REVIEW

Chondroprotective agents: are we being too dogmatic?

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Recent major guidelines to osteoarthritis treatment have ceased to recommend the use of chondroprotective drugs; this new standing is based on new data, but comes mostly from a reassessment of existing information through methods of evidence-based medicine; these were more rigorous, with significant changes in the search and inclusion criteria, minimum follow-up requirement and the use of the concept of minimum clinically important improvement. However, currently available data includes a wealth of high quality studies demonstrating long term symptomatic relief and additional benefits such as global efficacy that match results described for non steroidal anti-inflammatory drugs. It is an undisputed concept that osteoarthritis should be managed as an integrated package of care rather than through single treatments, ministered alone or in succession. Thus, when osteoarthritis is in fact managed through any single treatment in order to conduct a controlled trial, it logically follows that it would be difficult to produce significant symptomatic improvements. Moreover, it is well established that positive placebo effects are a significant entity in osteoarthritis research. Therefore, it seems unreasonable to disqualify statistically significant results favoring chondroprotective agents used as monotherapy vs. a powerful placebo and consider them to be "not clinically relevant".

We performed a review of the literature and found high quality data showing that chondroprotective agents are safe, effective and decrease the use of non-steroidal anti-inflammatory agents. We therefore suggest that recent guidelines are overly dogmatic.

KEYWORDS: Osteoarthritis; chondroprotective drugs; treatment.

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INTRODUCTION

Over the last two decades there has been great interest in the use of chondroprotective agents for osteoarthritis (OA) treatment, a promising field, with over five hundred reported studies. However, recently published major OA guidelines[1-3] ceased to recommend the use of such drugs to treat OA, based on new data, but mostly reassessing existing information through methods of evidence-based medicine that were more rigorous, with significant changes in the search inclusion criteria, minimum follow-up requirement and the use of the concept of minimum clinically important improvement.

Undoubtedly, scientific evidence relating to the capacity of chondroprotective drugs to modify OA progression is very limited. Thus, to apply the expression "disease-modifying osteoarthritis drug" to such chondroprotective agents would be an overstatement. However, a good many high quality studies show long term symptomatic relief and additional benefits of these agents, including global efficacy similar to that non steroid anti-inflammatory drugs (NSAIDs) and a carry-over effect (i.e., an effect that lasts for months even after treatment suppression) with the use of chondroprotective agents. The slow onset of action makes it more appropriate to use the expression "symptomatic slow acting drugs for osteoarthritis" when referring to such agents.

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Symptomatic Slow Acting Drugs for OA – What about them?

Nutraceuticals. Nutraceutical is a portmanteau of the words "nutrition" and "pharmaceutical" which has come into general use. The use of chondroitin sulphate and glucosamine as well as the relevance of their clinical efficacy is constantly under debate. A recent meta-analysis concluded that there is no structural modifying effect of these agents based upon trials using joint space narrowing as a clinical end point[4]. Other meta-analyses[5], including two trials, reported small to moderate protective effects of glucosamine sulphate on minimum joint space narrowing after 3 years in knee OA. This was in accordance with the first high quality Cochrane analysis of glucosamine treatment in OA[6]. Data relating to a recently published trial[7] indicate that glucosamine sulphate can prevent total knee replacement. Five systematic reviews examined the efficacy of chondroitin for knee OA. Results differed regarding symptom relief, with four[4,5,8,9] finding no significant benefit of chondroitin over placebo for pain, while one[10] finds a

large effect in favor of chondroitin, in that it produced a significant reduction in joint swelling and effusion during the GAIT study.

Some findings suggest that a combination of glucosamine and chondroitin sulphate could be more efficient than either in isolation[10,11,12]. A 2-year follow-up randomized controlled trial demonstrated that the combination resulted in a statistically significant reduction of joint space narrowing compared to placebo while chondroitin sulphate or glucosamine alone were without effect[11]. The American College of Rheumatology conditionally recommends that patients with knee OA should not use the glucosamine and chondroitin sulphate combination[1]. The Osteoarthritis Research Society International recently released new guidelines[3] that did not recommend the use of glucosamine and chondroitin sulphate. Despite the good quality of evidence, low risk score and good effect size, the expert panel's vote resulted in "uncertain" recommendation for symptom relief and "inadequate" recommendation for disease modification.

Collagen Hydrosylate is obtained from collagenous tissues and contains high levels of glycine, proline and hydroxyproline, amino acids essential for the stability and regeneration of cartilage[13]. This product is generally recognized as a safe food ingredient by regulatory agencies. There are only three randomized controlled trials in the literature[14-16]. All of them showed that the use of a collagen hydrosylate dietary supplement improves joint pain, mobility and reduces the need for analgesic medication.

