The role of synovitis in osteoarthritis

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Abstract: Osteoarthritis (OA) is the most common form of arthritis worldwide yet there is still a lack of effective treatments for this condition. Increasingly, attention has turned to the role of the synovium in OA as it is now recognized, in part from the use of modern imaging techniques, that synovitis is both common and associated with pain. This offers a target for treatment, for both symptom and potential structure modification. In this review we discuss the evidence for histological and imaging-detected synovitis and the current role of antisynovial therapies in OA.

Keywords: osteoarthritis, synovitis, histology, magnetic resonance imaging, ultrasound

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Introduction

Osteoarthritis (OA) is the most prevalent form of arthritis worldwide, a major cause of joint pain and disability and the most common reason for total hip and knee replacement. There are over 8 million people in the United Kingdom living with OA and a 2003 survey of almost 2000 people with OA found that 81% are in constant pain or are limited in their scope to perform everyday tasks. It is estimated that almost half of the adult population of the USA will have symptomatic knee OA by the age of 85, with the highest risk among those that are obese [Murphy *et al.* 2008]. OA also has huge economic implications due to an increasing number of joint replacements, increasing hospital charges and an ageing population [Kim, 2008]. In 2004 the USA national bill for hospital charges for hip/knee replacements was US$26 billion and, if the current trend persists, it is estimated that 600,000 hip replacements and 1.4 million knee replacements will be performed in the US in 2015 [Kim, 2008].

Despite this, there is still a real lack of safe and effective treatments for OA, barring surgery and acetaminophen, and further treatments are desperately required. Over recent years, attention has turned to the importance of synovitis in OA, although OA is not traditionally considered a classical inflammatory arthropathy, due to the relative lack of neutrophils in the synovial fluid and the lack of systemic manifestations of inflammation. OA symptoms however frequently include joint pain, swelling and stiffness, suggestive of at least local inflammation [Pelletier *et al.* 2001]. It is now recognized that synovitis is common in OA, both in early and late OA and this offers a potential target for treatment, both for symptom and potential structure modification.

Abnormalities in the osteoarthritis synovium

The gold standard for the diagnosis of synovitis is histology. The normal synovium is composed of 1–4 layers of cells which merge on their deep surface with a zone of loosely arranged fibrocollagenous tissue containing adipocytes, fibroblasts, mast cells and macrophages. The synovial membrane has an abundant blood and nerve supply running throughout the loose fibrocollagenous tissue.

Biopsies from the synovium of OA knees (taken at arthroscopy for knee pain or at joint replacement) have demonstrated several key changes in the synovium, which although more pronounced in advanced OA, are present from the earliest stages of the OA process [Loeuille *et al.* 2005; Smith *et al.* 1997; Myers *et al.* 1990]. These synovial abnormalities include:

- thickening of the lining layer;
- increased vascularity;
- inflammatory cell infiltration.

Synovial membrane histology in classical inflammatory arthritides such as rheumatoid arthritis (RA) is characterized by a wide heterogeneity. OA synovium also displays this spectrum of changes, although there is a lesser degree of inflammation than in RA. The OA spectrum ranges from marked hyperplasia of the lining

layer, with a dense cellular infiltrate composed largely of lymphocytes and monocytes, through to a synovial membrane which is thickened by fibrotic tissue [Haraoui *et al.* 1991]. Surface fibrin deposition and fibrosis within the synovium is common in OA, particularly in the later stages [Loeuille *et al.* 2005].

Direct comparison of the synovium between 12 OA subjects and 18 RA subjects at time of total knee replacement has shown more hyperplasia of the lining cell layer and cellular infiltrate in severe RA (treated with steroids and methotrexate) than in OA. However, in milder RA (subjects treated with nonsteroidal anti-inflammatory drugs [NSAIDs] only) the histological changes are similar to those seen in OA [Haraoui *et al.* 1991].

The synovitis seen in OA knees tends to be diffuse and is generally not localized to areas of chondral defects, although an association has been reported between chondral defects and associated synovitis in the medial tibiofemoral compartment of the knee [Ayral *et al.* 2005; Loeuille *et al.* 2005]. Interestingly, work by Blom and colleagues demonstrated that in an OA mice model, using an MMP3-knockout model, macrophage activation in the synovium is essential for cartilage damage via the production of matrix metalloproteinases (MMPs), suggesting that inflammation within the synovium may be pivotal for cartilage damage [Blom *et al.* 2007].

