Editors' pick

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As in previous years, the editors have made a personal selection of some of what for us have been highlights among the papers published in BJCP in 2012.

Oncotherapeutic biomarkers: from genetics to tumour volumes. Caveat lector!

During the last decade the term 'biomarker' has become very sexy and widely used. The NIH definition of a biomarker is 'a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention' [1]. Such characteristics are hugely diverse (for example genetic, biochemical, functional or anatomical). In oncology, as in many therapeutic areas, there is a burgeoning pressure to define and validate biomarkers that enhance our understanding of pharmacokinetics (PK) and pharmacodynamics (PD).

Since the publication of the human genome sequence in 2001, the disciplines of pharmacogenetics/pharmacogenomics have produced volumes of information about genetic biomarkers. Between 2001 and 2011 the *Journal* published a median of 21 (range 15–35) papers on pharmacogenetics/pharmacogenomics per year, and this area continued to expand in 2012. The drug influx transporter *SLCO1B3*, situated at the hepatocyte basolateral membrane, transports a wide range of xenobiotics, including docetaxel. The pharmacogenetic behaviour of *SLCO1B3* is not well characterized and previous *in vivo* and *in vitro* studies have reported conflicting data concerning the functional and clinical effects of *SLCO1B3* polymorphisms. The PK and PD of docetaxel show extensive inter-individual variability and an understanding of relationships between variants in the *SLCO1B3* gene could help explain this. Chew *et al.* [2] screened three different healthy Asian populations (Chinese, Malay and Indian; *n* = 56 each group) for polymorphisms in *SLCO1B3* and

then investigated the influence of haplotype-tag SNPs (htSNPs) on docetaxel (used as monotherapy) disposition in 50 Chinese patients with nasopharyngeal carcinoma. They reported a strong linkage disequilibrium pattern across a total of 88 *SLCO1B3* polymorphisms, and 15-htSNPs were identified. The *SLCO1B3* haplotypic region comprised seven htSNPs which were significantly associated with docetaxel clearance ($P = 0.003$). Conditional haplotype analyses revealed that the haplotypic constructs comprising the IVS4+76G>A, 699G>A (Met233Ile), IVS12-5676A>G and *347_*348ins. A polymorphisms accounted for approximately one quarter of the observed variability in docetaxel disposition (clearance and area under the plasma concentration-time curve, $AUC_{0-\infty}$, $r^2 = 29\%$ and 22% , respectively). Patients with the GAG*347ins.A haplotype were associated with a 30% decrease in docetaxel clearance compared with patients carrying the reference haplotype, GGA*347wt ($P = 0.025$). In contrast, a 50% higher docetaxel clearance was observed in patients carrying the GAG*347wt haplotype compared with those with the reference haplotype ($P = 0.002$). To judge from published data derived from different patient populations [3,4] some of the less strong associations may well depend on environment and on non-genetic aspects of ethnicity, and most importantly require replication.

Another group, led by Etienne-Grimaldi [5], examined associations of drug therapy-related candidate gene polymorphisms with treatment toxicity, clinical response, time to progression and overall survival, using a study-specific schedule of the combination of cetuximab-tegafur-uracil (UFT)-folinic acid-irinotecan, administered in 21 day cycles. A subgroup of 52 patients with advanced colorectal cancer who participated in the multicentre phase II CETUFTIRI trial (*n* = 61) consented to pharmacogenetic evaluation. The severest toxicity was linked to the epidermal growth factor receptor (EGFR) -191C > A polymorphism, with 71.1% grade 3–4 toxicity in CC patients vs. 28.6% in AC/AA patients ($P = 0.01$). A tendency to a better response was observed in patients carrying the thymidylate synthase

(TYMS) 3RG allele ($P = 0.029$) and those carrying the IgG Fc-gamma receptor 3A (FCGR3A) 158Val genotype ($P = 0.02$). The greater the score of favourable TYMS 3RG allele and FCGR3A genotypes, the better the response rate ($P = 0.009$) and the longer the overall survival ($P = 0.007$). The findings suggest that FCGR3A 158Phe > Val and TYMS 5' UTR polymorphisms may be important in determining the responsiveness and survival of advanced colorectal cancer patients treated with cetuximab-fluoropyrimidine-based chemotherapy, although caution is warranted because some of the comparisons were of modest significance and the size of the subgroup who underwent genotyping was relatively small. Again, there is an important need to replicate these findings and extend them by means of appropriately designed and analyzed genome-wide association studies.

