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Cryotherapy in inflammatory rheumatic diseases: a systematic review

Expert Rev. Clin. Immunol. 10(2), 000–000 (2014)

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The aim of this article was to review current evidence about cryotherapy in inflammatory rheumatic diseases (therapeutic and biological effects). For therapeutic effects, we performed a systematic review (PubMed, EMBASE, Cochrane Library, LILACS databases, unpublished data) and selected studies including non-operated and non-infected arthritic patients treated with local cryotherapy or whole-body cryotherapy. By pooling 6 studies including 257 rheumatoid arthritis (RA) patients, we showed a significant decrease in pain visual analogic scale (mm) and 28-joint disease activity score after chronic cryotherapy in RA patients. For molecular pathways, local cryotherapy induces an intrajoint temperature decrease, which might downregulate several mediators involved in joint inflammation and destruction (cytokines, cartilage-degrading enzymes, proangiogenic factors), but studies in RA are rare. Cryotherapy should be included in RA therapeutic strategies as an adjunct therapy, with potential corticosteroid and nonsteroidal anti-inflammatory drug dose-sparing effects. However, techniques and protocols should be more precisely defined in randomized controlled trials with stronger methodology.

KEYWORDS: cryotherapy • cytokines • DAS28 • enzymes • pain VAS

Inflammatory joint diseases, such as rheumatoid arthritis (RA), represent a major public health concern, with both synovial inflammation causing joint destruction, pain and disability [1] and systemic inflammation thought to increase cardiovascular risk and mortality [2,3]. Recently, progress in immunology provided new therapeutic targets and new drugs such as biologic agents allowing to achieve clinical remission and prevent joint destruction [4,5]. These treatments, however, remain expensive, with rare but potentially life-threatening side effects such as infections [6]. Long-term nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids also have a well-known toxicity [7]. So the development of adjunct therapies in order to spare biologic and corticosteroid doses is a key focus in these diseases.

Cryotherapy is used empirically in a wide range of rheumatic diseases as a symptomatic treatment, with well-known analgesic, anti-phlogistic, myorelaxing, vasoconstrictive, anti-inflammatory, enzyme-blocking and antioxidative effects [8–10]. It can be used not only in inflammatory joint diseases (such as crystal-

induced arthritis, spondyloarthritis and RA [10] but also in such painful rheumatic condition as osteoarthritis [8,9], fibromyalgia [11], shoulder capsulitis [12] and muscle damage [13]. Whole-body cryotherapy (WBC) also showed effects on bone biomarkers [14]. This adjunct treatment is cheap (at least for local cryotherapy [LC]) and generally well tolerated [15,16]. Technical modalities (local/general application, duration, number of sessions [17], and physical form) are very diverse and lack standardization [18]. This widespread use contrasts with a poor level of evidence [18]. Cryotherapy has been shown to decrease intra-articular temperature (T°C) in human knees to 30°C [19,20]. This intrajoint temperature is in the same range as therapeutic mild hypothermia used in several other medical fields. Mild hypothermia (28–34°C) has shown anti-inflammatory effects in healthy subjects [21,22] and in very diverse pathologies such as cerebral ischemia in humans [23] and murine models [23,24], traumatic tissue injury in murine models [25,26] and humans [27], hemorrhagic shock in rats [28], cardiac arrest in humans [29], coma in pigs [30],

coronary artery or cardiopulmonary bypass in humans [31], aortic ischemia/reperfusion in mice [32], mechanical ventilation in rats [33,34], postexercise hyperthermia in humans [35], age-related macular degeneration in culture experiments using a retinal cell line [36] and pancreatitis in rats [37]. These studies showed potential effects on important molecular/cellular mechanisms involved in synovial inflammation and joint destruction such as proinflammatory cytokines [21,25,38], VEGF [36], enzymatic pathways (metalloproteinases [39,40], collagenase [41], adhesion molecules (ICAM-1) and white blood cell infiltrate formation in rats [42] and humans [43], oxidative stress in rats [24] and humans [44], norepinephrine in humans [24,45,46]. This suggests potential therapeutic effects in inflammatory rheumatic diseases such as RA, as some of these molecular pathways are known to be related to pain, disease activity scores including 28-joint disease activity score (DAS28), biological inflammation and radiologic joint damage.

The aim of this article is to review data and evidence concerning cryotherapy's effects in inflammatory rheumatic diseases.

First, we performed a systematic review of the literature about cryotherapy's therapeutic effects in rheumatic inflammatory joint diseases. The primary endpoints were pain assessed by visual analogic scale (VAS) and DAS28. The secondary endpoints were tolerance and molecular anti-inflammatory effects of cryotherapy in these diseases.

Cryotherapy effects on pain & disease activity in rheumatoid arthritis: systematic review

Methods

We followed the PRISMA statement checklist for meta-analysis and systematic review quality criteria [47].

Searching

We used PubMed, EMBASE, LILACS and Cochrane library databases. Keywords 'cryotherapy,' 'cryotherapy arthritis,' 'cryotherapy inflammation,' 'cold,' 'cold arthritis,' 'cryostimulation' and 'WBC' were used alone and in combination. We considered articles with available abstracts in English, German, Spanish, French language and in referenced journals from their inception to March 2013. We also manually screened references cited in the selected articles, considered abstracts from rheumatology congresses (ACR, EULAR since 2001).

As concerns unpublished data, we considered the International Standard Randomised Controlled Trial Number Register [101], The National Institute of Health [102] and the WHO [103]. The screening was performed by two independent reviewers with discussion when needed in order to reach consensus.

Eligibility & study selection

Selection criteria for cryotherapy therapeutic effect evaluation were studies including inflammatory rheumatic disease patients (i.e., RA, microcrystals, peripheral spondyloarthritis) treated with LC or WBC, with endpoints evaluating pain and joint disease activity (pain VAS, ESR, CRP, DAS28 and Doppler activity). Articles about postoperative joint cryotherapy and

infectious diseases were excluded. We selected original articles, abstracts, reviews and meta-analyses. Duplicates were removed.

Quality assessment

For cryotherapy therapeutic effects, we analyzed technical cryotherapy modalities in detail (physical form and device, duration, skin or joint temperature).

The methodology was also evaluated: study population, randomization, blinding, control groups (other therapeutic modalities such as pharmacological treatments, physical therapy, different cryotherapy techniques or placebo groups), withdrawal and dropout reporting, as well as potential confounders (corticosteroids, NSAIDs, biologics, physical exercise, kinesitherapy, BMI, considered joint) when assessed in the studies. Data extraction was performed by two independent reviewers.

Therefore, we assessed study quality based on specific validated scores depending on the study design. A JADAD 5-point scale was used for randomized controlled trials [48]. For non-randomized studies, we used the Newcastle–Ottawa Scale (NOS) system (0–9) [104]. Furthermore, a JADAD 11-point scale [48] was applied to all the selected studies whatever their design in order to compare them globally and to provide a general qualitative overview. Studies that scored six or higher using JADAD 11-point scale (3/5 with JADAD-5 and 5/9 with NOS) were considered to be of higher quality. This quality assessment was also performed by two independent reviewers.

Quantitative data synthesis

Most outcomes were continuous in nature (pain VAS, DAS28). When pooling data from different trials was possible, the principal measures of effect were means \pm SD (weighted mean differences before/after cryotherapy or relative to control groups when possible). Heterogeneity was assessed graphically with 95% confidence intervals and statistically tested using Fisher's variance comparison tests. Heterogeneity threshold was calculated for each primary outcome ($F = 2.73$ or greater was significantly heterogeneous for pain VAS in patients treated with LC, $F = 2.7$ for pain VAS in WBC-treated patients, $F = 2.73$ for DAS28 in LC-treated patients and $F = 3.12$ in WBC-treated patients). We used a fixed effect model. Pooled means \pm SD were compared before/after cryotherapy (within-group effect size; paired t tests; α risk 5%) and the mean differences before/after treatment were compared between cryotherapy-treated patients and control groups when available (between-group effect size; unpaired t tests; $\alpha = 5\%$; variance comparison using Fisher's test).

Data were analyzed using Statview[®] (SAS Institute Inc. Version 5.0) device. There were no *a priori* sensitivity and subgroup analyses. We also considered unpublished data in order to minimize publication bias.

Results

Flowchart

The Flowchart is shown in FIGURE 1.

Screening results

PubMed search (in English with abstracts) displayed 11,344 citations for 'cryotherapy' keyword on 4 March 2013. 'cryotherapy arthritis,' 'cryotherapy inflammation,' 'WBC,' 'cold,' 'cold arthritis,' 'cold inflammation,' 'cryostimulation' showed 67, 346, 331, 108,707, 733, 4355 and 31 results, respectively.

EMBASE database displayed 23,228 citations for 'cryotherapy' keyword, 22,632 results for 'cold,' 1784 results for 'cold arthritis,' 445 results for 'cryotherapy arthritis,' 95 results for 'WBC,' 17,445 results for 'cold inflammation,' 3402 results for 'cryotherapy inflammation' and 32 results for 'cryostimulation.'

The LILACS database displayed 230 results for 'cryotherapy' keyword, 1 for 'cryotherapy arthritis,' 7 for 'cryotherapy inflammation,' 52 for 'WBC,' 1479 results for 'cold' keyword, 6 for 'cold arthritis,' 19 for 'cold inflammation' and 34 results for 'cryostimulation.'

In EULAR congress abstracts, we found 17 and 132 abstracts related to 'cryotherapy' and 'cold,' respectively, since 2001 on EULAR website (ACR website: 21 abstracts related to 'cold' in 2006–2011, none related to 'cryotherapy').

The International Standard Randomised Controlled Trial Number Register website displayed 15 results for 'cryotherapy' keyword and 99 results for 'cold' keyword. The National Institutes of Health website displayed 188 results for 'cryotherapy' keyword (4 for 'cryotherapy arthritis,' 5 for 'WBC') and 645 results for 'cold' keyword (16 for 'cold arthritis'). The WHO website displayed 1830 results for 'cryotherapy' keyword (56 for 'cryotherapy arthritis,' 22 for 'whole body cryotherapy') and 3,020 results for 'cold' keyword (949 for 'cold arthritis').

Article selection process

First, articles were excluded on the basis of title and abstract: numerous records dealing with completely different scientific or medical fields such as dermatology, gynecology, urology, oncology, ophthalmology, infectious or lung diseases, chemistry, etc., very low temperature cell lysing-cryotherapy, local cryotherapy not applied to joints spine, etc. After duplicate removal, we found 511 records potentially dealing with cryotherapy in all types of joint diseases according to the titles and abstracts. After applying eligibility criteria, we screened 146 potentially relevant references in the field of therapeutic cryotherapy in inflammatory joint diseases.

Then, we excluded 124 articles for the following reasons: duplicates, articles related to postoperative cryotherapy, non-inflammatory diseases, nonrheumatologic diseases, with inadequate outcomes or endpoints, lacking accuracy in cryotherapy

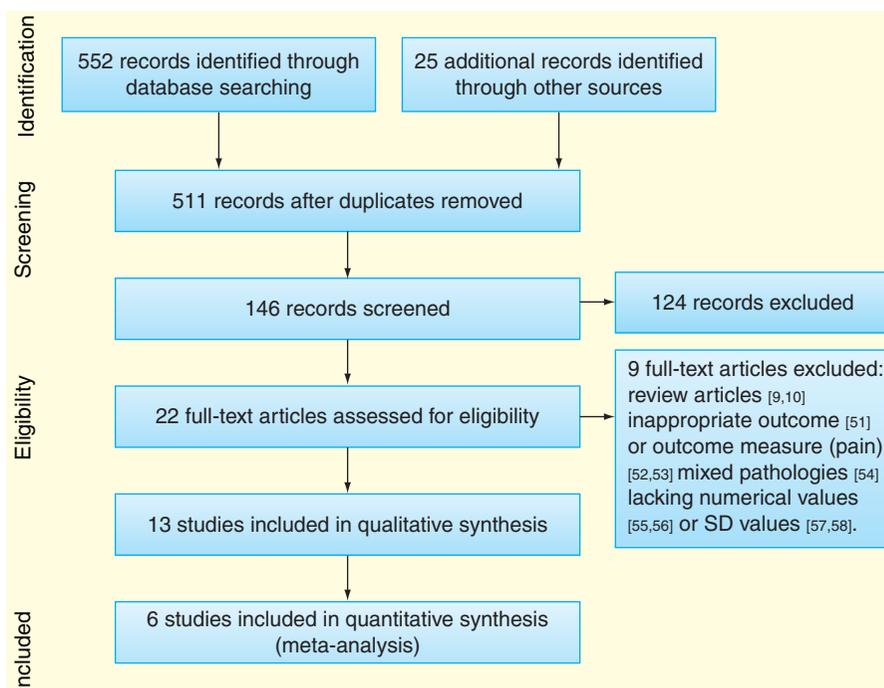


Figure 1. Flowchart.

