

Prevention of metacarpophalangeal joints structure damage in patients with psoriatic arthritis using secukinumab

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Background:

Psoriatic arthritis (PsA) is a chronic inflammatory joint disease associated with psoriasis. PsA is associated with distinctive clinical features including changes in skin and nails, peripheral arthritis, axial disease, dactylitis and enthesitis. Synovial inflammation in peripheral joints is the most prevalent feature of the disease ranging in severity from mild joint inflammation to disabling peripheral arthritis [1]. Within 2 years of diagnosis, radiological erosions were developed in 47% of the patients [2]. Without proper monitoring and treatment, it will lead to significant structure damage and loss of physical function, and even arthritis mutilans, which is the most severe destructive form of PsA [3]. Prevention of structural damage is one of the primary goals of treating PsA patients to maximise health-related quality of life [4].

Detection of bone erosions in PsA patients is usually achieved by conventional radiographs although the sensitivity is low [5]. High-resolution peripheral quantitative CT (HR-pQCT) is a novel technique for detailed bone microstructure analysis with high reproducibility in assessing bony erosions [6]. With its high spatial resolution of 130 µm, HR-pQCT exhibited a higher sensitivity in detecting erosion compared with radiograph and magnetic resonance imaging (MRI) [7]. Recently, Finzel et al. described an indirect method to assess volume based on measurements of the width and depth of the erosions using HR-pQCT [8]. Quantitative measurement of erosion volume can also be achieved [6]. Using this method, erosion repair under biological disease-modifying antirheumatic drugs (DMARDs) treatment has been demonstrated in patients with rheumatoid arthritis (RA) [8, 9]. Bone apposition at the margin of erosions (osteosclerosis) with the formation of a new cortical lining was associated with a decrease in erosion depth or width, which may indicate either periosteal or endosteal repair processes [8, 9]. Valid measurement of erosion volume using HR-pQCT will facilitate the testing of treatments that may help to heal erosion. Decrease in erosion volume and the presence of osteosclerosis on HR-pQCT could be promising markers for erosion healing.

Interleukin 17 (IL-17) is a proinflammatory cytokine which produced by type 17 helper T cells (Th17). It is now considered to be a key cytokine in the pathogenesis of a number of autoimmune disorders in humans including PsA [10]. IL-17 was also reported to be associated with the presence of joint erosion [11]. Recently, secukinumab, an anti-interleukin-17A monoclonal antibody, was reported to be effective in reducing disease activity and decreased the rate of radiographic joint damage compared with placebo [12]. However, whether healing of erosion could occur in PsA has never been evaluated.

On the other hand, osteophytes formation at the enthesal regions of the joints in PsA is distinctive feature compared with RA [13]. The formation of osteophytes is tightly regulated by anabolic pathways, which resembles the pathogenesis of new bone formation in ankylosing spondylitis (AS). Tumor necrosis factor (TNF) inhibition was unable to halt the structural progression in AS patients [14-16], it also lacked efficacy in stopping the progression of osteophytes in PsA patients [17]. Inhibition of IL-17 by secukinumab was effective in the treatment of both AS [18] and PsA [12]. Secukinumab also decreased the rate of radiographic joint damage regarding to erosion and joint space narrowing [12]. However, it is unknown if it has any effect in the progression of osteophytes. In an animal model, although over-expression of IL-17 alone failed to induce enthesal and periosteal bone formation, inhibition of IL-17 led to significant reduction of such bone formation in an IL-23 overexpression model [19]. Moreover, IL-17A accelerates bone formation by stimulating the proliferation and osteoblastic differentiation of mesenchymal progenitor cells after injury [20]. It is worth exploring if secukinumab could prevent the progression of osteophytes in PsA patients.

Aims and hypotheses to be tested:

Hypothesis

IL-17 inhibition by secukinumab could lead to healing of existing erosion, and prevent progression of osteophytes in PsA patients.

Aims

The aim of this randomized, double-blind, placebo-controlled study is to evaluate the protective effects of secukinumab on the healing of joint erosion and prevention of progression of osteophytes in PsA patients using HR-pQCT.

Objectives

Primary outcome

Difference in changes in the volume of erosions on metacarpophalangeal joints (MCP) 2-4 measured by HR-pQCT at 52 weeks between secukinumab and placebo group.

