

# Hand osteoarthritis—nonpharmacological and pharmacological treatments

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**Abstract** | Hand osteoarthritis (OA) is a prevalent disease with a high clinical burden. The number of clinical trials in hand OA is limited and, therefore, recommendations for the management of hand OA are mostly expert-based instead of evidence-based, and medication is often prescribed off-label. However, in the past 5 years, this ‘forgotten’ disease has attracted increasing attention and a number of high-quality clinical trials have now been performed, or are ongoing. The results from studies conducted to assess nonpharmacological treatment modalities indicate that educating patients about self-management, the provision of assistive devices and the application of splints for thumb base OA, are effective for pain and disability. For pharmacological management, more high-quality trials are needed, although evidence is available for short-term symptom alleviation of pain by topical and oral NSAIDs. The role of anti-inflammatory medication, such as corticosteroids and biologic agents, is controversial, and the same holds true for the efficacy of symptomatic slow acting drugs for OA. Disease modifying OA drugs (DMOADs) for hand OA are currently not available. The results from the ongoing pharmacological trials will increase our knowledge for evidence-based management of hand OA in the near future.

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## Introduction

Hand osteoarthritis (OA) is one of the most common OA phenotypes and the prevalence will increase further in the coming decades with ageing of the general population. Hand OA leads to pain, loss of function, a decrease in grip and pinch grip strength, and reduced quality of life—which results in unmet patient needs.<sup>1–4,5</sup> OA is caused by an imbalance between degradation and repair processes in cartilage, bone and synovial tissue.<sup>6</sup> Synovial inflammation corresponds to hand joint swelling and pain, and can be detected by ultrasonography and MRI.<sup>1,7,8</sup> Catabolic and proinflammatory mediators produced by synovial tissue cells lead to further cartilage matrix degradation.<sup>6</sup>

Hand OA consists of several subsets—including finger OA with nodes, thumb base OA and erosive OA—with their own risk factors, such as genetic and occupational factors, hypermobility and obesity.<sup>1,9</sup> Some of these risk factors could be modified or prevented, but no strategies that target risk factors have been investigated to date. In contrast to knee OA, for example, whether losing weight would be of value to patients with hand OA is currently unknown.<sup>10</sup> In hand OA, especially erosive OA, synovial inflammation is prevalent.<sup>11</sup> Anti-inflammatory medication, such as corticosteroids, disease modifying anti-rheumatic drugs (DMARDs) and biologic agents

are, therefore, hypothesized to be effective in patients with erosive OA and might even act as disease modifying OA drugs (DMOADs): they are increasingly investigated. Hand OA subsets often coincide and treatment decisions should reflect this overlap. For example, because thumb base OA contributes to pain and disability more than finger OA, treatment of thumb base OA should be emphasized, even if it coincides with finger OA.<sup>12–14</sup>

Personal factors, such as illness perception and coping strategies, are also important in perceived pain and disability in patients with hand OA. Therefore, management strategies linked to the cognitive-behavioural theory are important to investigate.<sup>15–18</sup> Patients with hand OA often perceive a lack of support and understanding of the impact of hand OA on the individual. Patients also, unfortunately, report insufficient availability of information with regard to management of their disease, and contradictory advice from different healthcare professionals about treatment options.<sup>19,20</sup> This inconsistency could be due to the limited number, and low-quality, of clinical trials to date in the hand OA field.<sup>21–23</sup> However, this ‘forgotten disease’ has attracted increasing attention in the last 5–6 years, which has resulted in the initiation of a number of high-quality trials.<sup>24</sup>

Currently, management strategies target symptom alleviation; no DMOADs are available. This Review summarizes state-of-the-art pharmacological and non-pharmacological management of hand OA in view of existing guidelines; surgical management is excluded. Trials performed in the past few years, as well as ongoing trials, are described. The efficacy of treatment

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**Key points**

- Evidence from high-quality clinical trials for the management of hand OA is limited and, therefore, recommendations are mostly based on expert opinion and medication is often prescribed off-label
- Education for self-management is effective for pain and disability; however, because the stand-alone result of education is small, it should be combined with other management strategies
- High-quality clinical trials now show that splints are effective in pain alleviation for thumb base OA, but the optimum splint type and instruction for use has not been defined
- Inflammation is frequently observed in hand OA, although anti-inflammatory drugs show ambiguous results and more research into the role of inflammation in hand OA is required
- Evidence for the efficacy of symptomatic slow acting drugs for OA is currently lacking—ongoing trials will contribute to our knowledge in the coming years
- Disease modifying activity is seldom investigated for hand OA; more long-term studies are needed to investigate disease modifying drug activity across hand OA subsets

