Study Title

Musculoskeletal Ultrasound Assessment of Therapeutic Response of Tofacitinib in Rheumatoid Arthritis Patients

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Musculoskeletal Ultrasound Assessment of Therapeutic Response of Tofacitinib in Rheumatoid Arthritis Patients

Pfizer Study Drug
Tofacitinib (Xeljanz®)

Support Provided By
Pfizer

Investigator
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Study Type
Open-label Pilot Study

Grant Request
We are requesting both funding and drug

Research Setting
Single Site at UCLA

Country of Primary Site
USA

Brief Study Synopsis:

A. Utility of Musculoskeletal Ultrasonography in RA Therapeutic Response

Advances in drug development of small molecules, biologic agents, and disease modifying anti-rheumatic drugs (DMARDs) have improved disease activity, quality of life, and imaging outcomes in rheumatoid arthritis (RA). Although radiographic assessments of joint space narrowing and erosions of the hands/feet are considered the gold standard imaging outcome measure, musculoskeletal ultrasound (MSUS) is quickly becoming a valuable imaging modality to diagnose rheumatic disorders and monitor therapeutic response.

MSUS use by rheumatologists is rapidly growing in the USA [4]. Ultrasound offers, for both patient and clinician, a safe, sensitive, cost-effective, and convenient modality for detection of synovitis. Importantly, sonography can be utilized at point of care and does not require use of contrast to detect vascularity. A recent ACR whitepaper outlined the current status of the use of sonography in American Rheumatology practice. This paper and others have summarized the validity of use of musculoskeletal ultrasound in RA clinical trials studying the response to therapeutic agents [5-7]. MSUS is more sensitive than x-ray in detecting erosions and it has the added advantage at inferring inflammation in synovial tissues by detecting blood flow in tissues without the use of contrast agents. We hypothesize that MSUS derived measurements of synovitis (power Doppler [PDUS] and grey scale synovial hypertrophy [GSUS]) will serve as an early imaging marker of rheumatoid arthritis (RA) clinical response to treatment with tofacitinib. Studies have yet to examine the utility of performing US to determine early RA therapeutic response in tofacitinib, thus a unique opportunity for investigation.

As stated earlier, radiographic assessments of joint space narrowing and erosions of the hands/feet (measures of damage) are considered the gold standard imaging outcome measurement, largely because these measures are validated to measure change in randomized controlled trials (RCTs), with change shown to be associated with function and disability. However, appropriate and judicious use of RA therapeutics has improved outcomes to the point that radiographic progression is halted in a majority of patients. In order to show a difference in structural damage between 2 active RA treatments arms with radiographs requires a large sample size, and more importantly, this lack of sensitivity doesn't allow use of radiographs to facilitate treatment decisions. Additional consideration for treatment decisions is that clinical composite measures such as DAS28, CDAI, and RAPID3 may not adequately reflect the totality of intra-articular inflammation contributing to joint damage. Understandably, the use of musculoskeletal US in detecting synovial vascularity and hypertrophy is rapidly becoming a valuable imaging modality to sensitively assess therapeutic response in RA [8, 9].

Sonography may also be useful in assessing response, where suppression of PDUS signal after administration of biologic agents suggests response to therapy [11, 14], and persistence of Doppler signal may predict the risk of progressive erosive disease. It is this feature that we hypothesize will be useful in determining which patients may or may not respond to tofacitinib. Kume et al demonstrated the rapid response to 8mg/kg (maximum dose 800mg) Tocilizumab in biological therapy naive RA

patients who were non responsive to low dose prednisone and methotrexate. The investigators were able to predict DAS28 response at 24 weeks based on Doppler activity at two weeks. Non responders did not show any change in Doppler activity at two weeks [15]. Similar findings have been reported by other investigators who treated patients with active RA with other biologic and DMARD agents, though not yet with tofacitinib [11-13].

B. Utility of Vectra DA in RA Therapeutic Response

Regrettably, there is no single laboratory, clinical or imaging measure that accurately anticipates response to therapy for patients with RA. Instead, complex composite disease activity measures (Disease Activity Score [DAS28/ESR]), quality of life measures (Health Assessment Questionnaire-Disability Index [HAQ-DI]), and x-ray progression of disease (Sharp Scores) are all used simultaneously as outcome measures in clinical trials. Understandably, there is a strong push to find appropriate and feasible biomarkers in patients with RA that can predict early response to therapy. Some biomarkers have been suggested for evaluating early therapeutic response, i.e. C-Reactive Protein (CRP); however, due to the poor specificity of the tests they have only been used in combination with other clinical and imaging measures. The ability to detect which RA patients will be responders would be a significant advance in the management of RA.

