Pharmacogenomic substudies of randomized controlled trials: consideration of safety outcomes

Ther Adv Drug Saf
2014, Vol. 5(2) 62–66
DOI: 10.1177/2042098613520030

Michael J. Sorich, Andrew Rowland and Michael D. Wiese

Although the definitions of personalized medicine and pharmacogenomics vary, most include the potential to better utilize biological characteristics (e.g. genetic variation or gene expression) of an individual to improve the selection of the most appropriate medicine and/or dose for treating that individual. Within this context, the goal may be to improve therapeutic response, decrease adverse effects and/or improve cost effectiveness. However, despite the clear potential, clinical translation of pharmacogenomics into routine medical practice has been slower and less extensive than had been generally anticipated.

Many reasons have been proposed for the poor clinical translation, and in reality it is likely due to a variety of reasons. However, one factor that appears to be of particular importance is the strength of evidence underlying claims of significant clinical utility of a given pharmacogenomic marker. That is, there is a growing expectation that prior to any substantial use of a pharmacogenomic marker there should be high quality evidence that the use of the pharmacogenomic marker will result in a significant improvement in health outcomes. Such evidence also forms the basis for high quality estimates of the cost effectiveness of introducing the pharmacogenomic test (see review, for example, by Sorich and colleagues [Sorich *et al.* 2013c]) – an assessment that is critical for funding a pharmacogenomic test in many healthcare systems [Deverka, 2009; Flowers and Veenstra, 2004].

Over the past 5 years there has been increasing discussion regarding what constitutes different levels of evidence for a pharmacogenomic marker and what level is required prior to routine use [Altman, 2011; Andre *et al.* 2011; Patterson *et al.* 2011; Simon *et al.* 2009; Teutsch *et al.* 2009]. Following the standard evidence-based medicine philosophy, prospective randomized controlled trials (RCTs) with appropriate clinical outcomes will provide the highest level of evidence for the clinical value of a pharmacogenomic marker. This presents an important dilemma as such studies are very uncommon for pharmacogenomic markers. The reason for this is not surprising – prospective RCTs that are well powered to detect important clinical outcomes are generally very expensive to undertake.

One example of an RCT where participants were randomised to use of a pharmacogenomic marker was with the antiretroviral abacavir. Abacavir was plagued by hypersensitivity reactions in up to 6% of treated patients, and in this study screening for the *HLA-B*5701* allele eliminated these hypersensitivity reactions [Mallal *et al.* 2008]. Prior to this trial the association between *HLA-B*5701* and abacavir hypersensitivity had been identified by two independent groups and observed in several noncontrolled environments, but retrospective methodologies, lack of control populations and racial diversification, small sample sizes and issues of overdiagnosis had led to uncertainty about its clinical utility.

Whilst this is a success story for pharmacogenomics, it is noteworthy that this study was supported by the manufacturer of abacavir. As in this case, the pharmaceutical industry can potentially develop evidence of a pharmacogenomic marker, but this will generally only occur for patented drugs where is there is clear strategic value in predicting variability between individuals (e.g. to achieve a higher price for the pharmaceutical or improve its competitiveness against alternative pharmaceuticals) which outweighs the reduction in market size [Davis *et al.* 2009]. Although such studies are the standard required for drugs prior to registration and clinical use, it seems unlikely that this will translate seamlessly to pharmacogenomics as the profitability of pharmacogenomic

Correspondence to:
Michael J. Sorich, PhD
Department of Clinical Pharmacology, Flinders University School of Medicine, Finders Drive, Bedford Park, Adelaide, South Australia, 5042, Australia
michael.sorich@flinders.edu.au

Andrew Rowland, PhD, BSc
Department of Clinical Pharmacology, Flinders University, Adelaide, Australia

Michael D. Wiese, PhD, BPharm
School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, Australia

markers is likely to be substantially less than that of a pharmaceutical agent. Although there are a vast number of pharmacogenomic markers that could be trialled, there is little incentive for the manufacturer to conduct these studies and it is unlikely that public funding will be sufficient for even those that, based on the results of observational studies, are prioritized as most promising.

