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Article

Pharmacogenomics of mycophenolic acid in kidney transplantation: Contribution of immune response-related genes

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Mycophenolic acid (MPA) inhibits IMPDH, involved in the guanosine nucleotides synthesis, and prevents DNA replication in immune cells. The repression of cell and humoral immunity by MPA induces allograft tolerance preventing acute rejection in solid organ transplantation. MPA is an effective and safe drug, but genetic and non-genetic factors have been implicated in the interindividual variability of drug response. Several studies have shown the impact of variants of pharmacokinetics or pharmacodynamics-related genes on MPA response in kidney transplantation. This review explored further the influence of genes involved in the immune response on clinical outcomes of kidney recipients on short- or long-term MPA treatment. Variants in genes related to T cell activation (*CD28*, *CTL4*, *ICOS*, *PDPC1*), pro-inflammatory cytokines (*IL2, IL6, IL12A, IL12B, TNF*, *IFNG*), immunomodulatory cytokines (*IL4, IL10, TGFB1*), and innate immune response (*CD14, TLR2, TLR4*) were shown to be associated with increased risk of acute rejection, graft function or survival, chronic graft nephropathy, viral infections or MPA-induced myelotoxicity. Some of the significant pharmacogenetic associations were confirmed by meta-analyses of kidney transplantation. These findings are suggestive that variants in immune response-related genes contribute to the variability of MPA response, and have potential application as biomarkers of acute rejection in kidney transplantation.

Keywords: Immunosuppressive therapy. Mycophenolic acid. Kidney transplantation. Pharmacogenomics. Immune response.

INTRODUCTION

Mycophenolic acid (MPA) is a potent antiproliferative drug prescribed broadly to prevent acute rejection in kidney transplantation. MPA is a reversible inhibitor of the inosine-5´-monophosphate dehydrogenase (IMPDH), an important enzyme involved in the *de novo* synthesis of guanosine nucleotides, which are essential for the proliferation of T and B cells (Bentata, 2020). Consequently, the depletion of the guanosine nucleotides by MPA prevents DNA replication and leads to repression of both cell and humoral-mediated immunity and induces tolerance to allograft in kidney transplantation (Staatz, Tett, 2014; Bentata, 2020; Da Silva *et al.*, 2017). MPA also reduces the recruitment and infiltration of lymphocytes and other cells into a transplanted organ, therefore reducing the inflammatory response and preventing organ rejection (Staatz, Tett, 2014). MPA is considered a safe drug but some adverse events can occur, such as gastrointestinal complications, myelotoxicity, susceptibility to infections and neoplasms (Staatz, Tett, 2014; Bentata, 2020).

Mycophenolate mofetil (MMF) and enteric-coated mycophenolate sodium salt (EC-MPS) are the prodrug forms of MPA. MPA is metabolized by

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UDP-glucuronosyltransferases (UGT) into MPA phenyl (MPAG, inactive) and acyl (AcMPAG, active) glucuronides, which are eliminated mainly in the urine (Kiang, Ensom, 2018; Ferreira *et al.*, 2020). Genetic and non-genetic factors influence the pharmacokinetics and pharmacodynamics of MPA, and it has been suggested to monitor MPA plasma levels to reduce the interindividual variability of its immunosuppressive response (Kiang, Ensom, 2018; Ferreira *et al.*, 2020).

The contribution of pharmacogenomics in the response to immunosuppressive drugs has been widely investigated. Several clinical studies have reported the influence of gene polymorphisms on the efficacy and safety of MPA suggesting their potential contribution in the management of transplant patients. Most of these studies approached the influence of pharmacokinetics and pharmacodynamics-related genes on MPA response in different populations (Zaza *et al.*, 2015; Genvigir *et al.*, 2017; Guo *et al.*, 2018; Li *et al.*, 2018; Genvigir *et al.*, 2020).

Mediators of the immune response, such as co-stimulatory molecules, cytokines and receptors, innate immune system and others, have been proposed to play important roles in immunologic tolerance of organ solid transplantation. Polymorphisms in genes involved in the immune response have been proposed as predictive factors of clinical graft outcomes in kidney transplantation (Stojanova, Pouché, Picard, 2016). This review explored the pharmacogenomic studies focused on immune response-related genes in kidney transplantation and the main clinical outcomes.

GENES RELATED TO T CELL ACTIVATION

T cell-mediated immune response plays an important role in immunological tolerance and allograft survival (Da Silva *et al.*, 2017). T cell activation is modulated by co-stimulatory molecules, including CD28 and inducible costimulatory (ICOS), as well as by negative regulators, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PDCD1, PD-1). Variants in genes encoding these molecules were proposed to contribute to acute rejection and other allograft outcomes (Stojanova, Pouché, Picard, 2016).

A previous excellent review explored genetic polymorphisms in the immune response, and discussed their correlation with delayed graft function (DGF), acute rejection (AR), chronic graft nephropathy, graft survival and other clinical outcomes in kidney transplantation (Stojanova, Pouché, Picard, 2016).

CD28, *ICOS*, *CTLA4* and *PDCD1* are the most studied genes involved in T cell activation (Figure 1), and the studies that reported significant influence on MPA-related clinical outcomes in kidney transplantation are shown in Table I.

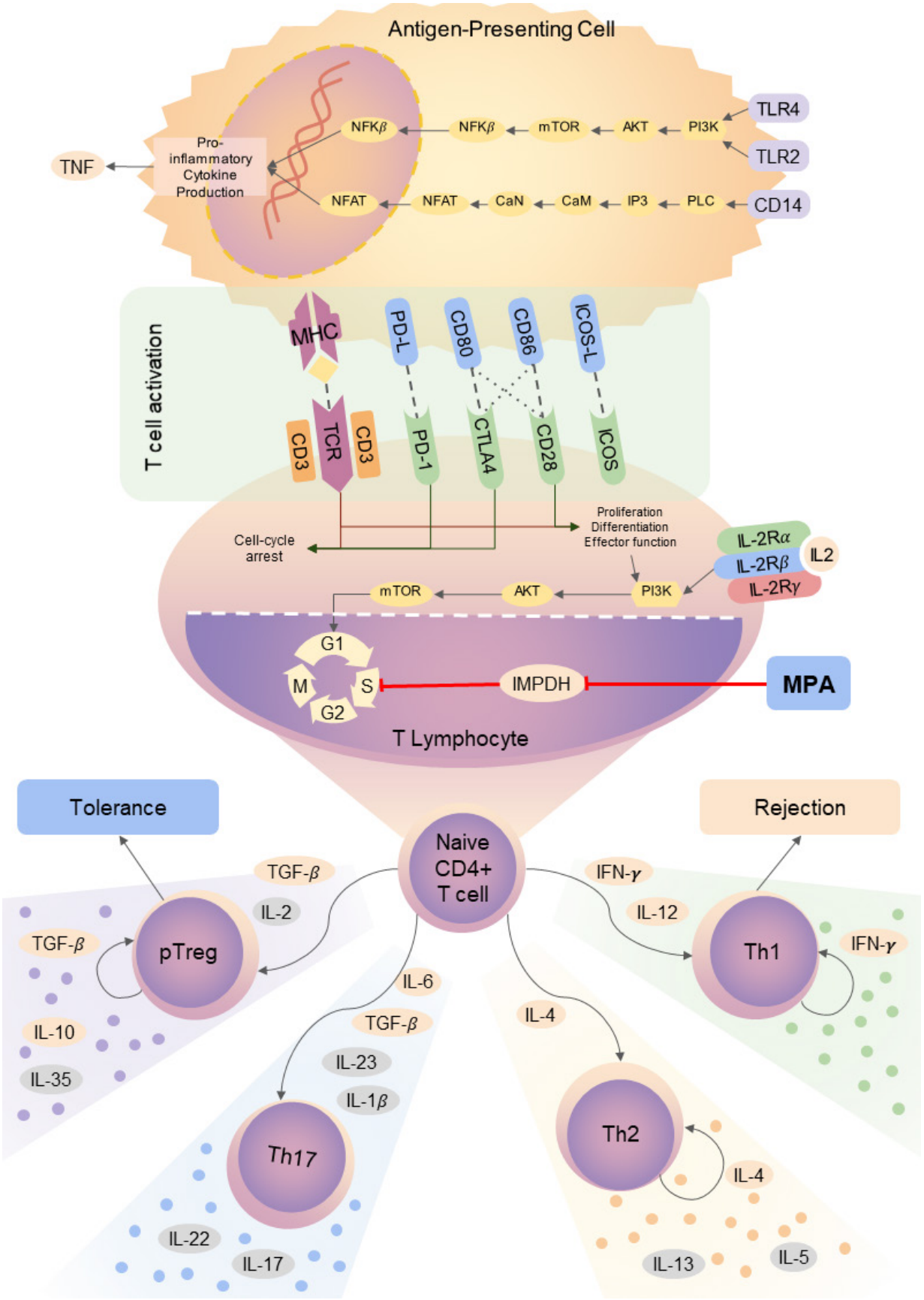

FIGURE 1 - Schematic representation of immune response-related genes involved in kidney transplantation.

