

GALACTOSAMINOGLYCURONOGLYCAN SULFATE (MATRIX) IN THERAPY OF TIBIOFIBULAR OSTEOARTHRITIS OF THE KNEE

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Summary: *To evaluate the efficacy and tolerance of galactosaminoglycuronoglycan sulfate (Matrix vials) in the therapy of tibiofibular arthritis of the knee, forty patients suffering from this illness at radiological stages 1 and 2 undergoing concomittant therapy with NSAIDS, were randomized into two groups of twenty. The treatment group received the drug under study and the control group received placebo. Treatment was carried out in double blind. The therapy protocol comprised 25 intramuscular injections (one injection twice a week). This cycle was repeated for 6 months, for a total of 50 injections. The patients were visited on days 0, 90, 180, 240, 330 and 360. At each visit the following symptoms were evaluated: spontaneous pain, pain on loading, on passive movement and on pressure; changes in NSAIDS posology were also recorded; lastly any possible side effects were noted. Analysis of results has shown a statistically significant higher therapeutic effect on treatment with Matrix for all the symptoms taken into consideration. No important side effects were noted, either local or systemic; in two cases only in the group treated with Matrix and in the same number in the control group slight dyspeptic symptoms were found to occur, but without requiring suspension or reduction in posology. Two patients in the Matrix group and one in the control group left the study for non-compliance with the type of administration. The good clinical results obtained, together with the excellent tolerance shown by the drug, suggest that Matrix may be the drug of choice in the "basic" therapy of osteoarthritis, with its efficacy being demonstrated in an increasing number of clinical studies.*

Introduction

As opposed to senile arthritis, which occurs in old age and is connected to the physiological ageing of cartilaginous tissue, primary osteoarthritis (OA), which presents in the age group between 45 and 55, is a true pathological process of cartilaginous tissue involving well-studied characteristic histological and biochemical alterations. The major factor at the basis of this condition is most certainly a defect in the elaboration of the structural macromolecules of the cartilage. These substances are

glycosaminoglycans (GAGs) which, when joined to a protein backbone (PG), constitute the interfibrillar basic substance of the cartilaginous matrix, i.e. the substance which fills the spaces in the collagen network.

Due to their capacity to absorb and desorb water molecules, by way of their functional group charges, PGs can modify the characteristics of cartilaginous tissue according to the charge, giving cartilage its typical hardness, elasticity, surface smoothness and capacity to absorb shocks due to mechanical stress (1-3). They are responsible for

the fundamental protective action via "excluded volume".

In osteoarthritic cartilage there is an increase in the catabolism of PG (4, 5). The degradation of GAGs is carried out by lysosomal enzymes released by leukocytes, with lysosomal elastase being of particular importance (6). The loss of interfibrillar substance causes the exposure of collagen fibres, which are in turn attacked by collagenases. In the final phases, the entire cartilage matrix dissolves and the damage extends to the tissue cells, with progressive atrophy of chondrocytes. An important phenomenon to be noted is the attempt by healthy chondrocytes to repair damage to tissue by increasing the synthesis and the release of GAGs into the extracellular matrix.

The exogenous administration of GAGs has been found to inhibit enzymatic degradation of both PG and collagen (7, 8). GAGs also inhibit the mediated inflammation of the complement (9), and in the last analysis have an anti-inflammatory action mechanism different from that of NSAIDs. Some GAGs such as chondroitin sulfate (CS) have been found effective in improving symptomatological aspects in patients with OA (10). Galactosaminoglycuronoglycan sulfate (GAGGS - Matrix), composed of chondroitin 4,6-sulfate has been found to be effective in the chondroprotective therapy of OA in numerous studies.

In this study it was decided to test Matrix administered by intramuscular route in the therapy of tibiofibular arthritis of the knee. The study was therefore carried out in double blind against placebo on forty patients suffering from this illness, receiving concomitant therapy with NSAIDs.

Patients and methods

The forty patients enrolled in the trial, aged between 60 and 65, were randomized into two groups of twenty patients each. One group was treated with Matrix (twelve women and eight men, mean

age 57.3 ± 3.9) and the other with placebo (physiological solution with the same viscosity and colour as Matrix) (ten women and ten men, mean age 55.2 ± 3.6). In all cases a diagnosis of tibiofibular arthrosis of the knee (stage 1-2) had been made during the previous 6 months; in both groups there were seven cases of stage 1 osteoarthritis and thirteen cases of stage 2 osteoarthritis. All patients were receiving therapy with NSAIDs. No patients using "chondroprotective" or corticosteroid drugs in the 6 months preceding the trial or patients with serious systemic pathologies were admitted to the trial.