How common is histological synovitis in osteoarthritis?

There is increasing evidence that synovitis is common in OA joints, particularly when the disease has been present for some time.

Microscopic changes in early osteoarthritis

A study of 29 people with knee pain and arthroscopic evidence of OA (chondropathy) but with no or minimal radiographic changes of OA demonstrated that over half have synovitis histologically, as defined by proliferation of the lining cells and increased mononuclear cell infiltration [Myers *et al.* 1990]. Work by Benito and colleagues in a smaller group of 25 patients demonstrated that early OA patients (normal XR with arthroscopic chondropathy) have a higher level of macrophage infiltration in the synovium, more blood vessel proliferation and higher markers of vascular proliferation than late OA patients (at the time of joint replacement) [Benito *et al.* 2005].

Microscopic changes in late osteoarthritis

A larger study of 104 subjects fulfilling American College of Rheumatology (ACR) criteria for OA collected synovial samples at time of total knee or hip replacement, and demonstrated extensive synovitis, as assessed by a semiquantitative score. Severe synovial inflammation was shown in 31%, with only 7 out of the 104 patients having no evidence of synovitis. Synovial inflammation was not confined to patients with extensive radiographic joint damage or end-stage disease. Lymphoid aggregates (usually suggestive of a classic inflammatory arthritis such as rheumatoid) were noted in the severely inflamed synovial samples [Haywood *et al.* 2003].

Smith and colleagues studied 36 patients with knee pain and a normal knee radiograph and 27 with severe knee OA needing joint replacement. Considerable variation in the synovial lining thickness of the synovial lining layer was seen, with some overlap between normal knees and early OA, however the scores for synovial cellularity, vascularity and inflammation were markedly increased in the OA synovium compared with normal knees, and with OA synovium at time of joint replacement showing the highest degree of change. Lymphoid aggregates in the synovium were not seen in normal tissue and only rarely in early OA, but were present in a third of severe OA synovial membranes, often resembling the synovial membranes of RA [Smith *et al.* 1997].

Cells and cytokines in the osteoarthritis synovium

Infiltration of the synovium with activated B cells and T lymphocytes and overexpression of pro-inflammatory mediators is common in both early and late OA [Benito *et al.* 2005]. Infiltration with B cells has been demonstrated in the synovium of half of OA knees in a group of 41 subjects fulfilling ACR criteria for knee OA, who presented with knee pain and/or joint swelling [Da *et al.* 2007]. Interestingly, work by Benito and colleagues demonstrated that patients with early OA have a higher level of mononuclear cell infiltration in the synovium compared with late OA, and higher expression of inflammatory mediators, including interleukin (IL)-1, tumour necrosis factor-alpha (TNF-α), vascular endothelial

growth factor (VEGF) and intercellular adhesion molecules [Benito *et al.* 2005].

Smith and colleagues detected the production of IL-α and β and TNF-α in a sample of 63 OA synovial membranes, taken at time of total joint replacement (late OA) and at time of arthroscopy for knee pain (OA diagnosis based on chondropathy). Levels of IL-1 and TNF were elevated in both early and late OA, however these cytokines increase in production with a statistically significant increase in moderate and severe OA ($p < 0.05$). This increase in cytokines is thought to be due to an increase in lining layer cells of the synovium [Smith *et al.* 1997].

There is also evidence for T-cell activation and the production of Th1 cytokines (for example, interferon-γ) in OA, with T cells and T-cell infiltrates seen in the synovial membrane [Sakkas and Platsoucas, 2007]. There is excessive production of cytokines and growth factors by the inflamed synovium and activated chondrocytes and these are thought to play a key part in the pathophysiology of OA [Goldring, 2001; Pelletier *et al.* 2001; Smith *et al.* 1997]. These factors may be initially produced by the synovial membrane and diffuse into the cartilage via the synovial fluid [Pelletier *et al.* 2001] (Figure 1).