DAS28: 28-joint Disease Activity Score (composite score including patient VAS for disease activity, acute-phase reactant (ESR or CRP), tender joint count and swollen joint score); LC: Local Cryotherapy; n: Number of articles; RCT: Randomized controlled Trial; SD: Standard Deviation; VAS: Visual Analogic Scale; WBC: Whole-body cryotherapy.

technical description or numerical data reporting, with full text not available and insufficient data in the abstract.

A Cochrane meta-analysis including five RCT about cryotherapy in RA [49–53] was published in 2001 and updated in 2011 [18]. None of these articles were appropriate to be used in our meta-analysis, as summarized in TABLE 1. Two of the studies were performed in operated patients [49,50]. The outcomes [46,47] or outcome measures were inappropriate to our analysis [49,52,53]. Cold application was also probably insufficient in intensity [49,50], in duration [51] or periodicity [51–53]. Furthermore, hot packs used in three of the studies [50,52,53] could have proinflammatory properties [20] and therefore do not seem to be relevant treatments for control group.

The remaining articles (22 articles including 8 RCTs for therapeutic effects) were assessed for further evaluation on the basis of full-text article when available. Nine articles were further excluded [9,10,51–58].

The 13 remaining studies were potentially appropriate to be included in a meta-analysis. There were five RCTs, two nonrandomized controlled studies, three studies comparing several cryotherapy techniques in parallel treatment arms and three noncontrolled studies. Seven articles dealt with local cryotherapy [8,59–64], four with WBC [65–68] and two with both (FIGURE 1) [69,70].

Characteristics of the studies selected for quantitative analysis (cryotherapy therapeutic effects)

Study characteristics and quality assessment results are summarized in TABLE 2.

Table 1. Cochrane meta-analysis [18]: review of the five randomized controlled trials about cryotherapy.

Pathology	Joint	Endpoints	Postoperative cryotherapy (yes/no)	JADAD score (/5)	Cryotherapy modality	Control group	Reason for Exclusion	Ref.
24 RA (ARA criteria)	Knees	– Joint circumference – Infrared thermography	No	2/5 R1B0W1	Crushed ice in damp towels (10 min daily for 10 days)	Contralateral joint (no cryotherapy)	– Endpoints – Insufficient cold exposure (duration)?	[51]
5 RA; 83 OA	Knees	– Pain (PCA use)	Yes	3/5 R2B0W1	Thermal pad (50°F vs 60°F vs 70°F); duration? periodicity?	None	– Postoperative cryotherapy – Insufficient cold exposure (temperature)?	[49]
14 chronic RA (definite or classic RA)	20 knees	– Pain (none = 0–5 = severe) assessed by two observers at the same time – Stiffness, range of movement, knee circumference, skin temperature, patient preference	No	1/5 R1B0W0	Ice packs in damp towels (20 min, once a day for 10 days)	Hot packs (cross-over)	– Pain assessment	[52]
Patients hospitalized for surgical procedures to the hand	30 hands	– Edema evolution over preoperative volume	Yes	2/5 (R1B0W1)	Cold water immersion (10°C for 4 min; twice a day for 1 day)	Hot packs (n = 15)	– Postoperative – Endpoints – Insufficient cold exposure (Temperature and duration)?	[50]
18 Recent RA (<5 years)	Shoulders	– Pain (Mc Gill questionnaire) – Range of movement	No	1/5 (R1B0W0)	Ice (20 min) + exercises program	Hot packs (n = 9)	– Pain assessment	[53]

This meta-analysis performed in 2001 and updated in 2011 mixed studies with cold or heat application. It showed no significant effect on pain (primary endpoint), joint swelling, medication intake, range of motion, grip strength or hand function. No harmful side effect was reported [18]. The five RCTs about cryotherapy had limitations: the studies showed a great heterogeneity as concerns cryotherapy methods, treated joints, outcomes, associated medications and physical exercise. The control groups were: hot packs in three studies and contralateral joint in one study. Heat application does not seem to be an appropriate control nor treatment group because it could increase joint inflammation and collagenase activity [20]. Cold exposure was probably insufficient in intensity and duration in some of the studies compared with more recent studies. ARA: American Rheumatism Association; B: Blinding; n: number of patients; OA: Osteoarthritis; PCA: Patient-controlled Analgesia; R: Randomization; RA: Rheumatoid Arthritis; W: Withdrawals (JADAD score). Data taken from the articles cited in this table.

Table 2. Therapeutic effects of cryotherapy: articles included in the meta-analysis (n = 6).

Pathology/ joints (n)	LC/WBC (n)	Cryotherapy modalities	Control group (n)	Relevant endpoints (for meta-analysis) and evaluation times	JADAD 5/ NOS JADAD11	Bias/confounders	Ref.
RA (60 patients)	- LC (n = 20) OR - WBC (-60°C; n = 20) - WBC (-110°C; n = 20)	- Cold packs or cold air on 5 joints (-30°C; 10–30 or 1–5 min) OR - WBC (-60°C OR -110°C; duration?) → Three-times a day; 7 days (20 applications)	None	- Pain VAS - DAS28 - ESR - CRP → Before; Day 7 'after the last cryotherapy' n = 20; 17; 17	R1B0W1 8/11	- Associated kinesitherapy - Corticosteroids (10/20; 14/20; 9/ 20); median dose 5 mg/day [2.5–15] - NSAIDs: 16/20; 17/20; 18/20 - DMARDs: 10/20; 9/20; 9/20 - 'cytostatics': 11/20; 14/20; 12/20 - No change in pharmacological treatment. - BMI: 25.7 ± 4 vs 24.6 ± 3.6 vs 28.3 ± 5.9 - Biologics, physical exercise, skin/ room TC: NA	[70]
RA (ACR; n = 40 patients)	- LC (2 modalities)	- Cold air (-30°C; 3 min; n = 20) OR - Liquid nitrogen vapours (-160°C; 3 min; n = 20) → Twice a day (knees in the morning, 4 h break, then hands) for 10 days	None	- Pain VAS - DAS28 → Before and after 10 days of treatment	S3C102 6/11	- Associated kinesitherapy and physical exercise - Corticosteroids 28/40 - DMARDs 40/40 - Biologics: none - No change in pharmacological treatment. - BMI: 28.4 ± 4.5 and 28.2 ± 2.3 - NSAIDs, skin/room TC	[63]
Early RA (n = 36 patients)	- LC (n = 20 patients)	- Cold air (-60°C; 15 min; 10 sessions; hands, knees or ankles) Included in a Complex Rehabilitation Program (40 min exercise, 40 min occupational therapy + 'Drug therapy'). Total duration?	- 'Drug therapy' only (n = 16)	- Pain VAS - DAS28 → Before and after treatment (10 days?)	S3C101 3/11	- Corticosteroids, NSAIDs, DMARDs, biologics, kinesitherapy, skin/room TC, BMI: NA	[64]
RA (n = 48 patients), AS (n = 12)	- WBC	- WBC (-110°C for 3 min; twice a day) → Average number of sessions: 15.8 ± 8.37	None	- Pain VAS - DAS 28 (48 patients) - BASDAI (12 patients) → Before and after treatment	S2C001 4/11	- Associated kinesitherapy and physical exercise. - No change in pharmacological treatment. - Corticosteroids, NSAIDs, kinesitherapy, physical exercise, skin temperature, BMI: NA	[66]

ACR: American College of Rheumatology (Diagnostic criteria for rheumatoid arthritis); B: Blinding; BASDAI: Bath Ankylosing spondylitis Disease Activity Index; C: Control groups; DMARD: Disease activity-modifying drug;
LC: Local Cryotherapy; NA: Not assessed; NSAID: Nonsteroidal anti-inflammatory drug; O: Outcome measurement (NOS score); Pain VAS: pain Visual Analogic; RA: Rheumatoid Arthritis; RCTs: R: Randomization;
S: Sampling; Scale DAS28: 28 joint-disease activity score (Composite score including patient VAS for disease activity, acute-phase reactant (ESR or CRP), tender joint count and swollen joint score); T: Temperature;
W: Withdrawals (JADAD score); WBC: Whole-body cryotherapy
Data taken from the cited articles.

Table 2. Therapeutic effects of cryotherapy: articles included in the meta-analysis (n = 6) (cont.).

Pathology/ joints (n)	LC/WBC (n)	Cryotherapy modalities	Control group (n)	Relevant endpoints (for meta-analysis) and evaluation times	JADAD 5/ NOS JADAD11	Bias/confounders	Ref.
RA (ACR; n = 32 patients)	- WBC (n = 15 patients)	- WBC (-110°C for 3 min; once a day) + kinesitherapy → 'Complex therapy' for 8 days	- Low frequency magnetic field (20-40 Hz; 5-7 mT; 20 min; n = 17 patients) + kinesitherapy	- Pain VAS - DAS28 → Before and after treatment (8 days)	S4C101 5/11	- Associated kinesitherapy - No change in pharmacological treatment. - Corticosteroids, NSAIDs, physical exercise, skin temperature, BMI: NA	[67]
RA (ACR ; n = 41 patients)	- WBC	WBC (-160°C; 3-5 min; twice a day (6 h interval) for 15 days) + active exercises (45 min)	None	- Pain VAS → Before and after treatment (15 days)	S3C101 3/11	- Associated kinesitherapy and physical exercise - No change in pharmacological treatment. - Corticosteroids, NSAIDs, DMARDs, biologics, skin temperature, BMI: NA	[68]

ACR: American College of Rheumatology (Diagnostic criteria for rheumatoid arthritis); B: Blinding; BASDAI: Bath Ankylosing spondylitis Disease Activity Index; C: Control groups; DMARD: Disease activity-modifying drug;
LC: Local Cryotherapy; NA: Not assessed; NSAID: Nonsteroidal anti-inflammatory drug; O: Outcome measurement (NOS score); Pain VAS: pain Visual Analogic; RA: Rheumatoid Arthritis; RCTs: R; Randomization;
S: Sampling; Scale DAS28: 28 joint-disease activity score (composite score including patient VAS for disease activity, acute-phase reactant (ESR or CRP), tender joint count and swollen joint score); T: Temperature;
W: Withdrawals (JADAD score); WBC: Whole-body cryotherapy
Data taken from the cited articles.

The endpoints were compared before and after cryotherapy.

Cryotherapy modalities (technique, temperature, duration and periodicity) were heterogeneous. The main potential confounders were assessed when possible: Corticosteroid, NSAID, disease activity-modifying drug (DMARD), biologic intake, kinesitherapy, physical exercise, room temperature. No serious adverse event was reported in any of the studies.

We could only perform a pooled quantitative analysis for two endpoints: pain VAS and DAS28 in RA patients. For that purpose, six studies were included in the quantitative data analysis (TABLE 2) [64,65,67-69,71]. Reasons for excluding the seven other studies [8,59-62,65,69] were: one duplicate [69], impossibility to combine data for power Doppler hypersignal endpoint due to different evaluation scores [59-61], as for gout patients: too different designs [8,62], one study mixed patients suffering from heterogeneous rheumatic diseases (inflammatory as well as noninflammatory) [65]. Straub and Hirvonen's studies were considered as duplicates as they were performed, at least partly, in the same patient cohort [69,70]. For WBC, we only considered -110°C-treated patients in Hirvonen's study [70].

Results: study quality assessment

Six studies including 257 RA patients were appropriate to be included in quantitative data synthesis. There was one RCT with 40 patients meeting the inclusion criteria [70], two controlled trials [63,64], two studies comparing parallel cryotherapy treatment groups [67,68] and one noncontrolled study [66].

The RCT scored 2 out of 5 (JADAD5 score) [70]. As for the five noncontrolled studies, the mean NOS quality score was 5 ± 1.2 [63,64,66-68]. Overall, the mean JADAD11 score for the six selected studies was 4.8 ± 1.9 . The quality scores for each study are displayed in TABLE 2.