The multi-biomarker disease activity (MBDA) blood test (VectraDA TM; Crescendo Bioscience, Inc., South San Francisco, CA) is currently commercially available to assess RA disease activity. Serum from peripheral blood is processed and assayed for 12 protein biomarkers (VCAM-1, EGF, VEGF-A, IL-6, TNF-RI, MMP-1/3, YKL-40, Leptin, Resistin, SAA, and CRP). An algorithm of these 12 markers is utilized to characterize RA disease activity on a scale of 1-100 (the higher the number represents more disease activity). Due to ease of performing and interpreting the test, many community rheumatologists utilize this test to evaluate disease activity in their RA patients. However, much more work is needed to fully validate the use of MBDA. Due to intriguing recent data, the MBDA is gaining more notice by academicians that this biomarker may aid in therapeutic management of the RA patient. Based on several studies, correlation between DAS28, SDAI, and CDAI with the MBDA is moderate to good ranging from 0.5-0.84. Curtis et al in 2012 published findings that the MBDA correlated well with seropositive and seronegative RA patients. In addition, changes in MBDA scores at 6-12 weeks were significantly associated with ACR50 response rates and change in DAS28-CRP. MBDA was also assessed in a subcohort of the CAMERA study at baseline and 6 mos. In a multivariate analysis, a modified MBDA score (without CRP) was an independent predictor of disease activity, while CRP was not. Lastly, in a study published by van der Helm-van Mil et al., MBDA cut off of $\leq$25 was associated with limited radiographic progression over 12 months in the Leiden Early Arthritis Cohort. Patients who were in DAS28-CRP remission but had >25 MBDA scores were at an elevated risk for continued radiographic progression.

C. Proposal: Utilization of Both MSUS and MBDA to Evaluate Response to Therapy with Tofacitinib

[redacted]

Brief Study Rationale/Objectives:

This is a pilot open-label trial of 25 RA patients treated with tofacitinib over 3 months. The patients meeting inclusion criteria will be started on tofacitinib 5mg po bid. Patients will be recruited from the UCLA Rheumatology Clinics. Inclusion criteria will include the following: meeting ACR 1987 RA criteria, DAS28≥3.2, age≥18, and PDUS≥10 (see below for more details). Patients who are deemed unsafe to enroll will be excluded. Ultrasound measures (PDUS/GSUS) and MBDA scores will be obtained at screen, baseline, 2 weeks, and 3 months. In addition, we will also obtain HAQ-DI, CDAI, and DAS28 at the same time points. In addition, we will have a 6 week visit for capturing adverse events, concomitant drugs, drug dispensation, and evaluation of adherence. Currently, there are several US measures to evaluate therapeutic response in RA patients that have been used in the literature. Some US studies evaluate all joints involved in RA, which is time consuming. At present, there is no consensus as to the ideal ultrasound scoring system. However, we will utilize a 34-joint US scoring system to evaluate response to therapy in this proposal (see Table 1). Our research team has expertise in MSUS (given several workshops/lectures nationally) and we have proficiency in designing/conducting MSUS clinical trials. We currently have 4 ultrasonography-rheumatologists at UCLA who are ACR certified in MSUS.

Table 1

JOINT	VIEW	Power Doppler Synovitis	B-mode Synovial Hypertrophy
[redacted]	[redacted]	X	X
[redacted]	[redacted]	X	X
[redacted]	[redacted]	X	X
[redacted]	[redacted]	X	X
[redacted]	[redacted]	X	X

[redacted]	[redacted]	X	X
	[redacted]	X	X

Primary Aims:
AIM 1: To determine whether MSUS inflammatory scores (PDUS and GSUS) or MBDA improve in response to treatment with tofacitinib over 3 months.

AIM 2: To assess the association between the change in ultrasound measures/MBDA and change in DAS28-ESR and/or CDAI.