Studies *in vitro* and *in vivo* have demonstrated that IL-1 and TNF-α are the predominant pro-inflammatory and catabolic cytokines involved in the initiation and progression of articular cartilage destruction in OA [Goldring, 2001]. These cytokines stimulate chondrocytes to produce chemicals such as MMPs, which degrade matrix proteins and collagen. Chondrocytes then produce further IL-1, which then further stimulates MMP production. In human OA samples, chondrocytes produce more TNF-α and TNF-α convertase enzyme than normal cartilage and express higher quantities of the p55 TNF-α receptor, suggesting that OA cartilage may be

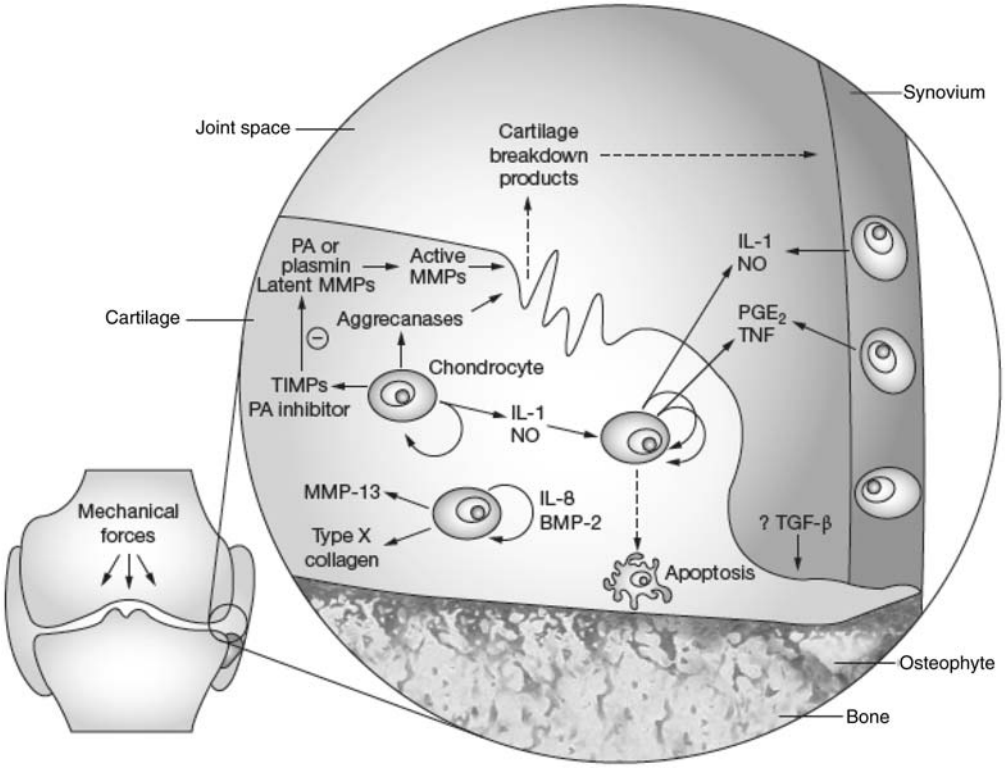

Figure 1. Schematic representation of key pathological events and potential targets for disease modification in osteoarthritis. Mediators that represent potential therapeutic targets have been identified in both synovial tissue and cartilage. Less well identified are targets derived from bone. BMP, bone morphogenic protein; IL, interleukin; MMP, matrix metalloproteinase; NO, nitric oxide; PA, plasminogen activator; PGE_2, prostaglandin E_2; TGF, transforming growth factor; TIMP, tissue inhibitor of metalloproteinase; TNF, tumour necrosis factor. (Adapted by permission from Macmillan Publishers Ltd: [*Nature Clinical Practice Rheumatology*] (Abramson *et al.* 2006), copyright (2006).)

more susceptible to damage from TNF-α than normal cartilage [Fernandes *et al.* 2002]. The increased levels of catabolic enzymes, prostaglandins, nitric oxide (NO) and other markers in OA fluids and tissues appear to be related to elevated levels of IL-1 and TNF-α [Goldring, 2001]. IL-6 is also upregulated during synovial inflammation and is produced by synovial cells, osteoblasts and chondrocytes and can be detected in synovial fluid samples taken from OA joints [Bonnet and Walsh, 2005].

Angiogenesis in the osteoarthritis synovium

Synovial and osteochondral angiogenesis are also features of OA and markers of angiogenesis in the synovium have been associated with histological synovitis, suggesting that angiogenesis may contribute to chronic synovitis [Walsh *et al.* 2007]. More recent work has concentrated on the potential role of VEGF in the OA synovium. VEGF is a potent stimulator of angiogenesis and macrophages and mast cells, present in abundance in chronically inflamed OA synovium, have been shown to produce VEGF [Bonnet and Walsh, 2005]. The authors hypothesize that production of VEGF by synovial macrophages is a possible molecular mechanism which exacerbates synovial angiogenesis and inflammation in OA [Haywood *et al.* 2003], although the exact regulation of angiogenesis in an OA joint is not yet completely understood [Ashraf and Walsh, 2008].

