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Chapter 5

Pharmacogenetics of Immunosuppressants in Solid Organ Transplantation: Time to Implement in the Clinic

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Abstract

Our aim in this chapter is to present the state of the art, including our own group research, in the field of immunosuppressant pharmacogenetics in the four main types of solid organ transplantation: kidney, heart, lung, and liver. The main focus will be on those findings in the field that have been widely investigated and then in those that are close to clinical implementation, mainly CYP3A5 genotyping for the adjustment of the initial tacrolimus dose. This recommendation will be discussed in more detail, explaining its clinical potential as well as its limitations. To end, a short opinion about the feasibility of implementation in the health systems as well as discussion about private companies selling pharmacogenetic tests will be presented.

Keywords: SNP, tacrolimus, pharmacogenetic-guided therapy, CYP3A5, ABCB1, precision medicine

1. Introduction

Since the first successful kidney transplantation was performed in the 1950s, great advances have been achieved in the control of immunosuppression and graft outcome, improving

drastically patient survival. Nowadays, the most common immunosupressant regimens in solid organ transplantation consist of a combination of a calcineurin inhibitor (CNI: cyclosporine [Cs] or tacrolimus [TAC]) with an antiproliferative agent such as mycophenolic acid (MPA: mycophenolate mofetil or mycophenolate sodium) or the less used azathioprine. Corticosteroids are also widely employed. Also, mTOR inhibitors [sirolimus (SIR) and everolimus (EVE)] have become common drugs in the prophylaxis of rejection after transplantation [1, 2]. Immunosuppressive agents have a narrow therapeutic index and substantial inter-patient variability, so achieving the optimal equilibrium between efficacy and an acceptable grade of toxicity is essential for the success of the treatment, and individualizing drug therapy has become an important goal.

Therapeutic drug monitoring (TDM) is indispensable for immunosuppressive agents dosing and reduces the pharmacokinetic component of variability by controlling drug blood concentrations. However, TDM is only possible after the drug is administered and steady state and patient's compliance are achieved; thus, complementary strategies are needed. The intra- and inter-patient differences in immunosuppressant dosage requirements and pharmacokinetics are attributable to several factors, such as kidney function, ethnicity, concomitant use of other drugs [3], and qualitative and quantitative changes of proteins whose activity plays key roles in the absorption, distribution, metabolism, and function of these drugs. In these last mentioned protein changes is where pharmacogenetics plays a crucial role: Functional changes of these proteins (transporters, metabolizing enzymes, target proteins, etc.) have been attributed to polymorphism in their coding genes [4, 5]. Single-nucleotide polymorphisms (SNPs) are the main type of polymorphisms involved in human genome variation. These are different alleles or variants that naturally occur at a determined position of a gene, the frequency of the less common allele in the population being not higher than 1%. For instance, in a concrete point of a determined gene, part of the population, let's say 80%, could have an adenine (A) or AA, and this would be the most frequent genotype at that genomic position, while 5% would have a thymine, being the variant and less frequent allele (TT genotype), and the rest 15% of the mentioned population would be heterozygous for the variant, AT genotype. Pharmacogenetics aims to determine the effect of those genetic variants regarding the efficacy and toxicity of drugs, and therefore, it may be able to predict patients' response to them. These genetic characteristics can be known for each single patient before the drug is administered, allowing the design of the best strategy to treat the patient, what we nowadays know as precision medicine.

In this scenario, it is also very important to take into account that in transplantation each patient actually contains two different genetic entities: the donor and the recipient. Therefore, the drugs administered to the recipient will be metabolized or excreted by the transplanted organ from the donor when we are talking about liver or kidney transplantation, respectively. But also in heart- or lung-transplanted patients, the effect of the donors' genotype could be seen if we find toxicities and/or efficacies directly related to these organs. This is the reason why more and more studies in transplantation pharmacogenetics consider both the donor and recipient genotypes to evaluate the response to treatment [6–9].

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2. The genes related to the immunosuppressants

Cs and TAC are metabolized by CYP3A subfamily in both enterocytes and hepatocytes. Cs is primarily metabolized by *CYP3A4* and in a lesser extent by *CYP3A5*, while TAC is mainly metabolized by *CYP3A5*. Both enzymes are characterized by great variations in their expression and activity caused by genetic variability but also by concomitant administration of drugs that act as inhibitors or inducers [4, 5, 10–13]. P450 (cytochrome) oxidoreductase (*POR*) has been suggested as an element that also influences *CYP3A5* activity.

The *ABCB1* gene encodes the efflux transporter P-glycoprotein (P-gp), which is responsible for the active transport and expulsion of multiple substances across cell membranes and is present in several tissues but mainly in excretory organs [14].This pump plays a major role in the pharmacokinetics of TAC and Cs. P-gp has been found to be present at high concentrations in enterocytes, and it is present in hepatocytes, kidney cells, and lymphocytes [15]. A 17% of the variability in oral clearance of Cs depends on the P-gp accounts in intestinal enterocytes [16]. In TAC, the level of *ABCB1* intestinal expression showed a strong inverse correlation with the TAC concentration/dose ratio [17]. Genotypes associated with lower P-gp function have been associated with greater drug absorption and higher blood concentration. The three most frequent *ABCB1* gene polymorphisms studied are the synonymous SNPs 1236C<T (rs1128503) and 3435C<T (rs1045642), as well as the nonsynonymous SNP 2677G<T/A (rs2032582). The variant TT genotype of these SNPs is proposed to result in decreased levels of mRNA expression and P-gp activity, although this point is still controversial.

Following administration, mycophenolate mofetil (MMF) or enteric-coated mycophenolate sodium is hydrolyzed to MPA, the active metabolite. MPA is metabolized in the liver, gastrointestinal tract, and kidney by uridine diphosphate gluconosyltransferases (UGTs). MPAG, the main metabolite, is a phenolic glucuronide, which has no pharmacological activity and is excreted into the urine via active tubular secretion and into the bile by multidrug resistance protein 2 (*MRP-2* or *ABCC2*). MPAG is de-conjugated back to MPA by gut bacteria and then reabsorbed in the colon, the so-called enterohepatic circulation pathway [18–21]. MPA acts as a selective inhibitor of inosine 5′-monophosphate dehydrogenase (*IMPDH*). Two isoforms of *IMPDH* exist and MPA is more active against type II (expressed primarily in malignant and activated lymphocytes) than against type I (predominantly found in normal, resting leukocytes) [22–25]. SNPs in these genes might affect the efficacy of MPA and therefore acute rejection in transplant patients.

