Comparison of efficacy and therapeutic safety of two treatments based on hyaluronic acid (Go-On and Hyalgan) in knee osteoarthritis

F. ARENSI
San Siro Clinical Institute, Milan

Aim. To compare the efficacy and therapeutic safety of two formulations of hyaluronic acid, in patients with knee osteoarthritis.

Methods. In this controlled, randomized, parallel-group study, 40 patients (30 females, 10 males, mean age 64 years), with diagnosis of knee osteoarthritis (OA) and pain severity over 20 mm on the Visual Analogue Scale (VAS), were assigned by randomization to one of the two study formulations of hyaluronic acid, Go-On (Go) and Hyalgan (Hy). The patients were treated with two intra-articular injections every week for 5 weeks with 3 months of follow-up. Symptoms and function parameters were assessed weekly until the fifth week and at 3 months of follow-up. At the end of the treatment, the physician’s and the patient’s overall evaluations were recorded.

Results. Pain, articular stiffness and joint function, as WOMAC index subscales, Lequesne index and general health state improved with both treatments and showed no statistically significant difference between formulations. Treatment tolerability was excellent. The physician’s evaluation on treatment efficacy was good in 55% of patients with both treatments as well as patient’s evaluation on acceptability was good in 55% of patients treated with Go and in 50% of patients treated with Hy.

Conclusion. It may be stated that the two formulations of hyaluronic acid employed in the treatment of knee OA exhibit a totally overlapping efficacy and therapeutic safety.

Key words: Osteoarthritis - Hyaluronic acid - Knee.

Osteoarthritis is one of the main causes of inability and is one of the most common pathologies of the musculoskeletal apparatus. Its etiopathogenesis is not totally known, it is surely multifactorial and genetic, constitutional and environmental factors are involved.

The objectives of the interventions on osteoarthritis are the following: patient’s education, pain relief, improvement of the articular function and delay of disease progression.

The pharmacological management of OA includes symptomatic treatments with analgesic, non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular steroids (“symptom-modifying drugs”) and with drugs which modify the articular structure (“structure-modifying drugs”), namely capable of acting on the anatomical damage of the joints with a positive impact on the disease progression.1,2

NSAIDs are the most common acute symp-
tomatic treatment of OA, but their use has a poor risk/benefit ratio and a resulting reduced long-term therapeutic safety with the potential worsening of the arthritic process, as they could interfere with the cartilage trophism.

In view of the disease characteristics, slow-acting symptomatic drugs (SYSADOA) find a rationale. Among them we mention oral glucosamine sulphate which is also capable of modifying the articular structure, and hyaluronic acid by intra-articular administration.3

Indeed, the American College of Rheumatology recommends to employ intra-articular injections of hyaluronic acid as an alternate to oral analgesics or to NSAIDs for the symptomatic treatment of pain correlated to the knee OA.4

Hyaluronic acid (HA) is a polysaccharide consisting of non-sulphurated chains including dimers of N-acetylglucosamine and glycuronic acid with a mean molecular weight of 4-5 million Daltons. HA is the main constituent of connective tissue in which it confers features of stability and elasticity to the articular structure. Indeed, it is able to lubricate the joint with a resulting protection of the articular heads and preventing the mechanical injury with an absorption of traumas conferring resistance to the cartilaginous tissue and hydration to the connective tissue.5

In osteoarthritis where the synovial fluid loses viscosity and ability of lubricating and absorbing shocks, with a resulting increase in the mechanical stress and loss of articular cartilage,6,8 HA acts as a lubricant and mechanical support. As hyaluronic acid formulations available for the treatment of arthritis may differ in molecular weight, origin and technique of administration, aim of this study was to compare the efficacy and therapeutic safety of two formulations of hyaluronic acid having different molecular weights, origins, and mode of administration in the treatment of OA of the knee.

**Materials and methods**

The present study was approached with a controlled, randomized, parallel-group experimental design.

