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CLINICAL RESEARCH PROTOCOL

Columbia University Medical Center

TITLE: Non-Steroidal Anti-inflammatory Drugs in Axial Spondyloarthritis: a Pilot Study

SHORT TITLE: NSAIDs in AS

PRINCIPAL INVESTIGATOR: [redacted] MD, MHS

1. PRECIS

Spondyloarthritis (SpA) is a group of inflammatory spine conditions that affects 0.5 - 1% of the population in the United States. Ankylosing spondylitis (AS) is the prototypical disease in this family. Non-steroidal anti-inflammatory drugs (NSAIDs) are the first line pharmacological treatment of SpA and AS. However, more than 20 different NSAIDs are available for use. It remains unclear whether any particular NSAID is more effective than others, or if individual patients respond to NSAIDs differently. To address this questions, I propose a series of n-of-1 trials of NSAIDs in patients with SpA, as a pilot study for a future multicenter trial. More specifically this study will:

- Evaluate the optimal treatment length for each NSAID – 4 weeks vs. 6 weeks.
- Evaluate whether a washout period is necessary between different NSAIDs.
- Evaluate the feasibility of remote collection of patient-reported outcomes (PROs).

Hypothesis 1: The change of pain score from week 4 to week 6 is not clinically significant, and 4 weeks of treatment is sufficient to determine efficacy of NSAIDs.

Hypothesis 2: Washout period is not necessary for assessing treatment response in a sequential design.

2. STUDY DESIGN AND METHOD

2.1 Study Overview

Study Design Each patient will be randomized to one of the four NSAIDs, indomethacin, diclofenac, meloxicam, and celecoxib, each for six weeks, together with an oral proton-pump inhibitor. In the initial visit, patient will be evaluated for eligibility and give consent to the study. All patients will undergo a one-week washout period without any NSAIDs, and have a re-evaluation of their eligibility. Eligible patients will be randomized to one of four NSAIDs, each for 6 weeks. The patients will have a one-week washout period, and be randomized to one of the other four NSAIDs. Based on sample size calculation (see details later), we plan to enroll 24 patients in this group.

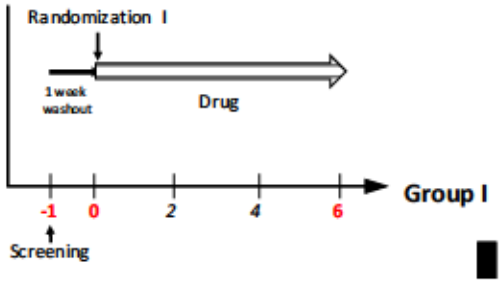

Figure. *Study Overview. Weeks labeled in red are the time points for clinical visits; weeks labeled in black are time points for remote collection of patient reported outcomes.*

Study population Study subjects will be outpatients who are seen at CUMC rheumatology clinic with a clinical diagnosis of AS by treating rheumatologists, or a diagnosis of axial SpA with a pelvis MRI with significant bone marrow edema on STIR sequences. Other inclusion criteria include 1) minimum of 18 years old; 2) are taking NSAIDs on a regular basis for AS or SpA (defined as more than 20 days in the past month), or having active symptoms that require initiation of NSAIDs; 3) if using antirheumatic drugs concomitantly, stable dose for the past three months; 4) have active disease after initial washout period, defined by BASDAI >=4/10, or back pain VAS >=4/10. Exclusion criteria include: patients who have concurrent rheumatic diseases other than AS or axial SpA; patients who have oral corticosteroid in the past two weeks; patients who have acute peripheral arthritis; patients with high fibromyalgia score; patients with extensive cardiac history, history of gastrointestinal bleeding that required blood transfusion, chronic kidney disease, or pregnancy. Use of low dose of aspirin (<100mg daily) is allowed in the study.

Study Drugs indomethacin ER 75mg (capsules) twice a day; diclofenac EC 75mg (tablets) twice a day; meloxicam 7.5mg (tablets) twice a day; celecoxib 200mg (capsules) twice a day. With omeprazole 20mg daily.