Azathioprine is employed in patients with intolerance to mycophenolate as an alternative antimetabolite. This prodrug is activated to 6-mercaptopurine in the erythrocytes, and thiopurine methyltransferase (*TPMT*) is the main enzyme for 6-mercaptopurine metabolism. Described *TPMT* polymorphisms produce a decreased enzyme function and a higher risk of side effects related to the 6-thioguanine formation such as bone marrow suppression. The Clinical Pharmacogenetics Implementation Consortium has published guidelines for the clinical implementation of *TPMT* genotype analysis in patients treated with azathioprine; likewise the US Food and Drug Administration label also recommends TPMT testing [26]. One study evaluated this association in liver transplantation, and aversely, its findings suggest that

TPMT, ITPA, and *MTHFR* genotypes do not predict adverse drug reactions, including bone marrow suppression [27].

Information about genetic variations affecting SIR and EVE response is still scarce. Both drugs are metabolized via *CYP3A4, CYP3A5*, and *CYP2C8* enzymes [28] and both are P-gp substrates. EVE is used as off-label immunosuppressive therapy in lung transplantation with CNI-associated renal insufficiency, skin neoplasms, and bronchiolitis obliterans syndrome [29, 30]. As the rest of immunosuppressive drugs, SIR and EVE have a narrow therapeutic index and a significant inter- and intra-individual pharmacokinetic variability.

Glucocorticoid-induced osteonecrosis is an important adverse event affecting transplant patients, leading to severe joint pain and limitations on physical activity. Numerous studies have reported that *ABCB1* polymorphisms are associated with glucocorticoid-induced osteonecrosis, as, for instance, in renal transplant patients [31]. A recent meta-analysis suggested that some *ABCB1* alleles may decrease the risks of corticoid-induced osteonecrosis [32].

Other clinical consequences, mainly long term, of immunosuppressants are being subject to really interesting pharmacogenetic studies: tumor development, fertility impairment, or hypertension [33–35].

3. Kidney transplantation

3.1. Calcineurin inhibitors

The expression of *ABCB1* in the kidney plays an important role in the renal elimination of metabolic waste products and toxins. It seems like after renal injury, *ABCB1* expression is upregulated, which may represent an adaptive response in the renal regeneration process. Also, it has been shown that treatment with CNI induces *ABCB1* expression both in vivo and in vitro, which could serve to protect the kidney from the injurious effects of CNIs by facilitating their extrusion [36]. A decrease in *ABCB1* levels of expression could lead to intrarenal accumulation of CNIs and predispose patients to the occurrence of CNI-related nephrotoxicity [37]. Capron et al. showed in a prospective study with 96 renal transplant recipients that *ABCB1* 1199G>A, 3435C>T, and 2677G>T/A (rs2229109, 1045642, 2032582, respectively) seemed to reduce the activity of P-gp increasing TAC peripheral blood mononuclear cell concentrations. Nevertheless, the impact of *ABCB1* SNPs on TAC blood concentrations was negligible [38]. In another study conducted in Asian renal transplant recipients, *ABCB1* C3435T was not an important factor in TAC pharmacokinetics [39]. The presence of *ABCB1* 3435T variant allele in the donor was related to a higher risk of histologic kidney damage [40], maybe due to a local drug accumulation.

In the meta-analysis conducted by Terrazzino et al. [41], no evidence of an effect of the *ABCB1* 3435C>T variant was detected on TAC Cmin/D, except for a modest effect limited to the first month after renal transplantation. In contrast, another meta-analysis conducted by Li et al. [42] showed that *ABCB1* 3435C>T could influence the TAC pharmacokinetics at different post-transplant times, so subjects with wild-type genotype showed lower Cmin/D than those

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carrying variant T allele. Results of a more recent meta-analysis published in 2015 in Cs-treated kidney transplant recipients indicated a significant difference of Cmin/D and Cmax/D between 3435CC and 3435TT genotype carriers ($p = 0.03$). Subgroup analysis by ethnicity demonstrated that in Asians, Cmin/D was lower in CC versus TT genotype carriers but did not vary for Caucasian recipients. This meta-analysis showed that patients with 3435CC genotype will require a higher dose of Cs to achieve target drug blood concentrations when compared with 3435TT carriers, especially in the Asian population and especially during the early and middle time periods after transplantation [43].

A polymorphism in intron 3 of *CYP3A5* (rs776746 or *CYP3A5**3) results in altered mRNA splicing that leads to a premature stop codon and hence a nonfunctional protein [11]. So, while *3/*3 carriers do not express the enzyme (nonexpressers), individuals carrying at least one functional *CYP3A5**1 allele express the enzyme (expressers) and are able to metabolize CNIs via *CYP3A5* [12]. Our studies in Spanish Caucasian population show that although *1/*1 genotype is rare and carried by only 1% of the population, 16% of transplanted patients and donors present *CYP3A5**1/*3 genotype and might have different dosage needs than *3/*3 carriers [13].