Results: heterogeneity assessment

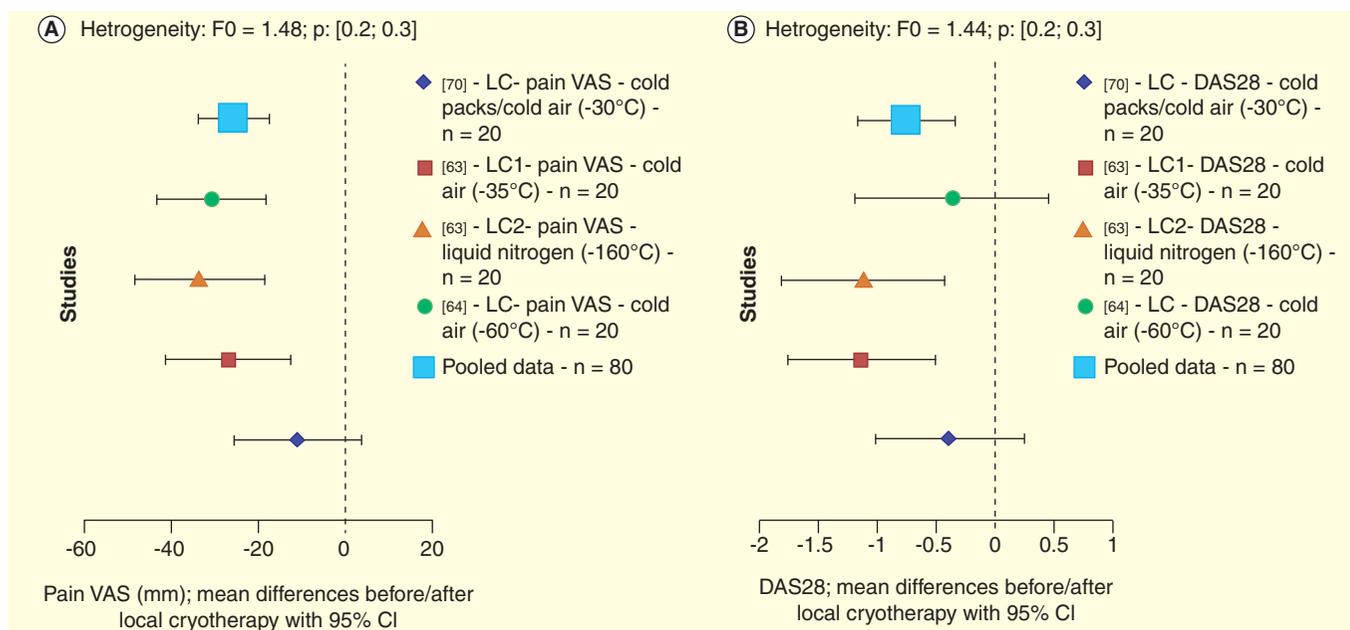
We could only perform quantitative analysis for two endpoints: pain VAS (mm) and DAS28 in RA patients after chronic application (7-15 days) (FIGURES 2 & 3) [63,64,66-68,70].

There was no significant heterogeneity between studies for pain VAS and DAS28 in LC or WBC-treated patients, as shown in FIGURES 2 & 3, displaying means and 95% confidence intervals. Fisher's tests showed $F_0 = 1.48$; p : [0.2; 0.3] for pain VAS after local cryotherapy (FIGURE 2A), $F_0 = 1.44$; p : [0.2; 0.3] for DAS28 after local cryotherapy (FIGURE 2B), $F_0 = 1.07$; p : [0.3; 0.5] for pain VAS after WBC (FIGURE 3A), $F_0 = 0.47$; p : [0.5; 0.9] for DAS28 after WBC (FIGURE 3B).

Paired t-tests were used to assess pain VAS and DAS28 evolution after cryotherapy.

As concerns local cryotherapy, the mean number of cold applications was 17.1 (ranging from 10 to 20), mean temperature of -70.3°C (-30 to -160) applied for 11.5 min (3-30).

As for WBC and pain VAS (mm), the mean number of applications was 20.2 (8-30) at a mean temperature of -126.5°C (-110 to -160) during 3.2 min (2-5).



AQ6 **Figure 2.** Effects of local cryotherapy on pain VAS (A) and DAS28 (B). Data taken from the cited articles.

Considering WBC and DAS28, the mean number of applications was 14.4 (8–20) at a temperature of -110°C during 2.8 min (2–3).

Results: primary outcomes (pain VAS & DAS28)

As concerns pain, LC (cold packs, cold air, liquid nitrogen applied on 1–5 joints) significantly reduced pain VAS (mm)

in 80 RA patients originating from three studies [63,64,70], with 20 of these patients were included in a RCT [70]. Mean pain VAS decreased from 59.10 ± 25.86 (95% CI: 42.17–75.63) to 33.55 ± 20.77 (95% CI: 26.07–56.33) after LC ($p < 0.000002$). WBC also significantly decreased pain VAS in 124 RA patients from 4 studies [66–68,70] (20 patients

300

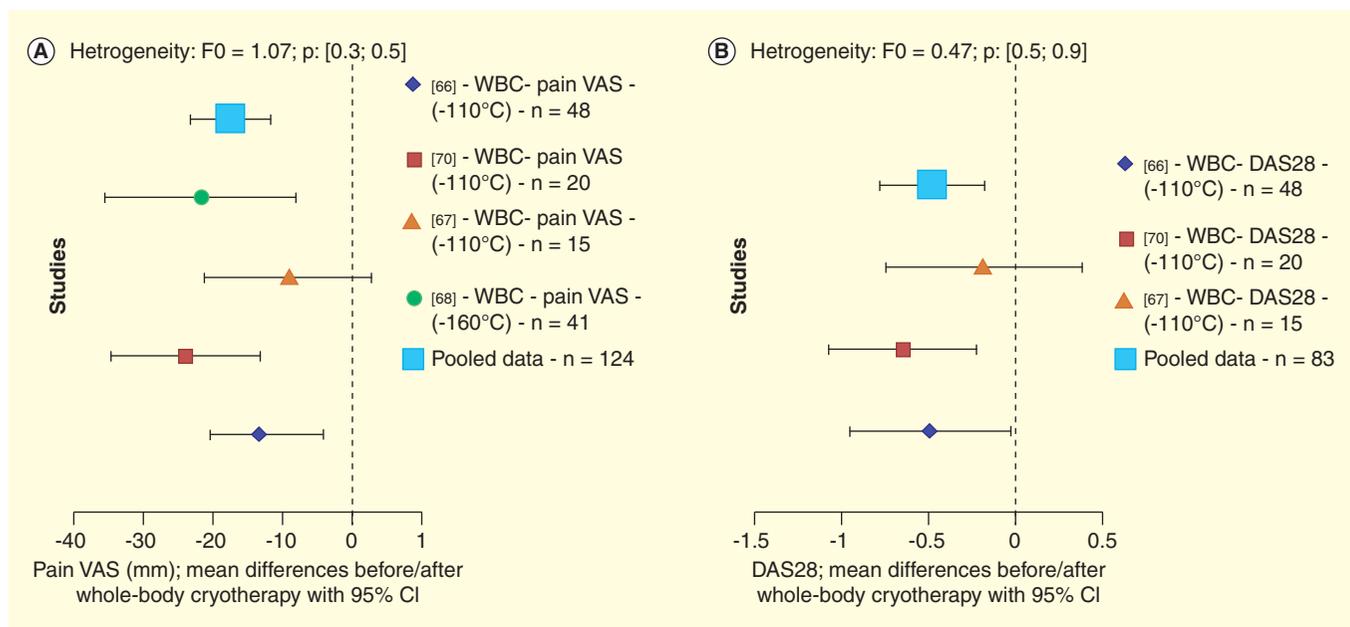


Figure 3. Effects of whole-body cryotherapy on pain VAS (A) and DAS28 (B). Mean differences in pain VAS (mm) or DAS28 before/after LC or WBC are represented for each of the six studies included in the meta-analysis [63,64,66–68,70], with 95% confidence intervals. Heterogeneity was also tested using Fisher's test (F_0 and p -values are shown on the graphs). Design of the studies: RCT [70], controlled trials [63,64], parallel cryotherapy treatment groups [67,68] and noncontrolled study [66].

DAS28: 28-joint disease Activity Score (composite score including patient VAS for disease activity, acute-phase reactant (ESR or CRP), tender joint count and swollen joint score); LC: Local Cryotherapy; n: Number of patients;

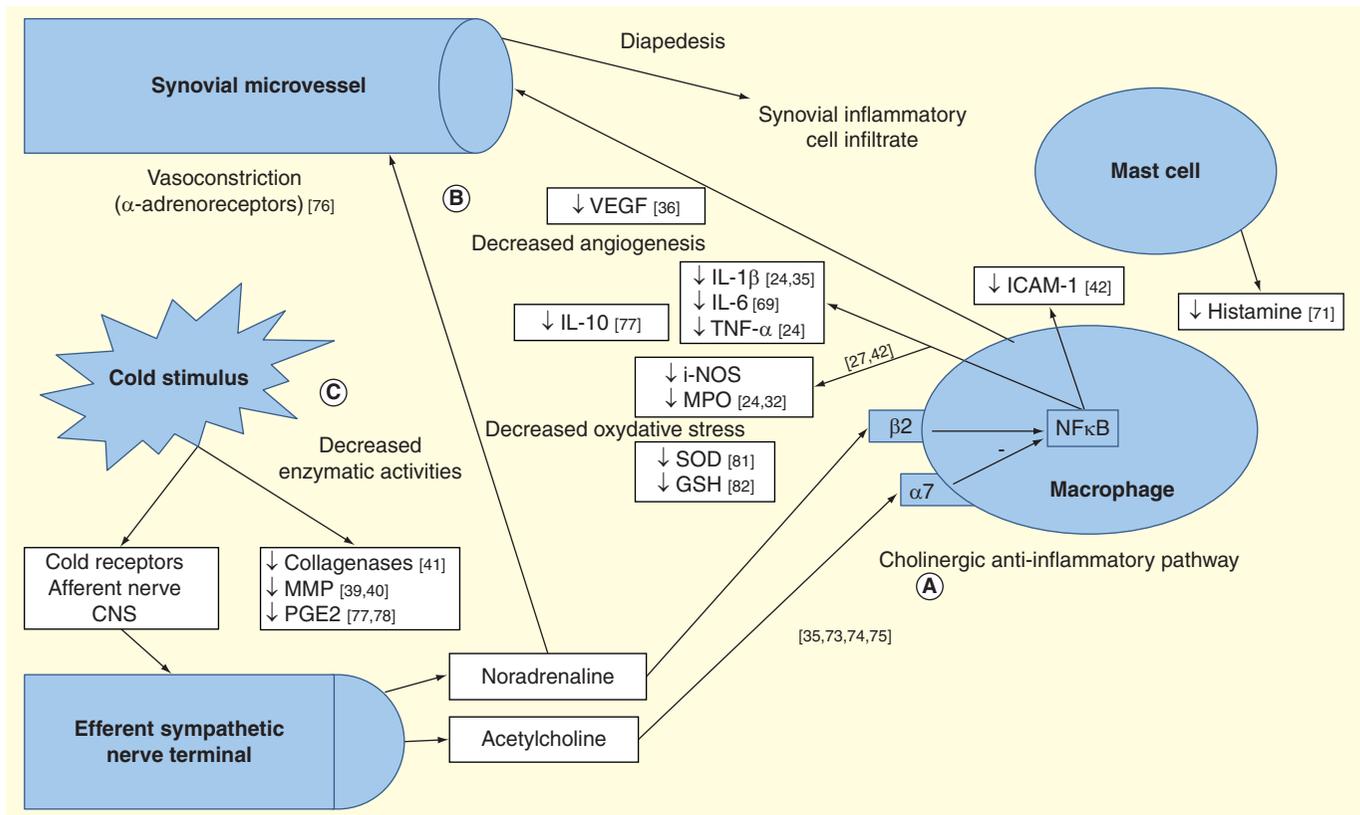


Figure 4. Molecular pathways involved in cryotherapy (proposed model). In RA, local and systemic inflammation promote neoangiogenesis which in turn favors inflammatory cell infiltrate and proinflammatory cytokine release. **(A)** After cold stimulation, the autonomic nervous system is activated [73] and efferent sympathetic neurons release acetylcholine that binds $\alpha 7$ nAChR receptor and noradrenaline that binds $\beta 2$ -adrenoceptor. These ligand–receptor interactions may then inhibit the NF κ B pathway and subsequently downregulate proinflammatory cytokine, oxidative stress agent and adhesion molecule gene transcription [23,35,38,73–75]. **(B)** Noradrenaline also induces vasoconstriction through α -adrenoceptor binding on the vascular wall [76], which could contribute to limit inflammation. Cryotherapy might also downregulate the expression of proangiogenic factors such as VEGF [36]. **(C)** Cryotherapy might also downregulate important enzymatic pathways involved in joint inflammation and destruction [39,59,77,78]. Citations refer to studies conducted in humans [23,35,39,41,69,71,73,76–79], human cell [41] or cell line [36] cultures, rats [24,38,40,42,80], mice [23,32], dogs [76] and two review articles [74,75]. ICAM-1: Intercellular Adhesion Molecule-1; i-NOS: Inducible NO-Synthase; MMP: Metalloproteinase; PGE2: Prostaglandin E2; VAS: Visual Analogic Scale; WBC: Whole-body Cryotherapy. Data taken from the articles cited below and in the figure.

originated from a RCT [66]. Mean pain VAS decreased from 53.15 ± 20.45 (95% CI: 49.55–56.75) at baseline to 35.64 ± 26.69 mm (95% CI: 30.94–40.34) after WBC ($p < 0.000002$).

