

reactions for each patient, besides demographic data. They answered a of quality of life questionnaire (SF-36) at the beginning of treatment and two months before starting.

Results During this period, 7 patients began treatment with CBD-THC, prescribed by neurologists. The average age was 40 years (± 8.2), 4 males and 3 females.

It was used for spasticity due to MS in two patients and it was off-label use for the rest of patients: two cases of refractory spasticity not caused by MS and three cases of neuropathic pain.

The quality of life improved 21%, showed by SF-36 questionnaire.

The average titration period was 26 days, the average dose used was 7.8 sprays/day (standard deviation 3.27) (min: 3 max 12), spread three times a day.

All patients, except for one, suffered adverse reactions, mainly mild or moderate dizziness (57% of them), dysgeusia (taste alteration) 29% and hypotension (14%).

Conclusions The quality of life has improved for our patients treated with CBD-THC.

As many adverse effects appeared and it was difficult to manage this drug the pharmacist's role assumed considerable importance; monitoring and pharmaceutical care is very necessary

No conflict of interest.

PHC-014 EXPLORATORY ANALYSIS OF 1,936 SNPs IN 225 ADME GENES FOR ASSOCIATION WITH BUSULFAN CLEARANCE IN ADULT HEMATOPOIETIC STEM CELL RECIPIENTS

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Background Busulfan is used in preparative regimens prior to stem cell transplantation (SCT). There is significant inter-patient variability in busulfan pharmacokinetics (PK) and outcome is related to exposure.

To date, only polymorphisms in genes encoding for glutathione-S-transferases have been studied; they could only explain a small portion of the variability in PK.

Purpose To investigate the role of other genetic variants on busulfan clearance by interrogating 1,936 variants in 225 genes that are involved in drug absorption, distribution, metabolism and excretion (ADME).

Materials and Methods 62 adult patients who received busulfan were genotyped using the Drug Metabolizing Enzymes and Transporters (DMET) array. Busulfan clearance was estimated with a limited sampling ($t = 2.5, 4$ hrs) PK model. Individual SNPs were associated with busulfan clearance. Top SNPs and haplotypes were replicated in an independent cohort ($n = 78$).

Results In the discovery cohort 7 variants (3 SNPs and 4 haplotypes) explained 64% (adjusted R^2) of variance in busulfan clearance ($p < 0.001$). These genetic variants, located in GSTA5, CYP2C19, CYP3A1 (2 haplotypes), ABCB4, SLC22A4 and SLC7A8, were replicated in the second cohort. One haplotype in GSTA5 (rs4715354 and rs7746993) remained statistically significant ($P = 0.025$) for correlation with busulfan clearance.

Conclusions This is the first study using an exploratory pharmacogenetic approach in 225 genes involved in ADME to explain the inter-individual variability in busulfan clearance. The GSTA5 haplotype was significantly correlated with busulfan clearance, both in the discovery and replication cohort. No additional genetic markers involved in drug metabolism and transport appear to be associated with busulfan clearance.

No conflict of interest.

PHC-015 IMPACT OF MDR1 POLYMORPHISMS ON THE ANALGESIC EFFICACY OF TRAMADOL IN PATIENTS AFTER MINOR SURGERY

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Background P-glycoprotein is a transmembrane transporter coded by the ATP-binding cassette sub-family B multi-drug resistance gene (MDR-1) gene. It influences the bioavailability, disposition and excretion of many drugs. Among the 50 SNPs of the MDR1 gene, more attention has been focused on the SNP at position 3435 in exon 26. Homozygous TT samples were associated with more than two-fold lower intestinal MDR1 expression levels compared with homozygous CC samples. A trial in patients suffering from chronic and cancer pain reported decreased opioid consumption in carriers of the 3435T allele. Our previous data suggest that the pharmacokinetics and therefore effectiveness of tramadol could be affected by MDR1 polymorphism C3435T.

Purpose To evaluate the possible effect of MDR1 polymorphisms on the analgesic efficacy of tramadol in realistic clinical settings.

Materials and Methods Pain intensity was assessed using a visual analogue scale at 2 and 24 hours after minor surgery in 156 patients. Polymorphisms and gene duplication in the MDR1 gene were analysed by PCR-RFLP (restriction fragment length polymorphism).

