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EULAR recommendations for intra-articular therapies

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ABSTRACT

Objectives To establish evidence-based recommendations to guide health professionals using intra-articular therapies (IAT) in adult patients with peripheral arthropathies.

Methods A multidisciplinary international task force established the objectives, users and scope and the need for background information, including systematic literature reviews) and two surveys addressed to healthcare providers and patients throughout Europe. The evidence was discussed in a face-to-face meeting, recommendations were formulated and subsequently voted for anonymously in a three-round Delphi process to obtain the final agreement. The level of evidence was assigned to each recommendation with the Oxford levels of evidence.

Results Recommendations focus on practical aspects to guide health professionals before, during and after IAT in adult patients with peripheral arthropathies. Five overarching principles and 11 recommendations were established, addressing issues related to patient information, procedure and setting, accuracy, routine and special aseptic care, safety issues and precautions to be addressed in special populations, efficacy and safety of repeated joint injections, use of local anaesthetics and aftercare.

Conclusion We have developed the first evidence and expert opinion-based recommendations to guide health professionals using IAT. We hope that these recommendations will be included in different educational programmes, used by patient associations and put into practice via scientific societies to help improve uniformity and quality of care when performing IAT in peripheral adult joints.

INTRODUCTION

Intra-articular therapy (IAT) is a cornerstone procedure extensively performed by different health professionals around the world. IAT is a key for treating adults with joint synovitis, effusion and pain of different origins such as inflammatory arthritis and osteoarthritis (OA).[1] Common injectables include glucocorticoids (GC), local anaesthetics, hyaluronic acid (HA), autologous blood products and radiopharmaceuticals.[2–7] Regardless of their efficacy and safety tested in clinical trials, in daily practice, a myriad of aspects may influence the outcome of IATs, such as the specific arthropathy, joint location and size, the setting and the procedure as well as the postprocedure care.

There is a wide variation in the way IAT are used and delivered in patients with arthropathies.[8 9] Health professionals may have different views and habits depending on training and access to IATs, and individual patients also have their own needs and preferences.[9 10]

To the best of our knowledge, no international and multidisciplinary effort has been made to develop evidence-based recommendations when performing IAT. To address this gap, EULAR (European alliance of associations for Rheumatology) established a taskforce with the aim of developing evidence-based recommendations to help guide health professionals using IAT in adult patients with peripheral arthropathies.

METHODS

The project adhered to the updated EULAR standardised operating procedures for the development of recommendations.[11] Methods included two face-to-face meetings, a series of systematic reviews (SR) and the production of Delphi technique-based consensual recommendations.

The task force (TF) comprised a convenor (JU), co-convenor (EN), methodologist (LC), 2 fellows (SCR-G and RC-M), 12 clinical experts from six European countries (rheumatologist, orthopaedic surgeon, nuclear medicine specialist and radiologist), 2 of whom belonged to EMEUNET (VV and ENi), 1 rheumatology nurse (JdlT-A), and one patient representative (IAP).

At the first face-to-face meeting, after presenting the evidence of an overview SR on the efficacy and safety of IAT,[12] the TF established the aims and scope and defined the functions, tasks and timing of the work programme, then prepared 32 'PICO' (population–intervention–comparator–outcome) questions relating to the topic area and carried out a ranking exercise to define priorities. To address the PICO questions, a series of SR were undertaken by the fellows under the supervision of the methodologist and the convenors, while an experienced librarian helped with the search strategies. Evidence was approached hierarchically by first identifying existing SR, appraising them using the AMSTAR-2 tool[13] and subsequently identifying and appraising individual studies in the situations where an SR to address a particular PICO question was not available. The results of the SR are being published elsewhere.[12]