In summary, the synovium in OA joints is abnormal, even from the earliest clinical stages, with production of inflammatory cytokines IL-1, IL-6, TNF-α and VEGF, infiltration of mononuclear cells, thickening of the synovial lining layer and fibrosis.

Modern imaging and osteoarthritis synovitis

Magnetic resonance imaging

MRI has been invaluable in improving our understanding of the role of the synovium in OA. Quantitative MRI markers of synovitis include synovial membrane thickness (commonly performed using segmentation and image analysis of individual MR slices), synovial fluid volume (also using segmentation techniques) and the rate of synovial enhancement after intravenous (IV) injection of contrast agent such as gadolinium-DTPA (diethylenetriamine penta-acetic acid). It has recently been demonstrated that volume acquisition of synovitis may also be combined with the rate of enhancement after IV contrast injection [Loeuille *et al.* 2009].

Intravenous contrast agents usually incorporate the heavy metal gadolinium, which distributes rapidly to vascular tissues. Inflamed (and therefore vascular) synovium is enhanced, with the signal intensity increasing in proportion to the concentration of gadolinium. It has been demonstrated that synovitis can be accurately quantified without using contrast [Pelletier *et al.* 2008] and recent concerns over the potential toxicity of gadolinium contrast in those with severe renal impairment means this area warrants further development. The use of IV contrast in MRI allows clear differentiation between synovitis and effusion in large joints, which may be more difficult to differentiate on noncontrast imaging, although ultrasound can differentiate between synovitis and effusion.

The frequency of synovitis in OA knees has been evaluated with MRI. Fifty two people with ACR criteria knee OA and a control group of 40 normal knees were imaged using noncontrast MRI to assess synovial thickening. Synovitis (as determined by synovial thickening) was observed in 73% of OA knees compared with 0% of the control group. Synovitis was also noted to be more likely with increasing K/L grade [Fernandez-Madrid *et al.* 1994]. This synovial thickening seen on MRI has been confirmed as histological synovitis in a small study by the same authors, of nine people, using arthroscopic sampling of the areas of MRI detected synovial thickening [Fernandez-Madrid *et al.* 1995]. A further study confirmed that MR detected synovial changes are confirmed as histological synovitis [Loeuille *et al.* 2005]. This study assessed 39 people with knee OA with both noncontrast MRI and arthroscopy to assess the synovium macroscopically and take over 100 biopsy samples for microscopic analysis. The grade of MR synovial thickening correlated well with the degree of macroscopic synovitis seen at arthroscopy ($r = 0.58$) and also with the degree of synovial changes seen microscopically ($r = 0.41$, $p < 0.0001$). The authors also noted that the distribution of synovitis was diffuse, with no statistical difference seen between those people with marked chondral changes and those with few chondral changes, suggesting again that synovitis is present from the earliest stages of OA and is not related purely to areas of cartilage damage [Loeuille *et al.* 2005]. Further work, in a study

of 15 subjects, demonstrated that synovial membrane which has a high rate of enhancement on MR imaging after administration of IV contrast was significantly associated with severe microscopic synovial vascular congestion [Loeuille *et al.* 2009].

Recent imaging studies have demonstrated an even higher frequency of imaging-detected synovitis in painful OA. A MRI study assessed 87 moderately symptomatic people meeting ACR criteria for knee OA using 1.5-T MRI. Pre- and post-gadolinium sequences of a single knee were evaluated for semiquantitative synovitis scores at nine intra-articular sites. Distribution of synovitis was extensive with 86% of subjects having synovitis at six or more sites [Conaghan, 2006].