Patients of both sexes, older than 40 years, with diagnosis of OA of the knee and pain severity over 20 mm of the Visual Analogue Scale (VAS), were randomly assigned to one of the two study formulations of sodium hyaluronate: Go-On (Go) and Hyalgan (Hy). Go contains 25 mg in 2.5 mL of sodium hyaluronate of a mean molecular weight of 1 400 Kda, and Hy contains 20 mg in 2 mL of sodium hyaluronate of molecular weight between 500 and 750 kDa. Go is supplied in pre-filled syringes while Hy is supplied in vials containing the solution for injection to be transferred to the syringe.

The patients were treated with two intra-articular injections a week for 5 weeks and afterwards were followed-up for 3 months.

The main exclusion criteria were the following: other rheumatic pathologies ongoing; remarkable anomalies of the hematologic, hepatic, renal or metabolic functions; development and previous manifestations of hypersensitivity reactions to the drug.

No other concomitant intra-articular therapies were allowed.

Before starting the treatment, the patients signed a written informed consent to undergo an infiltrative therapy with hyaluronic acid.

The study was carried out in agreement with the recommendations of Helsinki Declaration and its revisions.

The criteria of evaluation of efficacy, assessed at baseline, weekly until the fifth week and at 3 months of follow-up, were the following: WOMAC index (Western Ontario and McMaster Universities) expressed as total score and pain, stiffness and joint function subscales; Lequesne index for pain; movement restriction and ability of walking, and general health state evaluated with the VAS scale (0-100 cm; 0=worst – 100=excellent). Both function indices result from the sum of the scores corresponding to 24 questions of a questionnaire to which the patient should answer.

At the end of the study, the physician’s evaluation on the efficacy of the treatment and the patient’s evaluation on the treatment acceptance were assessed by a semi-quantitative scale from 0 to 4 (0=null, 1=poor, 2=fair, 3=good, 4=excellent).
Any side-effects occurring during the study, the time of onset, severity, duration and correlation, were recorded using an appropriate Case Record Form.

Statistical analysis

The statistical analysis was carried out with the analysis of variance with multiple pair comparisons.

Results

The study included 40 patients, equally divided into the two study treatments. The patients had homogeneous historical features and severity of the initial conditions in the two groups (Tables I, II).

Lequesne index improved versus the baseline in a progressive and constant way from the third week of treatment in both groups. The reduction of severity of the Lequesne index continued also in the three months of follow-up after discontinuation of the administrations, even reaching the statistical significance (P=0.04) versus the 5th week in patients treated with Go (Figure 1).

Pain, articular stiffness and function subscales of WOMAC index showed a similar pattern for both treatments with a clear-cut reduction of the score of severity in time (Figures 2-4). The improvement was appreciable from the third week of infiltrations for both the preparations and obtained the statistical significance from the 4th week keeping the result obtained until the end of the 3-month follow-up after the treatment discontinuation.

The global health state improved at the end of the treatment and of the follow-up period of 5.1% and 5.9% in the Go group and of 2.8% and 3.1% in the Hy group.
All the tested parameters revealed a statistically significant difference versus the baseline for both treatments, whereas no statistical difference was observed between the two formulations of hyaluronate.

During the treatment, three patients in both groups complained moderate gonalgia: 2 after the first week and one after 4 weeks of therapy in Go group and all after the first week of therapy in Hy group.

Concerning Go, the physician’s evaluation on treatment efficacy was excellent in 15% of patients and good in 55% of patients; for Hy, the physician’s evaluation was excellent in 20% of patients and good in 55% patients.

The patient’s evaluation on treatment acceptability was excellent in 10% of patients and good in 55% of cases for Go and excellent in 15% and good in 50% of cases for Hy.

**Discussion**

The results of the present study show that both treatments with hyaluronic acid were found to be likewise effective in knee OA.

Indeed, the two formulations have reduced the painful symptomatology and improved the articular function of knee OA and were found to be both well tolerated by the patients. A better handiness may be ascribed to Go as prepared in prefilled syringes, differing from Hy which requires a further passage for the transfer of the solution for injection from the vial to the syringe with a potential lower asepsis.

