Institution: University of Warwick

Unit of Assessment: B15 General Engineering

Title of case study: Kinetic modelling to optimise dialysis and improve kidney function in patients with multiple myeloma. (Case study B15.1)

1. Summary of the impact

Through the mathematical modelling of biomedical processes, outcomes for patients with multiple myeloma (a form of bone cancer that can lead to kidney failure, a major cause of morbidity) have been vastly improved, with the result that dialysis treatment may no longer be necessary alongside their myeloma treatment. Regaining kidney function for these patients improves their quality of life and results in significant cost savings for the NHS. Research into the modelling of the kinetics of whole antibodies produced by multiple myeloma patients (and others) has also had an impact on patient outcomes and clinical decisions. There have also been economic benefits for Gambro, a German company that sells products developed on the basis of the research results.

2. Underpinning research

A long-established research collaboration exists between the Biomedical and Biological Systems Laboratory (Engineering, Warwick), The Binding Site Ltd and the Department of Immunology (Birmingham). This work has primarily involved the application of Warwick's research into mathematical modelling of biomedical processes to the use of monoclonal antibodies for targeting tumours, for both diagnostic and therapeutic purposes. Since 2002, Warwick's research has been extended to antibody synthesis and the modelling of the kinetics of antibodies and free light chains based upon assay data that can be obtained only from The Binding Site Ltd. The Binding Site is a global specialist protein company providing immunodiagnostic assays for the global laboratory market.

Chappell (Head of Warwick group), Evans and EPSRC PhD student Hattersley (Warwick 2007-2009) performed engineering state space (compartmental) modelling in 2005-2006. This was based on multiple myeloma patients and used systems modelling and simulation techniques. These incorporated the effects of novel scheduling strategies and theoretically predicted that the use of alternative types of dialysis filter (High Cut Off/High Frequency (HCO/HF) filters) for longer initial dialysis sessions than were normally used would greatly increase the extraction of free light chains. The modelling performed was novel not only in terms of the generation of a mechanistic model of serum free light chain kinetics in humans, but also in being the first simulations to suggest that the use of alternative dialysis filters extracted excess serum-free light chains from myeloma sufferers [3, 4].

Warwick modelled the prevalence of free light chains in patients with multiple myeloma, and the effect of these light chains on kidney function on the outcome of certain forms of chemotherapy [1, 2]. Patients with multiple myeloma and severely reduced kidney function or kidney failure can become dependent on dialysis, which is an additional burden on their quality of life as well as being costly from an economic perspective. In order to improve the quality of life of such patients, a key objective is to remove the greatly increased amounts of the free light chains produced, permitting recovery of kidney function and hence a release from dialysis dependence.

This modelling work prompted a series of local clinical trials which took place between April 2006 and May 2008, in which multiple myeloma patients with kidney failure were treated using larger filters than previously used and over extended dialysis sessions, being up to 12 hours daily for a few weeks compared to the previous treatment of 3-4 hours 3 times per week potentially indefinitely [9]. The results of these trials were extremely encouraging, with 85% of patients recovering kidney function and no longer requiring dialysis treatment. The remaining 15% of patients had confounding symptoms with suggested clear reasons as to why they did not benefit from this optimised protocol.

The promising results obtained from these trials have now led to a Europe-wide series of clinical trials (EuLite, http://clinicaltrials.gov/ct2/show/NCT00700531), which are currently underway, with the results expected from January 2014 onwards. The modelling has also been applied to the treatment of other medical conditions such as rhabdomyolysis. A two compartment model has been developed by Warwick [5] to treat rhabdomyolysis patients undergoing dialysis for the removal of myoglobin. The application of the modelling, using Gambro filters removes myoglobin more effectively without the removal of other larger essential molecules.

