Institution: Newcastle University

Unit of Assessment: UoA1

Title of case study: Curing chronic granulomatous disease in children through early bone marrow transplant

1. Summary of the impact

Chronic granulomatous disease is a rare but very serious inherited disorder of the immune system that leaves sufferers vulnerable to potentially fatal bacterial and fungal infections. Researchers at Newcastle University demonstrated very high survival and cure rates following bone marrow transplantation for the disease and good quality of life for successfully transplanted patients. This led to a change in national clinical policy, and doctors at both specialist disease centres in the UK now recommend transplantation to families where previously they would not have done so. In the five years prior to 2008 there were only 11 transplants for chronic granulomatous disease in the UK and in the following five years, 36 transplants. 32 children are alive and cured of the disease.

2. Underpinning research

Key Newcastle University researchers

Dr Andrew Gennery, initially a Clinical Senior Lecturer and from 2009 Consultant and Clinical Reader and Professor Andrew Cant, then an Honorary Clinical Lecturer, led the studies in Newcastle and contributed to collaborative work as described below.

Background

Chronic granulomatous disease (CGD) is a severe inherited disorder of the immune system that usually becomes clinically apparent in the first few months of life. It is rare, with an incidence of 4 – 5 cases per million live births in Europe, so about four children are newly diagnosed each year in the UK and Ireland. Because of the rarity of the disease, patients are diagnosed at national specialised centres. In the UK these are the Great North Children's Hospital in Newcastle and Great Ormond Street Hospital in London. The disease results from any one of a number of defects in genes encoding subunits of the enzyme NADPH oxidase that result in loss of its catalytic activity. In healthy people the enzyme has an important role in the production of toxic oxygen species by immune phagocytes (principally neutrophils), a process that is required to kill many pathogenic bacteria and fungi. Patients with CGD are therefore very vulnerable to serious infection by these micro-organisms. Even for those patients who comply fully with the prophylactic regimen of anti-bacterial and anti-fungal drugs, rates of morbidity and mortality are high. A report published in 2008 on outcomes in UK patients estimated mortality to be 45% by age 30 years (Jones et al. (2008) PMID: 18410635).

Research

In 2002 several European centres, including Newcastle, published a survey of outcomes of bone marrow transplantation for CGD, covering procedures carried out at between 1985 and 2000 (R1). It was a project jointly conceived by Professor Andrew Cant, Professor Reinhard Seger (University Children's Hospital, Zurich) and Dr Alain Fischer (Necker Hospital, Paris). Cant contributed about a third of the patient data in the report. The report demonstrated high survival and cure rates following myeloablative transplantation (complete destruction of the recipient's own bone marrow before transplant) with matched sibling donors. Success rates were particularly high in younger patients and in those without established infection. The authors concluded that while bone marrow transplantation had previously been considered a risky intervention, only to be used in those patients where (in spite of prophylactic treatment) disease had become established on a severe course, it was now an appropriate option to consider early for affected children with matched sibling donors.

In 2009 Gennery and colleagues published an analysis of outcomes of bone marrow transplantation for the disease, this time covering a later period (1998 to 2007) and including patients transplanted with bone marrow from matched unrelated as well as matched sibling donors

(ten people in each group) (R2). Of the 20 patients transplanted, 18 were cured of the disease. Significantly, long term outcomes were comparable for those patients receiving marrow from matched unrelated donors and those from matched sibling donors. Complications during and after transplant only tended to occur in patients with pre-existing infection and/or inflammation.
In 2009 Gennery led a pioneering study into the under-researched area of the quality of life of CGD patients comparing those cured by bone marrow transplantation with patients managed conservatively (R3). The researchers looked at the quality of life of 47 patients, approximately half of whom were pre-transplant (median age 9 years) and the others post-transplant (median age 10 years). A validated paediatric quality of life questionnaire approach was used, involving both children and their parents. Across several domains, including physical, emotional, social and school functioning, children with the disease who had not been transplanted (n = 34) and their parents (n = 47) had significantly poorer quality of life than a control group of healthy children/parents. By comparison, transplanted children cured of the disease, and their parents, had a comparable quality of life to healthy controls.