TABLE I - Genes related to T cell activation in kidney recipients on MPA therapy with significant associations

Gene	Variant	Study Population	ISS regimen (follow-up)	Clinical outcomes[a]	Reference
CD28	rs3116496 (17T>C, c.243+17T>C)	270 adults (Poland)	MMF, CsA, CS (2 y)	17C: High Risk of AR	Pawlik *et al*., 2014
ICOS	rs10183087 (c.*2A>C) rs4404254 (c.*964T>C) rs10932037 (c.*1024C>T)	678 adults (Finland)	MMF, Tac, Aza, CsA, CS (8 y)	c.*2A and c.*964T: DGF or graft non-function c.*1024T: Low graft survival	Haimila *et al*., 2009
CTLA4	rs733618 (c.-1722T>C) rs4553808 (c.-1661A>G) rs5742909 (c.-318C>T), rs231775 (c.49A>G, p.Thr17Ala) rs3087243 (CT60G>A, c.*1148+236G>A) rs11571317 (c.-658C>T) rs16840252 (c.-1147C>T) STR (AT)n L>H	63 adults (Venezuela)	MMF, CsA, CS (3 y)	c.49G: High risk of AR	Gendzekhadze *et al*., 2006
		314 adults (Poland)	MMF, Tac, Aza, CsA, CS (5 y)	c.49AA/LL haplotype: Long-term graft function (eGFR).	Kusztal *et al*., 2010
		167 adults (China)	MMF, Tac, CsA, CS (6 m)	c.49G, c.-1722T, and TACGG haplotype: High risk of AR	Gao *et al*., 2012
		72 adults (Italy)	MMF, Tac, CsA, CS (6 m)	c.49AA, CT60AA and CCAA haplotype: AR	Canossi *et al*., 2013
		304 adults (China)	MMF, Tac, CsA, CS (1 y)	c.-1661GG and CGTAG and CGCAG haplotypes: Viral infection	Guo *et al*., 2013
		270 adults (India)	MMF, Tac, CsA, CS (3 y)	c.49GG and CT60GG: Symptomatic CMV infection, low CMV disease-free survival GCTTGG haplotype and STR H allele: Symptomatic CMV infection	Misra *et al*., 2015
		81 adults (Turkey)	MMF, Tac, CsA, mTORi, CS (6 m)	c.-318T: High risk of AR	Ruhi *et al*., 2015
		172 adults (Iran)	MMF, CsA, CS (7 y)	c.-1661AA: Low risk of AR (male patients)	Niknam *et al*., 2017
PDCD1	rs11568821 (c.627+189G>A) rs2227982 (c.644C>T, p.Ala215Val)	469 adults (France)	MMF, Aza, CNI, CS	rs11568821 A: High risk of CMV in seropositive patients	Hoffmann *et al*., 2010
		172 adults (Iran)	MMF, CsA, CS (7 y)	c.644CT: AR (male patients)	Niknam *et al*., 2017

[a]Significant association. AR: acute rejection; CMV: Cytomegalovirus; CNI: calcineurin inhibitor; DGF: delayed graft function; eGFR: estimated glomerular filtration rate; ISS: immunosuppressive; STR: short tandem repeat. Aza: Azathioprine; CsA: Cyclosporine; CS: Corticosteroids; MMF: mycophenolate mofetil, MPA: mychophenolic; mTORi: mTOR inhibitor; Tac: Tacrolimus.

CD28 & ICOS

The ***CD28*** rs3116496 (c.243+17T>C), an intronic variant also named 17T>C, was investigated in a cohort of adult kidney recipients on MMF therapy, and the 17C allele was associated with increased risk of AR (OR: 1.82, 95%CI: 1.13-2.94, $p<0.05$) but not with DGF or chronic graft nephropathy (Pawlik *et al*., 2014) (Table I).

Other studies reported a lack of association of the *CD28* 17T>C with AR, graft function or graft survival in adult patients (Kusztal *et al*., 2010) (Niknam *et al*., 2017). In the same way, the *CD28* upstream variant rs35593994 (c.-594G>A) was not associated with AR, graft function or graft survival, in a large cohort of adult kidney recipients (Haimila *et al*., 2009) (Table II).

Two meta-analyses explored variants in genes of co-stimulatory molecules and found an association of the *CD28* rs3116496 (C allele) with kidney allograft rejection (Han *et al*., 2014; Liu *et al*., 2017a). A recent systematic meta-analysis including data from previous meta-analyses and genome-wide association studies (GWAS) also reported *CD28* rs3116496 association with AR in kidney recipients, but the epidemiology credibility (cumulative evidence) was weak (Cargnin *et al*., 2020).

Haimila *et al.* (2009) investigated the influence of six ***ICOS*** variants rs11883722 (c.-693G>A), rs10932029 (c.58+173T>C), rs10183087 (c.*2A>C), rs4404254 (c.*964T>C), rs10932037 (c.*1024C>T) and rs4675379 (c.*1773G>C) on kidney transplantation outcomes in a large cohort of adult patients on long-term MMF therapy. The c.*2A and c.*964T alleles were associated with (DGF) or graft non-function, whereas the c.*1024T allele was associated with low graft survival. However, all *ICOS* variants did not influence the AR outcome (Haimila *et al*., 2009) (Table I). Another study explored the *ICOS* 1720C>T variant, which was not related to AR, graft function or survival in kidney recipients on long-term MMF therapy (Niknam *et al*., 2017) (Table II).

TABLE II - Genes related to T cell activation in kidney recipients on MPA therapy

Gene	Variant	Study Population	ISS regimen (follow-up)	Clinical outcomes	Reference
CD28	rs3116496 (17T>C, c.243+17T>C) rs35593994 (c.-594G>A)	678 adults (Finland)	MMF, Tac, Aza, CsA, CS (8 y)	c.-594G>A: no association with AR, graft function or survival	Haimila *et al*., 2009
		314 adults (Poland)	MMF, Tac, Aza, CsA, CS (5 y)	17T>C: no association with AR, graft function or survival	Kusztal *et al*., 2010
		270 adults (Poland)	MMF, CsA, CS (2 y)	17C: with DGF or chronic graft nephropathy	Pawlik *et al*., 2014
		172 adults (Iran)	MMF, CsA, CS (7 y)	17T>C: no association with AR or graft survival	Niknam *et al*., 2017
ICOS	rs11883722 (c.-693G>A) rs10932029 (c.58+173T>C) rs10183087 (c.*2A>C) rs4404254 (c.*964T>C) rs10932037 (c.*1024C>T) rs4675379 (c.*1773G>C) 1720C>T	678 adults (Finland)	MMF, Tac, Aza, CsA, CS (8 y)	c.-693G>A, c.58+173T>C, c.*2A>C, c.*964T>C, c.*1024 and c.*1773G>C: no association with AR	Haimila *et al*., 2009
		172 adults (Iran)	MMF, CsA, CS (7 y)	1720C>T: no association with AR or graft function or survival	Niknam *et al*., 2017

TABLE II - Genes related to T cell activation in kidney recipients on MPA therapy

