Italian Society for Rheumatology recommendations for the management of hand osteoarthritis

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SUMMARY

Hand osteoarthritis (OA) is a common and potentially disabling disease, with different features from hip and knee OA so that a specific therapeutic approach is required. Evidence based recommendations for the management of hand OA were developed by the European League Against Rheumatism (EULAR) in 2006. The Italian Society for Rheumatology (SIR) aimed to update, adapt to national contest and disseminate the EULAR recommendations for the management of hand OA.

The multidisciplinary group of experts included specialists involved in the management of patients with hand OA. In order to maintain consistency with EULAR recommendations, a similar methodology was utilized by the Italian group. The original propositions were reformulated in terms of a search query and for every recommendation a systematic search was conducted updating EULAR recommendations' review. The propositions were translated in Italian and reformulated basing on collected evidences and expert opinion. The strength of recommendation was measured for each proposition with the EULAR ordinal and visual analogue scales.

The original 11 propositions of EULAR recommendations were translated and adapted to Italian context. Further evidences were collected about non-pharmacological therapies, local treatments, intra-articular injection with SYSADOA and corticosteroids, and surgery.

The SIR has developed updated recommendations for the management of hand OA adapted to the Italian healthcare system. Their implementation in clinical practice is expected to improve the management of patients with hand OA.

Key words: *Hand osteoarthritis, Treatment, Recommendations.*

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INTRODUCTION

Hand osteoarthritis (OA) is a common condition (1) with a significant impact on the patient with regards to pain, disability and limitation in activities of daily living (2-4). Some clinical characteristics considerably differentiate OA in the hand from that in other sites, such as the hip and the knee, amongst which are a small correlation between radiological lesions and pain, and a large aesthetic impact (4). Moreover, the specific anatomical, functional and prognostic aspects lead to the postulation that the treatment modalities can themselves have a different impact from that observed in the large joints (5).

In 2006 a European League Against Rheumatism (EULAR) Task Force has issued evidence-based recommendations on hand OA (6). The Italian Society for Rheumatology (SIR), with the aim of facilitating the dissemination of the proposals in the Italian standpoint, has planned to adapt, update and disseminate the 2006 EULAR recommendations for the treatment of hand OA.

MATERIALS AND METHODS

Italian recommendations for the management of hand OA were developed by a multidisciplinary team of experts including rheumatologists and other specialists involved in the care of patients with hand arthritis, representatives of the Italian Society of Hand Surgery (SICM), the Italian Society of Physical Therapy and Rehabilitation (SIMFER), the Italian Interdisciplinary Society of Primary Care (SIICP), the Scientific Society of General Practitioners - Italian Federation of Family Doctors (Metis-FIMMG), the Italian Society of General Medicine (SIMG), the Italian Medical Association of Hydroclimatology, Talassotherapy and Physical Therapy (AMITTF) and the Italian Society of Orthopaedics and Traumatology (SIOT). The expert panel adhered to the same methodology of the 2006 EULAR recommendations task force in order to guarantee continuity and consistency in content.

The phases of the resolution were: translation of the recommendations, reformulation of propositions as search queries, evidence collection and critical evaluation, and definition of recommendations derived from available evidence and expert advice, adapted to Italian pharmaceutical formulary.

During the first phase, the recommendations were translated from English to Italian and the resulting proposals were evaluated by the internal expert panel. All propositions were rephrased as search queries according to the PICO (*Population-Intervention-Comparator-Outcome*) strategy.

The systematic literature review has been conducted by adhering to the same methodology of the 2006 EULAR guidelines in order to update the previous review in a consistent manner. The same search strategy was utilized for all recommendations by focusing on the keyword *hand arthritis*, as reported in the EULAR recommendations (Appendix 1 of 6). The review search has therefore been conducted to systematically identify all studies on hand OA while studies including patients with OA at other sites were not systematically sought. The search was undertaken on main electronic bibliographic databases (Medline, Embase and Cochrane Library) in a timeframe from 1/1/2006 (final EULAR revision date) to 15/7/2012, and restricting the search to publications in English or Italian and research conducted on human subjects. The search has been enhanced with manual search in the reference lists of the studies included from the electronic search.

Therefore, a specific selection of studies for each recommendation has been performed among studies included in the general literature review. Inclusion criteria have been defined for each query, and subsequently, an *ad hoc* data extraction table has been developed. The article selection for each query has been conducted by a single reviewer (MM, AB, MF and IP).

With regards to the study design, systematic reviews and meta-analyses, randomized controlled trials (RCT) and controlled studies were included for queries of efficacy and safety. Conversely, cohort stud-

Table I - Level of evidence.

Ia	Meta-analysis of randomized controlled trials
Ib	Randomized controlled trial
IIa	Controlled study without randomization
IIb	Quasi-experimental study
III	Non-experimental descriptive studies
IV	Expert committee reports or opinion or clinical experience of respected authorities, or both

ies, case control and cross-sectional studies were included for the risk factors queries. Case report, narrative reviews and editorials have been excluded for all queries.

Efficacy and security data on drugs reported in RCTs have been combined in meta-analyses where feasible and presented as standard mean deviations [SMD or effect size (ES)], Number Needed to Treat (NNT) or risk ratio (RR), and relative confidence intervals (CI) at 95%. From the clinical perspective, an ES of 0.20 is considered low, 0.5 as moderate and more than 0.80 as high. The NNT is the number of patients who have to be treated in order to obtain one positive outcome (or prevent one negative outcome), and therefore a lower value corresponds to greater efficacy. On the basis of the study design, the impact of risk factors has been expressed as RR or odds ratio (OR). The ES calculations and the

Table II - Propositions and relative strength of recommendation.

