Institution: Newcastle University

Unit of Assessment: UoA-1

Title of case study: Developing gene-guided dosing of warfarin to improve patient safety

1. Summary of the impact

Warfarin is an anti-coagulant drug prescribed to tens of millions of people in the UK and US who are at high risk of developing blood clots. Because individual sensitivity to warfarin varies in the population there is a risk of overdosing the drug and causing serious bleeding and even stroke in many people when starting treatment. In 1999 researchers at Newcastle University were the first to demonstrate a statistically significant link between a person's genotype and the appropriate dose of warfarin. In 2010 the US Food and Drug Administration (FDA) mandated inclusion of a table of dose recommendations based on genotype in the warfarin prescribing information leaflet accompanying the drug. Newcastle research forms the basis of the 2009 international standard algorithm for gene-guided dosing of warfarin. This approach has been adopted by large US medical centres and the FDA states that it will prevent 17,000 strokes a year in the US.

2. Underpinning research

Key Newcastle University researchers

At the time of the research Professors Ann Daly and Farhad Kamali were both Senior Lecturers in the Department of Pharmacological Sciences.

Background

Warfarin is an anti-coagulant drug used to prevent and treat many clotting disorders, that otherwise can lead to severe outcomes such as stroke. It is very commonly prescribed: over 10.1 million prescriptions of warfarin were written in 2012 in England, with approximately 1% of the UK population being prescribed this drug at any given time. 33.9 million prescriptions of the drug were dispensed in 2011 at retail pharmacies in the US (data from the NHS Information Centre and IMS Health).

It has long been known that age, race, gender, weight, and the presence or absence of co-morbidities (and associated medications) all influence patient sensitivity to warfarin. Choosing the correct starting dose of warfarin is a complex decision and once started, the dose will be adjusted to the optimum level by closely monitoring the clotting ability of the patient's blood over the course of several weeks. Overdosing a patient with warfarin dramatically increases the risk of bleeding, and can potentially also cause a stroke. Such overdosing is most likely in the first few months of treatment. The Food and Drug Administration reported in 2007 that warfarin was the second most common drug (insulin was the first) implicated in emergency room visits in the US, amounting to tens of thousands of trips per year (Lesko 2008 PMID: 18714317). Newcastle University researchers, in collaboration with American colleagues, realised that variable patient sensitivity to warfarin might have a genetic component and explored this in a clinical study.

Underpinning research

Newcastle University researchers were partners in the first clinical study, led by the National Cancer Institute in the USA, which explored the association between warfarin sensitivity and one variant allele of the gene CYP2C9 (which encodes a liver enzyme that breaks down warfarin). Although the results (Furuya et al. 1995 PMID: 8747411) did not reach statistical significance they showed an association between genotype and warfarin dose requirement. Subsequent research revealed that there are actually two common variant alleles relevant to warfarin sensitivity.

These findings led Daly and others to refine the clinical study methodology and explore more clearly the link between genotype and warfarin sensitivity. By focussing on a group of patients with a requirement for low doses of the drug they were, in 1999, the first to demonstrate a statistically significant association between CYP2C9 genotype and sensitivity to warfarin (R1). The study also confirmed that this group of patients needing a low dose of warfarin were significantly more likely to have suffered serious bleeding events whilst taking the drug.

In a 2005 study of 297 patients, each of whom was on a stable maintenance dose of warfarin,

Newcastle researchers assessed the genetic contribution of sensitivity to the drug, relative to known factors of age and body size. Consistent with their previous findings, patients with two copies of the most common allele of CYP2C9 required significantly higher doses than those possessing one or more variant alleles. The same study also reported a significant association between allelic variants of another gene - VKORC1 (which encodes the target of warfarin) - and warfarin dose requirement. On the basis of these results a novel warfarin dosing regimen incorporating CYP2C9 and VKORC1 genotype information, age and body size was developed and validated (R2). Newcastle researchers were then closely involved with the International Warfarin Pharmacogenetics Consortium in the production of a refined algorithm, published in 2009, following a trial involving 4,043 patients (R3).

Research involving Newcastle has continued, with Kamali and Daly leading work packages within the EU-PACT European multi-site randomised controlled trial of the safety and utility of genotype-guided dosing of anticoagulants involving 455 patients. Newcastle University researchers contributed to patient recruitment for the trial and led on (i) developing and validating a rapid (~2hr) point of care test for genotyping (R4) and (ii) developing an algorithm for genotype-guided dosing appropriate for the study (R5). The EU-PACT study has shown that patients dosed with warfarin based on CYP2C9 and VKORC1 genotype had on average a coagulation rate within the desired range for 67.4% of measurements in the first 3 months of treatment compared with 60.3% of measurements in the controls who received conventional dosing (R6). This difference was highly significant ($p<0.001$). Genotyped patients exceeded the safe clotting time in 2.3% of samples monitored, while the value for controls was 5.3% ($p<0.001$). The study found that genotyping improves the safety of warfarin treatment during initial dosing when adverse events are most common; time to stable dosage was 44 days for genotyped patients and 59 days in controls ($p<0.003$) (R6).

