TITLE: Celecoxib for Thyroid Eye Disease

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1. Abstract

- Thyroid eye disease (TED) is an autoimmume disorder in which autoantibodies against the TSH receptor attack orbital tissues, resulting in characteristic changes in eyelid position, globe position in the orbit, extraocular muscle balance, and optic nerve function. TED is a potentially blinding disease, and current treatments largely consist of nonspecific reduction of inflammation using corticosteroids or radiation therapy. The former treatment has significant morbidity, while the latter is controversial. Rituximab, which depletes CD20+ cells, has been used recently in severe disease but has evoked concern because of its cost and potential morbidity. Regardless of treatment, once TED progresses from its inflammatory phase to a more fibrotic, resolution phase, the orbital changes become fixed and can be modified only by surgery. We intend to use celecoxib (Celebrex), a non-steroidal anti-inflammatory drug approved by the Food and Drug Administration (FDA) for the treatment of pain, osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, as a treatment for active TED. *In vitro* data have shown that transformation of orbital fibroblasts into adipocytes is mediated by cyclooxygenase-2 (COX-2) via the PPAR-gamma pathway, and a single case report suggests that COX-2 inhibition can improve TED in the acute phase. Thus, we intend to evaluate the efficacy of COX-2 inhibition in the treatment of active TED and its ability to improve both the acute inflammatory signs and more permanent fibrotic changes of quiescent disease. We will enroll patients with active TED and treat them for 3 months (a characteristic period of disease activity) and compare this to standard treatments for mild TED (observation with only over the counter interventions such as lubrication with artificial tears) to assess efficacy.

2. Objectives (include all primary and secondary objectives)

- Study the effectiveness of celecoxib (Celebrex) in the reduction of orbital inflammation in patients with thyroid eye disease.
  - Primary outcome- reduction of clinical activity (by Clinical Activity Score (CAS) and VISA score (Vision, Inflammation, Strabismus, Appearance))
  - Secondary outcomes- improvement in proptosis, strabismus, and eyelid retraction, and TED quality of life questionnaire

3. Background

- Thyroid eye disease (TED) occurs in up to 50% of patients with Graves disease and to a lesser extent in Hashimoto thyroiditis. Autoantibodies to the TSH receptor [thyroid stimulating immunoglobulin (TSI) and TSH receptor antibody (TSHR Ab)] have cross-reactivity with similar antigens on the surface of orbital cell membranes. The basic pathogenesis of TED involves a cell-mediated inflammatory process that attacks orbital soft tissues, including adipocytes, fibroblasts, and extraocular muscle. Their binding results in recruitment of T-cells and monocytes (and B-cells to a lesser extent) and secretion of inflammatory cytokines. After an acute inflammatory phase, a chronic condition results from persistent tissue changes including extraocular muscle fibrosis and fat hypertrophy. Vision problems result when adipocyte proliferation leads to proptosis and corneal exposure, and extraocular muscle enlargement in addition to adipogenesis can cause compressive optic neuropathy. Proptosis is also disfiguring and can be remedied only by surgery after the inflammatory phase resolves; this can take 1-2 years without any medical intervention. Chronic TED responds only to surgical correction, and treatment in the acute phase can reduce morbidity. Current treatments of active TED involve nonspecific anti-inflammatory medications such as corticosteroids (with the attendant side effects) and orbital radiotherapy (controversial because of limited data supporting efficacy and theoretic risk of secondary malignancy). Recently, rituximab has been used in severe cases, but its expense and side effect profile have limited its utility.
- In addition to cytokines, activated T-cells produce ligands for peroxisome proliferator activated receptor (PPAR) gamma. These ligands include prostaglandins created via the cyclooxeganse-2 (COX-2) pathway. PPAR-gamma activation has been implicated in systemic adipogenesis in patients taking thiazolidinedione drugs for glycemic control, and *in vitro* studies of cultured orbital fibroblasts have shown that exposing cells to PPAR-gamma ligands such as specific prostaglandin analogues results in transformation of fibroblasts into adipocytes. This effect is more robust with TED fibroblasts than in cells isolated from control patients. Inhibiting the PPAR-gamma pathway *in vitro* with a selective COX-2 inhibitor blocks fibroblast transformation. A single case report in the literature also supports the possible *in vivo* efficacy of COX-2 inhibition in active TED.
- Based on these *in vitro* and *in vivo* findings, we propose to treat a cohort of patients with active TED using a selective COX-2 inhibitor, celecoxib (Celebrex), and to compare these patients to an observational control group. We hypothesize that celecoxib will reduce the severity of disease and/or prevent progression to proptosis, diplopia, and corneal exposure or compressive optic neuropathy. We will assess the effect of the treatment using validated clinical scoring tools, including the Clinical Activity Scale (CAS) from the European Graves Orbitopathy Group (EUGOGO) and the VISA (vision, inflammation, strabismus, appearance) scale of the International Thyroid Eye Disease Study (ITEDS) group. We will also use a validated Graves ophthalmopathy quality of life survey as a secondary outcome measure. Outcomes will be assessed at timepoints noted below with a 3-month period of treatment and follow-up for 1 year.