Proposition	VAS (95% IC)	A-B%
1. Optimal management of hand OA requires a combination of non- pharmacological and pharmacological treatment modalities individualized to the patient's requirements	97 (95-99)	100
2. Treatment of hand OA should be individualized according to: i) type of OA (nodal, erosive, post-traumatic); ii) risk factors (age, sex, adverse mechanical factors); iii) localization and severity of structural change; iv) presence of inflammation; v) level of pain, disability and restriction of quality of life; vi) comorbidity and co-medication (including OA at other sites); vii) wishes and expectations of the patient	95 (93-98)	100
3. Education concerning joint protection (how to avoid adverse mechanical factors) together with an exercise regimen (involving both range of motion and strengthening exercises) are recommended for all patients with hand OA	80 (73-87)	65
4. Thermal therapy, local application of heat (for example, paraffin), especially before exercise, and other physical therapies (for example, laser therapy, magnetotherapy and ultrasound) can be beneficial treatments	71 (63-80)	35
5. Splints for thumb base OA and orthoses to prevent/correct lateral angulation and flexion deformity are recommended	73 (65-81)	35
6. Local pharmacological treatments are preferred over systemic treatments, especially for mild to moderate pain and when only a few joints are affected. Topical NSAIDs and other anti-inflammatory preparations are effective and safe treatments for hand OA	71 (62-80)	53
7. Because of its efficacy and safety paracetamol (up to 3 g/day) is the oral analgesic of first choice and, if successful, is the preferred long term oral analgesic	79 (68-90)	76
8. Oral NSAIDs should be used at the lowest effective dose and for the shortest duration also in patients who respond inadequately to paracetamol. The patient's requirements and response to treatment should be reevaluated periodically. In patients with increased gastrointestinal risk, non-selective NSAIDs plus a gastroprotective agent, or a selective COX-2 inhibitor should be used. In patients with increased cardiovascular risk, coxibs are contraindicated and non-selective NSAIDs should be used with caution.	86 (82-90)	88
9. SYSADOA (for example, glucosamine, chondroitin sulphate, avocado soybean unsaponifiables, diacerhein, intra-articular hyaluronic acid) may give symptomatic benefit with low toxicity, but effect sizes are small, suitable patients are not defined and clinically relevant structure modification, and pharmacoeconomic benefits have not been established	72 (65-79)	29
10. Intra-articular injection of long-acting corticosteroid is effective for painful flares of OA, especially trapeziometacarpal joint OA	82 (77-88)	71
11. Surgery (for example, trapeziectomy, arthroplasty with ligament reconstruction and tendon interposition (LRTI) or arthrodesis) can be an effective treatment for severe thumb base OA and should be considered in patients with marked pain and/or disability when conservative treatments have failed	85 (78-92)	88

resulting meta-analyses have been created with Review Manager (Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011).

As in the EULAR guidelines, the level of evidence for efficacy has been assigned via a pre-established hierarchy according to the design of the studies included under each research query (7) (Tab. I). The search results for the clinical queries consisted of the highest level of evidence possible, and, when a systematic review of RCTs was available, the earlier review was updated. Queries on risk factors and adverse events were based both on RCTs and observational studies. Studies with direct evidence were considered first, *i.e.* evidence derived from studies on patients with hand OA about which the literature review has been compiled in a systematic manner; indirect evidence, i.e. evidence from studies conducted on subject with OA at other sites, such as the hip and knee, was only included when direct evidence studies were not available.

The strength of recommendation (SOR) was measured for each proposition by utilizing the EULAR A-E ordinal scale (A=fully recommended; B=strongly recommended; C=moderately recommended; D=weakly recommended; E=not recommended) and a visual analogue scale (VAS) from 0 to 100 mm (8), and by taking into consideration both the evidence (efficacy, safety and cost-effectiveness) and the clinical experience (feasibility, acceptability and tolerance). The results of each proposition were reported as mean of the VAS with 95% CI and as percentage of SOR *A or B* (Tab. II).

RESULTS

Recommendation #1

Optimal management of hand OA requires a combination of non-pharmacological and pharmacological treatment modalities individualized to the patient's requirements.

Level of evidence: IV.

Strength of recommendation (95% CI): 97 (95-99).

This proposition was solely translated to Italian since, via unanimous consensus, it was not deemed worth to be modified. Since there are no studies specifically designed to inform this statement, this statement is supported by expert opinion alone (level IV).

Recommendation #2

Treatment of hand OA should be individualized according to:

1) type of OA (nodal, erosive, post-traumatic);
2) risk factors (age, sex, adverse mechanical factors);
3) localization and severity of structural change;
4) presence of inflammation;
5) level of pain, disability and restriction of quality of life;
6) comorbidity and co-medication (including OA at other sites); vii) wishes and expectations of the patient.

Level of evidence: III; IV.

Strength of recommendation (95% CI): 95 (93-98).

This statement includes a number of clinical factors that may be relevant in guiding clinical management. It is known that there are OA subtypes, such as the erosive or inflammatory form, which is related to worse symptoms and outcomes (9). Evidence on the prognostic role of the disease features in hand OA is mainly based on observational studies.

With regards to the type of OA, various studies have evaluated the impact of erosive OA on disease outcomes such as pain, functional disability, radiological progression and aesthetic impact (10-16). These studies suggest that erosive OA is associated with an increased radiological progression at 6 years [RR (95% CI): 1.55 (1.04; 1.88)] (12), higher pain severity [ES (95% CI): 0.42 (0.08; 0.75)], functional disability [ES (95% CI): 0.47 (0.13; 0.81)] and a lower patient satisfaction rate on aesthetic outcomes [ES (95% CI): -0.67 (-1.01; -0.33)] (11).

Similarly, nodal OA seems to be associated with radiological progression at 6 years [RR (95% CI): 1.94 (1.37; 2.48)] (12). Conversely, patient sex does not seem

to significantly influence the outcome of hand OA (13).

The localization of OA can also affect the disease outcome: a cross sectional study on 308 patients with hand OA showed that involvement of both carpometacarpal and proximal interphalangeal joints was associated with higher pain severity [ES (95% CI): 0.67 (0.43; 0.91)] and functional disability [ES (95% CI): 0.60 (0.37; 0.84)] when compared to involvement of proximal interphalangeal joints alone (17); conversely, a prospective study with similar recruitment showed that the involvement of the thumb alone was not associated with a worse disease outcome when compared to involvement of other sites [RR for radiological progression at 6 years (95%CI): 1.16 (0.91; 1.36)] (12). With regards to structural change, higher radiological scores were associated with increased pain severity and functional disability (18).

The literature review did not identify any study which analyzed the impact of clinically-assessed inflammation on disease outcome. Studies utilizing diagnostic ultrasonography have shown an association between detected effusion or synovitis and an increase in severity of both pain and impact on quality of life (19, 20).

