ULTRASOUND IN PSORIATIC ARTHRITIS TREATMENT

UPSTREAM

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INTRODUZIONE

L'Artrite Psoriasica (PsA) è una malattia infiammatoria sistemica con impegno articolare ed extra- articolare. Attualmente, studi osservazionali prospettici su gruppi di pazienti affetti da PsA hanno identificato possibili fattori prognostici associati al raggiungimento della remissione. Sebbene la PsA comporti una disabilità funzionale comparabile a quella dell'artrite reumatoide, gli studi sui fattori prognostici su questa patologia risultano ancora limitati. Oltre ai tradizionali fattori prognostici clinici, in un prossimo futuro l'*imaging* ed in particolare l'ultrasonografia (US) potranno svolgere un ruolo chiave nell'identificare fattori prognostici aggiuntivi ai tradizionali fattori clinici. Negli ultimi anni il ruolo della diagnostica per immagini è infatti cresciuto e, ad esempio, le raccomandazioni della *European League against Rheumatism* (EULAR) hanno riconosciuto la maggiore sensibilità di US nel rilevare l'attività dell'impegno articolare periferico rispetto all'esame clinico. L'integrazione tra clinica e *imaging* sarà quindi un'importante sfida nel prossimo futuro.

OBIETTIVO PRIMARIO

Il presente studio si propone di valutare, in pazienti affetti da PsA con malattia periferica attiva che iniziano una nuova terapia, il valore aggiunto dell'US rispetto alla clinica nell'identificare i pazienti che raggiungono la Minimal Disease Activity (MDA) al sesto mese.

DISEGNO DELLO STUDIO

Lo studio segue un disegno osservazionale, prospettico e multi centrico.

SELEZIONE DEI CENTRI

Tutti i membri della Società Italiana di Reumatologia saranno invitati a partecipare allo Studio "*Ultrasound in PSoriatic arthritis TREatMent*" - UPSTREAM. Allo scopo di migliorare la validità e l'affidabilità dei risultati, i partecipanti saranno selezionati sulla base di tre pre-requisiti: disponibilità locale di un ecografo di alta fascia (inclusa la presenza di una sonda ad alta frequenza >14MHz); esercizio di *reliability* su immagini statiche con una riproducibilità elevata (kappa > 0.7) rispetto ad un "*gold standard scorer*"; valutazione della qualità delle immagini US delle lesioni tipiche per PsA.

PAZIENTI E METODI

CRITERI DI INCLUSIONE:

- Adulti > 18 anni con PsA (in accordo con i criteri della classificazione CASPAR);
- almeno un'articolazione coinvolta clinicamente (tumefatta e dolorabile);
- soggetti che iniziano un nuovo ciclo di terapia con FANS, iniezioni con steroidi (monoterapia), cDMARDs, bDMARDs, (inclusi *switch* e aumento di dosaggio) come da pratica clinica;
- se già in trattamento la terapia deve essere stabile nelle 6 settimane precedenti;
- firma del consenso informato.

VALUTAZIONE CLINICA

La valutazione clinica dei pazienti sarà effettuata in accordo con i principali domini proposti dal *Group for Research and Assessment of Psoriasis and Psoriatic Arthritis* (GRAPPA) e dell'*Outcome Measures in Rheumatology* (OMERACT).

VALUTAZIONE ULTRASONOGRAFICA

La valutazione ultrasonografica sarà effettuata da un medico esperto in ultrasonografia valutando 44 articolazioni, 36 tendini, 12 entesi e 2 borse secondo lo score elaborato per l'artrite psoriasica dal Gds di ecografia della Società Italiana di Reumatologia (US-score PsA-SIR).

RISULTATI ATTESI

UPSTREAM fornirà evidenza sui predittori clinici ed ecografici di risposta clinica, misurate come il raggiungimento della MDA in pazienti con PsA caratterizzata da artrite periferica attiva. L'identificazione dei fattori prognostici che permettono di ottenere una remissione o una bassa attività della malattia, permetterà una migliore selezione dei pazienti con fattori prognostici sfavorevoli ed un conseguente miglioramento della strategia di cura. Questo studio risponde alla necessità di un trattamento su misura che permetterà ai medici di applicare una medicina più efficace e personalizzata, focalizzandosi sulla utilità di un esame ecografico nella valutazione e nella gestione del paziente con PsA.

ABSTRACT

BACKGROUND

Psoriatic arthritis (PsA) is a systemic inflammatory disease with articular and extra-articular features. Establishing the prognosis of a patient with PsA is hence important to define the treatment strategy. Currently, observational and prospective cohort studies have identified prognostic factors correlating with the achievement of therapeutic response. Nevertheless, despite the importance of identifying prognostic factors in a disease with a functional disability comparable to rheumatoid arthritis, the studies are still limited. Furthermore in the last years the role of imaging has grown up and European League against Rheumatism (EULAR) recommendations on the use of imaging techniques recognize the high sensitivity of ultrasound (US) to detect disease activity better than clinical examination and integrating imaging in clinical practice is the challenge of the near future.

PRIMARY OBJECTIVE

In PsA with clinically active joint disease starting a new course of therapy, to evaluate the additional value of US-score over clinical examination in detecting patients achieving MDA at 6 months.

STUDY DESIGN

The study follows a multi-centre observational prospective cohort study design.

CENTRE SELECTION

All the members of the Italian Society of Rheumatology will be invited to participate to the "Ultrasound in PSoriatic arthritis TREatMent " - UPSTREAM study. In order to increase the validity and reliability of the results, the participants will be selected based on three prerequisites: local availability of a high level US machine including high level US probes (>14MHz); reliability exercise on static images with a kappa statistics value >0.7 compared with a 'gold standard' scorer; quality assessment of US images of PsA lesions.

PATIENTS AND METHODS

INCLUSION CRITERIA

- Adult > 18 years of age with PsA (PsA according to the Caspar classification Criteria with joint involvement)
- At least one joint clinically involved (both swelling and tenderness);
- prescription of new course of d NSAIDs (monotherapy), steroid intra-articular injections (monotherapy), cDMARD, bDMARDs, including switches or dose augmentations indicated by the treating rheumatologist according to usual clinical practice before US acquisition;
- Stable treatment before treatment modification (6 weeks);
- Signed informed consent form.

CINICAL ASSESSMENT

Patient's clinical assessment will be performed according to the core set of domains for PsA proposed by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and Outcome Measures in Rheumatology (OMERACT).

