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Therapeutic trials in hand osteoarthritis: a critical review

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Summary

Objective: To perform a critical review of the published therapeutic trials conducted in hand osteoarthritis (OA).

Method: A Medline research was performed to select the clinical trials in hand OA published since 1994.

Results: Twenty-five published studies were identified by this research, of which 10 were reported in abstract or short report forms. The trials were classified according to the study drug, and their methods and results examined. The critical analysis focuses on the design, the inclusion and efficacy criteria and the methodological limitations in all of these studies.

Conclusion: Methodological restrictions of the studies are elucidated, such as the need for a consensus on diagnosis of hand OA, the need of valid, reliable and sensitive to change clinical assessment tools and validated radiological assessment methods in order to conduct trials in the future. © 2000 OsteoArthritis Research Society International

Key words: Hand osteoarthritis, Therapeutic trials, Methodology, Critical review.

Introduction

The hand is commonly affected by osteoarthritis (OA). Several studies have been conducted on epidemiology, genetics, clinical and radiological presentations of hand OA. Conversely, we found only 25 therapeutic studies in hand OA. In this review, we report the principal characteristics of the 25 studies published, and perform a critical analysis of the methodologies used.

A previous review of the clinical trials conducted in hand OA was published in 1995.[1] The present review analyses trials published since 1994 and those not reviewed in the above-cited paper.

Summary and results of the trials

ORAL NON-STEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDS) (TABLE I)

Two studies of oral NSAIDs have been published. Seiler[2] included 41 patients with proximal interphalangeal joint (PIP) and distal interphalangeal joint (DIP) OA in a prospective, randomized, double-blind study of a 4-week treatment period and 4-weeks of follow-up. Patients were to have at least three painful joints and at least one acute inflamed Heberden node. Diagnosis of OA was ascertained by X-ray examination. The results showed that meclofenamate at 300 mg daily was more effective than placebo in improving pain measured on a scale ranging from 0=no pain to 3=severe pain, the number of painful joints and the number of inflamed nodes. Grip strength did not improve.

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In a prospective, randomized, double-blind trial conducted by Dreiser *et al.*,[3] 60 patients with X-ray documented OA of PIP, DIP and the first carpometacarpal (CMC1) joints were included. The sample size was calculated prior to study initiation. The study consisted of a 14-day treatment period and a 14-day follow-up. Patients needed to fulfill the following inclusion criteria: recent painful joint(s) of less than 15 days duration and pain on visual analog scale (VAS) of 40 mm or higher. The results showed that 1600 mg ibuprofen daily were more effective than placebo in improving spontaneous pain, pain on mobilization and on pressure, VAS score, and Dreiser's functional index for hand OA (FIHOA).

In these two studies, diagnosis criteria and disease activity were defined, but no primary criterion was specified. The pre-study calculation of the required sample size was performed only in Dreiser's study.[3]

OTHER TOPICAL NSAIDS (TABLE I)

Seven studies of topical NSAIDs have been published, of which four were in abstract form.

A prospective, randomized, comparative, double-blind trial of a 3-week treatment period and 3-weeks of follow-up, reported by Talke,[4] was performed in 60 patients with PIP and DIP OA. All of the patients had 'activated' Heberden's and Bouchard's arthritis. The results showed that topical etofenamate was as effective as oral indomethacin 150 mg daily, in improving pain at rest, pain on movement and on pressure using a VAS ($P<0.05$; $P<0.001$; $P<0.01$ respectively), joint circumference ($P<0.001$), range of motion ($P<0.001$), and grip strength using a Mannerfeld's intrinsic meter ($P<0.05$).

In another study, Guillaume[5] compared 5% ibuprofen gel with the gel vehicle (placebo) in a prospective, randomized, double-blind trial of a 14-day treatment period and 14 days

Table I
Design characteristics of therapeutic trials of oral or topical nonsteroidal anti-inflammatory drugs (NSAIDs) and of other topical drugs in hand OA

