Review

Potential role of arthroscopy in the management of inflammatory arthritis

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ABSTRACT

Despite its advantages in diagnosis, treatment and research, the role of arthroscopy in the management of rheumatic diseases has diminished due to the development of other less invasive means of joint assessment including advances in imaging techniques, e.g. ultrasound and magnetic resonance imaging. However, arthroscopy still provides invaluable information. By direct and precise internal inspection of a joint, arthroscopy allows the collection of synovial membrane samples (biopsies) of excellent quality, notably from the most representative pathological areas. Arthroscopy may also play a therapeutic role in the management of inflammatory arthritis (IA) by providing pain relief (lavage). Here we describe the procedure of knee arthroscopy under local anaesthesia, as well as an in situ visual assessment of synovial inflammation and its correlation with degree of histological and immunological abnormalities. With the emphasis being placed on early diagnosis and treatment initiation in patients with IA and as earlier initiation of targeted biologic therapies becomes more commonplace, the ability to predict which patients will respond to the different therapies available would be invaluable. Assessment of arthroscopic derived synovial biopsies has potential to play an important role in management of early IA in the future.

Introduction

Traditionally, arthroscopy has been the domain of orthopaedic surgeons, in view of the treatment opportunities they offer in the field of mechanical repair of joint instability or trauma (including meniscal suture, rotator cuff repair). However, next to its use in the orthopaedic field, the need for an arthroscopic inspection of a joint may arise during the management of inflammatory joint diseases. In addition to its therapeutic benefit in affording pain relief by synovial fluid aspiration and joint lavage, arthroscopy may be a diagnostic tool used to distinguish different form of inflammatory arthritides in specific situations and also a research tool, allowing for the collection of high quality biopsies under direct visualisation, while providing important information with respect to the local tissue environment. This review will elaborate on the technical aspect of knee arthroscopy and the value of synovial tissue biopsy in a clinical research setting. Considering the current, non-invasive alternatives to joint imaging, we will discuss the place of arthroscopy in the current management of inflammatory joint diseases and evaluate the benefit to risk ratio related to the exclusive type of information arthroscopy can provide.

Knee arthroscopy under local anaesthetic

The methodology described below is used in the department of Rheumatology at the University of Leeds, UK (1). Performing arthroscopy is not limited to surgeons, thus, it is possible for any registered medical practitioner to perform arthroscopies for rheumatology research purpose provided they fulfil regulations such as in France (i) to have received instruction and practised in an recognised training centre, (ii) to maintain professional education, and (iii) to perform this act under stringent conditions, including a dedicated operating room, and fulfil standards of inline with current clinical practice and established training guidelines (2). A survey of 36 rheumatology centres (33 returned survey) performing arthroscopy indicated that 73% of rheumatologists performing arthroscopy received

informal training from an orthopaedic or rheumatology colleague. Thirty-three percent had participated in the formal EULAR arthroscopy course and 39% had participated in an unspecified formal course.

Arthroscopy can only be performed after written fully informed consent is obtained from the patient, who must receive written details of the operative procedure and its complications. Potential complications of knee arthroscopy include post-procedure pain, infection or haemorrhage (see below).