The differential characteristics of the two sodium salts of hyaluronic acid are their origin and molecular weight. Sodium hyaluronate contained in Go is obtained from *Streptococcus equi* by fermentation processes and subsequent purification, whereas the one contained in Hy is extracted from rooster combs, with a further point in favor of Go concerning the risk/benefit ratio. The molecular weight of hyaluronic acid is optimal if between 500 and 4000 kDa, because it is physiological with a high binding affinity and, thus, capable of stimulating the production of endogenous hyaluronic acid. On the contrary, a molecular weight lower than 500 kDa has a weak binding affinity and does not stimulate the biosynthesis of hyaluronic acid.

Sodium hyaluronate contained in Go has a molecular weight 2-3-fold greater than the one contained in Hy: 1400 kDa versus 500-730 kDa. This aspect is an advantage for Go, because it makes Go more resistant to wear and decay with a better rheologic profile, which can be measured by the features of an optimal viscosity.

This study confirms that the viscosusplementation is a treatment useful in the therapy of knee osteoarthritis, thus contributing to block the degeneration of the joints involved by the arthritic disease.

Viscosity of synovial fluid is mainly due to
the presence of hyaluronic acid, whose features of viscoelasticity are, therefore, responsible for the protection, lubrication and stabilization of the cells and tissues during the articular motions.

In arthritic pathology, during the acute stage of the inflammatory process, the rheologic features of endogenous hyaluronic acid change and its molecular weight and concentration in the synovial decrease.

Therefore, the rationale of hyaluronic acid in the therapy of arthritis is based on the hypothesis that the supply of exogenous hyaluronic acid could replace the reduced articular lubrication and the lower abilities of shock absorption of endogenous hyaluronic acid during arthritis. The whole is supported by the real increase in viscosity of synovial fluid and the concentration and/or molecular weight of hyaluronic acid which could be observed in the animal model and in the arthritic patient treated by intra-articular route withy preparations containing hyaluronic acid.

Riassunto

Obiettivo. Confrontare l’efficacia e la sicurezza terapeutica di due formulazioni di acido ialuronico, in pazienti con osteoartrosi del ginocchio.

Metodi. Nello studio, controllato, randomizzato e per gruppi paralleli, 40 pazienti (30 di sesso femminile, 10 di sesso maschile, età media 64 anni), con diagnosto di osteoartrosi (OA) del ginocchio e gravità del dolore superiore a 20 mm di Scala Visuale Analogica (VAS) sono stati assegnati casualmente a una delle due formulazioni di acido ialuronico in studio (Go, Go-On e Hy, Hyalgan). I pazienti sono stati trattati con 2 iniezioni intrarticolari alla settimana, per 5 settimane con 3 mesi di follow-up. Sintomi e parametri funzionali sono stati valutati settimanalmente fino alla 5ª settimana e a 3 mesi di follow-up. Al termine del trattamento, medico e pazienti hanno espresso un giudizio complessivo sul trattamento.

Risultati. Il dolore, la rigidità e la funzionalità articolare, valutati nelle sottoscale dell’indice WOMAC, l’indice di Lequesne e lo stato generale di salute sono migliorati per entrambi i trattamenti e non hanno evidenziato alcuna differenza statisticamente significativa tra loro. La tollerabilità ai trattamenti è stata ottima. Il giudizio del medico è stato buono nel 55% dei pazienti, per entrambi i trattamenti; così come il giudizio del paziente è stato buono nel 50% dei pazienti trattati con Go e nel 50% dei pazienti trattati con Hy.

Conclusioni. Si può affermare che le due formulazioni di acido ialuronico utilizzate nel trattamento dell’OA del ginocchio mostrano un’efficacia ed una sicurezza terapeutica del tutto sovrapponibili.

Parole chiave: Osteoartrosi - Acido ialuronico - Ginocchio.

References