Tofacitinib for the Treatment of Non-Infectious Inflammatory Eye Disease

NCT03580343

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A Introduction

A1 Study Abstract

Non-infectious inflammatory eye disease, such as uveitis, is a chronic, auto-immune process that can occur in isolation or in the context of a systemic auto-immune condition. While corticosteroids are effective therapies, the side-effects of chronic steroid use require us to develop effective steroid-sparing therapies. There is only one FDA-approved steroid-sparing therapy for uveitis.

Tofacitinib is a small molecule that inhibits the signaling pathways of multiple inflammatory cytokines. It is already FDA-approved for the treatment of rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis. It is routinely prescribed by practicing rheumatologists at Washington University for diseases that place patients at risk for long-term disability.

We have successfully treated a patient with refractory uveitis with off-label use of tofacitinib after failure with multiple conventional steroid-sparing therapies (Paley *et al. in submission*). We plan to evaluate whether tofacitinib may have efficacy in a larger series of cases.

A2 Primary Hypothesis

Treatment with tofacitinib will limit ocular inflammation in the after steroids have been tapered off.

A3 Purpose of the Study Protocol

To evaluate whether tofacitinib has clinical efficacy as a steroid-sparing agent for patients with uveitis.

B Background

B1 Prior Literature and Studies

There are several lines of evidence to suggest that tofacitinib would be an effective agent in ocular inflammatory disease. For example, inflammatory cytokines that activate JAK/STAT signaling have been implicated in the pathogenesis of inflammatory eye disease (*1-3*). Furthermore, inhibitors of IL-2 (*4, 5*) and IL-6 (*6*), which activate JAK/STAT signaling, have had clinical efficacy in small studies of inflammatory eye disease. Tofacitinib has also been used topically to treat a mouse model of ocular inflammation (*7*). Additionally, tofacitinib has demonstrated clinical efficacy in rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis (*8-11*), which are associated with inflammatory eye disease. Thus, treatment of these patients with tofacitinib may trigger resolution of ocular inflammation by resolving the underlying systemic inflammatory disorder. Finally, reduced penetration of the blood-aqueous barrier may limit the efficacy of certain targeted therapies, such as etanercept and other biologic DMARDs. In contrast, a small molecule such as tofacitinib is likely to more efficiently cross of the blood-aqueous barrier.

B2 Rationale for this Study

Non-infectious inflammatory ocular disease is an auto-immune condition of unknown etiology. Although uveitis often responds adequately to corticosteroids, there are many patients for which this treatment is either inadequate or not tolerated. In addition, chronic steroid use leads to significant morbidity. We propose an open-label trial of tofacitinib for patients with non-infectious inflammatory eye disease.

A patient with inadequate response to treatment would manifest with uveitis activity by slit lamp examination determination of anterior chamber cellularity, vitreous haze or new lesions of the retina / choroid. Persistent inflammation can manifest as ocular hypertension (greater than 21 mmHg measured by tonometry), complicating chronic topical corticosteroid administration, leading to glaucoma and permanent visual loss or perforation of the eye (which also can lead to permanent visual loss). Moreover, systemic corticosteroids may be required at a dose unsafe for chronic administration. In these situations, an immunosuppressive medication is often added as a "steroid-sparing" agent. If and when there is clinical response to the added immunosuppressive, the oral and/or topical corticosteroid dose can be reduced or eliminated to avoid toxicity.

There is currently only one FDA-approved steroid-sparing therapy (adalimumab) for the treatment of uveitis. Furthermore, adalimumab is effective in only 40-60% of cases of uveitis (*12, 13*). As a result, additional steroid-sparing therapies are needed for these vision-threatening diseases.

