

High Intensity Laser Therapy in the treatment of gonarthrosis:

the first clinical cases and the protocol for a multicentric, randomised, double-blind study

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Arthrosis: state of the art

Cartilage possesses scarce reparative capacities and until several years ago spontaneous or therapeutic repair of an articular lesion was not considered possible. At the present time the most common cartilaginous pathology, Arthrosis (osteoarthritis) is the focus of great interest on a worldwide level and has become the “new frontier” not only for orthopaedics but also for rheumatology and rehabilitation, to which a great deal of energy and resources are dedicated.

Arthrosis is certainly the disease with the greatest increase in the number of cases in the western world in consideration of the general aging of the population.

The social and economic role of arthrosis is therefore potentially very high. Numerous drugs have been proposed for the therapy of arthrosis including:

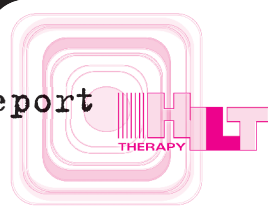
- the new FANS (selective inhibitors of the COX 2),

- basic drugs: DMOADs (Disease Modifying Osteoarthritis Drugs)

better known as chondroprotectors, theoretically capable of intervening in both the destructive and reparative process of the disease, which include galactosamineglucuronoglycan sulphate, diacerein, jaluronic acid.

The real effectiveness of the DMOADs still has to be demonstrated and the clinical impression is that these molecules represent the forerunners of a new generation of drugs.

Orthopaedics have developed a series of reparative surgical interventions of great interest aimed principally at knee-cartilage reconstruction.



The techniques are divided into two groups: bone marrow stimulation techniques and tissue transplant techniques. Worth noting among the marrow stimulation techniques are chondroabrasions, perforations and microfractures. These methods tend to stimulate the subchondrial bone and fill the cartilaginous lesions with fibrin coagula, rich in totipotent stem cells. These techniques give rise to the formation of fibrocartilaginous tissue (Type I collagen) with scarce mechanical capacities. These interventions are currently reserved for lesions of less than 2 cm², and are generally performed in arthroscopy, in one single diagnostic-surgical session.

Far more interesting are the tissular transplant techniques (homologous transplants, multiple or mosaicplastic autologous transplants, autologous transplants of periosteal flaps, autologous chondrocyte transplants), which aim at reconstructing the physiological hyaline cartilage (Type II collagen), with good mechanical capacities.

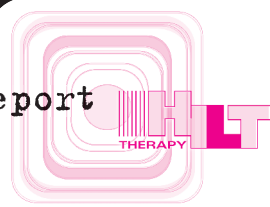
Amongst these techniques the implanting of autologous chondrocytes (ACI) has been particularly successful. This method consists essentially of arthroscopic extraction of the chondrocyte cells from areas not subjected to stress and transplanting of the same in the arthrotic lesions. This is carried out in 4 stages:

- 1) arthroscopic extraction of the cells;
- 2) creating of cell cultures in highly specialised laboratories
- 3) mounting of biomaterials deriving from the collagen
- 4) transplanting of the neo-tissue in the lesion.

These methods have opened futuristic scenarios which are already partially in progress. Mesenchymal cells deriving from the bone marrow and futuristic three-dimensional biomaterial deriving from hyaluronic acid (non-material materials) are already being tested in laboratories and animal models. These new surgical frontiers must not distract us however from the globality of the arthrosis problem.

Contra-indications to transplants

The presence of significant axial deviations (greater than normal varus or valgus knee greater than the norm of 5°) is considered as a mechanical



AUTHOR	AV.AGE/ PATIENT	NUMBER OF PATIENTS
Berruto	28	13
Gobbi	40	50
Cherubino	34.5	18
De Santis	33	24
Gualtieri	36	40
Faccini	33	16
Lo Bianco	34.5	36
Radosavjei	37	10

Table 1. Average age of clinical cases subjected to chondrocyte implant. From 1st G.I.R.C. convention Ischia 20-22 Sept.2001

