana vitrectomy on cystoid macular oedema associated with chronic uveitis: a randomised, controlled pilot study. The British journal of ophthalmology. 2006;90(16723360):1107-10.
21. Becker MD, Harsch N, Zierhut M, Davis JL, Holz FG. [Therapeutic vitrectomy in uveitis: current status and recommendations]. Der Ophthalmologe : Zeitschrift der Deutschen Ophthalmologischen Gesellschaft. 2003;100(10):787-95. Epub 2003/11/18. doi: 10.1007/s00347-003-0918-8. PubMed PMID: 14618350.
22. Stahn C, Buttgereit F. Genomic and nongenomic effects of glucocorticoids. Nat Clin Pract Rheumatol. 2008;4(10):525-33. Epub 2008/09/03. doi: 10.1038/ncprheum0898 ncprheum0898 [pii]. PubMed PMID: 18762788.
23. Edelman JL, Lutz D, Castro MR. Corticosteroids inhibit VEGF-induced vascular leakage in a rabbit model of blood-retinal and blood-aqueous barrier breakdown. Exp Eye Res. 2005;80(2):249-58. Epub 2005/01/27. doi: S0014-4835(04)00268-4 [pii] 10.1016/j.exer.2004.09.013. PubMed PMID: 15670803.
24. Vinores SA, Chan CC, Vinores MA, Matteson DM, Chen YS, Klein DA, et al. Increased vascular endothelial growth factor (VEGF) and transforming growth factor beta (TGFbeta) in experimental autoimmune uveoretinitis: upregulation of VEGF without neovascularization. J Neuroimmunol. 1998;89(1-2):43-50. Epub 1998/09/03. PubMed PMID: 9726824.
25. Fine HF, Baffi J, Reed GF, Csaky KG, Nussenblatt RB. Aqueous humor and plasma vascular endothelial growth factor in uveitis-associated cystoid macular edema. Am J Ophthalmol. 2001;132(5):794-6. Epub 2001/11/13. PubMed PMID: 11704050.
26. Weiss K, Steinbrugger I, Weger M, Ardjomand N, Maier R, Wegscheider BJ, et al. Intravitreal VEGF levels in uveitis patients and treatment of uveitic macular oedema with intravitreal bevacizumab. Eye (Lond). 2009;23(9):1812-8. Epub 2009/01/27. doi: 10.1038/eye.2008.388. PubMed PMID: 19169227.

27. van Kooij B, Rothova A, Rijkers GT, de Groot-Mijnes JDF. Distinct cytokine and chemokine profiles in the aqueous of patients with uveitis and cystoid macular edema. American journal of ophthalmology. 2006;142(16815285):192-4.
28. Cohen T, Nahari D, Cerem LW, Neufeld G, Levi BZ. Interleukin 6 induces the expression of vascular endothelial growth factor. J Biol Chem. 1996;271(2):736-41. Epub 1996/01/12. PubMed PMID: 8557680.
29. Jennings T, Rusin MM, Tessler HH, Cunha-Vaz JG. Posterior sub-Tenon's injections of corticosteroids in uveitis patients with cystoid macular edema. Jpn J Ophthalmol. 1988;32(4):385-91. Epub 1988/01/01. PubMed PMID: 3236561.
30. Helm CJ, Holland GN. The effects of posterior subtenon injection of triamcinolone acetonide in patients with intermediate uveitis. Am J Ophthalmol. 1995;120(1):55-64. Epub 1995/07/01. PubMed PMID: 7611330.
31. Antcliff RJ, Spalton DJ, Stanford MR, Graham EM, ffytche TJ, Marshall J. Intravitreal triamcinolone for uveitic cystoid macular edema: an optical coherence tomography study. Ophthalmology. 2001;108(4):765-72. Epub 2001/04/12. PubMed PMID: 11297495.
32. Karacorlu M, Mudun B, Ozdemir H, Karacorlu SA, Burumcek E. Intravitreal triamcinolone acetonide for the treatment of cystoid macular edema secondary to Behcet disease. Am J Ophthalmol. 2004;138(2):289-91. Epub 2004/08/04. doi: 10.1016/j.ajo.2004.02.053. PubMed PMID: 15289142.
