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PRECISION MEDICINE AND TARGETED THERAPIES:
REALITIES AND PERSPECTIVES

Incorporation of individual genetic and kinetic characteristics for pharmacological optimisation of drug therapies

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Notes are linked to the references page.

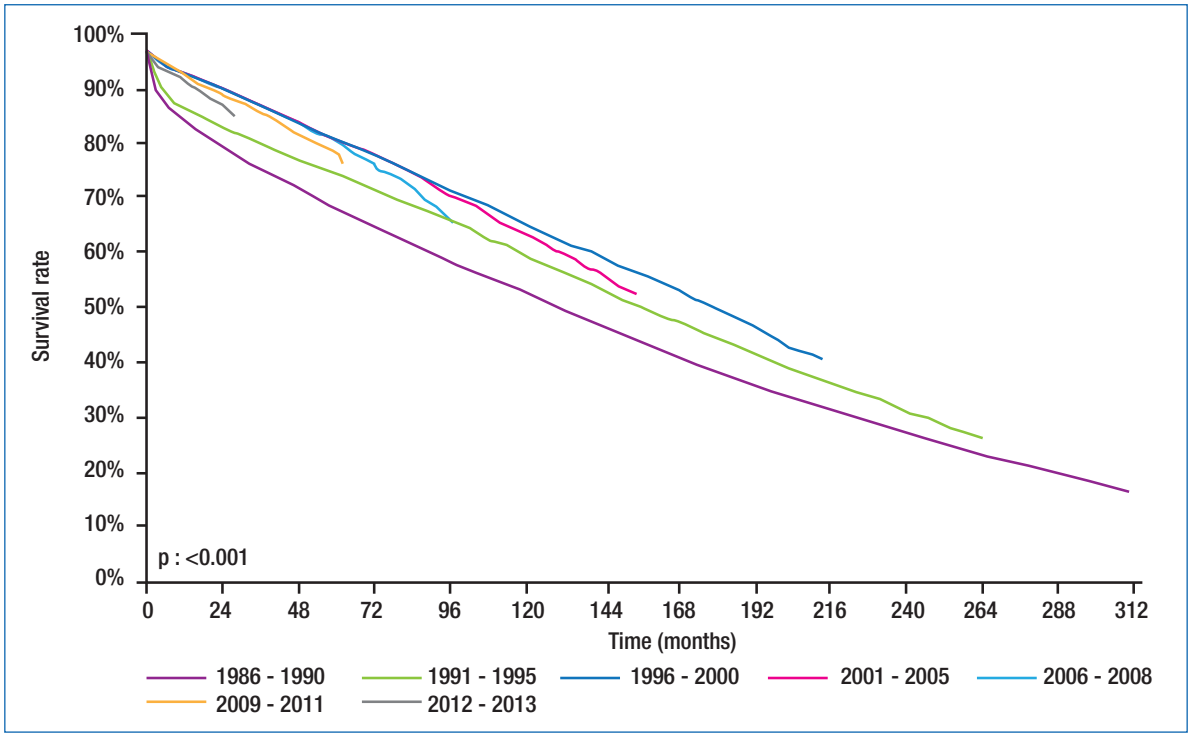
Immunosuppressive therapies used in transplantation have long been a preferred field of investigation for the development of personalised, or precision, medicine due to the wide variability of graft and patient survival, the narrow therapeutic window of the majority of immunosuppressive drugs, their pharmacokinetic interactions and the long-term toxicity of most of them.

Personalising treatments in organ transplantation is a long process that requires identification of the factors affecting response and tolerance to immunosuppressive therapy, developing tools and strategies to individualise therapy, validating them clinically, and then efficiently transferring them into routine practice. The impact of these interventions on graft survival, patient survival and quality of life, and even healthcare costs, can then be evaluated.

TREATMENT OPTIMISATION: THE EXAMPLE OF ORGAN TRANSPLANTATION

The 2014 Annual Report of the French Biomedicines Agency compared renal graft survival rates according to year of transplantation for time cohorts between 1986 and 2013. Figure 1 shows that graft survival gradually improved in each time period until the 1996–2000 cohort and then began to deteriorate in the early months after transplantation. The reason for this reversal is related to the widening of the acceptability criteria for grafts (‘marginal’ grafts) and for recipients (‘marginal’ recipients, such as those receiving organs from deceased non-heart-beating donors). While the profile of patients has changed greatly, all the immunosuppressive drugs used now were developed and licensed for cohorts dating, at best, to the years 1990–1995. The problem now is therefore to improve graft survival with the drugs we have available to us.

