

# EXPERT OPINION

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## Disease-modifying osteoarthritis drugs: *in vitro* and *in vivo* data on the development of DMOADs under investigation

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**Introduction:** Osteoarthritis is a disabling affliction, and disease-modifying osteoarthritis drugs (DMOADs) would be highly desirable adjuncts to symptomatic relief as they may delay the disease process.

**Areas covered:** This study is a comprehensive review of the recent literature on the efficacy of DMOADs in the treatment of OA. *In vitro* and *in vivo* evidence was collected using MEDLINE<sup>®</sup> (1950 to November 2012) and EMBASE (1980 to November 2012) databases. Several drugs have demonstrated DMOAD effects in OA. They can be divided into three groups based on their predominant mode of action: those targeting cartilage, inflammatory pathways and subchondral bone. OARSI guidelines recommend glucosamine and chondroitin sulphates and diacerein as DMOADs, and NICE will recommend glucosamine sulphate in the next update of guidelines. Exploration of improved outcome measures and identification of subgroups of patients most likely to benefit from different DMOADs are likely to be the most important areas of development over the coming years.

**Expert opinion:** It is expected that a wider range of prospective clinical studies will be embarked upon in the coming years. Trials including MRI as well as joint space narrowing (JSN) should be designed in a systematic manner, powered with sufficient numbers to demonstrate clinical benefit at different stages of disease.

**Keywords:** cartilage, disease-modifying osteoarthritis drug, joint replacement, joint space narrowing, joint space width, osteoarthritis, subchondral bone, synovium

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### 1. Introduction

Approximately 8.5 million patients suffer from osteoarthritis (OA) in the UK, making it the biggest cause of physical disability [1]. This figure is expected to rise as the population ages. In the 12 months preceding April 2012 there were over 84,000 hip replacements and 87,000 knee replacements performed in England, figures that have increased annually over the last decade [2].

Various agents have been developed to slow the progression of OA, and are collectively known as 'disease-modifying osteoarthritis drugs' (DMOADs). Guidelines by 'Osteoarthritis Research Society International' (OARSI) published in 2008 highlighted only glucosamine sulphate (GS) and chondroitin sulphate (CS) in knee OA, and diacerein in hip OA, as possible DMOADs [3]. Although the current 'National Institute for Health and Clinical Excellence' (NICE) guidelines for OA recommend no DMOADs, a review consultation performed in 2011 concluded that in knee OA, GS is recommended as a safe and

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**Article highlights.**

- Effective DMOADs would prove useful adjuncts to symptomatic relief in OA.
- Few DMOADs are recommended by regulatory authorities.
- Many DMOADs are in development that target cartilage, inflammatory pathways and subchondral bone.
- Identification of cohorts of patients likely to benefit from different DMOADs will likely lead to increased efficacy.
- Use of more sensitive and specific outcome measures will improve research in this area.
- Asymptomatic patients with early disease may be ideal candidates for treatment with DMOADs.

This box summarises key points contained in the article.

cost-effective option for symptomatic relief [4]. Guidelines by the American College of Rheumatology (ACR) published in 2012 do not recommend any DMOADs for the treatment of OA, indicating that there is still uncertainty in this area [5].

Joint space narrowing (JSN) on radiograph is currently the only validated primary outcome measure to show progression of OA. JSN has been shown to predict joint replacement in OA [6]. The Committee for Medicinal Products for Human Use (CHMP) published guidelines on the investigation of OA in 2010, concluding that JSN is still valid [7].

We present a review of the current literature with respect to DMOADs for the hip, knee and spine, and look at new areas of development with *in vitro* and *in vivo* evidence.

## 2. Methods

A literature search was performed on the current evidence for disease-modifying osteoarthritis drugs. The primary medical search engines used for the study were MEDLINE/OVID (1950–July 2012) and EMBASE (1980–July 2012) databases. Keywords and phrases such as ‘osteoarthritis’, ‘chondroitin’, ‘glucosamine’, ‘diacerein’, ‘doxycycline’, ‘mmp’, ‘matrix metalloproteinase’, ‘nitric oxide’, ‘growth factor’, ‘avocado’, ‘interleukin’, ‘disease modifying’, ‘structure’, ‘joint space width’, ‘jsw’, ‘tumour necrosis factor’, ‘tnf’, ‘trial’, ‘*in vitro*’ and ‘*in vivo*’ were used in differing combinations. Manual searches of key papers’ bibliographies supplemented database searches. Combination, truncation and explode functions were utilised to give the search greater depth. Abstracts were screened manually and excluded if not relevant to disease modification drugs for OA *in vitro*, *in vivo*, or in patient trials (Table 1). This review focuses on *in vitro* studies, *in vivo* studies and clinical trials of the effect of DMOADs on disease progression of OA.

## 3. Results

Several drugs have demonstrated DMOAD effects. They can be divided into three groups based on their predominant

mode of action: drugs targeting cartilage, inflammatory pathways and subchondral bone.

### 3.1 DMOADs targeting cartilage

#### 3.1.1 Matrix metalloproteinase inhibitors

Matrix metalloproteinases (MMPs) are biosynthesised in response to pro-inflammatory cytokines, chemokines and other proteins and assist with the regulation of inflammation and immunity [8]. They are thought to be involved in both physiological remodelling and pathological destruction of joint tissue. Therefore, control of MMPs may preserve the osteoarthritic joint.

##### 3.1.1.1 Tissue inhibitors of metalloproteinase

Production of MMPs may occur in any joint tissue. The active sites of MMPs may be bound by one of several regulatory proteins. The most abundant of these are ‘tissue inhibitors of metalloproteinase’ (TIMPs). Deficiency of TIMP-3 has been associated with OA in mice [9]. Several selective MMP inhibitors have been engineered from TIMP but their synthetic counterparts have been developed much further [10].

##### 3.1.1.2 Broad matrix metalloproteinase inhibitors

Early synthetic MMP inhibitors targeted a broad range of MMPs. An intervention trial of 35 patients looked at cartilage samples obtained at surgery after 3 weeks of treatment with oral ‘BAY 12-9566’ [11]. This suggested that treatment with the MMP-2, -9 and -3 inhibitor might increase matrix synthesis in knee cartilage. However, a randomised controlled trial (RCT) of oral ‘PG116800’, an MMP inhibitor, showed no significant effect on JSN at 1 year [12]. Joint space width (JSW) was measured in 401 patients at baseline and 12 months using knee radiograph. Musculoskeletal side effects were significantly increased in all of the treatment groups.

A range of previous studies have reported similar side effects with the use of broad MMP inhibitors, termed the ‘musculoskeletal syndrome’ (MSS). Their use in Phase III trials has therefore been limited. MSS causes painless loss of range of motion in the large joints, joint swelling, stiffness, soft tissue pain and Dupuytren’s contracture. The cause for MSS was initially thought to be a consequence of inhibition of one or more MMPs, but many drugs inhibit MMPs without causing MSS [13]. Recent suggestions implicate chelation of zinc as a consequence of zinc-binding groups used in the drugs. The cause is still unproven, but once identified may allow further exploration of MMP inhibitors.