4. Study Procedures

- Patients will be recruited from the Wilmer Eye Institute practices of the investigators.
- The exam will include a thorough history including a list a medications, health conditions previous surgeries and medical allergies (standard of care).

- The complete eye examination will measure visual acuity, eye movements (sensorimotor exam), visual fields, proptosis, pupil function, anterior segment evaluation, and lastly dilated fundus

exam to evaluate the potential subject's optic nerve. Photographs (external, eye movements, optic nerve) may be taken as needed. This eye examination is standard of care on any thyroid eye disease patient. Findings from the eye exam will be used to determine a CAS and VISA score. The CAS takes into account 7 manifestations (spontaneous retrobulbar pain, pain with eye movement, eyelid erythema, eyelid edema, conjunctival injection, chemosis, and caruncular swelling) with 1 point assigned for each positive finding. The VISA score ranges from 0-16 based on findings related to inflammation, strabismus, and eyelid changes and proptosis (appearance). Both scales were developed to assess features of active disease that might change with treatment.

- Study subjects will be randomly assigned to observation with no prescription treatment, or treatment with oral celecoxib 100 mg twice daily for 3 months. Patients will have a full clinical exam at baseline, 1 month, 3 months, 6 months, and 12 months, with additional clinical visits more frequently if indicated by disease course/activity. The proposed frequency of clinic visits is within standard of care for newly diagnosed active-phase TED.

- For those subjects randomized to the treatment group, baseline blood testing for blood counts, renal and hepatic function (BUN, Cr, AST, ALT, total bilirubin) will be obtained prior to starting the drug. Testing will be performed by a standard clinical laboratory and billed to insurance. Testing will be repeated at 1mo and 3mo after randomization/initiation of therapy for those receiving celecoxib. Abnormal BUN or creatinine (outside normal range) on lab testing or any previous/current kidney disease will be the criteria for labeling a patient as having impaired renal function. Abnormal liver enzymes (AST, ALT, bilirubin outside normal range) or previous/current liver disease will determine whether a patient is labeled as having impaired hepatic function. Monthly phone interviews also will be conducted by physician study team members to determine if other side effects, such as edema, may be occurring. Subjects will be asked specifically about peripheral swelling, any blood in urine or skin discoloration, or changes in exercise tolerance. Positive responses will trigger an unscheduled visit with the PI or co-investigator MD. Patients will be cautioned not to take additional NSAID medications while on Celecoxib, as this may increase the chance for adverse effects.

- Outcomes: The primary study outcome is reduction of clinical activity of TED, as determined by both the CAS and VISA scores. We will use both scales because there is currently disagreement as to which scale serves as a better overall assessment tool. Secondary outcome measures will include reduction of specific aspects of TED, including proptosis, diplopia, and eyelid retraction, as well as a validated TED-specific quality of life survey. These elements are captured in part by the 2 scales but also will be evaluated separately. Comparison of our primary and secondary outcomes between the treatment and control groups and with published studies of steroid treatment for TED may provide us with an indication of the relative efficacy of celecoxib treatment and whether further study is warranted. Treatment safety also will be assessed, and adverse events recorded. A recent prospective study of intravenous corticosteroid dosing for TED reported major adverse events in 10/159 (6.3%) of subjects and minor adverse events such as gastric distress, mild BP increase not requiring medication, and local skin reactions in about 25% of subjects. We anticipate a lesser incidence of minor or major adverse events based on the side effect profile of celecoxib in patients without co-morbidities placing them at higher risk (most TED patients are young and otherwise healthy). Occurrence of adverse events at a rate

greater than what has been reported for intravenous corticosteroid (an accepted method of TED treatment) would suggest that risk of celecoxib treatment exceeds any benefit.

- Biospecimens will be collected in this study, to include urine for a pregnancy test for female patients of childbearing age to determine eligibility, as well as blood as noted above that will be drawn by the clinical lab.

- Study length: Subjects will be followed for 12 months.

- Safety monitoring: As noted, baseline blood testing and phone surveillance will be performed. If abnormal results are found during drug treatment, then subjects will be advised to stop the medication and will be examined by the PI or other MD investigator. Adverse events will be reported to the IRB per institutional policy.

- Subjects may be taken out of the study if:
  - Staying in the study would be harmful.
  - Treatment required is not allowed in the study.
  - Those that fail to follow instructions.
  - Subjects become pregnant.
  - The study is cancelled.
  - There may be other reasons to take subjects out of the study that we do not know at this time.

