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Evaluation of Minimally Invasive, Ultrasound-guided Synovial Biopsy Techniques by the OMERACT Filter — Determining Validation Requirements

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ABSTRACT. ***Objective.*** Because limited data currently support the clinical utility of peripherally expressed biomarkers in guiding treatment decisions for patients with rheumatoid arthritis, the search has turned to the disease tissue. The strategic aim of the Outcome Measures in Rheumatology (OMERACT) synovitis working group over the years has been to develop novel diagnostic and prognostic synovial biomarkers. A critical step in this process is to refine and validate minimally invasive, technically simple, robust techniques to sample synovial tissue, for use both in clinical trials and routine clinical practice. The objective of the synovitis working group (SWG) at OMERACT 12 (2014) was to examine whether recently developed ultrasound (US)-guided synovial biopsy techniques could be validated according to the OMERACT filter for future clinical use recommendation.

Methods. The SWG examined whether current data reporting US-guided synovial biopsy of both large and small joints addressed the OMERACT filters of truth, discrimination, and feasibility.

Results. There are currently limited data examining the performance of US-guided synovial biopsy, mainly from observational studies. Thus, it remains critical to evaluate its performance, within the clinical trials context, against the current gold standard of arthroscopic biopsy, with particular reference to: (1) synovial tissue yield, (2) capacity to determine treatment response as measured by a validated synovial biomarker, and (3) tolerability of the procedure.

Conclusion. We summarize the discrete work packages agreed to as requirements to validate US-guided synovial biopsy and therefore lead to a global consensus on the use of synovial biopsy for research and clinical practice. (First Release June 1 2015; J Rheumatol 2016;43:208–13; doi:10.3899/jrheum.141199)

Key Indexing Terms:
SYNOVITIS BIOPSY RHEUMATOID ARTHRITIS ULTRASOUND

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In the past 2 decades the critical association between ongoing synovitis and structural damage in patients with rheumatoid arthritis (RA) has been recognized and has contributed to a paradigm shift in treatment with a sustained treat-to-target approach, now accepted as "gold standard" therapy[1]. In part fueled by the development of novel biologic agents, this approach has generated significant longterm improvements[2]. However, our ability to induce sustained remission and/or cure on an individual level remains limited, with insufficient information to guide selection of therapy based on prognosis and/or predicted response to treatment[3]. Because limited data currently support the clinical utility of peripherally expressed biomarkers[4,5,6,7], focus has turned to the use of synovial tissue biomarkers[8,9,10,11,12,13]. This is consistent with practice in other medical specialties such as oncology, where examination of pathobiological specimens from disease tissue have demonstrated prognostic value and are now integrated into standard care. In RA, however, synovial biopsy is not currently considered as a standard intervention in either routine care or in randomized controlled trials (RCT) for a variety of reasons[14]. Thus, the strategic aims and objectives of the Outcome Measures in Rheumatology (OMERACT) synovitis working group (SWG) are to develop a minimally invasive, simple, well-tolerated, and robust technique to sample synovial tissue from most patients/joints to use in turn to develop novel diagnostic/prognostic biomarkers[15,16].

The objective of the SWG at OMERACT 12 (2014) was, therefore, to examine whether recently developed ultrasound (US)-guided synovial biopsy techniques could be validated and recommended for future use to monitor therapeutic responses in RCT and/or for patient stratification.

Current Status on Synovial Tissue Acquisition

Acquisition of synovial tissue using an arthroscopic approach in RCT is currently recommended[14] based on: (1) extensive data confirming the safety and tolerability of the procedure[17,18,19], (2) its ability to sample synovial tissue from multiple sites within the joint, and (3) the means to sample joints with minimal synovitis[20]. However, outside of highly specialized centers, routine arthroscopic sampling of synovial tissue has not been widely adopted. This is due to a number of factors: technical training required for the procedure[19], economic cost of the required equipment and capacity/infrastructure[19,21], and the general acceptability of a relatively invasive technique to patients and/or their rheumatologists. Importantly, based on the recognition that small joint involvement is often prominent in early arthritis[22], and large joint involvement is associated with more severe and established disease[23], there is increasing interest in acquiring synovial tissue from small synovial joints[24,25] to understand the early stages of disease pathogenesis by clearly distinguishing mechanistic pathways, as well as to ensure the recruitment of representative RA cohorts into RCT. However, even with small-bore arthroscopy[26], the limitations of the procedure remain. Unless less-invasive techniques are validated, synovial biopsy is unlikely to be widely adopted.