Secondary outcomes

- 1) The percentage of erosions with healing determined using HR-pQCT on MCP 2-4 at 52 weeks including 1). A decrease in erosion volume of $\geq 0.4 \text{ mm}^3$ from baseline, and 2). The presence of grade 2 osteosclerosis at the margin of erosion.
- 2) Changes in depth and width of erosion using HR-pQCT at 52 weeks;
- 3) Marginal osteosclerosis (semi-quantitative and quantitative) using HR-pQCT at 52 weeks;
- 4) Changes in the height of osteophytes using HR-pQCT at 52 weeks;

Exploratory outcomes

- 1) Changes in van der Heijde-Sharp score on radiograph at 52 weeks.
- 2) Changes in patients-reported-outcomes (SF-36, AsQoL & DLQI) and functional disability (HAQ) at week 28 & 52

Plan of Investigation:

Subjects 120 biologic DMARDs naïve PsA patients attending the outpatient clinic of the Prince of Wales Hospital (PWH), Tai Po Hospital (TPH), Queen Elizabeth Hospital (QEH) and Tseung Kwan O Hospital (TKOH) who fulfilled the Classification Criteria for Psoriatic Arthritis (CASPAR), will be recruited. The main inclusion criteria are: 1) ≥ 18 years old; 2) without severe deformity in MCP joints which would influence the longitudinal assessment of HR-pQCT; 3) with active disease, which is defined as three or more than tender joints and three or more than swollen joints, despite previous treatment with nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs. These 120 patients will be screened for the presence of erosion at the head of MCP2-4 using HR-pQCT. The first 40 patients with erosion will be randomised in a 1:1 ratio to secukinumab (n=20) or placebo (n=20) group. Based on a study using high-resolution CT in 41 PsA patients, 41% of the patients had at least one erosion, and 90% of the erosions were in MCPs [5]. The resolution of the high-resolution CT is 0.4 mm, which is almost 5 folds lower than HR-pQCT (82 μm). Therefore, we estimated that over 1/3 of the PsA patients will have at least one erosion in MCPs. Thus, screening 120 patients using HR-pQCT should be adequate to recruit 40 patients with erosions on MCP 2-4.

All study procedures will be performed in PWH after recruitment from non-PWH site.

Randomisation will be performed using a computer-generated randomisation list provided by the hospital pharmacist, using a permuted blocks design with block sizes of 4 and 6. Allocation concealment will be ensured by the use of sequentially numbered, opaque, sealed envelopes. Treatment will be masked to patients and investigators.

Exclusion criteria are: 1) limited in ability to perform usual self-care, vocational, and avocational activities; 2) pregnancy; 3) previous therapy with biologic; 4) the presence of active inflammatory diseases other than PsA; 5) active infection in 2 weeks before randomization or a history of ongoing, chronic, or recurrent infections including tuberculosis; 6) history of hepatitis B & C; 7) history of malignant disease within the past 5 years (excluding basal cell carcinoma or actinic keratosis, in-situ cervical cancer, or non-invasive malignant colon polyps); 8) contraindications to secukinumab. The concomitant use of oral glucocorticoids (at a dose of ≤ 10 mg per day of prednisone or its equivalent) and methotrexate (at a dose of ≤ 25 mg per week) are permitted, provided that the dose will be stable.

The study will be approved by the Ethics Committee of the Chinese University of Hong Kong. Written informed consent will be obtained from all participants according to the Declaration of Helsinki and ICH-GCP guidelines.

Methods This is a 52-weeks, randomized, placebo-controlled, double-blind study. PsA patients will be randomised to either secukinumab or placebo group. All patients will be evaluated and treated according to the following protocol.

Study design

Treatment

The patients will be randomly assigned to the secukinumab group or placebo group. Patients will be followed-up at weeks 2, 4 and then every 12 weeks until week 52. Patients will receive subcutaneous placebo or secukinumab 150 mg once a week from baseline for 4 weeks, and then once every 4 weeks from week 4 onwards. The study flow is shown in Figure 1. Changes in the baseline treatment, e.g. the dosage of synthetic DMARDs (sDMARDs) including methotrexate, leflunomide, hydroxychloroquine, or sulfasalazine or the addition of a new sDMARD (individually or in combination), as well as changes in the dosage or the addition of steroids or nonsteroidal antiinflammatory drugs were allowed after week 28 if the patient cannot achieve minimal disease activity (MDA) (Table 1). For patients who had never been on anti-TNF but fulfilling the criteria for anti-TNF (Appendix 1), they can either pay out of pocket or can apply for the Samaritan Fund for financial assistance, provided they must pass a household-based financial assessment (http://www.ha.org.hk/visitor/ha_visitor_index.asp?Content_ID=10048&Lang=ENG&Dimension=100). Patients who have started anti-TNF treatment will be excluded from the efficacy assessment. Adverse effects will be recorded.