The knee joint is washed with povidine-iodine solution or alternative sterilising solution before being surrounded by drapes to ensure surgical sterility. The skin and soft tissue is anaesthetised by local injections of lidocaine and xylocaine-adrenaline subcutaneously using lateral and infra-patellar approach without touching the capsule to avoid modifying the vascularisation observed thereafter. Once the patient is in a dorsal decubitus position, the knee is aspirated and synovial fluid is collected. Following aspiration, without removing the needle, 10ml of local anaesthetic (lidocaine 1 or 2% or bupivicaine 0.25%) is injected followed by approximately 50 ml of warmed saline to ease insertion of the arthroscope into the joint. The arthroscope used for the knee can vary from 2.7 to 4.0 mm in diameter with 30° angle of view with the knee flexed at 90 degrees; a small incision is made at the lateral infrapatellar portal site down to the synovial membrane and the arthroscope sheath and blunt obdurator are inserted into the joint. After penetrating the capsule, the knee joint is slowly extended allowing the obdurator and sheath to pass cranially within the knee joint between the patella and the femur. The blunt obdurator is removed and the arthroscope inserted through the sheath into the knee joint. Approximately 1 litre of saline is required to perform full arthroscopic examination of the knee lasting nearly 20 minutes with the saline being attached to the irrigation port of the arthroscope port. The arthroscope is connected to a recording unit to enable direct visualisation of the synovial membrane on a video screen. A systematic examination of the synovial membrane including the peri-meniscal region (Fig. 1), patellofemoral and femorotibial cartilage surfaces (setting the knee in varus and valgus positions) is made with particular attention paid to two parameters: a) synovial vascularity (Fig. 1) and b) synovial proliferation (grainy or villous hypertrophy) (Fig. 1). An examination of the cartilage can then be carried out and any injuries evaluated according to different scores (3). In the absence of any specific risk factor, no anticoagulation therapy is needed, as joint immobilisation is not necessary. Following the procedure, a compression bandage is usually applied for 24h.

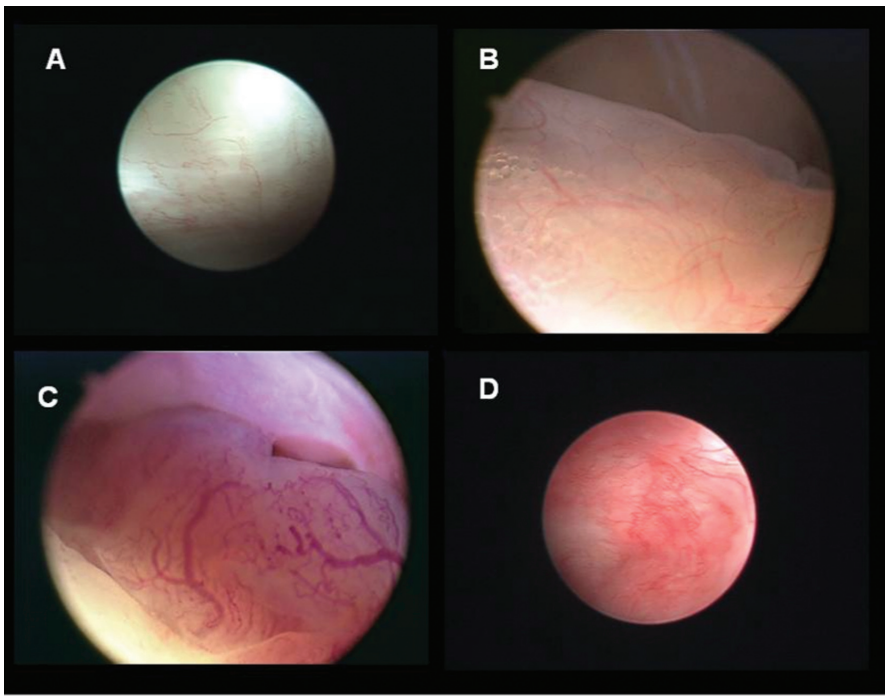

Fig. 1. Examples of synovial vascularity.
A Normal synovial membrane. **B** and **C** Increased vascular network observed in RA synovitis.
D Increased vascular network observed in reactive arthritis synovitis

With reduction in the diameter of arthroscopes (1.0–2.4mm) and increasing flexibility, mini-arthroscopy of smaller joints (wrist, metacarpophalangeal [MCP]) is possible. Good correlations between directly visualised level of inflammation and immunohistochemical (IHC) analysis of biopsy specimens from both small joint and knee biopsies, from the same patient, performed the same day, have been demonstrated. IHC analysis assessed number of infiltrating macrophages and T-lymphocytes and expression of interleukin-6 (IL-6) (4). However, the volume or number of synovial biopsies collected by mini-arthroscopy is significantly lower than those obtained from regular arthroscopy. Potential adverse effects of mini-arthroscopy of small joints include risk of capsular rupture. There has been an argument for performance of knee mini-arthroscopy exclusively for research purposes; however, small joint assessment may be invaluable especially in very early RA, where the knee joint may not be involved (5). Small joint arthroscopy is also important in visualising *in situ* deposition of sodium urate crystals in acute gout (6), and can be used to perform synovectomy of the wrist joint in RA patients with demonstrated clinical efficacy (7, 8).