Thus techniques using US to direct synovial tissue sampling are attractive: they are minimally invasive, applicable to both large and small joints, relatively inexpensive to perform, and technically simple. Two principal techniques for performance have been described: a portal and forceps (P&F) approach[27] and more recently, adaptation using a quick core needle[28]. Both techniques use US to locate a suitable area of synovial tissue to biopsy. The P&F approach uses a 14-16G introducer, guide wire, and coaxial sheath. The coaxial sheath remains *in situ* during the procedure and facilitates repeated introduction of biopsy forceps to the joint. Conversely, the US-needle biopsy (NB) technique uses either a 14- or 16-G needle repeatedly entered into the joint without requiring insertion of a relatively larger coaxial sheath (Figure 1).

Although US-guided biopsies may offer distinct advantages over arthroscopic sampling (Table 1), this approach cannot be recommended for use within RCT until it has been shown to fulfill the OMERACT filter of truth, discrimination, and feasibility.

MATERIALS AND METHODS

The SWG met at OMERACT 12 (2014) to discuss currently available data examining the performance of US-guided synovial biopsy against the OMERACT filters of truth, discrimination, and feasibility and to define future discrete work packages to validate the technique for use in clinical trials.

RESULTS

OMERACT Filter "Truth"

Synovial biopsy of large joints. US-guided synovial biopsies of large joints using a P&F[29,30] and NB approaches have been reported with success rates of 89–93%[28,30] for histopathological analyses and extraction of good-quality RNA from all samples reported. To overcome the heterogeneity of synovial tissue sampling in large joints, current OMERACT recommendations include acquisition from separate sites of at least 6 biopsies for histopathological and gene expression analysis, respectively[14]. Such a standard has not been evaluated for