**Table 1** | Overview of nonpharmacological treatment modalities in hand OA

Treatment	Placebo-controlled randomized trials	Systematic reviews	Treatment effect
Education	NA	Musculoskeletal pain, including hand OA <sup>33–35</sup>	Very small <sup>36</sup>
Assistive devices	NA	NA	NA
Splints for TB OA	Rannou <i>et al.</i> <sup>42</sup> Gomes Carreira <i>et al.</i> <sup>43</sup>	Kjeken <i>et al.</i> <sup>39</sup> Ye <i>et al.</i> <sup>40</sup> Valdes & Marik <sup>41</sup>	Short-term ES 0.37 (95% CI 0.03–0.71), long-term ES 0.80 (95% CI 0.45–1.15) <sup>39</sup>
Splints for DIP OA	Watt <i>et al.</i> <sup>45</sup>	NA	NA
Exercise	Garfinkel <i>et al.</i> <sup>110</sup> Rogers & Wilder <sup>111</sup> Lefler & Armstrong <sup>112</sup>	Kjeken <i>et al.</i> <sup>39</sup> Valdes & Marik <sup>41</sup>	Trials with high risk of bias, no meta-analyses performed Single trials: pain decreases, ROM and strength increases <sup>39</sup>
Local application of heat	NA	NA	NA

Abbreviations: CI, confidence interval; DIP, distal interphalangeal joint; ES, effect size; NA, not available; OA, osteoarthritis; ROM, range of motion; TB, thumb base.

is reflected by effect size—the difference in mean outcomes of the treatment and control group divided by the SD. When available, the effect sizes (or standardized mean differences) are reported. An effect size of 0.2 is considered small; 0.5, moderate; 0.8, large.<sup>25</sup>

**Existing guidelines**

Recommendations by the task force of EULAR (The European League Against Rheumatism) and technical expert panel of ACR (American College of Rheumatology) for the management of hand OA are available.<sup>26,27</sup> The NICE (National Institute for Health and Care Excellence) guideline recommends care and management for OA in general, including hand OA.<sup>28</sup> The lack of high-quality trials means that these recommendations for treatment are mostly based on expert opinion. Combining nonpharmacological and pharmacological treatment modalities, and tailoring treatment to the wishes and expectations of patients, is considered good

clinical practice and, therefore, recommended, even in the absence of evidence.

**Nonpharmacological treatment modalities**

Education, assistive devices, splints, exercise and thermal modalities are common nonpharmacological treatments for hand OA (Table 1). However, they are often used in combination, which makes it difficult to determine their individual efficacy. Nonpharmacological management is often provided by a multidisciplinary team, frequently including a physiotherapist, occupational therapist and rheumatology nurse specialist, but management can also be supplied by the primary care giver (general practitioner, rheumatologist or surgeon).<sup>20</sup> The implementation of these modalities has been suggested to improve with the engagement of healthcare professionals, such as nurse specialists, occupational therapists or practice nurses.<sup>29</sup> Patients also report that they are satisfied with consultations with nurse specialists.<sup>30</sup> Whether non-pharmacological treatment is optimally applied in an individual or group setting is unclear.

**Education**

Education aims to enhance patient understanding of OA diagnosis, disease course, objectives of treatment, self-help and the principles of joint protection and chronic pain. Misconceptions—that OA results from ageing and wear and tear (and, therefore, that nothing can be done), that OA inevitably progresses and that the symptoms cannot be alleviated are important to counteract.<sup>19,28,31</sup> Self-management strategies, frequently used by patients with hand OA,<sup>32</sup> are effective, as supported by several systematic reviews summarizing studies in a variety of chronic musculoskeletal pain conditions, including hand OA.<sup>33–35</sup> An overview of the systematic reviews showed that, although self-management is effective in addressing pain and function, effect sizes are very small and, therefore, clinically negligible.<sup>36</sup> In summary, while education is helpful, it has a small symptom alleviating effect.

**Assistive devices**

An increasing number of assistive devices, such as key turners, rubber grips, kitchen tools and zipper pulls, are available to help patients perform tasks and activities. These devices increase function and protect the joint from mechanical overloading.<sup>27</sup> Assistive devices are often provided in association with education<sup>37,38</sup> and they have not been investigated separately.

**Splints**

Splints are used to support, stabilize, protect or immobilize a painful osteoarthritic joint which, in patients with hand OA, is usually the thumb base. Numerous types of splint exist, both prefabricated and custom-made. Some splints only incorporate the first carpometacarpal joint, others the wrist or first metacarpophalangeal joint as well. The underlying working mechanism and expectations from wearing a particular splint (and how these translate to the design and instructions for use) are often unclear.<sup>39</sup> Guidelines for use vary from full-time

**Table 2** | Randomized controlled trials in hand OA investigating a combination of nonpharmacological treatments

Treatment	Subset of hand OA	n	Study duration (months)	Primary outcome	Treatment effect	Reference
Education, assistive devices, home exercise	ACR*	40	3	Grip strength	$P < 0.0005$ NNT 2 (1-6) <sup>26</sup>	Stamm, T. A. <i>et al.</i> <sup>46</sup>
Assistive devices, splints	ACR	70	3	Performance	Effect size 0.9 <sup>†</sup>	Kjeken, I <i>et al.</i> <sup>37</sup>
Education, assistive devices, home exercise, splints	ACR	151	3	Disability	No effect	Stukstette, M. J. <i>et al.</i> <sup>47,48</sup>
Education, exercise	ACR, TB	~250	6	Pain and disability	Preliminary: education effective, exercise not effective	Dziedzic, K. S. <i>et al.</i> <sup>49,50</sup>

\*Hand OA following the classification criteria of the ACR. †Based on adjusted mean differences between groups assessed by Canadian Occupational and Performance Measure. Abbreviations: NNT, number needed to treat; TB, thumb base; OA, osteoarthritis.

to use only during the day or night, or during activities or complaints.