Evaluation of disease activity and severity

At baseline and at each visit, we will quantify the extent of disease by evaluation of the multiple clinical domains of PsA. The following domains will be assessed: pain, physicians' and patients' global assessments, number of tender and swollen joints (using the 68 tender/66 swollen joint count), number of joints irreversibly damaged (baseline and week 52 visit only); enthesitis (13 sites for the MDA and 6 sites for the composite psoriatic disease activity index [CPDAI]); number of digits with dactylitis; levels of acute phase reactant including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, Bath ankylosing spondylitis disease activity index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) and the modified health assessment questionnaire (M-HAQ. For the skin domain, Psoriasis Area (BSA) and Psoriasis Activity and Severity Index (PASI) will be assessed in baseline and each visit. Quality of life will be assessed at baseline, week 28 and 52 which include HRQoL using the Short Form 36 (SF-36) Health Survey, the Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire [21] and Dermatology Quality of Life Index (DLQI). MDA will be used for assessment of treatment efficacy endpoint. A qualified dermatologist will be responsible for performing assessment of skin involvement (BSA, PASI and DLQI) of the patients. Composite disease activity will be assessed at baseline and at each visit according to the CPDAI (Table 2) [22]. In the CPDAI, disease activity is assessed in up to 5 domains; peripheral joints, skin, enthesitis, dactylitis and spinal manifestations. For each domain, instruments are used to assess both the extent of disease activity as well as the effect of involvement in that domain on patient function and health-related quality of life (HRQoL). CPDAI has been shown in the Psoriasis Randomised Etanercept Study in psoriatic Arthritis trial dataset to be able to distinguish treatment response between the two etanercept doses, and it can additionally measure changes in the skin and, therefore, to discriminate between two different doses of etanercept [23]. X-rays of the hands, wrists, feet, hip, cervical, lumbar and thorax spine will be performed at baseline and after 1 years for the evaluation of erosion.

Laboratory assessments and inflammatory markers

Laboratory assessments at baseline, week 28 and the end of study include fasting blood glucose, fasting lipid profile (total cholesterol, low-density lipoprotein-cholesterol [LDL-C], high-density lipoprotein-cholesterol [HDL-C], triglycerides), fibrinogen, and uric acid. Total cholesterol is measured by an autoanalyzer enzymatic method. HDL-C is determined enzymatically with polyethylene glycol-modified enzymes. LDL-C is calculated by the Friedewald formula. If the triglyceride levels exceed 4.0mmoles/liter, the LDL levels are measured directly by ultracentrifugal single spin analysis. A total of 20 ml research blood will be collected for later research use.

Safety Data Collection and Reporting

All possible side effect of the biologic and synthetic DMARDs used the study will be explained to the participants by the research nurse and the treating physician. To monitor the possible side effect, complete blood count, liver function tests and renal function tests will be performed every visit. Chest X-rays will be obtained at baseline and at the end of the study. The treating physician records all non-serious and serious adverse events, all reports of drug exposure during pregnancy, and all reports of misuse and abuse of the Novartis drug, other medication errors and uses outside of what is foreseen in the protocol, if necessary, make treatment adjustments in accordance with the protocol. Serious adverse events are defined as any adverse reaction resulting in any of the following outcomes: a life-threatening condition or death, a significant or permanent disability, a medically significant event, hospitalization or prolongation of hospitalization, a congenital abnormality, or a birth defect. All adverse events from this trial will be reported to local IRB and Health Authority by the investigator according per requirement as holder of certificate of clinical trial.