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To understand the patient's perspectives on IAT, a 44-item survey was developed, translated into 11 languages and disseminated to patients with rheumatic disease and their carers via the EULAR people with arthritis and rheumatism associations and via social media. To understand current clinical practice, a 160-item survey was developed and disseminated to a range of healthcare professionals via EULAR professional associations and social media. The results of these surveys will be published separately.[14] At the second face-to-face meeting, we discussed the evidence obtained from the SRs and surveys and formulated individual recommendations. These tentative recommendations were discussed and consequently rephrased if necessary. Then the agreement for each recommendation was anonymously tested in a first Delphi round from 0 to 10. Recommendations with an agreement greater than 65% were included for the next round. Those that did not reach 65% agreement were discarded and not included in the second round. One month after the second meeting, the third Delphi round was run electronically using SurveyMonkey. To remain in the set of recommendations after the second round, agreement needed to be greater than 80%. Finally, the methodologist added the level of evidence and grade of recommendation to each statement, according to the Oxford levels of evidence.[15]

The manuscript draft was reviewed by all TF members and pertinent comments were included. After that, it was submitted to the EULAR executive committee for review and approval.

RESULTS

Aim, users and scope

The TF agreed to establish recommendations to guide all healthcare professionals on practical aspects when undertaking IAT in adults with peripheral arthropathies. It was agreed that they would not include recommendations about use of individual therapies in specific diseases, for which guidelines currently exist.

Evidence results

The fellows addressed 32 PICO questions (see online supplemental table 1). An overview of SR of randomised controlled trials (RCTs) was performed up to July 2020 [12] The results from the other SRs that support specific recommendations are presented with the recommendation.

For the surveys, 200 patients responded and the results suggested a number of aspects about IAT that could be improved, including, for example, wider availability of IAT, attention paid to reduce pain from the procedure and better shared decision-making (SDM) including provision of information about the procedure.[14] The health professional survey was responded by 186 professionals, 77% of whom were rheumatologists, from 26 countries.[14] The specific results that support any recommendation are presented as supporting evidence.

Overarching principles and recommendations

The overarching principles with their agreement and the recommendations together with their agreement, level of evidence and grade of recommendation are summarised in table 1

Overarching principles

IAT are recommended and widely used in the management of joint diseases.

Any treatment, including IA injectables, should be given according to the best practice.

Table 1 Overarching principles and recommendations, with agreement and level of evidence and grade of recommendation (if applicable)

Overarching principles	A (%)		
I. IAT are recommended and widely used in the management of joint diseases.	98		
II.The aim of IAT is to improve patient-centred outcomes.	100		
III.Contextual factors are important and contribute to the effect of IAT.	93		
IV.IAT should be offered in the frame of full individualised information and a shared decision-making process.	97		
V. A variety of health professionals perform these procedures routinely.	94		
Recommendations	**A (%)**	**LE**	**GR**
1.The patient must be fully informed of the nature of the procedure, the injectable, and potential benefits and risks; informed consent should be obtained and documented according to local habits.	99	4	D
► An optimal setting for IAT includes:Professional, clean, quiet, private, well-lightened room. ► Patient in an appropriate position, ideally on a couch/examination table, easy to lie flat. ► Equipment for aseptic procedures. ► Aid from another HP. ► Resuscitation equipment close-by.	85	4	D
3.Accuracy depends on the joint, route of entry, and health professional expertise; if available, imaging guidance, for example, ultrasound, may be used to improve accuracy.	93	1B-2A	B
4.During pregnancy when injecting a joint one has to take into account whether the compound is safe for mother and baby.	98	4	D
5.Aseptic technique should always be undertaken when performing IAT.	98	3	C
6.Patients should be offered local anaesthetic explaining pros and cons.	75	3–4	D
7.Diabetic patients, especially those with suboptimal control, should be informed about the risk of transient increased glycaemia following IA GC and advised about the need to monitor glucose levels particularly from first to third day.	97	1B	A
8.IAT is not a contraindication in people with clotting/bleeding disorders or taking antithrombotic medications, unless bleeding risk is high.	89	3	C
9.IAT may be performed at least 3 months prior to joint replacement surgery, and may be performed after joint replacement following consultation with the surgical team.	88	3	C
10.The shared decision to reinject a joint should take into consideration benefits from previous injections and other individualised factors (eg, treatment options, compound used, systemic treatment, comorbidities…).	93	2	B
11.Avoid overuse of injected joints for 24 hours following IAT; however, immobilisation is discouraged.	94	1B	A

A, agreement; GR, grade of recommendation; IAGC, intra-articular glucocorticoids; IAT, intra-articular therapies; LE, level of evidence.