The first studies about the relationship between *CYP3A5* and CNI dosage in transplant recipients were published over 10 years ago. In 2003 Hesselink et al. [5] reported in kidney transplant recipients receiving Cs or TAC that TAC dose-adjusted trough levels were higher in *CYP3A5**3/*3 patients than in *1/*3 plus *1/*1 patients, but found no differences in Cs-treated patients. The same year, MacPhee et al. [44] also reported a reduced exposure to TAC in the first weeks after kidney transplantation in *CYP3A5* expressers, but found no difference in the rate of biopsy-confirmed acute rejection. Haufroid et al. [10] reported in 2004 that dose-adjusted trough concentrations were threefold and 1.6-fold higher in *CYP3A5**3/*3 patients than in *CYP3A5**1/*3 patients for TAC and Cs, respectively. Since then, several studies have shown that *CYP3A5* expressers require higher TAC doses than nonexpressers to achieve the same blood concentrations [45–50]. A pharmacogenetic substudy of a randomized-controlled trial where patients were treated with TAC, MPA, and corticosteroids compared *CYP3A5* expressers with *CYP3A5* nonexpressers. TAC doses were higher for expressers, whereas dose-corrected Cmin were lower for this group. This would mean that patients expressing *CYP3A5* need more TAC to reach target concentrations and have a lower TAC exposure. However, no differences in biopsy-proven acute rejection were found [51]. Regarding graft rejection, whereas some studies have found an association with *CYP3A5* genotype [52, 53], others have not shown this [54, 55]. In the case of nephrotoxicity, results are also controversial [47, 54, 56].

The first prospective randomized-controlled trial (by Thervet et al.) to compare the pharmacokinetic characteristics of TAC in patients receiving a fixed dose of the drug or a dose adapted according to the patient's *CYP3A5* genotype showed that, in the genotype-based group, a higher proportion of patients had values within the targeted Cmin at day 3 after initiation of TAC (43.2% vs. 29.1%; $p = 0.03$); they required fewer dose modifications and the targeted Cmin was achieved by 75% of these patients more rapidly [57]. No differences in clinical outcome were found, but the study population was at low immunological risk. A later randomized-controlled trial with similar pharmacogenetic-guided TAC starting dose found no differences

between groups in the percent of patients having a TAC exposure within the target range or the incidence of acute rejection [58].

Other authors have studied the influence of donors' genotype. Opposite to liver transplantation, donors' *CYP3A5* genotype seems to have no influence in CNI dose requirements to achieve target drug concentrations [56].

Several meta-analyses have been performed. The results of a meta-analysis performed by our group suggest a significantly lower TAC dose-normalized Cmin among *CYP3A5*1* allele carriers compared with carriers of the *CYP3A5*3/*3* genotype at weeks 1 and 2 and months 1, 3, 6, and 12 after kidney transplantation. Also *CYP3A5* expressers might have higher risk of acute rejection and chronic nephrotoxicity [59]. Terrazzino et al. [41] conducted another meta-analysis in which random-effects model showed significantly higher TAC Cmin/D in *CYP3A5*3/*3* compared with *CYP3A5*1* allele carriers, either in the overall analysis and when stratifying for ethnicity or time of posttransplantation (≤1, 3–6, 12–24 months). In the meta-analysis conducted by Tang et al. [60], *CYP3A5* expressers required higher mean TAC daily doses [95% confidence interval (CI), 0.033–0.056] than nonexpressers. In Cs-treated patients, a meta-analysis also showed that *CYP3A5*3* polymorphism is associated with Cs dose-adjusted concentration in renal transplant recipients [50].

Regarding *CYP3A4*, different studies have explored the impact of *CYP3A4*1B* on CNI pharmacokinetics. Gervasini et al. found that carriers of the *CYP3A4*1B* variant allele showed TAC Cmin that were on average 59% lower than in patients with the *CYP3A4*1/*1* genotype. Furthermore, among *CYP3A5**1 carriers, those also carrying the *CYP3A4*1B* allele showed the lowest dose-corrected Cmin, as compared with *CYP3A4*1*/*CYP3A5*3* carriers [61]. Other studies have shown the influence of this variant in TAC and Cs pharmacokinetics [46, 62], but results are still inconsistent [63, 64]. This variant has been reported to lead, in vitro, to increased transcription of the gene [65], but several authors attribute its observed effects to the fact that *CYP3A4*1B* is in strong linkage disequilibrium (LD) with the *CYP3A5*1* active allele, meaning that very frequently they are carried together. This could explain the inconsistencies of the reported associations with Cs and TAC pharmacokinetics, if only one of those two SNPs is addressed [1, 2]. Another functional SNP, located in *CYP3A4* intron 6 (*CYP3A4*22*, rs35599367, C>T), has been found associated with decreased mRNA hepatic expression and therefore decreased enzymatic activity and has also been correlated with the statin dose requirement for lipid concentration control [66]. This SNP was associated with altered TAC and Cs metabolism and dose-adjusted Cmin were higher for *22 carriers in a study carried out in 99 stable renal transplant recipients [67]. This difference was even higher when combining *CYP3A4*/*CYP3A5* poor metabolizer genotypes, for both TAC and Cs, and was reproduced in 185 kidney transplant recipients treated with TAC [68].

POR has been suggested as an element that influences *CYP3A5* activity. Carrying *28 allele was associated with increased dose of TAC in kidney transplant recipients. And an association for a higher daily dose requirement was found only in *CYP3A5* expressers [69]. Another study showed that *POR*28* allele is associated with increased in vivo *CYP3A5* activity for TAC in *CYP3A5* expressers, whereas *POR*28* homozygosity was associated with a significant higher CYP3A4 activity in *CYP3A5* nonexpressers for both TAC and Cs [70]. But other studies have

not replicated these results [71–73]. Also *POR*28* allele has been associated with increased risk of diabetes mellitus in patients treated with TAC [74].

Transplant patients receive a large number of drugs and the effect of concomitant drugs is important. Gastric protection is very common in transplant recipients. We conducted a study in 75 renal transplant recipients treated with TAC and omeprazole. This drug is mainly metabolized via *CYP2C19* and secondarily by *CYP3A4/5*. In patients carrying a nonfunctional *CYP2C19* variant, omeprazole inhibits TAC metabolism via *CYP3A5*, increasing TAC blood concentrations. The patients with *CYP2C19*2/*2* genotype showed a median posttransplantation hospital stay of 27.5 days (95%CI: 23–39), compared with 12 days (95%CI: 10–15) in patients with *CYP2C19*1/*1* or *1/*2* genotype. In the group of *CYP3A5* nonexpressers (expressers were excluded to avoid its influence), there was a direct correlation with an increase in Cmin/D TAC blood levels and *CYP2C19*2/*2* genotype, which also showed allograft delayed function (acute tubular necrosis in 3 out of 4 patients). So *CYP2C19*2/*2* variant indirectly elicits an increase of TAC blood levels in *CYP3A5* nonexpressers and may lead to adverse events [3].