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3. References to the research

Publications:

1. *C.A. Hutchison, P. Cockwell, S. Reid, K. Chandler, G.P. Mead, J. Harrison,* ***J. Hattersley, N.D. Evans, M.J. Chappell****, M. Cook, H. Goehl, M. Storr and A.R. Bradwell* "Efficient removal of immunoglobulin free light chains by haemodialysis for multiple myeloma: in-vitro and in-vivo studies. *Journal of the American Society of Nephrology,* 18(3) 886 – 895. (2007) DOI: 10.1681/ASN.2006080821 JIF: 8.288, 5yr JIF: 7.960, ERA: B, Citations: 58

2. *G. Pratt, G.P. Mead,* ***K.R. Godfrey, Y.Hu, N.D. Evans, M.J. Chappell****, R. Lovell and A.R. Bradwell*. "The tumour kinetics of multiple myeloma following autologous stem cell transplantation as assessed by measuring serum free light chains". *Leukemia and Lymphoma*, 47(1) 21 – 28. (2006) DOI: 10.1080/10428190500254216 JIF: 2.492, 5 yr JIF: 2.089, ERA: B, Citations: 10

3. ***N.D. Evans, J. Hattersley,*** *C. Hutchison, Y. Hu, K.R. Godfrey, A.R. Bradwell, G.P. Mead, and* ***M.J. Chappell***. **"**Modelling of haemodialysis in limiting serum free light chains in patients with renal failure", in: Proceedings of the 6th IFAC Symposium on Modelling and Control in Biomedical Systems 6(1) (D. Feng, O. Dubois, J. Zaytoon and E. Carson, eds), Reims, 20-22 September, 2006, Elsevier, Oxford, pp. 75-80) DOI: 10.3182/20060920-3-FR-2912.00018 (Full paper peer-reviewed international conference)

4. C.A Hutchison, A.R. Bradwell, M. Cook, K. Basnayake, S. Basu, S. Harding, J.G. Hattersley, **N.D. Evans**, **M.J. Chappell, P. Sampson, L. Foggensteiner, D. Adu and P. Cockwell.** "Treatment of acute renal failure secondary to multiple myeloma with chemotherapy and extended high cut-off haemodialysis. *Clinical Journal of the American Society of Nephrology* 2009*,* 4:745–754. DOI: 10.2215/CJN.04590908

5. **R. Keir, N.D. Evans**, C.A. Hutchison, M.R. Vigano, A. Stella, P. Fabbrini, M. Storr, **M.J. Chappell**. "Kinetic modelling of haemodialysis removal of myoglobin in rhabdomyolysis patients. *Computer Methods and Programs in Biomed*icine 2013 Aug 14. pii: S0169-2607(13)00252-6. DOI: 10.1016/j.cmpb.2013.07.017 [Epub ahead of print]

Patent:

6.

[text removed for publication]

4. Details of the impact The research has been widely recognised as not only having impacts on the health and welfare of patients but also resulting in economic benefits for healthcare providers and the industry supplier of dialysis filters.

Health outcomes: The research and trials demonstrated that HCO dialysis results in greater quantities of free light chains being removed from patients, which in turn improves the rates of renal recovery in myeloma patients with kidney failure.

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Quality of life: The outcomes of the research have clear impacts in terms of the well-being of the patients and their ability to lead more normal lives, without the need for dialysis. Normal dialysis takes 4-5 hours per session 3-4 times per week, potentially throughout the patients' lifetime. The new treatment, although requiring longer sessions (up to 12 hours daily for 3 weeks in total), significantly reduces the overall treatment time [7] clearly having an impact on the quality of life of patients with multiple myeloma in terms of treatment but also life expectancy.

Reach: In 2012, there were over 59,000 new incidences of multiple myeloma in the US, Japan,

France, Germany, Italy, Spain and the UK alone (approximately 0.8% of all cancers worldwide); 8% of these patients have severe kidney failure and will particularly benefit from this new treatment. The actual number of patients being treated in these 7 countries is higher due to the cumulative prevalence of multiple myeloma. On the basis of the increases over the last 5 years, it is estimated that the number of new incidences of multiple myeloma will increase by 47% by 2030 [8]. Therefore, the modelling work from Dr Chappell and colleagues in Warwick, which was instrumental in the optimisation of kidney dialysis for multiple myeloma patients, will have an increasing impact on patients with multiple myeloma.

'[text removed for publication]' The long-term outcomes for these patients is better than earlier literature suggests and two multicentre randomised controlled clinical trials (in the UK and Germany [10b]) are almost complete; these will signify the benefits when new literature is published [7].