33. Kok H, Lau C, Maycock N, McCluskey P, Lightman S. Outcome of intravitreal triamcinolone in uveitis. Ophthalmology. 2005;112(11):1916 e1-7. Epub 2005/09/21. doi: 10.1016/j.ophtha.2005.06.009. PubMed PMID: 16171868.
34. Young S, Larkin G, Branley M, Lightman S. Safety and efficacy of intravitreal triamcinolone for cystoid macular oedema in uveitis. Clin Experiment Ophthalmol. 2001;29(1):2-6. Epub 2001/03/29. PubMed PMID: 11272779.
35. Sorensen TL, Haamann P, Villumsen J, Larsen M. Intravitreal triamcinolone for macular oedema: efficacy in relation to aetiology. Acta Ophthalmol Scand. 2005;83(1):67-70. Epub 2005/02/18. doi: 10.1111/j.1600-0420.2004.00336.x. PubMed PMID: 15715560.
36. Sallam A, Comer RM, Chang JH, Grigg JR, Andrews R, McCluskey PJ, et al. Short-term safety and efficacy of intravitreal triamcinolone acetonide for uveitic macular edema in children. Archives of ophthalmology. 2008;126(2):200-5. Epub 2008/02/13. doi: 10.1001/archophthalmol.2007.59. PubMed PMID: 18268210.
37. Hogewind BFT, Zijlstra C, Klevering BJ, Hoyng CB. Intravitreal triamcinolone for the treatment of refractory macular edema in idiopathic intermediate or posterior uveitis. European journal of ophthalmology. 2008;18(18465727):429-34.
38. Androudi S, Letko E, Meniconi M, Papadaki T, Ahmed M, Foster CS. Safety and efficacy of intravitreal triamcinolone acetonide for uveitic macular edema. Ocul Immunol Inflamm. 2005;13(2-3):205-12. Epub 2005/07/16. doi: 10.1080/09273940590933511. PubMed PMID: 16019680.
39. Oueghlani E, Pavesio CE. Intravitreal triamcinolone injection for unresponsive cystoid macular oedema in probable Behcet's disease as an additional therapy. Klin Monbl Augenheilkd. 2008;225(5):497-9. Epub 2008/05/06. doi: 10.1055/s-2008-1027351. PubMed PMID: 18454410.
40. Choudhry S, Ghosh S. Intravitreal and posterior subtenon triamcinolone acetonide in idiopathic bilateral uveitic macular oedema. Clin Experiment Ophthalmol. 2007;35(8):713-8. Epub 2007/11/14. doi: 10.1111/j.1442-9071.2007.01578.x. PubMed PMID: 17997773.
41. Roesel M, Gutfleisch M, Heinz C, Heimes B, Zurek-Imhoff B, Heiligenhaus A. Intravitreal and orbital floor triamcinolone acetonide injections in noninfectious uveitis: a comparative study.

Ophthalmic research. 2009;42(2):81-6. Epub 2009/05/30. doi: 10.1159/000220600. PubMed PMID: 19478546.

42. Thach AB, Dugel PU, Flindall RJ, Sipperley JO, Sneed SR. A comparison of retrobulbar versus sub-Tenon's corticosteroid therapy for cystoid macular edema refractory to topical medications. Ophthalmology. 1997;104(12):2003-8. Epub 1997/12/24. PubMed PMID: 9400758.
43. Ferrante P, Ramsey A, Bunce C, Lightman S. Clinical trial to compare efficacy and side-effects of injection of posterior sub-Tenon triamcinolone versus orbital floor methylprednisolone in the management of posterior uveitis. Clin Experiment Ophthalmol. 2004;32(6):563-8. Epub 2004/12/04. doi: 10.1111/j.1442-9071.2004.00902.x. PubMed PMID: 15575824.
44. Venkatesh P, Kumar CS, Abbas Z, Garg S. Comparison of the efficacy and safety of different methods of posterior subtenon injection. Ocul Immunol Inflamm. 2008;16(5):217-23. Epub 2008/12/10. doi: 10.1080/09273940802209153 906501573 [pii]. PubMed PMID: 19065416.
