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Commentary

Comments on the discordant recommendations for the use of symptomatic slow-acting drugs in knee osteoarthritis

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Abstract

Despite the near concurrent publication by influential scientific organizations, there are important differences in interpretation of the evidence base and the conclusions derived from the recent Osteoarthritis Research Society International (OARSI) guidelines for the management of knee osteoarthritis, the American College of Rheumatology (ACR) guidelines (concerning also hip and hand osteoarthritis) and the algorithm recommendations by the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). This is particularly evident for the drug class of symptomatic slow-acting drugs in osteoarthritis. In this paper, we highlight these differences and try to understand where they derive from, proposing an evidence-based interpretation.

Introduction

Recommendations and guidelines for the management of osteoarthritis (OA) have been published by several different scientific organizations[1]. However, most of them are produced by national organizations, or are restricted to the use of specific interventions, such as physical therapy in many instances, or selected drug classes[1]. Thus, the most influential global, or at least continental, and comprehensive documents on all available interventions are those issued by the Osteoarthritis Research Society International (OARSI) for the management of knee osteoarthritis, the American College of Rheumatology (ACR) (concerning also hip and hand osteoarthritis) and, for Europe, the European League Against Rheumatism (EULAR) and the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Although there is relative general agreement on many OA management recommendations across organizations, controversies remain and are related to the use of some non-pharmacological interventions (e.g. acupuncture, knee braces, heel wedges) and, within pharmacological treatments, to the pharmacological class of symptomatic slow-acting drugs in osteoarthritis (SYSADOAs), mainly represented by glucosamine sulfate and chondroitin sulfate, and to some extent by intra-articular hyaluronic acid[1]. Such discrepancies have been increased by the recent publication of the OARSI guidelines update[2] that followed by slightly more than one year the recommendations issued by the ACR[3] and were published just before the algorithm recommendations by ESCEO[4] (while EULAR has not updated its 2003 recommendations for knee osteoarthritis yet).

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While discrepancies in non-pharmacological treatments are often related to the level of evidence and the difficulties in conducting randomized controlled trials for some interventions, for SYSADOAs there are important differences in interpretation of the evidence base and the conclusions derived therefrom. These differences may arise, in part, from the different regulatory status for some treatments in the USA compared to Europe. In this paper, we highlight these differences and try to understand where they derive from, proposing an evidence-based interpretation.

Glucosamine and chondroitin

Glucosamine and chondroitin were (conditionally) not recommended by the ACR mainly due to the lack of availability of prescription-quality preparations evaluated by the US Food and Drug Administration (FDA). The American market is indeed flooded by low quality food supplements not manufactured to pharmaceutical standards[5], with poor pharmacokinetic performance, used at variable and mostly ineffective dosages, the contents of which in some instances do not even correspond to the label claims[6]. In addition, they are not supported by high-quality clinical trials. Most importantly, rheumatologists, orthopedists and general practitioners are not made aware by their patients whether they are taking these food supplements, with the risk of drug interactions and other safety issues. This is less the case in Europe and in several other countries, where the original products (crystalline glucosamine sulfate and chondroitin sulfate) are available, are of pharmaceutical grade and are approved by the European Medicines Agency (EMA) or the relevant competent authorities as prescription drugs. Indeed, ESCEO was able to recommend prescription chondroitin sulfate and/or glucosamine sulfate as chronic background treatment in the first step of its algorithm guidelines for the management of knee osteoarthritis, based on the available evidence.

For glucosamine sulfate, most of the evidence has been reviewed in a recent Cochrane Review[7]. When all available studies are considered, efficacy on pain and function is clouded by high trial heterogeneity. In contrast, analysis restricted to high-quality trials with prescription glucosamine sulfate do show significant efficacy on pain and function without heterogeneity[7], contrary to studies performed with non-prescription glucosamine products that do not show any efficacy. Although modest, the long-term effect size of prescription glucosamine sulfate is statistically significant and clinically relevant[8] and in the same order of magnitude of other recommended but less tolerated drugs for much shorter treatments, or non-pharmacological options.

It is understandable that the ACR guidelines gave some emphasis to the negative results of the NIH-sponsored GAIT study[9] which had a high placebo effect and was performed with glucosamine hydrochloride, the most widely used glucosamine salt in non-documented US dietary supplements. Conversely, it is much less understandable why OARSI, which is a global scientific organization, decided to contradict its previous guidelines[10], where the difference in efficacy between glucosamine sulfate and hydrochloride was well reported, as also supported by pharmacokinetic evidence[11]. This is confusing for guideline users, since it is important to understand that a general reference to 'glucosamine' may not be adequate when prescription treatment is considered.