Collecting synovial biopsies

A small incision to puncture the synovial membrane at the lateral supra-patellar biopsy portal is made. The biopsy portal and blunt obdurator are inserted into the knee and a drain is attached at the biopsy portal site. Synovial biopsies of representative areas of inflamed synovial membrane are obtained under direct visualisation using grasping for-

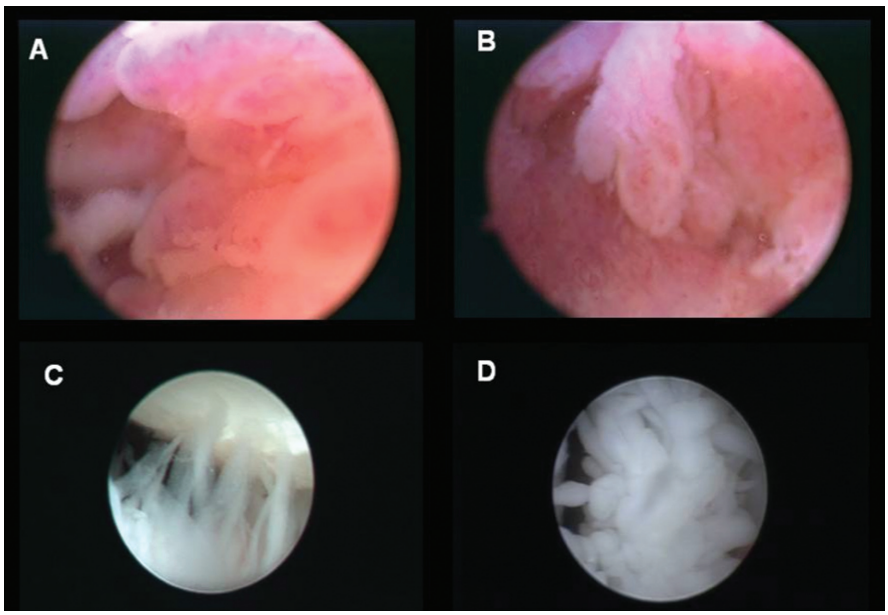

Fig. 2. Examples of synovial proliferation.
A and **B** Increase in volume of the RA synovial membrane with villous formation.
C and **D** Granular infiltrate of the synovial membrane.

ceps. Multiple samples (minimum 6) are usually obtained.

Synovial biopsy can be performed blindly without the help of an arthroscope in a strictly aseptic room dedicated to invasive procedures. Performed using a 4mm Parker Pearson trocar, it has the advantage of not requiring a full operating room, requiring a single IA incision, and may be coupled to lavage with saline (9). The main disadvantage is the inability to directly visualise the most relevant area to biopsy (10). The data obtained using such synovial biopsies are also more difficult to interpret because of direct effect of the mechanical force used to collect the tissue "by pushing" that can be confused with the effect of inflammatory arthritis.

Main complications

An important adverse event of arthroscopy is septic arthritis, hence the need for patient to be clearly informed before the procedure. Intravenous antibiotic prophylaxis one hour prior to knee arthroscopy was evaluated retrospectively using 3.231 operations (11). Results showed limited benefit, the infection rate being 0.15% in patients who received antibiotics *versus* 0.16% in other patients.