Several systematic reviews on the effect of hand splints for patients with hand OA have been published.<sup>39–41</sup> Kjeken *et al.* performed a meta-analysis of two studies (both with a low risk of bias)<sup>42,43</sup> in patients with painful thumb base OA. In both studies, patients used a rigid custom-made splint covering the thumb base and first metacarpophalangeal joint. The investigators reported an effect size on pain after short-term ( $\leq 45$  days) follow-up between the splint and control group of 0.37 (95% CI 0.03–0.71). After long-term ( $\geq 3$  months) follow-up, the effect size was 0.80 (95% CI 0.45–1.15). No effect on disability and pinch grip was observed. The instructions for use varied between the trials. Rannou and colleagues advised use during the night only, whereas Gomes Carreira and colleagues advised use during the day only.<sup>42,43</sup>

Distal interphalangeal (DIP) joint splints are available to protect and immobilize osteoarthritic painful DIP joints. The results from an open study of 25 patients suggest that DIP joint splints reduce pain,<sup>44</sup> and preliminary data from a controlled trial that compared pain in DIP joints with splints to DIP joints without splints also indicate an alleviating effect.<sup>45</sup>

In summary, splints can ease pain related to thumb base OA. Splinting of painful osteoarthritic DIP joints is thought to be effective, but further research should be performed. More high-quality studies that compare instructions for splint use, as well as the different types of splints, are needed.

### Exercise

A range of motion and strengthening exercises are recommended in guidelines for hand OA with the purpose of increasing pinch and grip strength, range of motion and stability of the first carpometacarpal joint. Studies that have investigated exercise have used different regimens and have generally been of low-quality. Systematic reviews provide some evidence that exercise might increase grip strength, although no meta-analysis could be performed.<sup>39,41</sup>

### Thermal modalities

Local application of heat, for example with paraffin wax or a hot pack, is (conditionally) recommended by both the EULAR task force and the technical expert panel of the ACR to alleviate pain and stiffness associated with OA.<sup>26,27</sup> The EULAR task force also recommend the use of thermal modalities before exercise.<sup>26,27</sup> These recommendations are based on expert opinion.

### Combination of nonpharmacological treatments

Nonpharmacological treatments are often used simultaneously (Table 2). Combining home exercise with either splints or education (including assistive devices), has been shown to improve the symptoms of patients with hand OA over control groups.<sup>38,46</sup> Combining exercise with education increased grip strength by 25% after 3 months, whereas no increase in grip strength was seen in the placebo group. Patient global hand function also increased compared with control participants, with the number needed to treat (NNT; the average number of patients that need to be treated for one to benefit compared with a control) of 2 (95% CI 1–6).<sup>26</sup>

Three high-quality trials have been performed, although the results were contradictory. Kjeken and colleagues randomized 70 patients with hand OA consulting secondary care to either provision of information and assistive technology (assistive devices and splints), or to information only.<sup>37</sup> The intervention was completed in a single session of approximately 2 h; 97% of patients in the intervention group received technical devices (the average number of devices per participant was 11) and 74% received splints. After 3 months, the Canadian Occupational and Performance Measure (COPM) improved significantly in the intervention group compared with the control group (effect size of 0.9). No difference was seen in pain scores, although there was a trend for improvement in function with a mean difference between groups of  $-0.3$  (95% CI  $-0.6\%$  to  $0.01\%$ ; effect size  $-0.5$ ).

By contrast, Stukstette and co-workers randomized 151 patients with hand OA consulting secondary care to a multidisciplinary care programme, including education