Reduced treatment costs: Because treated patients regain kidney function and are no longer dialysis dependent, the treatment is expected to have a significant economic impact on the NHS. The NHS treats approximately 4,500-4,800 patients with multiple myeloma every year (there are 3,000-3,500 new cases per year in the UK) of which 8% will require dialysis [9a]; around half of these patients are suitable for this new treatment. Dialysis costs the NHS £30-40k per year per patient [9b]. This new treatment will reduce the dialysis costs to the NHS for 85% of multiple myeloma patients to approximately £7,500-10,000 per patient equivalent to a saving of £3.8 million per year for the NHS alone [7].

Commercial and economic impacts: [text removed for publication]

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Public awareness and interest: Public awareness of the success of the new treatment is extending across the world from the UK to Australia and New Zealand as well as to the US. “Patients advocates (family etc) are finding the research on the web and are asking for it for their family members” [7]. Examples: The Myeloma Beacon; Kidney Friends; Helen Diller Family

Comprehensive Cancer Center; International Myeloma Foundation; Living with Multiple Lyeloma [14]. Dr John Hattersley (former PhD student (Section 2), is now Senior Research Fellow, Human Metabolic Research Unit, University Hospitals Coventry and Warwickshire NHS Trust.

Policy: If the results of the wider international trials, expected January 2014, are as positive as the earlier research, then there is likely to be a change in policy in several countries in relation to the treatment of multiple myeloma patients who also suffer from kidney malfunction or failure. The Health Policy Advisory Committee on Technology for Australia and New Zealand have produced a Technology Brief on the new procedure concluding it is effective and are awaiting further trial results [15]. It is expected that the full impact in clinical terms will develop over the next four to five years with the increase in patients (multiple myeloma and other conditions) being treated and benefiting from this change in treatment.

5. Sources to corroborate the impact

7. [text removed for publication]

8. Data Monitor Healthcare: 'Epidemiology: Multiple Myeloma Long survival and lack of curative drugs drives rises in myeloma treatable populations' by Sabada Dube *can be provided by HEI upon request*

9a. Book by A.R. Bradwell specifically acknowledging M Chappell and N Evans in Preface XV: Serum Free Light Chain Analysis (Plus Hevylite®) 6th Edition 2008 ISBN: 9780704427969
9b. NHS: 'In the UK, around 4,800 people are diagnosed with the condition each year' http://www.nhs.uk/Conditions/Multiple-myeloma/Pages/Introduction.aspx

10. Gambro webpages highlighting the application of the filters and HCO dialysers they are selling utilising the results of the research:
a. http://www.gambro.com/en/global/Therapies/Myeloma-Kidney-Therapy1/;
b.http://www.gambro.com/Global/Globalweb/Therapies/Myeloma/Documents/HCEN5379_3_Myeloma_low.pdf?epslanguage=en

11. [text removed for publication]

12. [text removed for publication]

13. Webpages of The Binding Site and the serum free light chain assays commercialised http://www.thebindingsite.com/hevylite; http://www.thebindingsite.com/freelite

15. The Myeloma Beacon 'New hemodialysis procedure …' May 27, 2009. http://www.myelomabeacon.com/news/2009/05/27/hemodialysis-improves-health-of-multiple-myeloma-patients/ February 27 2012 (German trial results): http://www.myelomabeacon.com/news/2012/02/27/high-cut-off-hemodialysis-helps-restore-kidney-function-in-multiple-myeloma-patients/
Kidney Friends: http://www.kidney-friends.net/showthread.php?tid=4352
Helen Diller Family Comprehensive Cancer Center: http://cancer.ucsf.edu/research/multiple-myeloma
International Myeloma Foundation: http://myeloma.org/ArticlePage.action?tabId=4&menuId=361&articleId=2859&aTab=-1
Living with Multiple Lyeloma: http://multiplemyelomablog.com/2010/04/high-cut-off-hemodialysis-hch-being-used-to-help-multiple-myeloma-patients-with-kidney-involvement.html

15. Centre for Healthcare Improvement, Queensland Health: Health Policy Advisory Committee on Technology Australia and New Zealand 'Technology Brief Theralite™ for treatment of renal failure in patients with multiple myeloma' http://www.health.qld.gov.au/healthpact/docs/briefs/WP094.pdf