Post-operative residual pain and sensation of anatomical displacement are also often reported post-procedure but usually can be treated effectively with simple analgesics such as acetaminophen and spontaneously resolve. IA injection of bupivacaine was efficient in reducing discomfort following knee arthroscopy but had limited efficacy in the wrist (12). Other complications are very rare, algodystrophy being one of them (13). Finally, vascular complications, even if rare, must always be investigated in case of acute post-operative pain using power Doppler examination.

Tolerance and safety of arthroscopies performed by rheumatologists compared to orthopaedic surgeons was evaluated using procedure from 33 centres worldwide (24 European, 10 in USA and 2 in Australia, 72 rheumatologists and 16.532 arthroscopies) (14). Similar numbers of arthroscopies were performed for diagnosis, treatment and research purposes. The most frequent complications described were haemarthrosis (0.9%), the majority occurring in procedures involving cartilage. The rate of intra-articular infection (0.1%) significantly correlated to the volume of saline used for joint irrigation. Other complications reported included iatrogenic damage from the procedure itself, deep venous thrombosis (0.2%) and nerve damage (0.02%). Complications in arthroscopies performed for rheumatology research purposes were nevertheless much less frequent than those described after orthopaedic arthroscopy procedures, which are notably more complex and lengthy, usually requiring general anaesthesia.

Arthroscopy for diagnosis

Arthroscopies were initially developed and used by orthopaedic surgeons for diagnostic purposes (15). The synovial membrane of healthy volunteers has a bright, white and smooth transparent membrane covering the articular capsule and presenting variable degree of fat deposition (16) (Fig. 1). The vascular network consists of regularly distributed thin and straight vessels. In rheumatoid arthritis (RA), several studies showed that the most severe synovitis is located close to the cartilage surface, at the level of the patella. Synovitis is easily identifiable and has characteristic features. Firstly, the number of blood vessels observed in an inflamed knee joint is greatly increased and morphologically vessels are more tortuous. Secondly, there is an increase in volume of the synovial membrane with oedema and villous formation resulting from the hyper-proliferation of the underlying layers of soft tissue (Fig. 2 A-B). Notably, there is a strong relationship between the number of vili observed *in vivo* and the extent of lymphocyte infiltration within the tissue detected in synovial biopsy (17). An intermediary state of inflammation consisting of a granular infiltrate is also described (Fig. 2 C-D). Regions of pigmentation corresponding to previous haemorrhage can also be seen. Fibrin can be deposited in a disorganised form or in small rice like deposits. The pannus, the proliferating synovial membrane which adheres to cartilage and is implicated in causing cartilage destruction (18), can be observed in Figure 3. The assessment of the pannus attachment to cartilage has been the object of several studies (19). TNF-alpha, IL-1, IL-6 and GM-CSF are detected at higher concentration in cells from the pannus-cartilage junction, particularly at the site of cartilage erosion in RA (20).

In clinical practice, arthroscopies and synovial biopsies (Fig. 4) are primarily

indicated in cases of a) "dry" monoarthritis or chronic arthritis, where the joint space is filled with inflamed synovial tissue with little fluid, b) to distinguish some rare causes of arthritis, c) in cases of septic arthritis, where regular lavage is performed until infection is resolved. Although rare, less than 2 cases per million inhabitants, pigmented villonodular synovitis (PVNS) has been described and commonly affects large joints including knees. Presence of PVNS can be a diagnostic biomarker of early IA (21). This condition is easily identified under arthroscopy due to the tan-brown colour of the synovial membrane caused by hemosiderin deposition (22). Similarly, the appearance of crystal arthropathy is typical, as shown in Figure 5, with *in situ* visualisation of calcium pyrophosphate crystals in chondrocalcinosis or uric acid crystals in gout.