Thus, it also not surprising that the vast majority of evidence developed for pharmacogenomic markers is at a much lower level of evidence. Much of the existing evidence comes from observational studies (often without all the control groups of interest), or studies with surrogate outcomes. It is often difficult to clearly evaluate clinical utility and cost effectiveness of pharmacogenomic markers using observational data [Khoury, 2010; Simon *et al.* 2009; Sorich *et al.* 2013a; Teutsch *et al.* 2009]. The use of observational data has only occasionally led to robust associations between pharmacogenomic markers and adverse drug reactions – notable examples include the association between *HLA-B*5801* and severe cutaneous adverse reactions with allopurinol [Hershfield *et al.* 2013] and *HLA-B*1502* and Stevens Johnson Syndrome/toxic epidermal necrolysis with carbamazepine [Leckband *et al.* 2013].

One of the most promising approaches to emerge in recent years is pharmacogenomic substudies of RCTs [Patterson *et al.* 2011; Simon *et al.* 2009]. These are essentially conventional RCTs that are subsequently re-analyzed to assess whether a pharmacogenomic marker influenced the response to treatment. Evidence from a pharmacogenomic substudy has a number of favorable characteristics, including comparison of treatments, randomized treatment allocation and blinded follow up of clinical outcomes. The retrospective nature of the genetic analysis for such studies means that they can be conducted relatively quickly and inexpensively, but this also places certain limitations and potential threats to validity. It has been proposed that under certain circumstances they may be considered level 1 evidence [Patterson *et al.* 2011].

The analysis, approach and associated caveats are generally very similar to the traditional subgroup analyses that accompany most RCTs [Assmann *et al.* 2000; Sun *et al.* 2010]. Subgroup analyses typically suffer from the risk of false positive results due to multiple hypothesis testing and poor reporting of which subgroup hypotheses are prespecified and which are *post hoc* exploration. The relatively recent advent of cheap micro-array technology to determine thousands of genetic variants further adds to the potential for multiple hypothesis testing and false positive results.

False negative results are also an issue as most RCTs are not sufficiently powered to detect differences in treatment response between subgroups. Thus, the availability of more than one pharmacogenomic RCT substudy answering the same clinical question is often required to confirm a finding or provide sufficient power to detect a meaningful difference.

In addition, RCTs are often primarily designed to assess the therapeutic effects of drugs, with identification of adverse effects being secondary. This influences both the consideration of power to detect safety events and the subsequent reporting of safety outcomes in publications of the RCT. There is a similar trend with respect to pharmacogenomic substudies which generally focus on whether a pharmacogenomic marker influences the efficacy of a drug. RCTs are often underpowered to detect many serious but rare adverse effects of drugs, and this is compounded by the availability of only a subset of the trial participants in the pharmacogenomic substudy. Additionally, it must be considered that the power to detect differences in efficacy between subgroups is generally lower than the power to detect an overall effect of a drug. Thus, for rare but serious safety concerns, pharmacogenomic substudies of RCTs are not likely to be sufficiently powered unless there are multiple RCTs than can be combined in a meta-analysis.

An additional issue that is specific to pharmacogenomic substudies is the risk that the substudy cohort used to assess the pharmacogenomic marker is representative of the overall trial cohort. Generally, only participants that have explicitly consented to the optional collection of a biological sample (e.g. blood or tissue) are available for subsequent pharmacogenomic analysis. In some cases only participants from certain sites (and therefore potentially limited ethnic groups) are offered the opportunity to provide a biological sample. In general, the smaller the proportion of the RCT included in the pharmacogenomic substudy, the greater the potential for bias.

A relevant pharmacogenomic substudy may not be possible for many pharmacogenomic markers

of interest. Older drugs (e.g. carbamazepine or allopurinol) may not have an RCT which has archived biological samples available to enable a pharmacogenomic substudy. It is also unlikely that a relevant RCT will be available to retrospectively assess markers which are proposed to guide the dose of a drug. In general, pharmacogenomic substudies of RCTs are more likely to be useful for questions of whether a pharmacogenomic marker can help select the best drug.

Three recent examples of pharmacogenomic substudies of RCTs are highlighted. These involve relatively common safety outcomes; bleeding resulting from use of clopidogrel, hypertension resulting from drugs targeting vascular endothelial growth factor (VEGF), and myopathy resulting from use of some statin drugs.