ULTRASOUND ASSESSMENT

Sonographic evaluations will be performed by expert ultrasonographers in 44 joints, 36 tendons, 12 entheses and 2 bursae according to the score developed for psoriatic arthritis by the study group ultrasound of the Italian Society of Rheumatology (US-score PsA-SIR)

EXPECTED RESULTS AND SIGNIFICANCE

The aim of this study is to identify clinical and US predictors of achieving MDA in PsA patients with active peripheral arthritis starting a new course of therapy. Identifying prognostic factors of achieving remission or low disease activity will allow a better selection of patients with poorer outcome and a following improvement of the therapeutic strategies. This study will respond to the need of tailoring treatment that would allow clinicians to practice a more effective and personalized medicine, optimizing the outcomes of patients with PsA as well as the treatments management, focusing on the clinical usefulness of US examination in PsA patient management.

BACKGROUND

Psoriatic arthritis (PsA) is a systemic inflammatory disease with articular and extra-articular features. Traditionally, five general patterns can be distinguished: symmetric polyarthritis, asymmetric oligoarthritis, mutilans arthritis, arthritis of the distal interphalangeal joints and spondylitis.[1] To date remission is considered to be the ultimate goal of therapy in PsA, however, due to the characteristics of the disease with involvement of different domains, remission may be difficult to achieve and maintain and so a minimal disease activity (MDA) could be an acceptable goal.[2,3] In view of the therapeutic target of remission or MDA, the identification of adverse prognostic factors and the best treatment strategy are two of the most important items in research agenda of PsA.[3]

Establishing the prognosis of a patient with PsA is hence important to define the treatment strategy. Currently, observational and prospective cohort studies have identified prognostic factors correlating with the achievement of therapeutic response. Nevertheless, despite the importance of identifying prognostic factors in a disease with a functional disability comparable to rheumatoid arthritis (RA), the studies are still limited.[4] Recently, Eder et al. demonstrated that overweight and obesity, female gender, old age and a longer duration of the disease were associated with a lower probability of achieving sustained MDA.[5] Furthermore, in accordance with the criterion the sooner the better in the Swedish Early Psoriatic Arthritis register, a shorter delay between the onset of symptoms and diagnosis was a predictor for MDA.[6] Moreover, low Health Assessment Questionnaire (HAQ) at baseline was identified with a better response in PsA.[7,8] Recently the RA-derived concept of treat-to-target (T2T) was applied in early PsA and this strategy significantly improved the therapeutic response.[9] Nevertheless, radiographic progression did not differ in the various strategies and also in the tight control group there were more adverse events and higher costs. Undoubtedly, the concept of T2T in PsA needs further studies, especially with longer follow up and larger samples.

In T2T strategies, it is necessary to quantify the disease activity and this is possible by composite indices. The heterogeneity of PsA including axial and peripheral involvement and specific features (i.e. dactylitis, enthesitis) as well as extra-articular features makes the use of a single composite index (e.g. Disease Activity for Psoriatic Arthritis-DAPSA, Composite Psoriatic Disease Activity Index-CPDAI) a challenge not resolved yet. An interesting possibility is to integrate musculoskeletal ultrasonography (US) with clinical examination to stratify patients and to decide treatments in a T2T strategy. In the last years the role of imaging is grown up and EULAR recommendations on the use of imaging techniques in chronic arthritis recognize the high sensitivity of US to detect disease activity better than clinical examination alone [10,11] although the utility of US in clinical practice is not supported by sufficient evidence yet.[12]

In PsA but also in chronic arthritis in general, integrating imaging in clinical practice is the challenge of the near future and for clinical feasibility it is essential to identify an US composite score that could explore all the domains of the disease, especially in the polymorphic PsA.

In 2012 *Gutierrez et al.* developed a Power Doppler composite score focused on joints, tendons, entheses, skin and nails and the final target was to define the overall disease activity.[13] The German US7-joints score is another viable tool for examining patients with chronic arthritis in daily practice. Developed mainly for RA, it was also effective for monitoring therapy in peripheral PsA.[14] More recently *Ficjan et al* developed two new US composite scores (PsASon-13 and PsASon-22), derived from a total ultrasound score (68 joints/14 enthesis) in order to have a high sensitivity to detect PsA features and a good feasibility in clinical practice.[15] However no simplified scores are fully validated in terms of content, construct and criterion so far. For this reason extensive US evaluations are needed to assess PsA in clinical practice and research.

AIM

The aim of this study is to identify clinical and US predictors of achieving MDA in PsA patients with active peripheral arthritis starting a new course of therapy.

Identifying prognostic factors of achieving remission or low disease activity will allow a better selection of patients with poorer outcome and a following improvement of the therapeutic strategies. Furthermore the possibility that US could be an added prognostic value makes this study a clear example of integration between the clinic and US. This study will respond to the need of tailoring treatment that would allow clinicians to practice a more effective and personalized medicine, optimizing the outcomes of patients with PsA as well as the treatments management.

STUDY OBJECTIVES

PRIMARY OBJECTIVE

In clinically diagnosed PsA with clinically active joint disease starting a new course of therapy, to evaluate the additional value of US-score (US-score PsA-SIR) over clinical examination in detecting patients achieving MDA at 6 months.

SECONDARY OBJECTIVES

In clinically diagnosed PsA with clinically active joint disease starting a new course of therapy:

- to evaluate the additional value of US over clinical examination in detecting patients:
  - achieving MDA at 12 months (including sustained)
  - achieving DAPSA remission at 6 and 12-months (including sustained)
  - achieving ACR remission at 6 and 12 months (including sustained)
  - with X-ray structural progression (mSVH score) at 12 and 24 months
  - with US structural progression (US-damage score) at 12 and 24 months
  - with functional worsening (ΔHAQ>0.23) at 12 and 24 months
  - with impairment of Health Related Quality of Life (HRQoL) at 12 and 24 months;
- to evaluate the relationship between time-integrated US-detected inflammation and US-detected damage at 12 and 24 months;
- to evaluate the comparative effectiveness of different treatment strategies on MDA, DAPSA remission, ΔHAQ>0.23, X-ray progression (mSvHS), US-inflammation score, US-damage score;
- to evaluate residual US activity in patients in MDA remission;
- to explore whether clinically-detected disease activity due to joint tenderness without swelling is related to joint or extra-articular US-detected inflammation evaluated by US;
- to explore clinical features and US-lesions related to X-ray detected bony apposition.

STUDY DESIGN

The study follows a multi-centre observational prospective cohort study design.