C Study Objectives

C1 Primary Aim

The primary endpoint will be treatment failure at week 24:

Treatment failure will be defined as

- Before or at week 8 (any one of the following criteria)
    - new inflammatory lesions relative to baseline
    - anterior chamber cell or vitreous haze > 0.5+ on SUN scale
    - worsening of visual acuity by two or more rows on ETDRS (Early Treatment of Diabetic Retinopathy Study) chart
- After week 8 (any one of the following criteria)
    - new inflammatory lesions relative to baseline
    - 2-step increase in anterior chamber cell or vitreous haze
    - worsening of visual acuity by two or more rows on ETDRS chart

Grade '0' will denote zero cells present per high power field or no vitreous haze and a change of full number grade will represent a "step change" (*e.g. a change from grade 1 to 0 is considered a 1-step change*).

C2 Exploratory Analysis

1. Treatment Failure According to Reason for Failure

- anterior chamber cell
- vitreous haze
- new retinal lesions
- worsening of best corrected visual acuity

2. Time to Treatment Failure
3. Cystoid Macular Edema
   - change of cystoid macular edema based on optical coherence tomography
4. Intraocular Pressure:
   - change in intraocular pressure as measured in mmHg during clinical evaluation
5. Improvement Visual acuity (best-corrected ETDRS chart-measured acuities)
   - a clinically significant change in visual acuity will be defined as an improvement by 2 lines in the ETDRS chart.
6. Angiography
   - Angiography will be assessed for clinically relavent patients (e.g. posterior or pan uveitis)
7. Cataract
   - Patients will be assessed for cataract formation

C3 Rationale for the Selection of Outcome Measures

Outcome measures for uveitis are based on previously published phase 3 trials for steroid-sparing agents in inflammatory eye-disease (*12, 13*). Measurement of intraocular pressure, cataract formation, cystoid macular edema and visual acuity are important to determine the improvement or worsening of secondary effects of active inflammatory disease.

D Investigational Agent

D1 Preclinical Data

Tofacitinib is a small molecule that reversibly inhibits Janus associated kinases (JAKs) with some selectivity for JAK1 and JAK3 (*14*). JAKs execute cytokine receptor signaling by phosphorylation and activation of signal transducers and activator of transcription (STAT) proteins, which subsequently dimerize, enter the cell nucleus, and initiate transcription of numerous inflammatory genes. Topical administration of tofacitinib has demonstrated efficacy in treating ocular inflammation in animal models (*7*).

D2 Clinical Data to Date

We successfully treated one patient with off-label use of tofacitinib for refractory uveitis (Paley *et al. in submission*). Tofacitinib is also clinically efficacious and FDA-approved for the associated systemic rheumatologic diseases, rheumatoid arthritis and psoriatic arthritis, which are associated with inflammatory eye disease (*8-10*). Treatment with tofacitinib leads to a clinical response starting at 4-8 weeks after initiation of therapy (*8-10*). Administration of tofacitinib is approved for 5mg twice daily or 11mg extended release for rheumatoid arthritis. This dose has been in clinical practice since its FDA approval in 2012 with 19,406 patient-years of accumulated safety data.

D3 Dose Rationale and Risk/Benefits

The planned use of this product uses the FDA-approved dose and route of administration for rheumatoid arthritis. Tofacitinib has more than 8 years of safety data from clinical trials and clinical use (*15, 16*). The risk of this medication is equivalent to the single FDA-approved steroid-sparing agent for uveitis, adalimumab (*8, 10, 12, 13, 15, 17*). Notable risks include infection, reactivation of tuberculosis and the development of malignancy. Benefits of tofacitinib included the protection of organs and tissues from autoimmune or inflammatory disease without the requirement for steroids.

E Study Design

E1 Overview or Design Summary

This study is a prospective, single-site, open-label investigation of tofacitinib for refractory uveitis. The study will be for 24 weeks, with potential 1-year extension for treatment responders. The patients will self-administer the medication.