Assessment All patients will have clinical assessments at initial screening visits (week -1) and at randomization (week 0). In addition, for Stage I, clinical assessments (Figure 1 in red) will be performed at week 6, and for Stage II, it will be performed at time when patients switch from one NSAID to another. Or, patients will be assessed clinically at the time when discontinue the NSAIDs prematurely due to lack of efficacy or side effects. Primary end points include spinal pain (VAS), patient global score (VAS), BASDAI, and BASFI. In addition, patient global assessment of response to therapy (PGART), by a 0-4 Likert scale, physician global assessment, ASDAS, CBC, ESR, CRP, adverse events will be collected at each clinic visit. For patients who discontinued their NSAID before 6 weeks, reasons for discontinuation will be assessed. At the end of the study, patients will be asked to give a preference of NSAIDs.

We will collect patient reported outcomes at week 2 and week 4 of each NSAID treatment, including spinal pain (VAS), patient global score (VAS), BASDAI (6 questions by VAS) and BASFI (10 questions by VAS). A link to the questionnaires will be emailed to patients via RedCap. By clicking the link, patients will be able to answer the questionnaires using either a mobile device or a desktop computer. If a patient does not respond in 24 hours, another email with link to questionnaires will be sent as a reminder. After three attempts, if there is still no reply, the patient will be contacted via phone to collect the answers to questionnaires. At the end of the study, we will survey the patients to have a qualitative assessment of remote collection.

2.2 Study Visits

	Week -1 ~ 0 (screen)	Week 0 (randomization)	2 weeks +/- 2 days (remote)	4 weeks +/- 2 days (remote)	6 weeks +/- 2 days (end of study)
	Visit 1	Visit 2			Visit 3
Background Questionnaire	X				
Eligibility Criteria Overview	X	X			

Informed Consent	X				
History/Physical Exam	X	X			
BASDAI	X	X	X	X	X
BASFI	X	X	X	X	X
Other PROs	X	X	X	X	X
Medication Questionnaires	X	X			X
ESR		X			X
CRP		X			X
Adverse Events			X	X	X
Blinded Treatment		X	X	X	X
Blood collection		X			X
Stool collection		X			X

Screening visit (Visit 1; Time ~ Week -1)

Length of visit: Approximately 1 hour

Potential subjects will have the study explained to them and provided the opportunity to ask questions about the study. All participants will provide written informed consent. Eligibility is confirmed through patient interview and review of past medical records by the study investigators. Subjects will have a medical history and physical examination. They will complete the Background Information, BASDAI, BASFI and questionnaires for other PROs for assessment of AS activity.

If patient's AS is not active based on inclusion criteria, the subject will exit the study. They would be eligible for re-screening in the future. Patients confirmed to have active disease will be eligible for the study, and will be asked to not taking any NSAIDs for 7 days, as the initial wash-out period. If they have not taken any type of NSAIDs, they are eligible for Visit 2 on the same day.

Questionnaires may be completed using paper forms and will be transfer to RedCap, which will serve as the study database.

Randomization (Visit 2; Time: Week 0)

Length of visit: approximately 1 hour

This visit provides subjects the opportunity to ask additional questions about the study, and the investigators to confirm ongoing disease activity of subjects. For the purposes of statistical analysis, this visit serves as the baseline visit. Subjects will have a medical history and physical examination. They have a clinical assessment of disease activity to ensure ongoing disease activity. If the disease is inactive, the subject will exit the study. They would be eligible for re-screening in the future if their treating rheumatologist plan to escalate their therapy.

Subjects confirmed with active disease will proceed with the following assessments. They will complete health self-assessments with BASDAI and BASFI questionnaires, Medication questionnaire, Health Status questionnaire. The BASDAI questionnaire has 6 questions and takes 3 minutes to complete. The BASFI questionnaire has 10 questions and takes 5 minutes to complete. The Health Status questionnaire includes the HAQ disability index, with 20 questions on physical function, and the SF-36 with 36 questions assessing physical and mental health. The health status questionnaire takes 15 minutes to complete. Fifteen milliliters of venous blood will be drawn for testing high-sensitivity CRP, sedimentation rate, HLA-B alleles, serum for storage for research purposes. In some patients, stool will be collected for future research purposes.

Confirmation of disease activity based BASDAI or pain VAS score is needed for subjects to receive a randomized treatment assignment and continue in the study. Randomized treatment assignment is made, and study medication is dispensed, together with a proton pump inhibitor, for a total of 6-week supply.

Follow-up Evaluation (Remote evaluation; Time: Week 2 and Week 4)

Length of completing questionnaires: 20 min.