These features contributed to diagnostis at time when alternative biomarkers are not fully available, even if Kraan *et al*. (23) showed that the immunohistochemical analysis of the synovial membrane from early arthritis patients can be used to differentiate RA from non-RA patients, with notably a high expression of macrophages, B- and plasma cells in RA synovium. The primary role of arthroscopy in diagnosis is currently in the initial management of patient with IA, particularly in patients with oligo- or mono-arthritis who do not meet the criteria for classification of RA or alternate inflammatory disease and whose immunological status is non-contributory. Differentiating patients who will evolve towards RA from other forms of IA using visual biomarkers has very important potential. Knee arthroscopy performed in 44 patients with early IA (<1 year of symptoms) (24) and in 100 with undifferentiated arthritis (25) demonstrated characteristic vascular and synovial membrane features depending on the diagnosis (notably RA, psoriatic arthritis and reactive arthritis). Using videotapes of knee arthroscopy, three independent observers successfully identified patients with a diagnosis of RA by characteristic synovial features of straight vessels with branching. Reactive or psoriatic arthritis demonstrated a different vascular pattern of thickened, tortuous vessels. These subjective visual features can be detected by experienced operators. However, arthroscopy is obviously not required for daily diagnosis of psoriatic and rheumatoid arthritis and is not part of any current diagnostic criteria. Further information was obtained using analysis of synovial biopsies which show differential gene expression dependant on diagnosis. A significant increase in the Fibronectin and the ReXS1 genes was demonstrated in patients with reactive arthritis compared with RA (26). RA synovium expresses both calmodulin and cellular apoptosis susceptibility (CAS) genes which encode proteins involved in calcuim signalling and cell division respectively (27). The identification of synovial biomarkers remains in constant evolution (28, 29). Markers such as the infiltration of particular subset of cells (plasma cells) or expression of survival factor (such as APRIL) are associated with RA patients with anti-citrillunated peptides antibodies (ACPA-positive patients) (30). The identification of a synovial biomarker which would allow early diagnosis of

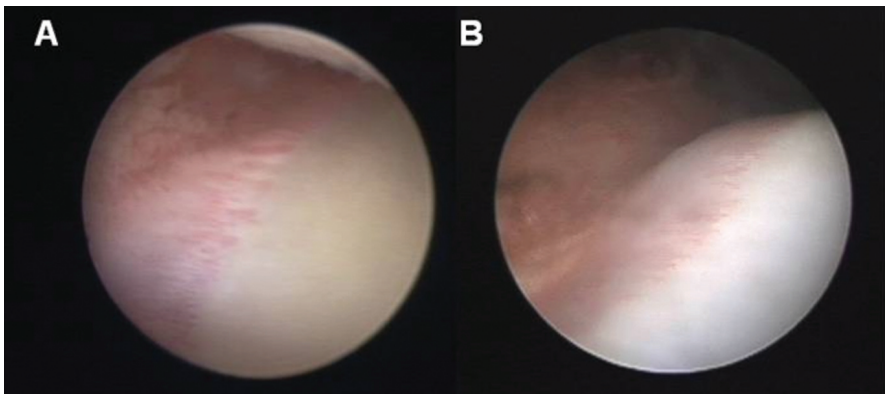

Fig. 3. Pannus observed in rheumatoid arthritis synovium.
A and **B** RA pannus.

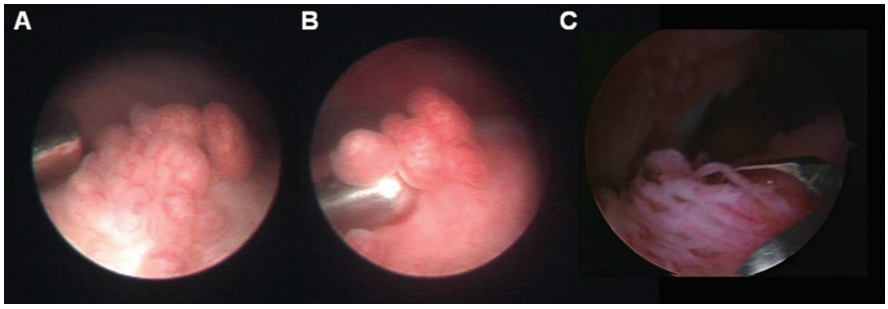

Fig. 4. Biopsy of the synovial membrane.
A, **B** and **C** Synovial biopsies.

