Institution: University of Glasgow

Unit of Assessment: Unit 1, Clinical Medicine

Title of case study: Improved clinical guidelines to manage postoperative infection risk in kidney transplant recipients

1. Summary of the impact

In 2012, around 19,500 kidney transplant operations were performed in the UK and USA. The greatest infection risk to transplant recipients is from cytomegalovirus (CMV), the standard 2–4 week treatment for which involves an average of 5 days as an inpatient, which can cost up to £13,000. University of Glasgow research has led to revised standards of care for the prevention and treatment of CMV disease in kidney transplant recipients (KTRs). First, that antiviral treatment with oral valganciclovir for 200 days can be used to prevent CMV disease in postoperative KTRs and is twice as effective as treatment for 100 days. Secondly, the team found that the use of oral valganciclovir was a practical and cost-effective alternative to intravenous ganciclovir for treatment of mild CMV disease in solid-organ transplant recipients. Since 2009, the use of these therapies has been recommended in key national and international guidelines for the care of KTRs. The research also provided the evidence base that was used for evaluating, and subsequently amending, the marketing authorisation of oral valganciclovir for use in preventative treatment of CMV disease in KTRs in the UK and USA.

2. Underpinning research

One of the paradoxes of the successful development of dialysis and transplantation for the treatment of end-stage renal failure is that affected patients are more likely to die of accelerated cardiovascular disease, malignancy and infection, than of renal failure. Roughly half the human population carries CMV, often asymptomatically due to the action of a healthy immune system. However, CMV is the leading infection risk to KTRs due to the use of immunosuppressant agents to prevent rejection. The resulting CMV disease is associated with significant risk of illness and death, along with an increased risk of kidney graft rejection and other opportunistic infections.

Research by Professor Alan Jardine (Professor of Renal Medicine, 1994–present) at the University of Glasgow contributed to two phase III, international, randomised controlled trials to: (i) evaluate the use of the oral antiviral drug valganciclovir as an alternative to intravenous ganciclovir for the treatment of CMV disease in solid-organ transplant recipients, and (ii) revise use of oral valganciclovir for the prevention of CMV disease in postoperative KTRs.

VICTOR trial

Between 2004 and 2006, Jardine was the UK lead for the 'Valganciclovir Compared to Ganciclovir iv in Patients With Cytomegalovirus Disease Who Are Solid Organ Transplant Recipients' (VICTOR) trial.[1] This study, and its subsequent sub-studies, was conducted by an international five-member executive steering committee, which included Jardine, in collaboration with Roche Pharmaceuticals. While the study comprised participants with different solid organ transplants (e.g. liver, heart or lung) around 74% of participants were KTRs.

Prior to the VICTOR study, treatment of CMV infection required frequent hospital admission for treatment with intravenous ganciclovir, which is both inconvenient for patients and expensive for health authorities. The VICTOR study was the first randomised controlled trial to compare the efficacy and safety of oral valganciclovir with intravenous ganciclovir in solid-organ transplant patients, and was conducted in a total of 321 patients across 42 centres worldwide. The study showed that oral valganciclovir is equivalent to intravenous ganciclovir therapy, with successful clearance of CMV disease at day 21 (45.1% valganciclovir versus 48.1% ganciclovir, P=0.05), rising to 85% of patients (85.4% valganciclovir versus 84.1% ganciclovir, P=NS) at day 49 of treatment.[1] The outcomes following treatment were evaluated after 1 year. This found that, independent of which treatment was used, detectable CMV virus had recurred (with or without associated disease) in 30% of participants, with CMV disease recurring in 15% of participants.[2]

IMPACT trial

Key to the management of CMV disease is prevention of infection with CMV, especially in high-risk patient groups (patients with no prior exposure to the virus who receive an organ from a CMV-infected donor). Before 2009, two strategies were used to prevent CMV infection in high-risk KTRs: rapid diagnosis and early therapy with an anti-viral agent (so-called "pre-emptive therapy") or universal prophylaxis with valganciclovir for 100 days. However, these approaches were associated with delayed-onset disease ("late-onset CMV") in one-third of patients after discontinuation of treatment.

Between 2006 and 2009, Jardine was on the steering committee of the 'Improved Protection Against Cytomegalovirus in Transplant' (IMPACT) trial.[3] This was a phase III trial designed by the group who performed the VICTOR study to assess the efficacy and safety of 100 day treatment versus 200 day treatment with oral valganciclovir in high-risk KTRs, with the aim of determining whether extended prophylaxis would prevent late-onset CMV disease. The trial included 326 high-risk KTRs across 65 study centres in 13 countries worldwide. The trial showed that 200 day prophylaxis prevented disease in 84% of high-risk KTRs for up to 1 year after surgery, with similar tolerability and safety compared with 100 day treatment. The incidence of CMV disease in the 200 day treatment group was 16% compared with 37% observed in the 100 day group; thus, doubling the length of prophylaxis reduces the incidence of CMV disease by 56%, relative to 100 day prophylaxis, an absolute risk reduction of 21%.[3]

These two trials have established that oral valganciclovir provides an equally effective treatment to intravenous ganciclovir for CMV disease, with no significant difference in safety profile, and that six months (200 days) of prophylaxis with oral valganciclovir improves the long-term outcome for KTRs, by reducing the incidence of late-onset CMV disease. They thus provide simplified treatment options, improving the clinical management of post-operative KTRs.