3. References to the research

(Newcastle authors shown in bold. Citations from Scopus as at July 2013.)

R1. **Aithal GP**, **Day CP**, **Kesteven PJL** & **Daly AK** (1999). Association of polymorphisms in the cytochrome P450 CYP2C9 with warfarin dose requirement and risk of bleeding complications. *Lancet* 353:717-719. DOI: 10.1016/S0140-6736(98)04474-2. **807 citations.**

R2. **Sconce EA, Khan TI, Wynne HA, Avery P, Monkhouse L, King BP, Wood P, Kesteven P, Daly AK & Kamali F** (2005). The impact of CYP2C9 and VKORC1 genetic polymorphism and patient characteristics upon warfarin dose requirements: proposal for a new dosing regimen. *Blood* 106:2329-2333. DOI: 10.1182/blood-2005-03-1108. **506 citations.**

R3. The International Warfarin Pharmacogenetics Consortium (2009). Estimation of the Warfarin Dose with Clinical and Pharmacogenetic Data. *N Engl J Med* 360:753-764. DOI: 10.1056/NEJMoa0809329. **558 citations**

R4. Howard R, **Leathart JBS,** French DJ, Krishan E, Kohnke H, Wadelius M, van Schie R, Verhoef T, Maitland-van der Zee A-H, **Daly AK** & Barallon R (2011). Genotyping for CYP2C9 and VKORC1 alleles by a novel point of care assay with HyBeacon (R) probes. *Clinica Chimica Acta* 412:2063-2069. DOI: 10.1016/j.cca.2011.07.013. **10 citations.** (Daly is the corresponding author)

R5. **Avery PJ**, Jorgensen A, Hamberg A, Wadelius M, Pirmohamed M & **Kamali F** (2011). A Proposal for an individualized pharmacogenetics-based warfarin initiation dose regimen for patients commencing anticoagulation therapy. *Clinical Pharmacology and Therapeutics* 90:701-706. DOI: 10.1038/clpt.2011.186. **10 citations.** (Kamali is the corresponding author and the first author is Senior Lecturer, Department of Mathematics and Statistics, Newcastle University.)

R6. Pirmohamed M, Burnside G, Eriksson N, Jorgensen AL, Toh CH, Nicholson T, Kesteven P, Christersson C, Wahlström B, Stafberg C, Zhang E, Leathart JB, Kohnke H, Maitland-van der Zee AH, Williamson PR, **Daly AK**, **Avery P**, **Kamali F**, Wadelius M (2013). A Randomized Trial of Genotype-Guided Dosing of Warfarin. *N Engl J Med* (publication online Nov 2013). (Kamali is joint senior author with Wadelius)

Key research grants

European Commission Biomedical Programme. 1996-8. £33 512. *Eurohepatotox.*

GenoType Ltd. 2001-4. £35 000. *A Study of Genetic Factors Affecting Warfarin Dose Requirements.*

European Commission FP7. 2007–13. £250 000 to Newcastle University. *European Pharmacogenetics of Anti-Coagulant Therapy (EU-PACT) study design.*

4. Details of the impact

Introduction of pharmacogenetic information to warfarin dosing advice

Several groups around the world made contributions to the body of evidence about the role of genetics in determining the warfarin sensitivity of patients, however it was the work published by Daly, Kamali and others in Newcastle that has been recognised as being fundamental. The Medical Director of the Barnes-Jewish Hospital Anticoagulation Service (who is also Professor of Medicine at Washington University, St Louis, USA) has said, '*The seminal paper published by Ann Daly at Newcastle University in 1999* [R1] *ignited the field of pharmacogenetic-based therapy*' (Ev a). The importance of the 2005 study [R2] has also been acknowledged, with the University of Illinois Hospital and Health Services Centre confirming that it '*formed a significant part of the evidence base that ultimately led to international clinical trials of gene-guided dosing of anticoagulants (including warfarin) being carried out*' (Ev b).

