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VISCOSUPPLEMENTATION IN OSTEOARTHRITIS

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ABSTRACT. Viscosupplementation is a new therapy for the treatment of OA and refers to the i.a. injection of hyaluronic acid (HA), a high molecular weight polysaccharide which is a major component of synovial fluid and cartilage, in order to relieve pain and improve function; In OA, the molecular weight and concentration of HA are diminished. The concept of viscosupplementation is based on the hypothesis that IA injections of HA could help restore the viscoelasticity of the synovial fluid and promote the endogenous synthesis of a higer molecular weight and possibly more functional hyaluronan, thereby improving mobility and articular function, and reducing pain. Hyaluronan and its derivatives to have a structure modifying action by retarding structural progression in OA of the knee is considered.

Keywords: osteoarthritis, hyaluronic acid, IA treatment

Osteoarthritis (OA) represents a major public health problem, holding the second position after cardiovascular diseases, its incidence and prevalence increasing with age. It begins as a degenerative disorder of the cartilage but affects the entire articulation, being manifested by pain and impaired joint function which develop progressively until invalidity, with major repercussions on the quality of life.

In this sense, ACR guidebooks from 2000 on OA determined the treatment pyramid in gonarthritis (after Hohberg and Creamer), which also mentions intra-articular (i.a.) treatment of viscosupplementation or steroids.

Hyaluronic acid (HA) – hyaluronan – is a negatively charged poly-anionic polysaccharide, also known as glycosaminoglycan which alternatively contains units of N-acetylglucosamine and molecules of sodium glucuronate. The chain of polysaccharides contains 12,000 units of disaccharides and has a molecular weight of 4-6 million. It is present in several extra-cellular compartments (aquos humour, umbilical cord, the extra-cellular matrix of the skin, cartilage, synovial liquid).

Hyaluronic acid is an important constituent of synovial liquid (SL) (2/4 mg/ml), playing an essential role in articular homeostasis by the functions it holds: contributes to joint lubrication, absorbs the impact on the joint surface, constitutes a permanent source of regeneration for joint tissue, confers analgesic and anti-inflammatory properties to the SL. The lyophil character of HA plays an important role the effects it has on the cell membrane; it is synthesized by chondrocytes and type-B synovicytes. In OA, the HA of SL is depolymerized with the diminishing of its molecular weight and of its visco-elastic properties, the cartilage becoming more vulnerable to lesion factors due to the alteration of the protective lubricating properties.

By **viscosupplementation** we understand the restoring of physiological and rheological conditions of the arthritic joint and of the respective tissues by i.a. injection with HA solutions; clinical improvement is based on the supplementation of the viscous and elastic properties of the pathological SA.

The effects of i.a. hyaluronic acid administration can be summed up as follows:

- creates a viscoelastic protection of articular surfaces (the synovial membrane and the cartilage);

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- covers the pain receptors in the articular capsule and diminishes their sensitivity;
- restores the filtering property of the SL;
- removes free oxygen radicals and inflammatory factors from the articular surface;
- inhibits the migration and phagocytosis of macrophages and granulocytes.

In vitro studies on synoviocytes coming from arthritic joints show that exogenous HA stimulates in vitro synthesis of this molecule and inhibits the release of arachidonic acid, and consequently E2 prostaglandin synthesis, induced by interleukin1. (T. Yasuda et al., 2005)

HA exerts an incidence on the adherence of proliferation, migration and leucocyte phagocytosis and gives protection against the cellular enzymes produced by reactivated oxygen radicals. HA induces the aggregation of fragmented proteoglycans in the cartilage, stimulates proteoglycan synthesis on adding chondroblast cultures, protein synthesis, sulphatic aminoglycan glycolysis both in fibroblasts and in chondroblasts (Bellamy N. et al., 2005).

There have been many **in vitro** studies carried out on various animals in which spontaneous arthritis was induced or which were subjected to various experimental methods, and which were administered i.a. HA. Thus, in rabbits, arthritis was induced by synoviectomy or vitamin A injection; in dogs, by cutting the crossed anterior ligament (the Kenneth method); in rats, by bradyquinine or PGE injection. Intra-articular infiltrations with HA had positive results in painful arthritic models, in the sense of preventing or delaying degenerative damage in the articular cartilage (Asari A. et al., 1998).

Intra-articular use of HA products with various molecular weights is currently used extensively in the therapy of OA. The first to conduct these experiments were Namiki et al., 1982; Balazs and Delinger, 1985; Dixon, 1988.

Among **HA pharmaceutical products** in the form of sodium hyaluronate we can mention:

- **Synvise** (Hylan G-F20, Hylan A+B 8mg+2mg/ml) in natrium chloride solution, GM=6,000,000 DA, PH=7.2, product of Genzime USA;
- **Hyalgan** (hyalart, polyrheumin) GM=500-730 KDA; product of Fidia, Italy;
- **Hyalgan** (20 mg/2 ml) CSC Pharmaceuticals Handels GmbH;
- **Ostenil** (sodium hyaluronate 1%, 10 mg/ml)GM=1,200,00 DA, produced by bacterial fermentation by TRB Chemedica;
- **Synovial** (HA 0.8%, 16 mg/2ml) GM-800-1,200 KDA, produced by IBSA, Switzerland;
- **Suplazyn** (NAD – the non-animal derived; NHD – non-heat degraded, 20 mg/2 ml) GM=500-750,000 DA, produced by Bioniche Pharma Group Limited;
- **Orthovisc** GM=1.7-2,000,000 DA, produced by Anika therapeutics Woburn Massachusetts;
- **Artz** GM=600-1,200,000 DA, produced by Seikagacu Tokyo Japan;
- **Adant** GM=600-1,2000,000 DA, produced by Maji Seika Japan;
- **Bio Hy** produced by Savient East Brunswick New Jersey;
- **Visciseal** 0.5 AH, 5 mg/ml, MW > 6.000.000 DA, produced by bacterial fermentation from animal protein, by TRB Chemedica;
- **Arthrum H** NaHA 40 mg/2 ml, sodium hyaluronate 2%, GM=2.4 million DA, produced by genetic engineering, biotechnological fermentation and associated with animal tissue extracts; product of LCA Pharmaceutical.

Several international multi-center studies, carried out in Europe, Canada, America and Australia, regarding the effectiveness of i.a. administration of HA products to a large number of patients, using the double-blind method, placebo or versus with i.a. Methylprednisolon, or concomitant or comparative administration with Naproxen, Sodium Diclofenac, mentioned the following **effects**, mainly in gonarthritis, plus three

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studies for the shoulder joint, two studies for the hip joint, and a recent study for the metatarsophalangeal joint of the index (Lussier A. et al., 1996, J.P.Raymond et al., 2002, Petrella R.Y. et al., 2002 , Altman R.D. et al., 1998):

1. **Improvement of symptoms**: relief of pain after 35 days, but mainly after 60 days of treatment (pain at rest, upon touch, during walking – VAS), stiffness, joint function (WOMAC, Lequesne index), with increased joint mobility observed by the physician and the patient; (Bellamy N. et al., 2005, Petrella R.Y. et al., 2002)
2. **Reduction of effusion and recurrences** mainly after 60 days of treatment, correlated with radiological alterations of cartilage damage and increased capacity of the synovial membrane to act as a barrier;
3. **X-ray** remains the golden standard of monitoring OA, according to the **Kellgren-Lawrence score**; the more recent use of surrogate markers **JSW – Joint Space Width** – greater than 4.6 mm, determined by computer digital image analysis system (DIA) during the repeated i. a. HA cycles, as well as **JSN – Join Space Narrowing** measurement, with an annual rate estimated between 0.22 – 0.6 mm/year. MRI shows the volume of the cartilage (Wluka et al. 2003; Jubb R.W. et al., 2003);
4. **Arthroscopic studies** showed the **reduction of chondropathy** in OA treated with i.a. HA (Listrat);
5. **Reduction of synovial inflammation** through the reduction of neovascularization and of the hemorrhagic effect (Frizzier et al.);
6. **Anti-inflammatory effect of HA**, especially of its immune-modulating effect, was obtained through the results of the cytologic exams with fluorescent-activated cells (FACS), carried out on SL cell populations: polymorphonuclear lymphocytes, T lymphocytes (CD3, CD4, CD8), activated T lymphocytes (CD3 + HLADR, CD3 + IL2R) – Corrado, Peluso, Durante, Palmieri, Savoia, Oriani, Tojana. The decrease of SL cellularity was correlated with the reduction of joint welding, and that of the activated cells was noted in the groups treated with i.a. HA, both for the lymphocyte population and for the monocyte-macrophage phenotypes, where there was also a significant decrease of the cell density of class II histocompatibility antigen expressed through fluorescence intensity, after HA therapy; (Mahee E. et al., 2002; Bellamy N. et al., 2005).
7. **Biochemical analyses in SL** after treatment show **the general decrease of the concentration of the various protein types** (total proteins, albumin, C3 fraction of the complement, immunoglobulins, antitripsin, transferin, ceruloplasmin. α1 – glycoprotein, α2 – macroglobulin) and of their ratio SL/plasma, carried out by high resolution electrophoresis, due to the decrease of their joint exudation and the repair of the barrier function of the synovial membrane. (Em.Corrado et al., 1995)
8. **Exogenous HA improves the rheological characteristics of SL**, brings back normal viscosity through its direct action and probably by stimulating synoviocyte synthesis, improving the quality of the mucin clot by increasing its concentration and molecular weight;
9. **it delays the development of cartilage damage**, with the repair of the surface layer, by decreasing proteoglycan depletion in the cellular matrix and protecting chondrocytes by preserving their viability and, implicitly, the regeneration process; (Gossec I. et al.,2004)
10. **The treatment with i. a. HA injections improves the quality of life**, reduces co-therapy excess and of systemic adverse reactions.

CONCLUSIONS

Successive, cyclical i.a. treatment with HA reduce pain and improve function in early stages of the arthritic disease.

In vitro and *in vivo* studies have shown that HA products induce structural alterations in the knee, influencing the progression of OA, by stimulating the synthesis of cartilage matrix, inhibiting degradation and apoptosis,

and contributing to the effectiveness of long-term treatment.

Clinical improvement in patients treated with HA cannot be accounted for only by the beneficial mechanism of the increased viscosity of SL, but mainly by the biological activity, especially by the control of the inflammatory processes and by the immune-modulating effect on the inflammatory cells, which become less active; the direct interaction with highly-specific HA receptors (CD44 receptors) can be considered the trigger element in this sense.

Hyaluronic acid plays a major role in maintaining articular homeostasis through the variations in its concentration and molecular weight.

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