Institution: University College London

Unit of Assessment: 1 – Clinical Medicine

Title of case study: Establishment of tacrolimus as the first choice calcineurin inhibitor for the immunosuppression regimen in liver transplant recipients

1. Summary of the impact (indicative maximum 100 words)

Research at UCL firmly established tacrolimus as the optimal calcineurin inhibitor to use in immunosuppressive regimens following liver transplantation. Compared to ciclosporin its use improved graft survival by 6% and patient survival by 7%. Assuming 550 liver transplants per year in the UK since 2008, we can estimate that, with 90% of patients treated with tacrolimus and 10% ciclosporin, tacrolimus-based immunosuppression has resulted in 165 grafts and 192 lives being saved during the period 2008-13.

2. Underpinning research (indicative maximum 500 words)

Long-term immunosuppression with calcineurin inhibitors (ciclosporin or tacrolimus) is essential for almost all patients undergoing liver transplantation. However, the optimum initial immunosuppression regimen was unknown by the late 1990s.

Previous immunosuppression trials had used rates and patterns of rejection as measures of drug efficacy. Results from such studies had shown lower rates of cellular rejection, steroid-resistant rejection, and chronic rejection in tacrolimus-treated patients compared to those receiving the old ciclosporin formulation. However this had been superseded by the microemulsified preparation with better bioavailability. Equally in liver transplantation the importance of acute cellular rejection was questioned as there appeared no correlation between such rejection and graft survival. Therefore patient and graft survival had become regarded as the most meaningful efficacy measures of immunosuppressive agents. At the time of the trial, results from follow-up of the early US and European studies suggested better survival rates for patients receiving tacrolimus than ciclosporin, although this was not a robust finding.

Beginning in the mid-1990s, Burroughs was the instigator and chief co-investigator of the TMC study together with O'Grady (King's College London). The investigators undertook a trial to assess the immunosuppressive efficacy of tacrolimus compared with micro-emulsified ciclosporin, with their protocol standardising all aspects of drug dosing and concomitant medication. The study showed that the clinical outcome at one year was better with tacrolimus-based immunosuppression.

The trial's primary outcome was the combined frequency (whichever occurred first) of death, retransplantation, or treatment failure for immunological reasons, analysed by intention to treat This was achieved in 62 (21%) of 301 patients in the tacrolimus group versus 99 (32%) of 305 allocated microemulsified ciclosporin (p=0·001). The authors recommended that tacrolimus should be the first choice of calcineurin inhibitor for patients receiving their first liver graft **[1]**. Three-year follow-up data confirmed the continued advantage of tacrolimus. A total of 62.1% of patients randomised to tacrolimus were alive at 3 years with their original graft and still on their allocated study medication, compared with only 41.6% in the ciclosporin limb **[2]**. A further randomised study comparing tacrolimus and ciclosporin as monotherapy, with no routine or maintenance steroids demonstrated that monotherapy provided adequate immunosuppression for 87% of tacrolimus versus 64% of ciclosporin patients **[3]**. Long-term follow up showed that tacrolimus monotherapy ab initio is a viable immunosuppressive strategy in liver transplantation and was associated with lower rejection rates and renal complications, compared to ciclosporin **[4]**. Finally, a systematic review to assess the effect of lower doses of tacrolimus on acute rejection rates and renal impairment confirmed that these are as effective and have fewer side effects **[5]**.

3. References to the research (indicative maximum of six references)

[1] O'Grady JG, Burroughs A, Hardy P, Elbourne D, Truesdale A; UK and Republic of Ireland Liver Transplant Study Group. Tacrolimus versus microemulsified ciclosporin in liver transplantation: the TMC randomised controlled trial. Lancet. 2002 Oct 12;360(9340):1119-25. http://dx.doi.org/10.1016/S0140-6736(02)11196-2

[2] O'Grady J, Hardy P, Burroughs AK, Elbourne D UK and Ireland Transplant Study group. Randomized controlled trial of tacrolimus versus microemulsified cyclosporine (TMC) in liver transplantation: post study surveillance to three years. Am J Transpl 2007;7:137-41 http://dx.doi.org/10.1111/j.1600-6143.2006.01576.x