Eligible patients would be those patients with a diagnosis of uveitis who meet the following criteria:

1) Disease sufficiently severe to require treatment with systemic corticosteroids, and
2) Referred from Ophthalmology to Rheumatology or Uveitis specialist for a steroid-sparing agent

For patients naive to oral steroid-sparing therapy (e.g., methotrexate, azathioprine, or mycophenolate), tofacitinib will be initiated as monotherapy. For patients who have failed or had only a partial response to oral steroid-sparing therapy, tofacitinib will be initiated as an add-on therapy. For patients intolerant to a conventional agent, tofacitinib will be initiated as replacement monotherapy. For patients who have failed biologic therapy (e.g. adalimumab), biologic therapy will be discontinued and tofacitinib will be initiated as replacement therapy without change to concurrent conventional steroid-sparing agents. Study visits will occur at baseline/enrollment, and weeks 4, 8, 12, 16, & 24 (+/- 2 weeks). Clinic visits may occur more frequently as determined by the treating physician. Laboratory monitoring (Table 1) will be obtained according to standard of care for drug toxicity monitoring. Clinical responses will be evaluated at 24 weeks, with the primary outcome defined as treatment failure.

All patients will undergo a predetermined oral steroid taper starting at 60mg of prednisone (or equivalent) and tapering over 14 weeks (Table 2). All patients will undergo a predetermined topical steroid drop taper starting at their current dose (Table 3).

Patients will have an ophthalmological evaluation by their treating ophthalmologist at Washington University. Steroid sparing therapy will be managed by rheumatologists or uveitis specialists at Washington University. All patients will be evaluated for an associated systemic rheumatologic condition.

E2 Subject Selection and Withdrawal

2.a Inclusion Criteria

- 18 years of age or older
- diagnosis of uveitis
- for patients with uveitis (documented in medical record):
    - prior treatment failure with adalimumab
    - medical contraindication to adalimumab
    - patient unable or unwilling to perform self-injections
    - patient unable to obtain adalimumab due to cost or insurance
- a clinical response to steroids
- active disease requiring at least 10mg of prednisone (or steroid equivalent) for 2 or more weeks
    - active disease is defined as any of the following
        - at least one active inflammatory chorioretinal or retinal vascular lesion
        - anterior chamber cell grade of 2+ or higher (according to Standardization of Uveitis Nomenclature Working Group criteria)
        - vitreous haze grade of 2+ or higher (according to National Eye Institute [NEI] criteria adapted by the Standardization of Uveitis Nomenclature Working Group)
- practice of preventative contraception for women of childbearing age

2.a Exclusion Criteria

- presence of an active or uncontrolled systemic rheumatologic disorder
- suspected or confirmed ocular infection
- chronic or recurring infections, such as HIV
- renal insufficiency, which would preclude safe administration of tofacitinib

2.b Ethical Considerations

There is one FDA-approved steroid-sparing therapy for uveitis (adalimumab). Tofacitinib and adalimumab are equally effective in treating the associated systemic disorder, psoriatic arthritis. For patients who have failed adalimumab, tofacitinib offers a reasonable alternative therapy.

Patients will have regular follow-up with both Ophthalmology and Rheumatology to monitor disease activity. Treatment with corticosteroids will be available for rescue therapy for all patients with uncontrolled disease.

Patients may be influenced to participate because an authority figure (their physician) may propose the study, however, steps that will be taken by the research team to minimize the possibility of coercion or undue influence during the consent process. The consent process will include full study disclosure, giving the patient a reasonable amount

of time to decide regarding participation and the opportunity to discuss with family and friends, and assuring the patient that they will receive the same quality of care regardless of study participation.

2.c Subject Recruitment Plans and Consent Process

Patients seen in the clinical offices of the Department of Ophthalmology & Visual Sciences and the Division of Rheumatology at Washington University will be consented in a private room within the clinical office.

2.d Randomization Method and Blinding

There is no randomization or blinding in this study.