As regards disease activity, LC significantly reduced DAS28 in 80 RA patients from 3 studies [63,64,70], with 20 patients included in a RCT [70]. Mean DAS28 decreased from 5.45 ± 1.37 (95% CI: 5.14–5.75) at baseline to 4.69 ± 1.16 (95% CI: 4.44–4.95) after LC ($p < 0.0001$), which could suggest a systemic effect of LC that was applied on several joints (4–6) in these patients. WBC also significantly reduced DAS28 in 83 RA patients from 3 studies [66,67,70], including 20 patients originating from a RCT [70]. Mean DAS28 decreased from 4.27 ± 0.83 (95% CI: 4.02–4.52) at baseline to 3.79 ± 0.81 (95% CI: 3.56–4.02) after WBC ($p < 0.002$).

Results: secondary outcomes (tolerance & physiological effects)

As concerns tolerance, no major adverse effect was reported in any of the screened studies. Cryotherapy is overall a well-tolerated treatment [8,9] compared with other adjunct therapies in RA such as corticosteroids and NSAIDs. The contraindications are patients with systemic lupus erythematosus, vasculitis, cryoglobulinemia, cold hypersensitivity, allergy or urticarial, cold-induced bronchospasm, Raynaud's phenomenon, acrocyanosis, sickle cell anemia, skin circulation disorders, paroxysmal cold hemoglobinuria, heart arrhythmia, symptomatic cardiovascular or lung disease, uncontrolled hypertension, advanced diabetes mellitus and cutaneous hypoesthesia. It should be avoided in patients with scleroderma, spinal cord injury or poor circulation (risk of skin lesions such as frostbite, chilblains or necrosis). Beyond a certain application duration threshold (for

Table 3. Local cryotherapy techniques.

	Physical form	Temperature	Pressure	Duration	Skin temperature	Ref.
<i>Local cryotherapy</i>						
Ice bags	Ice cubes, mixture of water and crushed Fee	0°C	Straps for compression	10–30 min 30 min	13–15°C in 15–30 min 1 G°C (minimal value)	[72] [20]
Cold packs prerefrigerated gels	Joint-shaped, flexibility (CryoCuff®; Polar Care®) Gel-filled cold pack (TMP Tiishaus® 12X29 cm	-15°C	+	10–30 min; three-times a day for 7 days 20 min; 5/day 20 min	22–24°C 5, 5°C	[69] [82] [58,59]
Gas (thermal shock)	– Cold air (filtered ambient air: no consumables) Cryo 5®: 40001/min	-30°C -20 to -30°C	0	5 min	9.7°C in 5 min	[19]
				10–30 min; 3/day; 7 days	?	[68]
				3 min	23.1°C after 1 min	[15]
				3 min	6°C	[58]
– Liquid Nitrogen vapors (Medivent®)	-160°C	0	6.5 min	9.8°C (minimal value)	[20]	
			3 min	17.9°C after 1 min	[15]	
– CO ₂ microcrystals (Cryotron®)	-78°C	50 bars (2–75 bars)	45 s–2 min (2/day); flare duration	7.3°C 2°C in 20–30S	[73] [8]	
			90s (3/day)	12°C	[83]	

instance, 20–30 min for cold packs, 2 min for CO₂ cryotherapy at -78°C as indicated in manufacturers' instructions for use), cryotherapy can be painful and proinflammatory. Anyway, specific instructions for use should be read carefully before using any cryotherapy device, especially as concerns maximal recommended application duration. During CO₂ cryotherapy, skin temperature must be kept above 2°C, gas blow must be performed at 10–15 cm from skin surface (4–6 cm for cold air) [15], the application area must be swept and ice crystal formation on skin surface must be avoided (frostbite, chilblain and burn prevention). Cold packs must not be in direct contact with the skin. Cryotherapy can also induce nerve lesions (it must be used with caution in the vicinity of superficial nerves) and slow wound healing.

As for cryotherapy, physiological effects in RA, LC may reduce joint temperature to about 30°C in healthy as well as arthritic human knees for 2 h [19,20].

Studies in animal models and other medical fields suggest that mild hypothermia (with local and/or core body temperatures around 30°C) may inhibit white blood cell infiltrate formation [42], proinflammatory cytokine gene transcription [23,30], enzymatic pathways such as collagenases [41], metalloproteinases [39,40], proangiogenic agents such as VEGF [36]. In RA, cryotherapy might decrease proinflammatory cytokine and proteolytic enzyme levels, but studies are rare. LC significantly decreased serum TNF-α and tended to decrease serum IL-6 levels in 40 RA patients [63]. LC and WBC tended to decrease serum IL-6 levels in 59 RA patients [69]. WBC significantly decreased serum histamine levels in 20 RA patients [71]. In experiments using RA synovial collagenase cultured with human collagen fibrils, the authors showed a four-time decreased collagen lysis at 33 versus 36°C [41]. In arthritic

zymosan-injected rabbits, ice chip application caused a non-significant decrease in cell infiltration and synovial hyperplasia [72]. These results hold strong therapeutic promises in RA. However, studies about cryotherapy's molecular effects in RA are scarce and heterogeneous, so we could not perform any quantitative data analysis.

Discussion

Pooling 6 studies including 257 RA patients, we show that chronic local or WBC (14–20 applications) significantly decreases pain VAS (mm) and DAS28 (within-group effect size).

As concerns control groups, 16 patients were treated with 'drug therapy' and compared with LC-treated patients [64] and 17 patients exposed to magnetic fields were compared with WBC-treated patients [67]. These control groups were poorly described, and the studies were not randomized, so we could not perform any comparison with pooled mean differences in cryotherapy-treated patients nor calculate any between-group effect size. We excluded control groups with heat application that has proinflammatory effects [20]. It is of course difficult to create placebo groups for cryotherapy. All the patients in the selected studies received associated pharmacological treatment. This drug therapy intake (NSAIDs, corticosteroids, DMARDs and biologics) was not precisely described in four out of six studies. However, RA treatment is quite standardized and pharmacological treatment protocols (drugs and doses) remained stable before and throughout the studies, so the variations in pain VAS and DAS28 scores are likely to reflect cryotherapy's effects as an adjunct therapy.

We pooled patients treated with different cryotherapy techniques, because group sizes were not sufficient for separate analyses, and because no significant difference for considered

Table 4. Ice-water and whole-body cryotherapy techniques.

Physical form		Temperature	Pressure	Duration	Skin temperature	Ref.
<i>Ice-water Immersion</i>						
Ice water		0–20°C	+	0–2°C for 20 s (three-times a week for 12 weeks)		[22,45]
<i>Whole-body cryotherapy</i>						
Cryogenic chambers	Dehydrated air (Criostream®)	-60°C to 140°C	0	2–3 min		[84]
	Cold air cooled by liquid nitrogen (Zimmer® KR2005N®)	< (1 or 2 acclimation chambers)		2 min (three-times/week; 12 weeks)	12–16°C (110*0)	[45]
				2 min; three-times a day; 7 days		[68]
		-130°C		3 min/day–10 days	11°C (forearm)	[81]

Data were taken from the cited articles.

endpoints was found between these techniques in studies using parallel treatment arms. Notably, we could not perform any subgroup analysis comparing cold packs (cooling) to gaseous cryostimulation in LC-treated patients due to insufficient sample sizes [63,70]. Cryotherapy protocols were quite heterogeneous (duration, intensity, considered joints, physical agents, temperature, duration and periodicity) as summarized in TABLE 2. The overall quality scores of the selected studies were quite low, but they reflect currently available evidence about cryotherapy. Studies were mainly limited by a lack of randomization and valid control groups. It is obviously difficult to find appropriate placebo groups for cryotherapy. Dropouts and withdrawals were also poorly reported. However, as cryotherapy is a very well-tolerated treatment, and as no major side effect was reported in any of the selected studies, the amount of missing data is likely to be very low.

Importantly, despite various cryotherapy modalities and potential confounders, the six selected studies showed very homogeneous results (FIGURE 2).

Unlike Welsh's Cochrane meta-analysis, we excluded articles dealing with postoperative cryotherapy, as surgery by itself might interfere with joint inflammation (TABLES 1 & 2).

Expert commentary & five-year view

Clinical practice and physiological rationale strongly suggest a potential interest of cryotherapy as an adjunct therapy in rheumatic inflammatory diseases.

Cryotherapy applied locally on an inflamed joint allows to reach a 30°C intra-articular temperature plateau, with a possibly 2–3 h remanent local hypothermia [19,20]. Studies conducted in other medical fields suggest that it might therefore downregulate such proangiogenic and proinflammatory pathways as VEGF, proinflammatory cytokines and enzymatic activities involved in synovial microvascular hyperplasia, joint inflammation and destruction (FIGURE 4).

Synovial and systemic endothelial dysfunction in RA induce pain, joint inflammation and destruction and increased cardiovascular morbidity and mortality. Cryotherapy, by upregulating

noradrenalin pathway, could downregulate IL-6 and i-NOS pathways, which are known to be involved in endothelial dysfunction an inflammation [3]. Further studies are needed to establish these molecular effects of cryotherapy specifically in RA. Studies in animal models such as collagen-induced arthritis or adjuvant-induced arthritis will certainly lead to a better description of cryotherapy effects on these promising molecular targets in the field of rheumatology, as already the case in neurology for instance, with well-known therapeutic effects of mild hypothermia after brain ischemia [23,24].

We could show a significant decrease in pain VAS (mm) and DAS28 in RA patients after chronic LC as well as WBC (within-group effect size). This result was remarkably constant among the six selected studies (FIGURE 2). However, we could not calculate any between-group effects size because available control groups were small and methodologically unsatisfying. Randomized trials with valid control groups and stronger methodology are required in order to measure this effect size more accurately.

In light of the results of this systematic review and considering a solid biological rationale, cryotherapy deserves to be evaluated as a full therapeutic option in patients without any corticosteroid, NSAID, DMARD, biologic or physical therapy.

Short-term cryotherapy effects should also be addressed. LC applied once to an inflamed joint has been shown to decrease synovial power Doppler hypersignal in RA, which is a good reflect of synovial neoangiogenesis and inflammation [60,61]. Our team is currently studying the effects of two local cryotherapy applications on synovial power Doppler hypersignal as well as synovial fluid cytokine and VEGF levels in arthritic patients.

In order to conduct these important studies, a better standardization of cryotherapy techniques will be required (TABLE 3). Optimal cryotherapy protocols need to be precisely defined (physical agent, temperature and duration periodicity). It is notably important to determine, for each cryotherapy technique, the therapeutic range and the cold intensity threshold beyond which it may become proinflammatory [10,20,59,69]. Gaseous LC might induce a more pronounced and acute decrease in tissue temperature (thermal shock) and cold packs a deeper

and more prolonged cooling. WBC is still expensive, but new techniques using filtered and cooled ambient air without any consumable will probably be cheaper and require less room space, allowing a more widespread use.