**Table 3** | Analgesics recommended in hand OA and evidence for efficacy

Treatment	Placebo-controlled randomized trials in hand OA	Systematic reviews in musculoskeletal pain, including hand OA	Efficacy in pain alleviation
Paracetamol	NA	NA	NA
Topical NSAIDs	Rothacker <i>et al.</i> <sup>113</sup> Altman <i>et al.</i> <sup>114</sup>	Derry <i>et al.</i> <sup>53</sup> Moore <i>et al.</i> <sup>54</sup> Lin <i>et al.</i> <sup>55</sup> Mason <i>et al.</i> <sup>60</sup>	Effect size 0.77 (0.32–1.22) <sup>53–55</sup> NNT 6.4–11 <sup>53–55</sup> NNT 3.1 (2.7–3.8) <sup>54</sup> NNT 4.6 (3.8–5.9) <sup>60</sup>
Topical capsaicin	McCarthy & McCarty <sup>57</sup> Schnitzer <i>et al.</i> <sup>58</sup>	Mason <i>et al.</i> <sup>59</sup> Zhang & Li Wan <sup>115</sup>	NNT 8.1 (4.6–5.9) <sup>60</sup>
Oral NSAIDs/COX-2 selective inhibitors	Grifka <i>et al.</i> <sup>61</sup> Dreiser <i>et al.</i> <sup>62</sup> Seiler <sup>63</sup>	Zhang <i>et al.</i> <sup>26</sup>	Effect size 0.40 (0.20–0.60) <sup>26</sup> NNT 3 (2–6) <sup>26</sup>
Tramadol	No trials in hand OA	NA	NA

Abbreviations: NA, not available; NNT, number needed to treat (95% CI); OA, osteoarthritis.

on self-management, joint protection, home exercise, assistive devices and splints, or to information only.<sup>47</sup> The intervention, supervised by one occupational therapist and one specialized nurse, comprised of four group sessions of 6–8 patients. No significant improvement was seen in any pain, function or grip strength outcome measure within the groups, although one third of participants reached the OMERACT-OARSI (Outcome Measures in Rheumatology-Osteoarthritis Research Society International) responder criteria.<sup>48</sup> Notably, no differences between the groups were observed.

Dziedzic and colleagues performed a two-by-two factorial randomized controlled trial in approximately 250 patients with hand OA in primary care. Four groups, who were provided with either joint protection, exercise, both protection and exercise, or only the provision of a leaflet (the control group), were compared. The intervention was supplied by an occupational therapist in a group setting during four visits. The preliminary results indicate that, in the control groups, 20–25% reached the OMERACT-OARSI responder criteria. Patients who received joint protection were twice as likely to meet the responder criteria after 6 months, but not after 3 months or 12 months. No such effect was seen in the group who received exercise.<sup>49,50</sup> The final results of the study are pending.

In summary, nonpharmacological treatment can be effective. Trials show, however, that combining various nonpharmacological treatment modalities in different settings can make it difficult to evaluate the individual efficacy of these programmes.

**Pharmacological treatments**

**Analgesics**

*Paracetamol*

Paracetamol (up to 4 g per day) is recommended as the primary choice of analgesics (Table 3), although no scientific evidence from trials in hand OA support this advice (except from one study, only published as an abstract).<sup>26,28,51</sup> This 3-group study included 88 patients with nodal hand OA that were treated with either

paracetamol (1.3 g three times a day [*n* = 29], placebo [*n* = 30] or hydroxychloroquine for 24 weeks. No difference was seen between the groups in reducing the number of tender joints or pain as scored on VAS (Visual Analog Scale).<sup>51</sup> The recommendation to use paracetamol is based on extrapolation from studies in knee and hip OA.<sup>52</sup> Moreover, paracetamol has the advantage of a favourable safety profile.

*Topical NSAIDs*

Several reviews have been published on the efficacy of topical NSAIDs for patients with hand OA.<sup>53–55</sup> Derry and colleagues, who focused on chronic musculoskeletal pain (including hand OA), found that topical NSAIDs were significantly more effective than placebo, especially in participants who received diclofenac. The NNT for ≥50% pain relief over 8–12 weeks compared with placebo was 6.4 for diclofenac solution, and 11 for diclofenac gel formulation. No difference was found between the efficacy of oral and topical NSAIDs, although local adverse effects, mostly mild skin reactions, were seen more often with topical than with oral NSAIDs. Gastrointestinal adverse effects were similar in patients on topical NSAIDs compared to placebo, and less than in patients on oral NSAIDs.<sup>53</sup> Lin and colleagues also reported short-term efficacy (after 1–2 weeks) in patients with hand OA receiving topical NSAIDs when compared to patients given placebo, with an effect size of 0.77 (95% CI 0.32–1.22).<sup>55</sup>

In summary, topical NSAIDs are effective in alleviating pain and are not associated with serious adverse effects. Topical NSAIDs are preferred as an analgesic over oral NSAIDs.<sup>26–28</sup>

*Topical capsaicin*

Capsaicin is the active compound that makes chilli peppers taste ‘hot’. It provides pain alleviation via counter irritation—by causing excitation of sensoneurons and enhancing sensitivity (perceived as burning or itching), which leads to reversible nerve degeneration with reduced sensitivity.<sup>56</sup> A positive effect of topical capsaicin was reported in a small placebo-controlled study of hand OA.<sup>57</sup> In addition, the results from a randomized placebo-controlled trial of 59 patients with hand OA, indicate that topical capsaicin (0.025%) is superior to placebo after 3 weeks and 9 weeks of treatment.<sup>58</sup> A systematic review of studies in patients suffering from pain owing to OA in several joint sites, and to rheumatoid arthritis, indicate a mean treatment response (~50% pain reduction) rate of 38% after 4 weeks in the capsaicin group versus a mean placebo response rate of 25%.<sup>59</sup>

