Symptomatic Management of Lyme Arthritis

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Protocol:

Short Title: Symptomatic Management of Lyme Arthritis

Full Title: Symptomatic Management of Lyme Arthritis: Feasibility and preliminary data study to compare symptomatic outcomes and side effects of adjunct scheduled NSAID therapy for Lyme arthritis versus scheduled acetaminophen or standard care

Brief description:

Lyme arthritis resolves with appropriate antimicrobial treatment in a majority of patients, but 10-20% of patients develop antibiotic-refractory Lyme arthritis with prolonged arthritis symptoms and treatment courses. Excessive up-regulation of the inflammatory process has been shown in patients with antibiotic-refractory Lyme arthritis. The over expressed proinflammatory cell mediators are downstream of NSAID inhibition, which would suggest initial inflammatory inhibition may be beneficial in these patients. While NSAIDs are known to reduce pro-inflammatory cell mediators early in the course of inflammation, research has shown that there are other cytokines that play a role in the healing after inflammation that are also inhibited by NSAIDs, and that NSAID use can delay healing.

It is not known if scheduled NSAID therapy will reduce, increase, or have no effect on the occurrence of refractory Lyme arthritis cases. The hypothesis of the study is that prescribing scheduled NSAIDs at the time of diagnosis of Lyme arthritis can prevent the development of the excessive inflammatory phase and decrease the number of patients with antibiotic refractory Lyme arthritis, or at least decrease the duration of persistent Lyme arthritis symptoms.

The pilot study design randomizes patients to scheduled NSAIDs, scheduled acetaminophen, or scheduled NSAIDs x 1 week than acetaminophen. Primary outcomes are duration of arthritis symptoms, number of refractory cases, side effects and compliance.

Specific Aims:

1. Demonstrate feasibility to ensure adequate patient enrollment and symptomatic follow-up of patients with Lyme arthritis.

2. Develop pilot data necessary for sample size and power calculations:

    a. Quantification of antibiotic-refractory Lyme arthritis in our population
    b. Symptomatic outcomes of patients with Lyme arthritis on scheduled NSAIDs versus those not placed on scheduled NSAIDs (duration to resolution and number of patients with resistant arthritis)
    c. Assess side effects of patients with Lyme arthritis placed on scheduled NSAIDs versus those not placed on scheduled NSAIDs
    d. Assess changes in resources (follow-up visits, further prescriptions) required for patients taking scheduled NSAIDs versus not taking scheduled NSAIDs

Background:

Lyme disease is the systemic tick-borne disease caused by Borrelia burgdorferi infection, and is endemic to an expanding portion of the United States. Lyme arthritis is a common presentation of Lyme disease. While Lyme arthritis resolves with appropriate antimicrobial treatment in most patients, 10-20% of patients develop antibiotic-refractory Lyme arthritis with prolonged inflammatory arthritis. Research suggests excessive up-regulation of the inflammatory process in patients with prolonged symptoms. The over-expressed proinflammatory cell mediators are downstream of NSAID inhibition, which would suggest NSAIDs may be beneficial in these patients. In fact, there is data that NSAIDs and/or disease-modifying anti-rheumatic drugs (DMARDs) may be beneficial in refractory Lyme arthritis cases, once diagnosed as refractory.
There are studies that show that NSAIDs in addition to inhibition of pro-inflammatory cell mediators, also inhibit prostaglandins that active during the healing phase of inflammation. Those studies have questioned whether NSAIDs can delay healing. This question has not been evaluated in acute joint inflammation, particularly in Lyme arthritis patients. It is possible that scheduled NSAID therapy would reduce inflammation early, but delay overall time to resolution of inflammation.
The hypothesis of the study is that prescribing scheduled NSAIDs at the time of diagnosis can prevent the development of the excessive inflammatory phase and decrease the number of patients with antibiotic-refractory Lyme arthritis, or at least decrease the duration of persistent Lyme arthritis symptoms. There are no known methods to identify patients at the time of diagnosis who will go on to develop antibiotic-refractory Lyme arthritis.

