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The SPECTRA Collaboration (Study grouP for xtrEme-Computed Tomography in Rheumatoid Arthritis) OMERACT Special Interest Group – Current Research and Future Directions

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Abstract:

Objective: High-resolution peripheral quantitative computed tomography (HR-pQCT) has potential to improve radiographic progression determination in clinical trials and longitudinal observational studies. The goal of this work is to describe the current state of research presented at OMERACT 2016, and ensuing future directions outlined during discussion among attendees.

Methods: At OMERACT 2016, SPECTRA introduced efforts to (i) validate HR-pQCT according to OMERACT guidelines - focusing on in rheumatoid arthritis (RA), and (ii) alternatives for automated joint space width (JSW) analysis. The SIG was presented to patient research partners, physicians/researchers and SIG leaders followed by a 40-minute discussion on future directions.

Results: A consensus definition for RA erosion using HR-pQCT was demonstrated through a systematic literature review and a Delphi exercise. Histopathology and perfusion studies were presented which explore the true nature of cortical breaks in HR-pQCT images, and provide Criterion Validity. Results indicate readers are able to discriminate between erosion and small vascular channels. Moderate reliability (ICC: 0.206-0.871) of direct erosion size measures was shown, which improves (>0.9) when only experienced readers are considered. Quantification of erosion size was presented for scoring, direct measurement and volumetric approaches, as well as a reliability exercise for direct measurement. Three methods for JSW measurement were compared, all indicating excellent reproducibility with differences at the extremes (i.e. near-zero and joint edge thickness).

Conclusion: Initial reports on HR-pQCT are promising, however to consider its use in clinical trials and longitudinal observational studies, it is imperative to assess the responsiveness of erosion measurement quantification.

Key Indexing Terms (MeSH): X-Ray Computed Tomography; 3-D Imaging; Arthritis,

Rheumatoid; Metacarpophalangeal Joint; OMERACT

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INTRODUCTION

Radiographic progression is a key outcome in randomized controlled trials for inflammatory arthritis. Unfortunately, the power of this assessment is limited in the early diagnosis and treat-to-target paradigm in RA, with most patients demonstrating little baseline joint damage or progression during trials. This is compounded with early timing of rescue therapies and limited exposure durations. In observational studies, plain radiography is the most feasible method for assessing damage progression, but only provides a 2D evaluation of a 3D surface, resulting in errors related to positioning and overlapping bony interfaces. Current radiographic scoring schemes are based on ordinal scoring of joint space width (JSW) and erosions, predisposing results to floor and ceiling effects, and significant progression is required to reach the incremental worsening threshold to detect score progression. For these reasons diagnostic imaging biomarkers with higher sensitivity to change, such as high-resolution peripheral quantitative computed tomography (HR-pQCT), could improve radiographic progression determination in clinical trials and longitudinal observational studies, as well as adding new outcomes for detection of pre-erosive bony changes (1), quantification of joint space narrowing, and assessment of bone densitometry and microarchitecture (2).

HR-pQCT is a relatively young imaging modality for quantitative evaluation of cortical and trabecular bone mineral density and bone microstructure, typically at the distal radius and tibia (3, 4). Quantitative measurements obtained with HR-pQCT are well established as biomarkers and outcome measures in osteoporosis research (5). HR-pQCT uses a very low irradiation dose (<5 μSv to image a 1 cm region of interest) and is approved by the US Food and Drug Administration. There are 70-75 sites worldwide, distributed on all continents, using either 82 or 60 μm isotropic resolution technology (SCANCO Medical AG, Brüttisellen, Switzerland). Advantages of HR-pQCT adoption in peripheral small joint imaging include high resolution, and detection of periarticular bone damage such as erosions, cysts, joint space narrowing and bone proliferations in inflammatory and degenerative disease not visualized sensitively with other imaging technologies such as plain radiography, ultrasound and magnetic resonance imaging (6, 7).