3. References to the research (Newcastle researchers in bold. Citations from Scopus as at July 2013)

R1. Seger RA, Gungor T, Belohradsky BH, Blanche S, Bordigoni P, Di Bartolomeo P, Flood T, Landais P, Müller S, Ozsahin H, Passwell JH, Porta F, Slavin S, Wulffraat N, Zintl F, Nagler A, **Cant A,** Fischer A (2002). Treatment of chronic granulomatous disease with myeloablative conditioning and an unmodified hemopoietic allograft: a survey of the European experience, 1985-2000. *Blood* 100(13):4344-50. DOI: 10.1182/blood-2002-02-0583. **110 citations.**

Cant had a significant role in producing output R1. He contributed about a third of the patient data to the study and to drafting the manuscript.

R2. Soncini E, Slatter MA, Jones LB, Hughes S, Hodges S, Flood TJ, Barge D, Spickett GP, Jackson GH, Collin MP, Abinun M, **Cant AJ, Gennery AR** (2009). Unrelated donor and HLA-identical sibling haematopoietic stem cell transplantation cure chronic granulomatous disease with good long-term outcome and growth. *British Journal of Haematology*. 145(1):73-83. DOI: 10.1111/j.1365-2141.2009.07614.x. **28 citations.**

R3. **Cole T**, McKendrick F, Titman P, **Cant AJ**, **Pearce MS**, Cale CM, Goldblatt D, **Gennery AR** (2013). Health related quality of life and emotional health in children with chronic granulomatous disease: a comparison of those managed conservatively with those that have undergone haematopoietic stem cell transplant. *Journal of Clinical Immunology.* 33(1):8-13. DOI: 10.1007/s10875-012-9758-0.

<u>Key research grants</u>

Newcastle upon Tyne Hospitals NHS Foundation Trust. Continuous funding (including for research) for the Supra-Regional Paediatric Bone Marrow Transplant Unit.

Bubble Foundation UK. 2009-10. £66 008. Pre-Doctoral Fellowship.
National Institute for Health Research. 2010–14. £248 459. *Chronic Granulomatous Disease: Clinical course, quality of life, cognitive outcome and cost benefit with conservative or curative treatment.*

4. Details of the impact

<u>Impact on UK policy and practice</u>
The impact of the Newcastle University-led research has been significant in the UK. First, as a matter of policy, almost all newly diagnosed CGD patients are now listed for bone marrow transplant. This is because transplantation as soon as possible after diagnosis is preferred since delay lengthens the period in which infections or inflammatory problems can become established. Such problems were shown by Newcastle research to be major risk factors for serious complications around the time of the transplant. Second, transplantation with bone marrow from a matched unrelated donor is now considered acceptable when matched sibling donors are not

available. This means that many more transplants are possible than was previously the case.
This approach to the treatment of new CGD cases pioneered at Newcastle has been adopted by the other UK specialist centre - Great Ormond Street Hospital. The Director of the Bone Marrow Transplantation Unit there has confirmed that practice at that hospital has changed as a result of Newcastle University research, saying,

> *'Undoubtedly up to 2009 we had a different approach to BMT* [bone marrow transplantation] *in CGD between the two NCG units* [Newcastle and Great Ormond Street] *with a much more conservative approach at GOS compared to Newcastle. Also without doubt your presentations at the NCG audit meetings and your publication of the excellent outcome of the Newcastle single centre experience of MSD/MUD* for CGD, convinced us to change our strategy to match yours.'* (Ev a) [*matched sibling donor and matched unrelated donor transplantation]

The effect of the changes in policy and practice are demonstrated in the number and type of bone marrow transplants carried out in the UK on patients with CGD (Ev b) and shown in table 1.

Table 1. Number of bone marrow transplants at the two UK centres, categorised by type.

	Matched	sibling	Matched	unrelated	Totals	
Years	Newcastle	GOS	Newcastle	GOS	Newcastle	GOS
1998-2002	9	2	2	2	11	4
2003-2007	1	1	6	3	7	4
2008-2012	2	2	21	11	23	13

As shown in table 1, the Newcastle centre has led on the practice of transplanting patients with CGD. What is also striking is the shift from using bone marrow from matched sibling donors to using that from matched unrelated donors. The effect of this has been to increase the total number of transplants carried out (a larger pool of available donors) and this is particularly notable in the data from Great Ormond Street. Of the 36 transplants between 2008 and 2013 32 children are alive and cured of the disease. It is thus clear that many children now have a significantly better quality of life, than would otherwise have been the case.