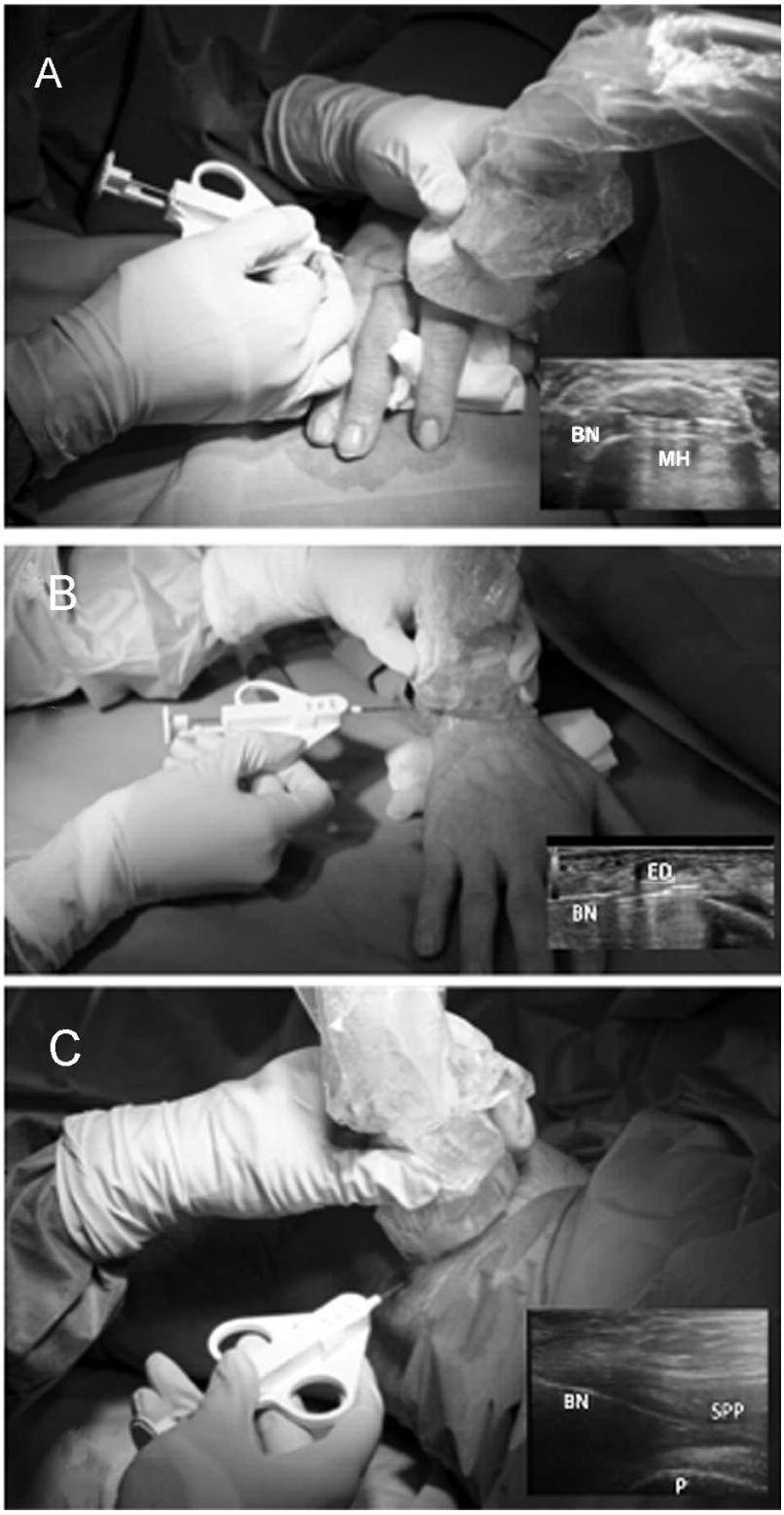

Figure 1. US-guided synovial biopsy. A. US-guided needle biopsy (NB) of the metacarpophalangeal (MCP) joint; inset shows transverse US image of biopsy needle (BN) insertion into MCP joint space (MH, metacarpal head). B. US-guided NB of wrist joint. Inset illustrates transverse image of biopsy needle insertion into wrist joint under extensor digitorum (ED) tendon. C. US-guided synovial biopsy of knee joint. Inset illustrates transverse image of biopsy needle insertion into suprapatellar pouch (SPP; P: patellar). US: ultrasound.

Table 1. Relative merits of techniques currently used in clinical trials to sample synovial tissue.

	Arthroscopy		US-guided P&F		US-guided NB	
	Joint Size					
	Large	Small	Large	Small	Large	Small
Validation	+++	+	+	++	+	+
Technically simple	+	+	++	++	+++	+++
Patient acceptability**	+++	*	*	*	+++	+++
Suitable for serial biopsies	+++	+++	*	*	++	++

*No data available; **No data available that directly compare techniques. P&F: portal and forceps; NB: needle biopsy; US: ultrasound.

either US-guided technique. Given the distinct differences in biopsy tools (i.e., forceps vs needle), it is also critical to evaluate the yield of synovial tissue (histopathological and RNA) between each technique and to compare these data against the current gold standard of arthroscopy.

Small joint biopsy. Data support the use of US-guided biopsy of small joints using both the P&F[27] and NB techniques[28]. However, in comparison with extensive validation data available for large joint biopsies, limited data are available for small joints. One report indicates that US-P&F biopsy of small joints[28] provides sufficient tissue for reliable histopathological assessment; however, this validation exercise was restricted to defining the biopsy area (rather than biopsy number) and therefore is difficult to extrapolate to routine practice. Further, given the interest in sampling small joints with minimal synovitis, particularly following effective treatment, it is also important to recognize that serial sampling using US-NB has been reported to be feasible[28] whereas US-P&F approach has not, primarily because of the challenge of inserting a larger coaxial sheath into minimally inflamed joints. As with large joints, currently there has been no systematic examination of overall yield of synovial tissue sampled using US-NB from small joints.