Results Variant allele 3435T was seen at a frequency of 58.3%. There were no statistically significant differences between MDR1 subgroups in basic demographic parameters. Mean VAS2h in groups C3435CC, C3435CT and C3435TT were 40.0 ± 11.8 ; 43.2 ± 17.9 , resp. 45.5 ± 16.1 mm ($P = \text{ns}$). Corresponding values for mean pain difference, defined as VAS2–24h were 19.3 ± 12.1 ; 21.3 ± 14.6 and 23.4 ± 15.4 mm ($P = \text{ns}$). Mean tramadol consumption was 2.47 ± 1.17 , resp. 2.62 ± 1.1 ; 2.42 ± 1.1 ; 2.44 ± 1.3 mg/kg ($P = \text{ns}$) during the 24 h period. There were no significant differences in the drug consumption, reporting of adverse reactions or need for rescue analgesics among the MDR1 genotype subgroups.

Conclusions Although there were approximately 20% higher mean pain difference values in the 3435TT group in comparison with the wild-type subjects, the between-group variation did not reach statistical significance.

No conflict of interest.

PHC-016 NILOTINIB VERSUS IMATINIB FOR THE TREATMENT OF PATIENTS WITH NEWLY-DIAGNOSED PHILADELPHIA CHROMOSOME-POSITIVE, CHRONIC MYELOID LEUKAEMIA IN THE CHRONIC PHASE

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Background Nilotinib is a BCR-ABL inhibitor designed to be more potent and selective than imatinib. Imatinib was the first of a new class of drugs that act by specifically inhibiting a tyrosine kinase receptor.

Purpose To assess the molecular response at 12 months from the start of nilotinib treatment, defined as BCR-ABL transcript levels on the International Scale of 0-1% or less by real-time quantitative PCR in a peripheral blood sample.

Materials and Methods We present data from the ENESTnd study. In ENESTnd, a phase 3, multicentre, open-label, randomised study, patients treated with nilotinib demonstrated higher and faster rates of major molecular response (MMR), more profound molecular response (MR), and complete cytogenetic responses (CCyR) compared with imatinib by 12 and 24 months. 282 adult patients were randomly assigned to receive nilotinib 300 mg twice daily, 281 to receive nilotinib 400 mg twice daily and 283 to receive imatinib. Patients were eligible if they had been diagnosed with chronic phase, Philadelphia chromosome-positive CML within the previous 6 months.

Results By 24 months after the start of treatment, significantly more patients had a MMR with nilotinib than with imatinib (201 with nilotinib 300 mg twice daily, 187 with nilotinib 400 mg twice daily and 124 with imatinib; $p < 0.0001$ for both comparisons). Significantly more patients in the nilotinib groups achieved a complete molecular response at any time than did those in the imatinib group (74 with nilotinib 300 mg twice daily, 59 with nilotinib 400 mg twice daily and 29 with imatinib; $p < 0.0001$ for nilotinib 300 mg twice daily vs. imatinib, $p = 0.0004$ for nilotinib 400 mg twice daily vs. imatinib).

Conclusions Nilotinib continues to demonstrate superiority vs. imatinib with faster and more profound molecular responses. These results support nilotinib as a first-line treatment option for patients with newly diagnosed Philadelphia chromosome-positive and chronic myeloid leukaemia.

No conflict of interest.

PHC-017 PHARMACOGENETIC STUDY ABOUT INFLUENCE OF A POLYMORPHISM IN GENE TRAILR1 IN RESPONSE TO INFlixIMAB IN PATIENTS WITH CROHN'S DISEASE (CD)

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Background Anti-TNF drugs show high inter-individual variability in efficacy and toxicity.

Currently there are no genetic, biochemical or environmental markers to predict response to treatment.

Purpose To assess the influence of gene polymorphism rs2230229 TRAILR1 as a genetic marker in response to treatment with infliximab in patients diagnosed with Crohn's disease (CD). Will it enable us to predict response and improve the effectiveness of the drug?