Goldmacher & Conklin [6] reviewed which tumour size measurements are the best biomarkers in assessing therapeutic response. Serial assessments of tumour burden is of paramount importance, be it in a clinical trial or as standard of care. Tumour size is most commonly evaluated by computed tomography or less frequently by magnetic resonance imaging. Traditionally, these evaluations have been based on linear measurements of tumour diameter(s). Even with updated consensus guidelines [7, 8], the performance and interpretation of such measurements have limitations related to technical, tumour morphology and reader variability. Goldmacher & Conklin make the case that measurements of tumour volumes may overcome some of the limitations of linear measurements, improving our ability to detect small changes in tumour size reliably. Work is in progress to optimize such volume measurements for the purposes of drug development and clinical care. There is also a need to develop optimal methods to merge tumour metabolism imaging (e.g. ^{18}F -Fluoro-2-deoxy-D-glucose positron emission tomography – PET) with anatomical imaging in determining tumour response to therapy. This is particularly important for modern targeted cytostatic anti-tumour drugs which cause disease stabilization rather than the tumour shrinkage caused by older cytotoxic agents [9, 10].

Clinical pharmacologists should bear in mind that the challenge concerning biomarkers is 'to devise biomarker tests that are reliable, reproducible, sensitive and specific' [11]. Much more clinical research is needed to achieve this in oncology as in other specialties.

Data-modelling-prediction-dosing (DMPD)

An increasingly important aspect of clinical pharmacology is the ability to access and/or generate core data, model the data, test and predict the effect of different clinical, patient-specific and drug scenarios to derive dosage modifications and thereby inform guidelines and drug informa-

tion sources. Four recent publications in the Journal [12–15] highlight the rich diversity of this DMPD paradigm, from ethnic differences in cytochrome P450 activities to dabigatran dosing, by way of topical drug application and prediction of foetal drug toxicity.

The field of drug metabolism has evolved from (qualitative) identification of enzymes (mainly CYPs and UGTs) that metabolize specific drugs to prediction of which enzyme(s) are the major ones responsible for drug clearance and, very importantly, quantitative *in vitro* to *in vivo* prediction of the whole body clearance of the drug. As well as helping to optimize dosing regimens early in drug development this can flag up risks of potential drug–drug interactions. The major player in the field, SimCYP, was co-developed by a distinguished former Chairman of the Editorial Board of this journal. Almost all of the work to date has been based on Caucasian data. Yang and colleagues [12] compared 30 Chinese and 30 Caucasian liver microsomes with respect to nine CYP enzyme specific reactions and found substantially lower (40–70%) intrinsic clearance ($V_{\max}/K_m$) values in the Chinese for CYPs 1A2, 2C9, 2C19 and 2E1 but not for CYPs 2A6, 2B6, 2C8, 2D6 and 3A. These core data expand our knowledge on inter-ethnic differences in PK by identifying which CYPs are important for drug specific metabolism in Chinese vs. Caucasians, and this large body of work will inform the world-wide development, testing and registration of new medicines whether discovered and developed in China or elsewhere.

Drugs are increasingly being developed for long term administration via topical routes of application to achieve systemic rather than solely local effects. Such topical application may be directed towards sites within the deeper dermal, subcutaneous or mucosal layers. However the mechanisms involved in deep tissue penetration remain unclear especially in humans. Diffusion, molecular weight, lipophilicity, the microvascular compartment and cutaneous blood flow are important, and there are major differences between humans and other animals. Dancik and colleagues [13] investigated the relative contributions of dermal diffusion and binding as determinants of dermal transport using excised human skin and six drugs of varying lipophilicity and plasma binding. They then compared lag times *in vitro* with published studies on *in vivo* dermis and deeper tissue transport kinetics and developed a physiological–PK model to describe the time dependence of the transport of two drugs (diclofenac, high plasma binding and nicotine, low plasma binding) using previously published human microdialysis data. They concluded that for lipophilic low protein bound drugs such as nicotine, tissue diffusion is the major mechanism, whereas for highly protein bound lipophilic drugs such as diclofenac convective, blood, lymphatic and interstitial transport are the major mechanisms, such that deep tissue concentrations peak earlier and may be several orders of magnitude greater than predicted by passive diffusion alone. This may help to explain why the topical application of NSAIDs for

musculoskeletal inflammation works so quickly and well.