Author(s) and references	Drug/control	Design	Patients	Inclusion criteria	Results
Oral NSAIDs					
Seiler[2]	Meclofenamate/ placebo	P DB R	41	PIP–DIP OA	Meclofenamate> placebo
Dreiser *et al.*[3]	1600 mg Ibuprofen/placebo	P DB R	60	PIP–DIP–CMC1 OA Flare <15 days VAS ≥40 mm	Ibuprofen>placebo
Topical NSAIDs					
Talke[4]	Etofenamate gel/1500 mg oral indomethacin	P DB R	60	PIP–DIP OA	Etofenamate=oral indomethacin
Guillaume[5]	Ibuprofen gel/ placebo	P DB R	64	PIP–DIP–CMC1 OA Flare <15 days	Ibuprofen>placebo
Augy[6]	Ketoprofen gel/ placebo	P DB R	60	PIP–DIP–CMC1 OA Flare <15 days	Ibuprofen>placebo
Bourgeois and Dreiser[7]	Niflumic acid gel/placebo	P DB R	202	PIP–DIP–CMC1 OA Flare <20 days VAS ≥40 mm	Niflumic acid>placebo
Gibeault and Wulwik[8]	Niflumic acid gel/dexamethasone	P R	60	CMC1 OA Flare <20 days VAS ≥40 mm	Niflumic acid=dexamethasone
Dougados and Nguyen[9]	Niflumic acid gel/placebo	P DB R	186	PIP–DIP OA	Niflumic acid=placebo
Thiesce and Dougados[10]	Diclofenac gel/ placebo	P DB R CO	20	DIP OA	Diclfenac=placebo
Other topical drugs					
Vuillemin[11]	Idrocilamide gel/placebo	P DB R	96	PIP–DIP–CMC1 OA	Idrocilamide>placebo
McCarthy and McCarty[12]	0.075% capsaicin gel/placebo	P DB R	14	Digital OA, without precision	0.075% capsaicin gel>placebo
Schnitzer *et al.*[13]	0.025% capsaicin gel/placebo	P DB R	59	Hand OA, without precision	0.025% capsaicin gel>placebo
Chouchane *et al.*[14]	Dexamethasone gel/vehicle/placebo	P DB R	90	PIP–DIP–CMC1 OA Recent flare	Dexamethasone> vehicle or placebo

P=prospective; DB=double-blind; R=randomized; CO=cross-over; PIP=proximal interphalangeal; DIP=distal interphalangeal; CMC1=first carpometacarpal; OA=osteoarthritis.

of follow-up. Sixty-four patients with OA of one to three finger joints were included. Except for pain at rest, ibuprofen gel was more effective ($P<0.01$) than the vehicle in improving spontaneous pain measured on a VAS, pain on mobilization and on pressure, Dreiser's functional index for hand OA, swelling, and global physician and patient assessment.

In a prospective, randomized, double-blind trial of a 14-day treatment period and 14-days of follow-up, Augy and Poiraud[6] enrolled 60 patients with X-ray documented OA in the PIP, DIP or CMC1 joints. Patient enrollment criteria included a flare of less than 2 weeks duration, involving one to three finger joints. The results showed that a 2.5% ketoprofen gel was more effective ($P<0.05$) than placebo on pain measured by VAS and Lickert scale, pain on pressure, pain on mobilization, joint swelling, and functional impairment measured on a verbal scale rating from 0=none to 3=severe.

Bourgeois and Dreiser[7] enrolled 202 patients with painful PIP, DIP or CMC1 OA in a prospective, randomized, double-blind trial of a 14-day treatment period with a 14-day follow-up. The results showed that a 2.5% niflumic acid gel was more effective ($P=0.02$) than the gel vehicle (placebo) in improving spontaneous pain measured by VAS, global physician and patient assessments, pain at rest and on pressure, and the FIHOA.

A prospective, randomized trial was performed by Gibeault and Wulwik.[8] Sixty patients with a flare of less than 20 days duration, pain on VAS of 40 mm or higher, and X-ray evidence of PIP, DIP or CMC1 OA were treated for 14 days with 14 days of follow-up. The results showed that a 2.5% niflumic acid gel was as effective as a 0.5% dexamethasone gel in improving spontaneous pain, pain on pressure and on mobilization, range of motion and global patient assessment.

Dougados and Nguyen[9] compared the efficacy of a niflumic acid gel with the gel vehicle (placebo) in a prospective, randomized, double-blind trial of 7-day treatment period with 7-day follow-up in 186 patients with painful Heberden's or Bouchard's nodes. The results showed that spontaneous pain, pain on mobilization and on pressure measured by the VAS improved in both groups but with no difference between the groups.