Therefore, key steps to be addressed before US-guided needle biopsy of small joints can be recommended in RA include: (1) to define the minimum number of biopsies required per procedure to ensure accurate histopathological assessment and adequate RNA yield; and (2) to systematically address whether US-guided biopsy reaches these defined standards for small joints.

OMERACT Filter "Discrimination"

The number of sublining CD68+ macrophages remains the only validated synovial biomarker recommended by OMERACT, with data to indicate that it varies according to clinical response[31] and is not modulated by ineffective therapy[32]. Its performance, using arthroscopic biopsies within the setting of multicenter RCT, has been reported[33,34]. However, whether the sublining macrophage number obtained from synovial tissue using US-guided biopsies discriminates between clinical disease states and active therapy has not been reported, and examining this within the context of a clinical trial remains an important validation step.

OMERACT Filter "Feasibility"

When considering the feasibility for broad adoption of US-guided biopsy into RCT and routine clinical care, a crucial step will be determination of its acceptability to patients. Although there are data to support the safety of both US-NB[28] and US-P&F[30] and acceptable tolerability of US-NB in a small cohort[28], both will require further evaluation, including through the application of patient questionnaires within large RCT. Further, examining a "learning curve" for clinicians undergoing training in US-guided

Table 2. Summary of planned validation exercises to evaluate US-guided synovial biopsy versus arthroscopy according to the OMERACT filter.

OMERACT Filter	Standard to Assess Per Procedure	Procedures to Evaluate	Joints
Truth	Histopathological quality	US-NB, US-P&F	Large and small
	RNA yield	US-NB, US-P&F	Large and small
Discrimination	Sublining macrophage number versus clinical response	US-NB, US-P&F	Large and small
Feasibility	Patient acceptability	US-NB, US-P&F	Large and small
	Evaluation of performance in a multicenter clinical trial	US-NB, US-P&F	Large and small
	Defining learning curve for new operators	US-NB, US-P&F	Large and small

US: ultrasound; P&F: portal and forceps; NB: needle biopsy.

synovial biopsy by defining numbers of observed/supervised procedures would be of critical importance to permit the development of robust training requirements for trainees.

Applying US-guided synovial biopsy to RCT. Evidence from observational studies already indicate that synovial biomarkers can predict responses to biologic therapy in RA[9,35,36], and this hypothesis is currently being examined in 2 UK-wide RCT funded by: (1) the R4RA (National Institute for Health Research: Response, Relapse, Resistance to Rituximab study); and (2) STRAP (Stratification of Biologic Therapies for Rheumatoid Arthritis by Pathobiology study), jointly funded by the Medical Research Council and Arthritis Research UK. Such trials are critical to thoroughly examine whether synovial biopsy offers clinical utility in the unbiased environment of a RCT. This would address 1 of the core aims of the SWG, because US-guided biopsy is incorporated into both of the above RCT protocols, while the comparison of sampling methods with arthroscopy using descriptive, correlation, and reliability statistics will provide a unique platform to examine the performance of the procedures in the context of multicenter RCT. Critical research questions posed within the studies will also offer the opportunity to perform a resource use/economic impact assessment, as a core domain included within the recently revised OMERACT Filter 2.0 framework[37].

The principal research agenda set by the SWG at OMERACT 12 is to deliver the discrete work packages that will lead to a global consensus on the use of synovial biopsy for research and clinical practice. Further, a systematic literature review of currently available synovial biopsy techniques in the context of clinical trials will be performed. The discrete work packages are summarized in Table 2 and focus on validation of a minimally invasive synovial biopsy technique for both small and large joints in RA — critical to facilitate the group's overarching aim to identify synovial biomarkers for treatment response, diagnosis, and/or prognosis.

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