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EDITORIAL

Therapeutic regimens in interstitial lung disease guided by genetic screening: fact or fiction?

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Drug-induced pulmonary toxicity is a serious and expanding problem [1, 2]. Since the mid 1980s, the understanding of the metabolism of pharmaceuticals has increased substantially. Not least because of the introduction of molecular biological techniques, defects in drug-metabolising pathways have been elucidated. Nowadays, pharmacogenetics can guide the clinician in the choice of the best therapeutic regimen, resulting in ''personalised medicine'' [3].

A decreased drug efficacy and unexpected and serious adverse drug reactions (ADR) are major threats to patients and occur more frequently than expected. Considerable efforts are needed to treat these ADR [4]. Therefore, prevention of ADR is of utmost importance for the patient and the clinician. ADR can be due to inherited defects in drug activation, which mostly lead to decreased efficacy of the treatment, or to defects in drug-metabolising enzymes; the latter results in an exuberant concentration of toxic metabolites [5].

In the current issue of the *European Respiratory Journal*, PERRI *et al.* [6] report the case of a patient suffering from idiopathic pulmonary fibrosis treated with azathioprine who developed severe alveolar haemorrhage. The haemorrhage was caused by severe myelosuppression due to deficiency of thiopurine methyltransferase (TPMT). The increased bioavailability of thioguanine nucleotides results in increased cell death.

Mercaptopurine metabolism is a complicated cascade of reactions, in which several enzymes play an important role in the activation and detoxification of mercaptopurines [7, 8]. One of the most intensively studied enzymes in this pathway is TPMT, an enzyme which catalyses the transfer of the methyl group of *S*-adenosylmethionine to the thiol group on the mercaptopurine molecule [9]. Methylation of mercaptopurines is one of the detoxification reactions in mercaptopurine metabolism. The importance of this reaction is emphasised by the study of PERRI *et al.* [6]. In the field of pulmonary medicine, this is the first case report on mercaptopurine toxicity due to TPMT deficiency. In the literature, several reports are available on ADR caused by mercaptopurine therapy, commenced for different disease entities [10, 11]. In all described cases, the occurrence of severe pancytopaenia was the trigger for determination of red cell TPMT activity or molecular analyses to establish TPMT polymorphisms.

Since mid-2006, we have included pre-treatment screening for TPMT in our protocols for patients with interstitial lung disease who are intended to be treated with mercaptopurines as immunosuppressive therapy. When normal TPMT and inosine triphosphatase (ITPase) activities are found, we advise commencing mercaptopurine therapy with the prescribed dose. When a decreased activity of TPMT is reported, we advise to lower the mercaptopurine dose and, in the case of a complete deficiency, use of an alternative immunosuppressive therapy is recommended. During mercaptopurine therapy a full blood count has to be carried out at regular intervals to avoid leukopaenia or pancytopaenia.

The promise of pharmacogenetics, the study of the role of inheritance in individual variation in drug response, lies in its potential to identify the right drug and dose for each patient. Even though individual differences in drug response may result from the effects of age, sex, disease or drug interactions, genetic factors also influence both the efficacy of drugs and the likelihood of adverse reactions [12, 13]. The discussion of a pre-treatment screening strategy for mercaptopurine therapy is still ongoing. Genetic analyses of CYP 3A4 and 3A5, components of the CYP-P450 enzyme system, to determine fast and slow metabolisers in tarcolimus therapy in kidney transplants is accepted as state of the art [14]. The benefits of screening in the case of TPMT, and even more so with ITPase, are still controversial [15–17]. In pharmacoeconomical terms, prospective testing in the case of mercaptopurine treatment seems valid; the profits for both the patient and health insurance authorities exceed the costs of testing [18, 19]. The profit for the patient being the greatest: drug-induced morbidity can be avoided.

The case study of PERRI *et al.* [6] clearly points out the benefit of testing for defects in the mercaptopurine pathway, which we hope will become common practice in the treatment of interstitial lung diseases in the next few years.

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REFERENCES

1 Camus P, Fanton A, Bonniaud P, Camus C, Foucher P. Interstitial lung disease induced by drugs and radiation. *Respiration* 2004; 71: 301–326.