2.e Risks and Benefits

As with other immunosuppressive treatments to control autoimmune diseases, the patients will be at increased risk of infection (20%). Other risks include nasopharyngitis (3% to 14%), hypertension (2%), headache (4% to 9%), rash (6%), acne vulgaris (≥2%), increased serum cholesterol (5% to 9%), diarrhea (4% to 5%), gastroenteritis (4%), nausea (4%), urinary tract infection (2%), anemia (4%), herpes zoster infection (5%; including disseminated cutaneous, meningoencephalitis, ophthalmologic), increased creatine phosphokinase (3% to 7%), increased serum creatinine (<2%), upper respiratory tract infection (4% to 6%), and fever (≥2%).

Lymphoma and other malignancies have been reported in patients receiving tofacitinib

Tuberculosis (pulmonary or extrapulmonary) has been reported in patients receiving tofacitinib. Standard laboratory screening is performed in all patients to assess for latent / chronic infection, such as TB.

There is a risk associated with lack of efficacy. In the case of a treatment failure based on the primary outcome criteria, tofacitinib will be discontinued and the patient will be switched to an alternative steroid-sparing therapy at the discretion of the patient's treating physician.

Potential benefits include improved control of the ocular inflammatory disease, reduced corticosteroid usage, reduced intraocular pressure, improved visual acuity, and prevention of permanent vision loss. The participants may also derive benefit from contributing to medical research.

2.f Early Withdrawal of Subjects

Participants may withdraw at any time from the study. They will be asked to undergo an Early Exit Visit.

2.g When and How to Withdraw Subjects

Participants will contact the researcher if they wish to withdraw.

2.h Data Collection and Follow-up for Withdrawn Subjects

Participants who withdraw will no longer be followed in the study.

2.i Cessation of tofacitinib therapy

i Indications for cessation of tofacitinib therapy

- Laboratory abnormalities:
  - New elevation of ALT or AST > 3x upper limit of normal
  - New leukopenia with ANC < 1.5
  - New anemia with hemoglobin <7 g/dl or a decrease of > 3g/dl
  - New renal failure that would preclude the safe administration of tofacitinib
    - Patients may restart tofacitinib after recovery of renal function
- Clinical events:
  - Shingles or opportunistic infection:
    - Patients that develop an opportunistic infection or shingles may opt to (1) withdraw from the study or (2) hold tofacitinib while undergoing treatment with antivirals or antibiotics
  - Hospitalization due to tofacitinib
    - Any patient hospitalized secondary to treatment with tofacitinib as determined by a rheumatology research clinician.
  - Infection with tuberculosis:
    - Patients that develop active mycobacterium tuberculosis. All patients will have undergone screening with a PPD or interferon gamma release assay to rule out TB at the beginning of the study.
  - Treatment failure after week 8

ii Monitoring after tofacitinib cessation

- If a patient is not a treatment failure as defined by the primary outcome measure at the time of tofacitinib cessation, they will be monitored for disease relapse
- If a patient is a treatment failure at the time of tofacitinib cessation, they will be switched to another steroid sparing agent at the discretion of their treating physician
- Patients who discontinue tofacitinib treatment will remain in the study and be followed to obtain safety data.

2.j Adjustment of tofacitinib therapy

i Indications for dose reduction of tofacitinib therapy to 5mg daily

- moderate to severe renal impairment
- ESRD requiring hemodialysis
- moderate hepatic impairment

E3 Study Drug

3.a Description

Tofacitinib is a small molecule that inhibits Janus kinase (JAK). Specifically, it inhibits JAK1 and JAK3 and to a lesser extent JAK2. This inhibition occurs downstream of multiple pro-inflammatory cytokines, such as IL-2, IL-6, & IFN, and explains the anti-

inflammatory effects of tofacitinib. It has demonstrated clinical efficacy in multiple inflammatory disorders: rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis.

3.b Treatment Regimen

Tofacitinib will be taken as extended release, 11mg, once daily.

3.c Method for Assigning Subjects to Treatment Groups

All subjects will be in the same treatment group.