Heterogeneity was reported as an issue for chondroitin sulfate trials too, but this is an obvious consequence of a number of studies being performed with different formulations or dosages and with different quality standards. On the other hand, OARSI itself acknowledges that the effect size on pain is always statistically significant: the only meta-analysis claiming a non-significant and

non-relevant effect in large high-quality studies[12] fails to acknowledge that two out of the three selected studies were ≥24 month trials for disease modification: patient characteristics in these trials make it difficult to see a symptom effect beyond 6–9 months[13], a sustained efficacy durability that was anyway never achieved by other symptomatic drugs beside chondroitin sulfate or glucosamine sulfate. Trial selection was also an issue in another network meta-analysis of both medications[14] highly criticized by the scientific community, whose negative conclusions were censored by the journal editor because they were considered not supported by the data[15].

OARSI decided not to overtly recommend glucosamine (sulfate) and chondroitin for symptom-modification and classify the evidence as 'uncertain': we find fault in not recognizing the differences between the evidence-based prescription drugs and other not well documented products. Finally, although this is not an approved indication, it is regrettable that OARSI could not even acknowledge the favorable data on the potential for joint structure modification of the prescription SYSADOAs, thus neglecting the evidence: this is at odds with the meta-analysis reported in the OARSI guidelines[16], that attributes a clinically relevant, statistically significant and homogeneous effect size in radiographic joint space narrowing to both chondroitin sulfate and (after three years of treatment, while the first year results were surprisingly considered more important in the OARSI document) glucosamine sulfate.

Hyaluronic acid

The case is much simpler for intra-articular hyaluronate, since this drug/medical device is available with the same quality and status in the USA, Europe and elsewhere, although in different formulations and with different molecular weight of the active ingredient. Indeed, both ACR and ESCEO recommend the use of hyaluronic acid after previous pharmacological (including non-steroidal anti-inflammatory drugs [NSAIDs]) or non-pharmacological treatments have failed to control symptoms[3,4]. Indeed, most trials and consequent meta-analyses document a small to moderate effect size in this difficult patient population. As reported in the OARSI guidelines, the efficacy of intra-articular hyaluronic acid on knee pain is longer lasting than that of intra-articular corticosteroids and the absolute effect size ranges between 0.37 and 0.46 in the two most recent meta-analyses available[17,18]. Even the latter of these two studies, a sponsored meta-analysis[18], showed such favorable results, including a clinically relevant effect size in the primary endpoint and similar data in a number of sensitivity analyses concerned with trial quality. However, the authors of this meta-analysis decided to rely mainly on the selective evidence of doubtful efficacy in a single secondary analysis, finally casting doubts on the efficacy of intra-articular hyaluronic acid in their conclusions. In addition, they also concluded that treatment with hyaluronic acid may be jeopardized by systemic adverse events that were apparently reported in a very small proportion of trials only and are actually never observed in common clinical practice: indeed, this finding was criticized for a possible lack of methodological rigor in the analysis[19]. OARSI decided to rely more on the conflicting conclusions of this meta-analysis[18] than on the actual evidence, thus assigning also to hyaluronate an 'uncertain' role in the management of knee osteoarthritis that may wrongly decrease physicians' confidence in this treatment. This is also at variance with a new network meta-analysis, showing that intra-articular hyaluronic acid is more effective than oral NSAIDs for knee OA pain[20].

Conclusions

While the OARSI guidelines suffer from a generalized approach that does not take into account the full evidence on some treatments and especially SYSADOAs, American and European recommendations are not free from criticism. Actually, the ACR guidelines are very much concerned with the US situation and may to a great extent not be applicable in Europe. Conversely, ESCEO attempted for the first time to devise an algorithm for the sequential application of interventions, rather than a mere exposition of the absolute evidence: while this approach may improve the currently scarce dissemination and implementation of OA management guidelines[1], the scientific literature still lacks in many cases appropriate evidence of sequential treatments after failure of the previous intervention.

One of the possible drawbacks of guidelines such as those issued by OARSI or ACR is that they conclude with either 'conditional' or 'uncertain' recommendations for the vast majority of the interventions considered, making it difficult for the practicing physician to select which agents or treatment modalities should be used. Conversely, adoption of an algorithm such as the one proposed by ESCEO allows prescribers to put the evidence into perspective and use a logical approach in sequentially applying the interventions. In such a way, the course of treatment is modified according to the patient's response.

With regard to the case of SYSADOAs, with all caveats connected to the 'uncertain' label that, as acknowledged by OARSI, does not necessarily have negative implications, as a global organization OARSI should have probably highlighted the differences in the pharmaceutical quality and regulatory status of SYSADOAs in the different regions, with the consequent differences in the available evidence. Similarly, a recommendation more in line with that of American and European guidelines for intra-articular hyaluronic acid might have better reflected current global evidence. In fact, prescription quality glucosamine sulfate and chondroitin sulfate have

satisfactorily demonstrated their efficacy and safety in the early and long-term management of knee osteoarthritis and indeed a more detailed analysis of the actual evidence allowed ESCEO to suggest adoption of the original prescription formulations of SYSADOAs in the very early steps of knee OA management. Moreover, there are few doubts about the favorable role of intra-articular hyaluronic acid in the treatment of more advanced stages of the disease, as described by the latest evidence.