In a prospective, randomized, cross-over trial of seven-day treatment period with a seven-day follow-up duration performed by Thiesce and Dougados,[10] 20 patients with painful Heberden nodes were enrolled. The results showed that diclofenac gel was not superior to the gel vehicle (placebo) in improving pain, function (index not specified) or global assessment.

Table II
Design characteristics of therapeutic trials of symptomatic slow-acting drugs on OA, of hydroxychloroquine and of miscellaneous treatments in hand OA

Author(s) and references	Drug/control	Design	Patients	Inclusion criteria	Results
Symptomatic slow acting drugs in OA					
Pastinen *et al.*[15]	Periarticular GAG-PS/placebo	P DB R	29	PIP–DIP–CMC1 OA	GAG-PS>placebo
Jonsson *et al.*[16]	Intramuscular pentosan-ps/placebo	O	12	Digital OA, without precision	Pentosan-ps>placebo
Verbruggen *et al.*[17]	Oral chondroitine sulfate/placebo	P DB R	119	PIP–DIP–MCP OA	Chondroitin sulfate>placebo
Wang *et al.*[18]	Oral chondroitine sulfate/placebo	P DB	34	PIP–DIP OA	Chondroitin sulfate>placebo
Rovetta and Monteforte[19]	GAGs/placebo	P DB R	24	PIP–DIP–CMC1 erosive OA	GAGs>placebo
Verbruggen *et al.*[20]	Xylanpolysulfate per os/placebo	P DB R	50	Digital OA	Xylanpolysulfate> placebo
Hydroxychloroquine (HCQ)					
Robertson *et al.*[21]	HCQ	Retrospective	7	PIP–DIP–MCP–CMC1 OA	HCQ effective
Bryant *et al.*[22]	HCQ	Retrospective	8	PIP–DIP erosive OA	HCQ effective
Punzi *et al.*[23]	HCQ/NSAIDs or analgesics	P R	15	PIP–DIP erosive OA	HCQ effective
Miscellaneous treatments					
Flynn *et al.*[24]	Cobalamin+folate/ folate/placebo	P DB R CO	26	PIP–DIP–CMC1 OA	Cobalamin+folate> folate or placebo
Garfinkel *et al.*[25]	Yoga/usual treatment	P R	25	PIP–DIP OA	Yoga>usual treatment
Graber *et al.*[26]	Berthollet/ibuprofen gel	P R	116	Digital OA Dreiser≥5	Berthollet>ibuprofen gel

P=prospective; DB=double-blind; R=randomized; CO=cross-over; O=open; PIP=proximal interphalangeal; DIP=distal interphalangeal; CMC1=first carpometacarpal; MCP=metacarpophalangeal; OA=osteoarthritis.

In all of these seven studies, diagnosis criteria and disease activity were never well-defined. A primary criterion was specified only in the trial performed by Dougados and Nguyen.[9] There was no pre-study calculation of the sample size performed.

OTHER TOPICAL DRUGS (TABLE I)

Idrocilamide gel, an agent with muscle relaxant properties, was compared to the gel vehicle (placebo) in a prospective, randomized, double-blind trial of a 7-day treatment period with a 7-day follow-up performed by Vuillemin.[11] Ninety-six patients with a flare of PIP, DIP and CMC1 OA were enrolled. Idrocilamide gel was found to be more effective than placebo on pain assessed by a self-evaluated score, and on improvement in mobility.

Capsaicin was evaluated in two trials. The first, a prospective, randomized, double-blind trial was performed by McCarthy and McCarty[12] in 14 patients with painful PIP, DIP and CMC1 OA for 4 weeks with a 4-week follow-up. Diagnosis of OA was based on 'classical findings on examination' which include evidence of OA nodes. The 0.075% capsaicin gel was found to be more effective than the gel vehicle (placebo) in improving joint tenderness as measured by a standardized dolorimeter ($P<0.02$), and pain assessed by VAS ($P<0.02$). No differences were found in changes of grip strength, morning stiffness or joint swelling. In this study, a group of RA patients was also included. Results were given on 267 joints in 14 patients. The second trial was a prospective, randomized, double-blind study of 9-week treatment duration period with 9-weeks of follow-up, performed by Schnitzer *et al.*[13] Fifty-nine patients with painful hand OA were enrolled. Diagnosis of OA was based on physical, biological and X-ray examinations. The results showed that 0.025% capsaicin cream was superior to placebo in improving joint tenderness ($P=0.01$), pain on a VAS ($P=0.01$), joint swelling, function using a verbal scale ranging from 0 to 3, and grip strength.