Gene	Variant	Study Population	ISS regimen (follow-up)	Clinical outcomes	Reference
CTLA4	rs231775 (c.49A>G, p.Thr17Ala) rs733618 (c.-1722T>C) rs4553808 (c.-1661A>G) rs16840252 (c.-1147C>T) rs11571317 (c.-658C>T) rs5742909 (c.-318C>T), rs3087243 (CT60G>A, c.*1148+236G>A) rs11571319 (c.*1440G>A) STR (AT)n L>H	100 adults (Canada)	MMF, Tac, Aza, CsA, CS (1 y)	c.-318C>T and c.49A>G: no association with AR, graft failure or patient death	Dmitrienko *et al*., 2005
		63 adults (Venezuela)	MMF, CsA, CS (3 y)	c.-1722C>T, c.-1661A>G and c.-318C>T: no association with AR or chronic rejection	Gendzekhadze *et al*., 2006
		678 adults (Finland)	MMF, Tac, Aza, CsA, CS (8 y)	*CTLA4* c.49A>G, c.-318C>T, c.-1661A>G and CT60A: no association with AR, graft function or survival	Haimila *et al*., 2009
		314 adults (Poland)	MMF, Tac, Aza, CsA, CS (5 y)	c.49A>G, c.-318C>T and STR (AT) n L>H: no association with AR and graft function or survival	Kusztal *et al*., 2010
		72 adults (Italy)	MMF, Tac, CsA, CS (6 m)	rs11571319G>A: no association with AR	Canossi *et al*., 2013
		81 adults (Turkey)	MMF, Tac, CsA, mTORi, CS (6 m)	c.49A>G, c.-1661A>G and CT60G>A: no association with AR	Ruhi *et al*., 2015
		172 adults (Iran)	MMF, CsA, CS (7 y)	c.49A>G, c.-1722T>C and c.-318C>T: no association with AR and graft survival	Niknam *et al*., 2017
PDCD1	rs2227982 (c.644C>T, p.Ala215Val) rs2227981 (c.804T>C, p.Ala268=) rs11568821 (c.627+189G>A)	678 adults (Finland)	MMF, Tac, Aza, CsA, CS (8 y)	c.804T>C and c.627+189G>A: no association with AR, graft function or graft survival	Haimila *et al*., 2009
		172 adults (Iran)	MMF, CsA, CS (7 y)	c.804T>C and c.627+189G>A: no association with graft survival	Niknam *et al*., 2017

AR: acute rejection; CMV: Cytomegalovirus; CNI: calcineurin inhibitor; DGF: delayed graft function; eGFR: estimated glomerual filtration rate; ISS: immunosuppressive; STR: short tandem repeat. Aza: Azathioprine; CsA: Cyclosporine; CS: Corticosteroids; MMF: mycophenolate mofetil, MPA: mychophenolic acid; mTORi: mTOR inhibitor; Srl: sirolimus; Tac: Tacrolimus.

CTLA4 & PDCD1

The ***CTLA4*** rs231775 (c.49A>G, Thr17Ala) missense variant was associated with increased risk of AR in adult kidney recipients on MMF therapy (c.49G allele, OR: 5.5, 95%CI: 0.96-31.44, p<0.05) (Gendzekhadze *et al*., 2006), (OR: 1.72, 95%CI: 1.01-2.93) (Gao *et al*., 2012; Canossi *et al*., 2013) (Table I). On the other hand, c.49A>G was not associated with AR in small (Dmitrienko *et al*., 2005; Ruhi *et al*., 2015) (Niknam *et al*., 2017) and large cohorts of adult kidney recipients (Haimila *et al*., 2009; Kusztal *et al*., 2010) (Table II).

Upstream and intronic variants in *CTLA4* were also investigated in various pharmacogenetic studies. Canossi *et al.* (2013) also explored the *CTLA4* rs16840252 (c.-1147C>T), rs5742909 (c.-318C>T), rs3087243 (c.*1148+236G>A, also named CT60G>A) and rs11571319 G>A variants and found association of the CT60AA

genotype and CCAA haplotype with increased risk of AR adult kidney recipients on MMF treatment. Likewise, Gao *et al.* (2012) assessed five variants in the *CLTA4* and found an association of the rs733618 (c.-1722T>C) T allele and TACGG haplotype with AR in adult patients. Moreover, Ruhi *et al.* (2015) investigated four *CLTA4* variants and the T allele of the rs5742909 (c.-318C>T) was associated with increased risk of AR OR: 3.45, 95%CI: 1.13-10.56, p<0.05). Conversely, the *CTLA4* rs4553808 (c.-1661AA genotype) was reported to reduce the risk of AR in male kidney recipients (Niknam *et al.*, 2017) (Table I).

Other studies reported lack of association of the *CTLA4* c.-318C>T, c.-1147C>T, c.-1661A>G, c.-1722T>C, CT60G>A or rs11571319 (c.*144G>A) variants with AR in small (Dmitrienko *et al.*, 2005; Gendzekhadze *et al.*, 2006; Gao *et al.*, 2012; Canossi *et al.*, 2013; Ruhi *et al.*, 2015; Niknam *et al.*, 2017) and large cohorts (Haimila *et al.*, 2009; Kusztal *et al.*, 2010) of kidney recipients treated with MMF. The *CTLA4* (AT)n L>H is a short tandem repeat (STR), which was also not related to AR in adult kidney recipients (Kusztal *et al.*, 2010) (Table II).

The impact of *CTLA4* variants on chronic rejection and graft function and survival was also explored in kidney recipients on MMF therapy. The c.49AA/LL haplotype was associated with long-term graft function, assessed by the estimated glomerular filtration rate (eGFR), in adult patients (Kusztal *et al.*, 2010) (Table I). On the other hand, none of the *CTLA4* variants c.49A>G, c.-318C>T, c.-1661A>G, c.-1722T>C, CT60G>A and STR (AT)n) L>H were associated with chronic rejection (Gendzekhadze *et al.*, 2006), graft function, survival or failure, or patient death (Dmitrienko *et al.*, 2005; Haimila *et al.*, 2009; Kusztal *et al.*, 2010; Niknam *et al.*, 2017) (Table II).

Two studies explored the impact of *CTLA4* variants on the incidence of viral infection in adult kidney recipients on MMF therapy. Guo *et al.* (2013) analyzed five variants and reported association of the c.-1661GG genotype (OR: 4.88, 95%CI: 1.70-13.67, p<0.05) and the haplotypes CGTAG and CGCAG with increased risk of viral infection, but not with bacterial infection. Misra *et al.* (2015) also explored the influence of seven polymorphisms on the incidence of cytomegalovirus (CMV) infection in adult patients. They found association of the variants c.49A>G (c.49GG, OR:2.46, 95%CI: 1.10-5.52, p<0.05) and CT60G>A (CT60GG, OR: 2.78, 95%CI: 1.21-6.39, p<0.05), as well as the GCTTGG haplotype and STR (AT)n H allele were associated with symptomatic CMV infection. Moreover, c.49A>G and CT60G>A were also associated with reduced CMV disease-free survival in this cohort (Misra *et al.*, 2015) (Table I).

Several meta-analyses explored the impact of *CTLA4* variants on AR and other outcomes in kidney transplantation. *CTLA4* rs231775 (c.49A>G) was found to increase the risk of AR, DGF or overall survival, suggesting its involvement in the susceptibility to AR or DGF in kidney recipients (Duan *et al.*, 2012; Misra *et al.*, 2014; Gao *et al.*, 2015; Liu *et al.*, 2017a; Yang *et al.*, 2017b). *CTLA4* rs733618 (c.-1722T>C), rs3087243 (CT60G>A) and STR (AT)n L>H (AT)n variants were also associated with AR or DGF, whereas the c.-318C>T and other upstream variants showed no impact on AR and other outcomes (Duan *et al.*, 2012; Han *et al.*, 2014; Misra *et al.*, 2014; Liu *et al.*, 2017a; Yang *et al.*, 2017a). Recently, a re-analysis of data from several meta-analyses and GWAS also reported the association of the *CTLA4* c.49A>G and c.-1722T>C variants with AR in kidney recipients, but the cumulative evidence was weak (Cargnin *et al.*, 2020).

The *PDCD1* rs2227981 (c.804T>C, p.Ala268=) and rs11568821 (c.627+189G>A), synonymous and intronic variants respectively, were explored in kidney transplantation, but no association was found with AR, graft function or graft survival in a large cohort adult patients on MMF therapy (Haimila *et al.*, 2009). Lack of association between these variants and AR and graft survival was also reported in kidney recipients on long-term MMF treatment (Niknam *et al.*, 2017) (Table II). Interestingly the missense variant *PDCD1* rs2227982 (c.644C>T, p.Ala215Val) increased the risk of AR in male adult patients (CT genotype, OR: 3.19, 95%CI: 0.92-11.01, p<0.05) (Niknam *et al.*, 2017) (Table I). Two meta-analyses investigated these *PDCD1* variants as predictors of AR in kidney transplantation, but no association was found with allograft rejection suggesting that they are not conspicuous risk factors for developing AR (Han *et al.*, 2014; Liu *et al.*, 2017a).

The *PDCD1* rs11568821 was associated with increased risk of CMV in seropositive patients (A allele, OR: 2.54,

95%CI: 1.25-5.15, p=0.010) (Hoffmann *et al*., 2010) (Table I). This finding was also reported in a recent systematic review that assessed variants in cytokine genes in kidney transplantation (Sakharkar, Deb, Mashayekhi, 2020).