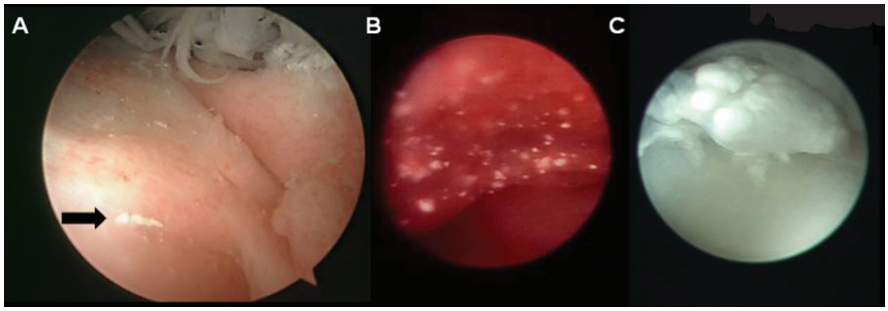

Fig. 5. Crystal arthropathies.
A Calcium pyrophosphate crystals of chondrocalcinosis. **B** Uric acid crystals of gout. **C** Crystals of chondrocalcinosis.

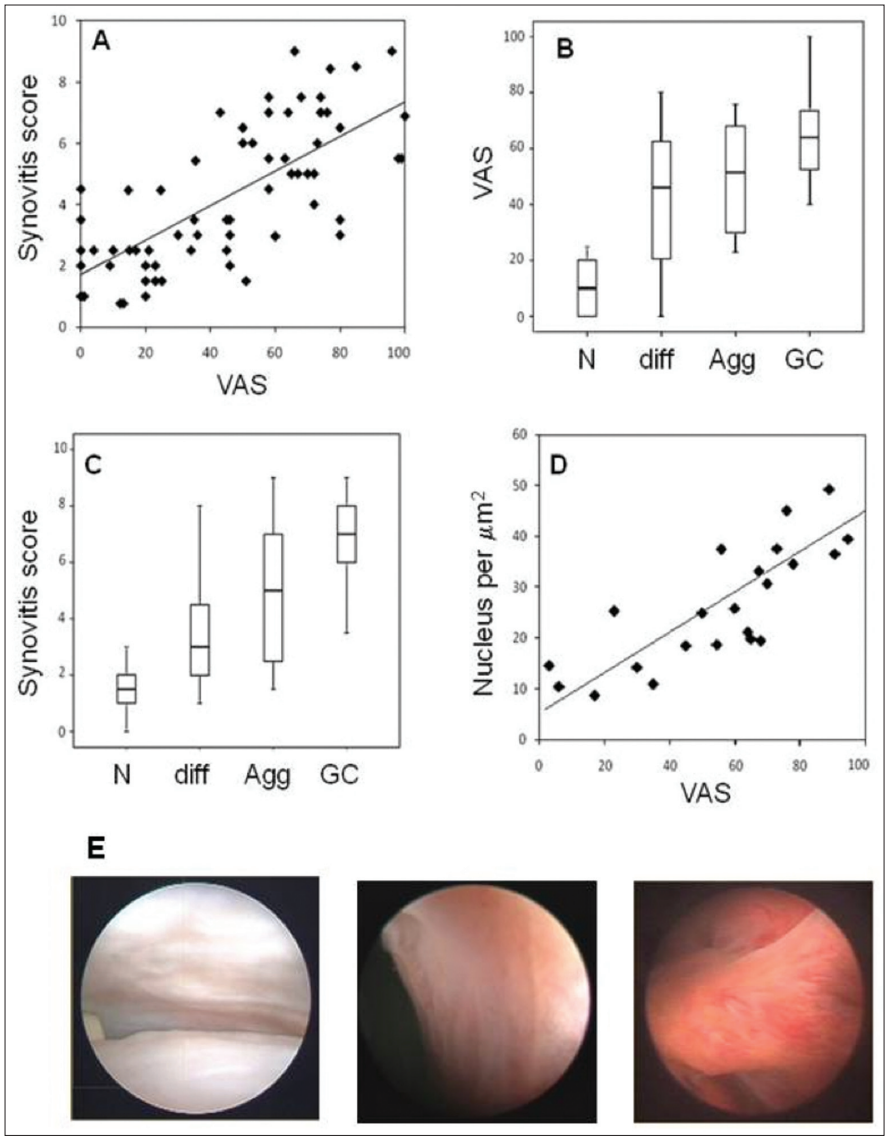

Fig. 6. Synovitis scores and aspects.
A Histological synovitis score developed to quantify the synovial membrane lining layer thickness, stromal cell proliferation and infiltration, which has close correlation with arthroscopic VAS.
B Correlation between arthroscopic VAS and tissue architecture (normal, diffuse, aggregate or tertiary germinal centre) as well as synovitis score (**C**). **D** Correlation between the number of nucleus per µm^2 and arthroscopic VAS. **E** Aspects of low, intermediate and high arthroscopic VAS.

ACPA-negative RA would greatly improve management of this patient cohort.

Therapeutic aspect of arthroscopy

As described above, the arthroscopic procedure involves lavage with at least 1 litre of saline. Arthroscopic lavage can be complemented by a pain relief procedure with intra-articular injections of corticosteroid and/or anaesthetic (bupivacaine) for rapid analgesic effect. A randomised trial notably showed increased efficacy of lavages with administration of corticosteroids during arthroscopy compared to intra-articular injection of corticosteroid alone following joint aspiration (31).

With the advent of targeted biological therapies, the indication of synovectomy in IA has become less prominent. Synovectomy performed during arthroscopy is employed in septic arthritis (32) and for pain relief in resistant RA (33). Local synovectomy with hexatrione can be considered for the treatment of resistant monoarthritis, possibly coupled with a lavage under local anaesthesia in addition to the introduction or intensification of therapy.

Arthroscopy and synovial biopsies as research tools

Obtaining high quality synovial biopsies from the most representative areas in the joint cavity is the major advantage of arthroscopy, currently unparalleled and allowing the study of many parameters (34). Ultrasound (US) is very useful for evaluating the thickness of the synovial membrane using gray scale and identify the most inflamed region with power Doppler (35-37). The implementation of US-guided synovial biopsies is, however, technically challenging and requires the assistance of two operators. Moreover, even though the resolution of US images is constantly improving, it does not provide a direct macroscopic view of the sites to be biopsied.