Figure 1. Graft survival rates according to year of transplantation (French Biomedicines Agency, Annual Report 2014)



TRANSLATIONAL RESEARCH STRATEGY FOR THERAPEUTIC OPTIMISATION IN ORGAN TRANSPLANTATION

Organ transplantation is characterised by a wide variability of therapeutic response, with good outcomes in some patients and unsatisfactory outcomes in others. In such a situation, translational research is necessary: it is by going back and forth from patient to laboratory that an answer can be found to the questions raised by this variability. First of all, it is important to understand the reason for the variability and to identify the factors, pharmacokinetic and pharmacogenetic factors in particular, which influence the individual response and tolerance to immunosuppressants and their combinations. In a second step, it is necessary to develop tools of precision medicine that take these factors into account, in order to try to offer a given patient the right treatment at the right dose. These tools will then have to come out of the laboratory to undergo clinical validation and be put to use in transplantation clinics so that patients can benefit. It will then be time to assess the impact of introducing these tools on patient and graft survival, quality of life and health economics.

PHARMACOGENETICS OF IMMUNOSUPPRESSANTS

The enzymes that metabolise sirolimus, mycophenolate mofetil, tacrolimus and ciclosporin explain a small part of the interindividual variability of blood concentrations for the same dose of these drugs.

Cytochrome P4503A5

Cytochrome P4503A5 (CYP3A5) is an enzyme system present in the intestine and liver. It is responsible for the biotransformation of ciclosporin, tacrolimus, sirolimus and everolimus. It has the characteristic of being expressed in only 10–20% of white Europeans as opposed to 80% of sub-Saharan blacks. This difference stems from a single nucleotide polymorphism in intron 3 of CYP3A5, which leads to a non-functional enzyme, CYP3A5*3[1]. At least one wild-type CYP3A5*1 allele is necessary for biotransformation of the above immunosuppressive drugs. It should be noted that expression of CYP3A5 leads to a doubling of activity of the CYP3A enzyme family, which is responsible for 80% of drug biotransformation.

Tacrolimus and CYP3A5

Tacrolimus is a major substrate of CYP3A5, and observational studies have clearly confirmed that transplant recipients who express this enzyme require a higher dose to achieve a therapeutic trough concentration[2]. Patients carrying one active CYP3A5*1 allele require a tacrolimus dose one and a half times higher, and those carrying two active alleles need an almost threefold higher dose[3].

