The current state of cartilage transplantation

The avascular and aneural structure of cartilage is both its downfall and its saviour. The very features that limit the capacity of articular cartilage to self-repair make it an ideal candidate for tissue engineering. While more traditional techniques have relied upon the stimulation of natural processes, tissue engineering has opened a whole new chapter in the modern treatment of cartilage defects.

AUTOLOGOUS CHONDROCYTE TRANSPLANTATION

In 1994, the news that cartilage defects could be biologically treated was published in the *New England Journal of Medicine* (Brittberg et al, 1994). Matts Brittberg and colleagues had pioneered the new technique and called it autologous chondrocyte implantation or transplantation (ACI/ACT). The team from Gothenburg, Sweden, gained ethical permission and began a programme of ACT in patients with cartilage defects of the knee. The first patients were treated in 1987, and their results were reported in the 1994 paper. A 90% success rate was stated with promising histology.

Despite early cynicism the technique gained in popularity, especially in the USA, and by 2001, 6000 patients worldwide had been treated by this method.

ACT IN THE UK

The use of ACT has been limited in Britain, mainly because of the expense. The report from the National Institute of Clinical Excellence (2000) stated:

> **'Autologous cartilage transplantation (ACT) should not currently be used for routine primary treatment of articular cartilage defects of the knee joint. ACT should only be performed as part of a properly structured clinical trial.'**

With centres such as that of the authors in Oswestry developing their own chondrocyte culture facilities and running trials, ACT is likely to undergo a rigorous assessment of its efficacy before it becomes more widely available. As a result most orthopaedic centres are currently unable to offer ACT as an option on the NHS and must refer what they consider suitable patients to a tertiary centre.

A STRATEGIC APPROACH

In order to develop the technique of ACT in Oswestry, a collaborative group of basic scientists and surgeons formed. The 'Oscell' group includes cell biologists, biochemists, clinical engineers, pathologists, radiologists and surgeons. Weekly meetings have enabled the group to assess current practice and monitor patient progress. A database has also been constructed to record information on every patient undergoing ACT. This combined approach has improved the quality of data collected and has provided a forum in which this new technique can be evaluated both clinically and scientifically.

This approach has recently undergone further expansion, with the development of 'Eurocell', a Europe-wide group. Centres involved include Oswestry, Gothenburg, Barcelona, Ghent, Tromso and Freiburg. With European Union backing a Eurocell database is under development and weekly teleconferences are held between centres to continue to improve understanding of this new technique.

THE PROCEDURE

Preoperatively the patient is assessed, the joint is fully examined, a thorough history of any previous procedures is recorded and a magnetic resonance imaging (MRI) scan is performed.

Outcome measures used at Oswestry include the knee-specific Lysholm and KOOS scores, and SF-36 as a general health assessment. All are self-administered by the patient. These are completed preoperatively and at annual postoperative intervals. ACT is a two-stage procedure usually involving an arthroscopic cell harvest and then an arthrotomy for patching of the defect and cell transplantation 3 weeks later.

The first stage

At the arthroscopy, a full assessment is made of the joint. In order to have a successful outcome the joint must be stable and in alignment. All compartments are visualized as well as making a thorough assessment of the defect to be treated. From a low weight-bearing area of the joint a 250 mg biopsy of cartilage is taken using a deep gouge or a mosaicplasty punch. The sample is taken to the laboratory, where the cartilage matrix is enzymatically digested, releasing the chondrocytes. These cells are then transferred into culture medium and are allowed to divide and increase in number. The process takes about 3 weeks after which the cells are ready for transplantation (Harrison et al, 2001).

The second stage

At the arthrotomy, the knee is opened via a parapatella approach and the defect is located. The defect is then debrided down to the subchondral bone, however, it is important that the base is not breached. The margins of the defect are curetted back to healthy cartilage, so that the fine sutures used do not 'cut-out'. Once debrided, the defect is measured and a template is made. From this, the size of the patch can be marked out on the periosteum. The patch is taken from the proximal tibia, and it is sutured over the defect using absorbable sutures, the edges are then sealed with fibrin glue. Once the surgeon is satisfied that, on testing by injecting Hartman's solution, the patch is watertight, the cultured cells are injected beneath the periosteal patch and the injection site is closed with a purse string suture.