While antibiotic-refractory Lyme arthritis has been studied at a microbiologic/cytokine level as well as evaluated in terms of treatment once patients have been deemed antibiotic refractory, to our knowledge there are no published studies evaluating prevention. With no literature looking at the question of NSAIDs for the prevention of antibiotic refractory Lyme arthritis, this pilot study is needed to adequately calculate sample size and power calculations for a large-scale multicenter study. There is anecdotal data from the Rheumatology and Infectious Disease departments at our institution that early scheduled NSAIDs may decrease refractory cases, but there has been no formal evaluation into this question. Retrospective evaluation is challenging since the medications in question (NSAIDs) are over the counter, and clinicians may or may not recommend scheduled or intermittent NSAID therapy at the time of initial diagnosis without documentation, and certainly without prescriptions in the medical record. Many patients with REFRACTORY Lyme arthritis are placed on NSAIDs but given the question of delayed healing with inhibition of prostaglandins during the healing phase of inflammation, the question of whether NSAIDs are beneficial in patients to prevent refractory arthritis is worthwhile rather than the current process of variable NSAID prescription. This work is important to delineate optimal timing and duration of NSAIDs given the research that shows the anti-inflammatory effects during healing can potentially delay recovery in other inflammatory conditions.

Study Design:

300 patients will be enrolled in a randomized active treatment-controlled trial.

Inclusion criteria:

Study patients are eligible for inclusion is they are >or= to 3 years and <18 years of age with arthritis and the clinical team is ordering a Lyme test. Patients will remain eligible for analysis if their Lyme test is positive.

Exclusion criteria:

Patients will be secondarily withdrawn from analysis and instructed to stop study medication if their Lyme test is negative.
Underlying diagnosis of rheumatoid or recurrent arthritis
Already on scheduled NSAIDs
Anything that restricts the prescription of naproxen or acetaminophen:
• Hypersensitivity to naproxen (for example: anaphylactic reactions, serious skin reactions) or any component of the formulation; history of aspirin induced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs, underlying kidney or liver impairment
• Already taking daily NSAIDs (naproxen or ibuprofen) or daily acetaminophen

• Hypersensitivity to acetaminophen or any component of the formulation; severe liver impairment or severe active liver disease

Research activities

Patients 3-17 years of age suspected to have Lyme arthritis (physician diagnosed arthritis and evaluation with a Lyme EIA with reflex western blot) will be enrolled in the study and receive randomization to adjunct treatment arms in addition to their standard of care antibiotic treatment.
Patients will be enrolled in the emergency department, primary care center, or infectious disease clinic where they have their initial point of contact for the diagnosis of Lyme arthritis.
Adjunct Treatment arms: Children will be randomized 1:1:1 to three treatment groups

1. Group 1 - Scheduled naproxen bid x 28 days or until symptom resolution. Dose of naproxen will be 5-7.5 mg/kg/dose. (per prescription table) doses by weight in prescription table in attached documents- maximum prescribed: 1000 mg/day of naproxen.
2. Group 2 - Scheduled acetaminophen qid x 28 days or until symptom resolution. Dose of acetaminophen will be 15 mg/kg/dose. (per prescription table) doses by weight in prescription table in attached documents- maximum prescribed: 2600 mg/day of acetaminophen.
3. Group 3 -Scheduled naproxen bid x 7days, then acetaminophen qid x 21 days or until symptom resolution. (at the same doses and maximums as above)
4. Patients who refuse enrollment for randomization will be offered consent to follow-up only arm (current standard of care treatment)

Prescriptions given to the families for symptomatic medications (naproxen and/or acetaminophen) can be filled in any pharmacy the family chooses.

Outcomes:

1. Feasibility of enrollment and data collection
2. Number of patients with antibiotic-refractory arthritis
3. Days until joint symptom resolution
4. Compliance with medication (and other medications taken)
5. Side effects
6. Days until return to baseline function
7. Need for repeated medical appointments/care seeking

Methods:

Enrollment visit - obtain written informed consent then randomize to one of three treatment arms.
- collect standardized physical examination
- symptom assessment Day 0

Outcomes 2-5 to be collected by text surveys at days from enrollment: 1, 3, 7, 10, 14, 21, 28, 60:
o Joint redness/swelling
o Joint function
o Joint pain
o Compliance with medication
o Side effects
o Overall function versus baseline

A phone call may be made if the text survey is not filled out within 24 hours of sending.
Outcome 6 and 7 to be evaluated through electronic medical record follow-up at 30, 60, 180 days (and every 30 days as needed in antibiotic-refractory cases, until symptoms resolve up to 1 year)