GENES RELATED TO PRO-INFLAMMATORY CYTOKINES

Cytokines have an important role in the immune response by participating of the Th1 and Th2 responses after T cell activation. Th1 lymphocytes contribute to inflammation by secreting pro-inflammatory mediators, such as interleukin (IL) 2, IL-6, IL-12, tumor necrosis factor-alpha (TNFα) and interferon-gamma (IFNγ) (Figure 1), which are involved in cell-mediated immunity and allograft rejection (Stojanova, Pouché, Picard, 2016; Da Silva *et al*., 2017). On the other hand,, Th2 lymphocytes are immunomodulatory cells that facilitate allograft tolerance by secreting anti-inflammatory cytokines that regulate cellular and humoral responses and contribute to allograft protection (Stojanova, Pouché, Picard, 2016).

The **IL-2** was initially characterized as a T cell growth factor and has a unique linking role between adaptive and innate immune response. During the early stage of immune response, the T cell activation induces the expression of IL-2, which promotes proliferation and differentiation of T and B cells. (Stojanova, Pouché, Picard, 2016; Da Silva *et al*., 2017; Bendickova, Fric, 2020).

The **IL-6** is a pro-inflammatory pleiotropic cytokine and a mediator of the acute phase responses that regulates inflammatory events. It is involved in leukocyte trafficking, T-cell proliferation, B-cell differentiation and survival. It is produced by endothelial cells, fibroblasts, monocytes, and macrophages in response to different stimuli during systemic inflammation (Stojanova, Pouché, Picard, 2016).

The **IL-12** is a potent pro-inflammatory cytokine composed of the IL-12A (p35) and IL-12B (p40) subunits, which are encoded by *IL12A* and *IL12B*, respectively. IL-12 is an essential inducer of Th1 cell response, as well as the activation and link the innate and acquired immune responses (Smith, Humphries, 2009).

The **TNFα** is produced by activated macrophages and T cells. It is involved in inflammation, activating endothelial cells, up-regulating cell adhesion molecules and participating in the recruitment of different leukocytes (Stojanova, Pouché, Picard, 2016).

The **IFNγ** is produced by Th1 lymphocytes and other adaptive and innate immune cells. It activates macrophages, increases the T cell activation, and induces cytotoxic activities and apoptosis (Stojanova, Pouché, Picard, 2016; Da silva *et al*., 2017).

Variants in genes encoding these pro-inflammatory cytokines have been proposed to impact acute rejection and other kidney transplant outcomes in patients treated with MPA and the significant results are shown in Table III.

TABLE III - Genes related to cytokines and immune innate response in kidney recipients on MPA therapy with significant associations

Gene	Variant	Study Population	ISS regimen (follow-up)	Clinical outcomes[a]	Reference
Pro-inflammatory cytokines					
IL2	rs2069762 (-330T>G, c.-385T>G)	50 adults (Japan)	MMF, Tac, CS (1 y)	-330TT: Chronic graft nephropathy	Satoh *et al*., 2007

TABLE III - Genes related to cytokines and immune innate response in kidney recipients on MPA therapy with significant associations

Gene	Variant	Study Population	ISS regimen (follow-up)	Clinical outcomes[a]	Reference
IL6	rs1800795 (-174G>C) rs10499563 (-6331T>C)	92 adults (Czech Republic)	MMF, Tac, Srl, CsA, CS (1 y)	-174G: Chronic graft nephropathy	Viklický *et al*., 2004
		100 adults (Iran)	MMF, CsA, CS (4 m)	-174G: High risk of AR	Karimi *et al*., 2012
		154 adults (Australia)	MMF, Tac, CS (2 w)	-6331CC: High risk of AR	Hu *et al*., 2020
IL12A	rs568408 (c.*121G>A)	918 adults (USA)	MMF, Tac, CsA, CS (6 m)	rs568408 A: Time to MMF-related anemia	Jacobson *et al*., 2011
IL12B	rs3212227 (c.*159T>G, 1188A>C)	469 adults (France)	MMF, Aza, CNI, CS	rs3212227 C: High risk of CMV infection	Hoffmann *et al*., 2008
		253 adults (France)	MMF, Aza, CNI, CS	rs3212227 C: High risk of CMV infection	Hoffmann *et al*., 2009
		469 adults (France)	MMF, Aza, CNI, CS	rs3212227 C: High risk of CMV infection in seropositive patients	Hoffmann *et al*., 2010
		152 adults (Serbia)	MMF, Tac, CsA, CS (1 y)	1188AA: Low risk of DGF	Perovic *et al*., 2018
TNF	rs1800629 (c.-488G>A, -308G>A**)**	63 adults (Venezuela)	MMF, CsA, CS (3 y)	-308A: Low risk of chronic rejection	Gendzekhadze *et al*., 2006
		237 adults (CAESAR study)	MMF, CsA, CS (1 y)	-308A: High risk of AR	Grinyó *et al*., 2008
		207 children & adolescents (Poland)	MMF, Tac, Aza, CsA, CS (1 y)	-308G: MMF-induced myelotoxicity (leukopenia).	Grenda *et al*., 2009
		286 adults (Spain)	MMF, Tac, CS (1 y)	-308A: High risk of AR	Sanchez-Fructuoso *et al*., 2016
		146 adults (Brazil)	MMF, Tac, CsA, CS (10 y)	-308G: Low eGFR	Alves *et al*., 2020
IFNG	rs2430561 (874T>A, c.115-483A>T) rs2069718 A>G (c.367-895T>C) rs12369470 T>C	100 adults (Iran)	MMF, CsA, CS (4 m)	874T: Hihg risk of AR	Karimi *et al*., 2012
		247 Hispanic adults (USA)	MMF or EC-MPS, Tac, Srl, CsA, CS (3 y)	874A: High risk of CMV infection, low CMV infection-free survival	Vu *et al*., 2014b
		556 Hispanic adults (USA)	MMF, Tac, mTORi, CsA, CS (6 y)	874TT: Low risk of AR, high graft survival time with BKV infection 874TT and rs2430561, rs2069718, rs12369470 AGT haplotype: Low risk of BKV infection	Vu *et al*., 2014a
Immunomodulatory cytokines					
IL10	rs1800872 (-592C>A, c.-627A>C)	237 adults (CAESAR study)	MMF, CsA, CS (1 y)	592AA: High risk of AR	Grinyó *et al*., 2008

TABLE III - Genes related to cytokines and immune innate response in kidney recipients on MPA therapy with significant associations

Gene	Variant	Study Population	ISS regimen (follow-up)	Clinical outcomes[a]	Reference
TGFB1	rs1800471 (915G>C, c.74G>C, p.Arg25Pro)	100 adults (Canada)	MMF, Tac, Aza, CsA, CS (1 y)	rs1800471 (25Pro): High risk of graft failure	Dmitrienko *et al*., 2005
Immune innate response					
CD14	rs2569190 (-260C>T, -159C>T)	142 adults (Iran)	MMF, Tac, Aza, CsA, CS (5 y)	-159TT: High risk of AR and graft loss, and low graft survival	Abdolvahabi *et al*., 2018

[a]Significant association. AR: acute rejection; BKV: BK polyomavirus; CMV: Cytomegalovirus; CNI: calcineurin inhibitor; DGF: delayed graft function; EC-MPS: enteric-coated mycophenolate sodium; ISS: immunosuppressive; Aza: Azathioprine; CsA: Cyclosporine; CS: Corticosteroids; MMF: mycophenolate mofetil, MPA: mychophenolic acid; mTORi: mTOR inhibitor; Srl: sirolimus; Tac: tacrolimus.

IL2, IL6, IL12A & IL12B

Two variants in the *IL2*, rs2069762 (c.-385T>G, also known as -330T>G) and rs2069763 (c.114G>T, p.Leu38=) were explored in adult kidney recipients on MMF therapy. Satoh *et al.* (2007) reported association of the *IL2* -330TT genotype with chronic allograft nephropathy (OR: 4.57, 95%CI: 1.04-20.11, p<0.05) in a small cohort of Japanese adult patients (Table III). The *IL2* -330T>G and c.114G>T variants were also investigated as predictive markers of AR, but no association was found in adult kidney recipients from the open-label, multicenter study [Cyclosporine Avoidance Eliminates Serious Adverse Renal-toxicity (CAESAR)] (Grinyó *et al*., 2008). In the same way, *IL2* -330T>G was not related to AR in adult patients from the FDCC study (Chen *et al*., 2014), and in other cohorts on short-term MMF treatment (Cilião *et al*., 2017; Hu *et al*., 2020). Lack of association between the variant *IL2* rs2069762 (-330T>G) and risk of acute renal graft rejection was confirmed in a meta-analysis of eight case-control studies (Hu *et al*., 2015) (Table IV).