Arthroscopic visual analogue score (VAS)

Research using arthroscopy and synovial biopsies has benefited from the development of a semi-quantitative scoring system to accurately measure local inflammation and tissue hyperplasia, assess synovial vascularisation and membrane proliferation. This score requires the analysis of several representative sites in the joint to construct an arthroscopic visual analogue score (VAS) of the local inflammation on a 0–100mm scale (24). Inter-observer correlations are high between experienced operators. Arthroscopic VAS accurately represents inflammation in the joint and significantly correlates with CRP levels in patients with RA. However, poor correlation was seen with the disease activity score incorporating 28 joints (DAS28) (38). We showed that tissue markers of inflammation were also closely associated with arthroscopic VAS in RA synovial biopsies, including the quantification of the synovial membrane infiltration by macrophage (CD68) and T-lymphocyte (CD3) using IHC detection (38). A histological synovitis score was developed to quantify the synovial membrane lining layer thickness, stromal cell proliferation and infiltration (39). Using this score we also demonstrated close correlation with arthroscopic VAS (Fig. 6A, n=70, r=0.681,

$p<0.0001$). The correlation noted previously between arthroscopic VAS and CRP was confirmed in this group (r=0.595, $p=0.003$). Tissue architecture was also assessed (normal, diffuse, aggregate or tertiary germinal centre) and showed correlation with VAS (Fig. 6B, n=65, r=0.560, $p<0.0001$) as well as synovitis score (Fig. 6C, n=45, r=0.682, $p<0.0001$). Using IHC, the number of nucleus per μm^2 was scored using digital image analysis and also correlated with arthroscopic VAS (Fig. 6D, n=24, r=0.723, $p<0.0001$) and synovitis score (r=0.785, $p<0.0001$). Representative images of low, intermediate and high arthroscopic VAS are presented in Figure 6E.