3.d Preparation and Administration of Study Drug

Preparation is not required. Study Drug will be provided by Pfizer, the manufacturer of the drug. The research team will provide pre-packaged bottles to the patients. Patients will self-administer the study drug.

3.e Subject Compliance Monitoring

Patients will be asked about medication adherence during regular clinical follow-up.

3.f Prior and Concomitant Therapy

All patients will be prescribed steroids with a uniform and pre-determined taper starting at prednisone 60mg daily (or equivalent) and tapering over 14 weeks to off.

Patients intolerant to an initial steroid-sparing therapy (e.g. methotrexate, azathioprine, or mycophenolate) will be started on tofacitinib and their prior steroid-sparing therapy will be discontinued. No other steroid sparing therapy will be initiated during the study period to avoid confounding of clinical efficacy.

Patients tolerant to prior steroid sparing therapy but with an incomplete control of their disease will have tofacitinib added to their steroid-sparing therapy. No other steroid sparing therapy will be initiated during the study period to avoid confounding of clinical efficacy.

Concomitant therapy with biologic steroid-sparing therapy such as adalimumab is prohibited due to the risk of infection.

3.g Packaging

Packaging will be provided by Pfizer, the manufacturer of the drug.

3.h Blinding of Study Drug

There is no blinding.

3.i Receiving, Storage, Dispensing and Return

The study drug will be shipped to the PI who will store the drug in a locked room at room temperature. An established and validated local temperature management system with temperature logs will be used to record the storage temperature. The research team will dispense the drug to the patients during their clinical visit.

F Study Procedures

F1 Screening for Eligibility

Clinicians on the research team will identify potential participants via a computerized search for relevant diagnoses and via clinical identification of uveitis during patient encounters. The clinician and/or research coordinator will discuss the study with potential participants either during the patient encounter. Consent will be signed prior to drug administration.

F2 Schedule of Measurements

Patients will have scheduled visits with a research clinician on weeks 0 (baseline), 4, 8, 12, 16, & 24 (+/- 2 weeks) as described in Table 1. These visits are standard of care for the treatment of uveitis. Measurements taken during these visits are part of standard of care.

Laboratory measurements for steroid-sparing therapy will be obtained according to Table 1.

F3 Initial Visit (week 0; baseline)

- Informed consent
- Inclusion/Exclusion criteria verification
- Medical history and Demographics
- Concomitant Medication collection
    - Dose of medications used to treat increased intraocular pressure
    - Dose of topical and/or systemic corticosteroids
- Ophthalmology data
    - Anterior chamber cell
    - Vitreous haze
    - Retinal lesions
    - Visual Acuity
    - Cystoid macular edema
    - Intraocular pressure
- Provide Subject Study Handout
- Provide Drug Package Insert
- Dispense Study Drug

F4 Subsequent visits (weeks 4, 8, 12, 16, 24 or Early Exit Visit)

- Concomitant Medication collection
    - Dose of medications used to treat increased intraocular pressure
    - Dose of topical and/or systemic corticosteroids
- Ophthalmology data
    - Anterior chamber cell
    - Vitreous haze
    - Retinal lesions
    - Visual Acuity

    - Cystoid macular edema
    - Intraocular pressure
- Adverse event collection
- Collection of used drug bottle and dispense of new drug bottle for use (drug accountability)

F5 Safety and Adverse Events

5.a Safety and Compliance Monitoring

Safety and compliance monitoring will be performed at each visit by research clinician in Rheumatology, e.g. Drs. Miner, Paley, Lee, & Brasington or Dr. Hassman in Ophthalmology.

Patients will return empty bottles of tofacitinib to demonstrate compliance.

5.b Medical Monitoring

i Investigator only

The principle investigator will review the study data every 6 months until study completion.