3.2. mTOR inhibitors

CYP3A5 genotype might explain part of the variability in SIR drug levels. In a few studies, *CY3A5* expressers showed increased dose requirements to achieve adequate blood trough levels of SIR in people with kidney transplantation as compared to *CYP3A5*3/*3* genotype. Also, *CYP3A5*3/*3* was associated with decreased metabolism of SIR and higher blood levels [75–77].

A study also showed that *CYP3A4*1B* carriers may require an increased dose of SIR as compared to patients with the *1/*1 genotype [75]. Preliminary data demonstrated that human liver microsomes carrying *CYP3A4*22* metabolized SIR at a significantly slower rate than noncarriers [1]. *ABCB1* genotype does not seem to be of relevance for mTOR inhibitor therapy, although patients with the CC genotype in 3435C>T or 1236C>T may have decreased total and low-density lipoprotein cholesterol when treated with SIR, as was shown by Sam et al. [78].

3.3. Mycophenolic acid

Several studies have reported the role of SNPs in the promoter region of *UGT1A9* in MPA pharmacokinetics and the risk of rejection, including gain of function SNPs -275T>A (rs6714486) and -2152C>T (rs17868320) [79]. Van Schaik et al. [80] showed in a study including 338 kidney transplant recipients that *UGT1A9* -275T>A and -2152C>T SNPs were associated to lower MPA exposure in patients receiving TAC and corticosteroids plus MMF. Additionally, in this study *UGT1A9*3* was associated with higher MPA exposure when MMF was given in combination with CNIs. In another study including 133 stable Caucasian renal transplant recipients, promoter SNPs -275T>A and -2152C>T were associated with lower MPA exposure, and additionally the carriers of these SNPs had higher incidence of gastrointestinal side effects [81]. *UGT1A8*3* and *UGT1A9*3* might influence MPA pharmacokinetics but occur with a very low allele frequency (<5%), so their clinical impact is limited [82]. *UGT1A8*2* might also be associated to less adverse gastrointestinal adverse events. *UGT2B7* has also been postulated

as a candidate biomarker of MPA pharmacokinetics, but no relevant results have been found yet.

Regarding *ABCC2*, MPAG is excreted in bile primarily by this transporter and this transport is essential for the enterohepatic circulation. *ABCC2* -24C>T (rs717620) has been associated with lower MPA clearance in patients with concomitant treatment with TAC [83]. *ABCC2* 1249G>A (rs2273697) was also related to higher MPA metabolite levels [84].

MPA is also substrate of organic anion-transporting polypeptides (OATPs), which are responsible for the entrance of MPA and MAPG into hepatocytes. This has been observed in vitro [85], but in vivo results are still contradictory [85–87]. Picard et al. [85] observed that the pharmacokinetics of both MPA and MPAG were significantly influenced by the *SLCO1B3* polymorphism 334T>G/699G>A in 70 renal transplant patients receiving combination treatment of MMF with either TAC or SIR, but not in 115 patients receiving MMF and Cs. Miura et al. [87] found a significant association between MPA excretion into bile and *SLCO1B3* 334T>G. The organic anion transporter polypeptide-1B1 (SLCO1B1) is involved in the liver uptake of MMF. In renal transplantation, the minor allele of SLCO1B1 (rs4149056) polymorphism was associated to lower MPA clearance than wild-type genotype, because this genotype reduces drug uptake [88].

The association of SNPs in IMPDH with MPA is not clear. *IMPDH1* rs2278294 allele T was found associated with decreased risk of biopsy-proven acute rejection [22, 89], but this was not found in other studies [23, 90]. Regarding *IMPDH2* rs11706052, allele G carriers who are treated with Cs and MMF may have an increased risk of biopsy-proven acute rejection and decreased response [82], but several other studies have not confirmed this association [24, 25].

4. Heart transplantation

Heart transplantation has experienced a great improvement in the last years. Survival among cardiac transplant recipients is estimated to be 83% 5 years posttransplantation as a result of improvements in immunosuppressant treatments, surgical technique, and reduction of adverse events [91, 92]. Nevertheless, still a considerable number of patients experience morbidity and mortality after transplantation. These outcomes could be related to genetic variability in genes that encodes transporters, metabolizers, or molecular targets of immunosuppressant therapy.

4.1. Calcineurin inhibitors

Most of the published studies analyzed the relationship between *ABCB1* polymorphisms and CNI pharmacokinetics. Regarding TAC, some studies found a relationship between wild-type *ABCB1* genotypes and reduced drug blood levels during the first 2 weeks after transplantation in adult patients [7] or after 6 and 12 months after transplantation in pediatric population [93]. However, several other studies did not find significant results [94–97]. Cs is also substrate of P-gp, and there are numerous reports of lesser cyclosporine blood concentrations with wild-

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type *ABCB1* genotypes [7, 97–100], although again other authors did not obtain significant differences [96]. The inconsistent influence of *ABCB1* genotypes on CNI therapies may be due to unique genetic populations or small sample size.

High CNI levels are related to the appearance of nephrotoxicity. Most of the studies did not detect association between *ABCB1* variants and renal function [95, 100–104]. On the other hand, in one of our last works, we obtained lower renal function in patients with AG genotype of a rarely studied polymorphism of *ABCB1* (rs9282564), related to higher Cs blood concentrations [97]. Besides, *ABCB1* wild-type genotype of 1236C<T SNP was correlated to lower risk of serious infections and lower Cs blood levels. Wild-type homozygosity for the 3435C<T and 2677G<T/A SNPs has been associated to increased steroid dependency after 1 year of heart transplantation in pediatric patients treated with TAC [105, 106], but this effect was not reproduced in a larger adult cohort of 337 patients with Cs therapy [100]. Wild-type genotypes of 3435C<T and 2677G<T/A were also correlated to higher risk of graft rejection in a large cohort of 170 adult recipients [107], although in smaller cohorts these effects were not reproduced [94, 100]. Other outcomes studied with these SNPs were new-onset diabetes [95] and plasma lipid concentrations [108]. Of these outcomes only higher LDL cholesterol pretransplant values were related to variant alleles of *ABCB1*, but this association was lost after transplantation.