Table 2 Eular recommendations in which IAT are mentioned

Joint/condition	EULAR recommendation
Knee osteoarthritis[86]	'Intra-articular injection of long acting GC is indicated for acute exacerbation of knee pain, especially if accompanied by effusion.' 'Hyaluronic acid (…) is probably effective in knee OA, but the size effect is relatively small, suitable patients are not well defined, and pharmacoeconomic aspects of that treatment are not well established'.
Gout[16]	'Recommended first-line options for acute flares are colchicine (…), oral corticosteroid (…) or articular aspiration and injection of corticosteroids.'
Rheumatoid arthritis[87 88]	'Monitoring should be frequent (…) therapy should be adjusted.' *Adjustment of therapy includes the optimisation of MTX (or other csDMARD) dose or route of administration, or intra-articular injections of GC in the presence of one or few residual active joints.
Hand osteoarthritis[89 90]	'Intra-articular injections of glucocorticoids should not generally be used in patients with hand OA, but may be considered in patients with painful interphalangeal joints'.
Acute or recent onset swelling of the knee[91]	'Intra-articular steroids should not be administered unless an appropriate diagnosis has been made and contraindications have been ruled out'.

csDMARD, conventional synthetic disease-modifying antirheumatic drugs ; GC, glucocorticoids; MTX, methotrexate; OA, osteoarthritis.

Dose and approach need to be defined for each indication and joint and might not be interchangeable across indications. Table 2 shows current EULAR recommendations in which IAT are mentioned.

The aim of IAT is to improve patient-centred outcomes.

Patient-centred outcomes are those relevant to the patient, such as benefits, harms, preferences or implications for self-management. While injectables are used mainly as a treatment to improve patient-centred outcomes, they can also be used to aid diagnosis and identify the origin of pain (eg, lidocaine test may be used to rule out joint vs referred pain).[1] The objective of therapy should be among the expected outcomes based on evidence. An example of an unclear objective is to use injectables to improve function in a joint without pain. Reduction of systemic medication can be also considered a patient and health provider aim.

Contextual factors are important and contribute to the effect of IAT.

Contextual factors such as effective communication, patient expectations or the setting in which the procedure takes place, which may influence the outcome of IAT. Additionally, one should recognise the magnitude of the placebo effect associated with this route of delivery.[16]

IAT should be offered in the frame of full individualised information and a SDM process

SDM implies the involvement of patients with their providers in making healthcare decisions that are informed by the best available evidence about options, potential benefits and harms, and that consider patient preferences. If not within a framework of SDM, any recommendation may not reach the expected effect.

A variety of health professionals perform these procedures routinely.

Depending on country regulations, IAT can be carried out by general practitioners, rheumatologists, traumatologists/orthopaedic surgeons, sports medicine specialists, radiologists, nuclear medicine specialists, trained nurses, physical therapists and occupational therapists, with varying levels of formal training.[14]

Recommendations

The patient must be fully informed of the nature of the procedure, the injectable and potential benefits and risks; informed consent should be obtained and documented according to local habits.

The TF agreed to include this general statement as the first recommendation on the basis that this frequent procedure is delivered by health professionals from many countries and that patients surveyed wanted to be informed prior to consent as an essential part of the SDM process.[14] Whether informed consent should be oral or written is beyond the scope of this project, furthermore, there was no preferred option in the patient survey. Essential information to be delivered includes the nature of the procedure, the potential benefit, side effects and postinjection care.

An optimal setting for IAT includes a professional clean quiet private well-lightened room, the patient in an appropriate position, ideally on a couch/examining table, easy to lie flat, equipment for aseptic procedures, aid from another HP and resuscitation equipment close by.

Contextual effects including the setting in which clinical care is delivered may impact on the outcome of clinical interventions. We could not identify any studies to help inform what the optimal setting for undertaking IAT therapy is. However, all these aspects may enhance the contextual effect. It was agreed that the main equipment required was a couch/examining table which could be adjusted, and equipment for aseptic procedures and resuscitation equipment close by. There was a discussion about the need to have another HP present as many countries or centres do not provide assistants.[14] A retrospective case series analysis showed a 2.6% overall rate for vasovagal reactions,[17] which may justify the help of others; however, in the healthcare professional survey, the large majority of professionals said that they never or seldom had vasovagal reactions.[14]

Accuracy depends on the joint, route of entry and health professional expertise; if available, imaging guidance, for example, ultrasound, may be used to improve accuracy.