We will collect patient reported outcomes at week 2 and week 4 after starting NSAID treatment, including spinal pain (VAS), patient global score (VAS), BASDAI (6 questions by VAS) and BASFI (10 questions by VAS), and a review of side effects. A link to the questionnaires will be emailed to patients via RedCap. By clicking the link, patients will be able to answer the questionnaires using either a mobile device or a desktop computer. If a patient does not respond in 24 hours, another email with link to questionnaires will be sent as a reminder. After three attempts, if there is still no reply, the patient will be contacted via phone to collect the answers to questionnaires.

Final evaluation (Visit 3, Time: Week 6)

Length of visit: 30-60 minutes.

Subjects will have a medical history and physical examination. Disease activity is assessed through physical examination and questionnaires. Three milliliters of venous blood will be drawn and tested for CRP and sedimentation rate. Patient will also be given questionnaire regarding user experience with remote collection of PROs.

2.3 Study Visits (Stage II)

The specific time for study visits will be based on results from Stage I.

2.4 Study Personnel

Subjects will be examined by the same rheumatologist throughout the study. Subjects will continue to receive standard AS care from their rheumatologist, who will make treatment

decisions based on his or her clinical judgment. The decision to change therapy because of increased AS activity or because of medication side effects will be the responsibility of the subject's rheumatologist. In some cases, the treating rheumatologist may also be the study investigator. In cases where the study investigator is not the treating rheumatologist, procedures for communicating about changes in AS activity and in medication will be established so clinical evaluations and withdrawal from blinded treatment (if necessary) can be done expeditiously.

2.5 Blinding and Unblinding

Subjects, their treating rheumatologists, study investigators will be blinded to treatment assignment. Study drug is prepared by the pharmacist at CUMC research pharmacy who is unblinded but has no direct interaction with subjects. Subjects will also be blinded to their laboratory test results.

Except in the event of an emergency, study drug codes will not be available to blinded personnel until after the conclusion of the trial during data analysis.

Unblinding may be required in the event of a suspected medication-related adverse event or medication-related complication, such as GI bleeding. For a subject who becomes unblinded for a medical emergency, he or she will discontinue study medication for the duration of the study but will remain in follow-up. All study investigators will be notified of the unblinding and information regarding the date, time, and reason for unblinding will be documented in the case report form.

2.6 Randomization

Subjects will receive a unique identifying number at study entry. For Stage 1, the study ID will be N101, N102, N103… For Stage 2, the study ID will be N201, N202, N203…Once assigned, a subject identifying number cannot be reused. At visit 2, enrolled subjects who meet eligibility criteria with confirmation of ongoing AS activity will receive a randomized treatment allocation. Subjects are randomized in a 1:1:1:1 ratio to receive one of the four study NSAIDs (celecoxib, meloxicam, diclofenac, indomethacin), respectively. The randomization table will be computer-generated, and will then be sent by a statistician who is not related to the study directly to the pharmacy department for treatment allocation. Randomization data will be kept strictly confidential—accessible only to authorized persons—until the time of unblinding.

4.7 Study Evaluation

Primary Endpoint: The primary endpoint of the study is the change of pain score on visual analog scale from Week 4 to Week 6. The null hypothesis that no clinically significant difference can be detected at week 4 and week 6.

Secondary Endpoint: The secondary endpoints include patient global score (VAS), BASDAI, and BASFI. In addition, patient global assessment of response to therapy (PGART), by a 0-4 Likert scale, physician global assessment, ASDAS, CBC, ESR, CRP, adverse events.

3. INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria:

Study subjects will be outpatients who are seen at CUMC rheumatology clinic with:

1. a clinical diagnosis of AS by treating rheumatologists, or a diagnosis of axial SpA with a pelvis MRI with significant bone marrow edema on STIR sequences;
2. minimum of 18 years old;
3. are taking NSAIDs on a regular basis for AS or SpA (defined as more than 20 days in the past month) and willing to withhold medication for one week; or having active symptoms that require initiation of NSAIDs;
4. if using antirheumatic drugs concomitantly, stable dose for the past three months;
5. have active disease after initial washout period, defined by BASDAI >=4/10, or back pain VAS >=4/10.

Exclusion Criteria:

1. Patients who have concurrent rheumatic diseases other than AS or axial SpA;
2. Patients who have oral corticosteroid in the past two weeks; patients who have acute peripheral arthritis.
3. Patients with a fibromyalgia score >= 13.
4. Use of low dose of aspirin (<100mg daily) is allowed in the study.

Study entry is not limited by gender or ethnicity. Children are excluded because inflammatory polyarthritis developing before age 16 is considered juvenile idiopathic arthritis and not AS.