The differences in TAC blood levels regarding the already explained CYP3A5 variants *1 or *3 were clearly observed in adult heart transplantation [95, 96, 98, 109, 110] and also in children [93, 94, 111]. However with Cs it was only described in our small cohort of 25 adult heart transplant patients, in which the CYP3A5*3/3* variant was associated to an increase in trough blood levels corrected by dose and body weight [98]. These results were not reproduced in two other similar studies (30 and 45 adult heart recipients) [96, 99].

Age and *CYP3A5* genotype were related to TAC concentration/dose ratio and dosing requirements in pediatric cardiac transplant population [94]. This was reflected in *CYP3A5* expressers, because when they were older than 6, the dosing requirements were more than 1.5 times lower than in *CYP3A5* expressers younger than 6 years. Besides CNI clearance, *CYP3A5*1* carriers were associated to higher estimated glomerular filtration rate after heart transplantation in a cohort of 160 adult recipients treated with TAC or Cs [102]. Other studies in cohorts of 53 and 60 adult cardiac transplants and 39 and 453 pediatric cardiac recipients did not find significant relationships between *CYP3A5* genotypes and renal outcomes [94, 97, 101, 103]. A study in a large cohort of 115 adult heart recipients did not find associations between CNI nephrotoxicity and *CYP3A5* genotypes, but it showed significant relationship with posttransplant kidney function in *CYP3A5*3/3** and *CYP2A6* (rs28399433) variants in European Americans (subgroup of 99 recipients) [104]. Other outcomes as steroid dependency, graft rejection, and risk of developing new-onset diabetes after transplantation were studied without significant relationships [94, 95, 106].

A study in 60 pediatric heart transplant recipients investigated the combined effect of *CYP3A5* and *CYP3A4*22* (rs35599367) [111]. *CYP3A* poor metabolizers (*CYP3A5*3/3* and CYP3A4*1/*22*) required 17% less TAC than intermediate (*CYP3A5*3/3* and CYP3A4*1/*1*) and 48% less than extensive metabolizers (*CYP3A5*1/1* or CYP3A5*1/3* and CYP3A4*1/*1*). This study also obtained similar effects with *CYP3A4*22* allele carriers alone in number of TAC doses to reach

target concentrations, but not in TAC concentrations and the dose-adjusted concentration. However, a later study in adult cardiac transplant patients treated with TAC (52 patients) or Cs (45 patients) did not find significant associations with *CYP3A4*22* variants [96] but showed that *POR*28* variant carriers had higher dose-adjusted TAC concentrations 3 and 6 months posttransplantation. This variant had previously been studied in kidney transplantation combined with *CYP3A5* expressers [112–114], with a contradictory effect compared to this effect in heart transplant recipients. Another *CYP3A* modulator is the pregnane X receptor encoded by *NR1I2* gene, whose SNP rs3814055 was studied by Lesche without changes in TAC clearance [96].

Other different CYP enzymes were studied in heart transplantation. *CYP2C8* and *CYP2J2* are expressed in the kidney and are involved in the metabolism of arachidonic acid–promoting kidney homeostasis. The *CYP2C8*3* variant was associated with a higher risk of nephrotoxicity in liver recipients treated with TAC or Cs [115]. In heart transplantation, *CYP2C8* variants were studied in a small cohort of 30 patients treated with maintenance therapy (Cs, EVE, prednisolone) and there were no differences in EVE dose requirements between *CYP2C8* genotypes [116].

4.2. mTor inhibitors

A report in adult heart recipients suggested that EVE blood levels were not related to *ABCB1* genotypes. No significant associations between *CYP3A5* poor expressers and EVE pharmacokinetics were observed either [110, 117]. *CYP2C8* variants were also studied in a heart transplantation cohort of 30 recipients without significant differences in EVE pharmacokinetics [116].

4.3. Mycophenolic acid

In pediatric heart transplantation, the gastrointestinal intolerance was reproduced with variant allele of *ABCC2* rs717620, causing MMF discontinuation [118]. Other toxicities associated to *ABCC2* SNPs were anemia (rs3740066) and leucopenia (rs17222723) [119].

Regarding serum levels of MPA and their metabolites, a study did not obtain significant relationships with *ABCC2* polymorphisms (34Ting LSL 2010). In a large pediatric cohort of 290 heart recipients, wild-type *ABCC2* (rs717620) genotype was correlated to higher risk of graft rejection and late rejection, both with hemodynamic compromise [120].

The influence of *UGT* SNPs on MPA plasma concentrations is moderate and must be analyzed along with *ABCC2* and *ABCB1* polymorphisms. In a cohort of 68 thoracic transplant recipients (36 lung and 32 heart transplants), two variants of *UGT2B7* (rs7439366 and rs73823859) and acyl-MPA glucuronide levels were associated in both cohorts [119]. In this study, two variants of *UGT2B7* (rs7668258 and rs73823859) showed a significant influence in thoracic graft rejection, as well as *UGT1A7* variant rs11692021 with anemia and *UGT* 3′UTR T1813 variant with leucopenia.

The presence of polymorphisms in IMPDH1 and IMPDH2 genes does not result in lower activity in all cases [121]. In a cohort of 59 pediatric cardiac transplant, two variants of IMPDH1

(rs2278294 and rs2228075) were associated to greater gastrointestinal toxicity [122]. On the other hand, this study also found that variant G of IMPDH2 (rs11706052) polymorphism was related to neutropenia that required dose holding. A posterior haplotype analysis repeated the association of IMPDH1 to gastrointestinal intolerance but this was not greater than individual IMPDH1 polymorphisms [122].

4.4. Azathioprine

In heart transplantation, heterozygotes for TPMT SNPs (rs1142345, rs1800460, rs1800462) were shown lower enzyme activity and earlier and higher rejection than wild-type genotypes, although without changes in leukopenia incidence [123].