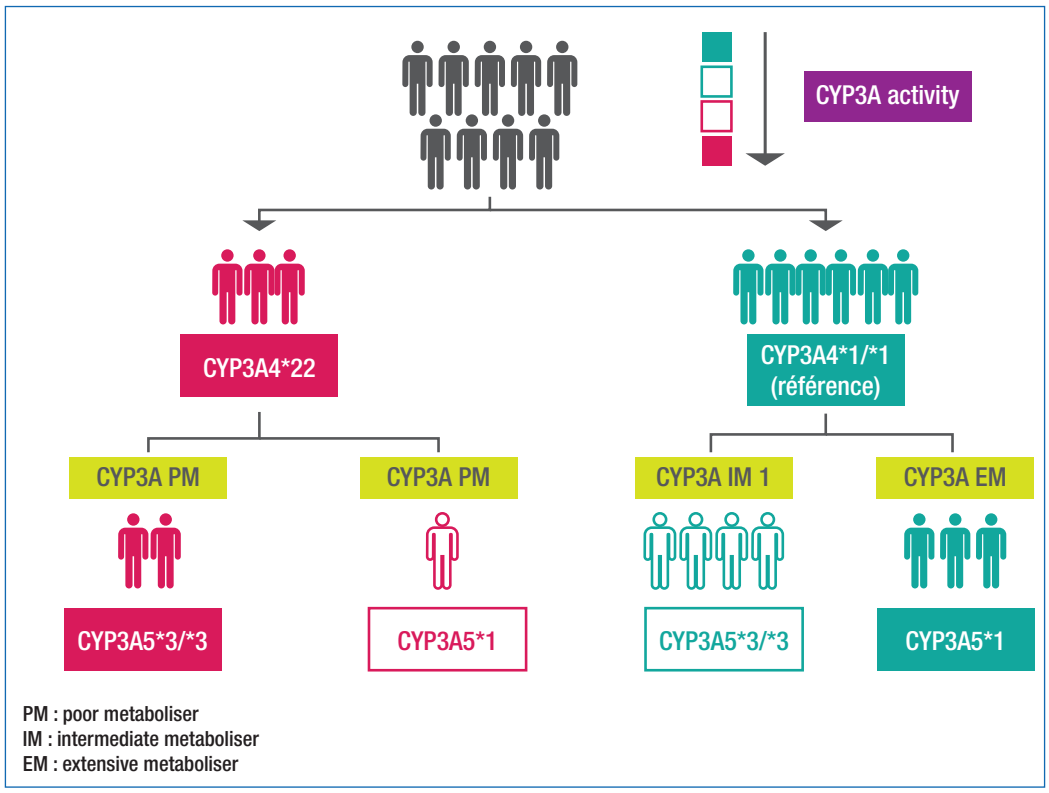
A French group led by Professor Thervet conducted a clinical trial involving pretransplantation genotyping[4]. Renal transplant recipients were randomly assigned to receive tacrolimus either according to CYP3A5 genotype or according to the standard daily regimen. The primary endpoint was the proportion of patients within the targeted therapeutic trough concentration after the administration of ten doses of tacrolimus. In the group receiving the adapted dose, a significantly higher proportion of patients had concentrations within the target range. Unsurprisingly, CYP3A5 expressors in the control group were under-dosed with the standard regimen. Patients expressing one inactive allele were in the lower therapeutic range and those expressing two alleles were above. Patients receiving the CYP3A5-adapted dose reached the target concentration range more rapidly and required significantly fewer dose modifications, which could translate into cost savings with fewer blood tests needed to measure tacrolimus levels (CYP3A5 genotyping: 78€; blood test: 32€).

However, no benefit in terms of survival of patients or grafts was observed at 3 months. A similar study by a Dutch group yielded the same results.

CYP3A phenotypes according to CYP3A5*3 and CYP3A4*22 genotypes

There are two CYP3A genes: CYP3A5 and CYP3A4. Recently, a polymorphism in CYP3A4, called CYP3A4*22, has been described. It is therefore necessary to consider both the CYP3A4 and CYP3A5 genotypes in order to identify the phenotypic group of patients. For example, a patient may be a double CYP3A4*22 and CYP3A5*3/*3 non-expressor (phenotypically, a poor metaboliser), a double CYP3A4*1/*1 and CYP3A5*1 expressor (extensive metaboliser) or belong to one of the two groups CYP3A4*22 and CYP3A5*1 or CYP3A4*1/*1 and CYP3A5*3/*3 (intermediate metaboliser) (Figure 2)[5].

Figure 2. CYP3A phenotypes as a function of CYP3A5*3 and CYP3A4*22 genotypes[6]



The existence of these phenotypic groups was not taken into account in the Thervet trial and could explain why no clinical benefit was observed. Currently, CYP3A5 genotyping is no longer widely used for adjustment of the first dose, but it is still used for patients with unusual pharmacokinetics, over or under-exposure, or unexpected drug interactions.