Participants will largely be recruited from CUMC rheumatology clinic. To identify potential subjects, investigators may search rosters of patients in the practice for subjects who meet the inclusion criteria. The number of patients screened and reasons for exclusion will be tabulated. Subjects may also be recruited by physician referral. Information about the study will be mailed to local rheumatologists and posted on the CUMC rheumatology website. We do not anticipate self-referral of subjects but eligible self-referred subjects will not be excluded.

Participants who completes the study, and express their interest to be enrolled for a second time to try a different NSAIDs would be allowed. However, one participants may not enter the study for more than two times.

4. MONITORING SUBJECTS AND CRITERIA FOR WITHDRAWAL

Subjects will be monitored for safety by the study investigator. Subjects will be interviewed regarding potential adverse events related to the study medication at each clinic visit and via emailed questionnaires, and will be asked to contact study investigators if any medication-related adverse events occur between study visits. In these cases, subjects will have a clinical assessment as indicated by the nature of the event. Subjects will be asked to contact investigator to report any worsening of arthritis symptoms during 6 weeks of treatment. Subjects will be asked to report any missed medication doses and reasons for missed doses.

Subjects will be withdrawn from study if they 1) worsening of symptoms, defined by increase in pain VAS by 10/100mm and increase of BASDAI by 1/10 at Week 4; or 2) develop adverse events related to the study medication; or 3) if they become pregnant; 4) they develop a comorbid illness that precludes treatment with NSAIDs.

Subjects may be withdrawn from the study if they fail to comply with study requirements, including failure to attend scheduled follow-up visits, to continue treatment, or to

answer email questionnaires. Reasons that a subject may discontinue participation in the study may include: protocol violation, adverse event(s), lost to follow-up, consent withdrawn, administrative problems, or death. Subjects may also be withdrawn at the discretion of the investigators.

5. DATA ANALYSIS

5.1 Statistical Analysis

The study is designed to test whether the change of pain score from 4 weeks to 6 weeks after initiation of NSAIDs is clinically important.

The primary analysis will be pooled result from patients randomized to different NSAIDs, and will be limited to patients who complete the 6-week study medications. The study is not designed to compare medication efficacy.

5.2 Sample size and Statistical Power

We will test the null hypothesis that no clinically significant difference can be detected at week 4 and week 6. For sample size calculation, we use paired *t*-test to compare the change of pain score from baseline to 4 weeks and 6 weeks. For α=0.05, two-sided, β=0.2, minimal clinically important difference for pain = 17/100 (20), standard deviation of change of pain score 22-30/100 (estimates from our systemic review), the sample size will be 15-26. Given the consideration that 1) patients who give the consents may not pass the screening visits, 2) unable to complete the study due to loss of follow up and/or medication side effects, we plan to recruit 40 patients.

6. HUMAN SUBJECT PROTECTIONS

6.1 Selection

All subjects will have AS, be age 18 years or older, and be active at screening visit. Subjects without a diagnosis of AS and those not active will be excluded. Pregnant women will be excluded due to potential side effect. Human subjects must be used for this study because the questions concern the treatment of AS in humans. Other vulnerable populations—those who may be easily coerced (e.g. prisoners) or unable to provide informed consent—will not be enrolled.

Subjects of both genders and all ethnic groups will be eligible to participate. Based on the epidemiology of AS, we anticipate that approximately 70% of subjects will be men and 30% will be women. We anticipate the distribution of ethnicities of subjects will reflect the distribution of ethnicities in the local community. There will be no exclusions based on gender or ethnicity.

6.2 Benefits and Risks

Benefits. Subjects may not receive any direct benefit from participating in this study. It is possible that subjects who participate and respond to the study drugs and achieve remission. Subjects may also benefit from receiving medication at no charge during the study period. All subjects may benefit from knowing they are helping us understand the management and pathogenesis of AS, which may help us better treat patients in the future.

Risks/Discomforts. Risks to subjects from the study medication are no different from the risks they have accepted when agreeing to be treated with NSAIDs. These include an increased risk

of GI bleeding, headache, hepatic and/or renal toxicity, increase of blood pressure. A risk specific to this research is worsening of spinal symptoms during the washout period (1 week), or no improvement on spinal symptoms within the study period (6 weeks). If a subject experiences increased symptoms of AS 2 weeks after initiation of treatment, they will receive prompt treatment by his or her rheumatologist, and may withdraw from the study.