Having established that MR can accurately detect synovial thickening and that this is confirmed as histological synovitis, it is important to understand the relationship between synovitis and symptoms. Three recent studies have demonstrated the relationship between synovitis in the knee and pain. Hill and colleagues evaluated the association of effusions, popliteal cysts, and synovial thickening with knee symptoms in 381 older persons with both knee pain and radiographic OA, 52 with no knee pain and radiographic OA, and 25 with neither pain nor radiographic changes [Hill *et al.* 2001]. All underwent MRI of one knee without the use of IV contrast. The authors noted that without IV contrast, synovitis may be underestimated and they attempted to distinguish between effusion and synovitis on MR images by oversampling knees with no or small effusions. Synovial thickening was measured as present or absent in three intra-articular areas by a trained reader, with a kappa for intra-observer reproducibility of 0.77. There was a significant association ($p = 0.006$) between synovitis and pain severity in those with knee pain and radiographic OA, after adjustment for radiographic change, BMI, age, sex and size of effusion. The mean pain score for those subjects with synovial thickening was 47 mm on a pain visual analogue scale (VAS), compared with a mean score of 28 mm for those without synovial thickening. There was also a significant increase ($p < 0.001$) in the frequency of both effusions (moderate or large) in the painful knees (54%) compared with those without pain (15%). Among those with small (grade 1) or no knee (grade 0) effusion, those with knee pain had a prevalence of synovial thickening of 73.6% compared with 21.4% of those without knee pain ($p < 0.001$, chi-squared) [Hill *et al.* 2001].

Further work by the same authors assessed the temporal relationship between synovitis and pain [Hill *et al.* 2007] in 270 subjects, all of whom had knee pain and radiographic OA, using MRI (without IV contrast) at baseline, 15 and 30 months. Synovitis was assessed at three sites using a semiquantitative score 0–3. Synovitis scoring was validated by comparison of synovitis scores of identical images with and without gadolinium contrast. Synovitis scores were identical in 13/20 cases, and underestimated in the non-contrast cases. Pain was assessed using a VAS for knee pain in the previous week. There was a significant correlation between change in total synovitis score and change in pain VAS score ($p < 0.001$, $r = 0.21$) [Hill *et al.* 2007].

A recent, large MRI study of 454 people (48% women, mean age 59) with OA knee, used contrast-enhanced MRI to assess the presence of synovitis. Synovitis was demonstrated in 80%. Moreover, the presence of extensive synovitis was associated with an adjusted odds ratio for severe knee pain of 9.2 (3.2–26.3) [Baker *et al.* 2010].

Ultrasound

Ultrasound can also be used to detect synovitis with much greater sensitivity than clinical examination. As with MRI, most studies have assessed knee OA, although hip OA and more recently, the role of ultrasound in hand OA have also been examined [Keen *et al.* 2008a].

A large EULAR study of 600 people with knee OA demonstrated synovial hypertrophy or effusion in 46% [D'Agostino *et al.* 2005]. Synovial hypertrophy was defined as synovial thickening of $\geq$4 mm and effusion recorded as present or absent based on the depth of fluid >4 mm or <4 mm in the suprapatellar recess. A further large cohort of 106 people aged between 35 and 55 assessed the ultrasound changes in early knee OA. All subjects had $\geq$3 months knee pain but the majority (87%) had either a normal radiograph but clinical features of OA, or mild radiographic OA (K/L grade 1) only. A third had synovial thickening (defined as $\geq$2 mm) and 27 had a suprapatellar effusion [Kumm *et al.* 2009].

A smaller study using ultrasound assessed 41 people with OA knee and demonstrated the

presence of synovitis (as demonstrated by synovial hypertrophy in the superior and lateral recesses) in 59% [Song *et al.* 2007] using a definition of synovial thickening of 'any degree of synovial thickening', rather than the stricter definition in the EULAR study. Using contrast-enhanced ultrasound increased this detection rate to 95% (on assessment of the superior recess). Unlike Hill and colleagues' MRI work, this study did not find an association between VAS pain and degree of synovitis, although the numbers in the study were small [Song *et al.* 2008].

Few studies have examined the OA hand using sensitive imaging techniques; however, the role of ultrasound in painful hand OA has recently been assessed. Thirty six subjects with painful hand OA underwent ultrasound imaging, which demonstrated that 46% had greyscale synovitis at baseline [Keen *et al.* 2008b]. Ultrasound also demonstrated that painful hand joints were significantly more likely to have synovitis than non-painful hand joints ($p < 0.001$), however the extent of changes in individual joints did not correlate with the degree of symptoms [Keen *et al.* 2008b].

Studies which use ultrasound to assess synovitis in the OA hip generally assess the response to treatment, such as intra-articular steroid. Studies have suggested that synovitis is detected in 59% of painful OA hips referred for intra-articular steroid [Robinson *et al.* 2007]. A reproducible, semi-quantitative scoring system for assessing OA changes in the hip joint, including synovitis, has been suggested [Qvistgaard *et al.* 2006b].