TABLE IV - Genes related to pro-inflammatory cytokines in kidney recipients on MPA therapy without significant associations

Gene	Variant	Study Population	ISS regimen (follow-up)	Clinical outcomes	Reference
IL2	rs2069762 (-330T>G, c.-385T>G) rs2069763 (c.114G>T, p.Leu38=)	237 adults (CAESAR study)	MMF, CsA, CS (1 y)	-330T>G and c.114G>T: no association with AR	Grinyó *et al*., 2008
		325 adults (FDCC study)	MMF, Tac, CsA, CS 1 y)	-330T>G: no association with AR	Chen *et al*., 2014
		246 adults (Brazil)	MMF, Tac, Srl, Aza, CsA, CS (6 m)	-330T>G: no association with AR	Cilião *et al*., 2017
		154 adults (Australia)	MMF, TAC, CS (2 w)	-330T>G: no association with AR	Hu *et al*., 2020

TABLE IV - Genes related to pro-inflammatory cytokines in kidney recipients on MPA therapy without significant associations

Gene	Variant	Study Population	ISS regimen (follow-up)	Clinical outcomes	Reference
IL6	rs1800795 (-174G>C) rs10499563 (-6331T>C)	63 adults (Venezuela)	MMF, CsA, CS (3 y)	-174G>C; no association with AR or chronic rejection	Gendzekhadze *et al*., 2006
		231 adults (Tunisia)	MMF-based ISS therapy (20 y)	-174G>C: no association with AR or chronic rejection	Dhaouadi *et al*., 2013
		92 adults (Saudi Arabia)	MMF, Tac, mTORi, CsA, CS (5 y)	-174G>C: no association with AR	Gaafar *et al*., 2014
IL12A	rs568408 (c.*121G>A)	918 adults (USA)	MMF, Tac, CsA, CS (6 m)	rs568408 A: no association with leukopenia	Jacobson *et al*., 2011
		189 adults (Dominos study)	EC-MPS, CsA, CS (6 m)	rs568408G>A: no association with AR, leukopenia, anemia or diarrhea	Woillard *et al*., 2014
IL12B	rs3212227 (c.*159T>G, 1188A>C)	50 adults (Japan)	MMF, Tac, CS (1 y)	1188A>C: no association with chronic graft nephropathy	Satoh *et al*., 2007
		253 adults (France)	MMF, Aza, calcineurin inhibitor, CS	rs3212227 C: no association with AR, DGF or graft survival	Hoffmann *et al*., 2009
		152 adults (Serbia)	MMF, Tac, CsA, CS (1 y)	1188AA: no association with leukopenia	Perovic *et al*., 2018
TNF	rs1800629 (c.-488G>A, -308G>A) rs361525 (c.-418G>A, -238G>A)	112 adults (Germany)	MMF, Aza, CsA, CS (1 y)	-308G>A: no association with AR	Weimer *et al*., 2003
		100 adults (Canada)	MMF, Tac, Aza, CsA, CS (1 y)	-308G>A: no association with AR, graft failure or patient death	Dmitrienko *et al*., 2005
		63 adults (Venezuela)	MMF, CsA, CS (3 y)	-308: no association with AR	Gendzekhadze *et al*., 2006
		50 adults (Japan)	MMF, Tac, CS (1 y)	-308G>A and -238G>A: no association with chronic graft nephropathy	Satoh *et al*., 2007
		100 adults (Iran)	MMF, CsA, CS (1 m)	-308G>A: no association with AR	Azarpira *et al*., 2009
		231 adults (Tunisia)	MMF-based ISS therapy (20 y)	-308G>A: no association with AR or chronic rejection	Dhaouadi *et al*., 2013
		92 adults (Saudi Arabia)	MMF, Tac, mTORi, CsA, CS (5 y)	-308G>A: no association with AR	Gaafar *et al*., 2014
		247 Hispanic adults (USA)	MMF or EC-MPS, Tac, Srl, CsA, CS (2 y)	-308G>A: no association with CMV infection	Vu *et al*., 2014b
		246 adults (Brazil)	MMF, Tac, Srl, Aza, CS (6 m)	-308G>A: no association with AR	Cilião *et al*., 2017
		152 adults (Serbia)	MMF, Tac, CsA, CS (1 y)	-308G>A: no association with AR, DGF or graft funcion	Perovic *et al*., 2018
		146 adults (Brazil)	MMF, Tac, CsA, CS (10 y)	-308G: no association with IL-6 and IL-10 plasma levels	Alves *et al*., 2020
		154 adults (Australia)	MMF, Tac, CS (2 w)	-308G>A: no association with AR	Hu *et al*., 2020

TABLE IV - Genes related to pro-inflammatory cytokines in kidney recipients on MPA therapy without significant associations

Gene	Variant	Study Population	ISS regimen (follow-up)	Clinical outcomes	Reference
IFNG	rs2430561 (874T>A, c.115-483A>T) rs2069718 A>G (c.367-895T>C) rs2870953 T>A rs12369470 T>C STR (126-134 bp)	100 adults (Canada)	MMF, Tac, Aza, CsA, CS (1 y)	STR: no association with AR, graft failure or patient death	Dmitrienko *et al*., 2005
		63 adults (Venezuela)	MMF, CsA, CS (3 y)	874T>A: no association with AR or chronic rejection	Gendzekhadze *et al*., 2006
		50 adults (Japan)	MMF, Tac, CS (1 y)	874T>A: no association with chronic graft nephropathy	Satoh *et al*., 2007
		100 adults (Iran)	MMF, CsA, CS (1 m)	874T>A: no association with AR	Azarpira *et al*., 2009
		296 adults (India)	MMF, Tac, CsA, CS (3 y)	874T>A: no association with AR	Singh *et al*., 2009
		231 adults (Tunisia)	MMF-based ISS therapy (20 y)	874T>A: no association with AR or chronic rejection	Dhaouadi *et al*., 2013
		92 adults (Saudi Arabia)	MMF, Tac, mTORi, CsA, CS (5 y)	874T>A: no association with AR	Gaafar *et al*., 2014
		247 Hispanic adults (USA)	MMF or EC-MPS, Tac, Srl, CsA, CS (3 y)	874T>A: no association with AR	Vu *et al*., 2014b
		152 adults (Serbia)	MMF, Tac, Srl, CsA, CS (1 y)	874T>A: no association with AR, DGF or graft function	Perovic *et al*., 2018
		600 adults (Spain)	MMF, Tac, CS (1 y)	874T>A: no association with CMV infection	Santiago *et al*., 2020

AR: acute rejection; BKV: BK polyomavirus; CMV: Cytomegalovirus; DGF: delayed graft function; EC-MPS: enteric-coated mycophenolate sodium; ISS: immunosuppressive; STR: short tandem repeat; Aza: Azathioprine; CsA: Cyclosporine; CS: Corticosteroids; MMF: mycophenolate mofetil, MPA: mychophenolic acid; mTORi: mTOR inhibitor; Srl: sirolimus; Tac: tacrolimus.

The intronic variant ***IL6*** rs1800795 (-174G>C) was investigated in kidney recipients on MMF therapy. An early study reported an association of the -174G allele with chronic graft nephropathy in a small cohort of adult patients (Viklický *et al*., 2004). Further, the -174G allele was found to increase the risk of AR (OR: 2.11, 95%CI: 1.00-4.44, p<0.05) in patients on short-term MMF treatment (Karimi *et al*., 2012) (Table III). On the other hand, this variant was not associated with AR or chronic rejection in other cohorts on long-term follow-up (Gendzekhadze *et al*., 2006; Dhaouadi *et al*., 2013; Gaafar *et al*., 2014) (Table IV). The ***IL6*** rs1800795 was assessed by a meta-analysis, but no association of the -174G allele (high producer) was found with AR in kidney recipients (Lv *et al*., 2012). A recent study explored the upstream variant *IL6* the rs10499563 (-6331T>C) and found an association of the -6331CC genotype (OR: 6.6, 95%CI: 1.7-25.8, p<0.05) with AR within two weeks of kidney transplantation (Hu *et al*., 2020) (Table III).

Variants in the 3´UTR of ***IL12A*** rs568408 (c.*121G>A) and ***IL12B*** rs3212227 (c.*159T>C, also named as 1188A>C) were assessed in adult kidney recipients. In a large cohort of patients, the ***IL12A*** rs568408 A allele was associated with time to MMF-related anemia (HR: 1.98, 95%CI: 1.39-2.82, p<0.001), but not with leukopenia, (Jacobson *et al*., 2011) (Table III). The *IL12A* c.*121G>A was also investigated in patients from the Dominos Study on short-term enteric-coated mycophenolate sodium (EC-MPS) treatment, but this

variant was not related to AR, leukopenia, anemia or diarrhea (Woillard *et al.*, 2014) (Table IV).