Diacerein. Diacerein, differently from traditional non-steroidal anti-inflammatory drugs, which inhibit prostaglandin synthesis is a slow acting, symptom modifying and perhaps disease-structure modifying drug for OA; its action occurs through interleukin-1 inhibition[17]. A Cochrane 2006 meta-analysis found a consistent benefit in pain improvement[18]. A 2010 systematic review and meta-analysis found statistically significant short-term benefits of diacerein for pain compared with placebo[19]. The authors suggested that diacerein might still be a safer alternative to non-steroidal anti-inflammatory drugs, which are associated with more severe adverse events. However, even this gold level evidence was insufficient to convince either the Osteoarthritis Society International or the American College of Rheumatology to recommend diacerein for OA treatment.

Bisphosphonates. Bisphosphonates could be chondroprotective by hindering the bone remodeling process. Higher doses of risedronate (15 mg/day) did not reduce the signs or symptoms of OA, but did reduce the marker of cartilage degradation (CTX-II), which may contribute to attenuation of radiological progression of OA[20]. However, there is some evidence that bisphosphonates are effective in the treatment of OA pain[21]. Along with other bisphosphonates, zoledronic acid has shown chondroprotective effects in animal models of OA[22] as well as a reduction in bone marrow edema and knee pain in a clinical trial[23].

Strontium Ranelate. Strontium ranelate, another drug used in the treatment of osteoporosis, may have anabolic effects on cartilage by directly promoting the formation of human cartilage matrix[24]. A three-year randomized controlled trial showed a chondroprotective effect and symptomatic improvement for knee OA[25].

Viscosupplementation. Viscosupplementation consists of the injection of exogenous hyaluronic acid into diarthrodial joints[26]. Clinical trials[27-29] and meta-analyses[30,31] have documented improvement in pain and function. Although previous Osteoarthritis Research Society International and American Academy of Orthopedic Surgeons guidelines supported viscosupplementation for knee osteoarthritis based on good quality studies[32], recently published guidelines no longer recommend this modality of treatment. The Osteoarthritis Research Society 2014 guidelines panel votes were influenced by inconsistent conclusions between the meta-analyses and conflicting results regarding the safety of intra-articular hyaluronic acid injections[3]. In the American Academy guidelines it was stated that although statistically significant outcomes were seen in studies using higher molecular weight hyaluronic acid preparations, these were not clinically significant, based on a lack of minimal clinically important improvement[2].

CONCLUSION

Osteoarthritis should be managed through an integrated package of care rather than by single treatments, alone or in succession. Core measures (patient education, exercise and weight loss) should be combined with other non-pharmacological treatments, such as orthoses, walking aids, acupuncture, and with pharmacological treatments. Thus, it is only to be expected that when osteoarthritis is managed with one single treatment in order to conduct a controlled trial, it would be difficult to produce significant symptomatic improvements. Moreover, it is well established that placebo effect in osteoarthritis is huge, with effect sizes sometimes exceeding 0.4. Therefore, we are talking about drugs that even administered as monotherapeutic agents, and even compared to a powerful placebo effect, still obtain symptomatic relief with statistical significance in a large cohort of studies. To dismiss such findings as "not clinically relevant" seems unrighteous. Present day reports contain a large number of high quality data showing that chondroprotective agents are safe, effective and lead to decreases in the use of non-steroidal anti-inflammatory agents. It may thus be argued that recently edited international guidelines may be excessively dogmatic.

RESUMO

"Guidelines" recentes produzidos por grandes entidades reumatológicas internacionais relativas ao tratamento da osteoartrite deixaram de recomendar o uso de medicamentos condroprotetores; estas novas recomendações baseiam-se em dados novos, mas principalmente em reavaliações de informações existentes, revisitadas através de métodos mais rigorosos de medicina baseada em evidências; estes novos métodos incluem mudanças significativas nos critérios de busca e de inclusão, com follow-up mínimo e na utilização do conceito de melhoria clinica minimamente importante. No entanto, dados atualmente disponíveis incluem uma abundância de estudos de alta qualidade, demonstrando alívio sintomático a longo prazo e benefícios adicionais, tais como a eficácia global a nível de resultados descritos para medicamentos anti-inflamatórios não esteroides. Por outro lado, é bem sabido que a osteoartrite deve ser gerida através de um pacote integrado de cuidados e não através de tratamentos, ministrados individualmente ou em sucessão. Por isso, quando a osteoartrite é tratada por meio de um

procedimento único, com a finalidade acadêmica de realizar um ensaio clínico controlado, não é de se esperar que apareçam melhorias sintomáticas significativas. Além disso, sabe-se também que efeitos placebo positivos são significativos na investigação de osteoartrite. Portanto, parece descabido exigir resultados clinicamente significativos, favorecendo agentes condroprotetores usados como monoterapia vs. um poderoso placebo e concluir que tais tratamentos "não são clinicamente relevantes".

Realizamos aqui uma revisão da literatura e encontramos uma abundância de dados de alta qualidade que mostram que os agentes condroprotetores são seguros, eficazes e capazes de diminuir o uso de agentes anti-inflamatórios não esteroides. Sugerimos, portanto, que as orientações recentes são excessivamente dogmáticas.

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