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National Institute for Clinical Excellence

National Institute for Clinical Excellence

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Technology Appraisal Guidance - No.16

National Institute for Clinical Excellence

Guidance on the Use of Autologous Cartilage Transplantation for Full Thickness Cartilage Defects In Knee Joints

December 2000

This document has been circulated to the following:

- Health Authority Chief Executives in England and Wales
- NHS Trust Chief Executives in England and Wales
- PCG Chief Executives
- Local Health Group General Managers
- Medical and Nursing Directors in England and Wales
- Physiotherapists in England and Wales
- Consultant Orthopaedic Surgeons in England and Wales
- NHS Director Wales
- Chief Executive of the NHS in England
- NHS Executive Regional Directors
- Special Health Authority Chief Executives
- Community Health Councils in England and Wales
- Patient advocacy groups
- Commission for Health Improvement
- NHS Clinical Governance Support Team
- Chief Medical and Nursing Officers in England and Wales
- Medical Director & Head of NHS Quality – National Assembly for Wales
- Clinical Effectiveness Support Unit - Wales
- Representative bodies for health services, professional organisations and statutory bodies, Royal Colleges

This Guidance is written in the following context:
This guidance represents the view of the Institute's Appraisal Committee, the membership of which is set out in Appendix A, which was arrived at after careful consideration of the available evidence. Health professionals are expected to take it fully into account when exercising their clinical judgement about the use of autologous cartilage transplantation for full thickness cartilage defects in knee joints. This guidance does not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

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Guidance on the Use of Autologous Cartilage Transplantation for Full Thickness Cartilage Defects In Knee Joints

1. Guidance

1.1 Autologous Cartilage Transplantation (ACT) is not currently recommended for routine primary treatment of articular cartilage defects of the knee joint in the NHS.

1.2 ACT should only be performed as part of a properly structured clinical trial, which, wherever possible, is randomised and adequately powered.

1.3 Exceptionally, ACT treatment may also be undertaken in centres participating in clinical trials of this procedure when other treatments for articular cartilage defects of the knee joint have already failed. Prospective follow up data from these cases should be collected within formal observational studies to audit the clinical effectiveness of ACT.

This section, Section 1, constitutes the Institute's guidance on the use of autologous cartilage transplantation for full thickness cartilage defects in knee joints. The remainder of the document is structured in the following way:

The full document and a Summary of Evidence are available from our website at www.nice.org.uk or by telephoning 0541 555 455 and quoting the reference number 22961.

Mae'r adran hon (adran 1) hefyd ar gael yn Gymraeg ar ein gwefan neu drwy gysylltu â 0541 555 455, rhif cyfeirnod 22964.

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2 Clinical Need and Practice

2.1 Normal hyaline cartilage provides a smooth surface at the ends of bones that allows virtually frictionless movement within the knee joint and acts as a shock absorber to cushion the bone from forces of more than five times the body's weight. Cartilage lacks blood and nerve supply, and has limited capacity for self-repair.

2.2 Cartilage damage can be caused directly from injury, often as a result of sporting activity, or spontaneously (a condition called osteochondritis dissecans). The natural history of hyaline cartilage lesions, or chondral fractures, that follow injury in humans is not known. Those experiencing symptoms with loss of hyaline cartilage of full thickness complain of knee pain, knee swelling, joint locking (i.e. a joint becomes stuck in one position) and giving way of the joint. Cartilage defects are usually diagnosed at arthroscopy, although they may be seen on MRI.

2.3 There are no reliable estimates of the prevalence of full thickness cartilage defects in the knee. Estimates from three consultees of the number of potential ACT operations in England and Wales range from 300 to 850 per year. The estimate of 300 is derived from a pro rata calculation of current USA treatment volumes. The estimate of 850 relies on a calculation that, of around 1,700 cases where other procedures are likely to have failed, about half could proceed with ACT.