3. References to the research

1. Asberg A *et al.* VICTOR Study Group. Oral valganciclovir is non-inferior to intravenous ganciclovir for the treatment of cytomegalovirus disease in solid organ transplant recipients. *Am. J. Transplant.* **7**, 2106–2113 (2007). doi:10.1111/j.1600-6143.2007.01910.x
2. Asberg A *et al.* Long-term outcomes of CMV disease treatment with valganciclovir versus IV ganciclovir in solid organ transplant recipients. *Am. J. Transplant.* **9**, 1205–1213 (2009). doi:10.1111/j.1600-6143.2009.02617.x
3. Humar A *et al.* The efficacy and safety of 200 days valganciclovir cytomegalovirus prophylaxis in high-risk kidney transplant recipients. *Am. J. Transplant.* **10**, 1228–1237 (2010). doi:10.1111/j.1600-6143.2010.03074.x

4. Details of the impact

In 2012, approximately 2,700 kidney transplants were performed in the UK and 16,812 in the USA. However, up to 50% of transplant recipients will have at least one infection within 1 year of transplantation. CMV is one of the most common infections in KTRs, and can lead to clinical disease involving fever, inflammation of the lungs, liver or gut, and also disruption of the local immune response, leading to secondary infections and long-term injury to or rejection of the transplanted kidney.

University of Glasgow research has helped to establish revised standards of care for the clinical management of the prevention (IMPACT trial) and treatment (VICTOR trial) of CMV disease in KTRs. These trials are cited in current guidelines around the world, supporting recommendations that include:

- Doubling the length of preventative (prophylactic) treatment with valganciclovir in KTRs from 100 days to 200 days, which has been shown to halve the relative incidence of CMV disease over 12 months.
- The use of oral valganciclovir as an alternative to intravenous ganciclovir in the treatment of

human CMV disease, which has been shown to be equally effective at eradicating disease in 85% of solid-organ recipients with non-life-threatening illness (74% of whom were KTRs).

Adoption of oral valganciclovir and extended prophylaxis in clinical guidelines

Since the publication of the IMPACT and VICTOR trials, the findings have been adopted to support recommendations for the management of KTRs in national and international guidelines. With the exception of Kidney Disease: Improving Global Outcomes (KDIGO; discussed later), all of the guidelines below cite the VICTOR trial to support oral valganciclovir as an alternative to intravenous ganciclovir to treat CMV disease, and cite the IMPACT trial to support the use of oral valganciclovir for 200-day (6-month) prophylaxis to prevent CMV disease in high-risk adult KTRs.

National guidelines

- The American Society of Transplantation is an organisation of more than 2,700 transplant clinicians, whose annual congress attracts in excess of 5,000 delegates from around the world. Its 2009 guideline 'Cytomegalovirus in solid organ transplant recipients' cites University of Glasgow research in the "CMV Prevention" (level 1 recommendation, ref. 26 and 32, p.S80) and "CMV Treatment" (ref. 12 and 39, p.S83) sections.[a]

- The British Transplantation Society (BTS) is the professional voice of transplantation in the UK, representing all healthcare professionals working with transplant patients. Their 2011 guidelines on 'Prevention and Management of CMV Disease after Solid Organ Transplantation' cite University of Glasgow research in the Prophylaxis (ref. 99, p.34-35) and Treatment (ref. 131, p.45) sections. The BTS guidelines provide further context, describing IMPACT as a '*landmark study*', and stating that, '*in practice, many units have begun to use oral valganciclovir prophylaxis to avoid the costs and inconvenience of hospital admission and/or home intravenous anti-viral therapy*." Likewise, they state that "*substantial clinical experience in recent years has reinforced that* [use of oral valganciclovir to treat CMV disease] *is an appropriate treatment strategy, which has the advantage of being able to offer management as an outpatient for a proportion of patients*.'[b]

- The Renal Association is the professional association for renal physicians and scientists in the UK, and has an active role in the development of renal services in the UK. In 2011, Prof. Jardine co-authored their guidelines on 'Post-operative Care of the Kidney Transplant Recipient'. The guidelines are intended for those healthcare professionals who care for KTRs, but who are not experts in transplant infectious disease. They cite University of Glasgow research as Prophylaxis recommendation 8.2.1 (level 1 recommendation, ref. 110, p.45-46) and Treatment suggestion 8.2.2 (ref. 112 and 113, p.45-46).[c]