Erosion assessment by HR-pQCT

Image acquisition

Metacarpal bone erosion will be assessed at MCP 2-4 of the more severely affected or the dominant hand if both hands are equally affected using a HR-pQCT system (XtremeCT; Scanco Medical AG, Bruttisellen, Switzerland). This system enables the simultaneous acquisition of CT slices with an isotropic resolution (voxel size) of 82 µm. HR-pQCT scanning will be performed by a single investigator who is blinded to all the clinical information of the patients. A single examination will be performed for measurements of MCP 2-4. An anteroposterior scout view will be used to define the region of interest (ROI). The scan region will be 80 slices distal and 242 slices proximal of the upper margin of the head of MCP3. Scan time will be around 8 min per patient and scan [8]. The scans will be performed at baseline and 52 weeks.

Erosion identification and measurement of the width and depth

Erosions are defined as sharply marginated bone lesions with juxta-articular localisation with a cortical break seen in at least two adjacent slices, which are often accompanied by loss of the adjacent trabecular bone. Erosions will be differentiated from physiological breaks indicating entry of blood vessels by the linear shape and occurrence on predilection sites. Pseudo-erosions, structures similar to cortical breaks presented by osteophytes, will be excluded [24]. Each of the erosions will be documented at baseline and 52 weeks. Assessment includes the palmar, ulnar, dorsal as well as the radial sides of MCP 2-4 heads investigating overall 322 2D HR-pQCT slices in the transversal, sagittal and coronal plane. Every erosion of each patient will be characterised by the maximal width and depth of the lesion in the axial, sagittal and coronal using the open source DICOM viewer Osirix V3.2 (Rosslyn, VA, USA).

Erosion volume

The volume of the erosions will be calculated according to the methodology published by Fouque-Aubert et al [6]. The volume of erosions (using the entire volume of interest) will be determined by manually defining the ROI including the erosion (V1) or excluding it (V2). The volume of erosions will be then calculated as: $V_{\text{erosion}} = V1 - V2$; $V = \sum(A_i * 0.082)$, where $A1_i$ or $A2_i$ is the area on slice i (mm^2), including or excluding erosion, and 0.082 mm is the thickness of slice (Figure 2).

Osteosclerosis

The signs of bone apposition at the margin of the erosion will be documented [8, 9]. Semi-quantitative scoring (0-2 scale) of osteosclerosis will be performed using coronal reconstructions as follows: grade 0 = 0%, grade 1 = 1-75%, grade 2 = 75-100% bone apposition along the surrounding bone (typical images were shown in Figure 3) [25]. Quantitative osteosclerosis will also be calculated by choosing the area (width =15 voxels) around bone erosion in MCP2-4 as ROI [26]. The density of the ROI will be calculated as the mean pixel attenuation of that area. 3D registration will be applied to obtain a consistent segmentation of the periosteal surface in the vicinity of the cortical break, which is highly important for accurate quantification of bone damage.

Defining the healing of erosion

This is the first study assessing erosion healing using HR-pQCT. Erosion healing is evidenced by a decrease in erosion volume and the presence of bone apposition at the margin of the erosion. Based on our preliminary data, the smallest detectable change of erosion volume, which was calculated on the basis of 29 individual erosions as suggested by Bruynesteyn et al. [27], was 0.4 mm^3 . Meanwhile, a grade 2 osteosclerosis means dramatic bone apposition at the erosion margin (>75%). Therefore, a decrease in erosion volume of $\geq 0.4 \text{ mm}^3$ from baseline, and the presence of grade 2 osteosclerosis at the surface of erosion at 52 weeks is considered as strong evidence of erosion healing.

Osteophytes

The maximal height of each osteophyte will be documented by assessing the maximal distance between the surface of the osteophyte and the original cortical bone surface using the open source DICOM viewer Osirix V3.2 (Rosslyn, VA, USA) [17]. The change of the maximal height between baseline and 52 weeks will be calculated.

Images will be evaluated by two independent readers blinded to the clinical data. Based on the post-hoc analysis of a 6-months open-label randomized-controlled trial conducted by us [28],

intra-observer reproducibility was 0.987, 0.994, 0.982, and 0.983 for erosion width, depth, volume and quantitative osteosclerosis, respectively. Inter-observer reproducibility as determined by intraclass correlation coefficient was: 0.977, 0.979, 0.962, and 0.974 for erosion width, depth, volume and quantitative osteosclerosis, respectively. Inter-reader agreement for the assessment of detecting the presence or the grade of osteosclerosis was also high (Kappa: 0.81~0.91).