Exploratory Aims:
AIM 3: [redacted]

AIM 4: [redacted]

Primary Endpoints
3 month change in MSUS power Doppler
3 month change in MBDA
3 month change in DAS28/ESR
3 month change in CDAI

MSUS Outcome measures: Total power Doppler synovitis score of 34 joints (range 0-102), Total B-mode synovial hypertrophy score of 34 joints (range 0-102), Composite of power Doppler + synovial hypertrophy of 34 joints (range 0-204)

Statistical Methods
Sample size is for the primary endpoint of change in PDUS scores from baseline to month 3.
We based our sample sizes on the ultrasound and disease activity data collected from another IIR (unpublished). Mean PDUS scores changed from 7.3 to 3.9 after 3 months of treatment with a standard deviation of the changes of 3.3. Assuming this same effect size and with 25 total patients we estimate 99% power to detect differences in PDUS from baseline to month 3 assuming a two-sided paired t-test with 0.05 level of significance. If 25% attenuation in effect size is observed, our sample of 25 will have 95% power to detect differences in PDUS from baseline to month 3 assuming a two-sided paired t-test with 0.05 level of significance.
A Pearson correlation coefficient of 0.51 was observed between PDUS and DAS28/ESR at baseline in the other IIR cohort. Based on this correlation coefficient, we estimate that we will have 77% power to detect correlation between DAS28/ESR and

PDUS with a sample size of 25, assuming a two-sided Pearson correlation with 0.05 level of significance.

Aim 1. We will use Wilcoxon signed rank tests to compare MSUS and MBDA scores between baseline and the 3 month time points.
Aim 2. We will use linear regression to model the outcomes of change (baseline - 3 months) in disease activity measures (DAS-28 and CDAI). The independent variables to be considered in these models will be change in MSUS/MBDA (baseline - 3 months) scores. Mixed effects models will also be used to assess the longitudinal association between disease activity and MSUS/MBDA scores.
Aim 3. We will use linear regression to model the outcomes of change (baseline - 3 months) in disease activity measures (DAS-28 and CDAI). The independent variables to be considered in these models will be change in MSUS/MBDA (baseline - 2 week) scores. For each of the outcomes we will use forward stepwise model selection to identify the best combination of MSUS/MBDA measures to predict response. We will assess the predictive ability of the marker by computing the model R-squared and the estimated prediction accuracy (median absolute residuals).
Aim 4. We will use Spearman correlation coefficients to evaluate the correlation between baseline, 2-week, and baseline-2 week MSUS scores versus MBDA.

Inclusion/Exclusion Criteria

Inclusion Criteria:

1) Patient must meet 1987 ACR criteria
2) Age $\geq$ 18 years of age
3) Baseline DAS28/ESR$\geq$3.2
4) Stable concomitant DMARDs for more than 1 month (methotrexate, leflunomide, plaquenil, sulfasalazine, or no DMARDs). However, if the patient is not on DMARD, history of DMARD use required. If not on DMARD, the patient can opt for monotherapy with tofacitinib or combination therapy.
5) Power Doppler score of >=10 (out of 34 joints assessed)
6) Female subjects of childbearing potential must test negative for pregnancy
7) Male and female subjects of childbearing potential and at risk for pregnancy must agree to use contraception throughout the study.
8) Negative QuantiFERON Gold test performed at screening
    a. This is required unless the subject has been adequately treated for active or latent tuberculosis or a negative QuantiFERON Gold was previously performed and documented within the 3 months prior to screening.
    b. A negative tuberculin skin test (TST) <5 mm induration can be substituted for the QuantiFERON Gold

Exclusion Criteria:

1) Active TB
2) Prednisone >10 mg
3) Pregnancy or breast feeding
4) Prior treatment with tofacitinib
5) Concomitant biologic therapy (TNF inhibitors, IL-6 inhibitors, etc.)

6) Active infection with HIV, hepatitis B or C, or herpes zoster
7) Subjects with any uncontrolled clinically significant laboratory abnormality or any of the following laboratory abnormalities:
    a. Evidence of hematopoietic disorder or hemoglobin <9 g/dL
    b. Absolute lymphocyte count <0.75 x 109/L (<750/mm3)
    c. Absolute neutrophil count <1.2 x 109/L (<1200/mm3)
    d. Platelet count <100 x 109/L (<100,000/mm3)
    e. Alanine aminotransferase (ALT), or aspartate aminotransferase (AST) >1.5 times the upper limit of normal (x ULN)
    f. Estimated GFR <40 ml/min
8) Subjects who have received live or live attenuated vaccines within 6 weeks prior to the first dose of study drug (or the zoster vaccine)
9) Subjects who require concomitant treatment with medications that are potent inhibitors of cytochrome P450 3A4 (CYP3A4), both moderate inhibitors of CYP3A4 and potent inhibitors of CYP2C19, and potent CYP inducers (See Appendix)

