Innovations in the intra-articular therapeutic management of osteoarticular pain

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ABSTRACT

Osteoarthritis (OA) is a chronic condition affecting millions of people worldwide. Pain and loss of mobility are the main symptoms of OA. Current treatments for OA include non-pharmacological, pharmacological and surgical approaches. Among the pharmacological treatments, intra-articular (IA) therapy is usually offered when systemic oral medication does not provide satisfactory pain relief. The agents most widely used in IA therapy are corticosteroids and hyaluronic acid (HA) preparations. Now, however, multiple novel IA treatments are emerging on the market and their clinical effectiveness is promising. The innovative therapies for OA include new HA preparations such as HYADD® 4 and hybrid association of high and low molecular weight HA (HL-HA). The evidence for the use of platelet-rich plasma (PRP) is increasing, even though unanswered questions remain. Moreover, there are new therapies combining HA with other agents: PRP, polyols (mannitol or sorbitol), chondroitin, or polynucleotides; and all have been trialled with positive results. Novel IA agents proposed for treating OA include clodronate, collagen and mesenchymal stem cell therapy. Finally, further aspects of IA therapy to consider are new drug delivery systems, cost-effectiveness for pain reduction, and appropriate choice of therapy for the phenotype and stage of OA.

KEYWORDS

Intra-articular agents, innovations, hyaluronic acid, osteoarthritis.

Introduction

Osteoarthritis (OA) is a chronic degenerative disease affecting joints and causing pain, stiffness and loss of function, which can lead to physical disability. It is a very common condition in modern societies [1,2], and its prevalence is especially high among the elderly, since age is the main risk factor for developing OA [3]. With increasing life expectancy and better quality of healthcare, we are now seeing more people living with this chronic condition for longer [4]. Therefore, the disease burden of OA is growing and can be expected to continue doing so in the immediate future.

OA is characterised by progressive damage to the articular cartilage and bone due to mechanical factors of "wear and tear" and the release of inflammatory cytokines, resulting in narrowing of the joint space [5]. The diagnosis of OA is based on a careful medical history, and examination and analysis of radiological evidence. A four-grade scale called the Kellgren-Lawrence Classification of Osteoarthritis is used to stage OA based on a plain radiograph [6]. The level of symptom control in OA is monitored through the use of validated patient questionnaires that measure the levels of pain, stiffness and disability. Examples are the Western Ontario and McMaster Osteoarthritis Index (WOMAC) [7] and Patient Global Impression of Improvement (PGI-I) [8].

The management of OA should be tailored to the specific patient and include conservative (non-pharmacological), medical (pharmacological), and surgical interventions. At the moment, there are no treatments able to reverse the damage sustained by the joint cartilage and hence provide a cure for OA. Instead, current treatment focuses on managing the symptoms, mainly pain [9]. Both non-pharmacological treatments (lifestyle modifications, weight loss, physical exercise, etc.) [10] and pharmacological treatments (topical, systemic and intra-articular) can be used. Topical non-steroidal anti-inflammatory drugs (NSAIDs), such as diclofenac gel preparations, can be especially useful in treating knee OA [5]. Systemic medications include oral paracetamol, NSAIDs and selective COX-2 inhibitors, as well as low-potency opioids such as codeine. Duloxetine was also investigated versus placebo and found to be of benefit [8]. Furthermore, intra-articular (IA) injections are usually offered to patients who have not achieved adequate pain control through lifestyle modifications and systemic therapy [11,12]. This modality of treatment has particular benefits such as increased local bioavailability, minimised systemic exposure, less frequent adverse effects (AEs), and reduced overall cost [13,14]. However, it has to be noted that IA therapy has its lim-

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itations; pain usually responds to IA therapy only at the initial and middle stages of the disease (Kellgren-Lawrence grades I-III), and the effect is minimal in severe forms of OA [15]. What is more, IA injections require precision and experience and, therefore, need to be performed by specialised medical personnel.