The study is registered at Open Science Framework.[16]

PARTICIPANTS

CENTRE SELECTION

All the members of the Italian Society of Rheumatology will be invited to participate to the UPSTREAM Study. In order to increase the validity and reliability of the results, the participants will be selected based on three prerequisites:

- local availability of a high level US machine including high level US probes (>14MHz);
- reliability exercise on static images with a kappa statistics value >0.7 compared with a ‘gold standard’ scorer;
- quality assessment of US images of PsA lesions.

PATIENT SELECTION

INCLUSION CRITERIA

- Adult > 18 years of age with PsA (according to the CASPAR classification Criteria)
- Clinically active arthritis, with at least one joint clinically involved (both swelling and tenderness) in patient not achieving the MDA;
- Subject newly prescribed NSAIDs (monotherapy), steroid intra-articular injections (monotherapy), cDMARD, bDMARDs as indicated by the treating rheumatologist according to usual clinical practice before US acquisition;
- Stable treatment before treatment modification (6 weeks);
- Signed informed consent form;

STUDY PROCEDURES

RELIABILITY EXERCISE

A total of 30 static images per US-lesion type (synovitis, enthesitis, tenosynovitis, erosion, bony apposition) with 50% of presence of lesions will be submitted to scoring through an on-line electronic platform. A reference atlas will be provided to the investigators before the exercise. A second exercise could be offered to investigators who did not achieve a minimum level of kappa after further training at one of the Centres of the PIs.

SCREENING VISIT

The aim of this visit is to identify a patient who might be suitable for inclusion in the study.

- Consent: Inform the patient about the nature and objectives of the study and obtain his/her written informed consent;
- Check inclusion/exclusion criteria;
- Check cumulatively CASPAR criteria since the onset of PsA;
- Assign patient number (PN) in sequential order, if the patient is suitable for the inclusion in the study.

BASELINE VISIT

The aim of this visit is to confirm that the patient is appropriate for inclusion in the study, determine disease activity state, undertake a complete high resolution ultrasound assessment and X-ray of hands and feet. If a X-ray has been already done within the 6 months before the study entry is not requested to perform a further scanning.

- Record in Case Report Form:
    1. demographic and life-style variables *(smoking, alcohol consumption, BMI)*;
    2. drug history (*including past adverse events*);
    3. typical comorbidities associated to PsA (*obesity, diabetes, hypertension, metabolic syndrome non-alcoholic fatty liver disease, IBD, uveitis, anxiety/depression*) and other comorbidities (*e.g. neoplasms, cardiovascular disease, Charlson comorbidity index*);
    4. onset of symptoms and disease duration;
    5. define clinical subset of PsA;
    6. CPR (mg/dl), ESR;
    7. RF, ACPA and HLA B27 (if available);
    8. treatment to be started;
- Procedures for psoriatic arthritis:
    1. Swollen (68) and Tender (66) Joints Count;
    2. Entheseal assessment;
    3. Tender Dactylitis Count;

- Procedures for psoriasis:
    1. Body Surface Area (BSA);
- Questionnaires:
    1. Physician completes VAS Physician global assessment of disease activity (joint and skin) 0-100;
    2. Patients completes pain VAS (0-100), global VAS (0-100), HAQ, BASDAI, PSAID12;
- US assessment:
    1. US-score PsA-SIR;
- X-ray assessment of hands and feet:
    1. Posterior-anterior radiographic assessments of hands and feet (electronic format)

3RD MONTH VISIT

The aim of this visit is to determine disease activity state, determine the compliance and safety of the therapy.

- Record in CRF:
    1. Therapy and dose;
    2. Check adverse events;
- Procedures for psoriatic arthritis:
    1. swollen (68) and tender (66) joints count;
    2. Entheseal assessment;
    3. Tender Dactylitis Count;
- Procedures for psoriasis:
    1. BSA;
- Questionnaires:
    1. Patients completes pain VAS (0-100), global VAS (0-100), HAQ.

6TH MONTH VISIT

The aim of this visit is to determine disease activity state and in particular the achievement of MDA, determine the compliance and safety of the therapy and undertake a complete high resolution ultrasound assessment.

- Record in CRF:
    1. Therapy and dose;
    2. Check adverse events;
    3. CRP, ESR;
- Procedures for psoriatic arthritis:
    1. swollen (68) and tender (66) joints count;
    2. Entheseal assessment;
    3. Tender Dactylitis Count;
- Procedures for psoriasis:
    1. BSA;
- Questionnaires:
    1. Physician completes VAS Physician global assessment of disease activity (joint and skin) 0-100;
    2. Patients completes pain VAS (0-100), global VAS (0-100), HAQ; PsAID12
- US assessment:
    1. US-score PsA-SIR

12TH MONTH VISIT

The aim of this visits is to determine disease activity state, determine the compliance and safety of the therapy, undertake a complete high resolution ultrasound assessment and assess radiographic progression;

- Record in CRF:
    1. Therapy and dose;
    2. Check adverse events;
    3. CRP, ESR;

- Procedures for psoriatic arthritis:
    1. swollen (68) and tender (66) joints count;
    2. Entheseal assessment;
    3. Tender Dactylitis Count;
- Procedures for psoriasis:
    1. BSA;
- Questionnaires:
    1. Physician completes VAS Physician global assessment of disease activity (joint and skin) 0-100;
    2. Patients completes pain VAS (0-100), global VAS (0-100), HAQ, PsAID12
- US assessment:
    1. US-score PsA-SIR
- X-ray assessment of hands and feet.
    1. Posterior-anterior radiographic assessments of hands and feet (electronic format)

24TH MONTH VISIT – END OF STUDY

The aim of this visit is to determine final disease activity state, current therapy and assess radiographic progression.