Using imaging to assess therapies

Imaging may be used to evaluate the effectiveness of therapies. A recent study demonstrated a reduction in ultrasound-detected synovial hypertrophy in 75% of recipients of intra-articular steroid for painful hip OA, although it should be noted that all subjects were selected on the basis of ultrasound-detected synovitis prior to receiving intra-articular steroid [Micu *et al.* 2010]. Ultrasound has also been used to assess synovial changes in hand OA after treatment with intramuscular steroid [Keen *et al.* 2010]. MRI may be used pre- and post-treatment to detect changes in synovial volume and enhancement although much of the current evidence is in subjects with the classic inflammatory arthritides [Clunie *et al.* 1999; Ostergaard *et al.* 1995].

Synovitis and osteoarthritis structural progression

There is certainly a pathophysiological rationale for synovitis being important in cartilage degradation, as discussed above. There is also evidence from imaging studies to suggest that synovitis has an important role in structural degradation of the OA joint. Ayral and colleagues assessed the importance of synovitis on structural progression in the medial tibial femoral joint in a large study of 422 subjects with knee OA. All underwent arthroscopy at baseline and 1 year and the primary outcome was the change in the arthroscopic chondropathy score. Synovial abnormalities were reported in 50% and subjects that had an 'inflammatory' appearance to synovium (21%) had an odds ratio (OR) for progression of the chondropathy score of 3.11 (1.07–5.69) [Ayral *et al.* 2005]. An MR study of 347 knees with minimal baseline cartilage damage has also demonstrated that the presence of synovitis or effusion was associated with an increased risk of fast cartilage loss, OR 3.36 (0.91–12.4) [Roemer *et al.* 2009]. Higher synovial volumes have also been shown to correlate with other measures of worsening OA, such as K/L score and joint space narrowing, in a small cohort of 44 subjects with knee OA who underwent contrast-enhanced MRI [Krasnokutsky, 2007].

A large, multicentre EULAR prospective study followed over 500 subjects with knee OA for 3 years following a baseline ultrasound examination. The primary endpoint of the study was a knee joint replacement. The multivariate analysis demonstrated that the presence of a joint effusion at baseline was a significant predictor of joint replacement at 3 years (hazard ratio [HR] 2.63) [Conaghan *et al.* 2010].

There is also evidence that raised systemic inflammatory markers have a role in future joint damage. C-reactive protein (CRP) levels (indicative of inflammation) are modestly but significantly increased in women with early knee OA and higher CRP levels predict those whose disease will progress radiographically over a period of 4 years, even after adjustment for weight, age and knee pain or injury [Spector *et al.* 1997]. Hyaluronic acid (HA) levels have been noted to be elevated twofold in people with OA compared with a control group and plasma HA levels correlated with an objective functional capacity score [Goldberg *et al.* 1991]. It has also been suggested that serum HA levels may predict

radiographic progression at 5 years, although poor sensitivity and specificity means this is not currently of clinical use [Sharif *et al.* 2000].

A recent longitudinal study of over 900 women has demonstrated that plasma IL-6 levels are significantly elevated (even after adjustment for age and BMI) in women who have radiographic OA than women without OA. Plasma IL-6 levels have recently been shown to be an independent predictor of radiographic knee OA progression over 15 years [Livshits *et al.* 2009].

Osteoarthritis analgesic therapies and synovitis

Nonsteroidal anti-inflammatory drugs

Randomized controlled trials have demonstrated that NSAIDs are efficacious at reducing pain in OA [Zhang *et al.* 2008]. This efficacy is thought to be due to an anti-inflammatory, or anti-synovial, effect. NSAIDs have been shown to reduce both joint pain and the size of effusion on MRI, in a small group of patients with knee OA [Brandt *et al.* 2006] and a large study of 200 people with painful and radiographic knee OA has demonstrated that ibuprofen reduces the markers of cartilage and synovium metabolism (including CTX-II) during an acute flare of painful knee OA [Gineyts *et al.* 2004].

Corticosteroids

Corticosteroids, in particular those given intra-articularly, are frequently used in the treatment of OA, and it is presumed that the corticosteroid mechanism of pain reduction is via an effect on the synovium [Jones and Doherty, 1996]. Corticosteroids inhibit the production of pro-inflammatory chemicals interleukins 1 and 6 and TNF-α as well as decreasing the expression of COX-2. Steroids also inhibit the generation, proliferation and activation of T cells, which have been shown to infiltrate the synovium in OA joints.