2.4 There is no uniform approach to managing hyaline cartilage defects in knees. The most common treatment options include a knee washout and debridement (trimming the loose tissue flaps), 'marrow stimulation techniques', various tissue grafts from outside the joint (for example rib or periosteum grafts), and grafts of normal cartilage cores from within an affected joint (mosaicplasty). Post-operative management of patients varies considerably. For example, the regimes for weight bearing, or of physiotherapy techniques, including the post-operative use of continuous passive motion (CPM), vary.

3 The Technology

3.1 ACT is a novel surgical approach used to treat full thickness cartilage defects in knee joints. Small grafts of normal cartilage removed from the edge of the diseased joint are treated in a laboratory to obtain cartilage cells. These are cultured to expand the cell population (by a factor of about 50) and re-implanted a few weeks later into areas where cartilage is denuded by disease. The aim of this procedure is to restore normal cartilage to the ends of bones and thereby restore normal joint function.

3.2 There is no consensus on the definition of the eligible population. ACT appears to be most appropriate for symptomatic patients between 15 and 40 years of age with full-thickness, weight-bearing cartilage defects of more than 2 square cm on the femoral articular surface. However, patients up to 55 years of age and, in some cases, defects of 1 to 2 square

cm, might also be considered eligible. Patients receiving ACT should also be required to adhere to a strict post-operative rehabilitation protocol. ACT is not suitable as a treatment option for patients with evidence of osteoarthritis.

4 Evidence

4.1 Evidence on effectiveness

4.1.1 There are no completed randomised clinical trials comparing outcomes with the alternative treatment modalities. Several randomised trials are currently under way, but it will be some time before these come to conclusion.

4.1.2 Forty-six reports on the use of ACT have been identified. Of these, only seventeen were case series (not necessarily of consecutive patients) that reported patient outcome data, involving a total of at least 2,600 patients, with a variable length of follow-up. Eight were abstracts of research only.

4.1.3 The Genzyme Tissue Repair Registry and the Swedish Registry are significant sources of data. The Genzyme Registry provides a case series data of over 1,500 patients followed up for up to 3 years, based upon voluntary participation, but with unknown selection biases. It is unclear what proportion of surgeons who utilise the technology contribute to the Registry. The Swedish Registry includes all 800 patients who have received the treatment, some of them followed for up to 9 years.

4.1.4 Assessment of the evidence on clinical efficacy is confounded by a number of factors including variations in patient characteristics, concomitant surgery and use of multiple interventions. With one exception, all studies reported an improvement in patient status, usually over a follow-up period of less than 2 years.

4.1.5 Outcomes were reported by using various disease-specific scales (e.g Lysolm, Cincinnati, Brittberg-Peterson scores). 70% of patients rated outcomes as 'good' or 'excellent' approximately 2 years after ACT surgery. Approximately 16% (8.6% to 21%) of patients required further arthroscopic surgical procedures during follow-up, and 3 to 7% were judged to have failed treatment. For other treatments, between 10% and 95% of patients were rated 'good' or 'excellent' 2 years after treatment.

4.1.6 The reported literature is subject to bias because of the inherent weaknesses of case series. In addition, the long-term impact of either conventional surgical treatments, or non-surgical treatment, is poorly documented.

4.1.7 Despite promising results from recent studies, it is not possible to draw a definite conclusion on the clinical effectiveness of this technology on the basis of available literature and in the absence of any evidence from randomised controlled trials. The results from trials presently under way should be awaited before any decision on the widespread usage of this technology is made, except for those indicated in paragraph 1.3 above.

4.2 Costs of ACT

4.2.1 Estimates of the cost of ACT, including cell culturing and surgery, are £3,200, £4,700 and £8,600, depending on which service provider is used for culturing the cells. Estimates suggest that the incremental cost over other treatments at two years is approximately £500 less than these initial costs.

4.2.2 In the event that 850 patients per year were to be offered ACT treatment as second-line therapy, following failure of other therapies, at a cost within the range of £4,200-£8,100, the additional cost to NHS would range from £3.6m to £6.9m per annum.

4.3 Evidence on cost-effectiveness

4.3.1 Given the lack of comparative evidence on clinical effectiveness, it is not meaningful to make any estimate of cost-effectiveness.