- Record in CRF:
    1. Therapy and dose;
    2. Check adverse events;
    3. CRP, ESR;
- Procedures for psoriatic arthritis:
    1. swollen (68) and tender (66) joints count;
    2. Entheseal assessment;
    3. Tender Dactylitis Count;
- Procedures for psoriasis:
    1. BSA;
- Questionnaires:
    1. Physician completes VAS Physician global assessment of disease activity (joint and skin) 0-100;
    2. Patients completes pain VAS (0-100), global VAS (0-100), HAQ, PsAID12
- US assessment:
    1. US-score PsA-SIR
- X-ray assessment of hands and feet:
    1. Posterior-anterior radiographic assessments of hands and feet (electronic format)

CLINICAL ASSESSMENT

The demographic variables describing the patients will be age, sex, ethnic group, family history, body weight, height and smoking. On enrolment in the study, a detailed medical history will be recorded mostly focusing on PsA (onset of symptoms, date of diagnosis), related treatment (current and previous medication, reason for withdrawal) and associated comorbidities (e.g. SpA spectrum comorbidities). To assess comorbidities, disease specific recommendations will be followed.[17]

To increase feasibility and reliability metabolic syndrome will be defined as follows: 1) BMI > 30 kg/m^2; 2) a diagnosis of type 2 diabetes mellitus and 3) a diagnosis of hypertension.[18]

Each patient considered eligible for the study will be classified according to clinical subset(s) of PsA:

1- Monoarticular or asymmetric oligoarthritis with or without dactylitis.
2- Symmetric polyarthritis similar to rheumatoid arthritis.
3- Classic psoriatic arthritis confined to distal interphalangeal joints of hands and feet.
4- Spondylitis with or without peripheral joint involvement
5- Arthritis mutilans

CLINICAL EFFICACY

Clinical response and clinical remission will be based on the following variables:

1- Minimal Disease Activity (MDA)
2- Disease Activity for Psoriatic Arthritis (DAPSA)
3- ACR response score

The sonographer should be blinded to minimize bias associated with disease activity score evaluation. In addition, every effort should be made to ensure that the same member of staff performs the disease activity assessment on successive visits for a given patient.

The MDA calculation will be based on the evaluation of 7 variables:

a) 68 tender joints count (≤1)
b) 66 swollen joint count (≤1)
c) BSA ≤3
d) Patient pain VAS (≤15 mm);
e) Patient global disease activity VAS (≤20 mm);
f) HAQ (≤0.5);
g) Leeds Enthesitis Index (LEI) tender entheseal points (≤1)

Patients will be classified as having MDA if they meet 5 out of these 7 criteria (value in brackets).

The DAPSA calculation is based on the evaluation of 5 variables:

a) 68 tender joints count
b) 66 swollen joint count
c) Patient's pain (VAS)
d) Patient's global disease activity assessment (VAS)
e) C-reactive protein

As a result the DAPSA index gives a value with:

- >28 indicating high disease activity
- 14-28 indicating moderate disease activity
- 4-13 indicating low disease activity
- ≤4 indicating complete remission

Using DAPSA the clinical response can be defined:

- Minor : 50% DAPSA change from baseline
- Moderate: 75% DAPSA change from baseline
- Major : 85% DAPSA change from baseline

The ACR20 response criteria require ≥ 20% [ACR50 ≥ 50% or ACR70 ≥ 70%] improvement in both the TJC and SJC, as well as a 20% improvement in 3 of the following 5 items:

1. patient global assessments of disease activity (VAS),
2. patient reported pain score (VAS),
3. physician global assessment (VAS),
4. Health Assessment Questionnaire (HAQ),
5. either ESR or CRP.

METHODS OF ASSESSMENT

Patient's assessment will be performed according to the core set of domains for PsA proposed by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and Outcome Measures in Rheumatology (OMERACT).[19,20]

Assessment of **Peripheral Joint Activity** will be performed using the 68 tender joint count and the 66 swollen joint count. Positive joints will be recorded and the total number of tender and swollen joints will be calculated. As it may be difficult to distinguish proximal inter-phalangeal (PIP) from distal inter-phalangeal (DIP) joint inflammation in the toes, if either the PIP or DIP of the toe is involved it should be marked as a PIP.

Patient global assessment (PtGA) and **Physician global assessement** (PGA) will be assessed by Visual Analogues Scores (VAS) as it is a reliable tool related to joint and skin disease activity. VAS **PGA of disease activity** (0-100)

Physicians will take into account both the severity of joint and skin disease when making the assessment on the scale. The left end corresponds to "completely inactive" and the right end to "highly active".

- VAS **PtGA of disease activity** (0-100)

The patients are instructed to rate their overall state of disease (joint and skin) on the scale. Recall period: past week. The left end corresponds to "completely inactive" and the right end to "highly active". The patients will mark their own assessment on the scales in the case report forms by themselves by placing a single vertical line through the bar.

- VAS **PtGA of pain** (0-100)

The patients will be instructed to rate their level of pain. Recall period: past week. The left end corresponds to "no pain" and the right end to "the worst pain imaginable". The patients will mark their own assessment on the scales in the case report forms by themselves by placing a single vertical line through the bar.

Physical function will be assessed using:

- **Heath Assessment Questionnaire Disability Index** (HAQ-DI).

There are 8 categories of functioning that represent different activities - dressing, rising, eating, walking, hygiene, reach, grip and usual activities. For each item there is a 4-level difficulty scale scored from 0-3, representing no difficulty (0), some (1) or much (2) difficulty, and unable to do (3). The highest component score in each category determines the category score, unless the patient uses aids or devices for, or receives assistance with activities in that category, in which case the relevant category score is increased to 2 if the maximum score was previously <2. The 8 category scores are averaged into an overall score from zero to 3, zero indicating no disability, 3 indicating complete disability.

Health Related Quality of Life (HRQoL) will be assessed using:

- Psoriatic Arthritis Impact of Disease (PsAID-12).

PSAID-12 includes 12 domains of health, each assessed by a single question with response on a NRS. Each NRS is assessed as a number between 0 and 10. The range of the final PsAID value is 0–10 where higher numbers indicate worse status. (Calculators and translations are available at http://www.eular.org/index.cfm?framePage=/st_com_clinical_tools.cfm).

Enthesitis is characterized by inflammation at sites of tendon, ligament, and joint capsule fibre insertion into bone, and is considered a pathophysiologically important aspect of PsA. For the purpose of the UPSTREAM study, enthesitis will be assessed using:

- the **Leeds Enthesitis Index** (LEI), an enthesitis index specifically developed for PsA;
- 4 additional entheseal sites.

LEI entheseal sites include the bilateral lateral epicondyles, medial femoral condyles, and Achilles tendon insertions. The 4 additional entheseal sites include: quadriceps insertion patella, inferior pole patella, tibial tubercle, insertion plantar fascia. Tenderness on examination is evaluated applying 4 kg/cm2 of pressure (enough to blanch the tip of the examiner's fingernail) and recording tenderness as either present (1) or absent (0) for each of the 6 sites, for an overall score range of 0–6. Higher count represents greater enthesitis burden.