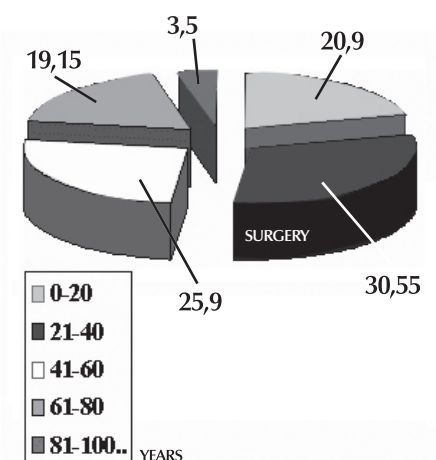


Fig. 1 - Distribution of arthrosis throughout the Italian population.

imbalance capable of compromising the positive results of the transplant; all deviations should be corrected in a preliminary manner. At the same time the absence of the meniscus due to previous menisctomies is considered as a potentially unfavourable situation for transplants. The simultaneous presence of multiple cartilaginous lesions calls for a careful assessment of the suitability of resorting to chondrocytary implanting or similar techniques.

More general conditions like overweight and an advanced age are other factors considered as very important in subjecting the patient to reparative surgery of the cartilage.

We only considered the patient's age since, as Pellaci states, if all these selective criteria were to be complied with, in practice, only very few patients would be proposed for this type of surgical treatment.

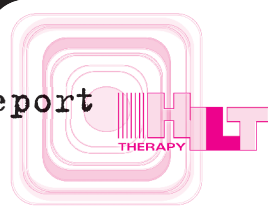
In international literature it is advised against performing transplants in patients over 55.

In actual fact, the age of the patients subjected to surgery is always low: at the recent convention of the Gruppo Italiano di Studio dei Processi Riparativi del Tessuto Osteo-Cartilagineo (G.I.R.C. – Italian Study Group of Reparative Processes of Osteo-Cartilaginous Tissue at Ischia 20-22 September 2001) the mean age of transplants resulted in being 34 years, with a minimum of 15 and a maximum of 40 (see table 1).

If we consider the wide range of the population over 55 we are able to realise how a univocal answer to arthrosis cannot be found in surgery alone (see fig. 1).

High Intensity Laser Therapy (HILT)

Over the last ten years numerous studies have been carried out indicating the biostimulating action of MID lasers. In particular, lasers have been accredited with the power to accelerate the healing of skin ulcers and bedsores. The Laser devices used until now have been low intensity with a wavelength of 600-900 nm, corresponding to the near infrared. Within this spectrum the Laser beam can be absorbed by the



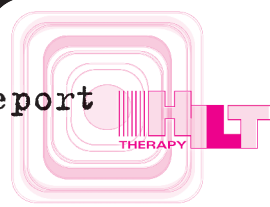
natural chromophores like melanin for example.

The CO₂ Laser represented the introduction of high intensity Laser in the medical field. Unfortunately, due to its wavelength (10,600 nm) it is completely absorbed by the water resulting in an extremely scarce penetration of the tissues.

Its action is prevalently analgesic, acting on the sensitive cutaneous nerve endings. We have recently analysed the physical properties of high intensity Nd:YAG Laser that has a wavelength of 1064 nm. At this frequency the Laser beam is easily diffused throughout the tissues. More specifically, the cartilaginous and bone tissues turn out to be excellent targets for this type of radiation. In the past this Laser was applied with continuous emission and given its high intensity there was a considerable increase in the heat produced with histolesive risks. This aspect obviously prevented its use. Approximately three years ago we developed a new Laser with pulsed wave emission capable of supplying high intensities without inducing heat effects and without causing cellular damage. We have tried to evaluate whether the Nd:YAG Laser had the same trophic effects in depth at the articular level that the MID lasers had already demonstrated to possess on superficial skin tissues. The results of the experimental studies performed on animal models and the in-vitro cellular studies carried out throughout 2000 and 2001, have demonstrated the possibility of stimulating the formation of hyaline cartilage by means of Laser stimulation. This fact has led us to consider the feasibility of clinical experimentation in humans.

Preliminary Clinical Study

For six months we have been carrying out a preliminary study at the Servizio di Recupero e Rieducazione Funzionale (Recovery and Functional Re-education Service) of the Rizzoli Institute of Orthopaedics, in the aim of exploring the investigation methods and therapeutic parameters most suitable for performing a double blind experimentation.