These studies will help to define cryotherapy's role in treatment strategies in RA and other joint inflammatory diseases, most probably as an adjunct therapy to DMARDs and targeted biologic treatments, along with corticosteroids and NSAIDs. Corticosteroid and NSAID toxicity represent a major public health concern, with numerous, well-known, side effects and complications. Cryotherapy used as an adjuvant therapy and applied using standardized and optimized protocols could help to spare corticosteroid and NSAID doses in these patients, and subsequently decrease cardiovascular, infectious, gastrointestinal morbidity and mortality. This treatment option may be of special interest in an increasing number of patients with NSAID and/or corticosteroid contraindications (cardiovascular diseases,

diabetes, kidney deficiency, etc). This dose-sparing effect should also be addressed and measured specifically in randomized controlled trials.

Local cryotherapy is a cheap and very well-tolerated therapeutic option, which can be easily performed at patient's home. In the future, it could contribute to reduce the economic burden and iatrogenicity related to the treatment of arthritic patients, especially for the elderly.

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Key issues

- Molecular pathways targeted by cryotherapy (proinflammatory cytokines, VEGF, cartilage-degrading enzymes) suggest interesting anti-inflammatory properties in rheumatic inflammatory diseases, which should be further investigated.
- Cryotherapy could be an interesting adjunct therapy in these diseases with a better safety profile as compared with corticosteroids and NSAIDs.
- By pooling six studies, we show that chronic local cryotherapy and WBC significantly reduce pain visual analogic scale and 28-joint disease activity score in rheumatoid arthritis (within-group effect size). However, methodological issues and a lack of control groups prevent from calculating any between-group effect size.

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<Article type:->Review

<LRH>-Guillot, Tordi, Mourot et al.

<RRH>-Cryotherapy in inflammatory rheumatic diseases

Cryotherapy in inflammatory rheumatic diseases: a systematic review

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Abstract

The aim of this article was to review current evidence about cryotherapy in inflammatory rheumatic diseases (therapeutic and biological effects).

For therapeutic effects, we performed a systematic review (~~Pubmed~~[PubMed](#), EMBASE, Cochrane Library, LILACS databases, unpublished data) and selected studies including non-operated and non-infected arthritic patients treated with local cryotherapy (~~LC~~) or whole-body cryotherapy (~~WBC~~).

By pooling ~~6~~[six](#) studies including 257 rheumatoid arthritis (RA) patients, we showed a significant decrease in pain ~~visual analogic scale~~[VAS](#) (mm) and ~~28-joint- disease activity score~~[disease activity \(DAS28\)](#) after chronic cryotherapy in RA patients.

For molecular pathways, ~~local cryotherapy~~[LC](#) induces an intra-joint temperature decrease, which might down-regulate several mediators involved in joint inflammation and destruction (cytokines, cartilage-degrading enzymes, pro-angiogenic factors), but studies in RA are rare.

Cryotherapy should be included in RA therapeutic strategies as an adjunct therapy, with potential corticosteroid and non-steroidal anti-inflammatory drug dose-sparing effects. However, techniques and protocols should be more precisely defined in randomized-controlled trials with stronger methodology.

KEYWORDS: ~~c~~[Cryotherapy](#); ~~c~~[cytokines](#); ~~c~~[DAS28](#); ~~c~~[enzymes](#); pain VAS; ~~DAS28~~; ~~cytokines~~; ~~enzymes~~

Inflammatory joint diseases, such as rheumatoid arthritis (RA), represent a major public health concern, with both synovial inflammation causing joint destruction, pain and disability [1] and systemic inflammation thought to increase cardiovascular risk and mortality [2,3]. Recently, progress in immunology provided new therapeutic targets and new drugs such as biologic agents allowing to achieve clinical remission and prevent joint destruction [4,5]. These treatments, however, remain expensive, with rare but potentially life-threatening side-effects such as infections [6]. Long-term nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids also have a well-known toxicity [7]. So the development of adjunct therapies in order to spare biologic and corticosteroid doses is a key focus in these diseases.

Cryotherapy is used empirically in a wide range of rheumatic diseases as a symptomatic treatment, with well-known analgesic, antiphlogistic, myorelaxing, vasoconstrictive, anti-inflammatory, enzyme-blocking, and anti-oxidative effects [8–10]. It can be used not only in inflammatory joint diseases (such as crystal-induced arthritides, spondyloarthritides, and rheumatoid arthritis RA [10]), but also in such painful rheumatic condition as osteoarthritis [8,9], fibromyalgia [11], shoulder capsulitis [12], and muscle damage [13]. Whole-body cryotherapy (WBC) also showed effects on bone biomarkers [14]. This adjunct treatment is cheap (at least for local cryotherapy [LC]) and generally well-tolerated [15,16]. Technical modalities (local/general application, duration, number of sessions [17], physicalland physical form) are very diverse and lack standardization [18]. This widespread use contrasts with a poor level of evidence [18]. Cryotherapy has been shown to decrease intra-articular temperature (T°C) in human knees to 30°C [19,20]. This intra-joint temperature is in the same range as therapeutic mild hypothermia used in several other medical fields. Mild

hypothermia (28–34°C) has shown anti-inflammatory effects in healthy subjects [21,22] and in very diverse pathologies such as cerebral ischemia in humans [23] and murine models [23,24], traumatic tissue injury in murine models [25,26] and humans [27], haemorrhagic shock in rats [28], cardiac arrest in humans [29], coma in pigs [30], coronary artery or cardiopulmonary bypass in humans [31], aortic ischemia/reperfusion in mice [32], mechanical ventilation in rats [33,34], post-exercise hyperthermia in humans [35], age-related macular degeneration in culture experiments using a retinal cell line [36], and pancreatitis in rats [37]. These studies showed potential effects on important molecular/cellular mechanisms involved in synovial inflammation and joint destruction such as pro-inflammatory cytokines [21,25,38], VEGF [36], enzymatic pathways (metalloproteinases [39,40], collagenase [41]), adhesion molecules (ICAM-1) and white blood cell infiltrate formation in rats [42] and humans [43], oxidative stress in rats [24] and humans [44], norepinephrine in humans [24,45,46]. This suggests potential therapeutic effects in inflammatory rheumatic diseases such as RA, as some of these molecular pathways are known to be related to pain, disease activity scores including ~~28-joint-disease activity score (DAS28)~~, biological inflammation and radiologic joint damage.

The aim of this article ~~study~~ is to review data and evidence concerning cryotherapy's effects in inflammatory rheumatic diseases.

First, we performed a systematic review of the literature about cryotherapy's therapeutic effects in rheumatic inflammatory joint diseases. The primary endpoints were pain assessed by visual analogic scale (VAS) and ~~28-joint-disease activity score (DAS28)~~. The secondary endpoints were tolerance and molecular anti-inflammatory effects of cryotherapy in these diseases.

<H1> Cryotherapy effects on pain ~~and~~ & disease activity in rheumatoid arthritis: systematic review

<H2> Methods

We followed the PRISMA statement checklist for meta-analysis and systematic review quality criteria [47].

<H3> Searching

We used PubMed~~pubmed~~, EMBASE, LILACS and Cochrane library databases. Keywords “cryotherapy”, “cryotherapy arthritis”, “cryotherapy inflammation”, “cold”, “cold arthritis”, “cryostimulation”, and “WBC” were used alone and in combination. We considered articles with available abstracts in English, German, Spanish, French language and in referenced journals from their inception to March 2013. We also manually screened references cited in the selected articles, considered abstracts from rheumatology congresses (ACR, EULAR since 2001).

As concerns unpublished data, we considered the International Standard Randomised Controlled Trial Number Register [101]website (<http://www.controlled-trials.com/isrctn>), The National Institute of Health [102]website (<http://www.clinicaltrials.gov>), and the WHO website (<http://www.who.int/ictrp/search/en>)[103]. The screening was performed by two independent reviewers with discussion when needed in order to reach consensus.

<H3> Eligibility ~~and~~ & study selection

Selection criteria for cryotherapy therapeutic effect evaluation were studies including inflammatory rheumatic disease patients (i.e., RA, microcrystals, peripheral spondyloarthritides) treated with LC or WBC, with endpoints evaluating pain and joint

disease activity (pain VAS, ESR, CRP, DAS28, and Doppler activity). Articles about post-operative joint cryotherapy and infectious diseases were excluded. We selected original articles, abstracts, reviews, and meta-analyses.

Duplicates were removed.

Quality assessment

For cryotherapy therapeutic effects, we analyzed technical cryotherapy modalities in detail (physical form and device, duration, skin or joint temperature).

The methodology was also evaluated: study population, randomization, blinding, control groups (other therapeutic modalities such as pharmacological treatments, physical therapy, different cryotherapy techniques or placebo groups), withdrawal and dropout reporting, as well as potential confounders (corticosteroids, NSAIDs, biologics, physical exercise, kinesitherapy, BMI, considered joint) when assessed in the studies. Data extraction was performed by two independent reviewers.

Therefore, we assessed study quality based on specific validated scores depending on the study design. A JADAD 5-point scale was used for randomized controlled trials [48]. For non-randomized studies, we used the Newcastle-Ottawa Scale (NOS) system (0-9) [1204]. Furthermore, a JADAD 11-point scale [48] was applied to all the selected studies whatever their design in order to compare them globally and to provide a general qualitative overview. Studies that scored 6 or higher using JADAD 11-point scale (3/5 with JADAD-5 and 5/9 with NOS) were considered to be of higher quality. This quality assessment was also performed by two independent reviewers.

Quantitative data synthesis

Most outcomes were continuous in nature (pain VAS, DAS28). When pooling data from different trials was possible, the principal measures of effect were means \pm SD (weighted

mean differences before/after cryotherapy or relative to control groups when possible). Heterogeneity was assessed graphically with 95% confidence intervals and statistically tested using Fisher's variance comparison tests. Heterogeneity threshold was calculated for each primary outcome ($F_{\text{test}} \geq 2.73$ or greater was significantly heterogeneous for pain VAS in patients treated with LC, $F_{\text{test}} = 2.7$ for pain VAS in WBC-treated patients, $F_{\text{test}} = 2.73$ for DAS28 in LC-treated patients and $F_{\text{test}} = 3.12$ in WBC-treated patients). We used a fixed effect model. Pooled means \pm SD were compared before/after cryotherapy (within-group effect size; paired t tests; α risk 5%) and the mean differences before/after treatment were compared between ~~eryotherapy~~~~cryotherapy~~-treated patients and control groups when available (between-group effect size; unpaired t tests; $\alpha = 5\%$; variance comparison using Fisher's test).

Data were analyzed using Statview[®] (SAS Institute Inc. Version 5.0) device. There were no a-priori sensitivity and subgroup analyses. We also considered unpublished data in order to minimize publication bias.

<H12>Results

<H23>Flowchart

The Flowchart is shown in **FIGURE 1**.

<H24>Screening results

~~PubMed~~~~Pubmed~~ search (in English with abstracts), displayed 11,344 citations for “cryotherapy” keyword on ~~the 4th,~~ March, ~~the 4th,~~ 2013. “cryotherapy arthritis”, “cryotherapy inflammation”, “WBC”, “cold”, “cold arthritis”, “cold inflammation”,

“cryostimulation” showed 67, 346, 331, 108, 707, 733, 4,355 and 31 results respectively.

EMBASE database displayed 23,228 citations for “cryotherapy” keyword, 22,632 results for “cold”, 1,784 results for “cold arthritis”, 445 results for “cryotherapy arthritis”, 95 results for “WBC”, 17,445 results for “cold inflammation”, 3,402 results for “cryotherapy inflammation” and 32 results for “cryostimulation”.

The LILACS database displayed 230 results for “cryotherapy” keyword, 1 for “cryotherapy arthritis”, 7 for “cryotherapy inflammation”, 52 for “WBC”, 1,479 results for “cold” keyword, 6 for “cold arthritis”, 19 for “cold inflammation” and 34 results for “cryostimulation”.

In EULAR congress abstracts, we found 17 and 132 abstracts related to “cryotherapy” and “cold” respectively, since 2001 on EULAR website (ACR website: 21 abstracts related to “cold” in 2006–2011, none related to “cryotherapy”).