Carriage of a loss-of-function (LoF) allele for the CYP2C19 enzyme (primarily the *CYP2C19*2* or *CYP2C19*3* alleles) has most commonly been assessed as a potential predictive marker of therapeutic response to clopidogrel therapy [Holmes *et al.* 2011; Mega *et al.* 2010; Sorich *et al.* 2013b]. CYP2C19 is thought to be important in the activation of clopidogrel, which is a prodrug. Reduced activation of clopidogrel associated with a CYP2C19 LoF allele may therefore lead to reduced risk of hemorrhage in addition to the reduced therapeutic effect. Thus, an assessment of effect on both adverse and therapeutic effects of clopidogrel is important to inform the relative benefit and harms for individuals with and without a LoF allele. Genetic substudies of the CHARISMA, PLATO, CURE, ACTIVE A and TRITON 38 trials have contributed insight into the role of CYP2C19 LoF alleles on bleeding risk with clopidogrel [Bhatt *et al.* 2012; Mega *et al.* 2009; Pare *et al.* 2010; Sorich *et al.* 2010; Wallentin *et al.* 2010]. However, due to differences in definition of bleeding events between trials and significant heterogeneity between study results the relationship remains unclear [Holmes *et al.* 2011; Sorich *et al.* 2012].

Anti-VEGF therapies such as bevacizumab are useful in the treatment of a number of cancers. They are high-cost drugs and significant effort has been applied to identifying a pharmacogenomic marker that can predict individuals who will and will not benefit from such therapy [Eng *et al.* 2012]. A range of pharmacogenomic markers have been assessed, including VEGF polymorphisms, and a number of different plasma biomarkers [Lambrechts *et al.* 2013]. Hypertension is the most common grade 3–4 adverse effect of anti-VEGF therapies and as such pharmacogenomic markers of hypertension risk are also of interest [Schneider *et al.* 2012]. Some but not all pharmacogenomic substudies of anti-VEGF RCTs have included assessment of putative pharmacogenomic markers of hypertension [Escudier *et al.* 2011; Lambrechts *et al.* 2012; Schneider *et al.* 2008]. The secondary consideration of hypertension outcomes, small subsets of the RCT cohorts and variability in the definition and recording of hypertension are barriers to the development and confirmation of evidence of pharmacogenomic markers for anti-VEGF induced hypertension.

A polymorphism in a member of the solute carrier organic anion transporter family (SLCO1B1) potentially influences risk of myopathy with some statin drugs. Pharmacogenomic substudies of the SEARCH, HPS and JUPITER RCTs have provided valuable insight into the role of SLCO1B1 and potential differences between different statin drugs and doses [Danik *et al.* 2013; SEARCH Collaborative Group, 2008]. Although this is a positive step, research to identify and validate pharmacogenomic markers of differential statin therapeutic effect has received much greater attention. In comparison, at least 10 pharmacogenomic substudies of statin RCTs have assessed markers of efficacy [Ference *et al.* 2011; Hoffmann *et al.* 2011; Maitland-van der Zee *et al.* 2007]. The low risk of myopathy in RCTs (compared with observation data of 'real world' use) may partially explain the smaller number of studies focusing on safety outcomes [Fernandez *et al.* 2011]. This highlights another potential issue in the use of pharmacogenomic substudies of RCT to develop evidence for safety outcomes.

In conclusion, the debate around the appropriate evidence threshold for pharmacogenomic markers will likely continue for the foreseeable future. Pharmacogenomic substudies of RCTs will likely become more common and, for common drug safety outcomes, these studies may be of value in validating the clinical utility of proposed pharmacogenomic markers. However, pharmacogenomic substudies of RCTs are unlikely to help the evidence development of rare but serious drug adverse effects.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not for-profit sectors.

Conflict of interest statement

The authors declare no competing interests.

References

Altman, R. (2011) Pharmacogenomics: 'noninferiority' is sufficient for initial implementation. *Clin Pharmacol Ther* 89: 348–350.

Andre, F., McShane, L., Michiels, S., Ransohoff, D., Altman, D., Reis-Filho, J. *et al.* (2011) Biomarker studies: a call for a comprehensive biomarker study registry. *Nat Rev Clin Oncol* 8: 171–176.

Assmann, S., Pocock, S., Enos, L. and Kasten, L. (2000) Subgroup analysis and other (mis)uses of baseline data in clinical trials. *Lancet* 355: 1064–1069.

