Institution: University of Sheffield

Unit of Assessment: 1 - Clinical Medicine

Title of case study: Safer treatment of childhood leukaemia through improved delivery of thiopurine drugs

1. Summary of the impact

A routine test to screen for patients genetically disposed to serious side effects from treatment with thiopurine drugs has been widely adopted following research by the Academic Unit of Clinical Pharmacology at the University of Sheffield. The test has spared patients painful and potentially life-threatening sepsis, and saved the considerable associated treatment costs which have been estimated to be over £9,000 per patient for a 17 day hospital stay. It has also led directly to a change in clinical guidelines and recommendations in both the USA and UK.

2. Underpinning research

During the period 1993 to 2003, Dr Lynne Lennard (Reader in Pharmacology, Department of Human Metabolism, University of Sheffield) together with John Lilleyman (Honorary Professor and Consultant Haematologist, Sheffield Children's Hospital and, from 1995, Professor of Paediatric Haematology, Barts and The London) investigated the wide variations in clinical response to a drug used in the chemotherapy of childhood leukaemia. The drug was called 6-mercaptopurine, a thiopurine drug. A dose of drug that was too toxic in one child could be ineffective in another child. A genetic defect was identified and studied, as part of clinical trials, over the subsequent decade.

Research included within these studies includes the description of the genetic defect causing abnormal metabolism of thiopurine drugs at the molecular level, that is the identification of the major defective variant forms of the enzyme thiopurine methyltransferase (TPMT) (R1), the connections between the inheritance of the variant TPMT enzyme, variable mercaptopurine metabolism, drug induced toxicity and the long-term drug effect, i.e. the outcome of treatment (R2), and the development of drug dosage schedules to enable drug therapy in patients with defective TPMT enzyme (R3, R4).

Research in Sheffield

From 1993 to 2000, Lennard, working with Lilleyman, identified the drug metabolites that caused excess cytotoxicity in children treated with thiopurine drugs as part of their chemotherapy for acute lymphoblastic leukaemia (ALL). Excess production of these toxic metabolites caused bone marrow failure (the bone marrow stops producing blood cells). Lennard developed and published methodologies for the measurement of the enzyme defect for use in routine tests in 1994 (R5), and modified these in 2006 (R6). This enabled the development of drug dosage schedules for those patients very sensitive to thiopurine drugs (low TPMT enzyme activity; no drug is removed by the enzyme TPMT and too much drug is then made into toxic metabolites) and those constitutionally resistant to standard drug doses (very high TPMT activities; too much drug is removed by TPMT and insufficient cytotoxic metabolites are made) (R2, R3, R4).

Collaborative studies

During 1993 to 1997, Lennard worked on a collaborative study with Richard Weinshilboum (Dept Pharmacology, Mayo Clinic, Rochester, USA), and identified the genetic error in the TPMT enzyme (R1). This enabled the establishment of genotype assays to detect TPMT deficiency.

Clinical trials

From 1997 to date, working within a series of clinical trials with Lilleyman and Vora (from 1995 Honorary Professor of Haematology and Consultant Haematologist, Sheffield Children's Hospital) formal studies were undertaken to establish the links between the amount of inherited TPMT enzyme, the production of cytotoxic drug metabolites and thiopurine drug toxicity and efficacy. The trials were called MRC ALL97 (which ran from 1997 to 2002) and ALL 2003 (2002 to 2011); thiopurine-based treatment lasts for 2 to 3 years, so the last child recruited will finish treatment in

2014. The Sheffield Clinical Pharmacology Unit (led by Lennard, funded by Leukaemia and Lymphoma Research) were responsible for the organisation and implementation of the Thiopurine Studies within these trials. Lilleyman and Vora were the Chief Investigators for ALL97 and ALL2003 respectively.

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

R1. Otterness D, Szumlanski C, **Lennard L**, Klemensdal B, Aarbakke J, Park-Hah J, Iven H, Schmeigelow K, Branum E, O'Brien J, Weinshilboum R. Human thiopurine methyltransferase pharmacogenetics: gene sequence polymorphisms. Clin Pharmacol Ther 1997; 62: 60-73. PubMed ID: 9246020

R2. **Lilleyman JS, Lennard L**. 6-Mercaptopurine metabolism and risk of relapse in childhood acute lymphoblastic leukaemia. The Lancet 1994; 343: 1188-1190. doi: 10.1016/S0140-6736(94)92400-7

R3. **Lennard L**, Gibson BES, Nicole T, **Lilleyman JS**. Congenital thiopurine methyltransferase deficiency and 6-mercaptopurine toxicity during treatment for acute lymphoblastic leukaemia. Archives of Disease in Childhood 1993; 69: 577-579. PubMed ID: 8257179

R4. **Lennard L**, Lewis IJ, Michelagnoli M, **Lilleyman JS**. Thiopurine methyltransferase deficiency in childhood lymphoblastic leukaemia: 6-mercaptopurine dosage strategies. Med Ped Oncol 1997; 29 252-255. PubMed ID: 9251729