Several published SRs and RCTs report that ultrasound improves accuracy in delivery of IAT though clinical outcomes are similar to those of landmark-guided IAT.[18–21] When using anatomical landmarks (blinded injections), each peripheral joint has different routes of entry. The best approach for a certain joint cannot be recommended except for the knee in which an SR showed that the superolateral approach was more common and resulted in the highest pooled accuracy rate of 91% (95% CI 84% to 99%) in patients with different arthropathies.[22] Aspiration of synovial fluid helps ensure that the needle is in the joint.[23 24] Expertise in the procedure is important and appreciated by the patient, as highlighted in the survey, and it is clearly dependent on practice and appropriate training.[14 25]

During pregnancy when injecting a joint one has to take into account whether the compound is safe for mother and baby.

IAT during pregnancy is often performed to treat local arthritis when indicated and the benefit/risk ratio in this setting may be superior to that for systemic therapy. Most of the compounds in routine practice can be used except for radiopharmaceuticals, which are contraindicated during pregnancy.

Aseptic technique should always be undertaken when performing IAT.

The risk of septic arthritis following IAT is very low. However, while historically the risk estimates for septic arthritis postintra-articular GC varied from 0.005% to 0.0002%, a recent study showed that the current risk could be higher (0.035 %, three per 7900 procedures).[26] We have found no studies comparing different aseptic techniques during IAT on subsequent risk of infection. Surgical gloves, skin preparation with alcohol, iodine disinfectant or chlorhexidine and changing needles between drawing the drug and injecting it into the joint are indirectly supported by their benefit in other common procedures, such as blood cultures and surgery.[27 28]

Patients should be offered local anaesthetic explaining pros and cons.

The main reasons for using local anaesthetics in IA T are to reduce discomfort during the procedure and to extend pain reduction effect. Local anaesthetics may be applied on the skin, infiltrated in the subcutaneous tissue, along the needle path into the joint, or injected into the joint, alone or mixed with GC. Topical anaesthetics such as eutectic mixture of local anaesthetic cream, lidocaine 2.5% and pilocarpine 2.5% or ethyl chloride spray, can reduce pain from the needle as demonstrated in children in one RCT.[29] Several TF members suggested ethyl chloride spray, a nonsterile coolant aerosol, might increase infection risk when not applied correctly, but we failed to find any evidence for this. A high-quality SR showed that warmed local anaesthetic (37°C) reduces local infiltration pain compared with injecting at room temperature, irrespective of whether the local anaesthetic was buffered or not.[30] Anaesthetic infiltration while advancing the needle into the joint does not minimise procedural pain, as suggested in a retrospective analysis performed in US-guided hip injections for MR arthrography.[31] Several RCTs in knee and hip OA have shown that the combination of GC and local anaesthetic improves pain longer than only injecting local anaesthetic.[32 33] Some TF members raised concern about the effect of lidocaine on cartilage. We found a study, by Ravnihar *et al*, on knee cartilage obtained from biopsies, that showed no differences in chondrocyte viability and morphology and population doublings after a single injection of lidocaine, and we failed to identify in vivo evidence of cartilage toxicity.[34] One last aspect on anaesthetics would be allergic reactions. Patients should be asked about previous allergic events prior to the procedure.

Diabetic patients, especially those with suboptimal control, should be informed about the risk of transient increased glycaemia following IA glucocorticoid injection and advised about the need to monitor glucose levels particularly from first to third day.