##### 3.1.1.3 Selective matrix metalloproteinase inhibitors

Recent research into the pathophysiology of OA implicated MMP-13, and therapies have been sought to selectively inhibit it. MMP-13 has a physiological tissue-remodelling role in health and pathological involvement in OA. It hydrolyses type II collagen and cleaves extracellular matrix, connective tissue and fibrinogen. Highly selective MMP-13

**Table 1. Human trials with DMOADs under investigation.**

Refs.	Year	Study	Size	Target and proposed action	Agent	Method	Results	Conclusion
[63]	1995	Huskinson <i>et al.</i> Effects of antiinflammatory drugs on the progression of osteoarthritis of the knee. LINK Study Group. Longitudinal Investigation of Nonsteroidal Antiinflammatory Drugs in Knee Osteoarthritis	n = 812	Knee OA Inflammatory pathways	Indomethacin 25 mg TDS PO. Tiaprofenic acid 300 mg BD PO. Placebo	JSW measured with radiograph at baseline and 12 months	40 of 85 in indomethacin group deteriorated vs 19 of 85 in the placebo group (p = 0.009). No statistically significant difference found between tiaprofenic acid and placebo (p = 0.308)	Indomethacin increased the rate of radiological deterioration of JSW but tiaprofenic acid did not
[28]	1998	Uebelhart <i>et al.</i> Effects of oral chondroitin sulfate on the progression of knee osteoarthritis: a pilot study	n = 42	Knee OA Cartilage – Promotes regeneration and inhibits degeneration	Chondroitin sulphate 800 mg OD PO. Placebo	JSW measured with radiograph at baseline and 12 months	Placebo group mean JSW reduced from 0.51 to 0.46 mm (p < 0.05). No significant change in JSW in CS group. Difference between groups significant (p < 0.01)	Chondroitin sulphate decreased rate of radiological deterioration of JSW
[34]	2001	Reginster <i>et al.</i> Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial	n = 212	Knee OA Cartilage – Promotes regeneration and inhibits degeneration	Glucosamine sulphate 1500 mg OD PO. Placebo	JSW measured with radiograph at baseline, 12 and 36 months	Placebo group had progressive JSW narrowing with mean loss after 3 years of 0.31 mm. There was no significant joint space loss in the GS group: 0.06 mm (0.22 to 0.09). Difference between two groups was significant (p = 0.038). Minimum JSW difference significant (p = 0.002)	Glucosamine sulphate decreased rate of radiological deterioration of JSW
[43]	2001	Dougados <i>et al.</i> Evaluation of the structure-modifying effects of diacerein in hip osteoarthritis: ECHODIAH, a three-year, placebo-controlled trial. Evaluation of the Chondromodulating effect of diacerein in OA of the hip	n = 507	Hip OA cartilage – promotes regeneration and inhibits degeneration. Also inhibits destruction of subchondral bone	Diacerein 50 mg BD PO. Placebo	JSW measured with radiograph at baseline and 36 months	238 patients dropped out mainly due to adverse events in the diacerein group (25 vs 12% with placebo) and because of inefficacy in the placebo group (14 vs 7% with diacerein. JSW deterioration was significantly lower with diacerein (mean 0.18 mm/year vs 0.23 mm/year with placebo (p = 0.042)	Diacerein decreased rate of radiological deterioration of JSW

Table 1. Human trials with DMOADs under investigation (continued).

Refs.	Year	Study	Size	Target and proposed action	Agent	Method	Results	Conclusion
[51]	2002	Lequesne <i>et al.</i> . Structural effect of acovado/soybean unsaponifiables on joint space loss in osteoarthritis of the hip	n = 163	Hip OA cartilage – inhibits degeneration	ASU 300 mg OD PO. Placebo	JSW measured with radiograph at baseline and 24 months	No significant difference in JSW between the two groups. Those patients with JSW worse than median at baseline, saw significant benefit from ASU vs placebo (p = 0.01)	ASU did not decrease the rate of radiological deterioration of JSW. <i>Post-hoc</i> analysis demonstrated significant benefit in subgroup of patients with severe OA
[61]	2002	Wluka <i>et al.</i> . Supplementary vitamin E does not affect the loss of cartilage volume in knee osteoarthritis: a 2 year double blind randomised placebo controlled study	n = 136	Knee OA cartilage – inhibits degeneration	Vitamin E 500 IU. Placebo	Cartilage volume measured with MRI at baseline and 24 months	No significant difference in cartilage volume loss in either group	Vitamin E did not decrease the rate of deterioration of MRI-measured cartilage volume
[33]	2002	Pavelka <i>et al.</i> . Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomised, placebo-controlled, double-blind study	n = 202	Knee OA Cartilage–Promotes regeneration and inhibits degeneration	Glucosamine sulphate 1500 mg OD PO. Placebo	JSW measured with radiograph at baseline, 12, 24 and 36 months	Placebo group JSW narrowing was 0.19 mm after 3 years. There was no significant change in JSW in the GS group. Significant difference between groups (p = 0.001)	Glucosamine sulphate decreased rate of radiological deterioration of JSW
[77]	2003	Raynauld <i>et al.</i> . Safety and efficacy of long-term intraarticular steroid injections in osteoarthritis of the knee: a randomised, double-blind, placebo-controlled trial	n = 68	Knee OA – inflammatory pathways	Triamcinolone 40 mg IA 3 monthly. Placebo	JSN measured with radiograph at baseline and 12 and 24 months	At 1- and 2-year follow up, no significant difference noted in JSN	Triamcinolone did not decrease the rate of radiological deterioration of JSW
[31]	2004	Uebelhart <i>et al.</i> . Intermittent treatment of knee osteoarthritis with oral chondroitin sulfate: a one-year, randomised, double-blind, multicenter study vs placebo	n = 120	Knee OA – Cartilage Promotes regeneration and inhibits degeneration	Chondroitin sulphate 800 mg OD PO (treated for 3 months twice per year). Placebo	JSW measured with radiograph at baseline and 12 months	CS treatment had preserved joint space surface area (p = 0.03) and mean JSW (p = 0.03) but not minimum JSW (p = 0.1)	Intermittent treatment with chondroitin sulphate decreased rate of radiological deterioration of JSW

Table 1. Human trials with DMOADs under investigation (continued).

