

Pharmacogenetics — its impact on drug development and evaluation

The science programme started with an overview of personalised medicine in health care. Dawn Connelly and Hannah Pike report

Setting the scene for personalised medicine in health care, Allen Roses, worldwide vice-president of genetics at GlaxoSmithKline, US, described the impact of pharmacogenetics on drug development.

He explained that DNA samples now obtained from patients during clinical trials can be stored and later analysed when an adverse event of interest arises. In his safety studies, Dr Roses has confirmed that it is possible to recognise a single nucleotide polymorphism profile related to an adverse event with as few as 10 to 20 adverse event cases. Future trials can be tailored according to patients' genotypes.

Sir Alasdair Breckenridge, chairman of the Medicines and Healthcare products Regulatory Agency, explained that the benefits of conducting phase III trials only in patients with the appropriate genotypes are that they are smaller, faster and less expensive. "The promise of pharmacogenetics is that you can take patients, all of whom have the same diagnosis, and you can remove by appropriate tests both non-responders and toxic responders, leaving a population you can treat," he said.

Sir Alasdair explained that the US Food and Drug Administration and the European Medicines Agency have introduced the con-



Sir Alasdair Breckenridge highlights pharmacogenetic regulatory challenges

cept of briefing meetings with drug sponsors early in development. They discuss the pharmacogenetic issues that are emerging and encourage the industry to share non-validated, early data without prejudice to the overall drug development, he said.

He also highlighted a regulatory challenge of these emerging therapies in that pharmacogenetic drugs and the tests (classed as de-

vices) that mandate their use are regulated by different systems within Europe. This leads to an unco-ordinated approach to their approval, he said.

Chris Ham, professor of health policy and management at the University of Birmingham, discussed the implications of patient choice for health services. He predicted that, with the rise of patient choice, there is likely to be a much stronger focus on marketing within the NHS. "NHS organisations will put more effort into finding out what patients want and finding out what the public wants, and I consider that to be a good thing," he said. He also believes that the NHS will take the opportunity to improve customer care.

He finished by saying that the future agenda needs to focus on relationships within the clinic, because that is where choice is particularly important. "It is fundamentally about a partnership between patients and health care professionals, including pharmacists. As we see a further decline in paternalism that partnership will become more a relationship of equals," he said. "Essentially, I am arguing for a renewed focus on shared decision-making between patients and health care professionals. That is the territory where I hope choice will develop in the future."

Pharmacogenetic testing in personalised medicine

Pharmacogenetics has had a limited clinical impact in preventing adverse drug reactions (ADRs), Munir Pirmohamed, professor of clinical pharmacology at the University of Liverpool, told participants. We do not know the qualitative contribution of genetic factors to the predisposition of ADRs, or the relative contribution of pharmacokinetics or pharmacodynamics in preventing ADRs, he said.

Reasons for this include poor study design, poor clinical and pharmacological phenotyping, and inadequate genotyping.

Drug response is a multigenic and multifactorial response, he explained, and yet most studies have adopted a case-control design, so are retrospective. Although this is a cheaper method, such studies may miss important events such as the environmental factors that have an impact on ADRs, he warned. Professor Pirmohamed said that a prospective cohort study design needs to be considered. Furthermore, there is a tendency to mix clinical end points together and treat them as one, which naturally produces differing results.

Clinical phenotyping (ie, the clinical characterisation of the patients involved in studies) has also been badly done in the past. "If you do not have an accurate clinical phenotype, any genotype you have will be completely useless," he said.

Professor Pirmohamed also emphasised the importance of pharmacological phenotyping. He said that researchers tend to forget the importance of pharmacology in the bigger picture. "You really need to know about how a drug is handled and disposed of etc, before you try to apply pharmacogenetics to it."

Professor Pirmohamed described how his team is undertaking research into genes in the warfarin pathway. The end point is to look at gene-environment interactions and gene-gene interactions, plus cost effectiveness, to see if they can improve warfarin therapy within the NHS. Their aim is to develop an algorithm that can be used in anticoagulant clinics to identify a patient's maintenance dose requirements.

In the following presentation, William Newman, clinical senior lecturer in medical genetics at St Mary's Hospital, Manchester, told participants that pharmacogenetics and molecular profiling can be useful in aiding appropriate prescribing in oncology.

Although chemotherapy is individualised, with the dose calculated according to the patient height and weight, better methods are still needed to select the most appropriate treatment and dose for each patient. There is a role for pharmacogenetics in oncology because of the narrow therapeutic window for chemotherapy, the high cost, and the problems of toxicity with high doses and limited efficacy with low doses.

Dr Newman said that in the future pharmacogenetic testing will be used more widely in oncology, such as the use of simple tests for example, mouthwashes or blood samples to predict the toxicity and efficacy of drugs in individual patients. Requirements for these tests include that they are sensitive and specific, and technically feasible and inexpensive.