The therapeutic protocol was 25 intramuscular injections (1 injection twice a week). This cycle was repeated after 6 months, for a total of 50 injections. The patients were visited on days 0, 90, 180, 240, 330 and 360. During the medical examinations the following signs of spontaneous pain, measured by the Scott-Huskisson analog visual scale, on passive movement and on pressure, measured on a scale from 0 to 3 (worsened, stationary, improved, greatly improved) were recorded; changes in permitted NSAIDs posology were also recorded (diclofenac, cinnoxicam, naproxen, tenoxicam or ketoprofen). Both the patient and the researcher expressed a final opinion regarding the efficacy of the therapy (worse, stationary condition, average improvement and substantial improvement). The efficacy of the treatment was evaluated by the Student's t test for pain, and by the chi square test for opinions expressed by the patient and researcher.

Lastly, possible side effects were recorded, including questioning of the patients expressly regarding the following symptoms:

- pain, swelling and bruising at the injection site;
- onset of dermatosis at the injection site;
- itching at the injection site (immediately, after several hours, after several days);
- feeling of illness after the injection;
- swelling after the injection (eyelids, genitals, oral-pharyngeal mucosae)

- pyrosis, dyspepsia, loss of appetite, intestinal disorders;
- bleeding from anus/rectum;
- tachycardia;
- sensation of facial heat;
- epistaxis;
- onset of ecchymosis or petechia;
- visual disorders.

Results

Four patients (two in the Matrix group and two in the control group) left the study due to low compliance with the prolonged intramuscular treatment. All the other patients terminated the protocol and were evaluated in the results of the study.

The course of spontaneous painful symptoms is shown in Fig. 1. It can be seen how therapy with placebo, after improvement in the initial phase, leads eventually in the closing phases of the study to a situation similar to that found at start of treatment; in the group treated with Matrix however, the improvement in symptoms is significantly higher in all follow-ups carried out ($p < 0.01$) and at termination of treatment when compared to start-up. Figure

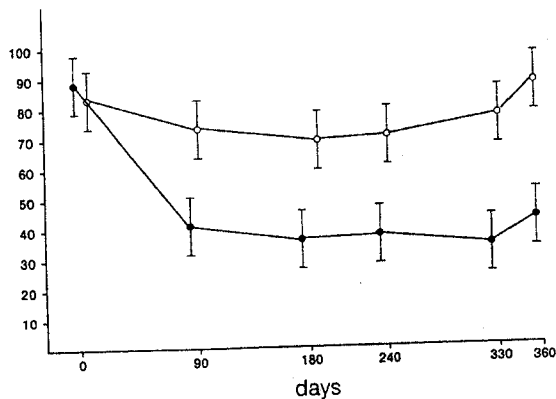
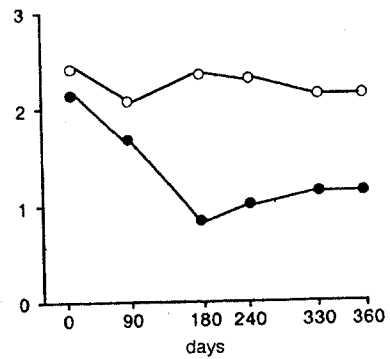
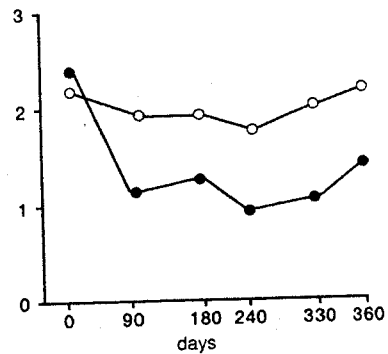


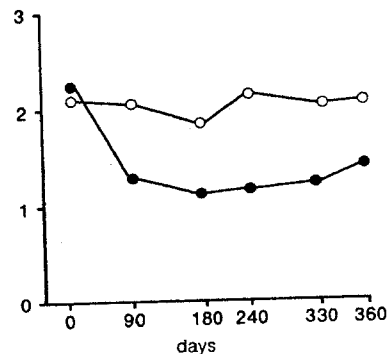
Fig. 1 Spontaneous pain measured using the Scott-Huskisson analog visual scale in mm ($\bar{x} \pm s.d.$); (●) patients treated with Matrix, (○) patients treated with placebo.



PAIN ON LOADING



PAIN ON PASSIVE MOVEMENT



PAIN ON PRESSURE

Fig. 2 Algo-functional index of arthritis of the knee ($\bar{x} \pm s.d.$) (●) patients treated with Matrix, (○) patients treated with placebo.