Pilot studies in inflammatory arthritis conditions demonstrated that scanning protocols were well tolerated by patients with active inflammation and those with chronic joint changes. Because motion artefact is a concern in image acquisition, scanning protocols were developed, along with position holders to stabilize the area of interest. Patient positioning and image acquisition takes 5-10 minutes compared to other imaging modalities such as conventional CT (10-15 Minutes) or MRI (20-45 minutes). Costs for one measurement by HR-pQCT varies between countries, but are comparable to a standard bone densitometry (DEXA) scan.

From this early pilot work, independent labs began to test the application of HR-pQCT for imaging peripheral joints. Some initial publications described visible pathological manifestations (6), while others compared findings at different stages of rheumatoid arthritis (8, 9) as well as different types of inflammatory arthritis, degenerative arthritis, and normal states (10, 11). Since then, 44 individual studies using HR-pQCT for arthritis assessment have been published or presented as abstracts (12), and led to the involvement of the SPECTRA collaboration in the formal OMERACT validation process. The collaboration is a global network of rheumatologists, clinicians, epidemiologists, engineers, radiologists, fellows, students, physicists, paediatricians, and industry partners. The inaugural SPECTRA meeting in Calgary in 2011 focused on standardizing

image acquisition across centres (13). Since then, membership has grown to 20 investigative sites from 5 continents, demonstrating clear interest in applying this technology in arthritis assessment for clinical research. The principal aims of SPECTRA are to (i) investigate HR-pQCT for arthritis assessment in clinical trials, (ii) validate HR-pQCT as a new imaging modality in clinical trials using OMERACT's incremental validation process, and (iii) harmonize SPECTRA's global efforts for efficiency.

SPECTRA adheres to the OMERACT filter 1.0 incremental validation process - truth, feasibility, discrimination, and filter 2.0, pathophysiological manifestations (14). The goal has been to target evaluation for findings sensitive to change in biologically relevant intervals not captured by current imaging techniques, and improve the correlation of imaging findings to function, which is significantly delayed with existing technologies. The aim of this work is to describe the current state of research as presented at OMERACT 2016, and the ensuing future directions outlined during the discussion among attendees.

MATERIALS AND METHODS:

At OMERACT 2016 in Whistler, Canada in May 2016, SPECTRA introduced HR-pQCT as a new imaging modality for outcome measures in clinical trials and longitudinal observational studies in a Special Interest Group (SIG). The collaboration's current research in validating HR-pQCT according to OMERACT guidelines was presented, focusing on the definition and evaluation of erosion in RA, and an automated algorithm for JSW analysis.

The SIG was presented to patient research partners, physicians/researchers and SIG leaders at OMERACT 2016. Following a 20-minute presentation, a 40-minute discussion on important next steps and future directions was moderated by two SIG leaders, with the other two SIG leaders collecting minutes.

RESULTS:

The SPECTRA SIG at OMERACT 2016 was attended by two patient research partners, 16 physicians/researchers and four SIG leaders.

Current State of Research

Pathophysiological Manifestations Visible with HR-pQCT

Table 1 shows current and ongoing research efforts presented at the SIG, as well as future research directions allowing conformity to OMERACT guidelines.

1. Definition and evaluation of erosions in RA

A consensus definition for RA erosions visualized by HR-pQCT was deemed an essential first step towards development of measurement frameworks. A systematic literature review was presented, and identified multiple approaches for defining erosion in HR-pQCT images (8, 15-17). These are consistent in that a cortical break must be present, and was expanded to assert that the break must be visible over multiple slices and in multiple planes. Erosion shape definition was also important (18), and differentiation between erosions and vessel channels was deemed necessary, Figure 1.

Eleven readers reviewed the definition and performed two scoring exercises to further refine it. A final scoring exercise on 58 joints gave 90% agreement on erosion presence, kappa 0.52 (95%CI 0.37-0.63) for all readers (of varying experience), and for experienced readers, kappa 0.76 (19). Experienced readers were those with greater than 5 years'

experience. These results were presented to 11 separate investigators and a Delphi exercise was performed. Results indicated 100% acceptance of the proposed definition.

