Final Report Summary - EU-PACT (A pharmacogenomic approach to coumarin-anticoagulant therapy)

Executive summary:

Bleeding due to oral vitamin K (coumarins) is a leading cause of drug-related death. It is therefore extremely important to improve the use, effectiveness and safety of coumarin therapy. We aimed to test whether pre-prescription genotyping improves the use of coumarins in clinical practice. We developed new coumarin dosing algorithms to determine individualised dose requirement at the initiation of coumarin therapy based on genetic factors and a number of patient characteristics. We will assess the safety and cost effectiveness of individualised therapy through a randomised clinical trial. Alongside this we will also assess the utility of a state-of-the-art genotyping instrument for rapid use by medical staff in the clinic.

Patient inclusion in the Netherlands started on 1 November 2010. Sweden, the United Kingdom and Greece started in 2011. Patient inclusion in Germany and Austria has started on October 2012. This delay was caused by the fact that the IRB needed the validation of the genotyping instrument that came available the summer 2011 and because the IRB needed a sponsor in the Netherlands. For University Utrecht, this was initially not possible, but the legal offices of the participating centres have eventually found a solution.

In total we have included 456 patients in the warfarin arm of the trial, 170 patients in the phenprocoumon arm, and 381 patients in the acenocoumarol arm. The original trial target was to recruit 986 patients in each arm. The trial sample size was calculated based on historical clinical data from Liverpool. However, a recent analysis of EU-PACT trial data demonstrated that the primary study outcome could be achieved by a significantly smaller sample of patients; the new calculations showed that with 200 patients in each of the two trial arms the study will have 80 % power to detect a difference in time within target therapeutic range (TTR) in the first 3 months of therapy (primary outcome) of about 0.06 to 0.07 between the standard treatment and the study intervention. The new power calculation was ratified by the trial DSMB.

A draft of the statistical analysis plan is currently being drawn up and which will need ratification by the drug safety monitoring board (DSMB) for final adoption. It is anticipated that once approved it will take about two months to carry out the statistical analysis of the trial data.

The plan is to complete the final analyses by mid-autumn 2013. As the data for the trial have not been analysed we do not know at this stage whether the incorporation of genetic data in the dosing algorithm improves the safety of anticoagulation therapy in newly diagnosed patients with thromboembolic disease. In any event the outcome of the trial will be of major interest to the academic and clinical community. We fully intend to publicise the results of the EU-PACT trial through presentations at international scientific conferences and publications in high-impact peer-reviewed journals.

The expected results are that dosing according to a genotype guided dosing algorithm will improve the safety of the patients by reducing the risk on thromboembolic events and (major) bleedings. We expect an impact on the health of European
citizens, on European scientific competitiveness and on the European economy.

Project context and objectives:

Introduction

Bleeding due to oral vitamin K antagonists (coumarins) is a leading cause of drug-related death. It is therefore extremely important to improve the use, effectiveness and safety of coumarin therapy. We aimed to test whether pre-prescription genotyping improves the use of coumarins in clinical practice. Improved dose prediction and stability of anticoagulation will help to reduce the frequency of one of Europe's most common causes of drug-related hospital admissions and death.

Since the risk of bleeding due to over-anticoagulation occurs largely at the initiation of therapy, knowledge of a patient's genotype and other environmental factors could be beneficial to the planning of an induction regimen likely to avoid this. Based on our existing data on the factors which affect dose requirements we will develop new coumarin dosing algorithms which will determine individualised dose requirement at the initiation of coumarin therapy based on genetic factors and a number of patient characteristics. We will then assess the safety and cost effectiveness of individualised therapy through a randomised clinical trial. Alongside this we will also assess the utility of a state-of-the-art genotyping instrument for rapid use by medical staff in the clinic.

Objectives

The objectives of the EU-PACT project are:

(1) To develop algorithms for individualised coumarin dosing.
(2) To validate the new rapid point-of-care test (POCT) for genotyping of CYP2C9 and VKORC1 by LGC HyBeaconTM technology.
(3) To perform clinical trials to compare the safety of the new dosing algorithms with standard care for the anticoagulants warfarin (United Kingdom, Sweden), phenprocoumon (Germany, Austria, Netherlands) and acenocoumarol (Netherlands, Greece). Genotyping for CYP2C9 and VKORC1 will be performed before the start of coumarin therapy to tailor dose according to genotype.
(4) To determine whether individualised dosing of the coumarins based on genotype is a cost-effective procedure.
(5) To develop an archive of deoxyribonucleic acid (DNA) samples in each country linked to high quality clinical data which can be used to identify genetic variants that determine why patients are either resistant or sensitive to the anticoagulants.

Project Results:

Description of work performed

During the first period we have finished the trial protocol. The study design of the trial is published in Pharmacogenomics in 2009 (1). Because of the many differences between clinical care in the 6 different countries, this was more complicated than predicted. However, finally all countries received approval for conducting the trial. Germany and Austria have faced many problems regarding sponsorship, and approval was only granted in September 2012. Furthermore, algorithms have been designed that can be used for individual coumarin dosing. In the Netherlands, 2 cohorts of coumarin users (phenprocoumon and acenocoumarol) with a total of more than 1 000 patients were included in the pre-EU-PACT study. In these cohorts we have developed the algorithms both with and without genotype information that can be used in the two arms of the trial (2). These algorithms were validated in an independent dataset (3). Also for the warfarin arm an article was published on the algorithms that were used (4).
Furthermore, LGC developed the assay to use POCT to genotype the CYP2C9 and VKORC1 polymorphisms. The assay has been validated and the results are published in Clin Chim Acta (5).