International guidelines

- KDIGO is an independent group with a core mission of developing and implementing clinical guidance in kidney disease with an international focus. The 2009 KDIGO guideline on 'The care of kidney transplant recipients' cites University of Glasgow research under recommendation 13.2.3.2 (level 1 recommendation, ref. 312, p.S48); the guidelines pre-date publication of IMPACT. Whilst they give a strong recommendation, they describe the evidence of the VICTOR trial as 'D' (low) due to the absence of patients with life-threatening CMV disease. However, they clarify in their rationale that, '*At this point, most experts would be willing to use oral therapy to treat adult KTRs with mild CMV disease*.'[d]

- The Transplantation Society is the leading international society of physicians, surgeons and scientists involved in the transplantation of organs and tissues. Its 2010 guideline 'International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation' was developed using a consensus group of 45 experts from 15 countries worldwide, which also included Jardine. These guidelines cite University of Glasgow research to support Prophylaxis (level 1 evidence, ref. 88, p.785) and Treatment (level 1 recommendation, ref. 33 and 87, p.787) recommendations.[e]

The implementation of the Transplantation Society's International Consensus guidelines was surveyed in 2011, a year after publication, receiving responses from 155 transplant clinicians, representing 126 clinical centres in 41 countries. Feedback from 73% of respondents represented kidney transplant practice. Of all respondents, only 99 specified which antiviral they use in high-risk patients, but of these, 86% used oral valganciclovir, and just over half of them used it for a period of 200 days.[f]

Amendment of licenses by medicines regulators

For medicines to be used in a modified way, the national medicines regulatory bodies must amend the relevant licenses. The IMPACT trial resulted in amendment of licenses for use of valganciclovir for preventing CMV disease in KTRs by UK medicines agencies[g-i] and the United States Food & Drug Administratio[n], providing the option of extended 200 day treatment with oral valganciclovir. Whilst the UK Medicines and Healthcare products Regulatory Agency[i] refers to the outcomes of the study in its amendment, the statutory advisors to the Scottish and Welsh governments (Scottish Medicines Consortium[g] and the All Wales Medicines Strategy Group[h]) published their detailed evaluation of the IMPACT evidence.

The Scottish Medicines Consortium's role is to license (or amend licenses for new indications) those drugs that are both clinically effective and represent good value for money. This ensures that drugs meeting these requirements are accepted for routine use and have access to NHS funding. The Scottish Medicines Consortium evaluated the comparative efficacy and safety of 100 day versus 200 day treatments, citing the IMPACT study,[3] including an analysis of the cost-effectiveness of using the drug, based on a cost-utility model provided by the manufacturers of valganciclovir (Roche). These data supported the amendment to the license, on the basis that an additional 100 days of preventative treatment was considered to offer both clinical and economic value. A 200 day treatment is currently being used in the two renal transplant units in Scotland (Glasgow Western and Edinburgh Royal and infirmaries).[g]

5. Sources to corroborate the impact

a. Humar A & Snydman D. & the AST Infectious Diseases Community of Practice. Cytomegalovirus in solid organ transplant recipients. *Am. J. Transplant*. 9, (Suppl 4): S78–S86 (2009). doi:10.1111/j.1600-6143.2009.02897.x.
b. British Transplantation Society Guidelines for the Prevention and Management of CMV Disease after Solid Organ Transplantation, 3rd edition, August 2011.
c. Baker R, Jardine A & Andrews P. Post-operative Care of the Kidney Transplant Recipient (2011) The Renal Association guidelines (Section 8.2).
d. KDIGO clinical practice guideline for the care of kidney transplant recipients. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. *Am. J. Transplant*. 9: S1–S155 (2009). doi:10.1038/ki.2009.377.
e. Kotton CN et al. & Transplantation Society International CMV Consensus Group. International consensus guidelines on the management of cytomegalovirus in solid organ transplantation. *Transplantation* 89, 779–795 (2010). doi:10.1097/TP.0b013e3181cee42f.
f. Le Page AK. International Survey of Cytomegalovirus Management in Solid Organ Transplantation After the Publication of Consensus Guidelines. *Transplantation* 95, 1455–1460 (2013). doi:10.1097/TP.0b013e31828ee12e.
g. Valganciclovir (SMC No. 662/10), Scottish Medicine Consortium, January 2011.
h. All Wales Medicines Strategy Group (AWMSG) review and amendment granted (June 2011).
i. Valganciclovir (SPC-DOC_PL 00031-0829 / 00031-0599, tablet), amendment to Medicines and Healthcare Products Regulatory Agency, June 2011.
j. FDA (August 2010) | News article.