Risks related to phlebotomy and intravenous catheter placement include temporary pain at the site, local bruising, and low probabilities of infection, dizziness, and fainting. Standard aseptic technique will be used. Physical risks related to radiography include exposure up to 0.0012 rem, which is less than one-third of one percent of the average level of natural background radiation exposure to a United States resident over one year (0.36 rem).

Interventions. Participants will continue to receive standard medical care from their rheumatologist and/or primary care physician.

Confidentiality and Disclosure. Information obtained in this study will be available only to study investigators. All clinical data will be stored in locked cabinets and in secured computer files and storage media. RedCap will be regulated by password protected access, with viewing privileges restricted to database administrator and the PI or designees. Computer files will include a unique subject identifying number to allow for coded data analysis by statisticians. The key linking subjects' identities with the study number will be kept securely by the Principal Investigator. All publications and reports will be based on aggregate data and will not contain identifying information about individual subjects.

Subjects will be informed that their data and samples will be retained for future studies. They will also be informed of their right to have their blood samples destroyed at any time in the future, but any study data will be retained.

6.3 Adverse Event Reporting

At each study visit, safety assessments will consist of monitoring and recording all adverse events (whether volunteered by the subject, discovered by investigator inquiry, or detected through physical examination, laboratory testing or other means) on the adverse event page of the case report form. An adverse event is defined as any unfavorable or unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome, or disease which occurs during the study, having been absent at baseline, or, if present at baseline, appears to worsen. As much as possible, each adverse event will be described by: (1) its duration, (2) the severity grade (mild, moderate, severe), (3) its relationship to the study drug (suspected/not suspected), and (4) the action(s) taken and, as relevant, the outcome. All adverse events will be followed as appropriate. Events involving adverse drug reactions, illnesses with onset during the study, or exacerbations of pre-existing medical illnesses will be recorded. Exacerbation of pre-existing medical illnesses, excluding the disease under study, is defined as a clinical manifestation (symptoms and/or signs) of the illness that indicates a significant increase in the severity of the illness as compared to the severity noted at the start of the trial. It may include worsening or increase in severity of symptoms and/or signs of the illness, increase in frequency of symptoms and/or signs of an intermittent illness, or the appearance of a new manifestation and/or complication.

Serious adverse events (SAE) are defined as any untoward medical occurrence that results in death, is life-threatening (defined as at immediate risk of death in view of the

investigators), requires hospitalization longer than 24 hours or prolongs existing hospitalization, results in permanent, persistent or significant disability/incapacity, results in a congenital anomaly or birth defect, or is any other condition which in the judgment of the study investigators represents a significant hazard. All study investigators will be notified immediately of any SAE. SAEs at any study site will be reported in writing within 7 days to CUMC IRB in the case of death or life-threatening serious adverse events, and within 15 days of occurrence for all other forms of SAE.

Expected, non-serious adverse events related to the study procedures will not be reported. These include risks related to phlebotomy—temporary pain at the site of the needle-stick, local bruising, dizziness, fainting, and local infection. Unexpected, non-serious adverse events represent those not meeting the criteria for SAE noted above. These events, occurring at any study site, will be included in the summary report of all adverse events and presented to the DSMC for review at scheduled times and at the annual IRB review.

6.4 Safety and Monitoring

The Principal Investigator will have overall responsibility for monitoring scientific integrity and patient safety for the full duration of the study.

While the risks and safety concerns for the current study are small to minimal, the PI will nonetheless meet weekly with the research coordinator and staff in CUMC Rheumatology Clinic to discuss study accrual and progress, patient safety and adverse events, and data management and security. These issues will be addressed annually for protocol renewal and for progress reports required for the Institutional Review Boards at CUMC. In the unlikely event that an adverse event during study procedures were to occur, an adverse event report will be generated and completed by the PI for submission to the CUMC Institutional Review Board.

7. REFERENCES

1. Ward MM, Kuzis S. Medication toxicity among patients with ankylosing spondylitis. Arthritis Rheum. 2002 Jun 15;47(3):234–41.

20. Tubach F, Ravaud P, Martin-Mola E, Awada H, Bellamy N, Bombardier C, et al. Minimum clinically important improvement and patient acceptable symptom state in pain and function in rheumatoid arthritis, ankylosing spondylitis, chronic back pain, hand osteoarthritis, and hip and knee osteoarthritis: Results from a prospective multina. Arthritis Care Res. 2012 Nov;64(11):1699–707.