5.c Definitions of Adverse Events

Any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Some possible adverse event include:

1. Drug Reaction
    - This includes a rash, drug hypersensitivity or allergic reaction.
2. Laboratory abnormality
    - Elevation of ALT, AST, or creatinine on complete metabolic panel above baseline and three times above the upper limit of normal
    - Decrease of white blood cell count, absolute neutrophil count, hemoglobin, platelet count below baseline and below the normal range
    - Increase of blood lipid and cholesterol levels above baseline and above the normal range
3. Infection
    - This includes bronchitis, influenza, nasopharyngitis, pharyngitis, rash, upper respiratory tract infection, and urinary tract infection.
4. Malignancy
    - Any new diagnosis of malignancy during the study period will be recorded.
5. Hospitalization
    - Any hospitalizations during the study period and the primary diagnosis for hospitalization will be recorded.

5.d Classification of Events

i Relationship

The definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website: http://www.hhs.gov/ohrp/policy/advevntguid.html

ii Severity

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website: http://evs.nci.nih.gov/ftp1/CTCAE/About.html

iii Expectedness

Unanticipated problems are defined as:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied.
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

5.e Data Collection Procedures for Adverse Events

Patients will be interviewed about adverse events during scheduled follow-up. Laboratory studies will be reviewed at each visit.

5.f Reporting Procedures

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at any WU, BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

5.g Adverse Event Reporting Period

These events must be reported to the IRB within 10 working days of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within 1 working day of the occurrence of the event or notification to the PI of the event.

5.h Post-study Adverse Event

Post-study adverse events will be identified through routine follow-up of these patients with chronic diseases by their treating physicians.

F6 Study Outcome Measurements and Ascertainment

1. Inflammatory lesions will be based on optical coherence tomography (OCT) and slit lamp exam by the treating ophthalmologist
2. Anterior chamber cell will be measured according to Standardization of Uveitis Nomenclature (SUN) Working Group criteria; scores range from 0 to 4+, with higher scores indicating more cells visible in the anterior chamber and greater severity of uveitis (*18*)
3. Vitreous haze will be measured according to National Eye Institute [NEI] criteria adapted by the SUN Working Group; scores range from 0 to 4+, with higher scores indicating greater severity of uveitis (*19*)
4. Visual acuity will be measured by Early Treatment Diabetic Retinopathy Study chart
5. Cystoid Macular Edema will be measured by Optovue OCT
6. Angiography will be performed with the Optovue OCT
7. Intraocular Pressure will be measured with a Goldmann applanation tonometer by the treating ophthalmologist
8. Cataract formation will be assessed on physical exam by the treating ophthalmologist

G Statistical Plan

G1 Sample Size Determination and Power

This is a pilot study evaluating the off-label use of tofacitinib for the treatment of non-infectious inflammatory eye disease. A maximum of 5 patients with uveitis will be enrolled. All analyses will be descriptive in nature.

G2 Interim Monitoring and Early Stopping

The study Principal Investigator will monitor for serious toxicities on an ongoing basis. Once the Principal Investigator becomes aware of an adverse event, he will report the adverse event to the HRPO according to institutional guidelines. The trial will be stopped early if the number of serious toxicities exceed the expected rate (*15*). For example, the trial will be stopped if there are 3 or more cases of shingles while on tofacitinib therapy.

G3 Analysis Plan

All analysis will be descriptive. We expect 40-60% of patients to meet the primary endpoint in each arm similar to adalimumab in the treatment of noninfectious uveitis. This is in contrast to the placebo arm, which had a treatment failure rate of 80% at 24 weeks (*12*).

Patients will by analyzed by intent to treat when all 5 patients in a treatment arm have either completed 6 months of therapy or discontinued therapy due to study withdrawal or indications for treatment cessation.

G4 Statistical Methods

All analysis will be descriptive. This study is not powered to draw statistical conclusions.

G5 Missing Outcome Data

Patients with missing outcome data in the primary endpoints will be censored for the initial analysis for efficacy.

G6 Unblinding Procedures

There is no blinding in this study.

