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The discrepancy between recommendations and clinical practice for viscosupplementation in osteoarthritis: mind the gap!

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Abstract. – Recently AAOS, ACR and OARSI revised their recommendations for the management of knee osteoarthritis (OA) and for hand, knee and hip joints. During ISIAT (International Symposium on Intra-Articular Treatments) 2013 round table on recommendations about the use of intra-articular Hyaluronic Acid (IAHA) in OA, several considerations were elaborated by the ISIAT Technical Expert Panel (TEP) regarding discrepancy between recommendations and clinical practice. The ISIAT TEP gathered the following eight suggestions regarding the drawing of recommendations on the use of IAHA in OA and its comparison with other treatments. It is necessary to merge data coming from both RCTs and registers. Only studies with a strong level of evidence should be taken into account. A common threshold of efficacy should be assessed for comparing treatments. Evaluation of hard outcomes is essential. The effect size of placebo as comparator should be attentively considered in RCTs. Particular attention should be given to different phenotypes of OA that may possibly respond differently to each treatment. Compliance and long-term side effects of different therapeutic approaches should be evaluated. Pharmacoeconomic evaluation should be performed on the long term.

Key Words:
Hyaluronic acid, Osteoarthritis, Guidelines, Recommendations.

Introduction

Osteoarthritis (OA) is the most common joint disease affecting adult patients worldwide. Its incidence grows together with ageing of population and there are intrinsic and extrinsic risk factors promoting its development. OA is also a major cause of disability around the world[1].

Recently American Association of Orthopedic Surgeons (AAOS) and the American College of Rheumatology (ACR) revised their recommendations for the management of knee OA and for hand, knee and hip respectively[2,3].

AAOS recommendations regarding the management of knee OA[2] report with a recommendation whose strength was defined as "strong" that they cannot recommend the use of intra-articular hyaluronic acid. This recommendation was obtained after the examination of 14 studies (three high-strength studies and 11 moderate-strength studies) and was based on the lack of evidence of efficacy and not on potential harm induced by such kind of treatment. They report that meta-analysis in meaningfully important difference units (MID) showed that the global effect was estimated to be less than 0.5 MID units, thus indicating a low likelihood that an appreciable number of patients achieved clinically important benefits in the outcomes. Meta-analyses of WOMAC (Western Ontario and MacMaster Universities Arthritis Index) pain, function, and stiffness subscales scores found statistically significant treatment effects, but still none of the improvements met the minimum clinically important improvement "thresholds".

ACR revised guidelines for the management of OA[3] are divided for the three different joints examined. Regarding knee OA, ACR reports that

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the Technical Expert Panel (TEP) cannot recommend the use of intra-articular hyaluronans, except for selected cases. Similarly, regarding hip OA, the TEP reported that no recommendations were made for intra-articular hyaluronates, duloxetine, or topical NSAIDs because of the lack of data from RCTs on either benefit or safety at the time of the TEP meeting.

In 2007 last published OARSI recommendations reported how corticosteroids for IA use may have a role in patients suffering from synovial effusion and/or inflammation, while IAHA are effective for symptomatic relief, with a level of evidence and a strength of recommendation of 64%. New OARSI guidelines for the management of knee OA[4] report with a classification of "uncertain" the use of HA for IA injection. Concerns regarding safety are also reported and data on this topic are drawn from the same studies, with the same low level of evidence, as other guidelines. Interestingly, studies reporting on the safety of IAHA drawn from national registers were not taken into account for the global evaluation of safety profiles of viscosupplementation[5]. Previous recommendations from OARSI included the use of corticosteroids injection in cases of inflammation, while HA was suggested as effective for symptomatic relief with a level of evidence and a strength of recommendation of 64%.

AAOS and ACR guidelines were recently reported and commented at ISIAT 2013, International Symposium on Intra-articular Treatments, held in October 3rd-5th in Barcelona (Spain) by an international panel of clinicians dealing with intra-articular treatments.

During ISIAT round table on recommendations about the use of IAHA in OA, several considerations were elaborated by the ISIAT TEP regarding the drawing of actual and future recommendations on the use of HA for intra-articular administration in patients affected by OA. Some key points were established by the TEP regarding eventual problems in drawing previous recommendations and regarding future ones.

From a methodological point of view, it is interesting to notice that such recommendations, although coming from international organizations, differ from those coming from other international organizations, such as those from EULAR[6], or may be more similar to those reported by other organizations, such as NICE[7]; such recommendations should be unique, as they should all consider the same studies and with the same methodology, but this is not the case. Studies included in meta-analyses performed in order to draw such guidelines are often different, as well as methodologies used for their analysis or for the thresholds used for defining the levels of efficacy. This may explain why results of meta-analysis are so different. For example, acetaminophen is still the first line drug for all organizations but not for NICE, and there is not accordance between the algorithm of therapy, although all recommendations insist on the tailoring of therapy for the single patient. Furthermore the risk of paracetamol, especially the one on cardiovascular system has been recently challenged and needs further precautions in case of long term use of paracetamol in patients with recognized cardio vascular risks[8].