Within the previously mentioned pre-EU-PACT study we performed several studies to investigate the possibility of optimising the dosage of acenocoumarol and phenprocoumon for the individual patient.

We evaluated the possible gene-gene interaction between CYP2C9 and VKORC1, because the combination of variation in both these genes might have different impact compared with variation in one of the genes. We investigated 3 different outcomes, the maintenance dose, time to severe overanticoagulation (INR > 6), and time to achieve stability, but no significant interactions were found (6).

Furthermore, we investigated the effect of genetic variation in GATA-4 a gene encoding for a CYP2C9 transcription factor. We indeed found an association between GATA-4 single nucleotide polymorphisms (SNPs) and the acenocoumarol maintenance dose, however the effects were small and the results could not be replicated in an independent dataset. No significant association was found for phenprocoumon. Genetic variation in the investigated GATA-4 SNPs therefore does not seem relevant for clinical implementation (7).

Other SNPs that were hypothesised to affect the coumarin maintenance dose were SNPs in CYP4F2 (metabolism Vitamin K) and SNPs in CYP3A4 (metabolism coumarins). CYP3A4*1B is the most common variant allele, but in our study it was not associated with the phenprocoumon and acenocoumarol maintenance dosages. CYP3A4*22 which is a more recently identified functional SNP within CYP3A4 was associated with the phenprocoumon maintenance dose, but because of the small effect the clinical value seems to be low. The same holds true for the CYP4F2 variant alleles. In the pre-EU-PACT dataset for phenprocoumon there was indeed a significantly increased maintenance dosage for the carriers of the variant alleles. For acenocoumarol there was a trend towards an increased maintenance dosage, but the difference was not statistically significant. The clinical relevance seems to be very low (8).

We also studied the effects of several commonly used drugs on the maintenance dose of the coumarins. In the Netherlands over 10 % of the population used a statin in 2010. Simultaneous use with coumarins occurs regularly. Therefore we also evaluated the effect of statin use on the dose. We found decreased acenocoumarol maintenance dose requirements when patients used concurrently either atorvastatin, simvastatin, pravastatin or rosuvastatin. We did not find an effect on the phenprocoumon dose requirements (9). Furthermore we evaluated the effect of co-use of (es)omeprazole. Our study showed that a lower phenprocoumon dose is required for users of (es)omeprazole (10).

Furthermore, we investigated the duration of the effect of VKORC1 and CYP2C9 genotypes on anticoagulation therapy. Patients with polymorphisms in CYP2C9 and VKORC1 had a higher risk of overanticoagulation (up to 74 %) and a lower risk of underanticoagulation (down to 45 %) in the first month of treatment with acenocoumarol, but this effect diminished after 1 - 6 months. For phenprocoumon the effect could only be measured in the first month of therapy (11, 12).

For the pharmaco-economic analyses, we have identified a health economist from every participating country willing to contribute to the EU-PACT trial. Cost parameters for country specific analyses have been gathered (13). To obtain knowledge about the available information on the cost effectiveness of pharmacogenetic-guided dosing in treatment with coumarin derivatives, literature research has been performed (14). The conclusion of the literature review was that current data is not sufficient to determine whether or not pharmacogenetic-guided dosing of coumarins is cost effective. The results of clinical trials such as EU-PACT are needed. A definite analysis plan for the results from the EU-PACT trial will be written in the coming months. This document will describe the steps to be taken for data collection, data management and statistical analysis. When the statistical analyses have been performed for the clinical effectiveness in the EU-PACT trial, also a report on the cost effectiveness will be published.
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The plan is to complete the final analyses by mid-autumn 2013. As the data for the trial have not as yet been analysed we do not know at this stage as to whether the incorporation of genetic data in the dosing algorithm improves the safety of anticoagulation therapy in newly diagnosed patients with thromboembolic disease. In any event the outcome of the trial will be of major interest to the academic and clinical community. We fully intend to publicise the results of the EU-PACT trial through presentations at international scientific conferences and publications in high impact peer reviewed journals.

References


Potential impact:

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Impact on the health of European citizens: The proposed individualised dosing algorithms have the potential to benefit all patients requiring coumarin therapy, especially if the rapid near-patient testing proves reliable and consistent. Whilst this approach does not obviate the need for international normalisation ratio (INR) monitoring or further dosage adjustments, it could potentially reduce the time required to reach target INR, improve the stability of anticoagulation control, reduce the number of treatment failures, and the number of dosage titrations, thus reducing the inconvenience and expense associated with frequent INR monitoring. It is envisaged that the new dosing regimen can later be adopted more widely by other anticoagulant clinics Europe-wide and elsewhere if successful.

Impact on European scientific competitiveness: The importance of pharmacogenetics has been better recognised in other regions than Europe, in particular by the United States of America (USA) and Japan, also resulting in substantial initiatives to extend the knowledge base of the subject in various disease areas. In order to improve European research and reverse these trends, substantial European Union (EU) projects into pharmacogenetics seems to be urgently needed.

Impact on European economy: This clinical trial will examine the impact of knowledge of the CYP2C9 and the VKORC1 genotype is needed to show whether genotyping of these factors will actually reduce the cost of health care in Europe.
List of websites: The website of the EU-PACT project is http://www.eupact.org. On this homepage, some background information can be found and links for patients and for researchers to obtain more detailed information. Researches can find programmes, standard operating procedures (SOPs), protocols etc. on the password protected page.

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