PHARMACOKINETICS OF IMMUNOSUPPRESSANTS, OPTIMISED THERAPEUTIC DRUG MONITORING AND TRANSFER TO THE CLINIC

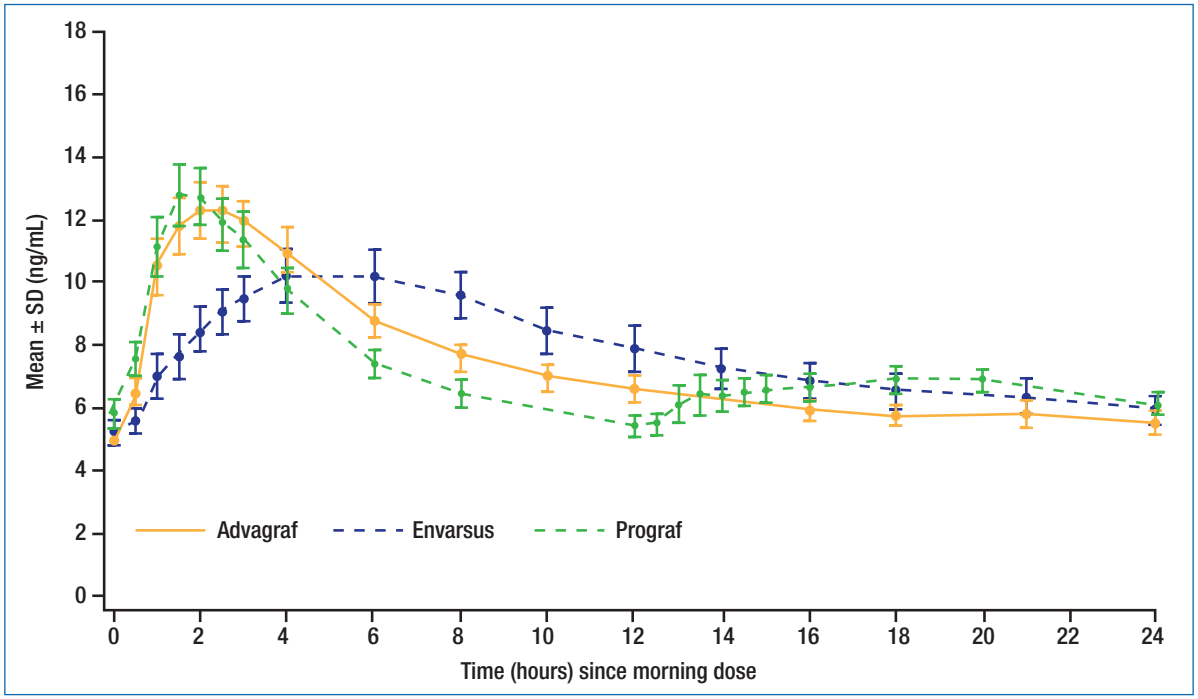
Our group has assayed immunosuppressant blood concentrations using reference methods, and then developed innovative pharmacokinetic models, conducted proof-of-concept clinical trials, and transferred these models into the clinic.

Pharmacokinetic monitoring of tacrolimus

Tacrolimus is the most widely prescribed immunosuppressive drug in transplantation. Figure 3 depicts the pharmacokinetic profiles of its three main formulations[7]. Prograf® is an immediate-release formulation whereas Advagraf® and Envarsus® are extended-release formulations.

Trough concentration monitoring is currently the most widely used method to guide the exposure index and determine the need for dose adjustments. These curves (Figure 3) show that in reality, trough concentrations reveal nothing about the very different pharmacokinetic profiles of these three formulations, and it would be preferable to measure an area under the curve (AUC) over the whole dose interval. This was stated by the 2012 European Consensus Conference[8], which recommended that the inter-dose AUC, i.e. the mean drug concentration, be used to determine the exposure index.

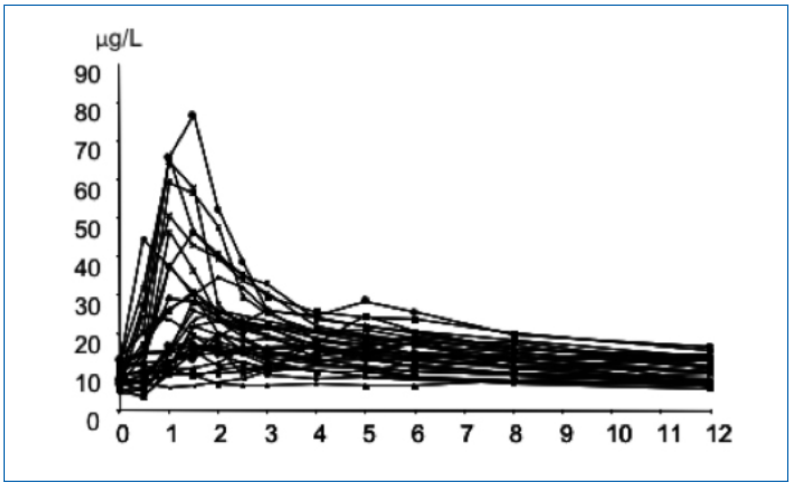
Figure 3. Normalised pharmacokinetic profile of Prograf (dose conversion: Envarsus – 30%, Advagraf + 8%)[7]



Pharmacokinetic modeling of Prograf

Figure 4 illustrates the large diversity of individual pharmacokinetic profiles for Prograf with secondary peaks after the initial absorption peak[9], which led us to design a complex pharmacokinetic model with bimodal absorption.