Chouchane *et al.*[14] performed a prospective, randomized, double-blind trial of a 7-day treatment period with 7 days of follow-up in 90 patients with a flare of PIP, DIP or CMC1 OA. The results showed that dexamethasone gel was more effective than both the salicylate vehicle ($P<0.01$) and placebo ($P<0.05$) in improving pain on VAS (spontaneous pain, pain at night, pain on pressure and on mobilization), in improving function using a verbal scale ranging from 1 to 3 and patient global assessment.

In these four studies, neither the disease activity, nor the primary criterion were well-defined. There was no pre-study calculation of the sample size performed. Diagnosis criteria were defined only in the Schnitzer's study.[13]

SYMPTOMATIC SLOW-ACTING DRUGS IN OA (SY-SADOA) AND DISEASE MODIFYING DRUGS IN OA (DMOADS) (TABLE II)

Six studies including four abstracts or short reports of Sy-SADOA or DMOAD in hand OA were identified.

Twenty-nine patients with painful PIP, DIP and CMC1 OA were included in a prospective, randomized, double-blind trial performed by Pastinen *et al.*[15] Their OA was diagnosed by both clinical and radiological findings. Nine periarticular injections of glycosaminoglycan polysulfate (GAG-PS) given over 13 weeks were found to be more effective than placebo in improving morning stiffness

(P=0.01), grip and pinch strength as measured by a dynamometer (P<0.01), function using a verbal scale ranging from 0 to 3 (P<0.01), but not pain on VAS. The end-point assessment took place 26 weeks after the injections.

Four weekly intramuscular injections of pentosan polysulfate (3 mg/kg) were assessed in an open study by Jonsson *et al.*[16] in 12 patients with 'severe symptomatic hand OA'. Pentosan polysulfate was found to be effective in relieving pain, improving grip strength, improving scores of the 'ISHOA hand disability scale' (statistics not provided), but not on OA activity assessed by scintiscan performed 10 days after drug administration. The criteria used for the diagnosis of OA were not specified.

Oral chondroitin sulfate was more effective than placebo in two studies. The first was a prospective, randomized, double-blind study performed by Verbruggen *et al.*[17] on 119 patients with PIP, DIP and CMC1 OA diagnosed using X-ray features. The structural effect of chondroitin sulfate at 1200 mg daily compared with placebo was assessed by a radiological scoring during a 3-year follow-up. The results showed that a comparable number of patients in both treated and placebo groups developed OA in non-previously involved joints. However, a significantly lower incidence with regard to the number of patients showing new erosive OA of the finger joints was observed in the treated group.

The second trial performed by Wang *et al.*[18] in 34 patients with painful PIP and DIP OA was prospective, randomized, and double-blind. Oral chondroitin sulfate at 1200 mg daily was compared with placebo. The results showed that chondroitin sulfate was more effective than placebo on pain assessed by VAS (P<0.05), grip strength (P<0.05), but not on circumference of joints. Twenty per cent of the previously unaffected joints in the treated group developed OA, vs 15% in the placebo group during a two-year follow-up with a radiological assessment. There was no significant difference between the groups in the development of OA in joints previously unaffected.

A prospective, randomized, double-blind trial performed by Rovetta and Monteforte[19] compared the efficacy of galactosaminoglycuroglycan sulfate (GAGs) to placebo in 24 patients with 'frank' painful erosive PIP, DIP or CMC1 OA. Diagnosis of erosive OA was based on X-ray findings. The results showed that oral GAG was more effective than placebo on measures of pain, and joint erosions, but not on joint scintiscans performed 2 years apart in parallel to the clinical and radiological assessments. It must be noticed that there were fewer joint erosions in the treated group compared to the placebo group at baseline.