45. Byun YS, Park YH. Complications and safety profile of posterior subtenon injection of triamcinolone acetonide. J Ocul Pharmacol Ther. 2009;25(2):159-62. Epub 2009/03/17. doi: 10.1089/jop.2008.0087. PubMed PMID: 19284323; PubMed Central PMCID: PMC19284323.
46. Leder HA, Jabs DA, Galor A, Dunn JP, Thorne JE. Periocular triamcinolone acetonide injections for cystoid macular edema complicating noninfectious uveitis. Am J Ophthalmol. 2011;152(21652023):441-8.
47. Hirano Y, Ito T, Nozaki M, Yasukawa T, Sakurai E, Yoshida M, et al. Intraocular pressure elevation following triamcinolone acetonide administration as related to administration routes. Jpn J Ophthalmol. 2009;53(5):519-22. Epub 2009/10/23. doi: 10.1007/s10384-009-0692-5. PubMed PMID: 19847609.
48. Jonas JB, Degenring RF, Kreissig I, Akkoyun I, Kamppeter BA. Intraocular pressure elevation after intravitreal triamcinolone acetonide injection. Ophthalmology. 2005;112(4):593-8. Epub 2005/04/06. doi: S0161-6420(04)01787-7 [pii] 10.1016/j.ophtha.2004.10.042. PubMed PMID: 15808249.
49. Smithen LM, Ober MD, Maranan L, Spaide RF. Intravitreal triamcinolone acetonide and intraocular pressure. Am J Ophthalmol. 2004;138(5):740-3. Epub 2004/11/09. doi: S0002-9394(04)00817-7 [pii] 10.1016/j.ajo.2004.06.067. PubMed PMID: 15531307.
50. Gillies MC, Simpson JM, Billson FA, Luo W, Penfold P, Chua W, et al. Safety of an intravitreal injection of triamcinolone: results from a randomized clinical trial. Arch Ophthalmol. 2004;122(3):336-40. Epub 2004/03/10. doi: 10.1001/archopht.122.3.336 122/3/336 [pii]. PubMed PMID: 15006845.
51. van Kooij B, Rothova A, de Vries P. The pros and cons of intravitreal triamcinolone injections for uveitis and inflammatory cystoid macular edema. Ocul Immunol Inflamm. 2006;14(2):73-85. Epub 2006/04/07. doi: 10.1080/09273940500545684. PubMed PMID: 16597536.
52. Maca SM, Abela-Formanek C, Kiss CG, Sacu SG, Benesch T, Barisani-Asenbauer T. Intravitreal triamcinolone for persistent cystoid macular oedema in eyes with quiescent uveitis. Clin Experiment Ophthalmol. 2009;37(4):389-96. Epub 2009/07/15. doi: 10.1111/j.1442-9071.2009.02033.x CEO2033 [pii]. PubMed PMID: 19594566.
53. Gillies MC, Islam FM, Zhu M, Larsson J, Wong TY. Efficacy and safety of multiple intravitreal triamcinolone injections for refractory diabetic macular oedema. Br J Ophthalmol. 2007;91(10):1323-6. Epub 2007/04/05. doi: bjo.2006.113167 [pii] 10.1136/bjo.2006.113167. PubMed PMID: 17405800; PubMed Central PMCID: PMC2000996.
54. Roth DB, Verma V, Realini T, Prenner JL, Feuer WJ, Fechtner RD. Long-term incidence and timing of intraocular hypertension after intravitreal triamcinolone acetonide injection. Ophthalmology. 2009;116(3):455-60. Epub 2009/01/23. doi: 10.1016/j.ophtha.2008.10.002 S0161-6420(08)01022-1 [pii]. PubMed PMID: 19157561.

55. Das-Bhaumik RG, Jones NP. Low-dose intraocular triamcinolone injection for intractable macular oedema and inflammation in patients with uveitis. Eye (Lond). 2006;20(8):934-7. Epub 2005/08/13. doi: 6702063 [pii] 10.1038/sj.eye.6702063. PubMed PMID: 16096656.