Refs.	Year	Study	Size	Target and proposed action	Agent	Method	Results	Conclusion
[44]	2004	Pham <i>et al.</i> Evaluation of the symptomatic and structural efficacy of a new hyaluronic acid compound, NRD101, in comparison with diacerein and placebo in a 1 year randomised controlled study in symptomatic knee osteoarthritis	n = 301	Knee OA cartilage – promotes regeneration and inhibits degeneration. Also inhibits destruction of subchondral bone	Hyaluronic acid (NRD101) IA x3. Diacerein 50 mg BD PO. Placebo	JSW measured with radiograph at baseline and 12 months	No significant difference in JSW found between groups	Neither HA nor diacerein decreased rate of radiological deterioration of JSW
[30]	2005	Michel <i>et al.</i> Chondroitins 4 and 6 sulfate in osteoarthritis of the knee: a randomised, controlled trial	n = 300	Knee OA – cartilage Promotes regeneration and inhibits degeneration	Chondroitin sulphate 800 mg OD PO. Placebo	JSW measured with radiograph at baseline and 24 months	Placebo JSW narrowing 0.14 mm after 2 years (p = 0.001 compared with baseline). No significant change in JSW in CS group. Difference between the two groups were significant for mean JSW (p = 0.04) and minimum JSW (p = 0.05)	CS decreased the rate of radiological deterioration of JSW
[58]	2005	Brandt <i>et al.</i> Effects of doxycycline on progression of osteoarthritis. Results of a randomised, placebo-controlled, double-blind trial	n = 431	Knee OA cartilage – inhibits degeneration	Doxycycline 100 mg BD PO. Placebo	JSW measured with radiograph at baseline, 16 and 30 months	Doxycycline group placebo 0.45 mm narrowing. Difference between groups 0.15 mm (p = 0.03)	Doxycycline decreased the rate of radiological deterioration of JSW
[81]	2005	Spector <i>et al.</i> Effect of risedronate on joint structure and symptoms of knee osteoarthritis: results of the BRISK randomised, controlled trial	n = 284	Knee OA Subchondral bone – inhibits degeneration	Risedronate 5 mg OD PO. Risedronate 15 mg OD PO. Placebo	JSW measured with radiograph at baseline and 12 months	7 patients receiving placebo and 4 of patients receiving 5 mg risedronate exhibited detectable progression of disease vs 1 patient receiving 15 mg risedronate (p = 0.067)	Risedronate decreased the rate of radiological deterioration of JSW
[79]	2006	Bingham <i>et al.</i> Risedronate decreases biochemical markers of cartilage degradation but does not decrease symptoms of slow radiographic progression in patients with medial compartment osteoarthritis of the knee: results of the two-year multinational knee osteoarthritis structural arthritis study	n = 2483	Knee OA Subchondral bone – inhibits degeneration	Risedronate 5 mg OD PO. Risedronate 15 mg OD PO. Risedronate 35 mg once/week PO. Risedronate 50 mg once/week PO. Placebo	JSW measured with radiograph at baseline, 12 and 24 months	No significant difference in JSW or symptom control in any group	Risedronate did not decrease the rate of radiological deterioration of JSW

Table 1. Human trials with DMOADs under investigation (continued).

Refs.	Year	Study	Size	Target and proposed action	Agent	Method	Results	Conclusion
[55]	2007	Manicourt <i>et al.</i> Effect of treatment with the cathepsin-k inhibitor, balicatib, on cartilage volume and biochemical markers of bone and cartilage degradation in patients with painful knee osteoarthritis	n = 223	Knee OA cartilage – inhibits degeneration. Also inhibits degeneration of subchondral bone	10 mg Balicatib OD PO. 25 mg Balicatib OD PO. 50 mg Balicatib OD PO. Placebo	Cartilage volume measured with MRI at baseline and 6 months	No significant difference amongst groups at 6 months in cartilage volume	Balicatib did not decrease the rate of deterioration of MRI measured cartilage volume
[88]	2007	Bruyere <i>et al.</i> Effects of strontium ranelate on spinal osteoarthritis progression	n = 1105	Spinal OA Subchondral bone – inhibits degeneration and promotes regeneration	Strontium ranelate 2 g OD PO. Placebo.	OA score (JSW, osteophytes and sclerosis) measured with radiograph at baseline and 36 months	9.9% (SR) vs 17.1% (Placebo) experienced progression of OA over 3 years. SR reduced OA score by 42% (p = 0.0005)	SR decreased rate of deterioration of radiographic OA score
[12]	2007	Kizeski <i>et al.</i> Development of musculoskeletal toxicity without clear benefit after administration of PG-116800, a matrix metalloproteinase inhibitor, to patients with knee osteoarthritis: a randomised, 12-month, double-blind, placebo-controlled study	n = 401	Knee OA cartilage – inhibits degeneration	PG-116800 25 mg BD. PG-116800 50 mg BD. PG-116800 100 mg BD. PG-116800 200 mg BD. Placebo	JSW measured with radiograph at baseline and 12 months	No statistically significant decrease in rate of JSW Narrowing in any group	PG-116800 did not decrease rate of radiological deterioration of JSW
[82]	2007	Buckland-Wright JC <i>et al.</i> A 2 yr longitudinal radiographic study examining the effect of a bisphosphonate (risedronate) upon subchondral bone loss in osteoarthritic knee patients	n = 1232	Knee OA Subchondral bone – inhibits degeneration	Risedronate 5 mg PO OD. Risedronate 15 mg PO OD. Risedronate 50 mg PO once/week. Placebo	JSW measured with radiograph at baseline and 24 months	vertical trabeculae number increased significantly in the 50 mg group (p < 0.05)	Risedronate preserved the structural integrity of the subchondral bone
[35]	2008	Rozendaal <i>et al.</i> Effects of glucosamine sulfate on hip osteoarthritis: a randomised trial	n = 222	Hip OA cartilage – Promotes regeneration and inhibits degeneration	Glucosamine sulphate 1500 mg OD PO. Placebo	JSW measured with radiograph at baseline and every 3 months for 24 months	JSW narrowing did not differ significantly between the two groups after 24 months (mean difference 0.029)	Glucosamine sulphate did not decrease rate of radiological deterioration of JSW

Table 1. Human trials with DMOADs under investigation (continued).

Refs.	Year	Study	Size	Target and proposed action	Agent	Method	Results	Conclusion
[78]	2008	Neogi <i>et al.</i> The effect of alendronate on progression of spinal osteophytes and disc-space narrowing	n = 200	Spinal OA Subchondral bone – inhibits degeneration	Alendronate 5 mg PO OD for first and second year. Alendronate 10 mg PO OD third year. Placebo	Disc space width and osteophytes measured with radiograph at baseline and 36 months	Osteophyte score significantly better in alendronate group (p = 0.04). The adjusted mean change disc space was less in the alendronate group vs placebo for the whole spine (p = 0.2), particularly when limited to the lumbar spine (p = 0.04)	Alendronate decreased the rate of radiographic disc space narrowing and osteophyte formation
[62]	2009	Raynaud JP <i>et al.</i> Protective effects of licofelone, a 5-Lipoxygenase and cyclo-oxygenase inhibitor, vs naproxen on cartilage loss in knee osteoarthritis: a first multicentre clinical trial using quantitative MRI	n = 355	Knee OA Inflammatory pathways	Licofelone 200 mg BD. Naproxen 500 mg BD	JSW and cartilage volume measured with MRI and knee radiograph at 6, 12 and 24 months	No significant difference in JSW as measured by knee radiograph. Significant differences in global knee cartilage volume loss (p < 0.001) with intention to treat analysis	Licofelone decreased the rate of decrease of cartilage volume measured with MRI. This study proves the superiority of quantitative MRI over x-ray examinations in a multicentre clinical trial
[36]	2008	Sawitzke AD <i>et al.</i> The effect of glucosamine and/or chondroitin sulfate on the progression of knee osteoarthritis: a report from the glucosamine/chondroitin arthritis intervention trial	n = 572	Knee OA – Cartilage Promotes regeneration and inhibits degeneration	Glucosamine sulphate 500 mg TDS. Chondroitin sulphate 400 mg TDS (alone or in combination). Celecoxib 200 mg OD. Placebo	JSW measured with radiograph at baseline and 24 months	Placebo group JSW loss 0.166 mm. No significant difference in mean JSW loss in any treatment group by comparison	Glucosamine and chondroitin did not decrease the rate of radiological deterioration of JSW. However, knees with K/L grade 2 radiographic OA appeared to have the greatest potential for modification with these treatments