Functional disability due to hand OA seems to be associated with a worse quality of life (21), while OA at other sites does not seem to influence the radiological progression at the hand (22).

In conclusion, some clinical factors, such as the presence of the erosive and nodal subtypes, radiological and functional severity, and involvement of multiple joint groups, show an association with a worse outcome of hand OA in observational studies (level III); for other clinical characteristics, this statement is supported by expert opinion alone (level IV).

Recommendation #3

Education concerning joint protection (how to avoid adverse mechanical factors) together with an exercise regimen (involving both range of motion and strengthening exercises) are recommended for all patients with hand OA.

Level of evidence: IV.

Strength of recommendation (95% CI): 80 (73-87).

While the 2006 EULAR recommendations supported this proposition on expert opinion alone, the literature review update has included a number of studies which analyzed the efficacy of physical exercise in hand OA; however, the substantial heterogeneity of physical therapy interventions and outcome measures did not permit their combined analysis.

Table III - Studies on the efficacy of exercise and joint protection in the treatment of hand osteoarthritis.

Author (year)	No.	Duration	Design	Intervention	Comparator
Exercise and/or joint protection					
Dziedzic (2012)	257	1 year	RCT	Education + joint protection + exercise	Education
Garfinkel (1994)	27	10 weeks	RCT	Yoga	No treatment
Lefler (2004)	19	6 weeks	RCT	Exercise	Placebo
Rogers (2009)	76	48 weeks	RCT crossover	Exercise	Placebo
Stamm (2002)	40	3 months	RCT	Joint protection + exercise	Placebo
Passive mobilization					
Villafañe (2012)	60	2 months	RCT	Median nerve mobilization	Placebo
Villafañe (2012)	28	2 weeks	RCT	Passive mobilization of trapezio-metacarpal joint (Maitland)	Placebo
Villafañe (2011)	29	2 weeks	RCT	Passive mobilization of carpo-metacarpal joints (Kalteborn)	Placebo
Splint and exercise					
Boustedt (2009)	40	1 year	CCT	Joint protection +splint + exercise	Joint protection
Stukstette (2011)	151	3 months	RCT	Education +splint + exercise	Education
Wajon (2005)	40	6 weeks	RCT	Splint + exercise	Splint + exercise

RCT, randomized controlled trial; CCT, controlled clinical trial.

The simultaneous evaluation of numerous physical therapy interventions did not permit to identify the specific effect of the various components. Moreover, according to Cochrane criteria, the majority of the studies carried a high risk of bias (23). The included studies were subdivided in three categories according to the evaluated therapy: physical exercise and/or joint protection (24-28), passive mobilization techniques of the joints or of the nerves of the hand (29-31) and combined physical exercise and joint splinting (32-34) (Tab. III).

Among the studies of the first group, in which the employment of physical exercise and/or joint protection were evaluated, a non-randomized controlled trial of 27 patients analyzed a 10-week yoga program and showed a significant reduction in pain severity [ES (95% CI): -1.30 (-2.13;-0.48)] and an increase in range of motion [ES (95% CI): 1.32 (0.49; 2.14)] in the treatment group, although no significant between-group difference in functional improvement and grip strength was found. A 3-month RCT of 40 patients on a combined program of physical exercise and joint protection has shown a significant increase in grip strength in treated patients [ES (95% CI): 4.46 (3.26; 5.66)] while a significant reduction in pain severity and improvement in function did not result (28). Conversely, recent data suggest greater overall improvement, with respect to a decrease in pain severity and functional disability, in patients on a combined program of physical exercise and joint protection when compared to control patients (24). The other studies did not however show a significant effect of physical exercise on the recorded outcomes (26, 27).

In a RCT on 60 patients, Villafane and colleagues have shown a significant decrease in pain severity and an improvement in grip strength secondary to passive mobilization of the radial nerve (29); a significant decrease in pain levels but no improvement in grip strength were shown in 2 RCT utilizing passive mobilization techniques on the trapeziometacarpal (30) and the carpometacarpal (31) joints. These studies however, despite their adequate methodology, have limitations related to sample size, advanced age of the participants and representation of the studied populations.

Lastly, a 1-year non-randomized controlled trial of 40 patients with trapeziometacarpal joint OA compared a combined program of joint protection, physical exercise and joint splintage to joint protection alone (32). A significant reduction in pain severity èES (95% CI): 0.75 (0.06; 1.44)+, improvement in function èES (95% CI): 0.98 (0.27; 1.68)+ and decrease in stiffness èES (95% CI): 0.88 (0.18; 1.58)+ were observed in the combined program group when compared to the control group at long term (even at 1 year) follow-up, while grip strength did not show any significant between-group difference. Conversely, another study did not show significant improvement in pain severity and functional disability in patients who were on a combined program of physical exercise and joint splinting rather than education alone (33); in the same way no significant difference was shown between two exercise regimens which included different types of splints (34). However, the results of the studies included in the last group do not permit to identify the distinct effects of physical exercise and joint splinting, and therefore do not provide direct evidence of the efficacy of one or the other intervention.

In conclusion, there is no direct evidence of the efficacy of joint protection and physical exercise in the management of hand OA. Data derived from the included studies do not provide comparable results and consequently do not permit the comparison of the effect of the various interventions. Therefore, this proposition is supported by expert opinion alone (level IV).

Recommendation #4

Thermal therapy, local application of heat (for example, paraffin), especially before exercise, and other physical therapies (for example, laser therapy, magnetotherapy and ultrasound) can be beneficial treatments.

Level of evidence: Ib; IV.

Strength of recommendation (95% CI): 71 (63-80).