10 patients have been selected (mean age 50 years, min. 41 years, max. 65 years, 5 females, 2 males) affected with primitive arthrosis.

Clinical tests

The clinical tests considered most suitable were as follows.

The W.O.M.A.C. (Western Ontario and Mc Master Universities Index), consisting of a clinical functional test specifically for osteoarthritis (the W.O.M.A.C. is the only test among those used in an international context to have been validated for Italy). It is easy to implement and explores both the functional attitude of the arthrosic knee and the patient's daily activity.

The IKDC test is a functional test of the knee consisting of a section with the patient's subjective assessment of his/her own conditions in relation to his/her daily and/or sporting activities, and a clinical and objective assessment by the physician. It is extremely valid in the event of the patient having been subjected to arthroscopy or being a candidate for reparative knee surgery, for which he/she has not been considered in the final assessment of the pilot study.

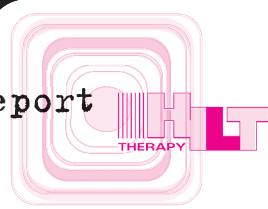
V.A.S. (*Visual Analogic Scale*) is the traditional scale for a quantitative assessment of pain which consists of a simple test with easy acquisition and comparability.

As laboratory analyses the following classical phlogistic tests were implemented: ESR, PCR, α 1glycoprotein, as well as several Interleukin and ChemiKine assays like: IL1 β , IGF 1, IL8 and RANTES, as an expression of the metabolic activity of the articular environment affected by arthrosis.

Instrumental diagnostic tests

As an initial sidetracking from the arthrosis we performed a conventional X-ray of the knee in an antero-posterior position under stress, after which we classified the lesions using the Ahlbach's guide.

The patients classified under grades II and III were then subjected to a nuclear magnetic resonance.



DEGREE	RADIOGRAPHIC ALTERATIONS
I	Slight reduction in height of the femurotibial space (<50%)
II	Obliteration of the femurotibial space (>50%)
III	Moderate bone wearing away (<7 mm.)
IV	Significant bone wearing away (>7 mm.)
V	Significant bone wearing away with articular sub-dislocation

Magnetic resonance

A last generation MR device with 1.5 T was used. Where possible we compared photographic images of the arthrosic lesions obtained with arthroscopies, with the images obtained from the various MR sequences.

From the numerous tests conducted, the most suitable weights for defining the arthrosic alterations were the sequences in T2 and the SPGR suppressed fat performed according to sagittal and coronal planes. Subsequently, it was considered opportune to use the three-dimensional methods for volumetric acquisitions.

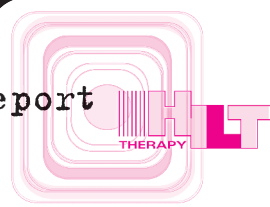
Ultrasonography

The most suitable optical “windows” of the patients in the preliminary study were assessed via ultrasonography in order to allow for the diffusion of the Nd:YAG Laser.

These windows resulted in being the internal and external hemi-rima of the knee bent to 90° for the anterior chondyles and the internal and external hemi-rima of the knee in the popliteus hollow at maximum extension for the posterior chondyles. In order to access the posterior face of the patella the best lateral and middle windows appeared with the knee bent to 30°.

Therapeutic protocol

As a therapeutic protocol a total of 2500 m Joule were delivered in pulsed waves with manual scansion with a last generation Nd:YAG Laser with an average intensity of 6 W. The treatment was carried out once a day



for 15 days over a period of three weeks (excluding holidays). After three months the entire therapeutic cycle was repeated. At the beginning (T0) and at the end (T1) of the first cycle, and likewise at the beginning (T2) and at the end (T3) of the 2nd cycle of treatment the algo-functional assays (W.O.M.A.C. and V.A.S.) and the laboratory tests: ESR, PCR, 1 α glycoprotein, IL 1 β , IL 8, h-RANTES and IGF-1 were carried out.

State of progress

Seven out of the 10 patients selected completed all the clinical instrumental tests envisaged.

Clinical tests

The clinical tests VAS and WOMAC evidenced a constant improvement of both the algic and functional symptomatology.