Dactylitis, or "sausage digit," is characterized by swelling of an entire finger due to synovitis, tenosynovitis, enthesitis, and soft tissue edema. For the purpose of the UPSTREAM study, dactylitis will be assessed using:

- **Tender Dactylitis Count.**

Each of 20 fingers will be evaluated. The clinician marks which fingers are affected on a diagram displaying fingers and toes. The clinician squeezes the affected fingers with moderate pressure and documents the patient's response: 0 = no tenderness, 1 = tender.

Spinal assessment will be performed using:

- **Bath Ankylosing Spondylitis Disease Activity Index** (BASDAI).

The BASDAI consists of a 1 - 10 scale measuring discomfort, pain, and fatigue (1 being no problem and 10 being the worst problem) in response to six questions asked of the patient pertaining to the five major symptoms of AS: Fatigue - spinal pain – peripheral activity - morning stiffness duration - morning stiffness severity. To give each symptom equal weighting, the average of the two scores relating to morning stiffness is taken. The resulting 0 to 50 score is divided by 5 to give a final 0 – 10 BASDAI score.

Blood tests will be performed locally. ESR and CRP will be determined at each protocol time point and collected along with reference ranges.

SAFETY MONITORING

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease) in a subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a specific medicinal product.

DEFINITION OF SAE

An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

· is fatal or life-threatening
· results in persistent or significant disability/incapacity
· constitutes a congenital anomaly/birth defect
· requires inpatient hospitalization or prolongation of existing hospitalization.

ULTRASONOGRAPHIC ASSESSMENT

Sonographic evaluations will be performed by expert ultrasonographers on the same day of clinical assessment and must invariably be performed after the clinical decision to change the patient's treatment. Furthermore, results of ultrasonographic evaluation should not be taken into account for the choice of treatment.
Grey scale (GS) and power Doppler (PD) sonography will be performed in 44 joints, 36 tendons, 12 entheses and 2 bursae (US-score-PsA-SIR) using a high standard US machine and multi-frequency linear transducers (high frequency probe at least 14 Mhz).
In the absence of a definition of the ultrasound **bone proliferation** in PsA, we propose to use the OMERACT definition of osteophyte (formation of excess bone at the joint margins). [21, 22] Score dichotomous: 0 – Absent, 1 – Present.
In accordance with Terslev L. et al [23] the elementary lesions considered to evaluate **enthesitis** were: hypoechogenicity (indicate increased thickness with blurring of the tendon margins); increased thickness of tendon insertion; enthesophyte (the step up of the bony prominence at the end of the normal bone contour is marked with white arrowheads); calcifications; bone erosion at the enthesis; Doppler at enthesis <2 mm from the bone insertion. In addition to single elementary lesions, global definition of enthesitis will be recorded.

Erosions will be defined as an intra-articular discontinuity of the bone surface that is visible in 2 perpendicular planes. [24]

Sonographically the two criteria for the definition of **bursitis** have been represented by: pathological effusion into the bursae (shown as an anechoic material) and hypertrophy of the synovial membrane (displayed as material into the bursae, which can appear hypoechoic, isoechoic or hyperechoic compared with subcutaneous fat). Bursitis may also be characterized by the presence of the Doppler signal within the synovial proliferation. For some bursae as the bag deep infrapatellar bursa and deep Achilles bursa minimum fluid distension, in the absence of synovial proliferation, are considered physiological.
The presence of **Peritenon extensor tendon inflammation** (PTI) will be investigated at dorsal scans of 5 finger of the hands defined as abnormality characterized by hypoechoic swelling of the soft tissue surrounding the extensor digitorum tendon, with or without peri-tendinous PD signal. B-mode (GS-PTI) as well as PD-findings in perisynovial tissue (PD-PTI) graded with 0=absent or 1=present. [25]
Two criteria for active **articular inflammation** were evaluated by US: joint effusion and proliferation of the synovial membrane. In the majority of cases both phenomena appear concurrently and we decided to include both in a combined measure. [26] The level of **synovitis** was obtained modifying the score described by D'Agostino MA: [27] In gray scale synovitis (GS-S): Grade 0 = no synovitis, grade 1 = minimal synovitis (below or approximately at the level of bony joint line), grade 2 = moderate synovitis (above level of bony joint level but without complet distension of joint capsule, forming concavity of upper joint surface), grade 3 = severe synovitis: above level of bony joint line with distension of joint capsule (forming convexity of upper surface). In PD synovitis (PD-S): Grade 0 = no flow in the synovium (gray scale area), grade 1 = up to 3 single spots signals or up to 2 confluent spots or 1 confluent spot + up to 2 single spots, grade 2 = vessel signals in less than half of the area of the synovium (< 50%), grade 3 = vessel signals in more than half of the area of the synovium (> 50%).
Tenosynovitis can be defined on B-mode as abnormal anechoic and/or hypoechoic (relative to tendon fibres) tendon sheath widening which can be related to both the presence of tenosynovial abnormal fluid and/or hypertrophy. Definition of tendon sheath effusion can be as follows: presence of abnormal anechoic or hypoechoic (relative to tendon fibres) material within the synovial sheath, either localised (eg, in the synovial sheath cul-de-sacs) or surrounding the tendon that is displaceable and seen in two perpendicular planes. Definition of tenosynovial hypertrophy can be as follows: presence of abnormal hypoechoic (relative to tendon fibres) tissue within the synovial sheath that is not displaceable and poorly compressible and seen in two perpendicular planes. Tenosynovitis can be characterised on Doppler mode by the presence of peri-tendinous Doppler signal within the synovial sheath, seen in two perpendicular planes, excluding normal feeding vessels (ie, vessels at the mesotenon or vinculae or vessels entering the synovial sheath from surrounding tissues) only if the tendon shows peritendinous synovial sheath widening on B-mode.

The grade of tenosynovitis should be assessed in both longitudinal and transverse planes. A four-grade semiquantitative scoring system (ie, grade 0, normal; grade 1, minimal; grade 2, moderate; grade 3, severe) can be used to score tenosynovitis on B-mode. The grade of tenosynovitis should be assessed in both longitudinal and transverse planes.

A four-grade semiquantitative scoring system (ie, grade 0, no Doppler signal; grade 1, minimal; grade 2, moderate; grade 3, severe) can be used to score pathological peritendinous Doppler signal within the synovial sheath.

- grade 0, no signal;
- grade 1, peritendinous focal signal within the widened synovial sheath (ie, signals in only one area of the widened sheath), seen in two perpendicular planes, excluding normal feeding vessels;
- grade 2, peritendinous multifocal signal within the widened synovial sheath (ie, signals in more than one area of the widened sheath), seen in two perpendicular planes, excluding normal feeding vessels;
- grade 3, peritendinous diffuse signal within the widened synovial sheath (ie, signals filling most of the widened sheath), seen in two perpendicular planes, excluding normal feeding vessels.