H Data Handling and Record Keeping

H1 Confidentiality and Security

Consents will be scanned into the medical record. Original hard copies of consents will be secured under two keys and two locks in a locked file-cabinet within a locked office. Prospective clinical data will be collected during the study and entered into RedCap (a HIPAA compliant and password-protected database.) All aspects of the medical record will be analyzed including age, sex, office visit data, phone number, MRN, chief complaint, history of present illness, past medical and surgical history, past ocular history, medications, allergies, exam findings, studies including images, ultrasound, and radiographic studies, laboratory data, diagnosis, assessment and plan as well as clinical outcomes.

H2 Training

All researchers have undergone confidentiality and ethical training through Washington University.

H3 Records Retention

Electronic records of patient treatment will be stored in the electronic medical record (EMR) and in RedCap. Consents will be scanned into the EMR. This will be saved for the lifespan of the EMR and RedCap. Hard copies of records (e.g. consents) will be kept for 3 years after completion of the trial.

I Study Monitoring, Auditing, and Inspecting

I1 Study Monitoring Plan

The investigators will meet weekly to review study data to detect early evidence of unanticipated harm to subjects. The review will focus on safety data including but not

limited to serious adverse drug events, drug exposure, laboratory test results, and vital signs measurements asa well as the rate of treatment failure.

I2 Auditing and Inspecting

2.a Audits

In order to guarantee that the conduct of the study is in accordance good clinical practice and the national laws, audits may be performed at the study sites to be carried out by an independent auditor. In addition, for-cause audits may be scheduled. The investigator agrees to give the auditor access to all relevant documents for review.

2.b Inspections

Inspections of the study sites may be performed by the local or regulatory authorities at any time during or after completion of the study. The investigator agrees to give the inspectors access to all relevant documents for review.

J Study Administration

J1 Organization and Participating Centers

Principle Investigator: Lynn Hassman, MD, PhD
Co-Investigator: Michael Paley, MD, PhD

See IRB submission for complete list of participating clinicians.

This is a single-site study at Washington University.

J2 Funding Source and Conflicts of Interest

The funding source is departmental for the physicians. Dr Brasington receives speaking fees for Pfizer. Dr Brasington will be a treating physician. He will identify and consent patients for study enrollment and manage their steroid-sparing therapy. However, Dr Brasington will not be scoring the amount of inflammatory eye disease or be involved in primary analysis of the study data. He will not be in a position to influence the outcome of the trial.

J3 Subject Stipends or Payments

Subjects will not receive Stipends or Payments.

J4 Study Timetable

Planned Start Date: November 1st, 2018
Planned Completion Date: May 31st, 2020

K Publication Plan

The results of this study will be submitted for publication to a peer-reviewed journal.

L Attachments

L1 Tables

Table 1. Schedule of Laboratory measurements

	Week					
	0	4	8	12	16	24
Clinic visit	X	X	X	X	X	X
CMP & CBC	X	X		X		X
Lipid Panel	X					X
Hepatitis B	X					
Hepatitis C	X					
PPD / IGRA*	X					

*IGRA: Interferon-gamma release assay a.k.a. T spot for TB

Patients with Hepatitis B & C serologies within the past 5 years will not need repeat labs.

Patients with a PPD / IGRA in the past 12 months will not need repeat labs.

Table 2. Oral steroid (prednisone or equivalent) taper

Week	Prednisone dose (mg/day)
0	60
1	60
2	50
3	40
4	30
5	20
6	15
7	12.5
8	10
9	7.5
10	5
11	4
12	3
13	2
14	1
15	0

Table 3. Prednisone Drop Taper Schedule – patient-specific wherever they start

Dose (# of drops/day) per Week

12
10
8
6
5
4
3
2
1

L2 Informed consent documents

See separate informed consent document.

L3 Patient education brochures

See separate informed consent document.

L4 Questionnaires or surveys

Patients will not be required to complete questionnaires or surveys.

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