**Table 1. Human trials with DMOADs under investigation (continued).**

Refs.	Year	Study	Size	Target and proposed action	Agent	Method	Results	Conclusion
[29]	2009	Kahan et al. Long-term effects of chondroitins 4 and 6 sulfate on knee osteoarthritis: the study on osteoarthritis progression prevention, a two-year, randomised, double-blind, placebo-controlled trial	n = 622	Knee OA – Cartilage Promotes regeneration and inhibits degeneration	Chondroitin sulphate 800 mg OD. Placebo	JSW measured with radiograph at baseline, 12, 18 and 24 months	Significant reduction (p < 0.0001) in minimum JSW loss between CS and placebo. Percentage of patients with radiographic progression ≥ 0.25 mm was significantly reduced in the CS group compared with the placebo group (p < 0.0005)	Chondroitin sulphate decreased rate of radiological deterioration of JSW
[52]	2009	Maheu et al. Evaluation of the structure-modifying effect of avocado-soybean unsaponifiables (ASU expanscience) in hip osteoarthritis (OA): Results of the ERADIAS study, a 3-year prospective, randomised, double blind, placebo controlled trial	n = 399	Hip OA cartilage – inhibits degeneration	ASU 300 mg OD. Placebo.	JSW measured with radiograph at baseline and 36 months	No difference in minimum JSW between groups. Number of progressors (deemed ≥ 0.5 mm) 40% in ASU group and 50% in placebo group (p = 0.039)	ASU reduced the percentage of JSW-deteriorating patients compared to placebo
[47]	2010	Mc Alindon et al. Clinical trial of vitamin D to reduce pain and structural progression of knee osteoarthritis	n = 146	Knee OA cartilage – inhibits degeneration of subchondral bone	Vitamin D3 2000 IU OD. Titrated for serum vit D > 30 ng/ml. Placebo	JSW measured with radiograph at baseline and 12 months. MRI used to assess cartilage volume and thickness at baseline, 12 and 24 months	No significant difference in any outcome measure in either group (p > 0.05 for all groups)	Vitamin D supplementation at a dose sufficient to elevate serum levels above 30 ng/ml did not decrease rate of radiographic JSW deterioration of cartilage volume measured with MRI
[32]	2011	Wildi Lm et al. Chondroitin sulphate reduces both cartilage volume loss and bone marrow lesions in knee osteoarthritis patients starting as early as 6 months after initiation of therapy: a randomised, double blind placebo-controlled pilot study using MRI	n = 69	Knee OA – Cartilage Promotes regeneration and inhibits degeneration	Chondroitin sulphate 800 mg OD. Placebo	Cartilage volume and bone marrow lesions assessed by MRI at baseline, 6 and 12 months	The CS group showed significantly less cartilage volume loss than the placebo group at 6 months for global knee (p = 0.030), lateral compartment (p = 0.015) and tibial plateau (p = 0.002), with significance persisting at 12 months. Significantly lower bone marrow lesions for the CS group at	CS treatment significantly reduced cartilage volume loss and bone marrow lesions, measured with MRI

Table 1. Human trials with DMOADs under investigation (continued).

Refs.	Year	Study	Size	Target and proposed action	Agent	Method	Results	Conclusion
[92]	2011	Karsdal <i>et al.</i> Oral calcitonin demonstrated symptom-modifying efficacy and increasing cartilage volume: results from a 2-year phase 3 trial in patients with osteoarthritis of the knee	n = 1169	Knee OA Subchondral bone – inhibits degeneration. Also increases regeneration and inhibits degeneration of cartilage	Calcitonin (oCT) 0.8 mg BD. Placebo	JSW measured with radiograph at baseline and 24 months	12 months in lateral compartment (p = 0.035) and lateral femoral condyle (p = 0.044) JSW unchanged in both groups (p = 0.97). There was significant difference in cartilage volume (p = 0.012)	oCT did not decrease the rate of radiological deterioration of JSW. Cartilage volume was significantly increased in the oCT group iNOS inhibition decreased the rate of radiographic deterioration of JSW over 48 weeks, but this effect was not sustained at 96 weeks
[54]	2012	Hellio le Graverand-Gastineau <i>et al.</i> A 2-year randomised, double-blind, placebo-controlled, multicentre study of an oral selective inos inhibitor in subjects with symptomatic osteoarthritis of the knee	n = 1048	Knee OA cartilage – inhibits degeneration	SD-6010 50 mg PO OD. SD-6010 200 mg PO OD. Placebo	JSW measured with radiograph at 48 and 96 weeks	Loss of JSW at 48 weeks was significantly less with SD-6010. 50 mg and 200 mg gave 40.1 and 51.3% reduction in loss of JSW at 48 weeks (p = 0.032 and p = 0.081 respectively). After 96 weeks there was insignificant reduction in both groups	ZA decreased MRI measured bone marrow lesions
[83]	2012	Laslett <i>et al.</i> Zoledronic acid reduces knee pain and bone marrow lesions over 1 year: a randomised controlled trial	n = 59	Knee OA subchondral bone – inhibits degeneration	ZA 5 mg. Placebo	Bone marrow lesions measured with MRI at baseline, 6 and 12 months	Reduction in BML seen in ZA group compared with placebo at 6 months (p = 0.044)	
[89]	2013	Reginster <i>et al.</i> Efficacy and safety of strontium ranelate in the treatment of knee osteoarthritis: results of a double-blind, randomised placebo-controlled trial	n = 1683	Knee OA Subchondral bone – inhibits degeneration and promotes regeneration	Strontium Ranelate 1 g PO OD. SrRan 2 g PO OD. Placebo	JSW measured with radiograph at 12, 24 and 36 months	Treatment with SrRan was associated with less progression of cartilage degradation, decrease in JSW was -0.23 (SD = 0.56) mm with 1 g/day; -0.27(SD = 0.63) mm with 2 g/day and -0.37(SD = 0.59) mm with placebo; p < 0.001 for 1 g/day and p = 0.018 for 2 g/day	SrRan 1 and 2 g/day decreased the rate of radiographic deterioration of JSW

inhibitors were developed to be free from zinc-chelating functional groups, thus minimising potential causes of MSS, e.g., 'ALS 1-0635' [14]. Rats treated with this drug did not show signs of MSS, whereas rats receiving a broad MMP inhibitor did. Treatment with 'ALS 1-0635' in a rat model caused 67% reduction in cartilage degradation vs placebo in induced OA *in vivo*. Research into MMP inhibitors is ongoing. However, Phase III evidence for the clinical use of MMP inhibitors as DMOADs is lacking. Non-zinc-chelating, MMP-13-selective inhibitors offer an exciting area of development. Such drugs may provide DMOAD effects without causing MSS, a syndrome that has previously held back research in this area.