Physical therapies could be of benefit for patients with hand OA. The main objectives to which these modalities should aim are the relief of pain and stiffness and the increase in strength and range of motion.
Seven RCTs from the literature review support this statement; all were conducted on patients with hand OA, were of a duration varying from 3 to 13 weeks, and analyzed the efficacy of various interventions. Of these, 4 RCTs were derived from a 2011 systematic review which evaluated the effect of the various modalities on pain, joint function and overall physical condition of patients with hand OA (35).
Specifically, these studies evaluated the efficacy and safety of the following modalities: acupuncture (36), laser therapy (37, 38), infrared heat (39, 40), paraffin with topical analgesics (41) and magnetotherapy with balneotherapy (42) (Tab. IV). There were no significant results with regards to the considered outcomes (pain, musculoskeletal function, grip strength, range of motion, stiffness) except that for the last two studies.
In the 4-week study of Myrer (41) on 35 patients the efficacy of the paraffin and topical analgesics was compared to that of the paraffin alone and therefore the difference in effect probably represented the effect of topical anaesthetics alone. The study showed a significant decrease in pain severity [ES (95% CI): 0.97 (0.26; 1.67)] and increase in hand function [ES (95% CI): 0.97 (0.26; 1.67)] in the group treated with paraffin and topical anaesthetics when compared to the patients treated with paraffin alone.
On the other hand, the 13-week study of Horvath (42) on 63 patients compared the efficacy of balneotherapy with magnetotherapy to that of magnetotherapy alone: in this case therefore, the difference in effect probably represented the role of balneotherapy. The combination of balneotherapy and magnetotherapy resulted in a greater improvement in pain severity [ES (95% CI) 0.82 (0.18; 1.45)] and grip strength [ES (95% CI): 0.70 (0.07; 1.32)] when compared to the application of magnetotherapy alone.
In conclusion, thermal balneotherapy seems to reduce pain severity and improve grip strength in patients with hand OA (level Ib). The local application of heat and that of other physical modalities are supported by expert opinion alone (level IV).

Recommendation #5
Splints for thumb base OA and orthoses to prevent/correct lateral angulation and flexion deformity are recommended.
Level of evidence: Ib; IV.
Strength of recommendation (95% CI): 73 (65-81).
There was no literature on RCTs comparing standard care or placebo to the use of orthoses at the time of publishing of the 2006 EULAR recommendations. The first RCT on trapeziometacarpal joint orthoses was published in 2009 (43) and the literature review update identified another study published in 2010 on a similar intervention (44). Both studies were RCTs in which the use of orthoses in trapeziometacarpal joint OA was compared to standard treatment.

Table IV - Studies on the efficacy of physical therapies in the treatment of hand osteoarthritis.

Author (year)	No.	Duration	Design	Intervention	Comparator
Basford (1987)	81	3 weeks	RCT	Laser	Placebo
Dickens (1989)	13	2 weeks	RCT	Acupuncture	Transcutaneous electrical nerve stimulation (TENS)
Favaro (1994)	48	Not reported	RCT	Infrared radiation	Placebo
Brosseau (2005)	88	6 weeks	RCT	Laser	Placebo
Stange-Rezende (2006)	45	3 weeks	RCT Crossover	Infrared radiation	No treatment
Myrer (2011)	35	4 weeks	RCT	Paraffin + topical analgesics	Paraffin
Horvath (2012)	63	13 weeks	RCT	Magnetotherapy + balneotherapy	Magnetotherapy

RCT, randomized controlled trial.

The first study was conducted on 112 patients and was of one-year duration, whereas the second one recruited 60 patients and was of 6-month duration. The main outcome of both studies was a VAS decrease in pain severity, while disability, pinch and grip strength were secondary outcomes.
Overall, data analysis showed a statistically significant decrease in medium-long term pain at 6 months ES (95% CI): -1.07 (-1.74; -0.4) by Gomes Carreira, and at 1 year ES (95% CI): -0.69 (-1.10;-0.28) by Rannou), although no significant between-group differences were observed in levels of disability, pinch and grip strength. In both studies, the effect of splinting on trapeziometacarpal dislocation was not analyzed. However, expert opinion recommends that splinting is used during rest (from activity or during sleep) since the device maintaining the joint in a functional position would prevent and correct dislocation of the thumb in trapeziometacarpal joint OA.
In conclusion, RCTs show that the use of a splint or of orthoses during night time or during rest is beneficial in the reduction of pain severity in trapeziometacarpal joint OA (level Ib). Expert opinion suggests that the indication for the prevention and correction of the dislocation of the thumb should be recommended (level IV).

Recommendation #6

Local pharmacological treatments are preferred over systemic treatments, especially for mild to moderate pain and when only a few joints are affected. Topical NSAIDs and other anti-inflammatory preparations are effective and safe treatments for hand OA.
Level of evidence: IIb; IV.
Strength of recommendation (95% CI): 71 (62-80).
The Italian group of experts has omitted the mention of capsaicin since it is not available in the Italian pharmaceutical formulary.
From a 2004 RCT meta-analysis on topical NSAIDs, a subanalysis on hand OA studies has shown that topical NSAIDs have a higher efficacy in pain relief when compared to placebo [ES (95% CI): 0.77 (0.32; 1.22)] and also have a similar efficacy to that of oral NSAIDs (ES [95% CI): -0.05 (-0.27; 0.17)] (45). However, the studies included in the subanalysis are of a short duration and show an efficacy of topical NSAIDs higher than placebo in the first 2 weeks, but similar to placebo at 1 month (46-49). The updated literature review has identified other studies on hand OA. In the 21-day study of Widrig on 198 patients, in which the effects of Arnica and ibuprofen gels were compared, no significant difference in pain relief resulted (50). In the 8-week study of Altman on 385 patients, in which the effect of diclofenac sodium gel was compared to that of a placebo, diclofenac showed greater pain relief efficacy despite that this difference seemed to progressively decrease (51). Finally, the comparative study of Jain between topic corticosteroids and placebo did not provide applicable data since the study design was deemed as providing a high risk of bias (52).
With regards to data on safety, the 2004 meta-analysis conducted by Lin showed that topical NSAIDs did not portray a higher risk of gastrointestinal adverse effects than placebo [RR (95% CI): 0.81 (0.43; 1.56)] (45). Two post-hoc analyses included in this review show that diclofenac gel 1% (53) and diclofenac solution 1.55% DMSO (54) are both safe and well tolerated and that their main possible adverse effect is a local cutaneous reaction; there was indeed no observed significant difference when compared to placebo in respect to systemic adverse effects or specifically to adverse effects in the gastrointestinal tract.
In conclusion, topical NSAIDs are an effective therapeutic choice in patients with mild to moderate pain and when only a few joints are affected (level IIb). Their safety profile makes topical NSAIDs indicated for patients with comorbidities or those with a high risk of cardiovascular and gastrointestinal events (level IV) since, with the exception of local cutaneous reactions, they do not seem to cause more adverse effects than placebo (level Ib).