4.5. Other genes: the immunomodulatory pathway

The immune response and acute transplant rejection could be influenced by cytokines and growth factors; hence regulating cytokine production is a strategy to minimize rejection. Of these, the most studied in heart transplantation is the transforming growth factor- ß1 (*TGF-ß1*), because this inductor of the collagen has profibrotic activity during the progression of glomerulonephritis, consequence of CNI nephrotoxicity. Polymorphisms in the *TGF-ß1* promoter region produced a reduction of *TGF-ß1* level [124]. In a large cohort of 237 cardiac transplants, the presence of variants of two *TGF-ß1* polymorphisms (rs1800470 and rs1800471) was associated to CNI-induced end-stage renal failure [125]. However, in two smaller cohorts and a larger pediatric cohort, these two SNPs were not related to renal outcomes [101, 103, 126]. Other polymorphisms included in one of these studies an SNP in the protein kinase C-β gene (*PRKCB*; rs11074606), a gene implicated in the renin-angiotensin-aldosterone intracellular signaling, was related to posttransplant estimated glomerular filtration rate [126].

Polymorphisms in cytokine genes (*TNF-α, TGF-ß1, IL-10, IL-6, and INF-γ*) were also analyzed regarding steroid dependency. Of these SNPs, only *IL-10* polymorphisms (rs1800896, rs1800871, rs1800872) were associated as independent risk factor with steroid dependency at 1 year after heart transplantation [106]. In a large multiethnic cohort of 300 pediatric cardiac transplant patients, acute rejection at 5 years was related to the combination *VEGF* high (rs699947, rs833061, rs2010963), *IL-6* high (rs1800795), and IL-10 low (rs1800896, rs1800871, rs1800872) expression genotypes, but not with *TNF-α* (rs1800629) [127].

The nucleotide-binding oligomerization domain containing 2 (*NOD2/CARD15*) encodes a protein involved in intracellular pathogen recognition and lymphocyte activation. In our latest study we observed a tendency of association between CC genotype in NOD2/CARD15 (rs2066844) and increased graft rejection [97].

A new gene that was studied in heart transplantation was the connective tissue growth factor (*CTGF*), whose expression has been shown to be induced in in vitro models of chronic heart allograft rejection. Carriers of the C allele of rs6918698 SNP were associated to high risk for the development of cardiac allograft vasculopathy, a surrogate marker for chronic rejection [128].

5. Lung transplantation

Lung transplantation has become an alternative option for a variety of end-stage pulmonary diseases, including cystic fibrosis, idiopathic pulmonary fibrosis, pulmonary arterial hypertension, bronchiolitis, or advanced chronic obstructive pulmonary disease. Hardy performed the first human lung transplantation in 1963 but the recipient survived only 18 days. In the 1980s, the introduction of Cs generated renewed interest in this area, and in 1986, Dr Joel Cooper reported the first successful single lung transplant. Since the early 1990s, more than 30,000 lung transplants have been performed around the world.

The increasing success of thoracic transplantation is largely attributable to the development of effective immunosuppressive regimens. However, it remains as one of the solid organ transplant with the worst outcomes, with less than 80% 1-year survival and less than 70% after 3 years [129]. Several reasons for these poor results have been identified; some of them are shared with other solid organ transplants, including acute rejection and drug treatment toxicity. Lung-transplanted patients are a particularly difficult group to study: Immunosuppressive treatment variations and the way they are administered (intravenous and oral) during the first weeks post transplantation make changes in blood concentration difficult to evaluate. On the other hand, patients with cystic fibrosis, one of the main groups of lung transplantation patients, present high absorption variability, leading to lower immunosuppressive drugs blood levels [130]. It should be noticed that most of the lung transplant studies have not considered this variable in their analyses, potentially leading to erroneous results. This complexity has made this group of patients less studied than other groups such as heart, liver, or kidney transplantation. However, some relevant findings have been published.

Contradictory results have been reported regarding the effect of *ABCB1* polymorphisms on TAC disposition in lung transplantation. Wang et al. [131] reported an association between *ABCB1* haplotype and TAC blood concentration. This result has been replicated in subsequent studies [132]. However, other authors have not found this relationship [5, 45]. It should be noticed that these two studies did not considered the concomitant effect of *CYP3A5* genotype, which has shown to have important effects in this group of patients [133].

Initial studies have demonstrated a positive association between TAC dosing and the CYP3A5 gene polymorphism in heart and adult lung transplant patients [5, 131]. The CYP3A5 *3/*3 nonexpresser patients have a higher TAC level/dose than the CYP3A5 *1/*1 or *1/*3 enzyme expressers. Several authors have recommended that CYP3A5 expressers should initially get double dose of TAC than the administered to CYP3A5 nonexpressers [44], but this proposal should be tested thoroughly in lung transplantation before initiation in clinical practice.

No relevant information related to SNP variations and MPA concentrations in lung transplantation has been published. In a 51 patients study, we found that those patients with heterozygous at *ABCC2* rs3740066 had lower MPA blood concentrations than homozygotes [132]. However, large study sizes are needed to confirm these results.

Schoeppler et al. [134] in 65 lung transplant recipients did not find associations between several polymorphisms, in genes including *ABCB1, CYP3A5, CYP3A4, CYP2C8*, and EVE blood

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concentration. The author concluded that genotyping lung transplantation patients for these polymorphisms is unlikely to be helpful for clinicians in optimizing EVE therapy. However, the small number of patients included makes necessary new studies to confirm this hypothesis. In the last years, SIR has been introduced as an alternative immunosuppressive therapy for lung transplantation patients [135, 136], but still no information has been reported about pharmacogenetics of this drug in lung transplantation.

The process of chronic rejection is a pathologic process very different to acute rejection, and almost all lung transplant patients at 4 years posttransplantation have some evidence of chronic rejection [137]. Whether the chronic rejection process either directly or indirectly involves P-gp is unknown but is a possibility worth to be explored.