Erosion assessment by radiographs

Radiographs at baseline and 52 weeks will be obtained and assessed by one radiologist and one rheumatologist who are masked to treatment groups. Radiological progression will be assessed using the van der Heijde modification of the Sharp score. The van der Heijde modified Sharp score evaluates erosions in 16 joints in each hand and wrist, and six joints in each foot. These erosions are scored on a scale of 1–5 in the hands depending on the surface area affected and 0–10 in the feet. Total erosion scores range from 0 to 160 in the hands and 0 to 120 in the feet. Joint Space Narrowing (JSN) is assessed in 15 joints in each hand and wrist, and six joint in each foot on a scale of 1–4. The score of JSN ranges from 0 to 120 in the hands and from 0 to 48 in the feet.

Data processing and analysis Statistical analyses will be performed using the Statistics Package for Social Sciences (SPSS). Data will be analysed in an intention-to-treat manner. Patients who discontinued treatment or violated treatment protocol will be excluded from analysis. Missing data are assumed missing at random and will be treated using a multiple Imputation method [29]. Based on the pilot study and our previous experience, the missing data is estimated to be less than 5%. Descriptive statistics will be used for demographic and clinical variables included frequencies, means and standard deviations, median and interquartile range. T-test, Mann-Whitney U test and Chi-square test will be used to evaluate differences in baseline characteristics between secukinumab group and placebo group. Changes of the outcome measurements between groups will be tested using t-test, Mann-Whitney U test, repeated measures analysis of variance (ANOVA) or Chi-square test where appropriate. Multivariate linear or logistic regression will be used to explore the association between the use of secukinumab and outcome measurements adjusting for baseline characteristics. A 2-tailed probability value of $p < 0.05$ is considered statistically significant.

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Table 1. The minimal disease activity (MDA) criteria of Coates, *et al* (1). Patients are deemed to be in MDA when they meet 5 of 7 of the criteria.

Feature	Cutoff
Pain by VAS, 0–100	≤15
Global disease by VAS, 0–100	≤20
HAQ, 0–3	≤0.5
Tender joint count	≤1
Swollen joint count	≤1
PASI, 0–72	≤1
OR body surface area involved, 0–100%	≤3
Enthesitis	≤1

VAS: visual analog scale; HAQ: Health Assessment Questionnaire (2); PASI: Psoriasis Area and Severity Index (3). Enthesial sites assessed include the bilateral first costochondral joints, seventh costochondral joints, posterior superior iliac spines, anterior superior iliac spines, iliac crests, proximal insertion of Achilles tendons, and the fifth lumbar spinous process.

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Table 2. Modification of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis grid proposed for the Composite Psoriatic Disease Activity Index (1)*

	Not involved (0)	Mild (1)	Moderate (2)	Severe (3)
Peripheral arthritis		≤4 joints (swollen or tender); normal function (HAQ <0.5)†	≤4 joints but function impaired; or >4 joints, normal function	>4 joints and function impaired
Skin disease		PASI ≤10 and DLQI ≤10	PASI ≤10 but DLQI >10; or PASI >10 but DLQI ≤10	PASI >10 and DLQI >10
Enthesitis#		≤3 sites; normal function (HAQ <0.5)†	≤3 sites but function impaired; or >3 sites but normal function	>3 sites and function impaired
Dactylitis		≤3 fingers; normal function (HAQ <0.5)†	≤3 fingers but function impaired; or >3 fingers but normal	>3 fingers and has function impaired
Spinal disease		BASDAI <4; normal function (ASQOL <6)	BASDAI >4 but normal function	BASDAI >4 and function impaired