The International Standard Randomised Controlled Trial Number Register website displayed 15 results for “cryotherapy” keyword and 99 results for “cold” keyword. The National Institutes of Health website displayed 188 results for “cryotherapy” keyword (4 for “cryotherapy arthritis”, 5 for “whole WBC”), and 645 results for “cold” keyword (16 for “cold arthritis”). The WHO website displayed 1,830 results for “cryotherapy” keyword (56 for “cryotherapy arthritis”, 22 for “whole body cryotherapy”), and 3,020 results for “cold” keyword (949 for “cold arthritis”).

<H24> Article selection process

First, articles were excluded on the basis of title and abstract: numerous records dealing with completely different scientific or medical fields such as dermatology, gynaecology, urology, oncology, ophthalmology, infectious or lung diseases, chemistry, etc., very low temperature-cell lysing-cryotherapy, local cryotherapy not applied to joints (spine, etc.).

After duplicate removal, we found 511 records potentially dealing with cryotherapy in all

types of joint diseases according to the titles and abstracts. After applying eligibility criteria, we screened 146 potentially relevant references in the field of therapeutic cryotherapy in inflammatory joint diseases.

Then, we excluded 124 articles for the following reasons: duplicates, articles related to postoperative cryotherapy, non-inflammatory diseases, non-rheumatologic diseases, with inadequate outcomes or endpoints, lacking accuracy in cryotherapy technical description or numerical data reporting, with full text not available and insufficient data in the abstract.

A Cochrane meta-analysis including ~~5~~five RCT about cryotherapy in RA [49–53] was published in 2001 and updated in 2011 [18]. None of these articles ~~was~~ere appropriate to be used in our meta-analysis, as summarized in **TABLE 1**. Two of the studies were performed in operated patients [49,50]. The outcomes [46,47] or outcome measures were inappropriate to our analysis [49,52,53]. Cold application was also probably insufficient in intensity [49,50], in duration [51] or periodicity [51–53]. Furthermore, hot packs used in ~~3~~three of the studies [50,52,53] could have pro-inflammatory properties [20] and therefore do not seem to be relevant treatments for control group.

The remaining articles (22 articles including 8 RCTs for therapeutic effects) were assessed for further evaluation on the basis of full-text article when available. Nine articles were further excluded [9,10,51–58].

The 13 remaining studies were potentially appropriate to be included in a meta-analysis.

There were ~~5~~five RCTs, ~~2~~two non-randomized controlled studies, ~~3~~three studies comparing several cryotherapy techniques in parallel treatment arms, ~~and~~ ~~3~~three non-controlled studies. Seven articles dealt with local cryotherapy [8,59–64], ~~4~~four with WBC [65–68], ~~and~~ ~~2~~two with both **(FIGURE 1)** [69,70] ~~(FIGURE 1)~~. —————

~~—~~ <H24> Characteristics of the studies selected for quantitative analysis (cryotherapy therapeutic effects)

Study characteristics and quality assessment results are summarized in **TABLE 2**.

The endpoints were compared before and after cryotherapy.

Cryotherapy modalities (technique, temperature, duration, ~~—~~ and periodicity) were heterogeneous. The main potential confounders were assessed when possible: Corticosteroid, NSAID, disease activity-modifying drug (DMARD), biologic intake, kinesitherapy, physical exercise, room temperature. No serious adverse event was reported in any of the studies.

We could only perform a pooled quantitative analysis for ~~2~~ two endpoints: pain VAS and DAS28 in RA patients. ~~On~~ For that purpose, six studies were included in the quantitative data analysis (**TABLE 2**) [64,65,67–69,71] ~~(TABLE 2)~~. Reasons for excluding the ~~7~~ seven other studies [8,59–62,65,69] were: ~~1~~ one duplicate [69], impossibility to combine data for power Doppler hypersignal endpoint due to different evaluation scores [59–61], as for gout patients: too different designs [8,62], one study mixed patients suffering from heterogeneous rheumatic diseases (inflammatory as well as non-inflammatory) [65]. Straub and Hirvonen's studies were considered as duplicates as they were performed, at least partly, in the same patient cohort [69,70].

For WBC, we only considered ~~—~~ 110°C-treated patients in Hirvonen's study [70].

~~—~~ <H23> Results: study quality assessment

Six studies including 257 RA patients were appropriate to be included in quantitative data

synthesis. There was one RCT with 40 patients meeting the inclusion criteria [70], ~~2~~two controlled trials [63,64], ~~2~~two studies comparing parallel cryotherapy treatment groups [67,68] and one non-controlled study [66].

The RCT scored ~~2~~out of 5 (JADAD5 score) [70]. As for the five non-controlled studies, the mean NOS quality score was ~~5~~+/- ± 1.2 [63,64,66–68]. Overall, the mean JADAD11 score for the ~~6~~six selected studies was ~~4.8~~+/- ± 1.9. The quality scores for each study are displayed in **TABLE 2**.

~~H23~~Results: heterogeneity assessment

We could only perform quantitative analysis for ~~2~~two endpoints: pain VAS (mm) and DAS28 in RA patients after chronic application (~~7~~to ~~15~~ days) (**FIGURES 2 & 3**) [63,64,66–68,70]. (~~FIGURES 2 and 3~~).

There was no significant heterogeneity between studies for pain VAS and DAS28 in LC ~~nor~~ WBC-treated patients, as shown in ~~FIGURES 2 and & 3~~, displaying means and 95% confidence intervals. Fisher's tests showed $F_0 = 1.48$; p: [0.2-; 0.3] for pain VAS after local cryotherapy (**FIGURE 2A**), $F_0 = 1.44$; p: [0.2-; 0.3] for DAS28 after local cryotherapy (**FIGURE 2B**), $F_0 = 1.07$; p: [0.3-; 0.5] for pain VAS after WBC (**FIGURE 3A**), $F_0 = 0.47$; p: [0.5-; 0.9] for DAS28 after WBC (**FIGURE 3B**).

Paired t-tests were used to assess pain VAS and DAS28 evolution after cryotherapy.

As concerns local cryotherapy, the mean number of cold applications was 17.1 (ranging from 10 to 20), mean temperature of ~~-70.3~~-70.3°C (~~-30~~ to ~~-160~~) applied for 11.5 min (~~3~~to ~~30~~).

As for WBC and pain VAS (mm), the mean number of applications was 20.2 (~~8~~to ~~30~~) at a mean temperature of ~~-126.5~~-126.5°C (~~-110~~ to ~~-160~~) during 3.2 min (~~2~~to ~~5~~).

Considering WBC and DAS28, the mean number of applications was 14.4 (8-~~to~~-20) at a temperature of ~~-~~110°C during 2.8 min (2-~~to~~-3).

<H3>Results: primary outcomes (pain VAS ~~and~~ & DAS28)

As concerns pain, LC (cold packs, cold air, liquid nitrogen applied on 1-5 joints) significantly reduced pain VAS (mm) in 80 RA patients originating from ~~3~~-three studies [63,64,70], ~~with~~ (20 of these patients were included in a RCT [70]). Mean pain VAS decreased from 59.10 \pm 25.86 (95% CI: {42.17-75.63}) to 33.55 \pm 20.77 (95% CI: {26.07-56.33}) after LC ($p < 0.000002$). WBC also significantly decreased pain VAS in 124 RA patients from 4 studies [66,~~67~~,68,70] (20 patients originated from a RCT [66]). Mean pain VAS decreased from 53.15 \pm 20.45 (95% CI: {49.55-56.75}) at baseline to 35.64 \pm 26.69 mm ~~after WBC~~ (95% CI: {30.94-40.34}) after WBC ($p < 0.000002$).

As regards disease activity, LC significantly reduced DAS28 in 80 RA patients from 3 studies [63,64,70], with 20 patients included in a RCT [70]. Mean DAS28 decreased from 5.45 \pm 1.37 (95% CI: {5.14-5.75}) at baseline to 4.69 \pm 1.16 (95% CI: {4.44-4.95}) after LC ($p < 0.0001$), which could suggest a systemic effect of LC; ~~which~~-that was applied on several joints (4-~~to~~-6) in these patients. WBC also significantly reduced DAS28 in 83 RA patients from 3 studies [66,67,70], including 20 patients originating from a RCT [70]. Mean DAS28 decreased from 4.27 \pm 0.83 (95% CI: {4.02-4.52}) at baseline to 3.79 \pm 0.81 (95% CI: {3.56-4.02}) after WBC ($p < 0.002$).

<H2>Results: secondary outcomes (tolerance and physiological effects)

As concerns tolerance, no major adverse effect was reported in any of the screened studies.

Cryotherapy is overall a well-tolerated treatment [8,9] as compared to with other adjunct therapies in RA such as corticosteroids and NSAIDs. The contra-indications are patients with systemic lupus erythematosus, vasculitides, cryoglobulinemia, cold hypersensitivity, allergy or urticarial, cold-induced bronchospasm, Raynaud's phenomenon, acrocyanosis, sickle-cell anemia, skin circulation disorders, paroxysmal cold hemoglobinuria, heart arrhythmia, symptomatic cardiovascular or lung disease, uncontrolled hypertension, advanced diabetes mellitus, and cutaneous hypoesthesia. It should be avoided in patients with scleroderma, spinal cord injury or poor circulation (risk of skin lesions such as frostbite, chilblains or necrosis). Beyond a certain application duration threshold (For for instance, 20–30 minutes for cold packs, 2 minutes for CO₂ cryotherapy at –78°C as indicated in manufacturers' instructions for use), cryotherapy can be painful and pro-inflammatory. Anyway, specific instructions for use should be read carefully before using any cryotherapy device, especially as concerns maximal recommended application duration. During CO₂ cryotherapy, skin temperature must be kept above 2°C, gas blow must be performed at 10–15 cm from skin surface (4–6 cm for cold air) [15], the application area must be swept and ice crystal formation on skin surface must be avoided (frostbite, chilblain and burn prevention). Cold packs must not be in direct contact with the skin. Cryotherapy can also induce nerve lesions (it must be used with caution in the vicinity of superficial nerves) and slowed wound healing.

As for cryotherapy, physiological effects in RA, LC may reduce joint temperature to about 30°C in healthy as well as arthritic human knees for 2 hours [19,20].

Studies in animal models and other medical fields suggest that mild hypothermia (with local and/or core body temperatures around 30°C) may inhibit white blood cell infiltrate formation [42], pro-inflammatory cytokine gene transcription [23,30], enzymatic pathways such as collagenases [41], metalloproteinases [39,40], pro-angiogenic agents such as VEGF [36].

In RA, cryotherapy might decrease pro-inflammatory cytokine and proteolytic enzyme levels, but studies are rare. LC significantly decreased serum TNF- α and tended to decrease serum IL-6 levels in 40 RA patients [63]. LC and WBC tended to decrease serum IL-6 levels in 59 RA patients [69]. WBC significantly decreased serum histamine levels in 20 RA patients [71]. In experiments using RA synovial collagenase cultured with human collagen fibrils, the authors showed a 4-four-time decreased collagen lysis at 33°C versus 36°C [41]. In arthritic zymosan-injected rabbits, ice chip application caused a non-significant decrease in cell infiltration and synovial hyperplasia [72].

These results hold strong therapeutic promises in RA. However, studies about cryotherapy's molecular effects in RA are scarce and heterogeneous, so we could not perform any quantitative data analysis.

<H1>Discussion

Pooling 6 studies including 257 RA patients, we show that chronic local or WBC (14–20 applications) significantly decreases pain VAS (mm) and DAS28 (within-group effect-size).

As concerns control groups, 16 patients were treated with “drug therapy” and compared ~~to~~ with LC-treated patients [64] and 17 patients exposed to magnetic fields were compared ~~to~~ with WBC-treated patients [67]. These control groups were poorly described, and the studies were not randomized, so we could n't-not perform any comparison with pooled mean differences in cryotherapy-treated patients nor calculate any between-group effect-size. We excluded control groups with heat application, ~~which-that~~ has pro-inflammatory effects [20].

It is of course difficult to create placebo groups for cryotherapy.

All the patients in the selected studies received associated pharmacological treatment. This drug therapy intake (NSAIDs, corticosteroids, DMARDs, and biologics) was not precisely described in 4four/ out of 6-six studies. However, RA treatment is quite standardized, and pharmacological treatment protocols (drugs, and doses) remained stable before and throughout the studies, so the variations in pain VAS and DAS28 scores are likely to reflect cryotherapy's effects as an adjunct therapy.