If in addition to an abnormal peritendinous (ie, intra-sheath) signal there was an abnormal intratendinous signal seen in two perpendicular planes (ie, excluding intratendinous small isolated signals that can correspond to normal feeding vessels detectable by US), then grades 1 and 2 would be increased by one point [28].
Tendon damage can be defined on B-mode as internal and/or peripheral focal tendon defect (ie, absence of fibers) in the region enclosed by tendon sheath, seen in two perpendicular planes. The grade of tendon damage should be assessed in both longitudinal and transverse planes. [29]

The overall PsA-SIR US score will be calculated as the sum of the scores of every lesion at all sites (range 0-632).
The inflammatory PsA-SIR US subscore will be calculated as the sum of the scores of GS-sinovitis, PD-synovitis, GS-tenosynovitis, PD-tenosynovitis, GS-peritenotitis, PD-pertitenonitis, entheseal hypoechogenicity, entheseal thickness, entheseal PD, GS-bursitis and PD-bursitis at all sites (range 0-470).
The damage PsA-SIR US subscore will be calculated as the sum of the scores of joint erosion, bony proliferation, tendon lesion, enthesophytes, entheseal calcifications, entheseal erosions, at all sites (range 0-162).

RADIOGRAPHIC ASSESSMENT

Posterior-anterior radiographic assessments of hands and feet will be scored at a subsequent time point by two radiologists centrally using the van der Heijde modification of the Sharp score. The scoring will be performed pairwise, blinded to the sequence of the films and to the clinical data. Mean of two investigators will be taken as the final score for X-ray assessments.

STUDY VISIT/SCHEDULE

Study Period:	**Enrollment**	**Observation/Follow-up MONTHS**				
Visit	*Screening*	*Baseline*	*3*	6	12	24
Informed Consent	X					
Inclusion/Exclusion Criteria	X					
Socio-demographic data		X				
Life-style questionnaire		X				
Medical History		X				
Information treatment		X	X	X	X	X
ARTICULAR ASSESSMENT						
Tender (68) and swollen (66) joint count		X	X	X	X	X
Entheseal assessment		X	X	X	X	X
Tender Dactylitis Count		X	X	X	X	X
SKIN ASSESSMENT						
Body Surface Area (BSA)		X	X	X	X	X
BLOOD TEST						
RF/ACPA/HLA-B27		X				
ESR/CRP		X		X	X	X
PATIENT GLOBAL AND PAIN ASSESSMENT						
Pain VAS		X	X	X	X	X
Global VAS		X	X	X	X	X
PHYSICIAN'S GLOBAL ASSESSMENT						
Physician's Global VAS		X		X	X	X
PATIENT SPINAL ASSESSMENT						
BASDAI		X				
PHYSICAL FUNCTION						
HAQ		X	X	X	X	X
HEALTH-RELATED QUALITY OF LIFE						
PsAID-12		X		X	X	X
US IMAGING						
US-score PsA-SIR		X		X	X	X
CR IMAGING						
X ray (hands-feet)		X			X	X
ADVERSE EVENTS			X	X	X	X

STATISTICAL ANALYSIS PLAN

VARIABLES: OUTCOME MEASURES

PRIMARY:

- MDA at 6 months

SECONDARY

- MDA at 12 months, sustained MDA at 6 AND 12 months
- DAPSA <3.3 at 6 months, 12 months, 6 AND 12 months
- ΔmSvH 0-12 and 0-24 months
- ΔHAQ 0-12 and 0-24 months
- ΔPSAID 0-12 and 0-24 months
- US-score PsA-SIR damage subscore at 0-6-12 months

US PREDICTORS

- US-score PsA-SIR
- US-score PsA-SIR inflammation subscore
- US-score PsA-SIR damage subscore

CLINICAL PREDICTORS

Based on the relevant literature clinical variables to be considered in the model include:

- Demographic and environmental factors:
  - Age
  - Gender
  - Smoking
  - BMI
- Clinical factors:
  - subset of PsA
  - time from symptoms onset to diagnosis
  - disease duration
  - disease activity (DAPSA and BASDAI)
  - HAQ score
  - tender joints / pain
  - comorbidities (FM, MetS)
- Serological factors:
  - Acute phase reactants
- Therapy factors:
  - Treatment (NSAIDs, steroids, DMARDs)

DESCRIPTIVE ANALYSES

Descriptive data will be provided for all outcomes according to data type; number of patients (N), mean, standard deviation (for interval data), median 25% and 75% quartiles (for ordinal data). Frequency (absolute and relative) distributions will be provided for categorical data. Two-sided p-values will be presented throughout.

PRIMARY ENDPOINT ANALYSIS

Prediction of 6 months MDA will use multivariate adjusted logistic models. A baseline model will include all the clinical variables. US predictors will be added as covariates to the clinical variables, assuming an additive model. The derived ß coefficients were used to calculate prognostic indices, thereby creating weighted prediction models.

Model performance will be evaluated by C-indices (area under the ROC curve, AUC), net reclassification indices (NRI), integrated discrimination improvement (IDI), and plotted ROC curves. NRI can be used to compare the clinical impact of different models (it is a comparison of the proportion of subjects with disease who have appropriately increased risk scores with the new model, and the proportion of subjects without disease who have appropriately decreased risk scores with the new model). IDI represents desired improvements in average sensitivity corrected for undesirable increases in 1-specificity, it therefore compared whether the new models improved sensitivity without affecting specificity.[30]

Data management and analysis will be performed using RedCap, R, Stata.

SECONDARY ENDPOINT ANALYSES

- to evaluate the additional value of US over clinical examination in detecting patients:
  - achieving MDA at 12 months
  - achieving sustained DAPSA remission at 6 and 12-months
  - achieving DAPSA remission at 6 and 12 months
  - achieving ACR Remission remission at 6 and 12 months
  - with X-ray structural progression (mSVH score) at 12 and 24 months
  - with US structural progression (US-damage score) at 12 and 24 months
  - with functional worsening (ΔHAQ>0.23) at 12 and 24 months
  - with impairment of HRQoL at 12 and 24 months

The same approach followed for the primary endpoint will be followed to evaluate

EXPLORATORY ANALYSES

- to evaluate the relationship between time-integrated US-detected inflammation and US-detected erosions at 12 and 24 months
- to evaluate the comparative effectiveness of different treatment strategies on MDA, DAPSA remission, ΔHAQ>0.23, X-ray progression (mSvHS), US-inflammation score, US-damage score.
- to evaluate the comparative effectiveness of different treatment strategies on MDA, DAPSA remission, ΔHAQ>0.23, , X-ray progression (mSvHS), US-inflammation score, US-damage score.