5 Implications for the NHS

5.1 Wherever ACT is trialled, the NHS should require specific surgical training and high quality cell production facilities for the manufacture of chondrocytes. As a minimum, the latter should comply with the Good Manufacturing Practice (GMP) for Medicinal Products as set out in volume 4 of the Rules Governing Medicinal Products in the European Community. Quality control within the laboratories manufacturing the chondrocytes is exceedingly important, as any contamination could lead to extremely poor outcomes, which would put the procedure as a whole at risk. Strict monitoring of compliance with the GMP rules will therefore be necessary.

6 Further Research

6.1 The evaluation of the clinical effectiveness of ACT must be carried out, wherever possible, in the context of properly conducted and adequately powered randomised clinical trials. There is a need to define the patient population (i.e. age groups, type and size of lesion) for whom this procedure is likely to be the most beneficial. There is a particular need for a trial or trials comparing ACT against the best alternative treatment for patients who have had a previous simple debridement that has not relieved symptoms. Currently, a number of trials are being conducted worldwide, including

comparisons of ACT with periosteal graft and with periosteal graft alone, and comparisons of ACT with drilling and with mosaicplasty.

6.2 Methodologically robust cost effectiveness studies should be carried out, either as part of, or based upon, the effectiveness data of studies proposed in 6.1.

6.3 Research to date has focused on the surgical procedure itself and not on the rehabilitation of these patients. This also remains an area for further research to inform the true clinical and cost effectiveness of this intervention.

6.4 Centres that carry out ACT should be responsible for collecting follow-up data for their patients.

6.5 Standards for the pre- and post-operative management of these patients will need to be developed within the context of the research environment. Appropriate outcome measures to be used for evaluation and benchmarking of services also need to be agreed.

7 Implementation

7.1 Trusts should review their current practice against the guidance. ACT should only be carried out in the context of properly conducted trials. Exceptionally, Trusts may consider carrying out ACT as indicated in paragraph 1.3.

8 Clinical Audit Advice

8.1. Surgeons should be encouraged to collect prospective long-term outcome data on those patients who will in the future undergo, or who have to date undergone, ACT.

9 Review of Guidance

9.1 This guidance will be reviewed in November 2003

Andrew Dillon
Chief Executive
December 2000

APPENDIX A

Appraisal Committee Members

The Appraisal Committee is a Statutory Committee whose members sit for 3 years. They are supplemented by technology specific experts as indicated in Appendix B.

Professor R. L.Akehurst
Dean, School of Health Related Research
Sheffield University

Professor David Barnett (Chairman)
Professor of Clinical Pharmacology
University of Leicester

Professor Sir Colin Berry
Professor of Morbid Anatomy
St Bartholomew's and Royal London School of Medicine

Dr Sheila Bird
MRC Biostatistics Unit, Cambridge

Professor Martin Buxton
Director of Health Economics Research Group
Brunel University

Professor Yvonne Carter
Professor of General Practice and Primary Care
St Bartholomew's and Royal London School of Medicine

Dr Karl Claxton
Lecturer in Economics
University of York

Professor Duncan Colin-Jones
Professor of Gastroenterology
University of Southampton

Ms Sarah Cowley
Professor of Community Practice Development
Kings College, London

Dr Nicky Cullum
Reader in Health Studies
University of York

Mr Chris Evennett
Chief Executive
Mid-Hampshire Primary Care Group

Ms Jean Gaffin
Formerly Executive Director
National Council for Hospice and Specialist Palliative Care Service

Mrs Sue Gallagher
Chief Executive
Merton, Sutton and Wandsworth Health Authority

Dr Trevor Gibbs
International Medical Operations Director
Glaxo-Wellcome R&D Ltd

Mr John Goulston
Director of Finance
The Royal Free Hampstead NHS Trust

Professor Philip Home
Professor of Diabetes Medicine
University of Newcastle

Dr Terry John
General Practitioner
St James Health Centre, London

Dr Diane Ketley
Clinical Governance Programme Leader
Leicester Royal Infirmary

Dr Mayur Lakhani
General Practitioner, Highgate Surgery, Leicester and
Lecturer, University of Leicester