Application of capsaicin can, however, lead to local adverse effects and nerve degeneration might not be totally reversible.<sup>56</sup> In summary, topical capsaicin is recommended,<sup>26–28</sup> although evidence of efficacy is limited. Notably, the NNT is 8.1 (95% CI 4.6–5.9)—almost twice that for topical NSAIDs, which is 4.6 (95% CI 3.8–5.9).<sup>60</sup>

*NSAIDs/COX-2 selective inhibitors*

Oral NSAIDs or cyclo-oxygenase (COX)-2 selective inhibitors, in the lowest effective dose for the shortest

**Table 4** | Overview of placebo-controlled randomized trials in hand OA investigating anti-inflammatory drugs

Drug	Subset of hand OA	n	Study duration (weeks)	Primary outcome	Treatment effect	Reference
<b>Intra-articular corticosteroids</b>						
Triamcinolone	TB	40	12	Pain	No effect	Meenagh <i>et al.</i> <sup>71</sup>
Betamethasone	TB	60*	4	Pain	No effect	Heyworth <i>et al.</i> <sup>72</sup>
Triamcinolone	TB	200*	26	Pain	Preliminary: no effect	Mandl <i>et al.</i> <sup>75</sup>
<b>Systemic corticosteroids</b>						
Prednisolone 3 mg daily + dipyridole	ACR <sup>‡</sup>	83	6	Pain	10.2 (95% CI 1.6–18.7) <sup>§</sup>	Kvien <i>et al.</i> <sup>76</sup>
Prednisolone 5 mg daily	ACR <sup>‡</sup>	70	4	Pain	No effect	Wenham <i>et al.</i> <sup>78</sup>
<b>Biologic agents</b>						
Intra-articular infliximab monthly	Erosive	10	12	Pain	Pain reduced in treated, not in control joints	Fioravanti <i>et al.</i> <sup>80</sup>
Subcutaneous adalimumab 40 mg every 2 weeks	Erosive	60	52	Radiological progression	No effect	Verbruggen <i>et al.</i> <sup>81</sup>
Subcutaneous adalimumab 40 mg at 0 and 2 weeks	ACR <sup>‡</sup>	85	6	Pain	No effect	Chevalier <i>et al.</i> <sup>82</sup>

\*Including patients randomized to a third group, being intra-articular hyaluronic acid. †Hand OA following the classification criteria of the American College of Rheumatology. ‡AUSCAN pain (scale 0–100), mean difference (95% CI) between groups. Abbreviations: ACR, American College of Rheumatology; TB, thumb base.

duration, are recommended after failure on paracetamol or topical analgesics.<sup>26–28</sup> These recommendations are based on three placebo-controlled trials of patients with hand OA,<sup>61–63</sup> in which the researchers reported efficacy from 2–4 weeks. A meta-analysis of two trials<sup>61,62</sup> is suggestive of an effect size of 0.40 for pain relief (95% CI 0.20–0.60) and an NNT of 3 (95% CI 2–6). A major concern regarding the use of oral NSAIDs and COX-2 selective inhibitors is their gastrointestinal and cardiovascular toxicity profile, which is particularly relevant as patients with hand OA are often elderly with comorbidities.

#### Tramadol

No studies in hand OA with tramadol have been performed and its use is conditionally endorsed by one recommendation.<sup>27</sup> However, opioids (including tramadol) can cause adverse effects including nausea, vomiting, dizziness and constipation, leading to safety concerns for its use, particularly in the elderly.<sup>64,65</sup>

### Anti-inflammatory drugs

#### Intra-articular corticosteroids

Intra-articular corticosteroid injections are frequently given in clinical practice, particularly for patients with OA in the thumb base joint, to alleviate pain (Table 4).<sup>66</sup> Evidence from high-quality trials is limited, and the procedure is potentially harmful. Therefore, the technical expert panel involved in the 2012 ACR recommendations “conditionally recommends not using intraarticular corticosteroids.”<sup>27</sup> Eight studies have been performed in patients with various stages of thumb base OA. However, six of these studies were open, and five involved 40 (or fewer) participants.<sup>67–74</sup> In half of the studies, injections were guided by radiography<sup>67,70,71</sup> or ultrasonography.<sup>73</sup> The corticosteroids given to patients in these studies were

methylprednisolone,<sup>68,74</sup> triamcinolone<sup>69–71,73</sup> or sodium betamethasone sodium phosphate–betamethasone acetate.<sup>72</sup> Sometimes, injections were combined with rest and splinting. The investigators of the open studies reported alleviation of pain in 43–95% of patients after 4–6 weeks, although the effect was often unsustainable (wearing off at 3 months in a considerable portion of patients). Whether or not patients with less radiographic damage respond better to therapy is controversial.<sup>68,70,73</sup>