Budding et al. [138] found an association between complement regulatory gene *CD59* polymorphism and the pathogenesis of acute rejection in lung transplantation. *HLA-G* haplotypes have also been associated with increased graft survival and decreased rejection episodes in lung transplantation [139]. NOD/CARD15 has been related with graft organ survival outcomes of transplanted patients [140, 141], but information in lung transplantation is scarce.

6. Liver transplantation

The concept that a single gene polymorphism could affect patient survival in a complex patient population is difficult to conceive. However, a study by Hashida et al. [142] suggested that patients who had high amounts of *ABCB1* mRNA had a significantly poorer patient survival than the patients with low amounts of *ABCB1* mRNA. Patients with the *ABCB1* 2677GG, 1236 CC, and 3435CC genotypes would have greater function of the drug transporter associated with lower TAC bioavailability and level/dose ratio, but the evidence remains uncertain. Some studies in Caucasian patients [143, 144] have not reported association between both variables; however a meta- analysis reported a significative association between ABCB1 C3435T and C/D ratio TAC, although with a low quality of evidence [145]. Other *ABCB1* polymorphisms do not seem to relevantly influence TAC pharmacokinetics.

In summary, there is not sufficient information to support prospective clinical trials about TAC dosing based only in these polymorphisms, but they may be good candidates for combined analyses of polymorphisms affecting the inter-individual variability in TAC pharmacokinetics among *CYP3A5* expressers.

6.1. Influence of donor versus recipient genotype

Pharmacokinetic studies in liver transplant recipients are complex due to the fact that the recipient's intestinal genotype and the donor liver genotype may act together influencing the overall drug disposition. Several studies have evaluated the effect of donors and recipients *CYP3A5* 6986A>G. They had showed that nonexpresser recipients grafted with *CYP3A5* nonexpresser donors had the largest TAC C/D ratio and this genetic effect changed over time

since transplantation [146–149]. These results suggest that the organ influencing TAC disposition may change from the native intestine (recipients) in the early phase following transplantation to the graft liver (donors) in the stable phase, when the transplanted organ has gained the recovery of metabolic function.

In view of this and many more studies published through the years, there is enough evidence to carry out studies to assess the prescription of TAC based on both the donor and the recipient *CYP3A5* genotype [150]. The recipient *ABCB1* and donor *CYP3A5* genotypes may also act together in overall drug disposition. Previous studies have evaluated the effect of recipients' *ABCB1* C3435T or G2677T/A genotype and graft *CYP3A5* genotype. We published a meta-analysis [151] showing that donors with *CYP3A5* nonexpresser genotype had a TAC blood C/D ratio (concentration normalized for daily dose received on a body weight basis) 1.3 to 2 times higher than *CYP3A5* expressers, during the first month after transplantation. When the C/D ratio was analyzed with regard to the recipient genotype, this polymorphism variant also affected the pharmacokinetics, although its effect was less pronounced (1.1 to 1.4 times higher). The quality of evidence was at least moderate.

Regarding *CYP3A4*, its association with the TAC dose requirement or trough dose-adjusted concentrations has not been demonstrated. Recently a study in renal transplantation reported that only a significant influence of *CYP3A4*22* on Cs pharmacokinetics was found, but this effect is not high enough to justify dose modification based on *CYP3A4*22* [152]. There are not similar studies in liver transplantation, and current knowledge about this polymorphism does not justify the genotyping of this SNP to assist in selecting the best initial dose.

Influence of the *CYP3A5* 6986A> G SNP on the pharmacokinetics of Cs also remains uncertain [153]. Monostory et al. evaluated the effect of donors' *CYP3A5* genotype and *CYP3A4* expression in the blood concentrations and dose requirements of CNIs in liver transplant recipients. They reported that recipients transplanted with liver grafts from *CYP3A4* low expresser donors carrying also *CYP3A5 *3 /*3* required about 50% lower dose of Cs or TAC than that of the patients with grafts from donors expressing *CYP3A4* at the normal level [154]. So, estimating a donor' s *CYP3A4* expression combined with *CYP3A5* can have predictive power regarding the recipient's medication options and may refine the immunosuppressant therapy facilitating the appropriate dosage for each individual recipient.

Influence of ABCB1 3435C> T, 1236C> T, and 2677G> T/ A SNPs on the pharmacokinetics of Cs remains uncertain, with inconsistent results to date. Higher Cs exposure at a given dose was found in liver transplant recipients with the 3435CT heterozygous variant genotype compared with the 3435CC wild-type genotype [155]. However, other studies reported contradictory results. Jiang et al. [156] conducted a meta-analysis and they failed to demonstrate a correlation between *ABCB1* C3435T and pharmacokinetics of cyclosporine.

Respect to the combined effect of CYP3A5 and ABCB1 polymorphism in donors and recipients regarding Cs, there are no studies published to date.

No relevant studies regarding mTor inhibitors or mycophenolate pharmacogenetics in liver transplantation have been found either.

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6.2. Impact of pharmacogenetics on clinical outcomes

Acute rejection: Acute cellular rejection occurs in 20 to 35% patients during the first 2 weeks after liver transplantation. The impact of SNPs of drug transporter proteins and metabolizing enzymes needs to be further analyzed, as studies about the impact of *CYP3A5* showed controversial results [157] and no correlations have been found regarding *CYP3A4* and *ABCB1* polymorphism [158, 159]. Maybe, the efficiency on TAC routine TDM may partly abrogate the polymorphism clinical impact on drug exposure and acute graft rejection.

Acute nephrotoxicity occurs in 30 to 90% patients. It is due to vasoconstriction of the afferent arterioles, a dose-dependent and reversible effect. Its etiology had been associated with relatively higher systemic exposure to CIs, but recent studies could not confirm this association, which could explain why the evidence does not support an effect of *CYP3A4*, *CYP3A5*, and *ABCB1* on this clinical outcome.