Osteoarthritis is a Chronic Disease

Clinicians dealing with IAHA administration may easily dissent with such guidelines for several reasons. First of all, patients from RCTs deeply differ from patients clinicians meet during clinical practice. This is the already reported difference between randomized clinical trials and real practice, where patients do not stop existing at the end of the study, but may come over and over for more than 10 years. This gives clinicians a completely different perspective on efficacy and safety profiles of compounds studied in RCTs. OA is a chronic disease and the perspective of clinicians dealing with such patients may be deeply different from results obtained by short term follow-up RCTs. Guidelines should be drawn not only from RCTs, that are essential to understand several aspects of the examined drugs, but also from registers of clinical practice. Data on efficacy and safety profiles drawn from registers may add relevant information differing from those extracted by meta-analyses of RCTs. It would be more appropriate to draw guidelines from registers and RCTs, instead of taking into account only RCTs, as such guidelines would reflect more precisely true profiles of IAHA in terms of efficacy and safety.

Guidelines reporting that the first line of treatment is acetaminophen, when applied to clinical practice, would lead us to use it on a small part of patients: many of OA patients have cardiovascular, gastrointestinal and metabolic (such as hepatic) impairments that would make systemic drugs unavailable mainly for long time, so only topical NSAIDs or IAHA would be available options, but there are no consideration on that in any recommendations.

The Need of High Levels of Evidence

Drawing recommendations from meta-analyses may methodologically be erroneous for some reasons: metanalysis should consider the strength in terms of evidence of each study included, or there is a concrete risk of evaluating poor level of evidence studies as high level of evidence studies. Furthermore, the evaluation of the obtained effect is to consider differently in a chronic disease such as OA, and maybe the effectiveness threshold had to be carefully reconsidered[9].

The Need of Common Thresholds for Efficacy and Safety Evaluations

Recent recommendations have been stated mostly on the recent Rutjes publication in Ann Intern Med in 2012. There are some key points to reconsider in the study from Rutjes et al[10], where the threshold for efficacy was arbitrarily set and the relevance of side effects reported in poor level of evidence studies was overestimated. As reported in the review from Bannuru et al[11], if only good quality studies are included, the efficacy of IAHA raises far above acceptable threshold for a disease such as OA. The efficacy level of acetaminophen is 0.1, while efficacy profiles of IAHA for both metanalyses (Rutjes et al and Bannuru et al) are above that level, but still, in recommendations from all guidelines except for NICE ones, acetaminophen nevertheless represents first line therapy.

The Relevance of "hard" Outcomes

The rate of TKR is worldwide increasing and it may further increase if the offer of non-surgical options decreases. This risk is certainly the most worrying since it may be associated with severe complications[12].

Regarding the choice of endpoints, an evaluation on structural damage of disease should be performed on the long term, while this is very difficult during RCTs, due to follow-up times usually shorter that 1 year; investigating the results on the progression of the disease may be even more relevant than reporting results on patients' symptomatic state. Before stating whether a treatment is effective or not it in OA, it would be recommended to understand what is expected to be the outcome in terms of joint function on the long term, in other words to prevent joint failure. A previous study from Reynauld et al[13] reported how a "hard outcome", such as need for TKR, may be predicted when merging clinical data with imaging data, such as data coming from MRI. In this sense, hard outcomes such as need for surgical joint replacement should be considered when drawing recommendations regarding the use of various therapeutic options. Although some previous studies suggested that the use of IAHA may delay total joint replacement, no studies are available regarding patients undergoing to NSAIDs or pain killers. Moreover, several studies demonstrated how the use of IAHA may reduce the use of NSAIDs or pain killers in patients affected by OA with a reduction of their side effects and a considerable impact on costs.

The Problem of a Proper Comparator

Other concerns regard comparators. A clear analysis of what should be considered as a placebo in RCTs should be performed. Several studies report on good efficacy profiles of intra-articular injection of saline solution, considered as control arm. This is to take into account when comparing effect of active arms, be it steroids, HA or other compounds. In a meta-analysis from Zhang et al[14], placebo seemed to be effective in OA with an effect size (ES) of 0.51 for pain relief, when rescue medications were allowed, and with an ES raising to 0.71 in those trials where rescue medications were not allowed, but this was observed only for subjective outcomes such as pain, joint stiffness and self-reported function. This study also stated that apparent determinants of effect size of placebo seemed to be the baseline severity, the expected strength of the treatment, the route of delivery and the sample size. The consideration of solely subjective symptomatic outcomes may induce to think that active arm compounds do not offer a relevant benefit in the management of OA while investigating difference in terms of structural clinical outcomes could lead to different evaluation against saline solution injection[15]. Also, in the protocol of RCTs, sham injection as control arm should be considered in order to draw real differences for IA administration of products. Sham injection will not alter, as saline solution may do, intra-articular environment and consequently it is more suitable as control arm.