A histopathology study was presented, which explores the true nature of cortical breaks in HR-pQCT (Criterion Validity), and provides anatomic data supporting the SPECTRA definition. A perfusion study with barium sulphate was presented, which correlates linear cortical channels with penetrating blood vessels (20). This data confirms the SPECTRA definition of erosion and that HR-pQCT can distinguish bone erosion from small vascular channels; a critical distinction for discrimination between healthy controls and individuals with early RA, who exhibit both physiologic vascular channels and small bone erosions (20).

Multiple approaches to measure erosion have been identified (21) – using either a semi-quantitative score, a direct measurement from 2D images, or volumetric approximation. Given that volumetric methods are not widely available, results from direct measurement were presented. Consensus was reached on a standard approach, which was tested for reliability in the RELEX-1 reading exercise. Moderate reliability was obtained (perpendicular width RMSCV 12.3%, ICC 0.206; axial width RMSCV 20.6%, ICC 0.665; perpendicular depth RMSCV 24.0%, ICC 0.783; axial depth RMSCV 22.2%, ICC 0.871) (19). ICCs increased to >0.9 for experienced readers only. Plans for a second study investigating responsiveness of the direct measurement approach (RELEX-2), as well as automated quantitative strategies consistent with the SPECTRA definition were described.

2. Joint Space Width

JSW is an indirect measure of arthritis disease activity. A systematic literature review was presented which identified published approaches to joint space measurement (15, 22, 23). Specifically, three techniques for high-throughput, robust, reproducible, fully-automated, quantitative 3D measurements of JSW from HR-pQCT derived data have been published (15, 22, 23).

In order to standardise JSW measurement among the SPECTRA consortium, a study has been performed to reach consensus on one method; either one of the three published or a hybrid. The methods were compared to test JSW measurement reliability (i) across a spectrum of RA disease (early to late), (ii) in scan/rescan (including re-positioning), and (iii) for the same joints measured on the two HR-pQCT devices available commercially (XtremeCT and XtremeCT II, Scanco Medical AG). Results indicate excellent reproducibility, with all three methods able to discriminate JSW across a spectrum of disease, and mean and minimum JSW estimates comparable between them. This comparison revealed that maximum JSW estimates were significantly different between the three methods, while minimum JSW reliability was sensitive to scan/rescan errors, particularly in joints with substantial narrowing, due to differences in handling zones with zero or near-zero thickness, Figure 2. There was no difference in JSW when measured using the two models of HR-pQCT.

DISCUSSION:

SIG Discussion & Future Research Directions

Following presentation of current research, future research directions were discussed. A consensus emerged that it is now imperative to perform a longitudinal study assessing the responsiveness of erosion measurement quantification, where one scoring method, direct measurement or automated measurement, must be selected which gives reliable

estimates of change over time and with treatment. If a manual method is selected, calibration of readers is required. Consequently, identification of disease specific cut-offs in erosion and JSW metrics, compared to normal findings in healthy controls, is necessary. Furthermore, it was recommended that performance of HR-pQCT be tested for detecting and quantifying pathological manifestations in comparison to other modalities (e.g. ultrasound, MRI) (18, 21), as well as other rheumatological diseases; e.g. osteoarthritis, psoriasis and psoriatic arthritis, and crystal arthropathies. Translation of the methods to other sites of interest, for example the wrist (23) or metatarsophalangeal joints, would also aid in increasing sensitivity to detect activity in site-specific diseases.

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Figure Legends

Figure 1. HR-pQCT image of the metacarpophalangeal head, transverse view. Arrows indicate examples of (a) an erosion and (b) a vessel channel.

Figure 2. (a) and (b) Two examples of HR-pQCT images of the MCP II joint at different stages of arthritis disease, and (c) and (d) their corresponding joint space masks. Colours indicate where each of the three algorithms (1, 2, 3) had full (white), partial (orange, purple, green) or no agreement (yellow, red, blue) in defining the joint space mask volume. Joint space volume for (a) was 90, 94 and 70 mm^3, and (b) 106, 114, 87 mm^3, for algorithms 1, 2 and 3, respectively.