Figure 4. Diversity of individual pharmacokinetic profiles with frequent rebounds[9]



How, in these conditions, can drug exposure be determined and the dose adjusted accordingly? In routine practice it is not possible to take 12 blood samples to measure the AUC. We therefore used a statistical technique combined with pharmacokinetic parameters, known as Bayesian estimation, which allowed us to develop pharmacokinetic models of immunosuppressant drugs with only three sampling times: 0, 1 and 3 hours post-dose[9-11].

These Bayesian estimators can accurately estimate pharmacokinetic Prograf profiles in different patient groups, including lung transplant recipients with and without cystic fibrosis (see Figure 5) and renal transplant recipients with and without gastroparesis, i.e. slow gastric emptying (see Figure 6).

Figure 5. Bayesian estimator of AUC 0–12 h for Prograf in two lung transplant recipients with cystic fibrosis[9-11]

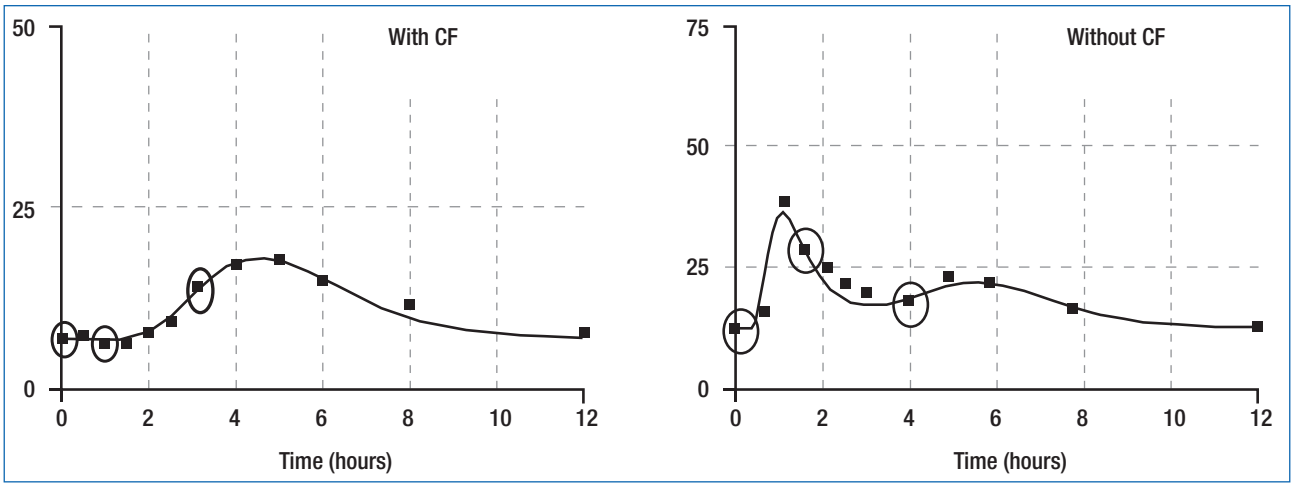
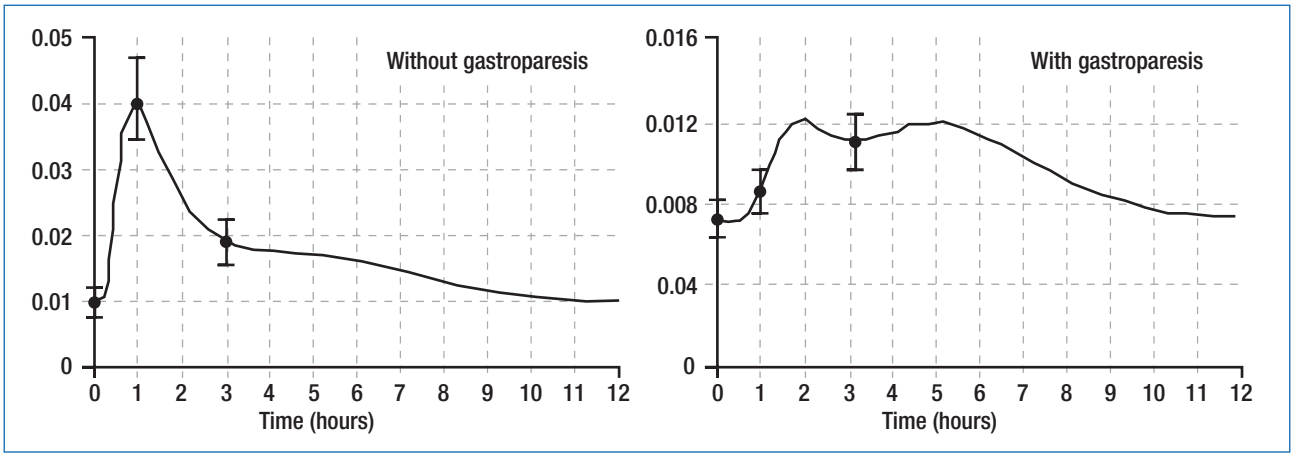