### 3.1.2 A disintegrin and metalloproteinase with thrombospondin motifs inhibitors

Degradation and loss of aggrecan, an integral part of extracellular matrix in cartilage tissue, occurs in OA. Some members of the 'a disintegrin and metalloproteinase with thrombospondin motifs' (ADAMTS) family, a group of peptidases found in mammals and invertebrates, are aggrecanases, and have been shown to have a pathological role in OA in mice [15]. Double knockout of ADAMTS-4 and -5 has been shown to protect against surgically induced OA in mice, and these proteins also cause aggrecanolytic in human OA [16]. An ADAMTS-4 and -5 inhibitor 'AGG-523' was shown to reduce aggrecan fragments in joint injury in a rat model [17]. This potential DMOAD is the only ADAMTS inhibitor that has completed Phase I clinical trials but published results are not yet available.

### 3.1.3 Growth factors

Growth factors are a group of proteins whose purpose is to stimulate cellular division, growth and differentiation. Several operate within articular cartilage in health, and controlling them may allow repair of cartilage to improve its function. Following two growth factors are currently involved in clinical trials: 'Human recombinant FGF18' and 'human recombinant BMP-7' (marketed under the name OP-1). The latter is a recombinant form of one of 20 bone morphogenetic proteins (BMPs), a group of growth factors expressed in many tissues including articular cartilage and bone [18]. BMP-7 has been shown to have strong pro-anabolic as well as anti-catabolic effects. *In vitro* studies showed that OP-1 causes synthesis of cartilage extracellular matrix proteins and opposed catabolic mediators. Animal studies show that OP-1 can stimulate growth of new but poorly structured cartilage in sheep with OA [19]. Phase I trials have been completed on intra-articular (IA) BMP-7, which suggested improvement of symptoms vs placebo [20]. Phase II trials have been completed with BMP-7 although the results have not yet been released. FGF-18 has been shown to stimulate repair of damaged cartilage in rat OA [21]. Phase I and II trials with FGF-18 have been performed, but results are not yet available.

### 3.1.4 Glucosamine and chondroitin

GS and CS are normal constituents of cartilage. GS is an amino sugar and is a component of many glycosylated proteins and lipids, and chondroitin is a glycosaminoglycan whose presence within cartilage may provide much of its resistance to compression. Supplementation of both GS and CS is recommended by OARSI and GS will soon be recommended by NICE. All recommendations are for symptomatic relief, but they may also act as DMOADs.

GS appears to affect both anabolic and catabolic mechanisms of cartilage remodelling. It has been shown to facilitate the production of proteoglycan components when radiolabelled GS is added to cultured chondrocytes [22]. It has also been shown to down-regulate MMP-13 activity in chondrocytes and human mesenchymal stem cell cultures and increase matrix production by bovine chondrocytes [23]. It inhibits production of 'tumour necrosis factor alpha' (TNF- $\alpha$ ), 'interleukin-1 beta' (IL-1 $\beta$ ) and 'prostaglandin E2' (PGE2). Reduction of TNF- $\alpha$  and IL-1 $\beta$  disrupts cartilage homeostasis and prevents the normal growth factor-driven repair of cartilage seen in OA [24]. PGE2 is a major catabolic factor in OA and is involved in cartilage degradation and chondrocyte apoptosis [25].

CS has been shown to reduce production of bone remodelling factors 'osteoprotegerin' (OPG) and 'receptor activator of nuclear factor kappa-B ligand' (RANKL), and also inhibit MMP-3 synthesis [26]. CS suppresses ADAMTS-4 and -5, reduces collagenase-3 and MMP-13 gene expression, and increases production of TIMP-1 and TIMP-3 gene expression in articular chondrocytes *in vitro* [27].

Several RCTs have reported significant DMOAD effect of CS in knee OA [28]. Kahan *et al.* (2009) reported the largest study to date; 622 patients were given either 800 mg CS or placebo orally once per day [29]. Radiographs were taken at baseline, 12, 18 and 24 months. JSN was significantly less in the CS group ( $p < 0.0001$ ), as was reduction in pain ( $p < 0.01$ ). A study by Michel *et al.* (2005) compared 300 patients by knee radiograph to determine mean JSW and minimum JSW [30]. Differences were significant for both outcomes ( $p = 0.04$  and  $0.05$  respectively). Uebelhart *et al.* (2004) gave 120 patients either 800 mg CS or placebo once per day for 3 months, followed by a 3-month break, with a further 3 months of treatment [31]. Significant differences were seen in joint space surface area ( $p = 0.03$ ) and mean JSW ( $p = 0.03$ ) but not minimum JSW. This evidence was supported in the recent study using MRI [32]. Sixty-nine patients were randomised to receive either 800 mg of CS or placebo once per day. Significant improvement was found in the CS group for cartilage loss globally in the knee ( $p = 0.03$ ), lateral compartment of the knee ( $p = 0.015$ ) and tibial plateaus ( $p = 0.002$ ) at 6 months. This was still significantly different at 12 months.

Trials involving GS have also shown DMOAD effects in the knee. Most recently, Pavelká *et al.* (2002) randomised 200 patients with knee OA, to receive 1.5 g GS or placebo

once per day [33]. JSN measured by knee radiograph was significantly different over 3 years ( $p = 0.001$ ). Reginster *et al.* (2001) treated 202 patients with 1.5 g GS or placebo, and also found significant differences between the two groups for minimum JSW and mean JSW at 3 years ( $p = 0.002$  and  $p = 0.038$  respectively) [34]. Rozendaal *et al.* (2008) treated 222 patients with either 1.5 g glucosamine sulphate or placebo but found there to be no significant difference in hip JSN at 24 months [35].

The GAIT trial divided 572 patients to compare 1.5 g glucosamine hydrochloride (GH) per day and 1.2 g CS per day, alone or in combination, with placebo [36]. Differences in JSN at 24 months were not significant in any group compared with placebo although some improvement was noted in patients with 'Kellgren/Lawrence' (K/L) grade 2 disease. A review of glucosamine in 2007 concluded that GH does not appear to confer the same benefit as GS in OA, and that care should be made in selecting preparations, as purity varies considerably [37]. Results of trials using European GS, which is regarded as a medication and is therefore rigorously quality-controlled, should not be extrapolated to less pure nutritional supplement preparations found in the US and Canada.

In a meta-analysis of CS and glucosamine, Wandel *et al.* concluded that neither drug was effective as a DMOAD, but were widely criticised [38]. Large-scale RCTs of 200 patients or more were included, which looked at CS and GS preparations alone or in combination. Ten trials were included, six of which investigated JSN in 1835 patients. The authors concluded that there was poor heterogeneity between trials, and that the reductions in JSN were very small. Criticisms were raised that the conclusions were not supported by the data [39].

A study of 275 patients was performed in 2008 to follow up on two previous studies of glucosamine sulphate [40]. The Kaplan–Meier analysis indicated that there was a significant reduction in total knee replacement in patients who had been treated with glucosamine sulphate ( $p = 0.026$ ).

There is evidence that both GS and CS slowed progression of OA, and extension studies on large numbers of patients will add to this body of evidence.