Recommendation #7

Because of its efficacy and safety paracetamol (up to 3 g/day) is the oral an-

algesic of first choice and, if successful, is the preferred long term oral analgesic.
Level of evidence: IV.
Strength of recommendation (95% CI): 79 (68-90).
There are no RCTs comparing paracetamol to placebo which show its efficacy in patients with hand OA even though paracetamol has been indicated for hand OA for decades. Evidence in support of its use is mainly extrapolated from studies on OA at other sites, such as the hip and the knee. A 2009 Cochrane meta-analysis on the use of paracetamol in patients with hip or knee OA showed that paracetamol has a significantly higher efficacy in pain relief than a placebo (ES (95% CI): -0.13 (-0.22; -0.04)), even though its efficacy is less than that of NSAIDs (55). A *head-to-head* comparative trial between paracetamol and dexketoprofen trometamol in the treatment of hand OA showed a superior efficacy for the dexketoprofen-trometamol group with regards to reduction in stiffness but not pain (56); moreover, a N-of-1 trial compared paracetamol and celecoxib in patients with OA at different sites, including the hand, and overall 80% of patients did not report any different effect between the two preparations (57).
However, clinical judgment, apart from efficacy, has to also consider the adverse effects and cost of drugs. In the above-mentioned Cochrane meta-analysis, paracetamol did not show a higher risk of adverse effects than that of the placebo [RR (95% CI): 1.02 (0.89; 1.17)], and also a lower gastrointestinal risk with respect to non-selective NSAIDs [RR (95% CI): 1.47 (1.08; 2.00)] (55). Moreover, data regarding possible paracetamol nephrotoxicity are not decisive, and, at the allowed dosages, hepatotoxicity does not seem to be of concern; on the other hand a clear increase in cardiovascular risk has not been stated even if several studies on the hypertensive effect of paracetamol have been published. Therefore, paracetamol portrays an acceptable balance between risks and benefits and can be considered as first-line analgesic drug in chronic pain conditions, such as OA.

With regards to the use of other analgesics, our literature review did not permit the identification of trials in which these drugs have been studied as an indication for hand OA. A 2009 meta-analysis on the use of tramadol in hip and knee OA has shown a significantly higher efficacy on pain relief when compared to placebo despite the higher risk of both mild and serious adverse effects (58). Similarly, a 2007 meta-analysis on the use of opioid drugs in the treatment of OA at different sites has shown a significant reduction in pain severity [ES (95% CI): -0.79 (-0.98; -0.59)] and functional disability [ES (95% CI): -0.31 (-0.39; -0.24)] in treated patients when compared to patients on a placebo; however, opioids use was associated with an increased risk of adverse events with a NNT of 5 (4 for strong opioids, 9 for weak opioids) (59). The Italian expert group has deemed relevant the mention of Law 38 of the 15th of March 2010 and emended on the 31st of March of the same year, which states the possibility to prescribe opioid drugs in the treatment of pain related to chronic degenerative diseases; since that, the prescription of other analgesics can be a therapeutic option in patients not responding to paracetamol.
In conclusion, the efficacy of paracetamol in the management of hand OA has not been shown directly. The proposition is supported by extrapolative evidence from study conducted on OA at other sites (level Ia) and expert opinion (level IV). Although the analgesic effect of paracetamol is inferior to that of NSAIDs, paracetamol is safer and cheaper and therefore is to be considered as first-line analgesic treatment in patients with hand OA. Overall, the proposition is mainly supported by expert opinion (level IV).

Recommendation #8
Oral NSAIDs should be used at the lowest effective dose and for the shortest duration also in patients who respond inadequately to paracetamol. The patient's requirements and response to treatment should be re-evaluated periodically. In patients with increased gastrointestinal risk, non-selective

NSAIDs plus a gastroprotective agent, or a selective COX-2 inhibitor should be used. In patients with increased cardiovascular risk, coxibs are contraindicated and non-selective NSAIDs should be used with caution.
Level of evidence: Ia; IV.
Strength of recommendation (95% CI): 86 (82-90).
As in the published 2006 recommendations, it was not possible to identify any study which specifically analyzed oral NSAIDs use as an indication for hand OA. In the previous recommendations there were only 3-controlled placebo studies on the use of NSAIDs in hand OA. These trials have analyzed the efficacy of meclofenamate (100 mg t.i.d. for 4 weeks in 41 patients), ibuprofen (800 mg daily for 2 weeks in 60 patients) and lumiracoxib (200 mg or 400 mg daily for 4 weeks in 594 patients). All 3 trials have shown superior efficacy of NSAIDs when compared to a placebo (60-62). From a re-analysis of the data derived from 2 of the 3 studies an ES (95% CI) of 0.40 (0.20; 0.60) in reduction in pain severity with a NNT (95% CI) of 3 (2; 6) were noted.
The updated literature review has identified a study conducted by Yelland and colleagues (57) on a population of patients with OA including a subgroup of patients with hand OA. This N-of-1 trial compared the efficacy of paracetamol and celecoxib by evaluating the individual responses of the participants. Overall, 80% of patients did not report any difference between the two drugs for all included outcomes (pain, functional disability, stiffness, and adverse events).
Additional information can be derived from a meta-analysis conducted in 2009 (55) which compared the efficacy of paracetamol at a dose of 1g for 3 or 4 times daily to that of NSAIDs (including ibuprofen, diclofenac, artrotec, celecoxib, naproxen, rofecoxib) in patients with hip or knee OA. Overall, the efficacy of NSAIDs was reported to be superior to that of paracetamol in pain relief (ES (95% CI): -0.25 (-0.33; -0.17)); moreover, NSAID use has shown to be superior to paracetamol use with regards to the outcomes of function and overall health condition (according to both patient and doctor). There were no reported differences with regards to safety. Detailed analysis of the gastrointestinal risk profile has however shown a statistical difference with regards to treatment cessation due to adverse effects with a RR (95% CI) of 2 (1.05; 3.81) for NSAIDs with respect to paracetamol. The renal and cardiovascular safety profiles were not analyzed in this review in light of the rare occurrence of these adverse effects and of the small sample size and the overall short average duration (6 days to 2 years) of the included trials, which have not permitted proper analysis of these events.
In line with the previous recommendations, it is appropriate to point up that, since the risk of severe gastrointestinal toxicity is dose-dependent and incremental with age, the indication of NSAIDs for hand OA is to be restricted. Various measures were recommended for gastrointestinal protection with the aim of optimising NSAID use: NSAIDs with proton pump inhibitors (PPIs); NSAIDs with H2-antagonists; NSAIDs with misoprostol; selective COX-2 inhibitors (including both COX-2 selective and COX-2 specific, or *coxib*). There is well-documented evidence that these strategies reduce the risk of gastrointestinal ulcers (55-63). However, extreme caution is necessary to adhere to these strategies since they also carry a potential risk of toxicity (64-66). It seems that cardiorenal toxicity may be a class related side effect of NSAIDs rather than specific of coxibs use, however there is lack of the necessary evidence. In consideration of all risks and benefits, the option of oral NSAID use should be based on the individual conditions of the patient and the decision to use them is to be taken only after an exhaustive and open discussion with the patient.
In conclusion, NSAIDs are effective in the symptomatic treatment of hand OA (Ia). However, NSAIDs carry the risk of serious adverse gastrointestinal effects. Even though the majority of the gastroprotective measures (concomitant prescription of PPIs and the use of selective COX-2 inhibi-