IA GC can provoke transient hyperglycaemia, which may cause risk to patients with diabetes mellitus by raising blood glucose to hyperglycaemic levels. One SR of critically low quality, including 76 patients, showed that blood glucose levels increase during day 1–3 postinjection though no severe adverse events such as hyperosmolar hyperglycaemic state or ketoacidosis were encountered.[35] Twu *et al* prospectively analysed 70 diabetic patients requiring IA GC and observed that preinjection haemoglobin A1C had a significant effect on postinjection blood, whereas corticosteroid dose, body mass index, insulin use and the number of injections had no significant effect on the elevation of blood glucose.[36] Also, an RCT showed that extended release triamcinolone acetonide may increase glycaemia less than the standard triamcinolone acetonide (14.7 mg/dL vs 33.9 mg/dL),[37] and so it could be an alternative for poor controlled diabetic patients. Finally, although diabetes predisposes to native and prosthetic joint infection,[38–40] none of the studies on IA GC in patients with diabetics reported postprocedure infections.[35–38 41–43]

IAT is not a contraindication in people with clotting/bleeding disorders or taking antithrombotic medications, unless bleeding risk is high.

Our literature review identified 15 observational studies including 1428 patients (1425 haemophilia and 3 Von Willebrand disease) subjected to more than 10 000 procedures (all of which were performed after appropriate factor replacement) including radioisotopes, triamcinolone, HA and other products, revealed only two hemarthroses and three soft-tissue bleeds in one study; thus, IAT appears to be a low-bleeding risk procedure in patients with clotting-impairing haematological disease.[44–57] Based on seven observational studies, the estimated periprocedure bleeding risk in patients on antithrombotic drugs (antiplatelet agents, low-molecular weight heparin, warfarin or direct oral anticoagulants) was found to be between 0% and 2%.[58–63] One of the larger studies, retrospectively reviewed 640 procedures (arthrocentesis and joint injections) in 514 patients taking warfarin; they found no significant difference in early and late complications in patients receiving therapeutic warfarin (INR 2–3) compared with nontherapeutic levels (INR <2).[61] In another large retrospective study, no bleeding was reported in 1050 procedures performed in 483 patients on rivaroxaban (52%), apixaban (31%) or dabigatran (17%).[62] Several panellists suggested that local pressure to prevent bleeding may be more important after injecting deeper joints than superficial ones.

IAT may be performed at least 3 months prior to joint replacement surgery and may be performed after joint replacement following consultation with the surgical team.

We identified six SRs, one of low quality and five of critically low quality, assessing safety issues of IA GC prior and following joint replacement.[64–69] Evidence was not conclusive of an increased risk of infection with IA GC injection in the hip or knee prior to total joint arthroplasty. Three retrospective studies examined whether this was a matter of a 'safe window'. The rate of prosthetic infections 3 months after surgery was significantly larger in the groups that had injections 0–3 months prior to total hip or knee arthroplasty, but not if the injections were separated from the surgery longer than 3 months; however, the difference was not strikingly large (from 0.5% to 1.0%, with background risk from 1.04% to 2.5%).[70–72]

Another important issue is whether it is safe to inject GC in a prosthetic joint. In a retrospective medical record review that aimed to assess the risk of acute infections in patients with total knee prosthesis,[73] the authors found a 0.6% infection rate in 1845 GC IA injections performed in 736 patients (1 infection in every 625 infiltrations). A recent single-centre retrospective study showed no joint infections at a minimum of 1-year follow-up in 184 patients with total knee prosthesis (31% received two to

five GC injections).[74] Both studies pointed out that IA GC injections in prosthetic joints should be avoided in routine practice and considered by orthopaedic surgeons after strict screening of prosthetic infection.

The shared decision to reinject a joint should take into consideration benefits from previous injections and other individualised factors (eg, treatment options, compound used, systemic treatment, comorbidities…).

IATs have been tested for different doses, frequencies and intervals. However, high-quality studies that aimed to evaluate the long-term effect of repeating IA injections are scarce. There are no clear evidence-based recommendations as to the appropriate number of IA injections from a risk benefit perspective for most indications. We found two RCT in knee OA, comparing IA GC every 3 months for 2 years versus saline, one showing gain in symptoms and no deleterious effect on cartilage volume,[75] and the other showing no difference in pain and greater progression of cartilage volume loss with GC.[76] A general accepted rule, though based on no research evidence, is to avoid more than 3–4 GC injections in the same joint per year. An SR on long-term effect of repetitive IA HA showed sustained or further pain reduction with repeated courses of HA and no serious adverse effect.[77]

Avoid overuse of injected joints for 24 hours following IAT; however, immobilisation is discouraged.