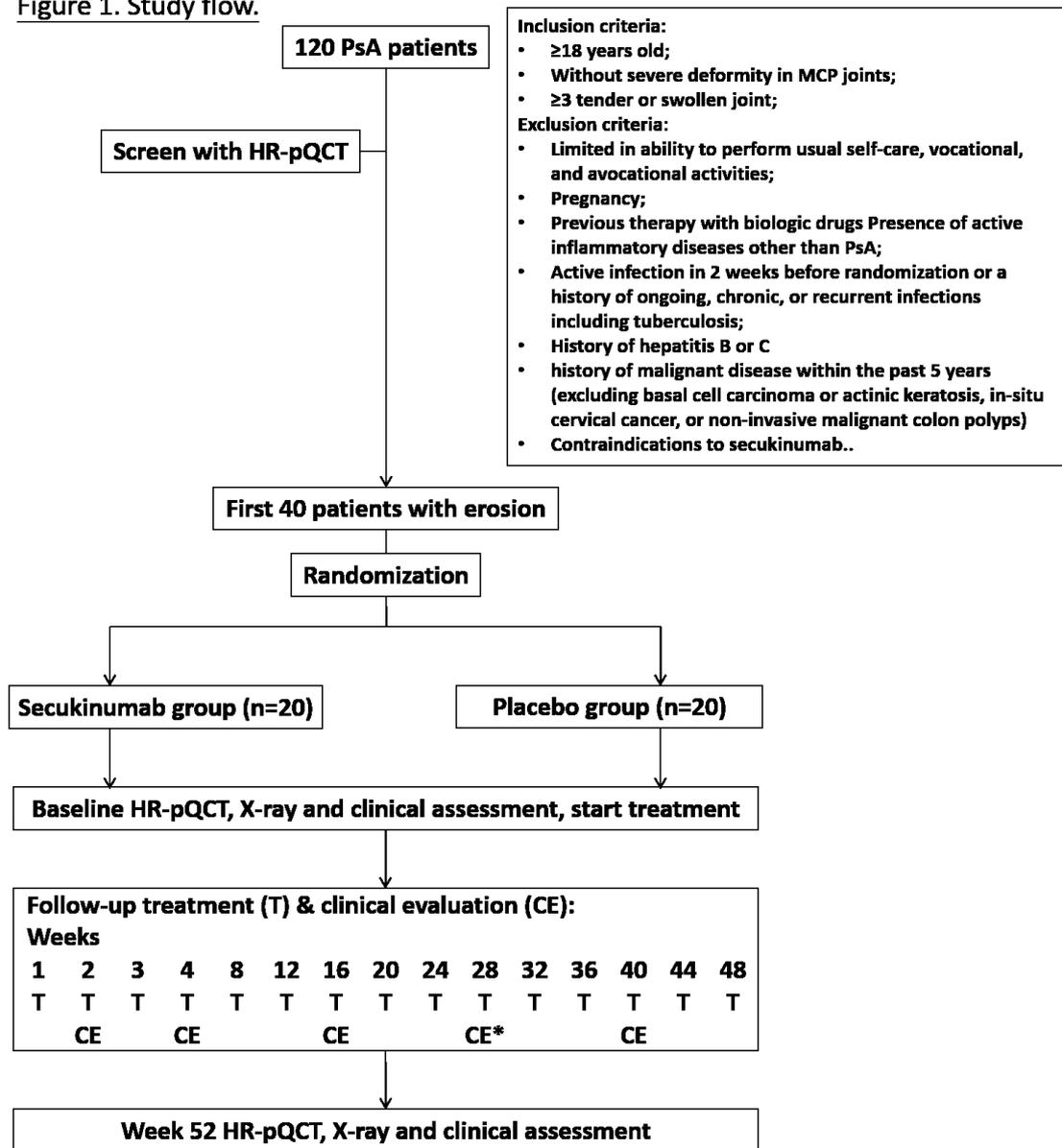
HAQ = Health Assessment Questionnaire (2); PASI = Psoriasis Area and Severity Index (3); DLQI = Dermatology Quality of Life Index (4); enthesitis# is assessed according to the Leeds enthesitis index (6 sites) (5), BASDAI = Bath Ankylosing Spondylitis Disease Activity Index (6); ASQOL = Ankylosing Spondylitis Quality of Life Questionnaire (7). † HAQ only counted if clinical involvement of domain (joint/enthesitis/dactylitis) is present.