There is good evidence for the short-term effectiveness (up to 4 weeks) in recipients of intra-articular IA steroid to the knee joint [Arden *et al.* 2008; Bellamy *et al.* 2006; Gossec and Dougados, 2004]; those with a knee joint effusion demonstrating a better response [Arden *et al.* 2008]. There are a number of studies confirming the effectiveness of intra-articular steroid for the painful OA hip [Lambert *et al.* 2007; Robinson *et al.* 2007; Qvistgaard *et al.* 2006a; Margules, 2001].

There is a lack of randomized controlled trials assessing the use of intra-articular steroid in the hand, particularly to the first carpometacarpal (CMC) joint, for which there is anecdotal evidence [Dieppe, 1991]. The only randomized controlled trial of intra-articular steroid to the first CMC joint noted no significant difference between steroid and placebo although the study was terminated early due to difficulty in recruitment [Meenagh *et al.* 2004].

Recently an observational open-label study has confirmed the effectiveness of intramuscular steroid for the treatment of painful hand OA. Thirty six patients with confirmed and symptomatic hand OA were given an intramuscular 120 mg methyl prednisolone injection. Ultrasound imaging assessed the degree of synovitis before and after steroid. A significant proportion (67%) of patients had an improvement in symptoms at 4 weeks, with 45% having a sustained reduction in pain at 12 weeks [Keen *et al.* 2010] and there was a trend for responders to have higher baseline levels of synovitis.

One study has looked at the use of oral steroids in hand OA, using a novel drug (CRx-102) combining oral prednisolone (3 mg) and dipyridamole, used to potentiate the action of the steroid [Kvien *et al.* 2008]. This 6-week randomized, placebo-controlled study of 83 people with painful hand OA had a primary outcome as the reduction in hand pain from baseline to 6 weeks, using the validated AUSCAN questionnaire. This study demonstrated a significant reduction in the 48-hour joint pain score at 6 weeks ($p = 0.02$). This may suggest a role for oral steroids in symptomatic relief of hand OA although it should be noted that this study did not evaluate steroid alone *versus* placebo.

Disease-modifying antirheumatic drugs in osteoarthritis

There is limited published evidence for the use of any disease-modifying antirheumatic drugs (DMARDs) in OA. Gold and hydroxychloroquine have been shown to reduce NO production in chondrocyte culture and OA cartilage, suggesting they may have an anti-inflammatory mechanism in OA [Vuolteenaho *et al.* 2005]. Although there is very limited published evidence for the use of hydroxychloroquine in OA [Bryant

et al. 1995], there is much anecdotal evidence that hydroxychloroquine may help sub-groups of patients.

Animal studies in OA have suggested a possible role for methotrexate in reducing cartilage damage in a rabbit model [Neidel *et al.* 1998; Mannoni *et al.* 1993].

There are two small studies of the use of methotrexate in human OA. The first, a placebo-controlled study of 89 patients used a small dose of 7.5 mg methotrexate for painful knee OA and did not demonstrate any reduction in pain at 4 months [Holanda, 2007]. Subjects taking methotrexate required less analgesia (paracetamol) than the placebo group. The second used 10 mg methotrexate weekly for 2 months, for painful hand OA, and demonstrated a significant improvement in pain at 2 months [Pavelka, 2006].

Anti-TNFs in osteoarthritis

There are few publications regarding the use of anti-TNF agents in OA. A larger, well-conducted study of 160 patients evaluated the effects of a single injection of intra-articular anakinra (an IL-1 receptor antagonist) to the symptomatic OA knee. No difference was seen between anakinra and placebo, although there was a trend to an improvement in pain score in the treatment group at 4 weeks, compared with placebo [Chevalier *et al.* 2009].

There is limited evidence for the potential effectiveness of systemic adalimumab and for intra-articular infliximab in small studies of painful hand OA [Fioravanti *et al.* 2009; Magnano *et al.* 2007].

Summary

Synovitis is very common in the OA joint and has been associated both with symptoms and with structural progression. Many of the current effective treatments used for OA have an antisynovial effect but further large-scale clinical trials are needed to confirm the role of antisynovial agents in symptom and structure modification.

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Conflict of interest statement

None declared.

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