Venue: PYRAMID 2
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1515-1630 hr

Symposium 6A: Therapeutic drug monitoring

S6A-1. Quality control of therapeutic drug monitoring

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It is essential that laboratories performing drug measurements that are used to guide dose adjustments ensure that their results are consistent over time and compare with those produced by other laboratories performing the same assay. There are several therapeutic areas in which therapeutic drug monitoring (TDM) of drugs in plasma or blood have been shown to be of clinical value. These include, antiepileptic, antibiotic, anti-HIV, antiarrhythmic, anti-cancer, antidepressive and immunosuppressive drug therapy. These drugs are mostly classed as critical-dose drugs, for which relatively small changes in their concentrations in plasma or blood lead to significant changes in efficacy or toxicity. If clinicians are to be able to make an informed decision on dose changes, and to achieve consistency of results across multiple sites, the quality of the drug measurement is of considerable importance. Key quality issues are calibration accuracy and reproducibility of the analytical technique. This presentation will use data on comparative assay performance from external proficiency testing schemes to show that there is often a tendency to concentrate on reproducibility, rather than absolute accuracy, especially in relation to immunoassay kits, biased due to cross-reactivity with metabolites of the target analyte. The availability of HPLC/MS has highlighted the differences between chromatographic and immunoassays and promoted comparative studies on the utility of these assay techniques for routine drug monitoring. A driving force in this process has been the use of HPLC/MS for the measurement of immunosuppressive drugs, and examples will be presented from this and other therapeutic areas that show the impact of methodology on the final result. It will be concluded that insufficient attention has been paid to the issue of assay calibration as part of the validation process, and its contribution to consistency of assay performance. Rectifying this problem requires constant vigilance by both laboratory scientists and the diagnostics industry.

S6A-2. Therapeutic drug monitoring of antiretroviral drugs

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The human immunodeficiency virus type 1 (HIV-1) was identified and characterised 20 years ago and as an infectious disease-causing agent, HIV-1 is now one of the most common causes of death worldwide. Four classes of pharmacological agents are now available for the treatment of HIV: nucleoside/nucleotide reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI) and entry inhibitors. Current treatment of HIV involves the use of a combination of two or more of these classes to suppress viral replication known as highly active antiretroviral therapy or HAART. Treatment of human immunodeficiency virus (HIV) with antiretroviral therapy (ART) reduces morbidity and mortality, suppresses plasma viral load, and restores immune function, but numerous obstacles can limit the success of this therapy. After starting triple drug regimens (ART) approximately 40% of people treated in the clinic setting will experience therapeutic failure (viral rebound) within two years of starting treatment. Furthermore, drug-related

toxicity has been shown to be the dominant factor in discontinuation of ART where 36% of 862 patients discontinued their first antiretroviral regimen after 45 weeks of treatment and 58% of the discontinuations were due to drug-related toxicity. The therapeutic strategy of giving the same dose to all patients ignores the striking and well known inter-patient pharmacokinetic variability seen for these agents in this population. Substantial drug-drug interactions in these people and the significant impact of the disease itself on drug absorption, distribution and elimination mean that the potential for people to receive suboptimal or toxic concentrations of these drugs cannot be overlooked. It is therefore no longer acceptable to assume that one dose fits all. Therapeutic drug monitoring (TDM) has the goal of promoting optimal drug treatment by maintaining drug concentrations within a "therapeutic range", above which there is an increased risk of toxicity and below which there is a high probability that the drug will be ineffective. TDM of ART remains controversial, but is clearly undervalued and misunderstood by many clinicians.

S6A-3. Immunosuppressive drug monitoring

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Currently numerous combinations of immunosuppressants are being evaluated with the goal to improve efficacy (rejection rates) and to reduce chronic overimmunosuppression. Immunosuppressive drug monitoring (TDM) plays an essential role in the optimization of such new regimens. In the field of analytical techniques specific LC-MS/MS methods are emerging as practical alternatives to the highly automated immunoassays. In maintenance renal transplant recipients C_2-monitoring may be a valuable tool to detect overexposure to cyclosporine (CsA). Trough level monitoring will presumably be useful to guide therapy with the new modified-release tacrolimus (MR-4) designed for once-daily administration. TDM of mycophenolic acid (MPA) is not fully established. Total MPA monitoring in particular on day 3 posttransplant can predict rejection risk in renal transplant recipients (minimum recommended threshold for MPA AUC: 30 mg x h/L). Various interactions between MPA and other agents (e.g. cyclosporine, antacids, metronidazole, norfloxacin, steroids and rifampin) have been documented all of which decrease MPA exposure. *UGT1A9* SNPs in the promoter region are associated with decreased MPA exposure. Free MPA AUC seems to be useful to predict the risk for leukopenia and infection. The MPA acyl glucuronide has proinflammatory properties that may play a role in the pathogenesis of non-infectious diarrhoea. For pharmacodynamic monitoring of MPA various biomarkers have been proposed: the activity of the target enzyme IMPDH and markers of lymphocyte proliferation or activation. Recent results from the FDCC trial show that MMF dose adjustments based on day 3 and day 10 abbreviated AUCs were not able to increase the percent of patients reaching early MPA target exposure. Investigators seemed reluctant to adjust the MMF dose based on MPA $AUC_{0\text{-}12h}$. However, results from the Apomygre study systematically using Bayesian forecasting for dosage individualisation have shown that a significantly lower incidence of acute rejection can be achieved in patients treated with an individualized dose adapted to the MPA $AUC_{0\text{-}12h}$ (target: 40 mg x h/L) compared to a fixed-dose regimen. MPA TDM can be useful in heart transplantation were there is minimal tolerance for rejection episodes and in liver transplant recipients were there are large variations in inter- and intrapatient responses. It can also be useful in renal transplantation in cases of higher rejection risk. From exposure-response studies in renal transplant recipients therapeutic windows could be defined for sirolimus trough blood levels (4 - 12 µg/L for triple therapy and 12 – 20 µg/L for dual therapy) and for everolimus combined with steroids and CsA (3 – 8 µg/L).