Remarkably, the efficacy of corticosteroid injections over placebo has not been reported to be beneficial in randomized controlled trials of patients with hand OA.<sup>71,72</sup> Meenagh and colleagues did not recruit the number of patients required to satisfy the power calculation; 40 patients were equally distributed to receive either 5 mg intra-articular triamcinolone hexacetonide, or intra-articular saline. Pain did not decrease significantly in either group and there were no differences between the groups, although patient global assessment improved after 4–12 weeks in both groups.<sup>71</sup> Heyworth and colleagues compared 22 patients receiving injections of 1 ml sodium betamethasone sodium phosphate–betamethasone acetate with 18 patients receiving saline injections, and with 20 patients receiving intra-articular hyaluronic acid. All patients also received splints for 2 weeks. In both the corticosteroid group and the placebo group, pain and disability decreased after 2 weeks and 4 weeks, but no difference was seen between these groups.<sup>72</sup> Adverse effects, including pain, bruising, mild skin atrophy and hypopigmentation at the injection site, have been reported.

In summary, insufficient data exist to conclude on the efficacy of intra-articular corticosteroids for patients with thumb base OA. The preliminary data from a placebo-controlled trial comparing intra-articular triamcinolone

with saline or hylan G-F 20 show no efficacy of interventions over placebo,<sup>75</sup> although the final results are not yet available.

#### Systemic corticosteroids

The efficacy of systemic low-dose prednisolone has been investigated in three studies of patients with hand OA, with equivocal results. Kvien and colleagues investigated administration of 3 mg prednisolone in combination with dipyridole (increasing dosage of dipyridole to 400 mg) per day for 6 weeks compared to placebo in a double-blinded randomized trial of 83 patients with hand OA (with at least one swollen and at least one tender joint and a score of  $\geq 30$  mm on the AUSCAN [The AUStralian CANadian Osteoarthritis Hand Index] pain scale).<sup>76</sup> Dipyridole has been shown to selectively amplify prednisolone's anti-inflammatory and immunomodulatory effects. Pain and function improved significantly in the intervention group compared to the placebo group. The mean difference between the groups in the intention-to-treat population was 10.2 (95% CI 1.6–18.7) for the VAS pain scale.

Keen and colleagues treated 36 patients with 120 mg methylprednisolone intramuscularly in an open study.<sup>77</sup> After 4 weeks, pain and function improved and 69% of the patients met the OARSI responder criteria. To study the underlying mechanisms, ultrasonography was performed. No effect of methylprednisolone on synovial hypertrophy and power Doppler signal was seen after 4 weeks and, moreover, ultrasonographic inflammatory features did not predict response.

Wenham and co-workers compared 5 mg orally administered prednisolone per day with placebo during 4 weeks in a randomized double-blind trial of 70 patients with hand OA (with a AUSCAN pain scale [VAS] score  $\geq 40$  mm).<sup>78</sup> The researchers observed no difference in pain or function between the groups, and equal numbers of patients met the OARSI responder criteria in both groups. 0.2 Tesla MRI, used to study underlying working mechanisms of the drug, showed that 75% of patients had at least one hand joint with definite synovitis or effusion. These symptoms do not, however, predict OARSI response and, after 4 weeks of treatment with prednisolone, inflammatory features had changed minimally.

In summary, the efficacy of systemic corticosteroids as analgesics for patients with hand OA is unclear. Moreover, the studies by Keen *et al.* and Wenham *et al.* have taught us that inflammatory features, as a target for treatment, need further investigation.

#### Biologic agents

Three studies on the efficacy of TNF blockers for patients with hand OA have been published to date. The results from a small open label study of 12 patients with hand OA who were treated with adalimumab are suggestive of clinical efficacy.<sup>79</sup> The data from another small controlled study of 10 patients with erosive OA, where affected DIP and proximal interphalangeal joints were injected with infliximab or saline in the same patient, also indicate alleviation of pain after 12 months by TNF blockade.<sup>80</sup>

The efficacy of 40 mg adalimumab prescribed every 2 weeks has been compared to placebo in 60 patients for erosive progression. No difference in erosive progression between the groups was seen after 12 months, although notably, posthoc analysis revealed that, in joints with palpable soft tissue swelling (which was associated with erosive progression), adalimumab is associated with less erosive progression than placebo (odds ratio of 4.57; 95% CI 1.46–14.3;  $P = 0.009$ )<sup>81</sup>—findings that potentially indicate DMOAD activity.

The role of TNF blockers needs to be further elucidated. Trials have commenced and the results are currently pending. Preliminary data from a trial of 85 patients with hand OA who received 40 mg subcutaneous adalimumab injections at baseline and 2 weeks, or placebo, showed no effect on symptoms after 6 weeks, although in the adalimumab group, the number of swollen joints decreased compared to placebo (mean difference of  $-1.9$ ; 95% CI  $-3.2$  to  $0.6$ ;  $P = 0.006$ ).<sup>82</sup> The results from a 1-year trial (EudraCT 2007-003,994-18) to compare etanercept to placebo are also pending.