56. Jonas JB, Schlichtenbrede F. Visual acuity and intraocular pressure after high-dose intravitreal triamcinolone acetonide in selected ocular diseases. Eye (Lond). 2008;22(7):869-73. Epub 2007/02/17. doi: 10.1038/sj.eye.6702734. PubMed PMID: 17304257.
57. Angunawela RI, Heatley CJ, Williamson TH, Spalton DJ, Graham EM, Antcliffe RJ, et al. Intravitreal triamcinalone acetonide for refractory uveitic cystoid macular oedema: longterm management and outcome. Acta Ophthalmol Scand. 2005;83(5):595-9. Epub 2005/09/29. doi: AOS438 [pii] 10.1111/j.1600-0420.2005.00438.x. PubMed PMID: 16187999.
58. Sallam A, Taylor SR, Habot-Wilner Z, Elgohary M, Do HH, McCluskey P, et al. Repeat intravitreal triamcinolone acetonide injections in uveitic macular oedema. Acta Ophthalmol. 2012;90(4):e323-5. Epub 2011/09/15. doi: 10.1111/j.1755-3768.2011.02247.x. PubMed PMID: 21914149.
59. Menezo V, Lau C, Comer M, Lightman S. Clinical outcome of chronic immunosuppression in patients with non-infectious uveitis. Clin Experiment Ophthalmol. 2005;33(1):16-21. Epub 2005/01/27. doi: CEO904 [pii] 10.1111/j.1442-9071.2005.00904.x. PubMed PMID: 15670073.
60. Habot-Wilner Z, Sallam A, Pacheco PA, Do HH, McCluskey P, Lightman S. Intravitreal triamcinolone acetonide as adjunctive treatment with systemic therapy for uveitic macular edema. Eur J Ophthalmol. 2011;21 Suppl 6:S56-61. Epub 2011/01/01. doi: 10.5301/EJO.2010.6062 FAF60F5D-AF35-40A4-8BCB-3A28F23F419A [pii]. PubMed PMID: 23264330.
61. da Silva GR, da Silva Cunha A, Jr., Ayres E, Orefice RL. Effect of the macromolecular architecture of biodegradable polyurethanes on the controlled delivery of ocular drugs. J Mater Sci Mater Med. 2009;20(2):481-7. Epub 2008/10/15. doi: 10.1007/s10856-008-3607-y. PubMed PMID: 18853235.
62. Kuppermann BD, Blumenkranz MS, Haller JA, Williams GA, Weinberg DV, Chou C, et al. Randomized controlled study of an intravitreous dexamethasone drug delivery system in patients with persistent macular edema. Arch Ophthalmol. 2007;125(3):309-17. Epub 2007/03/14. doi: 125/3/309 [pii] 10.1001/archopht.125.3.309. PubMed PMID: 17353400.
63. Williams GA, Haller JA, Kuppermann BD, Blumenkranz MS, Weinberg DV, Chou C, et al. Dexamethasone posterior-segment drug delivery system in the treatment of macular edema resulting from uveitis or Irvine-Gass syndrome. Am J Ophthalmol. 2009;147(6):1048-54, 54 e1-2. Epub 2009/03/10. doi: 10.1016/j.ajo.2008.12.033 S0002-9394(09)00002-6 [pii]. PubMed PMID: 19268890.
64. Herrero-Vanrell R, Cardillo JA, Kuppermann BD. Clinical applications of the sustained-release dexamethasone implant for treatment of macular edema. Clin Ophthalmol. 2011;5:139-46. Epub 2011/03/09. doi: 10.2147/OPTH.S15783. PubMed PMID: 21383939; PubMed Central PMCID: PMC3045060.
65. Hunter RS, Lobo AM. Dexamethasone intravitreal implant for the treatment of noninfectious uveitis. Clin Ophthalmol. 2011;5:1613-21. Epub 2011/12/06. doi: 10.2147/OPTH.S17419 opth-5-1613 [pii]. PubMed PMID: 22140307; PubMed Central PMCID: PMC3225458.
66. London NJ, Chiang A, Haller JA. The dexamethasone drug delivery system: indications and evidence. Adv Ther. 2011;28(5):351-66. Epub 2011/04/16. doi: 10.1007/s12325-011-0019-z. PubMed PMID: 21494891.