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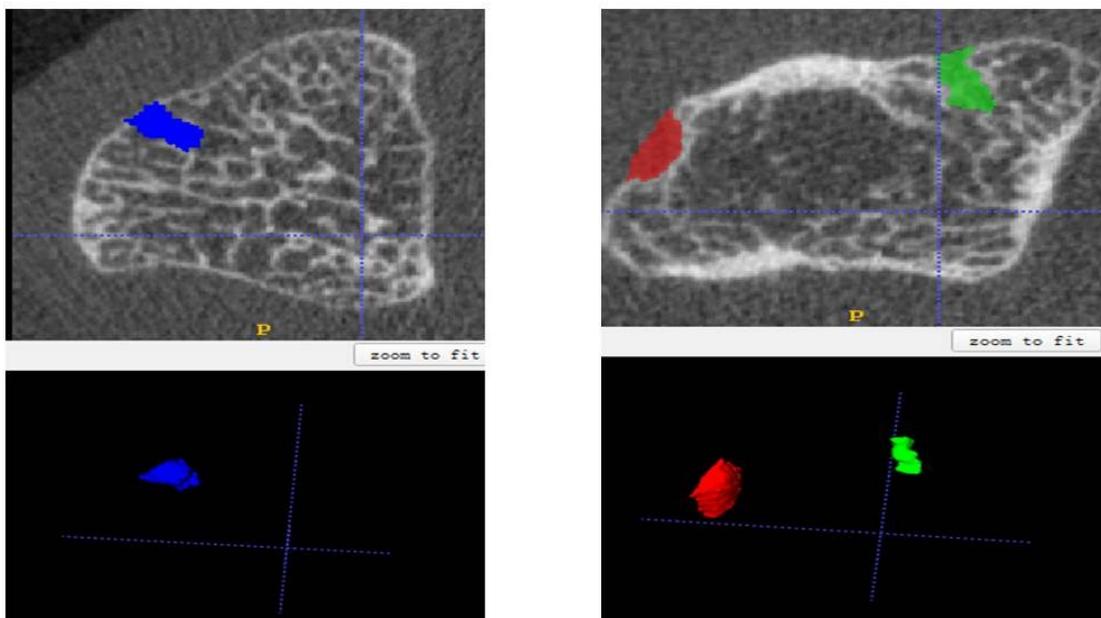
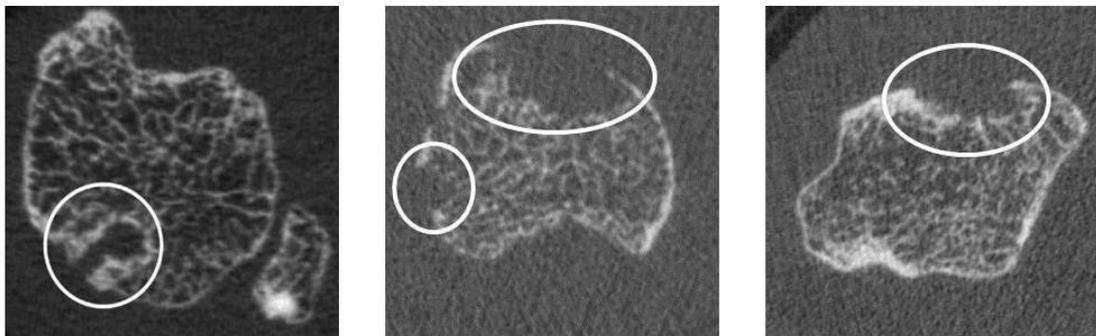
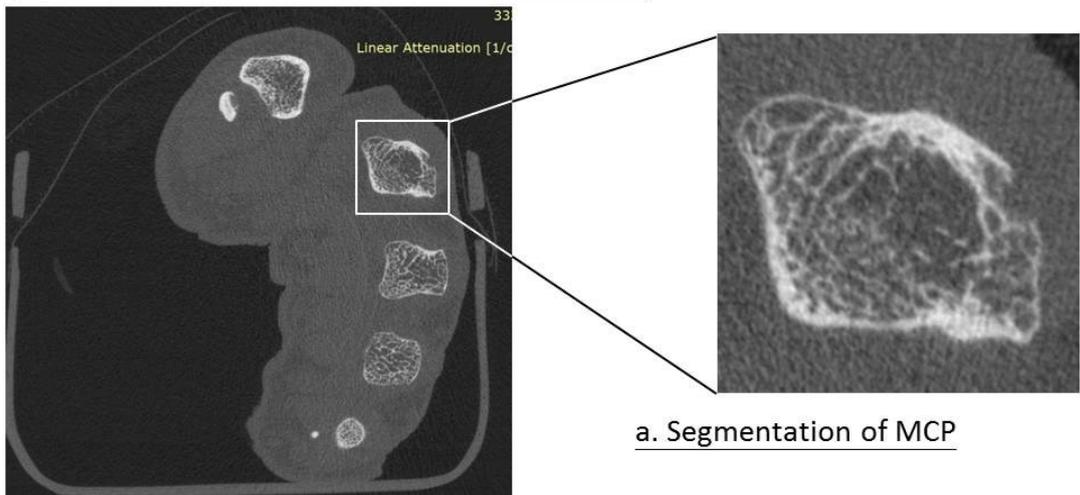
Figures:

Figure 1. Study flow.