Another interesting biologic agent is anakinra, an interleukin-1 receptor antagonist. A case series of subcutaneous administration of anakinra in three patients is suggestive of clinical improvement.<sup>83</sup> A trial is currently ongoing to compare intra-articular anakinra versus placebo for 24 weeks in patients with hand OA (EudraCT 2012-004,089-16).

#### Symptomatic slow acting drugs for OA

##### *Intra-articular hyaluronic acid*

Intra-articular hyaluronan is used to treat thumb base OA, but its efficacy in patients with hand OA has been less well studied than for patients with knee OA (Table 5). Eight out of nine studies that were set up to investigate the efficacy of hyaluronic acid in thumb base OA have been systematically summarized.<sup>84</sup> In seven of the eight studies, injections were given blindly; in one study, ultrasonography was used for guidance;<sup>85</sup> and in another, radiography was used for guidance.<sup>86</sup> The number of injections varied from 1–5 weekly and the majority of the studies lasted 6 months. Hyaluronan products with different molecular weights have been studied, but no direct comparison has been performed. Five open studies revealed a significant decrease in pain, four an improvement in disability<sup>85–88</sup> and one a benefit in grip strength.<sup>85</sup>

Four randomized controlled trials have also been published. Only one study, by Heyworth and colleagues, compared hyaluronate (2 injections with hylan G-F 20) with placebo (saline injections), although the authors found no difference between the groups.<sup>72</sup> Hyaluronate has also been compared with corticosteroid injections in four studies.<sup>72,89–91</sup> In two studies, corticosteroids were reported to be superior over hyaluronate in pain alleviation,<sup>90,91</sup> although no study reported superiority of hyaluronate.

Adverse effects, including pain, discomfort and swelling after the injections, can occur. Researchers have also reported that blind injections might result in more pain than fluoroscopic guided injections.<sup>92</sup> In summary,

**Table 5** | Placebo-controlled randomized trials in hand OA investigating symptomatic slow-acting drugs in OA

Drug	Subset of hand OA	n	Study duration	Primary outcome	Treatment effect	Reference
<i>Intra-articular hyaluronic acid</i>						
Hylan G F 20	TB	60*	4 weeks	Pain	No effect	Heyworth <i>et al.</i> <sup>72</sup>
	TB	200*	26 weeks	Pain	No effect	Mandl <i>et al.</i> <sup>75</sup>
<i>Hydroxychloroquine</i>						
200 mg bid	Nodal	88 <sup>†</sup>	24 weeks	Pain	No effect	McKendry <i>et al.</i> <sup>51</sup>
<b>CS</b>						
CS 1200 mg/day Intramuscular CpolyS 50 mg twice weekly for 8 weeks, every 4 months	Sympt. Rad. <sup>§</sup>	165	3 years	Radiological progression	No effect incident OA, suggested effect progression	Verbruggen <i>et al.</i> <sup>100</sup>
CS 800 mg/day	Erosive	24	2 years	Erosive progression	P=0.001	Rovetta <i>et al.</i> <sup>101,102</sup>
CS 800 mg/day	ACR <sup>  </sup>	162	6 months	Pain	-8.7 <sup>¶</sup> P=value 0.016	Gabay <i>et al.</i> <sup>103</sup>

There have been no clinical trials for the treatment of hand OA with methotrexate. \*Including patients randomized to third arm, being intra-articular corticosteroids. †Including patients randomized to third group, being acetaminophen. ‡Symptomatic OA of the finger joints with osteophytes and/or joint space narrowing with or without subchondral sclerosis on radiographs. §Hand OA following the classification criteria of the ACR. ¶VAS (Visual Analog Scale) pain (scale 0–100), mean difference between groups. Abbreviations: ACR, American College of Rheumatology; bid, twice daily; CS, chondroitin sulphate; OA, osteoarthritis; TB, thumb base.

insufficient data exist to conclude on the efficacy of hyaluronate for thumb base OA, however, data that are available do not support its efficacy. In accordance, the 2012 ACR panel “conditionally recommends not using intra-articular hyaluronates”<sup>27</sup>

#### Hydroxychloroquine

For many years rheumatologists have treated patients with hand OA with off-label hydroxychloroquine, especially when inflammatory signs are present in analogy to the treatment of inflammatory rheumatic disorders. However, evidence on the efficacy of hydroxychloroquine in these patients is scarce.