We pooled patients treated with different cryotherapy techniques, because group sizes were not sufficient for separate analyzes, and because no significant difference for considered endpoints was found between these techniques in studies using parallel treatment arms.

Notably, we could not perform any subgroup analysis comparing cold packs (cooling) to gaseous cryostimulation in LC-treated patients due to insufficient sample sizes [63,70].

Cryotherapy protocols were quite heterogeneous (duration, intensity, considered joints, physical agents, temperature, duration, and periodicity) as summarized in **TABLE 2**. The overall quality scores of the selected studies were quite low, but they reflect currently available evidence about cryotherapy. Studies were mainly limited by a lack of randomization and valid control groups. It is obviously difficult to find appropriate placebo groups for cryotherapy. Dropouts and withdrawals were also poorly reported. However, as cryotherapy is a very well-tolerated treatment, and as no major side effect was reported in any of the selected studies, the amount of missing data is likely to be very low.

Importantly, despite various cryotherapy modalities and potential confounders, the 6-six selected studies showed very homogeneous results (**FIGURE 2**).

Unlike Welsh's Cochrane meta-analysis, we excluded articles dealing with post-operative cryotherapy, as surgery by itself might interfere with joint inflammation (**TABLES 1 and & 2**).

<H1>Expert commentary ~~and~~ & five-year view

Clinical practice and physiological rationale strongly suggest a potential interest of cryotherapy as an adjunct therapy in rheumatic inflammatory diseases.

Cryotherapy applied locally on an inflamed joint allows to reach a 30^oC intra-articular temperature plateau, with a possibly 2–3 hour remanent local hypothermia [19,20]. Studies conducted in other medical fields suggest that it might therefore down-regulate such pro-angiogenic and pro-inflammatory pathways as VEGF, pro-inflammatory cytokines and enzymatic activities involved in synovial microvascular hyperplasia, joint inflammation and destruction (**FIGURE 4**).

Synovial and systemic endothelial dysfunction in RA induce pain, joint inflammation and destruction and increased cardiovascular morbidity and mortality. Cryotherapy, by up-regulating noradrenalin pathway, could down-regulate IL-6 and i-NOS pathways, which are known to be involved in endothelial dysfunction an inflammation [3]. Further studies are needed to establish these molecular effects of cryotherapy specifically in RA. Studies in animal models such as collagen-induced arthritis or adjuvant--induced arthritis will certainly lead to a better description of cryotherapy effects on these promising molecular targets in the field of rheumatology, as already the case in neurology for instance, with well-known therapeutic effects of mild hypothermia after brain ischemia [23,24].

We could show a significant decrease in pain VAS (mm) and DAS28 in RA patients after chronic LC as well as WBC (within-group effect-size). This result was remarkably constant among the ~~6~~ six selected studies (**FIGURE 2**). However, we could ~~not~~ not calculate any between-group effect-size because available control groups were small and methodologically unsatisfying. Randomized trials with valid control groups and stronger methodology are required in order to measure this effect size more accurately.

In light of the results of this systematic review and considering a solid biological rationale, cryotherapy deserves to be evaluated as a full therapeutic option, in patients without any corticosteroid, NSAID, DMARD, biologic ~~or~~ or physical therapy.

Short-term cryotherapy effects should also be addressed. LC applied once to an inflamed joint has been shown to decrease synovial power-Doppler hypersignal in RA, which is a good reflect of synovial neoangiogenesis and inflammation [60,61]. Our team is currently studying the effects of 2-two local cryotherapy applications on synovial power Doppler hypersignal as well as synovial fluid cytokine and VEGF levels in arthritic patients.

In order to conduct these important studies, a better standardization of cryotherapy techniques will be required (**TABLE 3**). Optimal cryotherapy protocols need to be precisely defined (physical agent, temperature, and duration periodicity). It is notably important to determine, for each cryotherapy technique, the therapeutic range and the cold intensity threshold beyond which it may become pro-inflammatory [10,20,59,69]. Gaseous LC might induce a more pronounced and acute decrease in tissue temperature (thermal shock), and cold packs a deeper and more prolonged cooling. WBC is still expensive, but new techniques using filtered and cooled ambient air without any consumable will probably be cheaper and require less room space, allowing a more widespread use.

These studies will help to define cryotherapy's role in treatment strategies in RA and other joint inflammatory diseases, most probably as an adjunct therapy to DMARDs and targeted biologic treatments, along with corticosteroids and NSAIDs. Corticosteroid and NSAID toxicity represents a major public health concern, with numerous, well-known, side-effects and complications. Cryotherapy used as an adjuvant therapy and applied using standardized and optimized protocols could help to spare corticosteroid and NSAID doses in these patients, and subsequently decrease cardiovascular, infectious, gastrointestinal morbidity and mortality. This treatment option may be of special interest in an increasing number of patients with

NSAID and/or corticosteroid contra-indications (cardiovascular diseases, diabetes, kidney deficiency, ~~etc.~~). This dose-sparing effect should also be addressed and measured specifically in randomized controlled trials.

Local cryotherapy is a cheap and very ~~well-well-~~tolerated therapeutic option, which can be easily performed at patient's home. In the future, it could contribute to reduce the economic burden and iatrogenicity related to the treatment of arthritic patients, especially for the elderly.

<H1> Key issues

- Molecular pathways targeted by cryotherapy (pro-inflammatory cytokines, ~~V~~VEGF, cartilage-degrading enzymes) suggest interesting anti-inflammatory properties in rheumatic inflammatory diseases, which should be further investigated.
- Cryotherapy could be an interesting adjunct therapy in these diseases with a better safety profile as compared ~~to~~ with corticosteroids and NSAIDs.
- By pooling ~~6~~ six studies, we show that chronic local cryotherapy ~~LC~~ and ~~WBC~~ WBC significantly reduce pain visual analogic scale ~~VAS~~ and 28-joint- disease activity score ~~DAS28~~ in rheumatoid arthritis ~~RA~~ (within-group effect-size). However, methodological issues and a lack of control groups prevent from calculating any between-group effect size.

<H1> Financial ~~and~~ & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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Figure and table legends

TABLE 1. Cochrane meta-analysis [18]: review of the 5-five Rrandomized controlled trialRCTs about cryotherapy.

<u>Pathology</u>	<u>Joint</u>	<u>Endpoints</u>	<u>Postoperative cryotherapy (yes/no)</u>	<u>JADAD score (/5)</u>	<u>Cryotherapy modality</u>	<u>Control group</u>
<u>24 RA (ARA criteria)</u>	<u>Knees</u>	<u>-Joint circumference</u> <u>-Infrared</u>	<u>No</u>	<u>2/5</u> <u>R1B0W1</u>	<u>Crushed ice in damp towels (10</u>	<u>Controlateral joint (no</u>

			<u>thermography</u>			<u>min daily for 10 days)</u>	<u>cryotherapy)</u>
<u>5 RA; 83 OA</u>		<u>Knees</u>	<u>-Pain (PCA use)</u>	<u>Yes</u>	<u>3/5 R2B0W1</u>	<u>Thermal pad (50°F vs 60°F vs 70°F)-; duration? periodicity?</u>	<u>None</u>
<u>14 chronic (definite or classic RA)</u>	<u>RA or</u>	<u>20 knees</u>	<u>-Pain (none = 0 to 5 = severe) assessed by 2two observers at the same time</u> <u>-Stiffness, range of movement, knee circumference, skin temperature, patient preference</u>	<u>No</u>	<u>1/5 R1B0W0</u>	<u>Ice packs in damp towels (20 min, once a day for 10 days)</u>	<u>Hot pack (cross-over)</u>
<u>Patients hospitalized for surgical procedures to the hand</u>		<u>30 hands</u>	<u>-EEdema evolution over preoperative volume</u>	<u>Yes</u>	<u>2/5 (R1B0W1)</u>	<u>Cold water immersion (10°C for 4 min; twice a day for 1 day)</u>	<u>Hot packs (n = 15)</u>
<u>18 Recent (<5 years)</u>	<u>RA</u>	<u>Shoulders</u>	<u>-Pain (Mc Gill questionnaire)</u> <u>-Range of movement</u>	<u>No</u>	<u>1/5 (R1B0W0)</u>	<u>Ice (20 min) + exercises program</u>	<u>Hot pack (n = 9)</u>

~~(Data taken from the articles cited in this table)~~

This meta-analysis performed in 2001 and updated in 2011 mixed studies with cold or heat application. It showed no significant effect on pain (primary endpoint), joint swelling, medication intake, range of motion, grip strength or hand function. No harmful side effect was reported [18].

The ~~5~~five RCTs about cryotherapy had limitations: the studies showed a great heterogeneity as concerns cryotherapy methods, treated joints, outcomes, associated medications and physical exercise. The control groups were: hot packs in ~~3~~three studies and ~~controlateral~~contralateral joint in one study. Heat application does not seem to be an appropriate control nor treatment group because it could increase joint inflammation and collagenase activity [20]. Cold exposure was probably insufficient in intensity and duration in some of the studies ~~as compared to~~with more recent studies.

ARA: American Rheumatism Association; B: Blinding; n: number of patients; OA: Osteoarthritis; PCA: Patient-controlled Analgesia; RCT: Randomized-controlled Trial;

R: Randomization; RA: Rheumatoid Arthritis; B: Blinding; W: Withdrawals (JADAD score).

Data taken from the articles cited in this table.

⋮

ARA: American Rheumatism Association;

RA: Rheumatoid Arthritis;

OA: Osteoarthritis;

PCA: Patient-controlled Analgesia;

n: number of patients

TABLE 2. Therapeutic effects of cryotherapy: articles included in the meta-analysis (n = 6).

<u>Pathology / joints (n)</u>	<u>LC--WBC (n)</u>	<u>Cryotherapy modalities</u>	<u>Control group (n)</u>	<u>Relevant endpoints (for meta-analysis) and evaluation times</u>	<u>JADAD 5/NOS JADAD1</u>	<u>Bias/-confounders</u>	<u>Ref.</u>
<u>RA (60 patients)</u>	<u>-LC (n = 20)</u> <u>OR</u> <u>-WBC (-60°C; n = 20)</u> <u>-WBC (-110°C; n = 20)</u>	<u>-Cold packs or cold air on 5 joints (-30°C; 10-30 or 1-5 min)</u> <u>OR</u> <u>-WBC (-60°C OR -110°C; duration?)</u> <u>→three-times a day; 7 days (20 applications)</u>	<u>None</u>	<u>-Pain VAS</u> <u>-DAS28</u> <u>-ESR</u> <u>=</u> <u>CRP →Before; Day 7</u> <u>'after the last cryotherapy'</u> <u>N = 20; 17; 17</u>	<u>R1B0W1</u> <u>8/11</u>	<u>-Associated kinesitherapy</u> <u>-Corticosteroids (10/20; 14/20; 9/20); median dose 5 mg/day [2,5-15]</u> <u>-NSAIDs: 16/20; 17/20; 18/20</u> <u>-DMARDs: 10/20; 9/20; 9/20</u> <u>-“cytostatics”:</u> <u>11/20; 14/20; 12/20</u> <u>-No change in pharmacological treatment.</u> <u>-BMI: 25,7 ±±/± 4</u>	<u>[70]</u>

						vs 24.6 ±±/± 3.6 vs 28.3 ±±/± 5.9	
						-Biologics, physical exercise, skin-/room T°C: NA	
<u>RA (ACR ; n=40 patients)</u>	<u>-LC (2 modalities)</u>	<u>-Cold air (-30°C; 3 min; n = 20)</u> <u>OR</u> <u>-Liquid nitrogen vapors (-160°C; 3 min; n = 20) →</u> <u>Twice a day (knees in the morning, 4 h break, then hands) for 10 days</u>	<u>None</u>	<u>-Pain VAS</u> <u>-DAS28</u> <u>→ Before and after 10 days of treatment</u>	<u>S3C1O2</u> <u>6/11</u>	<u>-Associated kinesitherapy and physical exercise</u> <u>- Corticosteroids 28/40</u> <u>- DMARDs 40/40</u> <u>- Biologics: none</u> <u>-No change in pharmacological treatment.</u> <u>- BMI: 28.4 ±±/± 4.5 and 28.2 ±±/± 2.3</u> <u>- NSAIDs, skin/room T°C</u>	[63]
<u>Early RA (n = 36 patients)</u>	<u>-LC (n = 20 patients)</u>	<u>-Cold air (-60°C ; 15 min; 10 sessions—; hands, knees or ankles)</u> <u>Included in a Complex Rehabilitation Program (40 min exercise, 40 min occupational therapy +</u> <u>“Drug therapy”²²).</u> <u>Total duration?</u>	<u>-“Drug therapy”²² only (n = 16)</u>	<u>-Pain VAS</u> <u>-DAS28</u> <u>→ Before and after treatment (10 days?)</u>	<u>S3C1O1</u> <u>3/11</u>	<u>-Corticosteroids, NSAIDs, DMARDs, biologics, kinesitherapy, skin-/room T°C, BMI: NA</u>	[64]
<u>RA (n = 48 patients), AS (n = 12)</u>	<u>-WBC</u>	<u>-WBC (-110°C for 3 min; twice a day)</u> <u>→ Average number of sessions: 15.8 ±±/± 8,37</u>	<u>None</u>	<u>-Pain VAS</u> <u>-DAS 28 (48 patients)</u> <u>-BASDAI (12 patients)</u> <u>→ Before and after treatment</u>	<u>S2C0O1</u> <u>4/11</u>	<u>-Associated kinesitherapy and physical exercise.</u> <u>-No change in pharmacological treatment.</u> <u>-Corticosteroids, NSAIDs, kinesitherapy, physical exercise, skin temperature, BMI: NA</u>	[66]