5. Inclusion/Exclusion Criteria

Eligibility criteria:

- *Recent diagnosis of thyroid eye disease (within the past 6 months)*
- *Have ocular symptoms or signs of TED with a CAS score of at least 3*
- *Ages 18-80 years*

Exclusion criteria:

- *Pregnancy*
- *Previous treatment with corticosteroid for TED for >2wks*
- *Previous treatment with orbital radiation for TED*
- *Impaired renal function*
- *Impaired hepatic function*
- *Treatment with antihypertensive medications except beta-blockers*
- *History of congestive heart failure, cardiac valvular disease, or coronary artery disease*
- *Allergy to NSAID or previous adverse reaction (ie. GI bleeding)*
- *Vision loss due to compressive optic neuropathy*

Target 40 participants will be enrolled in this study.

6. Drugs/ Substances/ Devices

Celecoxib (Celebrex) is a non-steroidal anti-inflammatory drug approved by the Food and Drug Administration (FDA) for the treatment of pain, osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. We will be using the recommended dosage of 100 mg twice a day over the course of 3 months. Celecoxib for TED is an off-label usage.

7. Study Statistics

The primary study outcome is reduction of clinical activity of TED, as determined by both the CAS and VISA scores. We will use both scales because there is currently disagreement as to which scale serves as a better overall assessment tool. Secondary outcome measures will include reduction of specific aspects of TED, including proptosis, diplopia, and eyelid retraction. These elements are captured in part by the 2 scales but also will be evaluated separately. Change in quality of life will be measured by a validated questionnaire as another secondary outcome measure. Comparison of our primary outcomes between treatment and control groups will provide us with an indication of the relative efficacy of celecoxib treatment. Treatment safety also will be assessed, and adverse events recorded. A recent prospective study of intravenous corticosteroid dosing for TRO reported major adverse events in 10/159 (6.3%) of subjects and minor adverse events such as gastric distress, mild BP increase not requiring medication, and local skin reactions in about 25% of subjects. We anticipate a lesser incidence of minor or major adverse events based on the side effect profile of celecoxib in patients without co-morbidities placing them at higher risk (most TED patients are young and otherwise healthy). Occurrence of adverse events at a rate greater than what has been reported for intravenous corticosteroid (an accepted method of TED treatment) would suggest that risk of celecoxib treatment exceeds any benefit. Observation of adverse events in excess of this rate during the treatment phase would require review, and consideration of early study termination. The changes in either the CAS or VISA score will be compared between the celecoxib and observation groups to determine whether a trend or significant difference can be found.

8. Risks

The study procedures, apart from the proposed treatment, carry no risk beyond that of standard clinical care. Celecoxib has well-described risks especially in certain patient populations, who will be excluded from this study as noted. Below is an enumeration of risks copied from the package insert:

- **Cardiovascular warning:** All prescription NSAIDs, like CELEBREX, ibuprofen, naproxen, and meloxicam have the same cardiovascular warning. They may all increase the chance of heart attack or stroke that can lead to death. This chance increases if you have heart disease or risk factors for it, such as high blood pressure or when NSAIDs are taken for long periods. Congestive heart failure and peripheral edema has also occurred in some patients has also been noted.
- **CELEBREX should not be used right before or after certain heart surgeries.**
- **Stomach and intestine risk:** All prescription NSAIDs have the same warning for serious stomach and intestine problems: They may cause ulcers and bleeding, which can occur without warning and may cause death.
- **Renal warning:** Long term use of NSAIDs, like CELEBREX, have resulted in renal papillary necrosis. Patients at risk are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, ACE inhibitors, and angiotension II inhibitors.

- **Serious skin and allergic reactions can occur with CELEBREX**. CELEBREX shold not be taken if one has had an asthma attack, hives, or other allergies to aspirin, other NSAIDs, or certain drugs called sulfonamides.

Risks of corticosteroid treatment are noted in section 7 with at least 25% of patients experiencing a minor or major adverse event. Orbital radiotherapy carries theoretic risk of ocular radiation toxicity (cataract formation, radiation retinopathy or optic neuropathy) and second malignancy occurrence, but the actual rate of such events is not known. Untreated, some patients with TED may have spontaneous improvement while others will progress to more severe manifestations. Increased disease activity at presentation is a predictor for progression, and we thus are including only subjects with clinical activity that may put them at risk for such changes. Treatment is effective only during the active phase of TED, and observation may result in irreversible proptosis or strabismus requiring subsequent surgery.

9. Benefits

The major benefit of the study is anticipated to be reduction of TED severity as measured by clinical activity assessment.

10. Payment and Remuneration

Subjects will not be compensated for participation.

11. Costs

Subjects will receive a separate Insurance and Research Participant Financial Responsibility Information Sheet (Sheet).

This Sheet will give subjects the following information:

- The drugs that are part of this research will be paid for by their insurance
- The required laboratory testing will be paid for by their insurance
- The standard eye examination, procedures and tests that will be performed will be billed to the subject and/or their health insurer. Subjects with health insurance will be responsible for any co-pays or deductibles not covered by their insurance. All planned visits with standard testing are consistent with standard of care and will be charged to insurance as usual.