### 3.1.5 Diacerein

Diacerein has been shown to reduce TNF- $\alpha$ , IL-1 $\beta$  and MMP-13 production in subchondral bone, *in vivo*, in patients with OA [41]. This may lead to beneficial influences on cartilage homeostasis and subchondral bone remodelling to prevent joint destruction. A Cochrane review was undertaken in 2009 to assess diacerein and its use in OA [42]. The authors included a range of clinical studies of which two were DMOAD trials. The reviewers reported that diacerein slows radiographic progression of hip OA but not knee OA. The earlier study of the two examined 507 patients with hip OA and assessed JSW on yearly x-ray for 3 years after treatment with 50 mg diacerein BD vs placebo [43]. JSN, in

patients completing 3 years of treatment, was significantly reduced with diacerein ( $p = 0.042$ ). The most frequent side effect was diarrhoea, which was experienced by 46% of the diacerein group and 12% of controls ( $p = 0.001$ ). Diarrhoea caused discontinuation of treatment more often in the diacerein group (12%) compared with the placebo group (2%). This visible and unacceptable side effect may have limited the validity of the double-blind design of the trial. The second trial investigated 301 patients with knee OA with 1 year of treatment with 50 mg BD diacerein vs placebo vs IA injections of hyaluronic acid [44]. No significant difference was demonstrated between groups indicating that diacerein did not demonstrate a DMOAD effect in this group of OA patients. A further study of 120 patients treated with diacerein has since suggested some structural benefit in knee OA [45]. A further trial is indicated in knee OA with larger patient numbers as 301 patients is relatively few, and cost–benefit analysis may lead to use of diacerein in hip OA in the future.

### 3.1.6 Vitamin D

Calcitriol, the active form of vitamin D, increases absorption of calcium from the intestine and resorption of calcium from bone. This increases the level of serum calcium. Vitamin D has been shown to contribute to production of MMP and PGE2 production, by chondrocytes, in osteoarthritic cartilage *in vitro*, and population-based studies have found that reduced levels are associated with low bone mineral density in OA sufferers [46]. Vitamin D supplementation has been shown to provide no benefit to symptoms or structure in knee OA in a RCT involving 146 patients [47]. Patients received either placebo or had their serum vitamin D titrated to  $> 30$  ng/ml. A Phase IV trial is underway to look at pain and function in patients undergoing unilateral total knee replacement who are treated with vitamin D, and will report on radiographic progression as a secondary outcome measure in 2014.

### 3.1.7 Avocado soybean unsaponifiables

'Avocado soybean unsaponifiables' (ASUs) prevent osteoblast-induced inhibition of matrix protein production *in vitro* and this effect may provide DMOAD effects [48]. ASU has been shown to inhibit IL-1 $\beta$  stimulation of stromelysin, IL-6, IL-8 and PGE2 and reduce collagenase synthesis in human articular chondrocytes *in vitro* [49]. *In vivo*, ASU significantly reduced cartilage degeneration in an OA model in mice [50].

Lequesne *et al.* (2002) studied 163 patients with hip OA, receiving either 300 mg ASU or placebo, over a 2-year duration [51]. The outcome measure of JSN was not significantly different between the two groups and DMOAD effects were not demonstrated, however *post-hoc* analysis found significant benefit in patients with severe OA. The ERADIAS study looked at 399 patients with hip OA, measuring JSN with pelvic AP radiograph taken at baseline and annually for 3 years [52]. Improvement was not seen in JSN on average, but there were significantly less cases with JSN in the ASU

group vs placebo ( $p = 0.039$ ). Both studies would suggest that some subgroups of patients may benefit from this therapy, and identification of suitable patients must be addressed before ASU can be considered clinically useful as a DMOAD.

### 3.1.8 Inducible nitric oxide synthase inhibitors

'Nitric oxide' (NO) is a free radical and causes damage to cartilage through several mechanisms including increasing the effects of MMPs, inhibiting matrix synthesis and causing apoptosis of chondrocytes. It has been shown that pro-inflammatory cytokines stimulate NO *in vitro* through the inducible nitric oxide synthase pathway (iNOS), and that synovium and cartilage stain positive for iNOS in OA but not in normal tissue. A selective iNOS inhibitor 'L-NIL' has been shown in a dog model of induced OA to prophylactically prevent progression of disease [53]. Selective inhibition of iNOS by L-NIL and the knock-on effect of reducing NO production caused less MMP, IL-1 $\beta$  and peroxynitrite within cartilage and synovium. A 2-year RCT recently showed that SD-6010 (a selective iNOS inhibitor) slowed progression of mild OA, but was not effective in severe radiographic OA [54]. Knee radiographs were taken at baseline, 48 and 96 weeks to assess JSW. Progression of JSN was reduced in the treatment group vs placebo at 48 weeks ( $p = 0.032$ ), but not sustained at 96 weeks ( $p = 0.081$ ). Alternative pathological mechanisms may have overcome the effect of NO inhibition between 48 and 96 weeks, so although this drug showed some efficacy in early OA, it is still unclear exactly which group of patients would see benefit from iNOS inhibition. For this reason further work is needed to identify patients most likely to benefit from this drug and to assess how large groups of such patients respond to this potential DMOAD.

### 3.1.9 Cathepsin K inhibition

Cathepsin K, a protease involved in bone resorption, cleaves type I and II collagen and degrades aggrecans (two mechanisms contributing to cartilage damage). Its expression in OA cartilage correlates with disease severity. Its inhibition was suggested as a potential mechanism of treatment for OA, but a trial with 223 patients treated with placebo or balicatib found no significant difference in cartilage volume measured by MRI at 6 months [55]. Side effects including hardening of the skin have been reported with use of balicatib and it has been suggested that this may be a class effect to be monitored for in further study [56].

### 3.1.10 Doxycycline

Doxycycline is a tetracycline antibiotic that is widely used, which also inhibits some MMPs and iNOS. Doxycycline inhibits collagenase and gelatinase *in vitro*, which are enzymes implicated in cartilage breakdown in OA. It has been associated with a reduction in early stage cartilage damage in rabbits *in vivo* [57]. A placebo-controlled RCT showed benefit in preserving JSW vs placebo with 40% less JSW loss in the index knee at 16 months ( $p = 0.027$ ) and 33% less at 30 months

( $p = 0.017$ ) [58]. The authors intended to determine if doxycycline would reduce the incidence of OA in the radiographically normal contralateral knee, with no effect demonstrated at 16 or 30 months. The authors suggested that doxycycline might interfere with specific matrix pathways with more importance in later stages of OA and so did not slow progression in normal knees. There is scope for further research in different stages of the disease, examining the relative effects this agent may provide in each. Currently, doxycycline should not be prescribed routinely.

### 3.1.11 Vitamin E

Vitamin E was identified as a potential DMOAD after *in vitro* study showed decreased cartilage matrix protein oxidation and degradation in the presence of the antioxidant [59]. In a rat model *in vivo*, a vitamin E-enriched diet significantly inhibited development of OA after IA injection of hydrogen peroxide [60]. A RCT involving 136 patients treated with either 500 units of vitamin E daily vs placebo over a 2-year period demonstrated no beneficial effect on cartilage volume measured with MRI [61].