Official guidance: By late 2007 (and so having an impact on practice from 2008 onwards) the US Food and Drug Administration had judged that the evidence on warfarin pharmacogenetics was sufficiently strong to warrant a change to the approved medication guide of warfarin (marketed as Coumadin). Since approximately one third of the population carries at least one genetic polymorphism that slows the breakdown of warfarin, there was a significant opportunity to apply the research findings and protect patient health by avoiding overdose. The regulator issued a safety alert that stated:

> *'FDA approved updated labeling to include pharmacogenomics information to the CLINICAL PHARMACOLOGY, PRECAUTIONS, and DOSAGE AND ADMINISTRATION sections of the prescribing information for the widely used blood-thinning drug, Coumadin. This new information explains that people's genetic makeup may influence how they respond to the drug. Specifically, people with variations in two genes may need lower warfarin doses than people without these genetic variations. The two genes are called CYP2C9 and VKORC1'* (Ev c)

In 2010 a substantial change was made to the drug medication guide that is included in the drug packaging when, at the request of the US Food and Drug Administration, a table displaying three ranges of warfarin doses based on CYP2C9 and VKORC1 genotype information was added (Ev d and Ev e).

Assisting practitioners: In 2009 the international standard algorithm for warfarin dosing was published in the *New England Journal of Medicine* (Ev f). The algorithm was a product of the work of the International Warfarin Pharmacogenetics Consortium. Newcastle University researchers Daly, Kamali and Sconce all contributed data to the paper that outlined the algorithm. Sources at centres in Chicago and Seattle have confirmed that the international standard algorithm was *'significantly underpinned'* (Ev b) by Newcastle research (R2) and that the Newcastle researchers had published '*the first algorithm on CYP2C9 and VKORC1 gene-guided dosing of warfarin*' (Ev g).

Application in the clinic

Interest in the pharmacogenetic approach to warfarin prescribing is increasing in clinics across the US, with large academic medical centres leading implementation. Since autumn 2010 the Vanderbilt University Medical Center in the US has been running the PREDICT programme, which aims to embed pharmacogenetic information in its approach to healthcare. So far the programme *'has included >12,500 subjects and warfarin-CYP2C9/VKORC1 is one of five drug-gene interactions currently* [being] *targeted.'* (Ev h)

The University of Illinois at Chicago has also provided a statement concerning practice at its medical centre:

> '*beginning in August 2012, all patients newly starting warfarin during hospitalization at our medical center are automatically genotyped for clinical care to assist with warfarin dosing. Nearly 300 patients have been genotyped to date.'* (Ev b)

Large-scale clinical trials

Clinical trials of gene-based dosing of warfarin, together involving thousands of people in the US and Europe, are currently in progress. Daly and Kamali contributed to the major European trial, EU-PACT (R6), which involved 455 patients. In the US, two large studies are ongoing: the WARFARIN study (approximately 3,800 patients, started August 2011) and the COAG study (around 1,020 patients, started September 2009) (Ev i).

The US Food and Drug Administration has estimated that gene-based dosing of warfarin will prevent 85,000 serious bleeding events and 17,000 strokes a year in the US (Ev j).

5. Sources to corroborate the impact

Ev a. Correspondence from a Professor of Medicine, Washington University Medical School, St Louis is available and contact details are available on request.

Ev b. Correspondence from an Associate Professor at the Department of Pharmacy Practice, University of Illinois at Chicago is available and contact details are available on request.

Ev c. US Food and Drug Administration (August 2007): Warfarin (marketed as Coumadin) – safety alert. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm152972.htm

Ev d. US Food and Drug Administration (January 2010): Coumadin (warfarin sodium) tablet and injection. Detailed View: Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER). http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm201100.htm

Ev e. Bristol-Myers Squibb website: Coumadin (warfarin) drug medication guide. http://packageinserts.bms.com/pi/pi_coumadin.pdf (Dosing table on page 2, column 2.)

Ev f. The International Warfarin Pharmacogenetics Consortium (2009). Estimation of the Warfarin Dose with Clinical and Pharmacogenetic Data. *N Engl J Med* 360:753-764. DOI: 10.1056/NEJMoa0809329. **558 citations**

Ev g. Correspondence from a Professor and Chair of Medicinal Chemistry at the Department of Medicinal Chemistry, University of Washington, Seattle is available and contact details are available on request.

Ev h. Correspondence from the Director of the Oates Institute for Experimental Therapeutics at the Vanderbilt School of Medicine is available and contact details are available on request.

Ev i. Trial information at clinicaltrials.gov

EU-PACT http://clinicaltrials.gov/ct2/show/NCT01119300

WARFARIN http://clinicaltrials.gov/ct2/show/NCT01305148

COAG http://clinicaltrials.gov/ct2/show/NCT00839657

Ev j. US Food and Drug Critical Path Initiative: Warfarin Dosing. http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm077473.htm