2 Nemery B, Bast A, Behr J, *et al.* Interstitial lung disease induced by exogenous agents: factors governing susceptibility. *Eur Respir J* 2001; 18: Suppl. 32, 30s–42s.
3 Eichelbaum M, Ingelman-Sundberg M, Evans WE. Pharmacogenomics and individualized drug therapy. *Annu Rev Med* 2006; 57: 119–137.
4 Kollek R, van Aken J, Feuerstein G, Schmedders M. Pharmacogenetics, adverse drug reactions and public health. *Community Genet* 2006; 9: 50–54.
5 Candelaria M, Taja-Chayeb L, Arce-Salinas C, Vidal-Milan S, Serrano-Olvera A, Dueňas-Gonzalez A. Genetic determinants of cancer drug efficacy and toxicity: practical considerations and perspectives. *Anticancer Drugs* 2005; 16: 923–933.
6 Perri D, Cole DEC, Friedman O, Piliotis E, Mintz S, Adhikari NKJ. Azathioprine and diffuse alveolar haemorrhage: the pharmacogenetics of thiopurine methyltransferase. *Eur Respir J* 2007; 30: 1014–1017.
7 Bakker JA, Drent M, Bierau J. Relevance of pharmacogenetic aspects of mercaptopurine metabolism in the treatment of interstitial lung disease. *Curr Opin Pulm Med* 2007; 13: 458–463.
8 Cara CJ, Pena AS, Sans M, *et al.* Reviewing the mechanism of action of thiopurine drugs: towards a new paradigm in clinical practice. *Med Sci Monit* 2004; 10: RA247–RA254.
9 Salavaggione OE, Wang L, Wiepert M, Yee VC, Weinshilboum RM. Thiopurine S-methyltransferase pharmacogenetics: variant allele functional and comparative genomics. *Pharmacogenet Genomics* 2005; 15: 801–815.
10 Gardiner SJ, Gearry RB, Barclay ML, Begg EJ. Two cases of thiopurine methyltransferase (TPMT) deficiency –a lucky save and a near miss with azathioprine. *Br J Clin Pharmacol* 2006; 62: 473–476.
11 Richard VS, Al-Ismail D, Salamat A. Should we test TPMT enzyme levels before starting azathioprine? *Hematology* 2007; 12: 359–360.
12 Meyer UA. Pharmacogenetics and adverse drug reactions. *Lancet* 2000; 356: 1667–1671.
13 Weinshilboum R. Inheritance and drug response. *N Engl J Med* 2003; 348: 529–537.
14 Op den Buijsch RA, Christiaans MH, Stolk LM, *et al.* Tacrolimus pharmacokinetics and pharmacogenetics: influence of adenosine triphosphate-binding cassette B1 (ABCB1) and cytochrome (CYP) 3A polymorphisms. *Fundam Clin Pharmacol* 2007; 21: 427–435.
15 van Dieren JM, van Vuuren AJ, Kusters JG, Nieuwenhuis EE, Kuipers EJ, van der Woude CJ. ITPA genotyping is not predictive for the development of side effects in AZA treated inflammatory bowel disease patients. *Gut* 2005; 54: 1664.
16 Winter J, Walker A, Shapiro D, Gaffney D, Spooner RJ, Mills PR. Cost-effectiveness of thiopurine methyltransferase genotype screening in patients about to commence azathioprine therapy for treatment of inflammatory bowel disease. *Aliment Pharmacol Ther* 2004; 20: 593–599.
17 Bierau J, Lindhout M, Bakker JA. The pharmacogenetic significance of inosine triphosphatase. *Pharmacogenomics* 2007; (In press).
18 Clunie GP, Lennard L. Relevance of thiopurine methyltransferase status in rheumatology patients receiving azathioprine. *Rheumatology* 2004; 43: 13–18.
19 Priest VL, Begg EJ, Gardiner SJ, *et al.* Pharmacoeconomic analyses of azathioprine, methotrexate and prospective pharmacogenetic testing for the management of inflammatory bowel disease. *Pharmacoeconomics* 2006; 24: 767–781.