Impact on international guidelines and practice

The European Society for Immunodeficiencies and European Group for Blood and Marrow Transplantation published guidelines in 2011 on bone marrow transplantation for treatment of primary immunodeficiencies, a class of diseases that includes CGD. The guidelines recommend a more conservative approach (a default position of anti-microbial prophylaxis) than that taken in the UK but they nonetheless incorporated Newcastle University research findings, describing excellent outcomes after transplants with matched unrelated donor material. The guidelines state that either of the inherited forms of CGD can be cured with transplants from matched sibling, matched unrelated and mis-matched unrelated donors (Ev c, p19). Two Newcastle research papers (R1 & R2) are listed among the five supporting references in the chronic granulomatous disease section of the guidelines document.
In the United States bone marrow transplantation is now increasingly preferred as a treatment for children with CGD. In a 2011 paper, clinicians at the National Institutes of Health cited the European and UK experience of transplantation (including R1 and R2) and concluded:

> *'allogeneic transplantation has improved dramatically over the last decade…. It has become a successful and sensible option for many patients with CGD that will likely treat and prevent both infectious and inflammatory complications.'* (Ev d)

Engagement with patient group

With a base in London, the UK CGD Society attracts members from all over the world (59% are from outside the UK). Around 150 people are now registering with the society each year. Their website www.cgdsociety.org is a source of information about the science of CGD, diagnosis, disease management and treatment, and acts as a portal to facilitate access of patients and their families to support services. Gennery has contributed significantly to material on the society website that explains bone marrow transplantation, including presenting a video in which he sets out to demystify bone marrow transplantation. There have been over 1200 page views on the bone marrow transplantation section of the society's website. A representative from the society has

described the impact of the Newcastle University research on patients:

> *'More families with young children are now actively considering* [bone marrow transplant (BMT)] *as a treatment option for CGD when their child is well rather than when they become seriously ill. This is a significant step forward and has been made possible by the advances and increased success of BMT for all primary immunodeficiencies, including CGD. Dr Gennery… has also added important knowledge about the impact of CGD on the quality of life of those affected and demonstrated how this and the growth and development of children returns to normal post BMT.'* (Ev e)

The change in approach by clinicians in the UK towards treatment of the disease is reflected in the information provided by the UK CGD Society to patients and their families. The society's *An introduction to bone marrow transplantation* for parents, which was approved in July 2013 by the CGD Society and a Specialty Doctor in bone marrow transplant at Great Ormond Street Hospital, states:

> *'A bone marrow transplant is now the recommended course of treatment for any child diagnosed with CGD. As with every medical procedure, there is a level of risk associated with a BMT. However, in most cases, experts consider this risk to be manageable.'* (Ev f)

Although the numbers of patients being treated is small, the two centres together have had a significant impact on CGD in the UK, reaching all those in need and contributing to the improved health and wellbeing of not only the children themselves, but also their wider families.

5. Sources to corroborate the impact

Ev a. Statement from the Director of Bone Marrow Transplantation, Great Ormond Street Hospital.

Ev b. Transplant figures available from the BMT data manager, Newcastle-upon-Tyne Hospitals Trust.

Ev c. EBMT/ESID guidelines for haematopoietic stem cell transplantation for primary immunodeficiencies (2011). http://www.esid.org/downloads/BMT_Guidelines_2011.pdf (Quotation from page 19.)

Ev d. Kang EM, Marciano BE, DeRavin S, Zarember KA, Holland SM, Malech HL (2011). Chronic granulomatous disease: overview and hematopoietic stem cell transplantation. J Allergy Clin Immunol. 2011 Jun;127(6):1319-26; quiz 1327-8. DOI: 10.1016/j.jaci.2011.03.028.

Ev e. Statement from the Research and Support Programme Manager, CGD Society.

Ev f. CGD Society (2013): An introduction to bone marrow transplantation. A guide for parents of children under the age of 18 who are affected by CGD. (Quotation from page 2. Supplied by the Society, available on request.)