<u>RA (ACR; n = 32 patients)</u>	<u>-WBC (n = 15 patients)</u>	<u>-WBC (-110°C for 3 min; once a day) + kinesitherapy → "complex therapy" for 8 days</u>	<u>-Low frequency magnetic field (20–40 Hz; 5–7 mT; 20 min; n = 17 patients) + kinesitherapy</u>	<u>-Pain VAS -DAS28 → Before and after treatment (8 days)</u>	<u>S4C1O1 5/11</u>	<u>-Associated kinesitherapy -No change in pharmacological treatment. -Corticosteroids, NSAIDs, physical exercise, skin temperature, BMI: NA</u>	<u>[67]</u>
<u>RA (ACR ; n = 41 patients)</u>	<u>-WBC</u>	<u>WBC (-160°C; 3–5 min; twice a day (6 h interval) for 15 days) + active exercises (45 min)</u>	<u>None</u>	<u>-Pain VAS → Before and after treatment (15 days)</u>	<u>S3C1O1 3/11</u>	<u>-Associated kinesitherapy and physical exercise -No change in pharmacological treatment. -Corticosteroids, NSAIDs, DMARDs, biologics, skin temperature, BMI: NA</u>	<u>[68]</u>

(Data taken from the cited articles):

RA: Rheumatoid Arthritis;

RCTs: R: Randomization, B: Blinding, W: Withdrawals (JADAD score);

Other study designs: S: Sampling; C: Control groups; O: Outcome measurement (NOS score);

Pain VAS: pain Visual Analogic Scale

DAS28: 28 joint-disease activity score (composite score including patient VAS for disease activity, acute-phase reactant (ESR or CRP_[53]), tender joint count and swollen joint score);

ACR: American College of Rheumatology (Diagnostic criteria for rheumatoid arthritis);

BASDAI: Bath Ankylosing spondylitis Disease Activity Index;

BMI: Body Mass Index (kg/m⁻²);

DMARD: disease activity-modifying drug; LC: Local Cryotherapy; n: number of patients; NA: Not assessed;

NSAID: Non-steroidal anti-inflammatory drug; T°C: Temperature (Celsius degrees)

LC: Local Cryotherapy;

WBC: Whole-body Cryotherapy

Data taken from the cited articles.

NA: Not assessed

T°C: Temperature (Celsius degrees)

BASDAI: Bath Ankylosing spondylitis Disease Activity Index

n: number of patients

TABLE 3. Cryotherapy techniques; Local cryotherapy techniques

(Data were taken from the cited articles).

Table 3A.: Local Cryotherapy (LC) techniques.

	Physical form	Temperature	Pressure	Duration	Skin temperature	Ref.
Local cryotherapy						
Ice bags	Ice- cubes, mixture of water and crushed Ice	0°C	Straps _____ for compression	10-30 min 30 min	13-15°C in 15-30 min 1 G°C (minimal value)	[20,72]
Cold packs Pre-refrigerated gels	Joint-shaped, flexibility (CryoCuff®; Polar Care®) Gel-filled cold pack (TMP Tiishaus® 12X29 cm	-15°C	±	10-30 min; 3 three-times a day for 7 days 20 min; 5/day 20 min	22-24°C 5, 5°C	[58,59,69,80]
Gas (thermal shock)	-Cold air (filtered ambient air; no consumables) Cryo 5: 40001/min	-30°C -20 to -30°C	0	5 min 10-30 min; 3/day; 7 days 3 min 3 min	9,7°C in 5 min [S4] 23,1°C after 1 min 6°C	[15,19,58,68]
	-Liquid Nitrogen vapors (Medivent®)	-160°C	0	6,5 min 3 min	9,8°C (minimal value) 17,9°C after 1 min	[15,20]

	-CO ₂ microcrystals (Cryotron®)	-78°C	50 bars (2-75 bars)	45 s-2 min (2-/day); flare duration 90s (3/day)	7..3°C 2°C in 20-30s 12°C	[8,73,81]
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Table 4: Ice-water and whole-body cryotherapy (WBC) techniques [55].

	Physical	Temperature form	Pressure	Duration	Skin temperature	Ref.
Ice-water Immersion						
Ice water		0-20°C	+	0-2°C for 20 s (three-times a week for 12 weeks)		[22,45]
Whole-body cryotherapy						
Cryogenic chambers	Dehydrated	-60°C to air	0	2-3 min 2 min (three-times/week; 12 weeks) 2 min; three-times a day; 7 days 3 min/day-10 days	12-16°C (110°0) 11°C (forearm)	[45,68,79,82]
	140°C <1 or 2 (Criostream acclimation®) chambers) Cold air cooled by liquid nitrogen -130°C (Zimmer® KR2005N®)					

Data were taken from the cited articles.

FIGURE 1. Flowchart.

LC: Local Cryotherapy

WBC: Whole-body Cryotherapy

VAS: Visual Analogic Scale

DAS28: 28 joint Disease Activity Score (composite score including patient VAS for disease activity, acute phase reactant (ESR or CRP), tender joint count and swollen joint score)

RCT: Randomized-controlled Trial

SD: Standard Deviation

n: number of articles

DAS28: 28-joint- Disease Activity Score (composite score including patient VAS for disease activity, acute-phase reactant (ESR or CRP), tender joint count and swollen joint score);

LC: Local Cryotherapy;

n: Number of articles; RCT: Randomized- controlled Trial;

SD: Standard Deviation;

VAS: Visual Analogic Scale;

WBC: whole-body cryotherapy.

n: number of articles

FIGURE 2^[R6]. Effects of local cryotherapy on pain VAS (**2A**) and DAS28 (**2B**). (Data taken from the cited articles).

FIGURE 3. Effects of whole-body cryotherapy on pain VAS (**3A**) and DAS28 (**3B**).

Mean differences in pain VAS (mm) or DAS28 before/after LC or WBC are represented for each of the six studies included in the meta-analysis [63,64,66–68,70], with 95% confidence intervals. Heterogeneity was also tested using Fisher's test (I² and p-values are shown on the graphs).

Design of the studies: RCT [70], controlled trials [63,64], parallel cryotherapy treatment groups [67,68], and non-controlled study [66].

CI: Confidence Interval

DAS28: 28-joint- Disease-disease Activity Score (composite score including patient VAS for disease activity, acute-phase reactant (ESR or CRP), tender joint count and swollen joint score);

LC: Local Cryotherapy;

n: Number of patients

i

FIGURE 4. Molecular pathways involved in cryotherapy (proposed model).

~~VAS: Visual Analogic Scale~~

~~WBC: Whole body Cryotherapy~~

~~(Data taken from the articles cited below and in the figure).~~

In RA, local and systemic inflammation promote neoangiogenesis which in turn favors inflammatory cell infiltrate and pro-inflammatory cytokine release.

(A) After cold stimulation, the autonomic nervous system is activated [73] and efferent sympathetic neurons release acetylcholine ~~which that~~ binds $\alpha 7n$ AchR receptor and noradrenaline that binds $\beta 2$ -adrenoceptor. These ligand-receptor interactions may then inhibit the NF κ B pathway and subsequently down-regulate pro-inflammatory cytokine, oxidative stress agent and adhesion molecule gene transcription [~~73,23,35,38,7374,35,75~~].

(B) Noradrenaline also induces vasoconstriction through α -adrenoceptor binding on the vascular wall [76], which could contribute to limit inflammation. Cryotherapy might also down-regulate the expression of pro-angiogenic factors such as VEGF [36].

(C) Cryotherapy might also down-regulate important enzymatic pathways involved in joint inflammation and destruction [39,59,77,78].

Citations refer to studies conducted in humans [23,35,39,41,69,71,73,76-789,81], human cell [41] or cell line [36] cultures, rats [24,38,40,42,820], mice [23,32], dogs [76] and ~~2-two~~ review articles [74,75].

~~CNS: Central Nervous System~~ ICAM-1: Intercellular Adhesion Molecule-1;

~~IL-6,-1 β , 10: Interleukin-6,-1 β , 10;~~

~~i-NOS: Inducible NO-Synthase;~~

MMP: Metalloproteinase;

NFκB: Nuclear Factor kappa B;

PGE2: Prostaglandin E2;

TNF-α: Tumor Necrosis Factor α;

VAS: Visual Analogic Scale; WBC: Whole-body Cryotherapy; VEGF: Vascular Endothelial Growth Factor

Data taken from the articles cited below and in the figure.

Abreviation list

BASDAI: Bath Ankylosing spondylitis Disease Activity Index; BMI: Body Mass Index

(kg/m²); CI: Confidence Interval ; CNS: Central Nervous System; CRP: C-reactive Protein

DAS28: 28 joint Disease Activity Score (composite score including patient VAS for disease activity, acute phase reactant (ESR or CRP), tender joint count and swollen joint score);

DMARD: Disease Activity Modifying Drug; ESR: Erythrocyte Sedimentation Rate (mm);

ICAM 1: Intercellular Adhesion Molecule 1; IL 6, 1β: Interleukin 6, 1β; i NOS: Inducible;

NO-Synthase; LC: Local Cryotherapy; MMP: Metalloproteinase; NFκB: Nuclear Factor

kappa B; NSAID: Non-Steroidal Anti-Inflammatory Drug; OA: Osteoarthritis; PGE2:

Prostaglandin E2; PnN: Neutrophil Polymorphonuclear; RA: Rheumatoid Arthritis; RCT:

Randomized-controlled Trial; SD: Standard Deviation; TNF-α: Tumor Necrosis Factor α

VAS: Visual Analogic Scale; VEGF: Vascular Endothelial Growth Factor; WBC: Whole-body Cryotherapy

RA: Rheumatoid Arthritis

LC: Local Cryotherapy

WBC: Whole-body Cryotherapy

~~VAS: Visual Analogic Scale~~

~~DAS28: 28 joint Disease Activity Score (composite score including patient VAS for disease activity, acute-phase reactant (ESR or CRP), tender joint count and swollen joint score)~~

~~ESR: Erythrocyte Sedimentation Rate (mm)~~

~~CRP: C-reactive Protein~~

~~TNF- α : Tumor Necrosis Factor- α~~

~~IL-6, 1 β : Interleukin-6, 1 β~~

~~PnN: Neutrophil Polymorphonuclear~~

~~VEGF: Vascular Endothelial Growth Factor~~

~~i-NOS: Inducible NO Synthase~~

~~NF κ B: Nuclear Factor kappa B~~

~~DMARD: Disease Activity Modifying Drug~~

~~NSAID: Non-Steroidal Anti-Inflammatory Drug~~

~~MMP: Metalloproteinase~~

~~PGE2: Prostaglandin E2~~

~~ICAM-1: Intercellular Adhesion Molecule-1~~

~~CNS: Central Nervous System~~

~~RCT: Randomized-controlled Trial~~

~~OA: Osteoarthritis~~

~~BMI: Body Mass Index (kg/m^2)~~

~~BASDAI: Bath Ankylosing spondylitis Disease Activity Index~~

~~SD: Standard Deviation~~

~~CI: Confidence Interval~~