tors) are able to reduce the NSAID adverse gastrointestinal effects (Ia), their safety profile is still not completely clear (IV).

Recommendation #9

SYSADOA (for example, glucosamine, chondroitin sulphate, avocado soybean unsaponifiables, diacerhein, intra-articular hyaluronic acid) may give symptomatic benefit with low toxicity, but effect sizes are small, suitable patients are not defined and clinically relevant structure modification, and pharmacoeconomic benefits have not been established.

Level of evidence: Ib - IV.

Strength of recommendation (95% CI): 72 (65-79).

Studies on the efficacy of the treatment of hand OA with symptomatic slow acting drugs for OA (SYSADOA) are few and evidence from the previous recommendations has often been extrapolated from studies conducted on patients with hip or knee OA. With regards to glucosamine, the updated review has included a study performed in 2012 (67) with a 6-week follow-up in which the higher efficacy of glucosamine with respect to the control (paracetamol) has been documented in pain relief and functional improvement.

Regarding chondroitin sulphate, the 2006 EULAR recommendations included two studies whose results were deemed as inconclusive: a non-randomized controlled trial (68) comparing the efficacy of combined chondroitin sulphate and naproxen to that of naproxen alone, and a RCT (69) in which chondroitin sulphate or chondroitin polysulphate were compared to a placebo in the prevention of radiological progression at 3 years. The first study (68) has not shown superior efficacy of the combined treatment on naproxen alone; the second one (69) has shown a significantly higher efficacy of the treatment with chondroitin polysulphate [NNT (95% CI): 8 (4; 166)] but not of the treatment with chondroitin sulphate [NNT (95% CI): 15 (-12; 15)] with respect to placebo in the prevention of radiological progression. Our review has

Table V - Studies on the efficacy of the treatment with *intra-articular* hyaluronic acid for hand osteoarthritis.

Author (year)	No.	Duration	Design	Intervention	Comparator
Fuchs (2004)	56	26 weeks	RCT	3 1 mL injections of HA (Ostelin mini)	3 1 mL injections of triamcinolone acetonide (Volon A10)
Bahadir (2009)	40	12 months	RCT	1 5 mg/0.5 mL injection of HA	1 20 mg/0.5 mL injection of triamcinolone acetonide
Figen (2009)	33	6 months	RCT	1 1 mL injection of Hylan G-F 20	1 1 mL injection of saline solution
Heyworth (2008)	60	24 weeks	RCT	1 1 mL injection of Hylan G-F 20 for 2 weeks	1 1 mL injection of saline solution, followed by 1 mL of celestone the following week OR 1 1 mL injection of saline solution every 2 weeks
Roux (2007)	42	3 months	RCT	1 1 mL injection of Sodium Hyaluronidate (Synovial) every 2 weeks	2 1 mL injections of Sodium Hyaluronidate (Synovial) every 2 weeks OR 3 1 mL injections of Sodium Hyaluronidate (Synovial) every 2 weeks
Schumacher (2004)	16	5 months	Prospective cohort	5 1 mL injections of HA 10 mg/mL (MW 500-730 kDa) every week	
Coaccioli (2006)	43	50 days	Prospective cohort	3 0.5 mL injections of HA every week	
Mandl (2006)	32	26 weeks	Prospective cohort	3 1 mL injections of Hylan G-F 20 every week	
Salini (2008)	18	1 month	Prospective cohort	1 1 mL ultrasound-guided injection of HA (MW 0.8-1*10^6 Dalton)	
Frizziero (2012)	58	6 months	Retrospective cohort	3 0.8 mL injections of 10 mg/ml HA (MW 500-730 kDa) every week	

RCT, randomized controlled trial; HA, hyaluronic acid.

identified another trial (70) on 162 patients in which treatment with chondroitin sulphate with respect to a placebo has shown superior efficacy at 6 months with regards to pain relief [ES (95% CI): 0.35 (0.04; 0.66)] and improvement in hand function [ES (95% CI): 0.43 (0.12; 0.75)].

There are no reported studies on the efficacy of the avocado-soya-unsaponifiables complex and diacerhein in the treatment of hand OA; in addition, for the latter, there are reported adverse gastrointestinal effects (diarrhoea).

The evidence supporting the treatment with *intra-articular* hyaluronic acid in the 2006 EULAR recommendations was extracted from a non-controlled study (71) on 16 patients treated for 5 week with a weekly *intra-articular* injection of sodium hyaluronate, and on a RCT (72) in which treatment with hyaluronic acid was compared with *intra-articular* steroid therapy. The updated review has included further studies: four RCTs (73-76), four prospective studies (77-79) and a retrospective study (80) (Tab. V).

The RCTs comparing trapeziometacarpal joint injections of hyaluronic acid to those of a saline solution have not shown statistical differences in the reduction of pain severity and function improvement between the two groups (73, 74) even if a statistically significant reduction in pain severity at weeks 12 and 26 with respect to the basal levels was recorded in the hyaluronic group (74). The studies comparing injections with hyaluronic acid and corticosteroids are discussed in proposition 10 (72, 74, 75).