Clinical trials in OA suffer from a large placebo effect[21] and most pharmacological treatments are shown to have, at best, a mild-to-moderate effect. This was confirmed in a very recent network meta-analysis[20] in which even the most widely prescribed oral NSAIDs had an effect size in the mild-to-moderate range over oral placebo, similar to that already described for prescription SYSADOAs in conventional, direct meta-analyses[8]. In this network meta-analysis[20], intra-articular hyaluronic acid emerged as the most effective treatment for knee OA pain, possibly thanks to the boost offered by the intra-articular placebo effect that hyaluronic acid was in any case able to overcome with a significant effect size, contrary to oral NSAIDs whose effect was not superior to that of intra-articular placebo.

In conclusion, while more studies are needed to further substantiate their precise effects, the availability of SYSADOAs such as glucosamine sulfate, chondroitin and hyaluronic acid widens the potential of the current physicians' armamentarium. An effort should be made by influential scientific organizations to share their expertise and find agreement on a treatment algorithm that puts the full evidence into perspective, extending the initial effort by ESCEO and putting physicians and specialists in the condition of prescribing the best available treatments for their patients.

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References

1. Nelson AE, Allen KD, Golightly YM, et al. A systematic review of recommendations and guidelines for the management of osteoarthritis: the Chronic Osteoarthritis Management Initiative of the U.S. Bone and Joint Initiative. Semin Arthritis Rheum 2014;43:701-12
2. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage 2014;22:363-88
3. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res 2012;64:465-74
4. Bruyère O, Cooper C, Pelletier J-P, et al. An algorithm recommendation for the management of knee osteoarthritis in Europe and internationally: a report from a task force of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). Seminars in arthritis and rheumatism 2014;43:253-63. Available at: http://dx.doi.org/10.1016/j.semarthrit.2014.05.014

5. Volpi N. Quality of different chondroitin sulfate preparations in relation to their therapeutic activity. J Pharm Pharmacol 2009;61:1271-80
6. Russell AS, Aghazadeh-Habashi A, Jamali F. Active ingredient consistency of commercially available glucosamine sulfate products. J Rheumatol 2002; 29:2407-9
7. Towheed TE, Maxwell L, Anastassiades TP, et al. Glucosamine therapy for treating osteoarthritis. Cochrane Database Syst Rev 2009;2:CD002946
8. Reginster JY. The efficacy of glucosamine sulfate in osteoarthritis: financial and nonfinancial conflict of interest. Arthritis Rheum 2007;56: 2105-10
9. Clegg DO, Reda DJ, Harris CL, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med 2006;354:795-808
10. Zhang W, Nuki G, Moskowitz RW, et al. OARSI recommendations for the management of hip and knee osteoarthritis: part III: changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthritis Cartilage 2010;18:476-99
11. Altman RD. Glucosamine therapy for knee osteoarthritis: pharmacokinetic considerations. Expert Rev Clin Pharmacol 2009;2:359-71
12. Reichenbach S, Sterchi R, Scherer M, et al. Meta-analysis: chondroitin for osteoarthritis of the knee or hip. Ann Intern Med 2007;146:580-90
13. Kahan A, Uebelhart D, De Vathaire F, et al. Long-term effects of chondroitins 4 and 6 sulfate on knee osteoarthritis: the study on osteoarthritis progression prevention, a two-year, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2009;60:524-33
14. Wandel S, Jüni P, Tendal B, et al. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. BMJ 2010;341:c4675
15. Groves T. Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. Report from post publication review meeting. BMJ 2011: published online 10 January 2011. Available at: http://www.bmj.com/rapid-response/2011/11/03/report-bmj-post-publication-review-meeting
16. Lee YH, Woo JH, Choi SJ, et al. Effect of glucosamine or chondroitin sulfate on the osteoarthritis progression: a meta-analysis. Rheumatol Int 2010;30: 357-63
17. Bannuru RR, Natov NS, Dasi UR, et al. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis – meta-analysis. Osteoarthritis Cartilage 2011;19:611-19
18. Rutjes AW, Jüni P, da Costa BR, et al. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. Ann Intern Med 2012;157:180-91
19. McAlindon T, Bannuru RR. Is viscosupplementation really so unsafe for knee OA? Nat Rev Rheumatol 2012;8:635-6
20. Bannuru RR, Schmid CH, Kent DM, et al. Comparative effectiveness of pharmacological interventions for knee osteoarthritis: a systematic review and network meta-analysis. Ann Intern Med 2015;162:46-54
21. Zhan W, Robertson J, Jones AC, et al. The placebo effect and its determinants in osteoarthritis: meta-analysis of randomized controlled trials. Ann Rheum Dis 2008;67:1716-23