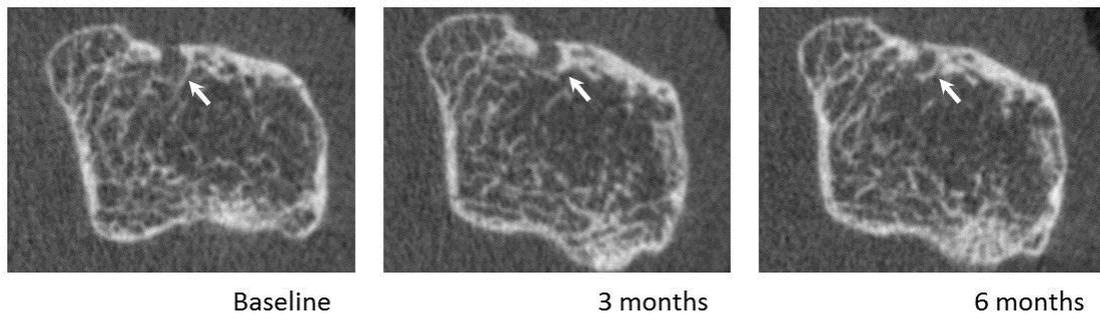
* Changes in the baseline treatment will be allowed since 28 weeks.

Figure 2. Quantification of the erosion volume .



Verosion= V1-V2; V =sum(A_i*0.082), where A_{1_i} or A_{2_i} is the area on slice i (mm²), including or excluding erosion, and 0.082 mm is the thickness of slice.

Figure 3. Osteosclerosis.



Typical images showing an erosion without osteosclerosis (Grade 0) at baseline, Grade 1 and Grade 2 osteosclerosis at 3 and 6 months in a pilot study, respectively.

Appendix 1. Criteria for application of The Samaritan Fund for patients with PsA

The biologic disease modifying anti-rheumatic drugs (DMARDs) are not reimbursed by the Hong Kong public healthcare system and are privately purchased by patients, which limit the use of these treatments. The Samaritan Fund provides financial assistance to these needy patients. The biologic DMARDs supported by Samaritan Fund for PsA patients are infliximab, etanercept, adalimumab, and golimumab. General principals in the use of Samaritan Fund for biologic DMARDs in PsA include:

1. Patients with arthritis fulfilling the Classification of Psoriatic Arthritis criteria (CASPAR classification criteria) for psoriatic arthritis (PsA); and
2. Persistent active disease as defined by: (1) ≥ 4 swollen joints; (2) ≥ 4 tender joints (dactylitis and enthesitis counted as one joint); AND (3) elevated ESR or CRP level, which should be made at 2 points at least 4 weeks apart; and
3. Failure of standard therapy: patients should have had an adequate trial of at least 3 standard DMARDs (Sulfasalazine, Methotrexate, Leflunomide and Cyclosporine A) in which Methotrexate must have been one unless contra-indicated.

Alternatively, patients with active spinal disease also eligible if:

1. Patient fulfilled the modified New York criteria for ankylosing spondylitis or the Assessment of SpondyloArthritis international Society (ASAS) classification criteria for spondyloarthritis; and
2. Persistent active disease

Active inflammation defined as BASDAI $>40/100$, or >4 swollen and tender joints

Patient global assessment $>40/100$; and

Physician global assessment $>40/100$; and

Objective evidence of an active disease, either:

- i. Elevation of acute phase reactants (either $ESR \geq 40$ mm/hr or $CRP \geq 20$ mg/L); or
- ii. A recent imaging study (such as MRI or bone scan) showing features of active disease (a formal report must be submitted with the application) – this does not apply for patient with pure oligoarthritis

3. Failure of standard therapy:

Three NSAIDs of different chemical classes at a maximal tolerated / recommended dose for at least 4 weeks for each agent used, (unless patient is contra-indicated to the use of NSAID or has developed significant adverse events rendering further use of NSAID not recommended) and

for patient with peripheral joint synovitis: must have had a trial of at least 2 standard DMARDs individually or in combination (Sulfasalazine, Cyclosporine, Methotrexate or Leflunomide).