The ***IL12B*** 1188A>C was associated with reduced risk of DGF (AA genotype, OR: 0.45, 95%CI: 0.21-0.96, p<0.05) (Table III), but this variant had no impact on AR or graft function in adult kidney recipients on MMF treatment (Perovic *et al.*, 2018). Earlier studies, also reported a lack of association of the *IL12B* 1188A>C with AR, DGF, graft survival, or chronic graft nephropathy (Satoh *et al.*, 2007; Hoffmann *et al.*, 2009) (Table IV). Three studies explored the influence of *IL12B* rs3212227 on CMV infection in a large cohort and the C allele as associated with increased risk of CMV infection, including in seropositive adult patients (C allele, OR=1.91, 95%CI: 1.10-3.30, p=0.021) (Hoffmann *et al.*, 2008; Hoffmann *et al.*, 2009; Hoffmann *et al.*, 2010) (Table III). This finding was also reported in a recent systematic review that assessed variants in cytokine genes in kidney transplantation (Sakharkar, Deb, Mashayekhi, 2020).

TNF

The *TNF* rs1800629 (c.-488G>A, also named -308G>A) is an upstream variant that was extensively explored in MPA-related pharmacogenomic studies. *TNF* -308A allele was associated with increased risk of AR in adult kidney recipients from the CAESAR study (OR: 2.18, 95% CI: 1.08-4.41, p<0.05) (Grinyó *et al.*, 2008) and from a Spanish cohort (OR: 2.78, 95%CI: 1.40-5.51, p<0.05) (Sánchez-Fructuoso *et al.*, 2016) on MMF treatment (Table III). Other studies reported no impact of the *TNF* -308G>A on AR in adult patients from different cohorts on short-term (Azarpira *et al.*, 2009; Cilião *et al.*, 2017; Hu *et al.*, 2020) or long-term on MMF therapy (Weimer *et al.*, 2003; Dmitrienko *et al.*, 2005). (Gendzekhadze *et al.*, 2006; Dhaouadi *et al.*, 2013; Gaafar *et al.*, 2014; Perovic *et al.*, 2018) (Table IV). Interestingly, the *TNF*H/TGFB1*H/IL10*H* haplotype, which includes the *TNF* -308A allele (H*), was associated with increased risk of AR (OR: 15.75. 95%CI: 0.98-528.85, p<0.05) and reduced graft survival in adult patients on long-term MMF therapy (Dhaouadi *et al.*, 2013).

An earlier meta-analysis of 28 studies reported that *TNF* -308G>A increased the risk of AR (GG genotype, OR: 1.39, 95%CI: 1.06–1.82, p=0.02) in kidney recipients (Hu *et al.*, 2011). A recent meta-analysis of 33 studies, including previous meta-analyses and GWAS, found *TGF* -308GG genotype associated with AR (OR: 1.41, 95%CI: 1.05–1.88, p=0.022) in kidney recipients, but the cumulative evidence was weak (Cargnin *et al.*, 2020).

TNF -308G>A was associated with reduced risk of chronic rejection (-308A allele, OR: 0.1, 95%CI: 0.005-1.64, p<0.05) in a small cohort of adult kidney recipients (Gendzekhadze *et al.*, 2006) (Table III). On the other hand, this variant did not increase the risk of chronic graft nephropathy (Satoh *et al.*, 2007) chronic rejection (Dhaouadi *et al.*, 2013), DGF or graft function (Perovic *et al.*, 2018), and graft failure or patient death (Dmitrienko *et al.*, 2005) in adult kidney recipients (Table IV). A recent study found *TNF* -308G allele carriers had low eGFR, but not with IL-6 and IL-10 plasma levels, in adult patients on long-term MMF therapy (Alves *et al.*, 2020). The variant *TNF* rs361525 (c.-418G>A, also named -238G>A) was also investigated in a small cohort of kidney recipients, but no impact was found on chronic graft nephropathy (Satoh *et al.*, 2007) (Table IV).

Grenda *et al.* (2009) reported association of the *TNF* -308G allele with leukopenia, an MFF-induced myelotoxicity, in a cohort of pediatric kidney recipients on one-year MMF treatment (Table III). The influence of *TNF* -308G>A on CMV infection was also explored, but no association was found in Hispanic adult patients on long-term MMF or EC-MPS treatment (Vu *et al.*, 2014b) (Table IV).

IFNG

The impact of the *IFNG* rs2430561, an intronic variant (c.115-483A>T, also named 874T>A), on clinical outcomes of kidney transplantation was also largely investigated. The *IFNG* 874T allele was associated with increased risk of AR (OR: 2.08, 95%CI: 1.12-3.88, p<0.05) in adult patients on short-term MMF therapy (Karimi *et al.*, 2012). Conversely, the *IFNG* 874TT genotype was

associated with reduced risk of AR (OR: 0.40, 95%CI: 0.19-0.85, p<0.05) and high graft survival time in adult kidney recipients on long-term treatment (Vu *et al.*, 2014a) (Table III). Other studies did not find an influence of the *IFNG* 874T>A on AR in small (Gendzekhadze *et al.*, 2006; Azarpira *et al.,* 2009; Gaafar *et al.*, 2014; Perovic *et al.*, 2018) and larger (Singh *et al.*, 2009; Dhaouadi *et al.*, 2013; Vu *et al.*, 2014b) cohorts of adult kidney recipients on MMF treatment (Table IV).

A meta-analysis of 13 case-control studies reported that carriers of the *IFNG* 874T allele (AT+TT genotypes) had an increased risk of AR (OR: 1.36, 95%CI: 1.07-1.73, p<0.05) in kidney recipients (Ge *et al.*, 2013). Similar results were found in two recent meta-analyses, which suggested the *IFNG* 874T>A as a relevant clinical biomarker for acute rejection in kidney transplantation (Cargnin *et al.*, 2020; Eiamsitrakoon *et al.*, 2020).

The *IFNG* 874T>A was also not associated with chronic rejection, chronic graft nephropathy or DGF and graft function in patients treated with MMF (Gendzekhadze *et al.*, 2006; Satoh *et al.*, 2007) (Dhaouadi *et al.*, 2013; Perovic *et al.*, 2018) (Table IV). Lack of association between *IFNG* 874T>A and chronic rejection in kidney transplantation was also reported in a recent meta-analysis (Eiamsitrakoon *et al.*, 2020).

An early study also investigated an *IFNG* STR (126-134 bp) but no association was found with AR, graft failure or patient death (Dmitrienko *et al.*, 2005). Other variants, such as rs2069718, rs2870953 and rs12369470, also did not influence AR and graft survival (Vu *et al.*, 2014a) (Table IV).

Three studies explored the impact of *IFNG* variants on susceptibility to viral infection in kidney recipients on MMF therapy. The *IFNG* rs2430561 (874A allele) was associated with increased risk of CMV infection (OR: 1.92, 95%CI: 1.18-3.11, p<0.05) and lower CMV infection-free survival (three-year follow-up) in adult patients on MMF or EC-MPS therapy (Vu *et al.*, 2014b). Another study also investigated four variants in the *IFNG* (rs2430561, rs2069718, rs2870953, rs12369470) and found association of the rs2430561 (874TT genotype, OR: 0.72, 95%CI: 0.40-1.20) and AGT haplotype (OR: 0.43, 95% CI: 0.25-0.73) with reduced risk of BK polyomavirus (BKV) infection in adult patients (Vu *et al.*, 2014a) (Table III). On the other hand, *IFNG* rs2430561 was not associated with the risk of CMV infection in a larger cohort of adult patients (Santiago *et al.*, 2020) (Table IV). A recent systematic review assessed variants in cytokine genes in kidney transplantation and reported an association between the *IFNG* 874T>A variant and CMV infection (Sakharkar, Deb, Mashayekhi, 2020).

GENES RELATED TO IMMUNOMODULATORY CYTOKINES

Immunomodulatory cytokines secreted by Th2 lymphocytes, such as IL-4 and IL-10, and transforming-growth factor β1 (TGF-β1) (Figure 1), which regulate negatively the T and B cell-mediated immune response, play important roles in the allograft tolerance, predominantly through their ability to inhibit T cell activation (Stojanova, Pouché, Picard, 2016; Li *et al.*, 2019). TGF-β1 is also involved in various biological processes related to cell growth, proliferation and differentiation, and fibrosis. Several studies investigated the influence of variants in *IL4*, *IL10* and *TGFB1* on MPA-related clinical outcomes in kidney transplantation with significant results shown in Table III.