Mr M Mughal
Consultant Surgeon
Chorley and South Ribble NHS Trust

Mr James Partridge
Chief Executive
Changing Faces

Professor Philip Routledge
Professor of Clinical Pharmacology
University of Wales

Professor Andrew Stevens
Professor of Public Health
University of Birmingham

APPENDIX B

Sources of Evidence

1. The following documentation and opinion was made available to the Committee:

a. Assessment Report:

- prepared by the West Midlands Development and Evaluation Service (Effectiveness of Autologous Chondrocyte Transplantation for Hyaline Cartilage Defects in Knees, July 2000)

b. Manufacturer/sponsor submissions:

- Genzyme Tissue Repair.
- Robert Jones and Agnes Hunt Orthopaedic and District NHS Hospital Trust
- Verigen Transplantation Service International AG

c. Professional/specialist group, patient/carer group and trade association submissions:

- Arthritis Care
- British Orthopaedic Association & Royal College of Surgeons – joint submission
- British Society for Rheumatology & Arthritis Research Campaign – joint submission
- Chartered Society of Physiotherapy

d. The external expert and patient advocate submissions:

- Ms. Judith Smart, Information Manager, Arthritis Care

APPENDIX C

Guidance on the use of autologous cartilage transplantation for full thickness cartilage defects in knee joints – patient information

The patient information in this appendix has been designed to support the production of your own information leaflets; you can download it from our web site (www.nice.org.uk) where it is available in English and Welsh. A printed version of this text is available in English/Welsh or English alone. If you would like copies of the printed leaflet please contact 0541 555 455, and quote the reference number 22966 for the English/Welsh version and 22965 for the English only version.

What is NICE Guidance?

The National Institute for Clinical Excellence (NICE) is part of the NHS. It produces guidance for both the NHS and patients on medicines, medical equipment and clinical procedures and where they should be used.

When the Institute evaluates these things it is called an appraisal. Each appraisal takes about 12 months to complete and involves the manufacturers of the drug or device, professional organisations and the groups who represent patients / carers.

NICE was asked to look at the available evidence on the use of autologous cartilage transplantation for full thickness cartilage defects in knee joints and provide guidance that would help the NHS in England and Wales decide when it should be used.

What is autologous cartilage transplantation?

Cartilage provides a smooth surface at the ends of bones that makes the movement within the knee joint easier and acts as a shock absorber to cushion the bone. Cartilage lacks blood and nerve supplies, and therefore has a limited ability to repair itself.

Cartilage damage can be caused directly from injury, for example from sports, or suddenly for no apparent reason. People who damage their cartilage often experience knee pain, knee swelling, joint locking (this is when a joint becomes stuck in one position) and the 'giving way' of the joint.

Autologous cartilage transplantation is a new procedure during which normal cartilage cells are collected from inside the knee and sent to a laboratory to grow for several weeks. Once they have grown, the knee is operated on and the cells are placed into the knee and sealed by a layer of tissue from the leg bone (tibia). This second operation requires a hospital stay of a day or two and following the operation the patient must have extensive rehabilitation treatment (including physiotherapy) and athletic activities and strenuous work are not permitted for between six months and a year.

Although there have been some promising results with this technique, there is not enough evidence to support its widespread use in people with cartilage damage in their knees. There are several other types of treatment available to repair cartilage damage in the knee.

What has NICE recommended on autologous cartilage transplantation?

NICE does not recommend the use of Autologous Cartilage Transplantation (ACT) for the treatment of cartilage defects of the knee joint in the NHS.

People should only have ACT as part of a clinical trial. If you need to have this type of operation, then your surgeon will discuss the details of the clinical trial with you before you agree to have the operation.

In exceptional cases, ACT treatment may be used for people who have had other treatments to repair the cartilage damage in their knee that have not worked. In these cases ACT should be carried out as part of a clinical trial.

Will NICE review its guidance?

Yes. This guidance will be reviewed in November 2003.

Further Information

Further information on NICE and the full guidance issued to the NHS is available on the NICE website at www.nice.org.uk. It can also be requested by telephoning 0541 555 455 and quoting reference number 22961.