The improvement of the outcome and survival of liver transplant patients has been associated with the occurrence of long-term chronic complication. One of them is chronic nephropathy, whose frequency is higher than in other solid organ transplants (5-year cumulative incidence of 20–37%) [160]. The main cause is local renal exposure of CNIs or their metabolites in kidney tissue, which is not necessarily associated to the CNI blood level [161]. Some studies have linked the inter-individual variability in kidney accumulation of CNIs to *ABCB1* and *CYP3A5* polymorphisms. There are two studies that detected significant association with *ABCB1* polymorphism in liver transplantation, but they have special characteristics. Hebert et al. [162] found a significant effect of *ABCB1* 2677, but the patients were treated with TAC and Cs, the latter with known increased risk of nephrotoxicity. Hawwa et al. [163, 164] found an association for the 3 *ABCB1* SNPs, albeit they studied children and did not evaluate potential confounding factors that could affect the creatinine clearance.

Respect to *CYP3A5*, Fukudo et al. [165] did not find a significant association in donors, although they only used changes in serum creatinine concentrations (and not creatinine clearance) for diagnosing chronic nephrotoxicity. Tapirdamaz et al. [166] reported that neither the *CYP3A5* 6989A>G nor *ABCB1* 3435C>T genotype of either donor or recipient was associated with risk of chronic kidney disease, but they did not consider as exclusion criteria other different causes of chronic kidney disease, so further studies are needed.

7. So, what can we actually do in the clinical practice?

After reviewing the state of the art with the most recent works published in each type of solid organ transplantation, which of all those findings does really have evidence enough to be implemented in the clinic? Currently, CYP3A5 association related to TAC dosage and metabolism is the only one classified with a level of evidence 1A by PharmGKB consortium (www.pharmgkb.org), with an actionable consequence: a dosing guideline proposed by the Clinical Pharmacogenetics Implementation Consortium (CPIC) [167]. The authors of this guideline underline that "…we are not recommending whether or not to test for CYP3A5

genotype in transplant, but we are providing recommendations on how to use CYP3A5 genotype information if it is known. Since it is typical clinical practice to achieve target blood concentrations as quickly as possible, we do recommend if CYP3A5 genotype is known, to individualize initial tacrolimus treatment using CYP3A5 genotype to guide tacrolimus dosing…" and also "Thus at present, there is no definitive evidence to indicate that genotype-guided dosing for tacrolimus affects long term clinical outcomes. However there is strong evidence to support its effect on achieving target trough whole blood concentrations, which is routine clinical practice for most centers…."

This considers that patients with at least one *1 allele (genotype GA or AA) being recipients of a kidney, heart, lung, or hematopoietic stem cell transplant and liver transplant patients where the donor and the recipient genotypes are identical, who are treated with TAC, would present lower dose-adjusted trough concentrations and decreased chance of achieving target concentrations, so they recommend to increase the starting dose 1.5 to 2 times the initially recommended starting dose (weight guided), not exceeding 0.3mg/kg/day, and then to use TDM to guide following dose adjustments. The same would apply for children and adolescents. Of course, other clinical factors influencing the treatment must be considered.

The association of *CYP3A5* rs776746 with Cs dosage and metabolism is classified with a level of evidence 2B by PharmGKB, with no further recommendations regarding genotype-guided dose adjustment.

7.1. And how can we have these analyses performed?

As in any field of knowledge that directly affects the improvement of health, even more if it deals with drug use, clinical applications arising from pharmacogenetics should be well regulated and should be given proper use. Both the patient and the doctor should be well informed of the scope and meaning of the data to be obtained. It is vital to know what we expect from pharmacogenetic analysis realistically, without creating false hopes.

In the last years, many private companies have developed "direct to consumer genetic analyses." Many of them analyze tens to hundreds of genetic variants and it seems like "the more, the better," but what can we do with that large amount of information? How do we interpret all those results? Is there enough knowledge about which is the biological meaning of each variant? And least but not last, what level of evidence does that knowledge have?

Regulatory agencies, academia, and industry agree in their worry about the alarm with regard to some proposals, which are clearly misleading for the consumer. Just a quick search on the Internet to realize that consumers can buy genotyping kits that offer scientifically implausible predictions, such as predicting vulnerability to sudden death in athletes, obesity, the ability to succeed in school, etc. The US committee SACGHS (the Secretary's Advisory Committee on Genetics, Health and Society) has issued several reports concerning this point, stressing the need to regulate this area of biomedicine to protect consumers. There are two excellent publications about Dr. J.P. Evans, illustrating the problem [168, 169].

Therefore, researchers still have a huge amount of work to do, to validate the associations proposed between certain SNPs and drug efficacy and toxicity and to discover new ones. These

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studies should finally be prospective and well designed and include the whole steps of the drug fate inside the organism, interactions, etc. and of course include accurate biostatistical and bioinformatic tools. The development of informatic tools to make pharmacogenetic results accessible and easy to interpret for clinicians is also a hot point. Only those associations with the highest level of evidence should be implemented in the clinical practice, as in our case *CYP3A5* rs776746 regarding TAC initial dosing.

8. Conclusions

The variability in solid organ transplantation therapy outcomes cannot be predicted only by clinical factors. Pharmacogenetics will help to implement personalized medicine based on patient data, clinical parameters, and genotypes. Evidences of the role of polymorphisms in some candidate genes have been established, as *CYP3A5* in pharmacokinetics of TAC, *TPMT* in clearance and toxicity of azathioprine, and possibly also *ABCB1* in CNI-associated nephrotoxicity. Besides, other genes related to immunosuppressant pathways are being studied, although their influence still has to be correctly validated. The relatively small size of some cohorts, the absence of ethnic subgroup analysis, or isolated analysis of some genes ignoring other genes that affect drug disposition could cause the inconsistent results obtained by different studies. These SNPs should be analyzed taking into consideration real biological pathways, as complete as possible, and the results should be validated in prospective studies involving larger groups of patients. Still, the biological consequences of many of the most studied SNPs seem to be the same, independently of the type of transplant studied. And also another consideration to keep in mind is the interest of studying both the donor and the recipient genotypes, again, in spite of the organ.

Certainly pharmacogenetics is already a reality in clinical application. To know about it and to understand its limits are unavoidable challenges that must be confronted by those who are responsible for the health of the population. Likewise, to establish the frames of cost-effectiveness for a feasible implementation is crucial for its real use in the clinical setting, in order to be used correctly and in a sustainable manner.

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