IL4 & IL10

Two studies assessed the upstream variant *IL4* rs2243250 (c.-589C>T, also named -590C>T) but no association was found with AR (Karimi *et al.*, 2012) or chronic graft nephropathy in small cohorts of adult kidney recipients on MMF therapy (Satoh *et al.*, 2007) (Table V). Lack of association between *IL4* -590C> and AR was also found in a meta-analysis that assessed six studies on kidney transplantation (Wu *et al.*, 2013).

TABLE V - Genes related to immunomodulatory cytokines in kidney recipients on MPA therapy without significant associations

Gene	Variant	Study Population	ISS regimen (follow-up)	Clinical outcomes	Reference
IL4	rs2243250 (-590C>T, c.-589C>T)	50 adults (Japan)	MMF, Tac, CS (1 y)	-590C>T: no association with chronic graft nephropathy	Satoh *et al*., 2007
		100 adults (Iran)	MMF, CsA, CS (4 m)	-590C>T: no association with AR	Karimi *et al*., 2012
IL10	rs1800896 (-1082A>G, c.-1117A>G) rs1800871 (-819C>T, c.-854T>C) rs1800872 (-592C>A, c.-627A>C) rs1800894 (-851C>T, c.-886G>A)	112 adults (Germany)	MMF, CsA, Aza (1 y)	-1082A>G, -819C>T and -592C>A: no association of with AR	Weimer *et al*., 2003
		100 adults (Canada)	MMF, Tac, Aza, CsA, CS (1 y)	-1082A>G: no association with AR, graft failure or patient death	Dmitrienko *et al*., 2005
		63 adults (Venezuela)	MMF, CsA, CS (3 y)	-1082A>G, -819C>T and -592C>A: no association with AR or chronic rejection	Gendzekhadze *et al*., 2006
		50 adults (Japan)	MMF, Tac, CS (1 y)	-592C>A: no association with chronic graft nephropathy	Satoh *et al*., 2007
		237 adults (CAESAR study)	MMF, CsA, CS (1 y)	-1082A>G, -851C>T and -819C>T: no association with AR	Grinyó *et al*., 2008
		100 adults (Iran)	MMF, CsA, CS (1 m)	-1082A>G: no association with AR	Azarpira *et al*., 2009
		231 adults (Tunisia)	MMF-based ISS therapy (20 y)	-1082A>G, -819C>T and -592C>A: no association with AR or chronic rejection	Dhaouadi *et al*., 2013
		325 adults (FDCC study)	MMF, Tac, CsA, CS (1 y)	-1082A>G and -592C>A: no association with AR	Chen *et al*., 2014
		92 adults (Saudi Arabia)	MMF, Tac, mTORi, CsA, CS (5 y)	-1082A>G, -819C>T and -592C>A: no association with AR	Gaafar *et al*., 2014
		247 Hispanic adults (USA)	MMF or EC-MPS, Tac, Srl, CsA, CS (2 y)	rs1800896 and rs1800872: no association with CMV infection	Vu *et al*., 2014b
		246 adults (Brazil)	MMF, Tac, Srl, Aza, CsA, CS (6 m)	rs1800872: no association with with AR	Cilião *et al*., 2017
		152 adults (Serbia)	MMF, Tac, CsA, CS (1 y)	-1082A>G, -819C>T and -592C>A: no association with AR, DGF or graft function	Perovic *et al*., 2018
		154 adults (Australia)	MMF, Tac, CS (2 w)	1082A>G and -819C>T: no association with AR	Hu *et al*., 2020

TABLE V - Genes related to immunomodulatory cytokines in kidney recipients on MPA therapy without significant associations

Gene	Variant	Study Population	ISS regimen (follow-up)	Clinical outcomes	Reference
TGFB1	rs1800470 (869T>C, c.29C>T, p.Pro10Leu) rs1800471 (915G>C, c.74G>C, p.Arg25Pro) rs1800469 (-509C>T, c.-1347T>C)	100 adults (Canada)	MMF, Tac, Aza, CsA, CS (1 y)	rs1800470 (p.Pro10Leu) and rs1800471 (Arg25Pro): no association with AR or patient death	Dmitrienko *et al*., 2005
		63 adults (Venezuela)	MMF, CsA, CS (3 y)	869T>C and 915G>C: no association with AR or chronic rejection	Gendzekhadze *et al*., 2006
		50 adults (Japan)	MMF, Tac, CS (1 y)	869T>C, 915G>C and -509C>T: no association with chronic graft nephropathy	Satoh *et al*., 2007
		237 adults (CAESAR study)	MMF, CsA, CS (1 y)	869T>C and 915G>C: no association with AR	Grinyó *et al*., 2008
		100 adults (Iran)	MMF, CsA, CS (4 m)	869T>C: no association with AR	Karimi *et al*., 2012
		231 adults (Tunisia)	MMF-based ISS therapy (20 y)	869T>C and 915G>C: no association with AR chronic rejection	Dhaouadi *et al*., 2013
		325 adults (FDCC study)	MMF, Tac, CsA, CS (1 y)	915G>C: no association with AR	Chen *et al*., 2014
		92 adults (Saudi Arabia)	MMF, Tac, mTORi, CsA, CS (5 y)	p.Pro10Leu and p.Arg25Pro: no association with AR	Gaafar *et al*., 2014
		246 adults (Brazil)	MMF, Tac, Srl, Aza, CsA, CS (6 m)	rs1800470 and rs1800471: no association with AR	Cilião *et al*., 2017
		200 adults (China)	MMF, Tac, Srl, CS (6 m)	rs1800470: no association with AR	Zheng *et al*., 2019
		154 adults (Australia)	MMF, Tac, CS (2 w)	-509C>T: no association with AR	Hu *et al*., 2020

AR: acute rejection; CMV Cytomegalovirus; DGF: delayed graft function; EC-MPS: enteric-coated mycophenolate sodium; ISS: immunosuppressive; Aza: Azathioprine; CsA: Cyclosporine; CS: Corticosteroids; MMF: mycophenolate mofetil; MPA: mychophenolic acid; mTORi: mTOR inhibitor; Srl: sirolimus; Tac: tacrolimus.

Several studies investigated ***IL10*** upstream variants rs1800896 (-1082A>G), rs1800871 (-819C>T) and rs1800872 (-592C>A) and rs1800894 (-851C>T) in MMF-treated kidney recipients (Table V). The -592C>A was the only variant associated with increased risk of AR (-592AA, OR: 4.71, 95% CI: 1.52–14.55, p<0.05) in adult patients from the CAESAR Study (Grinyó *et al.*, 2008) (Table III).

Other works also explored the *IL10* rs1800896, rs1800871 or rs1800872 variants but reported lack of association with AR in small (Weimer *et al.*, 2003; Dmitrienko *et al.*, 2005; Gendzekhadze *et al.*, 2006; Azarpira *et al.*, 2009; Gaafar *et al.*, 2014; Perovic *et al.*, 2018; Hu *et al.*, 2020) and larger cohorts (Dhaouadi *et al.*, 2013; Chen *et al.*, 2014; Cilião *et al.*, 2017) of adult patients. Likewise, *IL10* rs1800896, rs1800871 or rs1800872, did not impact on DGF or graft function (Perovic *et al.*, 2018), chronic rejection (Gendzekhadze *et al.*, 2006; Dhaouadi *et al.*, 2013), chronic graft nephropathy (Satoh *et al.*, 2007), graft failure or patient death (Dmitrienko *et al.*, 2005). *IL10* rs1800896 and rs1800872 were also assessed in kidney recipients and no association was found with susceptibility to CMV infection in adult patients on long-term MMF or EC-MPS treatment (Vu *et al.*, 2014b) (Table V).

An earlier meta-analysis assessed the impact of *IL10* -1082G>A, -819C>T and -592C>A variants in kidney transplantation and found the haplotype A-C-C (low expression) are associated (OR: 1.3, 95%CI: 0.9-1.6, p=00.44) with poor outcomes, such as graft failure, chronic allograft nephropathy, AR or chronic graft rejection (Thakkinstian *et al.*, 2008). Further

meta-analyses showed that *IL10* -1082G>A, -819C>T or 592C>A individual variants or haplotypes were not associated with increased risk of AR or chronic rejection (Xiong *et al*., 2015; Hu *et al*., 2016).