SAMPLE SIZE

The sample size calculation was done with the objective of minimizing the number of false positives (i.e the number of false non-responsive to treatment) in order to minimize the risk of over-treating patients who actually have a good response to therapy. Therefore, sample size was calculated to minimize this risk by 40% (null hypothesis H0) to 20% (alternative hypothesis H1), maintaining stable at 70% (both for the H0 for both the H1), the percentage of true positives (true unresponsive to therapy).

The simulations were carried out using the procedure rocsize Stata (by M. Pepe) [30], which allows to determine the power to detect an improvement in the ROC curve. The procedure requires the specification of the percentage of false positive and true positive both for the null hypothesis is for the alternative hypothesis and the percentage of positive / diseased.

Using the command rocsize 0.7 0.2, na (150) ndb (100) tpnull (0.7) fpnull (0.4) of Stata, 250 patients are sufficient to evaluate the performance of a model (and its ROC curve) with 90% power and 5% alpha. Specifically, we have assumed a 70% and a 20% of subjects true positives and false positives, respectively, according to the alternative hypothesis, a 70% and a 40% of subjects true positives and false positives, respectively, according to the null hypothesis, and a percentage of diseased of 60% (150 of 250 subjects).

Under the assumption of maximum attrition of 20%, the sample size will be increased to 300 patients. The same sample size is sufficient to precisely estimate a logistic model of achievement of a MDA (probability of 0.4 at 6 months) with 10 predictors (rule of thumbs).[31]

Based on the pre-study activities, 35-40 centres will be involved, 15 tertiary and 20-25 secondary rheumatology centres. Assuming 4 eligible patients/months for tertiary and 1/month in secondary centres, a 40% of enrolment rate, about 30 patients/months are expected.

ETHICS

This study will be conducted in accordance with all applicable laws and regulations including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), EU guidelines and the ethical principles that have their origins in the Declaration of Helsinki. The institutional review board (IRB)/independent ethics committee (IEC) must review and approve the protocol and informed consent form before any subjects are enrolled. Before any protocol-required procedures are performed, the subject must sign and date the IRB/IEC-approved informed consent form.

Clinical data (including AEs and concomitant medications) will be entered into a validated data capture system provided by the Italian Society for Rheumatology. The data system will include password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

PUBLICATION RULES

The study protocol will be submitted for publication and all the results of all the analyses stored at the https://osf.io/f8mrg.

Following completion of the study, the full results of this research will be published in a peer reviewed scientific journal. An Open Access publication policy will be applied.

As this is a multi-centre study, the results from individual centres must not be published prior to the publication of the entire study results and without prior agreement of the Steering Committee. For avoidance of doubt the first publication must be the responsibility of the Chief Investigators. A main authorship will be offered to all Local investigators who achieve the minimum target of 20 patients with complete clinical and ultrasound data at baseline and >80% of complete data at 6 months. All the other Investigators not reaching these criteria will be included in the collaborator's list or in the acknowledgements according to the table below.

Number of patients	*Sonographer*	*Clinician*
20	Author	Author
10-19	Author	Collaborator
5-9	Collaborator	Acknowledgment
<5	Acknowledgment	

All the investigators will be able to apply to investigator-initiated-studies using the entire data-set, being able to define the authorship according to International Committee of Medical Journal Editors Recommendations.[32]

[1] Moll JM, Wright V. Psoriatic arthritis. Semin Arthritis Rheum. 1973;3(1):55–78
[2] Coates LC, Helliwell PS. Validation of minimal disease activity criteria for psoriatic arthritis using interventional trial data. Arthritis Care Res. 2010 Jul 1;62(7):965–9
[3] Gossec L, Smolen JS, Ramiro S, Wit M de, Cutolo M, Dougados M, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. Ann Rheum Dis. 2015 Dec 7;annrheumdis – 2015–208337
[4] Sokoll KB, Helliwell PS. Comparison of disability and quality of life in rheumatoid and psoriatic arthritis. J Rheumatol. 2001 Aug;28(8):1842–6
[5] Eder L, Thavaneswaran A, Chandran V, Cook RJ, Gladman DD. Obesity is associated with a lower probability of achieving sustained minimal disease activity state among patients with psoriatic arthritis. Ann Rheum Dis. 2015 May;74(5):813–7
[6] Theander E, Husmark T, Alenius G-M, Larsson PT, Teleman A, Geijer M, et al. Early psoriatic arthritis: short symptom duration, male gender and preserved physical functioning at presentation predict favourable outcome at 5-year follow-up. Results from the Swedish Early Psoriatic Arthritis Register (SwePsA). Ann Rheum Dis. 2014 Feb;73(2):407–13
[7] Saber TP, Ng CT, Renard G, Lynch BM, Pontifex E, Walsh CAE, et al. Remission in psoriatic arthritis: is it possible and how can it be predicted? Arthritis Res Ther. 2010;12(3):R94
[8] Glintborg B, Ostergaard M, Krogh NS, Andersen MD, Tarp U, Loft AG, et al. Clinical response, drug survival, and predictors thereof among 548 patients with psoriatic arthritis who switched tumor necrosis factor α inhibitor therapy: results from the Danish Nationwide DANBIO Registry. Arthritis Rheum. 2013 May;65(5):1213–23
[9] Coates LC, Moverley AR, McParland L, Brown S, Navarro-Coy N, O'Dwyer JL, et al. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. The Lancet. 2015 Dec 19;386(10012):2489–98
[10] Colebatch AN, Edwards CJ, Ostergaard M, van der Heijde D, Balint PV, D'Agostino M-A, et al. EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis. Ann Rheum Dis. 2013 Jun 1;72(6):804–14
[11] Mandl P, Navarro-Compán V, Terslev L, Aegerter P, Heijde D van der, D'Agostino MA, et al. EULAR recommendations for the use of imaging in the diagnosis and management of spondyloarthritis in clinical practice. Ann Rheum Dis. 2015 Jul 1;74(7):1327–39
[12] Gutierrez M, Draghessi A, Bertolazzi C, Erre GL, Saldarriaga-Rivera LM, López-Reyes A, et al. Ultrasound in psoriatic arthritis. Can it facilitate a best routine practice in the diagnosis and management of psoriatic arthritis? Clin Rheumatol. 2015 Aug 23;34(11):1847–55
[13] Gutierrez M, Di geso L, Salaffi F, Bertolazzi C, Tardella M, Filosa G, et al. Development of a preliminary US power Doppler composite score for monitoring treatment in PsA. Rheumatol U K. 2012;51(7):1261–8
[14] Backhaus M, Ohrndorf S, Kellner H, Strunk J, Backhaus TM, Hartung W, et al. Evaluation of a novel 7-joint ultrasound score in daily rheumatologic practice: A pilot project. Arthritis Care Res. 2009;61(9):1194–201
[15] Ficjan A, Husic R, Gretler J, Lackner A, Graninger WB, Gutierrez M, et al. Ultrasound composite scores for the assessment of inflammatory and structural pathologies in Psoriatic Arthritis (PsASon-Score). Arthritis Res Ther. 2014 Oct 31;16(5):476
[16] UPSTREAM [Internet]. [cited 2016 Jan 16]. Available from: https://osf.io/f8mrg/
[17] Lubrano E, Cantini F, Costanzo A, Girolomoni G, Prignano F, Olivieri I, et al. Measuring psoriatic disease in clinical practice. An expert opinion position paper. Autoimmun Rev. 2015 Oct;14(10):864–74
[18] Labitigan M, Bahče-Altuntas A, Kremer JM, Reed G, Greenberg JD, Jordan N, et al. Higher rates and clustering of abnormal lipids, obesity, and diabetes mellitus in psoriatic arthritis compared with rheumatoid arthritis. Arthritis Care Res. 2014 Apr;66(4):600–7
[19] Gladman DD, Mease PJ, Healy P, Helliwell PS, Fitzgerald O, Cauli A, et al. Outcome measures in psoriatic arthritis. J Rheumatol. 2007 May 1;34(5):1159–66
[20] Gladman DD, Mease PJ, Strand V, Healy P, Helliwell PS, Fitzgerald O, et al. Consensus on a core set of domains for psoriatic arthritis. J Rheumatol. 2007 May;34(5):1167–70
[21] Hammer HB, Iagnocco A, Mathiessen A, Filippucci E, Gandjbakhch F, Kortekaas MC, Möller I, Naredo E, Wakefield RJ, Aegerter P, D'Agostino MA. Global ultrasound assessment of structural lesions in osteoarthritis: a reliability study by the OMERACT ultrasonography group on scoring cartilage and osteophytes in finger joints. Ann Rheum Dis. 2016 Feb;75(2):402-7.