67. Saraiya NV, Goldstein DA. Dexamethasone for ocular inflammation. Expert Opin Pharmacother. 2011;12(7):1127-31. Epub 2011/04/05. doi: 10.1517/14656566.2011.571209. PubMed PMID: 21457057.

68. Lowder C, Belfort R, Jr., Lightman S, Foster CS, Robinson MR, Schiffman RM, et al. Dexamethasone intravitreal implant for noninfectious intermediate or posterior uveitis. Arch Ophthalmol. 2011;129(5):545-53. Epub 2011/01/12. doi: 10.1001/archophthalmol.2010.339 archophthalmol.2010.339 [pii]. PubMed PMID: 21220619.
69. Myung JS, Aaker GD, Kiss S. Treatment of noninfectious posterior uveitis with dexamethasone intravitreal implant. Clin Ophthalmol. 2010;4:1423-6. Epub 2010/12/29. doi: 10.2147/OPTH.S15696. PubMed PMID: 21188153; PubMed Central PMCID: PMC3000767.
70. Miserocchi E, Modorati G, Pastore MR, Bandello F. Dexamethasone intravitreal implant: an effective adjunctive treatment for recalcitrant noninfectious uveitis. Ophthalmologica. 2012;228(4):229-33. Epub 2012/10/06. doi: 10.1159/000343060 000343060 [pii]. PubMed PMID: 23038070.
71. Querques L, Querques G, Lattanzio R, Gigante SR, Del Turco C, Corradetti G, et al. Repeated intravitreal dexamethasone implant (Ozurdex(R)) for retinal vein occlusion. Ophthalmologica. 2013;229(1):21-5. Epub 2012/09/26. doi: 10.1159/000342160 000342160 [pii]. PubMed PMID: 23006995.
72. Audren F, Tod M, Massin P, Benosman R, Haouchine B, Erginay A, et al. Pharmacokinetic-pharmacodynamic modeling of the effect of triamcinolone acetonide on central macular thickness in patients with diabetic macular edema. Invest Ophthalmol Vis Sci. 2004;45(10):3435-41. Epub 2004/09/29. doi: 10.1167/iovs.03-1110 45/10/3435 [pii]. PubMed PMID: 15452046.
73. Nussenblatt RB, Kaufman SC, Palestine AG, Davis MD, Ferris FL, 3rd. Macular thickening and visual acuity. Measurement in patients with cystoid macular edema. Ophthalmology. 1987;94(9):1134-9. Epub 1987/09/01. PubMed PMID: 3684231.
74. Sugar EA, Jabs DA, Altaweel MM, Lightman S, Acharya N, Vitale AT, et al. Identifying a clinically meaningful threshold for change in uveitic macular edema evaluated by optical coherence tomography. Am J Ophthalmol. 2011;152(6):1044-52.e5. Epub 2011/08/25. doi: 10.1016/j.ajo.2011.05.028. PubMed PMID: 21861971; PubMed Central PMCID: PMCPmc3223264.
75. Ferris FL, 3rd, Kassoff A, Bresnick GH, Bailey I. New visual acuity charts for clinical research. Am J Ophthalmol. 1982;94(1):91-6. Epub 1982/07/01. PubMed PMID: 7091289.
76. Kimura SJ, Thygeson P, Hogan MJ. Signs and symptoms of uveitis. II. Classification of the posterior manifestations of uveitis. Am J Ophthalmol. 1959;47(5 Pt 2):171-6. Epub 1959/05/01. PubMed PMID: 13649856.
77. Nussenblatt R, Whitcup, SM, Palestine, AG. Uveitis: Fundamentals and Clinical Practice. 2 ed. St. Louis: Mosby; 1996.
78. Nussenblatt RB, Palestine AG, Chan CC, Roberge F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. Ophthalmology. 1985;92(4):467-71. Epub 1985/04/01. PubMed PMID: 4000641.
79. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005;140(3):509-16. Epub 2005/10/01. PubMed PMID: 16196117.
80. The age-related eye disease study (AREDS) system for classifying cataracts from photographs: AREDS report no. 4. Am J Ophthalmol. 2001;131(2):167-75. Epub 2001/03/03. PubMed PMID: 11228291; PubMed Central PMCID: PMCPmc2032014.