Drug dosing in pregnant women is complicated by potential toxicity to the developing fetus. A key factor is the degree of fetal exposure to the drug which is a function of fetal drug input (maternal to fetal transfer) and elimination. Non-steroidal anti-inflammatory drugs (NSAIDs) can cause failure of closure of the ductus arteriosus and neonatal pulmonary hypertension. Animal studies are limited because profound species differences in placental biology limit successful prediction of human fetal PK. Shintaku and colleagues [14] attempted to predict quantitatively the toxicity to the human fetus at term of three NSAIDs (antipyrine, salicylic acid and diclofenac). They used previously published PK data obtained in adult women and separate transplacental kinetic data, and developed a physiological-PK model to simulate human fetal plasma concentration-time profiles. They then used rat PK, fetal and dose-response data to develop a plasma concentration-response relationship in that species. Response was quantitated as the ratio of the inner diameter of the ductus arteriosus to that of the pulmonary artery. A human fetal plasma concentration-response relationship was then obtained using a PK-PD model, and applied to predict fetal toxicity for the three NSAIDs. The ratio of the inner diameter of the ductus arteriosus to pulmonary artery was calculated to be 39% for diclofenac and less than 6% for antipyrine and salicylic acid; these differences agree with clinical reports of greater constriction of the ductus arteriosus with diclofenac than the other two drugs. Although somewhat intuitive, such modelling holds promise as a quantitative approach to predicting human fetal toxicity of new drugs and to improving drug utilization in pregnancy.

Dabigatran, one of the new anticoagulants, differs profoundly from warfarin, both in PK and PD. It is mainly (>80%) excreted unchanged in urine and is a direct thrombin inhibitor. Like warfarin it does have a narrow therapeutic index, pointing to a possible need for dose individualization, but is claimed to be easier to use than the older drug. The recommended prophylactic dose is reduced when creatinine clearance is $<50 \text{ ml min}^{-1}$ and in patients aged over 80 years. Chin and colleagues [15] believed that these dosing recommendations were oversimplified and (re)examined the issue using all the available clinical trial and PK-PD data and 'standard pharmacological principles' to avoid over- or under-dosing. They simulated two scenarios, one with a creatinine clearance of 51 ml min^{-1} and another with a normal serum creatinine but 90 years of age. Both could have received doses associated with 1.5 to 2-fold higher AUC than a reference patient from the clinical trials. They then developed dosing recommendations that took into account renal function and PK culminating in four different dosing schedules based on creatinine clearance thresholds. Their concept epitomizes the DMPD paradigm to optimize drug therapy. Whether this dosing schedule is being adopted or compared with the simpler recommen-

dation locally or internationally is not known, but potentially important for this rapidly increasingly utilized anticoagulant.

Drug safety

A fascinating aspect of drug safety stems from the occasional unexpected turn that serves as a sudden wake-up call. The sheer unpredictability of events, coupled with widely differing susceptibilities for adverse drug reactions amongst individuals means that one can never be fully confident about the potential for harm. Take for example the report by Michel *et al.* [16] regarding unexpected liver toxicity associated with flupirtine, a non-opioid analgesic that has been licensed in Europe for more than 30 years. In a proof of concept study (that one could reasonably describe as 'new uses for an old drug') patients with overactive bladder syndrome were randomized to flupirtine or placebo. During routine monitoring of liver enzymes in the double-blind phase, elevated liver enzymes (>3 times the upper limit of normal) occurred in eight patients. Seven of the eight proved to have been on flupirtine. Fortunately, the patients recovered fully, but the trial had to be stopped. Rigorous testing of a well-established drug in patients with varying susceptibilities or in a new setting may throw up unpleasant surprises!

Conversely, careful patient selection and appropriate monitoring may help avoid adverse outcomes, even with a drug such as spironolactone that has well-established potential for causing hyperkalaemia in the setting of renal dysfunction. Edwards *et al.* [17] conducted a trial of spironolactone 25 mg once daily in 115 patients with early stage chronic renal disease who were already taking angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists, and had no history of hyperkalaemia. After 40 weeks, deterioration of renal function was seen in <3% of patients, despite the progressive nature of chronic renal disease, while hyperkalaemia occurred in <1%. Patients had rigorous monitoring of renal function and electrolytes in the first 4 weeks, and biochemical changes were most apparent in those initial stages. Clearly these patients would generally be considered as 'high risk' for adverse effects with spironolactone, and it is interesting that careful recruitment and monitoring within a trial setting could inform us on how to use spironolactone safely. It is unclear whether such a low rate of adverse effects is achievable in real-life everyday practice, but it certainly is a worthy target.

Selective serotonin re-uptake inhibitors (SSRIs) have been recommended as first line pharmacological agents for the treatment of moderate to severe depression, mainly because of their perceived safety as compared with established agents such as tricyclic antidepressants. However, use of SSRIs in patients with high susceptibility for adverse effects (such as elderly people with dementia) may throw

up problems that may not have been seen in trials involving younger patients. Sterke *et al.* [18] retrospectively evaluated records from 248 nursing home residents with dementia and found that there was a significant dose-response relationship between injurious falls and SSRI use. This was particularly apparent in patients who were additionally taking anxiolytics or hypnotics. While there are clear limitations to the observational design of the study, it is unlikely that such patients will ever be recruited into randomized controlled trials where SSRIs and tricyclic antidepressants are compared directly.