Verbruggen *et al.*[20] performed a prospective, randomized, double-blind study in 50 patients with 'inflammatory' hand OA. A polysaccharide, xylanpolysulfate (XPS), given orally at 20 mg/kg twice a week, was more effective than placebo in relieving pain, morning stiffness, pain at night, function assessed by the 'Ghent' functional index during a 24-week follow-up. Grip strength and concomitant use of analgesics did not show any improvement.

Diagnosis criteria were defined only in the trials performed by Verbruggen *et al.*[17] and Rovetta and Monteforte.[19] Disease activity was specified only in Rovetta's study.[19] The primary criterion was specified in Jonsson *et al.*'s[16] and Verbruggen's[17] studies. The pre-study calculation of the required sample size was never performed.

HYDROXYCHLOROQUINE (TABLE II)

Three studies of hydroxychloroquine (HCQ) in erosive hand OA, including one abstract and one letter, are reviewed.

HCQ at a dose of 200–400 mg daily was effective in seven patients with evidence of erosive PIP, DIP or CMC1 OA on X-ray in an open retrospective study reported by Robertson *et al.*[21] Two patients had positive antinuclear antibodies (ANA) at baseline.

Bryant *et al.*[22] reported the results of an open, retrospective study. All patients had 'inflammatory arthritis' of PIP and DIP joints, with radiographic changes consistent with OA. The results showed that, among eight patients with erosive OA, HCQ at a 400 mg daily dosage resulted in an improvement of synovitis, morning stiffness and global assessment in six patients. Three of them had positive ANA at baseline.

Punzi *et al.*[23] performed a prospective, randomized, double-blind, and placebo-controlled trial, in 15 patients with 'inflammatory arthritis' of PIP and DIP joints, with radiological changes consistent with OA. Efficacy was assessed by clinical (Ritchie Index) and biological (sedimentation rate, interleukin-2 receptor level) tests with a 12-month follow-up. The results showed that HCQ was more effective than placebo on clinical and biological assessments.

Diagnosis criteria were defined in each of these three studies. Disease activity was not well-defined in Punzi's[23] trial. The primary criterion was never specified, nor the pre-study calculation of the sample size performed.

MISCELLANEOUS TREATMENTS (TABLE II)

In a prospective, randomized, double blind study performed by Flynn *et al.*[24] in 26 patients with PIP, DIP and CMC1 OA (ACR criteria, X-ray changes), 20 μg oral cobalamin combined with 6400 μg of folate was compared with folate alone or placebo. Severity of OA was designated clinically, as 'active' or 'inactive'. The results showed that the combination of vitamin B12 and folate was more effective than folate alone or placebo, in improving pain, morning stiffness, activity, psychological parameters, grip strength, and number of tender and painful PIP or DIP joints.

A yoga program was evaluated in 25 patients with painful PIP, DIP or CMC1 OA (ACR criteria) in a prospective randomized designed trial performed by Garfinkel *et al.*[25] The results showed that the yoga program combined with standard treatment was more effective than the usual treatment alone in improving pain, grip strength, motion, joint circumference, tenderness and hand function assessed by the Stanford hand assessment questionnaire.

In a prospective randomized trial performed at the Aix-les-Bains spa, a local treatment called *berthollet* was compared to ibuprofen gel. The trial was performed by Graber *et al.*[26] in 116 patients with painful PIP, DIP and CMC1 OA (ACR criteria) and a Dreiser's functional index score ≥5. The results showed that *berthollet* treatment was more effective than ibuprofen gel in improving pain, grip strength, joint circumference and global assessment at a 6-month follow-up.

Diagnosis criteria were defined in each of these three studies. Disease activity was not well-defined in Garfinkel's trial.[25] A primary criterion was specified only by Garfinkel.[25] No pre-study calculation of the sample size was performed.

Table III
Efficacy criteria and methodological limitations in therapeutic trials of oral or topical nonsteroidal antiinflammatory drugs (NSAIDs) and of other topical drugs in hand OA