Bhatt, D., Pare, G., Eikelboom, J., Simonsen, K., Emison, E., Fox, K. *et al.* (2012) The relationship between CYP2C19 polymorphisms and ischaemic and bleeding outcomes in stable outpatients: the CHARISMA genetics study. *Eur Heart J* 33: 2143–2150.

Danik, J., Chasman, D., MacFadyen, J., Nyberg, F., Barratt, B. and Ridker, P. (2013) Lack of association between SLCO1B1 polymorphisms and clinical myalgia following rosuvastatin therapy. *Am Heart J* 165: 1008–1014.

Davis, J., Furstenthal, L., Desai, A., Norris, T., Sutaria, S., Fleming, E. *et al.* (2009) The microeconomics of personalized medicine: today's challenge and tomorrow's promise. *Nat Rev Drug Discov* 8: 279–286.

Deverka, P. (2009) Pharmacogenomics, evidence, and the role of payers. *Public Health Genomics* 12: 149–157.

Eng, L., Azad, A., Habbous, S., Pang, V., Xu, W., Maitland-van der Zee, A. *et al.* (2012) Vascular endothelial growth factor pathway polymorphisms as prognostic and pharmacogenetic factors in cancer: a systematic review and meta-analysis. *Clin Cancer Res* 18: 4526–4537.

Escudier, B., Loomis, A., Kaprin, A., Motzer, R., Tomczak, P., Tarazi, J. *et al.* (2011) Association of single nucleotide polymorphisms in VEGF pathway genes with progression-free survival and blood pressure in metastatic renal cell carcinoma in phase 3 AXIS trial of axitinib *versus* sorafenib (AXIS trial). *Eur J Cancer* 47(Suppl. 1): abstract 7103.

Ference, B., Yoo, W., Flack, J. and Clarke, M. (2011) A common KIF6 polymorphism increases vulnerability to low-density lipoprotein cholesterol: two meta-analyses and a meta-regression analysis. *PLoS ONE* 6: e28834.

Fernandez, G., Spatz, E., Jablecki, C. and Phillips, P. (2011) Statin myopathy: a common dilemma not reflected in clinical trials. *Cleveland Clinic J Med* 78: 393–403.

Flowers, C. and Veenstra, D. (2004) The role of cost-effectiveness analysis in the era of pharmacogenomics. *PharmacoEconomics* 22: 481–493.

Hershfield, M., Callaghan, J., Tassaneeyakul, W., Mushiroda, T., Thorn, C., Klein, T. *et al.* (2013) Clinical Pharmacogenetics Implementation Consortium guidelines for human leukocyte antigen-B genotype and allopurinol dosing. *Clin Pharmacol Ther* 93: 153–158.

Hoffmann, M., März, W., Genser, B., Drechsler, C. and Wanner, C. (2011) Lack of association between the Trp719Arg polymorphism in kinesin-like protein-6 and cardiovascular risk and efficacy of atorvastatin among subjects with diabetes on dialysis: The 4D study. *Atherosclerosis* 219: 659–662.

Holmes, M., Perel, P., Shah, T., Hingorani, A. and Casas, J. (2011) CYP2C19 genotype, clopidogrel metabolism, platelet function, and cardiovascular events: a systematic review and meta-analysis. *JAMA* 306: 2704–2714.

Khoury, M. (2010) Dealing with the evidence dilemma in genomics and personalized medicine. *Clin Pharmacol Ther* 87: 635–638.

Lambrechts, D., Claes, B., Delmar, P., Reumers, J., Mazzone, M., Yesilyurt, B. *et al.* (2012) VEGF pathway genetic variants as biomarkers of treatment outcome with bevacizumab: an analysis of data from the AViTA and AVOREN randomised trials. *Lancet Oncol* 13: 724–733.

Lambrechts, D., Lenz, H., de Haas, S., Carmeliet, P. and Scherer, S. (2013) Markers of response for the antiangiogenic agent bevacizumab. *J Clin Oncol* 31: 1219–1230.

Leckband, S., Kelsoe, J., Dunnenberger, H., George, A., Tran, E., Berger, R. *et al.* (2013) Clinical Pharmacogenetics Implementation Consortium Guidelines for HLA-B genotype and carbamazepine dosing. *Clin Pharmacol Ther* 94: 324–328.