[3] Rolles K, Davidson BR, Burroughs AK. A pilot study of immunosuppressive monotherapy in liver transplantation: tacrolimus versus microemulsified cyclosporin. Transplantation 1999;68:1195-1209. http://www.ncbi.nlm.nih.gov/pubmed/10551650

[4] Cholongitas E, Shusang V, Germani G, Tsochatzis E, Raimondo ML, Marelli L, Senzolo M, Davidson BR, Rolles K, Burroughs AK. Long term follow up of immunosuppressive monotherapy in liver transplantation: tacrolimus and microemulsified cyclosporin. Clin Transplant. 2011 Jul-Aug;25(4):614-24. http://dx.doi.org/10.1111/j.1399-0012.2010.01321.x

[5] Rodriquez-Peralvares M, Germani G, Darius T, Lerut J, Tsochatzis E, Burroughs AK. Tacrolimus trough levels, rejection and renal impairment in liver transplantation: a systematic review and meta-analysis. Am J Transplantation 2012;12:2797-2814 http://dx.doi.org/10.1111/j.1600-6143.2012.04140.x

4. Details of the impact (indicative maximum 750 words)

Use of tacrolimus as the first line immunosuppression agent in liver transplantation had begun to climb from 1999 onwards, although trials at this stage had not demonstrated an unambiguous improvement over ciclosporin. The research by Burroughs firmly established tacrolimus as the optimal calcineurin inhibitor to use in immunosuppressive regimens following liver transplantation, and has thus changed standard clinical practice in the UK and worldwide. Tacrolimus-based immunosuppression has become the "gold-standard". The results of the trial were confirmed in a subsequent Cochrane meta-analysis of 16 trials which showed that treating 100 recipients with tacrolimus instead of ciclosporin would avoid acute rejection and steroid-resistant rejection in nine and seven patients, respectively, and graft loss and death in five and two patients **[a]**.

In the US, the Organ Procurement and Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR) Annual Data Report 2010 stated that; "*Immunosuppressive strategies based on tacrolimus and mycophenolate continue to be the dominant early regimen. In 2009, the alternative calcineurin inhibitor cyclosporine was used relatively infrequently (7.3%) compared with tacrolimus (85.8%)*" **[b]**. In 2011, they reported that; "*Initial immunosuppression for most recipients is tacrolimus and mycophenolate mofetil (MMF), commonly in conjunction with steroids… By 1 year after transplant, most patients are no longer taking steroids and are taking tacrolimus with or without MMF. With these immunosuppressive regimens, acute rejection occurs in less than 20% of recipients during the first year*" **[c]**. Of 14,658 patients transplanted between 2002 and 2010 in the US, 92% (13,515) were on tacrolimus **[d]**.

This landmark study therefore changed clinical practice and provided a clear benefit to patients. A 2006 meta-analysis of 16 trials demonstrated that tacrolimus reduced mortality by 15% and graft loss by 27% compared to ciclosporin **[e]**. Assuming 550 liver transplants per year in the UK since 2008, we can estimate that, with 90% of patients treated with tacrolimus and 10% ciclosporin, tacrolimus-based immunosuppression has resulted in 165 grafts and 192 lives being saved in total for the period 2008-13.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[a] Cochrane Database Syst Rev. 2006 Oct 18;(4):CD005161. Cyclosporin versus tacrolimus for liver transplanted patients. Haddad EM, McAlister VC, Renouf E, Malthaner R, Kjaer MS, Gluud LL. http://dx.doi.org/10.1002/14651858.CD005161.pub2

[b] http://srtr.transplant.hrsa.gov/annual_reports/2010/pdf/03_liver_11.pdf

[c] http://srtr.transplant.hrsa.gov/annual_reports/2011/pdf/03_%20liver_12.pdf

[d] Toso C, Merani S, Bigam DL, Shapiro AM, Kneteman NM. Sirolimus-based immunosuppression is associated with increased survival after liver transplantation for hepatocellular carcinoma. Hepatology 2010;51:1237-43. http://dx.doi.org/10.1002/hep.23437.

[e] McAlister VC, Haddad E, Renouf E, Malthaner RA, Kjaer MS, Gluud LL. Cyclosporin versus tacrolimus as primary immunosuppressant after liver transplantation: a meta-analysis. Am J Transplant. 2006 Jul;6(7):1578-85. http://dx.doi.org/10.1111/j.1600-6143.2006.01360.x