Since 1993, four small studies (three of which included <10 patients) with an open label design have investigated hydroxychloroquine in patients with hand OA.<sup>93–96</sup> The results from three of the four studies indicate that hydroxychloroquine could be useful in erosive or inflammatory hand OA.<sup>93,95,96</sup> In the mid-nineties, a randomized controlled trial compared hydroxychloroquine to NSAIDs and traditional analgesics over 12 months in 15 patients with hand OA. The clinical symptoms of patients on hydroxychloroquine, assessed by the Ritchie index, improved more than the clinical symptoms of patients on control medication.<sup>97</sup>

Another study, only published as an abstract, included 88 patients with nodal hand OA that were treated with either hydroxychloroquine (200 mg twice daily), paracetamol, or placebo for 24 weeks. No difference was seen between the groups in reducing the number of tender joints or pain as scored on VAS.<sup>51</sup>

At the moment, insufficient evidence exists to conclude on the efficacy of hydroxychloroquine in hand OA. In the near future, more data will become available out of placebo-controlled trials in the Netherlands (EudraCT 2010-019,684-11) and the United Kingdom.<sup>98</sup>

#### Methotrexate

Methotrexate is a well-known DMARD for use in rheumatoid arthritis and other inflammatory rheumatic disorders. Given the occurrence of synovitis in hand OA, methotrexate is also considered for use in patients with hand OA. However, little evidence is currently available to support its use for hand OA. In an open study of 21 patients with erosive OA, with at least one swollen proximal interphalangeal joint, 10 mg methotrexate was administered weekly. After 2 months, symptoms decreased significantly.<sup>99</sup>

In summary, at present, insufficient evidence exists to conclude on the use of methotrexate for patients with hand OA. In accordance, the technical expert panel for the ACR conditionally recommends not using methotrexate for hand OA management. In the future, more evidence will become available as a 12-month placebo-controlled trial is currently ongoing (EudraCT 2007-005,437-11).

#### Chondroitin sulphate

Chondroitin sulphate has been investigated in several randomized controlled trials. Verbruggen and co-workers published one report on two 3-year trials—one investigating oral chondroitin sulphate against placebo, the other investigating intramuscular chondroitin polysulphate against placebo.<sup>100</sup> Chondroitin sulphate does not prevent OA from occurring in previously normal joints, but a combined analysis indicates that patients on chondroitin sulphate show less radiographic progression during follow-up (although symptom relief was not considered). The results from a small ( $n = 24$ ) controlled study of low-quality, indicate that chondroitin sulphate decreases symptoms and erosive progression over 2 years.<sup>101,102</sup>

The efficacy of chondroitin 4-sulphate and chondroitin 6-sulphate on symptom alleviation has also been investigated in a 6 month placebo-controlled trial of 162 patients

with symptomatic radiographic hand OA fulfilling the ACR criteria.<sup>103</sup> The mean difference in patient assessment of global hand pain was 8.7 mm on a 0–100 mm VAS between the groups ( $P=0.016$ ). Hand function score and grip strength also improved significantly in the intervention group compared with the placebo group.

In summary, the data indicate that chondroitin sulphate could be effective in symptom alleviation and in reducing erosive progression, although more high-quality studies are needed to fully conclude the efficacy.

*Antiosteoporotic medication*

Antiosteoporotic drugs have been investigated in patients with OA, particularly in patients with knee OA. Studies in patients with knee OA to investigate risedronate gave ambiguous results, but subsequent randomized controlled studies with zoledronate and strontium ranelate indicated that antiosteoporotic drugs could be of value in OA.<sup>104–107</sup> The preliminary results from a 3-year randomized placebo-controlled trial in knee OA to compare the efficacy of two doses of strontium ranelate with placebo<sup>107</sup> show some effect of strontium ranelate. Hand symptom questionnaires and hand radiographs on patients with hand OA also indicate efficacy of strontium ranelate, although radiographic progression of hand OA in this trial was rather low.<sup>108,109</sup> Zoledronate, a bisphosphonate, is currently under investigation in a placebo-controlled trial in patients with hand OA (EudraCT 2010-019,119-24).

**Conclusions**

The unmet needs for patients with hand OA are high. Misconceptions—that nothing can be done, OA will inevitably progress and that the symptoms cannot be

alleviated—are prevalent. Nonpharmacological and pharmacological management strategies are available to alleviate symptoms for hand OA. The number of high-quality trials is limited, although evidence for some treatment modalities exists. For example, education and splints for patients with thumb base OA, and topical and oral NSAIDs, can alleviate symptoms. For pharmacological management, more high-quality trials are needed. The role of anti-inflammatory medication, such as corticosteroids and biologic agents, is controversial, and the same holds true for the efficacy of symptomatic slow acting drugs for OA. DMOADs for hand OA are currently not available. Proof-of-concept trials, even with negative results for efficacy, are urgently needed as they can enhance our insight into the underlying pathogenic mechanisms of hand OA by assessing process measurements, such as synovitis, effusion and bone marrow lesions (using MRI or ultrasonography), or degradation or synthesis products of joint tissue. Importantly, several ongoing pharmacological trials will contribute to our knowledge for evidence-based management of hand OA in the near future.

**Review criteria**

The PubMed database was searched for original articles in the English language focusing on management of hand osteoarthritis. Search terms used were “hand”, “osteoarthritis”, “management”, and all separate treatment modalities. The reference lists of identified articles were searched for additional papers. In cases where very little evidence on a particular subject was available, abstracts and articles not in English were included.

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