Figure 6. Bayesian estimator of AUC_{0-12h} for Prograf in two renal transplant recipients, one with gastroparesis

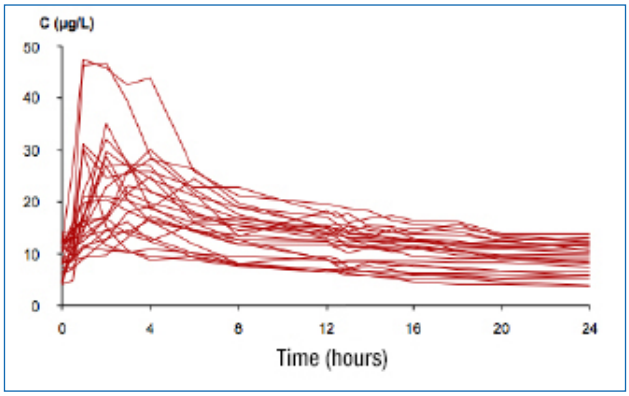


The different situations illustrate again how the measurement of trough concentrations gives only an extremely approximate reflection of drug exposure, whereas measurement of the mean concentration by the AUC gives a much more precise image.

Pharmacokinetic modeling and Bayesian estimator for Advagraf®

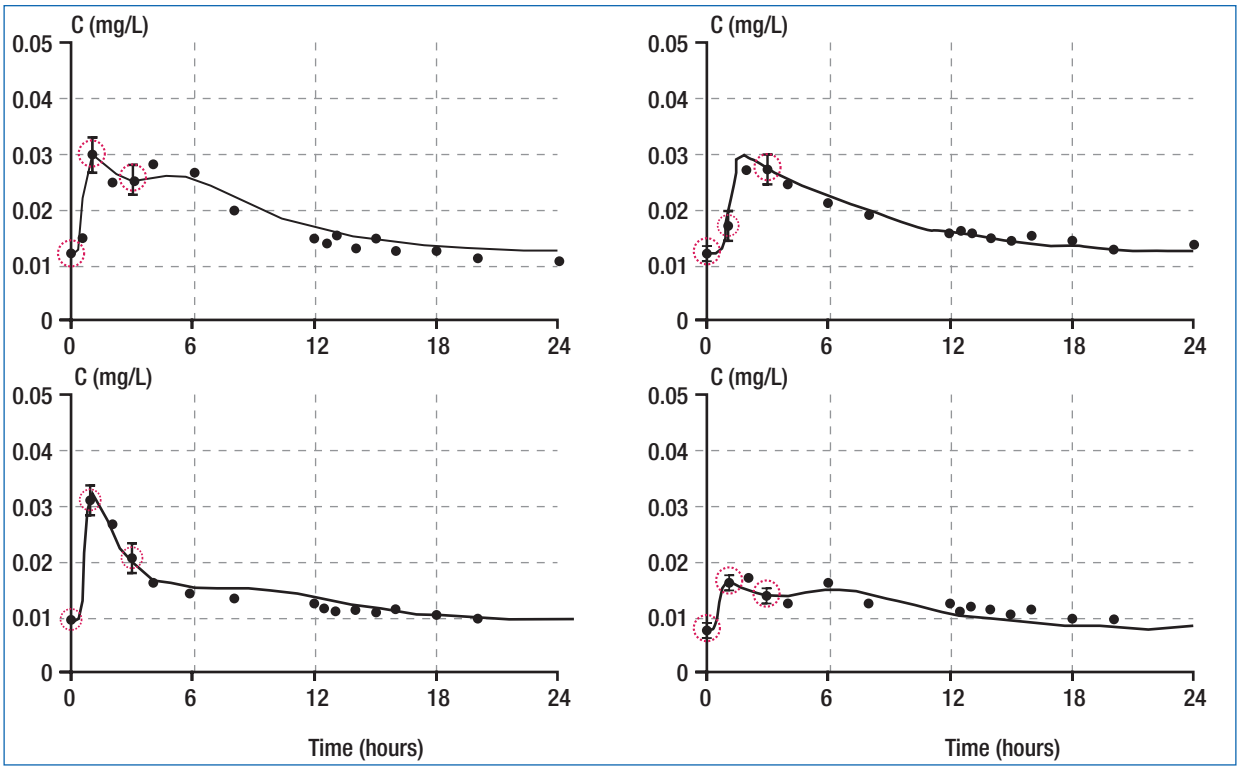
Like Prograf, the extended-release formulation of tacrolimus, Advagraf, is characterised by very wide inter-individual pharmacokinetic variability (see Figure 7)[12,13].