2 shows the course of painful symptoms after loading, passive movement and on pressure, evaluated on a numerical scale from 0 (no symptoms) to 3 (maximum intensity). Table I lists final opinions on modifications of each separate symptom, expressed at the end of the therapeutic cycle, according to the scale shown in the same table. The better results obtained with Matrix are also evident here. Such results are statistically significant, and were better than in placebo for all symptoms taken into consideration. No variations in radiological aspects were observed between the two groups.

Evaluation of the reduction in the consumption of NSAIDS showed no statistically significant differences between the two study groups, underlining a reduction in NSAIDS posology in the group treated with Matrix in contrast to unchanged consumption in the control group (Fig. 3). The overall opinion regarding the efficacy of the preparation (Table II) was in favour of Matrix over placebo.

As regards tolerance and onset of side effects, as mentioned above two patients left the study for poor compliance. In the group treated with Matrix, tolerance was considered excellent in fifteen cases, good in two (dyspepsia) and fair in one (pain at injection site). In the group treated with placebo, tolerance was excellent in sixteen cases and fair in two (pain at injection site). Laboratory tests showed no variations in the main parameters in both groups studied.

Discussion

Chondroprotective therapy is gaining increasing favour, as it is supported by physiopathological confirmation and positive clinical findings. The drug used in these trials is one of the most interesting, as it associates good therapeutic effects with excellent tolerance. In particular, in contrast to other similar preparations, Matrix does not give rise to any risk of the "heparinic" effect, thanks to its low sulfur content. Furthermore, the high level of deproteinization of the molecule guarantees against allergic reactions.

The use of Matrix has given very satisfactory results as regards reduction of painful symptoms and renewed functionality of the limbs. Of particular interest is the fact that these results have been obtained over a relatively short period of time; at the first check-up the difference compared to the control group was already significant. Treatment with NSAIDS in the study group decreased from start-up of the study, whilst controls showed no reductions in initial dosages; probably improvements in this aspect will require longer treatment times, after which reintegration of the basic substance of cartilage will have led to renewal of the integrity of the joint.

For the same reason it has not been possible to observe modifications in radiological aspects after two therapeutic cycles. However, improvements in

Table I Algo-functional index of arthritis of the knee. Evaluations^a carried out at the end of the therapeutic cycle (360 days) by simple semantic scale (mean \pm s.d.).

Symptom	Matrix		Placebo		p
	patients	score	patients	score	
Pain on loading	18	2.36 \pm 0.68	18	1.23 \pm 0.88	< 0.01
Pain on passive movement	18	2.11 \pm 0.69	18	0.81 \pm 0.54	< 0.01
Pain on pressure	18	2.42 \pm 0.88	18	1.17 \pm 0.74	< 0.01

^a Score used: worse = 0, stationary = 1, improved = 2, substantially improved = 3.

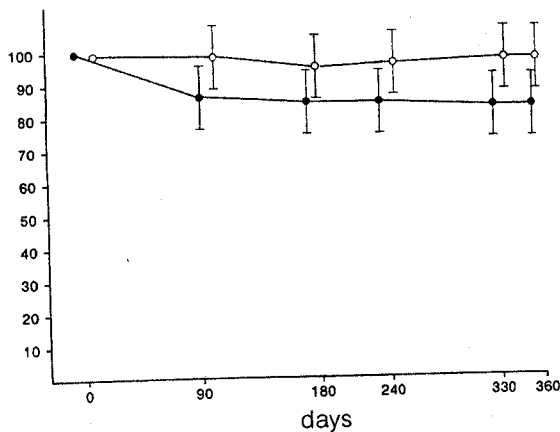


Fig. 3 Percentage reduction in NSAIDS consumption ($\bar{x} \pm s.d.$). (●) patients treated with Matrix, (○) patients treated with placebo.

Table II Overall evaluation of the efficacy of the preparations.

Treatment	Doctor	Patient
Matrix	2.4 ± 0.9	1.6 ± 0.8
Placebo	1.4 ± 0.6	1.2 ± 0.6

Score: worse = 0, stationary condition = 1, slight improvement = 2, substantial improvement = 3.

the clinical picture have always been significantly better than in controls, a sure indication of improved tissue trophism. This, very probably, was an aid to the anti-inflammatory action of Matrix, which has been well-documented experimentally.

Lastly, good compliance of patients with the type of therapeutic cycle must be mentioned. The protocol foresaw intervals between treatments such as to avoid excessive discomfort due to the intramuscular administration route.

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