At the end of the second Laser cycle the patients showed a reduction in pain equal to 51% (V.A.S.) and a reduction in the functional limitation (WOMAC) equal to 49%.

Lab tests

The classical phlogosis assays showed negligible variations with values always recorded within the normal range or very close to the same. Nevertheless it is worth pointing out how the trend of the ESR and PCR values, as well as the alpha 1 glycoprotein values appeared to be substantially similar. The values tended to rise after each Laser cycle and then return to the basic values again. The Nd:YAG Laser seems to have altered the quiescence of the articular environment. The scarce specificity of these classical indexes do not however allow us to understand further the metabolic alterations of the cartilaginous tissue.

The data obtained from the Lymphokin and ChemoKin assays appears far more significant. As regards the IL 1 β , which is the expression of the chondrolytic and pro-inflammatory activity at the level of the cartilaginous tissue, a constant diminishing trend from T0 to T3 has been



Fig. 2 - Measurement via NMR of the area of the ulcer.

observed. This datum is confirmed by the results obtained by the IGF-1, a growth and replicative activity factor of the chondrocytes. The trend of the IGF-1 in fact, has a slope which is opposed to the IL 1 β , with a growth in values from T0 to T3. The analysis of the h-RANTES ChemoKines and the IL 8, having a chemioactive and activating action of the neutrophils, has highlighted a decreasing trend from T0 to T3, which confirms the inhibiting action of the phlogosis factors by the Nd:YAG Laser.

Magnetic resonance

Via the MR the aim was to monitorise the morphological variations of the arthrosic knee treated with the Nd:YAG Laser. We initially tried to quantify any variations in the thickness of the incrustation cartilage of the femurotibial articulation.

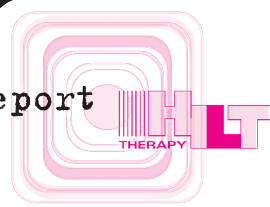
The measurement of the thickness of the cartilaginous mantles was problematic with the bidimensional technique used due to the presence of numerous artefacts caused by the oedema often present in the surface strata of the cartilage.

It was easier to measure the cartilaginous ulcer. The images acquired in two dimensions of an arthrosic ulcer before and after treatment with Nd:YAG Laser were processed electronically and compared by measuring the maximum diameter and the surfaces.

In the case described a marked reduction was noted in the diameter and extension of the area affected by the ulcer.

We have judged these images with caution in view of the difficulties involved in reproducing with exactness the positioning of the limb examined. Nevertheless, the patient in question recorded a pronounced improvement in his clinical conditions with regard to both pain and functionality of the knee in question.

At the bidimensional MR follow-up six months after the treatment corresponding to two months after the end of the 2nd cycle, four out of the seven cases currently completed showed improvement and three were unvaried. The most evident improvements were in the reduction of the trabecular bone oedema and the cartilage, and in one case in the reduc-



tion of the extension of the cartilage ulcer.

In the aim of obtaining a more reliable and reproducible volumetric measurement of the cartilaginous lesions we considered it necessary to carry out a three-dimensional acquisition by means of the MR, in order to be able to measure with reliability, also in the control group, the region of interest according to the greatest axis of development.

As a whole, the magnetic resonance, despite its limits, seems to be the only technique capable of documenting the structural modifications of the cartilage.

Arthroscopy is not a viable method of screening in a clinical experimental trial for both ethical and technical reasons.

The ethical reasons are those related to an excessive invasiveness of the examination compared to the benefits and consequently it can not be considered as a basic investigation to be carried out on patients enrolling in a double blind trial.

The technical reasons that limit the use of the arthroscopy are linked to the fact that the acquisition of a photographic image depends in a specific manner on prospective factors that are difficult to reproduce in a second trial.

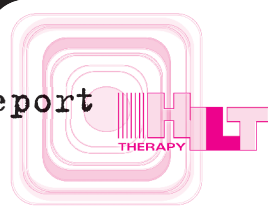
Yet arthroscopy is still useful to biopsic collection and therefore to assess the quality of cartilage. Considering that, we believe that it should be performed in few cases, after randomization of patients.