TGFB1

The *TGFB1* missense variants rs1800470 (869T>C, p.Pro10Leu) and rs1800471 (915G>C, Arg25Pro) have been explored in kidney recipients on MMF therapy. Several studies reported a lack of association of either *TGFB1* 869T>C and 915G>C variant with AR in adult kidney recipients on short-term MMF therapy (Karimi *et al*., 2012; Cilião *et al*., 2017; Zheng *et al*., 2019). These variants were also not associated with AR in adult patients on long-term MMF therapy (Dmitrienko *et al*., 2005; Gendzekhadze *et al*., 2006; Dhaouadi *et al*., 2013; Gaafar *et al*., 2014), as well as from the CAESAR study (Grinyó *et al*., 2008) and FDCC study (Chen *et al*., 2014). The upstream variant rs1800469 (-509C>T) in the *TGFB1* was also not related to AR in adult patients treated on two-week MMF treatment (Hu *et al*., 2020) (Table V).

Dmitrienko *et al.* (2005) found an association of the *TGFB1* 915G>C with increased risk of graft failure in adult kidney recipients on MMF therapy (Table III). On the other hand, the variants 869T>C, 915G>C or -509C>T variants had no impact on chronic rejection (Gendzekhadze *et al*., 2006), (Dhaouadi *et al*., 2013), chronic graft nephropathy (Satoh *et al*., 2007) or patient death (Dmitrienko *et al*., 2005) in adult patients (Table V).

Five meta-analyses explored the influence of *TGFB1* missense variants (869T>C and 915G>C) on AR in kidney transplantation. In an earlier study, the *TGFB1* 869TC genotype carriers had increased risk (OR: 1.5, 95%CI: 1.0-2.2, p=0.34) of combined poor outcomes (AR, chronic graft rejection, graft failure or chronic allograft nephropathy) (Thakkinstian *et al*., 2008). Further, *TGFB1* 869CC genotype was associated with increased risk of AR in kidney donors (OR: 1.47, 95%CI: 1.05-2.06, p=0.025) but not in kidney recipients (p>0.05) (Ge *et al*., 2014b). Lack of association between *TGFB1* +869T>C and +915G>C variants or haplotypes and AR susceptibility was also reported in other meta-analyses of kidney transplantation (Ge *et al*., 2014a; Li *et al*., 2019).

The *TGFB1* 869/915 TT/GG+TC/GG haplotype, classified as a high producer of TGF-β1 *in vitro* (Smith, Humphries, 2009), was associated with chronic graft nephropathy (OR: 3.6, 95%CI: 2.2-5.8, p<0.001), whereas the individual variants were not, in kidney recipients from eight studies (Liu *et al*., 2017b).

GENES RELATED TO INNATE IMMUNE RESPONSE

Proteins of the innate immune system, such as CD14 and Toll-Like Receptors (TLR), have an important role in pathogen recognition and activation of the innate immune response. TLR also can modulate T cell function and act as costimulatory receptors to enhance proliferation and/or cytokine production of in activated T cells (Figure 1). TLR2, TLR4 and the related molecule CD14 have been proposed to initiate inflammation and tissue injury, which may affect graft function and survival in solid organ transplantation (Stojanova, Pouché, Picard, 2016). Some studies investigated the influence of variants in *CD14*, *TLR2* and *TLR4* on MPA-related clinical outcomes in kidney transplantation and Table III shows the significant results.

CD14

The intronic variant ***CD14*** rs2569190 (c.-260C>T, also named -159 C>T) was explored in adult kidney recipients on long-term MMF therapy. Abdolvahabi *et al.* (2018) described the association of rs2569190 (-159TT genotype) with increased risk of AR (OR: 12.26, 95%CI: 4.02-37.31, p<0.05) and graft loss (OR: 8.75, 95%CI, 2.81-27.16, p<0.05) and reduced graft survival (Table III). Previous studies did not find an association of the *CD14* rs2569190 with AR, DGF, chronic graft nephropathy or graft survival (Viklický *et al*., 2004; Krüger *et al*., 2010; Krichen *et al*., 2013). This variant did not also contribute to the incidence of CMV and other infections (Krüger *et al*., 2010; Krichen *et al*., 2013) (Table VI).

Table VI - Genes related to innate immune response in kidney recipients on MPA therapy without significant associations

Gene	Variant	Study Population	ISS regimen (follow-up)	Clinical outcomes	Reference
CD14	rs2569190 (-260C>T, -159C>T)	92 adults (Czech Republic)	MMF, Tac, Srl, CsA, CS (1 y)	-260C>T: no association with chronic graft nephropathy	Viklický *et al*., 2004
		265 adults (Germany)	MMF, Tac, Aza, CsA, CS (6 y)	-159C>T: no association with AR, DGF, graft function and survival, or CMV and other infections	Krüger *et al*., 2010
		209 adults (Tunisia)	MMF-based ISS therapy (20 y)	-159C>T: no association with AR, chronic graft nephropathy or graft survival -159C>T: no association with incidence of urinary CMV and other infections	Krichen *et al*., 2013
TLR2	rs5743708 (c.2258G>A, p.Arg753Gln) rs3804100 (c.1350T>C, p.Ser450=)	265 adults (Germany)	MMF, Tac, Aza, CsA, CS (6 y)	rs5743708: no association with AR, DGF, graft function and survival, or CMV and other infections	Krüger *et al*., 2010
		142 adults (Iran)	MMF, Tac, Aza, CsA, CS (5 y)	rs5743708: no association with AR	Abdolvahabi *et al*., 2018
		154 adults (Australia)	MMF, Tac, CS (2 w)	c.1350T>C: no association with AR	Hu *et al*., 2020
TLR4	rs4986790 (c.896A>G, Asp299Gly) rs4986791 (c.1196C>T, p.Thr399Ile)	265 adults (Germany)	MMF, Tac, Aza, CsA, CS (6 y)	rs4986790 and rs4986791: no association with AR, DGF, graft function and survival, or CMV and other infections	Krüger *et al*., 2010
		209 adults (Tunisia)	MMF-based ISS therapy (20 y)	c.896A>G: no association with AR, chronic graft nephropathy or graft survival c.896A>G: no association with incidence of CMV and other infections	Krichen *et al*., 2013
		142 adults (Iran)	MMF, Tac, Aza, CsA, CS (5 y)	c rs4986790 and rs4986791: no association with AR	Abdolvahabi *et al*., 2018
		154 adults (Australia)	MMF, Tac, CS (2 w)	c.896A>G and c.1196C>T: no association with AR	Hu *et al*., 2020

AR: acute rejection; CMV Cytomegalovirus; ISS: immunosuppressive; Aza: Azathioprine; CsA: Cyclosporine; CS: Corticosteroids; MMF: mycophenolate mofetil; MPA: mychophenolic acid; Srl: sirolimus; Tac: tacrolimus.

TLR2 & TLR4

Three studies investigated ***TLR2*** variants in kidney recipients on MMF treatment. The missense variant *TLR2* rs5743708 (c.2258G>A, Arg753Gln) did not contribute to AR, DGF, graft function and survival, or CMV and other infections in adult patients on long-term follow-up (Krüger *et al*., 2010; Abdolvahabi *et al*., 2018). Likewise, a lack of association was found between the synonymous variant *TLR2* rs3804100 (c.1350T>C, Ser450S=) and AR in adult patients within the first two weeks of therapy (Hu *et al*., 2020) (Table VI).

The ***TLR4*** missense variants rs4986790 (c.896A>G, p.Asp299Gly) and rs4986791 (c.1196C>T, p.Thr399Ile) were explored, but no association with AR was found in adult kidney recipients on long-term (Krüger *et al*., 2010; Krichen *et al*., 2013; Abdolvahabi *et al*., 2018) and short-term (Hu *et al*., 2020) MMF therapy. Both variants had also no impact on DGF, chronic graft nephropathy, graft function and survival, or CMV and other infections (Krüger *et al*., 2010; Krichen *et al*., 2013) (Table VI).

CONCLUSIONS

Variants in genes related to T cell activation (*CD28*, *CTL4*, *ICOS*, *PDPC1*), pro-inflammatory cytokines (*IL2, IL6, IL12A, IL12B, TNF*, *IFNG*), immunomodulatory cytokines (*IL10, TGFB1*), and innate immune response (*CD14*) are associated with increased risk of acute rejection, graft function or survival, chronic graft nephropathy, viral infections or MPA-induced myelotoxicity in kidney recipients. These findings are suggestive that variants in immune response-related genes contribute to the variability of MPA response, and have potential application as biomarkers of acute rejection in kidney transplantation.

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AUTHOR CONTRIBUTIONS

Hirata RDC: Conceived, planned, searched the information, interpreted the data and wrote the manuscript.

Hirata TDC: prepared the figure and reviewed the manuscript.

Genvigir FDV, Cerda A, and Hirata MH: reviewed critically the manuscript.

All authors approved the final version.

CONFLICTS OF INTEREST

All authors declare no conflict of interest.

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