R5. **Lennard L**, Singleton HJ. High-performance liquid chromatographic assay of human red blood cell thiopurine methyltransferase activity. J Chromatogr B Biomed Appl. 1994;661:25-33. PubMed ID: 7866549

R6. **Lennard L**, Richards S, **Cartwright CS**, Mitchell C, **Lilleyman JS, Vora A**. The thiopurine methyltransferase genetic polymorphism is associated with thioguanine-related veno-occlusive disease of the liver in children with acute lymphoblastic leukaemia. Clin Pharmacol Ther 2006; 80: 375-383. doi: 10.1016/j.clpt.2006.07.002

4. Details of the impact

Sheffield research has led to the development of a routine test for the genetic defect regulating the use of 6-mercaptopurine, a thiopurine drug used to treat childhood leukaemia. Routine tests for this genetic defect are now recommended (and in some cases are mandatory) prior to starting thiopurine drugs. TPMT testing is one of the first pharmacogenetic analyses that has passed from research into routine clinical use and has become a textbook example of pharmacogenomic research.

Impact on health and welfare

The detection of thiopurine methyltransferase (TPMT) deficiency prior to the start of thiopurine treatment allows the early identification of the 1 in 300 genetically disposed to serious side effects from treatment with thiopurine drugs. Identifying TPMT deficiency spares patients painful and potentially life-threatening sepsis

In the UK, approximately 400 children and young adults are diagnosed with acute lymphoblastic leukaemia (ALL) per year. All these children are tested for TPMT deficiency prior to the start of thiopurine treatment. The thiopurine drug used is called 6-mercaptopurine; daily oral 6-mercaptopurine chemotherapy is taken for two (girls) or three (boys) years. The detection of TPMT deficiency prior to treatment allows immediate thiopurine dose reduction to 10% of the “normal” dose and so avoids catastrophic myelosuppression. TPMT-guided dose reduction for the drug 6-mercaptopurine allows the other chemotherapeutic drugs to be given at their maximum tolerated doses and avoids the withdrawal of chemotherapy (and the potential for the re-emergence of the leukaemia) that would have occurred if the full dose of mercaptopurine had been given to the TPMT deficient patient.

In addition, children with very high TPMT activities may not respond to standard doses of thiopurine drugs and require protocol-directed dose escalation to accumulate sufficient

concentrations of the cytotoxic and immunosuppressive metabolites (called thioguanine nucleotides). Monitoring of drug metabolite concentrations is clinically useful in this situation; assays initially developed by Lennard are now available in Clinical Pathology service laboratories internationally (S1, S2) to measure thiopurine drug metabolites in addition to TPMT genotype and activity. Thiopurine metabolite monitoring enables the child who forms sub-optimal amounts of cytotoxic metabolites due to high inherited TPMT (approximately 10% of patients) to be differentiated from the child who lacks thiopurine metabolites for other reasons (e.g. due to tablet taking problems), prior to dose escalation.

Changes to trial guidelines

The work by Lennard and Lilleyman, to identify the impact of the TPMT genetic polymorphism on the action of thiopurine drugs and the detection of TPMT deficiency, has led to changes in trial guidelines in both the UK and USA (S3, S4). The detection of TPMT deficiency prior to the start of mercaptopurine chemotherapy was incorporated into the protocol for the MRC ALL 2003 (recruitment 2003 to 2011) therapeutic trial for childhood ALL and it is an integral, mandatory, component of the current national trial, UK ALL 2011(recruitment from 2012). The Sheffield Clinical Pharmacology Unit (led by Lennard, funded by Leukaemia and Lymphoma Research; LLR) is responsible for the organisation and implementation of the thiopurine studies within these ALL trials; about 400 children are diagnosed annually.

Evidence of enhanced awareness of health risks and benefits by practitioners (NHS consultants)

The importance of inherited TPMT to thiopurine treatment outcome, initially demonstrated in children with ALL by Lennard and Lilleyman, has been translated to other disease states (S5). Thiopurine drugs are used extensively to control autoimmune conditions e.g. inflammatory bowel disease which affects approximately 180,000 people in the UK; potentially some 600 patients with TPMT deficiency who can be detected and thus patient care and the quality of life improved by avoiding severe and costly myelosuppressive adverse drug reactions. Overall, 67% of UK consultants test for TPMT prior to starting thiopurine based immunosuppression (S6). The cost of treatment and in-patient care for a severe episode of bone marrow failure due to thiopurine induced myelosuppression is over £9,000. The TPMT genotype test is currently £27 per patient thus the cost of detecting 1 patient with TPMT deficiency is slightly less than in-patient treatment, but TPMT testing enables a reduction in treatment-related morbidity and mortality and improved patient care. Treatment guidelines for dermatologists advocate TPMT testing (S7) whilst rheumatologists and hepatologists recommend TPMT testing (S8). The British National Formulary suggests that clinicians should consider TPMT testing.