Maitland-van der Zee, A., Boerwinkle, E., Arnett, D., Davis, B., Leiendecker-Foster, C., Miller, M. *et al.* (2007) Absence of an interaction between the angiotensin-converting enzyme insertion-deletion polymorphism and pravastatin on cardiovascular disease in high-risk hypertensive patients: The Genetics of Hypertension-Associated Treatment (GenHAT) study. *Am Heart J* 153: 54–58.

Mallal, S., Phillips, E., Carosi, G., Molina, J., Workman, C., Tomažič, J. *et al.* (2008) HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med* 358: 568–579.

Mega, J., Close, S., Wiviott, S., Shen, L., Hockett, R., Brandt, J. *et al.* (2009) Cytochrome P-450

polymorphisms and response to clopidogrel. *N Engl J Med* 360: 354–362.

Mega, J., Simon, T., Collet, J., Anderson, J., Antman, E., Bliden, K. *et al.* (2010) Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *JAMA* 304: 1821–1830.

Pare, G., Mehta, S., Yusuf, S., Anand, S., Connolly, S., Hirsh, J. *et al.* (2010) Effects of CYP2C19 genotype on outcomes of clopidogrel treatment. *N Engl J Med* 363: 1704–1714.

Patterson, S., Cohen, N., Karnoub, M., Truter, S., Emison, E., Khambata-Ford, S. *et al.* (2011) Prospective–retrospective biomarker analysis for regulatory consideration: white paper from the industry pharmacogenomics working group. *Pharmacogenomics* 12: 939–951.

Schneider, B., Shen, F. and Miller, K. (2012) Pharmacogenetic biomarkers for the prediction of response to antiangiogenic treatment. *Lancet Oncol* 13: e427–e436.

Schneider, B., Wang, M., Radovich, M., Sledge, G., Badve, S., Thor, A. *et al.* (2008) Association of vascular endothelial growth factor and vascular endothelial growth factor receptor-2 genetic polymorphisms with outcome in a trial of paclitaxel compared with paclitaxel plus bevacizumab in advanced breast cancer: ECOG 2100. *J Clin Oncol* 26: 4672–4678.

SEARCH Collaborative Group (2008) SLCO1B1 variants and statin-induced myopathy — a genomewide study. *N Engl J Med* 359: 789–799.

Simon, R., Paik, S. and Hayes, D. (2009) Use of archived specimens in evaluation of prognostic and predictive biomarkers. *J Natl Cancer Institute* 101: 1446–1452.

Sorich, M., Coory, M. and Pekarsky, B. (2013a) Indirect estimation of the comparative treatment effect in pharmacogenomic subgroups. *PLOS ONE* 8: e72256.

Sorich, M., Polasek, T. and Wiese, M. (2012) Systematic review and meta-analysis of the association between cytochrome P450 2C19 genotype and bleeding. *Thromb Haemost* 108: 199–200.

Sorich, M., Polasek, T. and Wiese, M. (2013b) Challenges and limitations in the interpretation of systematic reviews: making sense of clopidogrel and CYP2C19 pharmacogenetics. *Clin Pharmacol Ther* 94: 376–382.

Sorich, M., Vitry, A., Ward, M., Horowitz, J. and McKinnon, R. (2010) Prasugrel *versus* clopidogrel for cytochrome P450 2C19-genotyped subgroups: integration of the TRITON-TIMI 38 trial data. *J Thromb Haemost* 8: 1678–1684.

Sorich, M., Wiese, M., O'Shea, R. and Pekarsky, B. (2013c) Review of the cost effectiveness of pharmacogenetic-guided treatment of hypercholesterolaemia. *Pharmacoeconomics* 31: 377–391.

Sun, X., Briel, M., Walter, S. and Guyatt, G. (2010) Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. *BMJ (Clinical Research Ed.)* 340.

Teutsch, S., Bradley, L., Palomaki, G., Haddow, J., Piper, M., Calonge, N. *et al.* (2009) The evaluation of genomic applications in practice and prevention (EGAPP) initiative: methods of the EGAPP working group. *Genet Med* 11: 3–14.

Wallentin, L., James, S., Storey, R., Armstrong, M., Barratt, B., Horrow, J. *et al.* (2010) Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor *versus* clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. *Lancet* 376: 1320–1328.