Table 2

Procedure	**Pre-Treatment Screening Visit 1**	**During Treatment Visit 2 Baseline Visit**	**During Treatment Visit 3 2 Week Visit**	**During Treatment Visit 4 6 Week Visit**	**During Treatment Visit 5 12 Week Visit**	**Safety Follow-up**
Visit Time Window			+/- 2 weeks	+/-2 weeks	+/- 2 weeks	
Eligibility Assessments						
Informed Consent	X					
Inclusion/Exclusion Criteria	X	X				
Medical History	X					
Safety Assessments						
Chest X-ray (if not done within 3 mos)	X					
QuantiFERON(if not done within 3 mos) [a]	X					
Physical Examination	X					
Targeted Physical Examination		X	X		X	
Vital Signs	X	X	X	X	X	

Procedure	**Pre-Treatment Screening Visit 1**	**During Treatment Visit 2 Baseline Visit**	**During Treatment Visit 3 2 Week Visit**	**During Treatment Visit 4 6 Week Visit**	**During Treatment Visit 5 12 Week Visit**	**Safety Follow-up**
Concomitant Medication	X	X	X	X	X	
Assessment of Signs and Symptoms		X	X		X	
Adverse Events Assessment		X	X	X	X	X
CBC and Chem Panel Tests[3]	X	X	X	(X)	X	
Lipid Panel		X			X	
Cocci IgG, IgM EIA	X					
HIV, Hepatitis B and C Serologies (if not done within 3 mos)	X					
Rheumatoid Factor and CCP	X					
hsCRP	X	X	X		X	
ESR	X	X	X		X	
Urine Pregnancy Test	X	X	X		X	
Vectra DA		X	X		X	
Biomarkers	**X**	X	X		X	
Efficacy Assessments						
Joint Assessment	X	X	X		X	
MD Global	X	X	X		X	
Patient Global	X	X	X		X	
CDAI	X	X	X		X	
DAS28/ESR	X	X	X		X	
HAQ-DI and other questionnaires	X	X	X		X	
Ultrasound 34 joint Acquisition	X	X	X		X	

Procedure	Pre-Treatment Screening Visit 1	During Treatment Visit 2 Baseline Visit	During Treatment Visit 3 2 Week Visit	During Treatment Visit 4 6 Week Visit	During Treatment Visit 5 12 Week Visit	Safety Follow-up
Ultrasound 34 joint Scoring	X	X	X		X	

[a.] If QuantiFeron test cannot be performed, TB skin test can be done instead.

1. If a chest X-ray or CT scan of chest was done within the past 3 months, there is no need to repeat.
2. CBC and Chem panel laboratory tests do not have to be done if they were done within the past 4 weeks.
3. Hepatitis B and C serologies do not have to be done if they were done within the past 3 months.
4. Rheumatoid Factor and CCP test do not have to be done at screening if they were done previously.
5. CBC and Chem panel at the 6-week visit may be done per PI discretion.

** Study procedures may be repeated per PI discretion.

Target Enrollment
We plan to enroll 25 patients

Treatment Plan or Dosing Regimen
Open label tofacitinib 5mg po bid

Study Duration
3 months

Appendix: Prohibited Concomitant Medications

Prohibited drugs, including investigational compounds, require discontinuation for at least 7 days or 5 half-lives (whichever is longer) prior the baseline visit. Only systemically administered drugs listed below are prohibited; topical, ophthalmic, or intravaginal administration is allowed.

Prohibited Concomitant Medications

Potent CYP3A/CYP2C19 Inhibitors	Moderate or Potent CYP3A Inducers
Protease inhibitors:	Protease inhibitors:
indinavir (Crixivan)	efavirenz (Sustiva)*
nelfinavir (Viracept)	nevirapine (Viramune)*
ritonavir (Kaletra, Norvir)	Anticonvulsants:
Saquinavir (Invirase)	barbiturates*
Macrolide antibiotics:	phenobarbital*
clarithromycin (Biaxin, Prevpac)	phenytoin (Dilantin, Phenytek)
telithromycin (Ketek)	carbamazepine (Carbatrol, Tegretol)*
Other antibiotics:	Antibiotics:
chloramphenicol	rifampicin/rifampin (Rifadin, Rifamate)
Antifungals:	rifabutin (Mycobutin)*
fluconazole (Diflucan)	rifapentene (Priftin)*
voriconazole (Vfend)	
ketoconazole (Nizoral)	Antidepressants:
itraconazole (Sporanox)	St. John's Wort*
Antidepressants:	Other compounds:
fluvoxamine (Luvox)	modafinil (Provigil)
nefazodone (Serzone)	troglitazone (Rezulin)