REHABILITATION

Immediately postoperatively patients are placed in a straight leg splint for 4 hours. They are then commenced on continuous passive motion for 48 hours, gradually increasing the degree of flexion from 0–40°. After discharge, they are asked to follow a specially designed physiotherapy regimen. They are kept partially weight-bearing on crutches for 12 weeks and have a protocol of exercises to complete with their physiotherapist. The regimen is demanding and requires the patient's full cooperation.

RESULTS

Currently patients are assessed 1 year after their transplant. This involves clinical examination, repetition of outcome score forms, arthroscopic evaluation and MRI. The MRI allows assessment of the extent to which new tissue has filled a defect and gives some indication of the surface regularity and the condition of the underlying bone, e.g. the presence of subchondral cysts. At arthroscopy, cartilage appearance, cartilage stiffness and integration with the adjacent cartilage are assessed. A biopsy of graft tissue is also taken and sent for histology from which the morphology, organization and vertical integration of the tissue can be assessed (Richardson et al, 1999).

Results thus far have been encouraging. The Swedish group have reported 94 patients with 2–9-year follow-up, good to excellent clinical results were seen in 92% of isolated femoral condyle defects (Peterson et al, 2000). Comparable results have been reported from the Oswestry series, with up to 3 years follow-up (Ashton et al, 2001).

CURRENT STATE OF AFFAIRS

Despite the apparent success of the procedure, scepticism persists with many orthopaedic surgeons failing to accept the technique. There has been much controversy surrounding the lack of randomized controlled trials. However, several small randomized controlled trials are underway, and larger multicentred trials are being planned.

Other reasons cited include the prolonged rehabilitation programme this treatment requires when compared to other procedures used for treating cartilage defects. The rehabilitation is indeed much longer, although it would appear the long-term results of this treatment are superior to that achieved by other methods. Thus the prolonged rehabilitation is probably justifiable. The need to 'damage' healthy cartilage to obtain the harvest biopsy is also considered a disadvantage, as is the necessity to perform the procedure via an arthrotomy.

THE FUTURE

It would seem that the future of cartilage treatment is going to be exciting and innovative. As tissue engineering techniques improve a plethora of opportunities will present themselves. Scaffolds and artificial matrices are currently entering the marketplace and it is likely that in the near future these will be used pre-seeded with autologous cells. This would negate the need for arthrotomy if the scaffold could be cut to size, arthroscopically delivered and press fitted into the defect.

Artificial osteochondral plugs are also in the process of being developed. These would confer the advantage of being able to treat deep defects and large defects without the problems of donor site limitation or morbidity. Alternative sources of autologous chondrocytes are also under investigation; nasal cartilage, the pinna of the ear, the manubrial–sternal junction and costal cartilage have all been suggested as possibilities. Perhaps the most exciting prospect is the use of stem cells (Caplan and Bruder, 2001). The stem cells could be obtained from a bone marrow biopsy or perhaps even a simple blood sample, providing a population of precursor cells that could be persuaded to become chondrocytes.

In the long term it is hoped this technique could be developed to provide a method of resurfacing osteoarthritc joints. In the professional lifetime of the upcoming generation of orthopaedic consultants, the use of a custom-made fleece is envisaged. This will be seeded with autologous stem cells and arthroscopically introduced into a joint, and the true era of biological joint resurfacing will be upon us. **HM**

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KEY POINTS

- Articular cartilage is aneural and avascular and thus has limited capacity for self repair.
- Advances in tissue engineering will enhance and improve cartilage repair techniques, leading to a better repair tissue, with less invasive surgery.
- Randomized controlled trials are underway.
- A method of joint resurfacing developed from autologous cartilage transplantation may eventually result in biological joint replacement.