Figure 7. Pharmacokinetic profile of Advagraf[12,13]



With the same Bayesian estimators as for Prograf, we were able to model the pharmacokinetic profiles of Advagraf correctly from only three sampling times at 0, 1 and 3 hours post-dose (see Figure 8).

Figure 8. Bayesian estimator of AUC_{0-24h} for Advagraf: examples of different profiles[12]



Pharmacokinetic modeling and Bayesian estimator for Envarsus

Envarsus is a tacrolimus formulation with longer extended release than Advagraf and improved bioavailability. As with the other formulations, we designed a pharmacokinetic model and defined a limited sampling strategy

at 0, 8 and 12 hours post-dose. As pharmacokinetic curves were much flatter than with the other formulations, it was necessary to sample at later time points[14].

Feasibility of limited sampling strategies

The 0, 1 and 3-hour sampling strategy can be implemented with no problem at office visits or day hospital. On the other hand, the Envarsus sampling strategy at 0, 8 and 12 hours post-dose is only feasible in conventional hospitalisation.

However, the dried blood spot or DBS assay provides a practical solution to this problem: the patient collects a blood sample at home by finger prick and blots it onto filter paper, which is returned to us in a postage-paid envelope and used to measure drug concentrations. A clinical trial to validate this approach is currently in progress.

Feasibility of $AUC_{0-12\ h}$ or $AUC_{0-24\ h}$ calculations

We have created a secure web site, accessible only to healthcare professionals, which carries out these AUC calculations with limited sampling strategies. The site currently collects requests from around 140 transplant centres spread across all continents, including 70 in France. Our system, which involves validation of the results by expert pharmacologist, is able to recommend dosage adjustments for all the immunosuppressive drugs, in all types of transplantation, and in certain autoimmune diseases, with more than 200 Bayesian estimators developed over a 20-year period.

The platform proposes theoretical sampling times but the Bayesian estimators are very tolerant of schedule deviations provided that the exact times are known. For instance, if the recommended sampling times are 0, 1 and 3 hours, but the nurses can only take the samples at 0, 45 minutes and 4 hours, these changes simply have to be specified to us. The site has been in existence for 12 years, and celebrated its 100,000th request in September 2017.

CONCLUSION

A few genetic polymorphisms in the enzymes responsible for the biotransformation of immunosuppressive drugs can partly explain the pharmacokinetic and pharmacodynamic variability of these drugs.

Pharmacokinetic variability is taken into account by therapeutic drug monitoring, in particular by pharmacokinetic methods, and by individual dose adjustments. Genotyping of relevant polymorphisms (CYP3A5*3 and CYP3A4*22) has not shown an additional benefit in the ‘general’ population of transplant recipients, whether this is done pre-emptively to adjust the first dose or for subsequent dose adjustments (in particular, it does not improve the Bayesian estimator of AUC). On the other hand, it is useful to explain and understand special cases, such as very slow clearance or unexpectedly severe drug interactions.

The importance of pharmacodynamic variability (and its pharmacogenetic component) has yet to be elucidated.

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