Author(s)[ref]	Efficacy criteria	Methodological limitations
Oral NSAIDs		
Seiler[2]	Painful joint count; pain score (from 0 to 3); inflammatory Heberden nodes count; grip strength	D+. A+. P−. S−.
Dreiser *et al.*[3]	Patient and physician global assessment; VAS pain; pain on mobilization, on palpation; functional index; swelling; acetaminophen use	D+. A+. S+. No single main criterion
Topical NSAIDs		
Talke[4]	Patient and physician global assessment; pain at rest; on mobilization (scored from 0 to 10); circumference; range of motion, grip strength	D−. A−. P−. S−.
Guillaume[5]	VAS pain; pain on mobilization; on palpation; functional impairment; range of motion; pain at night; swelling; patient and physician global assessment	D−. P−. S−.
Augy and Poiraud[6]	VAS pain; range of motion; swelling; pain at night; compliance	D−. A−. P−. S−.
Bourgeois and Dreiser[7]	Patient and physician global assessment; VAS pain; pain at rest; on palpation; on mobilization; range of motion; functional index; acetaminophen use	D−. A−. S−. No single main criterion
Gibeault and Wulwik[8]	Patient and physician global assessment; VAS pain; pain on palpation; on mobilization; range of motion	D−. A−. S−.
Dougados and Nguyen[9]	VAS for spontaneous pain; pain on mobilization; pain on pressure	D−. A−. P+.
Thiesce and Dougados[10]	Global assessment; VAS pain; functional score	D−. A−. P−.
Other topical drugs		
Vuillemin[11]	Daily self-evaluation; pain; range of motion; global assessment	D−. A−. S−.
McCarthy and McCarty[12]	VAS pain; functional index (HAQ); morning stiffness; grip strength; swelling; pain on palpation	D−. A−. P−. S−. Results on 267 joints in 14 patients
Schnitzer *et al.*[13]	Joint tenderness; VAS pain; grip strength; swelling; functional index	D+. A−. P−. S−.
Chouchane *et al.*[14]	VAS pain; pain at night; on mobilization; on pressure; function score; swelling; global assessment	D−. A−. P−. S−.

VAS=visual analog scale; HAQ=health assessment questionnaire. D=diagnostic criteria; A=disease activity criteria; P=primary criterion; S=pre-study calculation of the required sample size; +=defined or specified; −=not specified or not well defined.

Critical analysis

Among the 25 studies, 10 were reported in abstract or short report format, providing much less information than full papers. Seventeen studies were prospective, randomized, double-blind trials; two used a cross-over design; two were retrospective; and three were open studies. Eighteen were placebo-controlled trials, three compared a topical NSAID with another drug, and four were controlled. For this review, we found no study assessing the efficacy of intra-articular corticosteroid injections, or the use of splints in hand OA, in particular for the thumb base.

CRITERIA FOR THE DIAGNOSIS OF HAND OA (TABLES III AND IV)

The criteria used for the diagnosis of OA were not specified in 12 of the reviewed trials. The clinical and/or radiological criteria for the diagnosis of OA were usually poorly defined or not specified. The ACR criteria for the classification and reporting of hand OA were used in only two studies. Patients with PIP, DIP and/or CMC1 OA were included in 10 trials. Nine trials included patients with PIP–DIP OA only, and one included patients presenting with CMC1 OA alone. The exact location of hand OA was not specified in five studies. As new trials are designed, the following questions regarding diagnosis of hand OA need to be addressed: should hand OA be defined similarly in trials assessing the symptomatic and structural effects of drugs? Should interphalangeal and CMC1 joints be combined in trials assessing symptomatic effects, or should they be studied separately?

INCLUSION CRITERIA (TABLES III AND IV)

Inclusion criteria of the reviewed trials typically state that 'painful', or 'inflammatory', or a 'flare' of hand OA was required for selection. However, in 18 out of the 25 studies, inclusion criteria were not specified or well defined. Only two studies required a specified level of measures of symptoms such as a minimal VAS pain score or Dreiser's functional index value (one trial). With the exception of two studies, the symptom activity was not well defined (inflammatory nodes, swelling, pain) and flare onset was not well described. Similar comments can be made concerning the severity of OA which was usually not clearly specified or well defined. As new trials are designed, the following questions need to be addressed: How should the symptom activity and/or severity criteria be measured in hand OA trials? What minimal VAS pain level should be used for selection criteria? What should the minimal number of painful joints be at entry? What should the minimal value of the functional index score be?