A new diagnostic or clinical technology has been adopted

As part of Lennard & Vora's current LLR funding, TPMT genotyping and thiopurine metabolite analysis (and guidelines for clinical interpretation) within the ALL 2011 trial was transferred from research laboratories into laboratories with Clinical Pathology Accreditation (CPA) within the NHS service sector; the transfer was successfully completed in July 2013. The interpretation guidelines for TPMT testing are disease specific (S9). In the UK thiopurine assays are now available at super-regional pathology centres (S2). In addition to the 400 children and young adults diagnosed with ALL per year, adults treated with thiopurine immunosuppression will also be tested, with the current take-up of TPMT testing approximately two thirds of the 180,000 adults diagnosed with inflammatory bowel disease.

Impact on public policy and services

Decisions by a health service or regulatory authority have been informed by research

The US Food and Drug Administration (FDA) directed label modifications for 6-mercaptopurine (July 2004) and azathioprine (July 2005) to reflect the pharmacogenetics of metabolism and recommends TPMT testing prior to initiating thiopurine therapy. Guidance in the UK from the National Formulary recommends that patients have their TPMT status checked prior to starting thiopurine drugs benefiting both the TPMT deficient individual (1 in 300) and the 11% of patients

who are heterozygotes and are at an increased risk of myelosuppression.

Evidence of improved cost-effectiveness

The cost-effectiveness of TPMT genotyping, for both UK and European ALL treatment protocols, was demonstrated prior to the widespread introduction of the test (S10). Routine TPMT testing prevents the TPMT precipitated episodes of profound myelosuppression that are caused by standard doses of thiopurine drugs in the TPMT deficient patient. TPMT testing prevents possible death from neutropenia-induced sepsis and thus improves the health-related quality of life. In a child with ALL, current costs (2013) of in-patient care due to thiopurine induced bone-marrow failure is approximately £200 (with drug support running at an additional £50 to £60) per night. Admission to the Intensive Therapy Unit (ITU) would be more expensive. This would be followed by the task of management of the bone marrow failure over a period of 6 to 8 weeks – this would entail the treatment of recurrent infections and associated use of expensive blood products. A total cost of about £10,000, or more, depending on the severity of the bone marrow failure and the recovery time.

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

S1. http://tinyurl.com/ll7588u corroborates TPMT testing available in the US

S2. http://www.cityassays.org.uk/tpmt.html is one of the 2 services in the UK and corroborates TPMT testing routinely available to the NHS.

S3. UK ALL2011 trial protocol. United Kingdom trial for children and young adults with acute lymphoblastic leukaemia and lymphoma. International standard randomised controlled trial number (ISRCTN) 64515327, Section 7.12.2 and Appendix 21. ALL2003 trial protocol. United Kingdom national randomised trial for children and young adults with acute lymphoblastic leukaemia. ISRCTN 07355119, Appendix C.

S4. Relling MV, Gardner EE, Sandborn WJ, Pui C-H, Stein CM, Carrillo M, Evans WE, Klein TE. Clinical pharmacogenetics implementation consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing. Clin Ther Pharmacol 2011;89:387-391. doi: http://dx.doi.org/10.1038/clpt.2010.320

S5. Roblin X, Oussalah A, Chevaux J-B, Sparrow M, Peyrin-Biroulet L. Use of thiopurine testing in the management of inflammatory bowel diseases in clinical practice: A worldwide survey of experts. Inflamm Bowel Dis 2011; 17:2480-2487. doi: 10.1002/ibd.21662

S6. Current use of pharmacogenetic testing: a national survey of thiopurine methyltransferase testing prior to azathioprine prescription, Fargher et al, Journal of Clinical Pharmacy and Therapeutics, 32, 2:187-195 doi: 10.1111/j.1365-2710.2007.00805.x

S7. Meggitt SJ, Anstey AV, Mustapa MF, Reynolds NJ, Wakelin S. British Association of Dermatologists' guidelines for the safe and effective prescribing of azathioprine 2011. Br J Dermatol 2011; 165: 711-734. doi: 10.1111/j.1365-2133.2011.10575.x

S8. Gleeson D, Heneghan MA. British Society of Gastroenterology (BSG) guidelines for management of autoimmune hepatitis. Gut 2012; 60:1611-1629. doi: 10.1136/gut.2010.235259

S9. Lennard L, Cartwright CS, Wade R, Richards SM, Vora A. Thiopurine methyltransferase genotype-phenotype discordance, and thiopurine active metabolite formation, in childhood acute lymphoblastic leukaemia. British Journal of Clinical Pharmacology, 2013, doi: 10.1111/bcp.12066 doi: 10.1111/bcp.12066

S10. van den Akker-van Marle M, Gurwitz D, Detmar D, Enzing CM, Hopkins MM, Gutierrez de Mesa E, Ibarreta D. Cost-effectiveness of pharmacogenomics in clinical practice: a case study of thiopurine methyltransferase genotyping in acute lymphoblastic leukaemia in Europe. Pharmacogenomics 2006; 7:783-792. doi: 10.2217/14622416.7.5.783