Many studies have investigated the effects of DMARDs and targeted therapies in patients with RA using arthroscopic synovial biopsies (40). The understanding of mechanism of response to abatacept was improved by the study of knee synovial tissue in 15 patients with RA before and after treatment (41). In addition to classical IHC study, a reduction in gene expression of different actors was also demonstrated (interleukin-1 and 6, matrix metalloproteinases 1 and 3 and interferon-gamma using real time PCR). The efficacy and safety of IA injection of anti-CD4 antibodies have been evaluated in 12 RA patients with knee synovial biopsies before and 6 weeks after treatment (42). Sequential synovial biopsies from 24 RA patients before and after infliximab treatment were also performed (43). No adverse events (severe infection or postoperative pain) were reported in these studies, even with a close sequence in time of 3 arthroscopies, suggesting limited risk for patients and providing arguments to obtain an agreement from ethics committees. The use of arthroscopic synovial biopsies for prediction of response to therapy was also investigated in 143 (44) and 51 (45) RA patients prior to treatment with infliximab. Pretreatment synovial levels of expression of TNF-alpha were predictive of good clinical response (reduction in DAS28 by at least 1.2 from baseline) in the first study (44), but were not confirmed in the other (45). However, significant reductions in TNF-alpha levels were correlated with reduced scores for synovial proliferation and vascularisation in patients with good *versus* non-response to treatment (45). Our group also showed correlation between good clinical response and absence of B-cells in the synovial membrane at 6 months following therapy with rituximab (46). More importantly, we showed that lack of response is associated with the presence of increased number of B-cells in synovial tissue prior to treatment (47). Interestingly, the assessment of rituximab's immunomodulatory synovial effects in RA (ARISE trial) among serial synovial biopsies (before and 8 weeks after rituximab infusions) showed a significant decrease in synovial B-cells after treatment, but only a small trend towards greater reduction among clinical responders (48).

While accepting that less invasive peripheral blood biomarker identification would be ideal, the ability to predict response to treatment through the study of synovial biopsies *in vitro* would be hugely beneficial to clinical practice especially in differentiating response to the ever-increasing armamentarium of available biological targeted therapies (49, 50).

Conclusion

Arthroscopic synovial biopsy seems promising in evaluating efficacy and mechanism of action of novel therapeutics and might play a role in the diagnostic process and choice of treatment in early inflammatory arthritis in the future. The ability to obtain good quality arthroscopic biopsies of the synovial membrane representative of the overall inflammatory state of the joint has greatly benefited key areas of research including evaluation of new biologic therapies. Nowadays, the development of ultrasound technology for joint imaging has notably improved the early diagnostic of disease such as RA. Grey scale images can detect synovitis and power Doppler signal detects vascularisation of the synovial membrane. Even the collection of synovial biopsy under US guidance allowing the selection of region of active synovitis is now possible. Tissue is however affected by the mechanical stress of extraction and histology and immunohistology (IHC) analysis is often impeded by haemorrhage. Despite these less invasive alternative means of assessment, arthroscopy retains an important role especially in specific cases of diagnostic uncertainty. In addition, the therapeutic benefit of arthroscopy (synoviectomy and lavage) is important in the management of patients, notably those with resistant disease. In the future, increasing numbers of targeted immunotherapies (TNF-α, IL-1, IL-6, IL-7, IL-17, B-cell, T-cell, BAFF) may justify the use of pre-treatment analysis of the synovial biopsy biomarkers to predict response to therapy and therefore prioritise choice of therapy (51).

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