A comparison of various treatment regimens (76) has not shown statistically significant difference with regards to pain severity or articular function in groups of patients which were respectively treated with one, two or three weekly *intra-articular* injections of hyaluronic acid for 2 weeks.

The prospective and retrospective studies on hyaluronic treatment in patients with trapeziometacarpal OA reported a significant reduction in pain and an improvement in hand function at one month (77, 78) and six months (79, 80) with respect to basal levels.

In conclusion, although new data in support of the efficacy of chondroitin sulphate for hand OA has been published (Ib), evidences present in literature are still inconclusive. There are no published data in the literature on avocado-soya-unsaponifiables complex, diacerhein and glucosamine as indications for hand OA. Despite the lack of evidence on the higher efficacy of hyaluronic acid injection than placebo in patients with symptomatic trapeziometacarpal OA, prospective studies show a reduction in pain severity and an improvement in function with respect to the pre-treatment period (III). Overall, the use of SYSADOA in the management of hand OA is supported by expert opinion (IV).

Recommendation #10

Intra-articular injection of long-acting corticosteroid is effective for painful flares of OA, especially trapeziometacarpal joint OA.

Level of evidence: III

Strength of recommendation (95% CI): 82 (77-88).

In the 2006 EULAR recommendations, the short term efficacy of *intra-articular* treatment with corticosteroids in patients with symptomatic trapeziometacarpal OA was supported by a non-controlled study (81), and not confirmed by a small RCT which compared the injection with triamcinolone acetonide to one with saline (82). Despite this, expert advice had considered the long-acting corticosteroid injection as an effective treatment for the inflammatory phase of OA, especially in that of the trapeziometacarpal joint.

Three RCTs (72, 74, 75) and 2 prospective studies (83, 84) were identified in the updated review. The three-arm RCT of Heyworth and colleagues (74), compared 3 *intra-articular* injections of combined betametasone sodium and betametasone acetate phosphate, Hylan G-F 20 and saline; there was no statistically significant difference between the 3 groups with respect to the following analyzed variables at 26 weeks: pain, grip strength, pinch strength and range of motion. The study of Bahadir and colleagues (75) compared 3 weekly

trapeziometacarpal injections of 20mg triamcinolone acetonide to 5mg sodium hyaluronate (*Ostenil*), showing major efficacy of the steroid at 1 month and 6 months with regards to a decrease in pain severity. Moreover, patients treated with corticosteroids experienced, with respect to basal levels, a statistically significant difference in VAS pain reduction at 12 months after the injection, while the decrease in pain among patients treated with sodium hyaluronate was only significant up to 6 months from the start of the study. A RCT comparing 10mg hyaluronic acid (*Ostenil mini*) and triamcinolone acetonide (72) has shown superior efficacy on pain of the *intra-articular* treatment with the steroid in the first weeks of the trial, while in the long term (26 weeks) no statistically significant differences in efficacy were observed between hyaluronic acid and the steroid. Conversely, observational studies have not shown any significant result on the considered outcomes (83, 84).

It is essential however to advise on the considerable heterogeneity among the included studies with regards to the amount of injected drug, the type of corticosteroid and the *intra-articular* injection techniques opted for since some studies utilized fluoroscopy- or ultrasound-guided injection (82-84).

In conclusion, despite the lack of direct evidence on the higher efficacy of corticosteroid injection with respect to that with saline solution in patients with symptomatic trapeziometacarpal OA, some studies have shown a decrease in pain severity and an improvement in function after treatment with corticosteroids (III). Hence, the multidisciplinary expert group has deemed it proper to consider long-acting corticosteroid injection as an effective treatment for hand OA, especially of the trapeziometacarpal joint.

Recommendation #11

Surgery (for example, trapeziectomy, arthroplasty with ligament reconstruction and tendon interposition (LRTI) or arthrodesis) can be an effective treatment for severe thumb base OA and should be considered in patients with marked pain and/or disability when conservative treatments have failed.

Level of evidence: III

Strength of recommendation (95% CI): 85 (78-92).

For ethical and methodological reason, there is no available literature on RCTs comparing thumb base surgery and placebo; on the other hand numerous studies support the option of undergoing surgery in cases refractory to conventional treatment. Various studies have been conducted in which different surgical procedures have been evaluated, for each of which there are recognized limitations and peculiarities.

In 2009, the *Cochrane Musculoskeletal Group* has published a systematic review (85) comprising 9 studies, 8 of which were RCTs and one was a prospective controlled study, with an overall total of 477 participants (range 15-183). The selected analyzed surgical procedures are the following: trapeziectomy, trapeziectomy with ligament reconstruction, trapeziectomy with ligament reconstruction and tendon interposition (LRTI), interposition arthroplasty, trapeziometacarpal arthrodesis and joint prosthetic implantation (Swanson and Artelon). From the literature review, the authors have concluded that it is not possible to identify the superior efficacy of one procedure on another with regards to pain, impact on function, overall health condition, range of movement and strength. With regards to adverse events, the authors have reported that median approach trapeziectomy was complicated by minor cases of adverse events with respect to trapeziectomy with LRTI [RR (95% CI): 2.20 (1.17; 4.12)].

A second systematic review (86) published in 2011 featured no quantitative data due to the heterogeneity of the included population samples and the differences between the various procedures and between the analyzed outcomes. However, even this review showed that there is no evidence on the superior efficacy of trapeziectomy with LRTI on trapeziectomy alone. With regards to the other procedures, the inclusion of a study on prosthetic joint implantation (87)

has shown that this procedure can be an option when considering the reported short term benefits, which are immediate joint stability and improvement in strength and range of movement; however, even the authors themselves suggest that the non-optimal methodology of the study necessitates the conduction of clinical trials to compare such procedure with others. Metacarpal osteotomy (88) is to be preferred in the initial phases of OA (I and II according to Eaton). Finally, the studies on carpometacarpal arthrodesis are of low quality and consequently do not permit comparative evidence of the superiority of this procedure on others.

In conclusion, surgery is an effective treatment in patients with trapeziometacarpal OA which is refractory to conventional treatment (level III). The currently available evidence is inconclusive on the higher efficacy and/or safety of the various procedures.