Most practitioners advise restricted activities. Studies have shown that 24–48 hour postinjection immobilisation, such as bed rest, joint splinting or bandages, add no benefit compared with normal activity after IAT, even when injecting radioisotopes.[78–83] Radioisotopic radiation leakage into extrasynovial tissue may be minimised by splinting during 48 hours.[78–80]

DISCUSSION

Herein, we present the first EULAR evidence-based recommendations to help guide health professionals who perform IAT in adult patients with peripheral joint disorders. We established 5 overarching principles and 11 recommendations addressing: patient information; procedure and setting; accuracy; routine and special antiseptic care; safety and precautions in special populations; efficacy and safety of repeated joint injections; the usage of local anaesthetics and aftercare. The main challenge faced by the TF has been the complexity of the topic and the paucity and controversy of the scientific evidence.

At the first meeting, it was very clear to the TF that there was a need for developing practical recommendations prior, during and after performing IAT, as this common procedure is performed by different clinicians and has not undergone a robust expert evidence-based evaluation. This ambitious and complex project required not only a well-designed broad systematic literature review, and an expert international panel, but also feed back from a broader group of health professionals and patients. We were fully aware that many of the accepted issues had little or no scientific support. Hence, we designed the surveys for back ground information from health professionals and patients coming from EULAR member countries. The respondents' opinions were presented with the results of the SRs for each pertinent research question. This helped the TF formulate low evidence (1, 2, 4 and 6) and moderately low evidence (5, 8 and 9) recommendations.

Recommendation 6, addressing the offering of local anaesthetics had the lowest agreement. The surveys revealed that approximately 50% of the health professional never use local anaesthetic, despite the fact that, in their respective survey, patients recurrently asked for a less painful or even painless procedure.[14] The low agreement was possibly due to the lack of scientific evidence on the benefit of local anaesthetics.

Recommendations with moderate evidence were 3 and 10. Part of recommendation 3 relating to the accuracy of IA injections says that "if available, imaging guidance, for example, ultrasound, may be used to improve accuracy". This part of the recommendation was worded as an open suggestion because many units neither have ultrasound machines nor physicians trained in joint ultrasonography. Noticeably when injecting a radiopharmaceutical, imagining is important to minimise extrasynovial radiogenic tissue necrosis.[84]

The identification of evidence was hampered by the large number of questions posed, the large number of potential populations and interventions as well as time constraints. We tackled it by using nine sensitive 'theme' search strategies and then organising the studies into the different questions.

These recommendations assume that 'best practice' is the rationale for IAT and for the selection of the compound. It was out of our scope to study and to compare the efficacy and safety of the specific IATs as well as to address the indications for the different arthropathies. When looking at contextual factors that may influence outcome, such as decrease in joint pain, we found that the procedure itself has an important placebo effect.[85] This should be considered not only in daily practice but also when interpreting the results of RCTs comparing IAT with systemic therapy or in observational studies on IAT. Another general aspect encountered was that the majority of the studies identified were conducted by orthopaedic surgeons and rehabilitation specialists and fewer by rheumatologists, and that most studies dealt with IA HA in patients with knee OA, while rheumatologists predominantly use IA GC.

Despite IAT being an important procedure and widely used for more than 70 years, many aspects of IAT still need to be assessed to increase our quality of care. These may include safe and cost-effective settings and procedures; whether ultrasound diagnosis and guidance improve outcome; better RCTs, and perhaps a real-life registry of IATs, like the arthroplasty registers.

As a disclaimer, this project was carried out before the COVID-19 pandemic outbreak, so it does not include specific safety measures to prevent SARS-CoV-2 viral infection nor measures to be used when having to deliver IAT to patients with COVID-19. Health professionals and patients should follow local country regulations and recommendations relating to this matter.

We expect these first recommendations to be included in different educational programmes, used by patient associations, and put into practice via scientific societies to help improve uniformity and quality of care when performing IAT in peripheral adult joints.

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