## 3.2 DMOADs targeting inflammatory pathways

### 3.2.1 Licofelone

Licofelone is a competitive inhibitor of cyclooxygenase (COX) and 5-lipoxygenase, and thus reduces destruction of matrix macromolecules. This may protect the joint from degeneration. A Phase III trial on licofelone (200 mg BD) showed that it significantly reduced knee cartilage loss measured by MRI over 12 and 24 months ( $p < 0.001$ ) [62]. Naproxen (500 mg BD) was used as the control group in this study, yet there has been no evaluation of the effect of naproxen or licofelone vs placebo on JSN. Indomethacin, an NSAID, caused increased rate of JSN in a trial of 812 patients ( $p = 0.009$ ) vs placebo [63]. There is no evidence that this effect carries over to other NSAIDs but lack of a placebo group is a significant weakness of this study. This is the only trial investigating licofelone as a potential DMOAD and promising results have been shown. Patients were followed up after 6 years to determine if the incidence of total knee replacement was different with licofelone treatment, and indeed, significant differences were noted; 64 patients treated with licofelone and 59 patients treated with naproxen were interviewed [64]. Sixty-one percent of patients undergoing TKR were treated with naproxen ( $p = 0.232$ ), indicating that treatment with licofelone may be beneficial and that MRI is likely to be an effective imaging modality. However, it would be prudent to compare licofelone to placebo before drawing conclusions.

### 3.2.2 Cytokines

Interleukin-1 $\alpha$  and IL-1 $\beta$  cause cartilage destruction *in vitro* and *in vivo*, partly through their potentiation of MMP synthesis, inhibition of TIMP production and induction of NOS [65]. Inhibition of IL-1 and TNF- $\alpha$  has been shown to result in down-regulation of MMP-1, MMP-3 and

MMP-13 expression and result in preservation of human cartilage *in vitro* [66]. In particular IL-1 $\beta$  appears to play a key role in cartilage homeostasis and repair. Blocking of IL-1 $\beta$  with 'IL- $\beta$  converting enzyme' (ICE) inhibition has been shown to slow progression of type II collagen-induced arthritis in mice [67]. 'Canakinumab', a human monoclonal antibody for IL-1 $\beta$ , has completed Phase II trials. There are no results for efficacy in human OA at this time, but it has been shown to suppress mouse cartilage damage *in vivo* [68]. Oral treatment with an IL-1 monoclonal antibody has been linked with a decrease in neutrophil count and may have indirectly caused the death of a study participant [69]. This is unacceptable for use in a nonfatal condition such as OA, and different modes of delivery such as IA should be considered [70].

### 3.2.3 Tumour necrosis factor antibodies

TNF blockers are used in rheumatoid arthritis (RA). RA is an inflammatory arthritis and TNF- $\alpha$  has a significant role on the pathophysiology that leads to joint destruction. TNF- $\alpha$  inhibits growth factor-mediated repair of cartilage in OA and up-regulates MMP gene expression, and therefore its inhibition may cause DMOAD effects [71]. A small pilot study suggested some improvement in some patients with 'adalimumab', a TNF- $\alpha$  monoclonal antibody [72]. Phase II trial evidence has shown that adalimumab slows progression of hand OA and Phase III trials are in progress [73]. 'Infliximab' has been associated with a reduction in anatomical lesion score after 1 year and has reduced the incidence of secondary OA of the hand in RA patients [74]. Completion of Phase III trials will hopefully give some information toward the efficacy of this class of drug in slowing OA progression.

### 3.2.4 Steroids

The ACR guidelines include IA corticosteroids for symptomatic relief. This practice was initially controversial, as injection of steroids into joints increased fissures and cysts in a rabbits *in vitro* [75]. Conversely, the effects of steroids *in vivo* have been shown to be protective [76]. In a RCT of 68 patients receiving IA injections of the steroid 'triamcinolone' every 3 months over a 2-year period, no significant differences were seen in JSW against placebo [77]. Consequently, steroids can be prescribed safely for symptomatic relief, but no evidence exists to support their use as DMOADs.

## 3.3 DMOADs targeting subchondral bone

### 3.3.1 Bisphosphonates

Bisphosphonates impair osteoclast activity, and therefore reduce physiological bone resorption, potentially protecting subchondral bone. Alendronate use in spinal OA has been studied in the FIT trial and was shown to slow progression of disc space narrowing (DSN) [78]. Two hundred patients had spinal radiographs at baseline and at 3 years after treatment with alendronate or placebo. Patients in the alendronate group showed fewer osteophytes on spinal radiograph ( $p = 0.04$ ) and less DSN ( $p = 0.2$ ), this was more significant

when taking into account only the lumbar spine ( $p = 0.04$ ). A number of authors have examined the use of risedronate in OA of the knee. In a large prospective Phase III study, risedronate (5 mg or 15 mg OD, or 35 mg or 50 mg once per week) has been shown to provide no significant effect on JSN as measured by plain knee radiograph vs placebo [79]. A total of 2483 patients in the KOSTAR trial had JSW measured at baseline, 12 and 24 months. Sub-analysis has been performed on the data from this trial, concluding that a biochemical marker of cartilage degradation, 'c-terminal crosslinked telopeptide type II collagen' (CTX-II), was decreased in the risedronate group [80]. The authors of this study argue that these findings may represent disease modification, and further work is required to clarify this. The BRISK trial further examined the use of risedronate in patients with OA [81]. In a prospective RCT, 284 participants were treated orally with 5 mg or 15 mg risedronate OD, or placebo. Plain radiographs of the knee were taken at baseline and after 1 year. The difference in JSN was not statistically significant. Risedronate has been shown to significantly preserve vertical trabeculae number in subchondral bone in patients in severe knee OA ( $p < 0.05$ ), and a RCT of zoledronic acid in knee OA demonstrated reduction in bone marrow lesions against placebo measured with MRI at 6 and 12 months ( $p = 0.044$ ) [82,83]. This mode of action would not necessarily preserve cartilage however, indicating that measurement of JSN may be a poor outcome measure for drugs affecting subchondral bone. Further work may demonstrate the clinical significance of preserving trabeculae number, although at present evidence for a clinical benefit for OA patients treated with bisphosphonates is lacking.

### 3.3.2 Strontium ranelate

'Strontium ranelate' (SrRan) increases osteoblast activity and survival, and regulates osteoclastogenesis *in vitro* and *in vivo* [84]. It decreases osteoclast activity causing increases in bone formation and decreases in bone reabsorption, and is approved by NICE for osteoporosis [85]. *In vitro*, study with normal and OA chondrocytes has shown SrRan to stimulate proteoglycan production and matrix formation [86]. *In vivo*, SrRan has been shown to reduce urinary CTX-II [87]. SrRan has been shown by Bruyere *et al.* (2008) to have DMOAD effects in spinal OA in women with osteoporosis and spinal OA [88]. Lumbar spine x-rays were taken at baseline and 3 years in 1105 patients, with a 40% reduction in the number of patients showing progression of cartilage degradation in the SrRan group vs placebo ( $p = 0.0005$ ). A Phase III RCT showed that SrRan was effective at reducing JSN in 1683 patients with knee OA ( $p < 0.001$  for 1 g/day and  $p = 0.018$  for 2 g/day) vs placebo [89]. This trial was only reported recently and cost-benefit analysis is awaited.