DISCUSSION

This document presents the SIR recommendations for the management of patients with hand OA based on the 2006 EULAR recommendations (6).

The 2006 EULAR recommendations on hand OA gathered for the recognized need to issue specific indications, which are distinct from those on hip and knee OA, in light of the multiple differences in anatomy, pathological history and the potentially different impact of treatment from that observed in other sites (5).

Similarly, following the organization of an Italian Consensus on the EULAR recommendations on the treatment of knee (89) and hip (90) OA, the SIR has deemed it a priority to update and adapt to the Italian pharmaceutical formulary the EULAR recommendations on the management of hand OA.

The Italian group has resolved to adhere to the EULAR methodology for data collection and evaluation of the strength of the recommendations in order to maintain the existing elements of strength. The systematic literature review has been updated by adhering to the same bibliographic research strategy opted for in the 2006 EULAR recommendations. The levels of evidence in support of the recommendations have been measured by adhering to the same hierarchical scale (7). Moreover, the strength of recommendation has been evaluated through the methodology recommended by the EULAR which assigns a level of evidence on the basis of a visual analogue scale and an ordinal scale. Such approach creates a summary of data on efficacy and safety which is combined with the clinical experience and therefore merges evidence and feasibility instead of merely providing grades of recommendations solely based on the design of the available studies; evaluation has been in fact based upon the opinion of experts who have taken into consideration the efficacy, safety, availability, substainability, logistical challenges and the acceptability of the therapeutic intervention in relation to the perspective of the patient.

Another strong point of the Italian recommendations was wide representation on the expert panel from the whole professional spectrum involved in the care of patients with hand OA, and from both the hospital and the community settings. However, as in the 2006 EULAR recommendations, the representation of the recommendations beneficiaries, that is, the patients affected from hand OA, was not included.

The Italian recommendations have some limitations, mainly with regards to data collection from literature. The compilation of the review from only one reviewer can lead to a heightened risk of loss or erroneous classification of the included studies. Additionally, the employment of validated scales for quality assessment was not ultimately utilized for a formal selection based on the level of quality acquired from this evaluation.

The systematic literature review has shown the scarcity of clinical studies in support of the recommendations which consequently leads to the high proportion of propositions supported by expert opinion alone. Likewise, the literature has shown lack of high

level evidence in support of various treatment options which consequently lead to a consensus frequently reached with fewer votes in favor: in 6 out of 11 recommendations the proportion of fully or strongly recommended evaluations was <75%. Moreover, the heterogeneous experience of the experts lead to different results on voting for the strength of recommendations and consequently the precision of confidence intervals was lowered.

During the recommendations development the need for better delineation of the various subsets of hand OA, which differ in both outcome and treatment regimens, became more evident. The systematic review update lead to the introduction and critical analysis of various new studies which however, in most cases, did not advance the level of evidence. For example, the analysis of 11 studies specifically evaluating the efficacy of physical exercise in hand OA did not permit the clear definition of treatment efficacy due to prominent heterogeneity among both treatment modalities and outcome measures; consequently, this prevented the increment in level of evidence for the corresponding recommendation. Comparable observations can be made on the new RCTs identified under recommendation 4 relating to the physical therapies. On the other hand, two new RCTs have lead to the classification of the use of splints and orthoses during sleep and rest under the Ib evidence level as an effective treatment for the alleviation of pain due to trapeziometacarpal OA.

With regards to SYSADOA utilization, our review has lead to the addition of another trial on treatment with chondroitin sulphate which showed efficacy in alleviating pain and increasing function at 6 weeks when compared to a placebo, while 9 studies have been added for the evaluation of *intra-articular* treatment with hyaluronic acid: 4 RCTs (73-76), 4 prospective studies (77-79) and a retrospective study (80), with respect to only 1 RCT on 16 patients featuring in the 2006 recommendations. RCTs comparing trapeziometacarpal injection with hyaluronic acid and saline solution, despite showing a statistically significant reduction in pain at 12 and 26 weeks with respect to initial levels, have not shown significant differences between the two groups. Nonetheless it is relevant to highlight that the RCTs included in the review utilized mainly subjective outcomes, and we do not know the effect on structural outcomes, which can be less influenced by the *placebo effect* (91). On the other hand both prospective and retrospective cohort studies on trapeziometacarpal hyaluronic acid injection report significant pain alleviation and improvement in hand function at 1 month (77, 78) and 6 months (79, 80) with respect to baseline levels. Moreover, 3 RCTs (72, 74, 75) and 2 prospective studies (83, 84) on the *intra-articular* administration of steroid-based products have been added, although a notable heterogeneity among these studies with regards to the amount injected, the type of corticosteroid, comparative treatment, evaluated outcomes, observation timeframes and *intra-articular* injection technique (fluoroscopic or ultrasound guidance) have made unequivocal extrapolation difficult. Lastly, even though the literature review identified another 9 RCT on the various practiced surgical interventions, the identification of superior techniques with regards to pain alleviation and/or functional impact was not possible due to heterogeneity among the studies. Therefore, an increment in level of evidence from the 2006 recommendations was not possible.

In a number of recommendations, in the absence of specific RCTs on hand OA, the recommendations were based upon scientific evidence regarding knee and hip OA. However it is well known that important differences exist between hand OA and that at the knee or the hip with regards to the impact of the disease due to anatomical factors, and also due to different grades of potential disability and functional alteration, natural history, prevalence and risk of disease progression, indicated modalities (*e.g.* topical preparations, injections) and different response to the same treatments (*e.g.* NSAIDS or SYSADOA). It is for these reasons that it is debatable whether extrapolations of data from hip and knee

studies offer a valid and universally acceptable basis for recommendations on the management of hand OA.
On the basis of these observations, the Italian expert group promotes and encourages the development of specific RCTs on the management of hand OA. It is moreover hoped that such studies are conducted in accordance to the 2006 recommendations for the conduction of clinical research on hand OA with the intent of improving the quality of future studies (92).

CONCLUSIONS

The SIR has developed 11 propositions based on the EULAR recommendations for the management of hand OA, rephrased in line with the availability of new evidence, clinical multidisciplinary experience and the Italian pharmaceutical formulary. The dissemination of the recommendations through the various Italian healthcare sectors and the implementation of the recommendations in clinical practice are to improve the care of patients with hand OA.

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