Materials and Methods Prospective observational study of all patients diagnosed with CD treated with infliximab at our hospital. The assessment of response to infliximab was performed using as criteria of clinical response a decreased questionnaire score CDAI (Crohn Disease Activity Index) at the 4th dose. Subsequently patients were considered to have responded if their CDAI decreased by 70 points or more with respect the baseline and at least 25% on the total score and clinical remission was achieved by a CDAI of less than 150 points. Biological response criteria were defined such as patient responders, partial responders or non-responders according to variation in levels of C-reactive protein (CRP) with regard to baseline at 3, 6 and 12 months. To detect polymorphism KASPAR probes were used in a PCR-based allele-specific competitive FRET technology using a computer and a real time PCR of Applied Biosystems 7500F in 96-well plate. All patients included in the study received a starting dose of infliximab 5 mg/kg at 0, 2 and 6 weeks after the start and then a maintenance dose every 8 weeks. Statistical analyses were performed with Epidat 3.1 and the level of significance was indicated by a p value of less than 0.05.

Results The study included a total of 40 patients. The mean age of the patients was 38.66 ± 13.98 years and 61.1% were female. The distribution for genotypes was 81.6% AA, 15.8% GA and 2.6% GG. Significant correlation wasn't found between genotypes or alleles of this polymorphism and clinical response to infliximab. Instead, statistically significant differences were shown for approximately 6 months of treatment when comparing patients with genotypes GG and GA/AA and a positive response ($p = 0.047$) when considering the biological response. Similarly patients with a G allele had a more frequent negative response than those with the A allele ($p = 0.043$). On the other hand, significant correlation was found between patients carrying the A allele and the positive response, at 3, 6 and 12 months based on biological response distribution.

Conclusions The results of our study show an association of this polymorphism with response to infliximab. Worst response rates are observed in patients carrying allele G diagnosed with CD. We need more studies on this polymorphism and with a larger sample size to confirm these findings.

No conflict of interest.

PHC-018 PHARMACOGENETIC STUDY AS A PREDICTOR OF EFFICACY AND TOXICITY IN PATIENTS WITH ADVANCED RENAL CELL CARCINOMA TREATED WITH SUNITINIB

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Background Sunitinib (SU) is an oral, small-molecule, multi-targeted tyrosine kinase receptor inhibitor that is approved for the treatment of renal cell carcinoma (RCC). However, several patients either do not respond to treatment, or they do, but they experience significant toxicity.

Purpose To find genetic markers of toxicity and efficacy using a commercially available DNA microarray genotyping system.

Materials and Methods 25 patients with newly-diagnosed metastatic RCC were evaluated prospectively from January 2010 to May 2011. Patients received SU in repeated 6-week cycles of 50 mg/day orally for 4 weeks, followed by 2 weeks off treatment. A total of 92 single nucleotide polymorphisms (SNPs) in 34 genes in the pharmacokinetic and pharmacodynamic pathways of drugs were analysed using the Drug inCode pharmacogenetic service. This test is performed from a saliva sample and uses a DNA microarray system. Polymorphisms in candidate genes, together with clinical characteristics, were tested by univariate analysis for association with the number of days of sunitinib treatment until the first reduction of dose, progression free survival (PFS) and overall survival (OS).

Results Patients with CYP1A2*1/*1, a low-metabolising genotype, needed dose reduction due to an increased risk of toxicity vs. *1F/*1F or 1F/1F* (Median time to dose reduction: 2.33 months vs. not reached during study period; $p < 0.006$). Patients with CYP2C19*1/*1, wild type genotype, had an increased risk of dose reductions due to toxicity versus other genotypes (Median time to dose reduction: 2.8 months vs. 9.73 months; $P < 0.021$). No statistically significant associations were observed among drug metabolising genes and PFS or OS.

Val(158)Met Catechol-O-methyltransferase (COMT) gene polymorphisms have been associated with PFS and OS. We found that Met/Met carriers, low metabolising allele, had longer PFS and OS compared to those with Met/Val (PFS not reached vs. 15 months; OS not reached Vs17.2 months) and Val/Val (PFS = 3.3 months; OS = 4.4 months) phenotypes ($P = 0.005$ for PFS and $P = 0.003$ for OS).