The Relevance of Different Phenotypes of Osteoarthritis

Since OA is a disease characterized by different stages and different features even in the same stage of disease, the characteristics of patients

must be taken into account. For example, the features of OA affecting an obese woman with a severe metabolic syndrome are completely different from OA affecting a young athlete. Meta-analyses cannot report on this, not only because they need a global evaluation of data, but also because studies taken into account do not report such data aborigine. Considering OA a single clinical entity is obviously wrong. OA may be considered as a multifactorial disease with extremely heterogeneous manifestations and may have different phenotypes of expression. Understanding what is the role of VS in different phenotypes of OA is essential for therapy tailoring. Identifying such phenotypes as a first step would be essential. As reported by Castañeda et al[16] in a recent publication, the heterogeneity of OA may affect the outcome from current therapies due to the inclusion in RCTs or other kind of studies of patients with diverse phenotypes and/or different stages of disease progression. In this sense it is recommendable to separately study different clinical and pathogenic phenotypes or subsets of OA.

A more Complete Analysis of Results Should Take into Account Also Pharmacoeconomic Evaluations

OA is a chronic disease, therefore, it is necessary not only to investigate results in terms of efficacy and safety over time, but also to evaluate and esteem costs related to long-term management of patients. Long term exposure to NSAIDs may have not only direct elevated costs, but also costs related to side effects such as bleeding or cardiovascular events[17]. It was already reported that the use of hyaluronic acid for intra-articular injection in patients affected by hip OA may reduce the need of NSAIDs consumption[18]. The morphinic and type 2 analgesics might be considered as rescue medications but unfortunately several recent trials show their bad tolerance which is not totally compatible with a long term use in a chronic disease such as OA. Moreover, it has been recently shown that opioids' consumption increases after stopping coxibs and this increase was correlated with an increased number of falls leading to a higher rate of femoral neck fracture in the elderly population[19]. In other words the alternate of strong analgesics may be not always valuable. More than that, considering costs related for therapy without tailoring therapy on disease stage or phenotype will eventually lead to a deep misunderstanding, and misuse, of therapies and relative costs. A differentiation of treatments depending on the stage of OA or depending on the cause of OA is essential in order to draw real pharmacoeconomic evaluations. Several evaluations on cost-effectiveness of HA have been performed, but as reported before, such evaluations are correct, in case of a chronic disease, only when performed on the long course. If several national health systems already reported on the high costs of IAHA, it is essential to draw data on the long course from national registries, in order to understand the real weight of different therapeutic options, such as rehabilitation, NSAIDs or IAHA/IA steroids. On the long course, cost related to such therapies may vary together with the course of disease or with the appearance of side effects related to such therapies. Costs related to NSAIDs side effects are considerable, as well as costs related to joint replacement, both direct costs related to intervention and costs related to adverse events, that as already reported in previous studies[19,20], may be very relevant.

Conclusions

The ISIAT TEP gathered the following suggestions regarding the drawing of recommendations on the use of IAHA in OA and on the evaluation of its use when compared with other possible treatments: (1) It is necessary to merge data coming from both RCTs and registers, as OA is a chronic disease: short-term follow up of RCTs cannot completely represent the complexity of such disease; (2) Only studies with a strong level of evidence should be taken into account and their relative strength should be considered when analysing data, especially on side effects. (3) Establishing common thresholds for efficacy and safety is essential for comparing treatments; (4) Evaluating hard outcomes such as structural progression of disease or progression to arthroplasty is essential; (5) In RCTs, placebo comparator should be attentively considered, as the use of saline solution may alter the IA environment; sham injection should be used as real placebo comparator; (6) Particular attention should be given to different phenotypes that may possibly respond differently to each treatment proposed; (7) Evaluating compliance and long-term side effects of different ther-

apeutic approaches is crucial for clinical practice; (8) Pharmacoeconomic evaluation (side-effects, need for surgical joint replacement, or further medications or assistance) should be performed on the long term.

Competing Interest

Prof. Migliore A declares he received grants as consultant from Pfizer, UCBPharma, Merck, Roche, Brystol-Myers-Squibb, IBSA, Sanofi-Aventis and Fidia Pharma. Dr. Bizzi E, Dr. Raman R and Dr. Herrero-Beaumont J declare they received grants as consultants from Pfizer and Brystol-Myers-Squibb. Prof. Chevalier X declares he received grants as consultant from Sanofi-Aventis, Servier, Genevriers, Pierre Fabre, SOBI, Smith and Nephews, Labbhra. Prof. Petrella RJ declares he received grants as consultant from Carbylan Biosurgery and Sanofi Biosurgery.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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