Currently, the mainstay of IA therapy involves corticosteroids and hyaluronic acid (HA) preparations [13], which are both approved by the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) [16]. Corticosteroids such as triamcinolone have been widely used for IA injections due to their potent anti-inflammatory properties. They were shown to provide rapid pain relief in patients with OA and to be effective in cases of synovitis [16,17]. However, the therapeutic effect of corticosteroids lasts only up to around 4 weeks, whereas HA preparations have been shown to have a positive effect at 4-24 weeks post injection [17].

Hyaluronic acid is a non-sulphated glycosaminoglycan normally found in articular cartilage and synovial fluid. It acts as a shock absorber and provides lubrication inside the joint, in addition to promoting cellular healing processes [18]. HA has been found to have chondroprotective, analgesic and anti-inflammatory actions [19]. There are multiple preparations of HA with different molecular weights currently used in IA treatment [16].

Here, we discuss innovative preparations of HA, combination therapies of HA with other agents, as well as novel agents.

Hymovis® (Intra-Articular HYADD® 4; Fidia Farmaceutici, Abano Terme, Italy) is a relatively new derivative of HA. It is a new hydrogel engineered for greater viscoelasticity and longer residence time. A network stabilized by reversible hydrophobic interactions confers high viscoelasticity and stability to a medium molecular weight (MW) HA derivative. The resulting three-dimensional hydrogel is particularly hygroscopic with distinctive viscoelastic and rheological properties. Hymovis® was investigated as a single injection in patients with knee and hip OA (Kellgren-Lawrence grades I-III), and displayed a good safety profile and led to significant reductions in pain, Laquense index and analgesic use [20]. Furthermore, it was shown to decrease pain by 46.0% at 12-month follow-up in patients with mild-to-severe knee OA (Kellgren-Lawrence grades II-IV) [21].

High and low molecular weight HA (Sinovial® HL; IBSA) is an innovative formulation of HA containing two types of HA: high MW HA (1.4-2.1 x 103 kDa) linked to low MW HA (65-110 kDa). Through a patented thermal process without chemical modification, a hybrid cooperative complex of HA is formed showing optimal viscosity and HA concentration. It was demonstrated to provide effective, fast, sustained and safe pain relief from 1 until 24 weeks post single IA injection in patients with knee OA grades II-III [22].

Platelet rich plasma (PRP) therapy uses centrifuged whole blood with a high concentration of platelets in IA injections to help regeneration of osteoarthritic joints. There are various, diverse modalities of PRP extraction and production and, in addition, the efficacy of PRP can vary from one individual to another (due to differing concentrations of cytokines and growth factors) [11]. Nevertheless, PRP has been shown to reduce pain in the short and medium term (6-12 months) when compared to other IA treatments, especially in subjects with early stage OA, most probably due to the regenerative potential of damaged cartilage [23]. When used as a combination therapy, PRP and HA demonstrated a slight advantage over the use of PRP alone and a better safety profile [24].

Moreover, addition of a polyol, such as mannitol or sorbitol, to HA has been trialled for the treatment of OA. Polyols are strong antioxidants which scavenge oxygen free radicals and can stabilise HA, leading not only to slower degradation of the HA, but also faster reduction of inflammation and pain [24,25]. After injection, the exogenous HA is rapidly degraded by the reactive oxygen species present in the OA joint, which reduces its clinical efficacy by shortening the residence time in the joint. Addition of polyols to HA creates a complex based on a dense network of hydrogen bonds without modifying the viscoelastic properties of HA. The neutralization of oxygen free radicals by mannitol is effective on both linear and cross-linked HA. As demonstrated in a double-blind controlled comparative trial versus HA alone, these properties of polyols are able to accelerate the onset and increase the level of analgesia, with a good profile of safety and local tolerability [26].

In addition, the use of HA in combination with chondroitin, which is an important constituent of extracellular cartilage matrix, has been proposed and subsequently applied in patients with knee OA, proving to be effective and safe in reducing pain, improving mobility and decreasing analgesic use [27].