The study is still in progress even if we have a clinical protocol which appears effective, and we are reassured by the first results achieved. They indicate a clinical and functional improvement for every treated patient.

Clinical study on patient

Moving from the experimental research and from the data of the preliminary study, we propose to perform a wider clinical study, in order to assess the chances of Nd:YAG Laser for the treatment of arthrosis.

We want now to begin a multicentric study which will allow us to col-



lect a good number of cases with a double blind design.

To do that we asked for the collaboration of the “Fondazione Don Carlo Gnocchi, Santa Maria agli Ulivi di Pozzolatico (FI)”, and of “CONI” - Bologna of the “Servizio di Radiologia dell’Ospedale Nuovo di Imola (BO)”. We will select from these operative units 100 patients affected by tibial-femoral arthrosis, or patellar-femoral arthrosis, age range 12-65. The selection method will be based on radiography assessment, since there is no reason to use a division based on arthroscopy. Radiography will be performed along the antero-posterior axis, under loading. Only patients affected by II and III stage arthrosis (which correspond to cartilage lesions showing a reduction of the joint space greater than 50%, and a mild bone wear, < 7 mm, respectively), following the Ahlback classification, will be admitted to treatment.

These patients will then undergo Magnetic Resonance with specific “weights” for the joint cartilage in order to confirm the presence and better assess the arthrosic lesions.

Images collected through this method will be then digitally elaborated in order to describe and, possibly, measure the qualitative and quantitative modifications of bone and cartilage components.

Then patients will undergo to *clinical tests*:

- W.O.M.A.C.: the Western Ontario and Mc Master Universities Index, functional clinical test specific for osteoarthritis
- 2000 IKDC, test for subjective functionality assessment by the patient and objective assessment by the clinician.

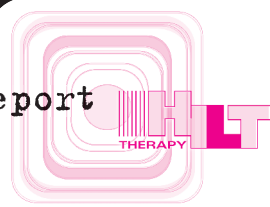
V.A.S. quantitative scale for the assessment of pain *Lab tests*:

to assess possible metabolic alterations

VES, PCR, (1-glycoprotein, IL 1 β , IL 8, IGF-1, TGF β , h-RANTES)

Patients will be randomly assigned to 2 groups.

- A => will undergo a minimum power He-Ne Laser treatment (1mW)
- B => will undergo Nd:YAG Laser treatment daily for 21 dd.



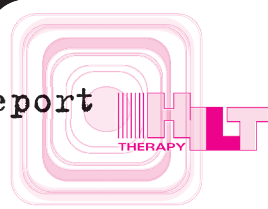
Laser devices will be provided with their own software which will assign randomly patients to treatment A or treatment B. After six months treatment (A or B) will be repeated. Every patients will be administered with a chondroprotective drug (galattoglucoronglycan sulfate 800 mg/day). Clinical tests will be repeated at the beginning and at the end of each of the two cycles. At the end, after twelve months from the beginning Magnetic Resonance will be repeated and the images collected will be compared with the previous one. All patients will be assessed again after 12 months through the lab tests and by Magnetic Resonance again 10 patients, randomly chosen, will be assessed through arthroscopic biopsic collections.

Therapeutic protocol

As far as the therapeutic protocol is concerned, Nd:YAG Laser will emit in pulse mode, with an average power approximatively equal to 9 W. The total energy, 3000 J, will be divided in this way: 500 J antero-lateral windows; 500 J antero-medial window; 500 J posterior-lateral window; 500 J posterior-medial window, 500 J medial patella; 500 J lateral patella, according to the individuated optical windows.

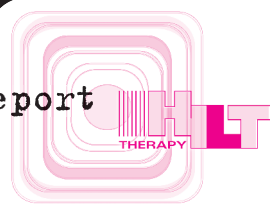
Performing this multicentric study we want to achieve important information about the clinical outcome after Nd:YAG Laser treatment, about the metabolic modifications of the treated osteoarthritis, and about the modification of the anatomic and pathologic conditions of the osteoarthritis treated lesions.

If the results achieved in vitro and on animal model were confirmed also on patients, interesting sceneries would open in osteoarthritis treatment, which would gain a new approach to improve effectively the quality of life.



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