81. Lehpamer B, Moshier E, Pahk P, Goldberg N, Ackert J, Godbold J, et al. Epiretinal membranes in uveitic macular edema: effect on vision and response to therapy. Am J Ophthalmol. 2014;157(5):1048-55. Epub 2014/02/04. doi: 10.1016/j.ajo.2014.01.020. PubMed PMID: 24487049; PubMed Central PMCID: PMCPmc4060278.
82. Ozurdex (package insert). Allergan, Inc. Irvine, CA 92612: 2013.

83. Triesence (package insert). Alcon. Fort Worth, TX 76134: 2008.
84. LUCENTIS (ranibizumab injection) (Package Insert). Genentech Inc. South San Francisco, CA 94080: February 2013.
85. Day S, Acquah K, Mruthyunjaya P, Grossman DS, Lee PP, Sloan FA. Ocular complications after anti-vascular endothelial growth factor therapy in Medicare patients with age-related macular degeneration. Am J Ophthalmol. 2011;152(2):266-72. Epub 2011/06/15. doi: 10.1016/j.ajo.2011.01.053. PubMed PMID: 21664593; PubMed Central PMCID: PMCPMC3143287.
86. Manatunga AK, Chen S. Sample size estimation for survival outcomes in cluster-randomized studies with small cluster sizes. Biometrics. 2000;56(2):616-21. Epub 2000/07/06. PubMed PMID: 10877325.
87. Ferris FL, 3rd, Miller KM, Glassman AR, Beck RW. A proposed method of logarithmic transformation of optical coherence tomography data for use in clinical research. Ophthalmology. 2010;117(8):1512-6. Epub 2010/04/07. doi: 10.1016/j.ophtha.2009.12.014. PubMed PMID: 20363505; PubMed Central PMCID: PMCPmc2916055.
88. Krzystolik MG, Strauber SF, Aiello LP, Beck RW, Berger BB, Bressler NM, et al. Reproducibility of macular thickness and volume using Zeiss optical coherence tomography in patients with diabetic macular edema. Ophthalmology. 2007;114(8):1520-5. Epub 2007/03/14. doi: 10.1016/j.ophtha.2006.10.055. PubMed PMID: 17353052; PubMed Central PMCID: PMCPmc2253719.
89. Lehpamer B, Moshier E, Goldberg N, Ackert J, Godbold J, Jabs DA. Subretinal fluid in uveitic macular edema: effect on vision and response to therapy. Am J Ophthalmol. 2013;155(1):143-9. Epub 2012/10/02. doi: 10.1016/j.ajo.2012.06.028. PubMed PMID: 23022159.
90. Diggle P HP, Liang K-Y, Zeger S. *Analysis of Longitudinal Data*. New York: Oxford University Press Inc.; 2002.
91. Gutierrez R. Parametric frailty and shared frailty survival models. The Stata Journal. 2002;2(1):22-44.
92. Tarwater PM, Mellors J, Gore ME, Margolick JB, Phair J, Detels R, et al. Methods to assess population effectiveness of therapies in human immunodeficiency virus incident and prevalent cohorts. Am J Epidemiol. 2001;154(7):675-81. Epub 2001/10/03. PubMed PMID: 11581102.
93. Keene ON, Jones MR, Lane PW, Anderson J. Analysis of exacerbation rates in asthma and chronic obstructive pulmonary disease: example from the TRISTAN study. Pharm Stat. 2007;6(2):89-97. Epub 2007/01/19. doi: 10.1002/pst.250. PubMed PMID: 17230434.
94. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine--reporting of subgroup analyses in clinical trials. N Engl J Med. 2007;357(21):2189-94. Epub 2007/11/23. doi: 10.1056/NEJMsr077003. PubMed PMID: 18032770.
95. Daniels MJ HJ. *Missing Data in Longitudinal Studies: Strategies for Bayesian Modeling and Sensitivity Analysis*. Boca Raton: Chapman & Hall/CRC; 2008.
96. Little RJA RD. *Statistical Analysis with Missing Data*. 2nd ed. New York: John Wiley & Sons; 2002.