Intra-articular injection of clodronate could be a further approach to OA. Clodronate is a non-nitrogenous bisphosphonate showing anti-inflammatory, analgesic and anti-erosive properties observed in animal models of OA. Its mechanism of action includes depletion of synovial lining cells, reduced production of chemokines (IL-1, TNF-α), growth factors (TGF-β, BMP 2/4) and metalloproteases (MMP 2/3/9) preventing synovial hyperplasia and proteoglycan loss, and reduction of joint inflammation, joint swelling, and osteophyte formation. From a clinical perspective, patients with knee OA treated with IA clodronate experienced improvements in pain and joint mobility. Therefore, clodronate has mechanisms of action different from those of HA and could be added to HA to interfere with the pathogenic processes of OA progression [28]. More studies on the combined use of HA plus clodronate are ongoing.

Highly purified polynucleotides have been tested in association with HA due to their water-binding properties and potential in promoting chondrocyte repair. This combination therapy showed significant improvement in pain and mobility over the use of HA alone, thus demonstrating a synergistic activity of polynucleotides and HA [29-31].

Another agent suggested for use in treatment of OA is collagen [32]. A double-blind randomized active-controlled clinical trial study showed non-inferiority of collagen versus HA in patients with knee OA in both management of pain and duration of the therapeutic action. A combination therapy of collagen and HA is still to be investigated.

What is more, studies of mesenchymal stem cell (MSC) therapy showed positive results for OA pain management [3,11]. However, MSC therapy is still speculative when considering the lack of standardization in cell preparation procedure, and differences in amplitude and duration of clinical effect of MSCs.

Despite the numerous clinical trials and research studies on the use of MSC in the treatment of knee OA [33-36], the literature offers no unanimous criteria regarding the collection/isolation, culture conditions and characterization, quality or administration of these stem cells. It is still necessary to define the cell dosage and MSC characteristics in order to compare clinical outcomes and efficacy of authorized cell therapy treatments. The massive gaps between clinical trials and the requirements of cell therapy regulatory bodies and the market explain the unavailability of this treatment for clinical use. Although it seems to be a promising form of therapy, its appropriate indication, effectiveness and safety need to be further investigated and on a larger scale.

From the safety perspective, these IA treatments generally have few AEs that, moreover, are local, minor and transient. No systemic or severe AEs are reported. However, the injection must be performed using strict aseptic procedures. Skin infections, systemic infections, haemorrhagic disorders and uncontrolled diabetes are the main contraindications to the IA approach.

Finally, we should not forget to mention the placebo effect and its significance in IA therapy comparative studies, as there is substantial evidence showing that it is stronger than in topical or oral therapies [11].

Discussion

Nowadays, the field of IA therapy is continuously developing and the scientific community as well as patients are hopeful that the advances will provide more effective and more easily available treatments for OA. For this reason, certain aspects of IA therapy must be carefully taken into consideration.

First, how might we improve the effectiveness of already existing products in achieving faster pain relief, increasing the magnitude of pain reduction, prolonging the duration of the analgesic effect and, consequently, enhancing the quality of life of our patients? New systems of IA drug delivery such as polymeric microparticles, nanoparticles and biomaterials can help to answer this question [37-39].

On the other hand, the use of combination therapy is associated with an increased cost, and so its cost-effectiveness should be assessed. It is crucially important to know whether the rise in cost is reflected in an equally significant increment in pain relief provided by any combination therapy [40].

Currently the most investigated joint is the knee and proper schedules of treatments for knee OA are available. In the case of the hip, shoulder and trapezio-metacarpal joints, investigative studies are less numerous. In particular, there is a lack of agreement about the proper dosage, in terms of volume and number of injections, for each joint.

Lastly, OA is an inherently diverse condition. Among the patient population, there are multiple phenotypes as well as different stages of disease progression [41]. Today, we should be asking more questions to know which therapeutic agents are most appropriate for which groups of patients and at which stages of the disease, in order to provide more effective, rapid and long-lasting pain relief, as well as functional improvements for our patients. At present, the evidence suggests that patients affected by initial or intermediate stage knee OA are those that could benefit more from the use of these agents. Also, patients with normal weight and routinely doing physical exercise could achieve the highest level of clinical efficacy.

Conclusion

The modern horizon for IA treatment of OA is promising with multiple novel therapies and a substantial number of clinical studies performed. Nevertheless, it will be crucial to undertake more focused, rigorous and larger-scale studies to understand which treatment options are most effective and most appropriate for which patients.

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