### 3.3.3 Calcitonin

Calcitonin is a hormone, which among other effects, opposes parathyroid hormone and therefore inhibits osteoclast bone

reabsorption. The mechanism by which this occurs is through binding to the calcitonin receptor on osteoclasts and changing their cytoskeletal structure. Calcitonin has been studied extensively *in vitro* and *in vivo*, and it appears to act on both bone and cartilage [90]. Treatment with calcitonin reduced urinary and serum biomarkers of OA in 41 knee OA patients [91]. Calcitonin was also shown to preserve cartilage volume in a trial looking at 1169 patients with knee OA, where significant benefit was seen in the calcitonin group vs placebo at 2 years ( $p = 0.012$ ) [92]. Calcitonin has not demonstrated significant effect on JSN and as such further evidence is needed before it can be proven to act as a DMOAD.

#### 4. Discussion

OA causes progressive pain and disability. Current treatments can be broadly divided into medical treatments, which target symptoms, or surgical treatments, which offer functional improvement by use of prosthetic joints. The risks of surgery and, in some joints, the limited lifespan of the prostheses, mean it is currently a last resort in the treatment of OA.

No DMOADs are yet recommended by NICE, although several are recommended by OARSI. A range of DMOADs have been discussed in this review, many of which still require further study. The development of DMOADs has the potential to reduce morbidity in large group of patients, and provides a significant financial incentive for public health services.

There have been significant limitations in DMOAD studies to date, including side effects, e.g., diarrhoea and MSS. This, in addition to long study durations required in assessing this slowly progressive disease, has caused loss to follow up which is an area for future improvement. Whereas laboratory research on agents *in vitro* and *in vivo* in animal models has yielded many possible drugs of interest, relatively few have demonstrated significant effects in humans. Reasons for this include that most of the models used have been on traumatically induced arthritis in relatively young rodents. OA is a disease most commonly found in ageing humans and as such it is unclear that such models are ideal. Recently developments including non-zinc-chelating selective MMP inhibitors may reduce side effects, and more sensitive and specific outcome measures including MRI and biomarkers of OA may reduce required study durations.

As new outcome measures are developed and validated for use, regulatory authorities should continue to develop up-to-date standardised protocols for outcome measures, to ensure results of each trial are valid and to avoid confusion amongst researchers. MRI has been used in the past as the primary outcome measure in some trials, but CHMP guidelines still recognise JSN as the primary outcome measure after consultation with several bodies including OARSI, the association of the European self-medication industry (AESGP), the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Group for the Respect of Ethics

and Excellence in Science (GREES) and the European League Against Rheumatism (EULAR). Although MRI has shown potential for evaluation of cartilage structure, there has been insufficient correlation with JSN, clinical symptoms and joint replacement to prove its clinical relevance. Study by Cicuttini *et al.* demonstrated that a 1% loss of tibial cartilage increased the risk of undergoing TKR over a 4-year period by 20% [93]. An OARSI working group concluded during 2011 that MRI is superior to knee radiograph in the measurement of disease progression in OA, and that MRI should now be considered the primary outcome measure in such research trials [94]. No further review has been performed by CHMP and therefore MRI should be strongly recommended as a secondary outcome measure.

Despite positive results demonstrating slowed progression of JSN with a range of agents, few studies have shown DMOAD effects alongside symptomatic and/or functional benefit. This lack of clinical benefit has important implications, as subsequent development and endorsement by clinical bodies may prove difficult if efficacy is in question. Cartilage is poorly innervated and as such, the pain experienced in OA is thought to come from other structures of the joint, such as synovium as the inflammatory process progresses. JSN may therefore not correlate well with pain, and this perceived weakness in the mechanism of action of DMOAD drugs which has limited their use in the past may not be as concerning as previously thought. A further complication may exist in that immobilisation may cause reduction in JSW, leading symptomatic drugs to have apparent DMOAD effects as function improves. This has not been the case to date but may be an issue to be aware of in the future.

#### 5. Conclusion

Evidence to support DMOADs does not yet give adequate support for their use in practice, but does suggest the concept is feasible with more development of different drugs and identification of the subgroups of patients in which to use them. Several agents have already proven DMOAD qualities, and others offer potential mechanisms *in vitro* and *in vivo* that are yet to be proven in clinical trials.

New outcome measures such as MRI and biomarkers will hasten advances in this area and will offer greater insight into the nature of patients' disease with regard to the different joint structures affected and the degree to which they are involved. Several significant challenges remain, but once overcome, this class of drug will represent the greatest milestone in the treatment of OA to date. An important step in future research with DMOADs is likely to be identification of groups of patients with similar features of disease. Several DMOADs have been suggested as having effects on select groups only; the characteristics of these groups are currently unknown. Linking appropriate patients to their most effective DMOAD will likely yield more benefit, as effects on a general OA population have so far been modest.

## 6. Expert opinion

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OA is likely to become an increasing burden in the coming decades. Although a range of agents have been developed to combat the progression of degenerate joint disease, there is still little reliable evidence that such agents will be successful. A lack of prospective, comparative, clinical data has meant that despite promising early data, only a small number of agents are recommended by NICE and OARSI.

Several biomarkers for OA have already been mentioned and in addition cartilage oligomeric matrix protein (COMP) has shown promise. In a study measuring COMP levels against MRI cartilage in symptomatic knee OA patients, a single increase in COMP corresponded with a sixfold increase in the risk of cartilage loss on MRI [95]. In the future biomarkers may allow sensitive and specific quantification of disease processes in the different structures of the joint to tailor DMOAD treatment to the target tissue. Evidence is needed to prove that biomarkers can predict OA in the asymptomatic patient, as this would allow selection of appropriate patients to receive early DMOAD treatment and hopefully receive maximal benefit.

Although DMOADs may not prevent pain in the latter stages of OA, it is feasible that their effect in preserving cartilage will lengthen the time before patients reach levels of debilitating pain, which would reduce their mobility and quality of life and cause them to seek a surgical alternative. A severely painful joint in relatively advanced disease is unlikely to respond to the disease-modifying treatment. However, intervention before this point, when patients are experiencing mild or intermittent symptoms, is likely to be

more beneficial. It remains to be seen whether intervention in the asymptomatic patients with very early degeneration would be worthwhile. In this scenario, screening programs would be required, which may be expensive, and alternative imaging modalities may be required. Static imaging may be superseded by new functional imaging techniques, to match specific structural weaknesses with functional limitations. Such sensitive evaluation of the joint may eliminate the need for such large study cohorts and long follow-up times which would speed up development significantly. Study endpoints are currently far from ideal, and development should be encouraged in this area. In parallel with clinical and radiological markers of disease progression, biomarker measurement may be of considerable use, offering a more accurate measurement of disease than direct visualisation of cartilage. However, research in this area is still in its infancy, and the clinical relevance has yet to be proven.

It is likely that a wider range of prospective clinical studies will be embarked upon in the coming years. Trials should be designed in a systematic manner, powered with sufficient numbers to demonstrate clinical benefit at different stages of disease. For example, there is evidence that doxycycline may provide symptomatic benefit in late-stage OA, with little effect in early disease. This may be true of other DMOADs, and further research is warranted to determine which patient subgroups benefit from each drug.

### Declaration of interest

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The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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