As always, vigilance is the key, and these three articles [16–18] serve as a timely reminder that it is best to avoid making assumptions.

News from the reviews

Several important and topical areas of clinical pharmacology and therapeutics have been tackled in the reviews section of the *Journal* in 2012. One such area is how to improve new drug development. This is a notoriously expensive process, costing the pharmaceutical industry billions of dollars each year, with an attrition rate of new chemical entities (NCEs) in excess of 95% as they progress through pre-clinical and, very much more expensively, clinical studies. Increasingly, PET imaging is being applied to assess whether new drugs reach target tissues, the relationship between drug plasma concentration and target occupancy, the effect of the drug on a particular biological process, and to provide patient-specific information for personalizing therapy. This has the potential to improve earlier decision making, reducing attrition in the later stages of development. This whole area was very comprehensively reviewed by Matthews and colleagues [9].

Alzheimer's disease has been much in the news, specifically because of the lack of effective treatments in slowing cognitive decline coupled with the relative lack of funding for research into this area of profound unmet need. This is despite its high prevalence in the elderly and attendant social and economic consequences. Salomone and colleagues reviewed the potential for novel 'disease-modifying' drugs to influence the progression of Alzheimer's disease [19]. Although none has yet succeeded in phase 3, the availability of new biomarkers, coupled with the ability to diagnose the pre-symptomatic phase of the disease more accurately, may allow such drugs to be used at a much earlier stage. Whether this will translate to a meaningful effect on disease progression and hence symptomatic deterioration remains to be seen.

Hypertension affects some 30% of the adult population and remains a major risk factor for stroke and coronary disease. Primary care physicians now routinely screen their patients and are incentivized to treat blood pressure to lower targets (current NICE guidelines state a target of 140/90 mmHg for people under the age of 80 years and

150/90 mmHg for those 80 years old and over). However, what to do for 'pre-hypertension' – that is to say, high blood pressure below the conventional threshold for antihypertensive drug treatment – remains unclear. Much evidence shows that there is a graded increase in risk as blood pressure increases, even from levels below 120/80 mmHg, but it is far from clear that drug treatment to targets below those currently recommended confers any meaningful benefit and such treatment can cause symptomatic hypotension. McInnes reviewed this area in detail [20], and convincingly argued that any changes in recommendations need to be considered only when robust adequately powered outcome studies become available.

Prescribing is an issue of ongoing interest and concern, partly because the kinds of practitioners allowed to prescribe are increasing, partly because of the increasing recognition that medication errors cause significant morbidity and in some cases mortality [21], and partly because of the increasing interest in personalized therapy. The October issue of the *Journal*, guest-edited by Derek Waller [22] was a themed issue devoted to prescribing, covering these as well as other important areas in the field. This collection of articles is a valuable resource that should be of interest and practical value to prescribers.

Fragments

Of all the content we publish in the *Journal* about one third is editorial material and commentaries. Most of what we publish is still 'hard core' clinical experimental pharmacology (39% of all papers) with PK, PD, drug interactions, pharmacogenetics and PK–PD studies as the most represented categories. Reviews (including systematic reviews) account for 15% of the total, and BJCP remains primarily an experimental journal with a healthy balance of other subjects.

We would like to reinforce some topics. Only 13 papers (5%) about clinical pharmacology in pregnancy and paediatrics put these categories in the incubator, especially as it is generally accepted that much more work should be done here. We hope to attract methodological papers in this area where so much new methodology is necessary. A star example, about adaptive trials in paediatric drug development, may help to reduce unnecessary drug exposure in children [23]. Authors willing to submit papers from these orphaned areas will get a sympathetic reception for their work.

The 'methods in clinical pharmacology' section is growing, with eight papers on a variety of subjects. Craig Hendrix showed what is possible by using clever models and imaging to measure how semen and microbicidal agents mix and meet in the colon, clearly of great importance for limiting the spread of HIV and other sexually transmitted diseases [24].

Research in clinical pharmacology is inherently translational, and we have created a special category which has

produced some gems this year. Olaf Weber and colleagues produced an outstanding example of how animal research can be quantitatively translated to human studies in two excellent papers on a cholesteryl ester transfer protein (CETP) inhibitor [25, 26]. We hope to publish many more papers in this category in years to come.

Competing Interests

There are no competing interests to declare.

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