EFFICACY ASSESSMENT CRITERIA (TABLES III AND IV)

More than 23 different efficacy criteria were used in the 25 trials. There was a range of one to eight criteria per study. The VAS for pain assessment was used in 16 studies. Other criteria often used were pain on mobilization, pain on pressure, pain at night, and morning stiffness. Grip strength measurements were also frequently used; however, the procedures were neither standardized nor identified. The functional indices also varied and were poorly

Table IV
Efficacy criteria and methological limitations in therapeutic trials of symptomatic slow-acting drugs on OA, of hydroxychloroquine and of miscellaneous treatments in hand OA

Author(s)[ref]	Efficacy criteria	Methodological limitations
Symptomatic slow acting drugs in OA		
Pastinen *et al.*[15]	Global assessment; morning stiffness; grip strength; pinch strength; VAS pain during the tests	D−. A−. P−. S−.
Jonsson *et al.*[16]	^{99m}Tc-diphosphonate uptake VAS pain; grip strength; hand disability scale	D−. A−. P+. S−.
Verbruggen *et al.*[17]	X-ray criterion: personal scoring; count of newly affected joints	D+. A−. P+. S−.
Wang[18]	X-ray changes after a 2-year follow-up; VAS pain; grip strength; joint circumference	D−. A−. P−. S−.
Rovetta and Monteforte[19]	Personal score=Ritchie index; number of central erosion; number of joints with a positive scintiscan; number of joint ankylosis	D+. A+. P−. S−.
Verbruggen *et al.*[20]	VAS pain; morning stiffness; pain at night; function score; 'Ghent' functional index; grip strength; pain on palpation; analgesics use	D−. A−. P−. S−.
Hydroxychloroquine		
Robertson *et al.*[21]	Global improvement; swelling	D+. A+. P−. S−.
Bryant *et al.*[22]	Morning stiffness; synovitis; erosions; patient global assessment	D+. A+. P−. S−.
Punzi *et al.*[23]	Ritchie index; erythrocyte sedimentation rate; soluble interleukin-2-receptor concentration	D+. A−. P−. S−.
Miscellaneous treatments		
Flynn *et al.*[24]	Grip strength; painful joint count; morning stiffness; compliance; patient and physician global assessment	D+. A+. P−. S−.
Garfinkel *et al.*[25]	Range of motion; grip strength; joint tenderness; circumference; VAS pain; function index (Stanford questionnaire)	D+. A−. P+. S−.
Graber *et al.*[26]	Dreiser's index; VAS pain; grip strength; swelling; physician global assessment	D+. A+. P−.

VAS=visual analog scale; D=diagnostic criteria; A=disease activity criteria; P=primary criterion; S=pre-study calculation of the required sample size; +=defined or specified; −=not specified or not well defined.

defined. Dreiser's functional index (FIHOA) was used in three studies. The following indices were used once: 'Ghent', health assessment questionnaire (HAQ), ISHOA(?), and the Stanford hand assessment questionnaire. Most studies failed to specify the primary evaluation criterion. This raises the question: what primary criterion should be used in trials in hand OA? If a functional index is required, which one should be used? It is important to answer these questions in order to standardize clinical trials in hand OA and to determine *a priori* anticipated, clinically relevant differences between the treatments groups. Moreover, this is necessary to calculate sample sizes of trials. In the trials reviewed, the number of patients ranged from seven to 202. The required sample size was determined in advance in only one trial.

ASSESSING STRUCTURE-MODIFYING DRUGS

Among the six studies reviewed, four were reported as abstracts or short papers. Only three of them presented results on long-term follow-up (more than 2 years), looking at changes in X-rays to assess structural effect. The minimum duration of trials measuring structural effects of drugs in hand OA is not currently known. Is X-ray assessment the best method to measure efficacy? Which radiological scoring method should be used to assess OA progression? These issues need to be addressed as future trials in the therapeutic treatment of hand OA are planned and conducted.

To summarize, the review of published data on hand OA raises more questions than it answers with regard to the evaluation of therapeutic agents. Despite the numerous methodological limitations reported above, most studies concluded that the tested drug was effective in improving hand OA symptoms. This review raises several issues, and the authors make the following recommendations: (1) A consensus needs to be reached on diagnosing hand OA, the definitions of the disease, its severity and symptom activity, allowing for standardized selection of patients; (2) primary and secondary evaluation criteria with appropriate, validated, reliable and sensitive tools need to be selected; (3) the now widely accepted guidelines for the conduct of clinical trials in OA,[27] should be adapted for further specific studies in hand OA.

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