[22] Mathiessen A, Haugen IK, Slatkowsky-Christensen B, Bøyesen P, Kvien TK, Hammer HB. Ultrasonographic assessment of osteophytes in 127 patients with hand osteoarthritis: exploring reliability and associations with MRI, radiographs and clinical joint findings. Ann Rheum Dis. 2013 Jan;72(1):51-6

[23] Terslev L, Naredo E, Iagnocco A, Balint PV, Wakefield RJ, Aegerter P, Aydin SZ, Bachta A, Hammer HB, Bruyn GA, Filippucci E, Gandjbakhch F, Mandl P, Pineda C, Schmidt WA, D'Agostino MA; Outcome Measures in Rheumatology Ultrasound Task Force.. Defining enthesitis in spondyloarthritis by ultrasound: results of a Delphi process and of a reliability reading exercise. Arthritis Care Res (Hoboken). 2014 May;66(5):741-8

[24] Wakefield RJ, Balint PV, Szkudlarek M, Filippucci E, Backhaus M, D'Agostino M-A, et al. Musculoskeletal ultrasound including definitions for ultrasonographic pathology. J Rheumatol. 2005 Dec;32(12):2485–7

[25] Gutierrez M, Filippucci E, Salaffi F, Di Geso L, Grassi W. Differential diagnosis between rheumatoid arthritis and psoriatic arthritis: the value of ultrasound findings at metacarpophalangeal joints level. Ann Rheum Dis. 2011 Jun;70(6):1111-4

[26] Scheel AK, Hermann KG, Kahler E, Pasewaldt D, Fritz J, Hamm B, Brunner E, Müller GA, Burmester GR, Backhaus M. A novel ultrasonographic synovitis scoring system suitable for analyzing finger joint inflammation in rheumatoid arthritis. Arthritis Rheum. 2005 Mar;52(3):733-43

[27] D'Agostino MA, Wakefield RJ, Berner-Hammer H, Vittecoq O, Filippou G, Balint P, Möller I, Iagnocco A, Naredo E, Østergaard M, Boers M, Gaillez C, Van Holder K, Le Bars M; OMERACT-EULAR-Ultrasound Task Force.. Value of ultrasonography as a marker of early response to abatacept in patients with rheumatoid arthritis and an inadequate response to methotrexate: results from the APPRAISE study. Ann Rheum Dis. 2016 Oct;75(10):1763-9

[28] Naredo E, D'Agostino MA, Wakefield RJ, Möller I, Balint PV, Filippucci E, Iagnocco A, Karim Z, Terslev L, Bong DA, Garrido J, Martínez-Hernández D, Bruyn GA; OMERACT Ultrasound Task Force*.. Reliability of a consensus-based ultrasound score for tenosynovitis in rheumatoid arthritis. Ann Rheum Dis. 2013 Aug;72(8):1328-34

[29] Bruyn GA, Hanova P, Iagnocco A, d'Agostino MA, Möller I, Terslev L, Backhaus M, Balint PV, Filippucci E, Baudoin P, van Vugt R, Pineda C, Wakefield R, Garrido J, Pecha O, Naredo E; OMERACT Ultrasound Task Force.. Ultrasound definition of tendon damage in patients with rheumatoid arthritis. Results of a OMERACT consensus-based ultrasound score focussing on the diagnostic reliability. Ann Rheum Dis. 2014 Nov;73(11):1929-34

[30] Pepe MS. The Statistical Evaluation of Medical Tests for Classification and Prediction [Internet]. Oxford University Press; 2003. (Oxford statistical science series). Available from: https://books.google.it/books?id=UHQoAgAAQBAJ

[31] Harrell FE, Lee KL, Mark DB. Multivariable Prognostic Models: Issues in Developing Models, Evaluating Assumptions and Adequacy, and Measuring and Reducing Errors. Stat Med. 1996 Feb 29;15(4):361–87

[32] International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals [Internet]. [cited 2016 Jan 16]. Available from: http://www.icmje.org/icmje-recommendations.pdf