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Review article

Immunosuppressive drugs and the gastrointestinal tract in renal transplant patients

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ABSTRACT

Gastrointestinal (GI) discomfort is common after renal transplantation and can be caused by the use of various immunosuppressive drugs. GI symptoms affect the quality of life, lead to an impaired graft survival and an increased mortality. Moreover, diseases and disturbances of the GI tract also affect the pharmacokinetics of immunosuppressive drugs. This review addresses the interaction between immunosuppressive agents and GI disorders.

The GI tract is involved in the metabolism of several immunosuppressive drugs. Calcineurin inhibitors, mTor inhibitors, and corticosteroids are subjected to metabolism by the intestinal cytochrome P450 (CYP3A) and by the drug efflux pump ABCB1. Mycophenolate is partly metabolized in the stomach and intestine and undergoes enterohepatic recirculation. Gastrointestinal disturbances can lead to a modified exposure to immunosuppressive drugs. In the first and second part of this review, we focus on the role of the GI tract in the pharmacokinetics of the immunosuppressive drugs and how to adjust immunosuppressive therapy in patients with vomiting, need for tube feeding, delayed gastric emptying, intestinal resection, and diarrhea.

In the third part, we review the GI adverse effects of the various immunosuppressive drugs, with special attention for diarrhea and dyspepsia.

Finally, we discuss the effects of drugs used for relief of GI complaints on the exposure to immunosuppressive agents.

Contents

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1. Introduction

The current practice in maintenance immunosuppressive therapy for renal allograft recipients is to make use of a combination of various drugs that interfere with different steps in the immune response. These drugs are generally classified according to their mechanism of action: calcineurin inhibitors (CNI) which consist of cyclosporine A (CsA) and tacrolimus, mammalian target of rapamycin (mTOR) inhibitors to which sirolimus and everolimus belong, antiproliferative drugs, which#spcent;include mycophenolate and azathioprine (AZA), and corticosteroids (CS).

Several factors, including diet, co-administration of drugs or herbs, and genetic features affect the blood concentration of these immunosuppressive drugs. It is not always recognized that disorders of the gastrointestinal (GI) tract like vomiting or diarrhea can also contribute to a modified exposure to immunosuppressive drugs. Moreover, some drugs that are used to treat these conditions can interact with the immunosuppressive agents.

GI adverse events, occurring in >80% of patients after renal transplantation, can also be a consequence of the use of immunosuppressive drugs [1]. The most commonly reported GI complaints are dyspepsia, abdominal pain, diarrhea, and constipation. GI complications, and particularly diarrhea, are associated with poor graft outcome and patient survival [2]. In addition, GI complaints can have detrimental effects on quality of life, which might result in reduced compliance with the immunosuppressive regimen. This in turn is a risk factor for graft failure#spcent;[3].

Knowledge on the effects of GI tract disorders on the pharmacokinetics of immunosuppressive drugs is essential for prescribing the optimal immunosuppressive regimen. Therefore, we will firstly discuss the role of the GI tract in the pharmacokinetics of the major immunosuppressive drugs. Secondly, we will address the consequences of GI disorders on the pharmacokinetics of immunosuppressive drugs and provide some practical recommendations how to adjust the treatment regimen in these circumstances. Thirdly, we will summarize the GI adverse effects of immunosuppressive drugs, and finally the effects of medical treatment of GI complaints on the pharmacokinetics of immunosuppressive agents will be highlighted.

2. Normal intestinal absorption and metabolism of immunosuppressive drugs

2.1. Calcineurin inhibitors, mTor inhibitors and corticosteroids

CsA and tacrolimus are available in different formulations with their own pharmacokinetic characteristics. There are two formulations of CsA available in capsules: oil based and micro-emulsion. In this review, we will only address the micro-emulsion formulation of CsA which is predominantly prescribed because of a better and more predictable oral bioavailability [4]. Three formulations of tacrolimus are yet available: regular, prolonged-release and prolonged-release with innovative drug delivery technology (LifeCyclePharma, LCP). With prolonged-release formulations, tacrolimus is released further along the GI tract and these formulations can be taken once daily. LCP-tacrolimus is a prolonged-release formulation with a higher bioavailability due to its specific drug delivery technology [5].

CNIs, mTOR inhibitors and CS are all metabolized primarily by CYP3A4 and CYP3A5. They are also substrates of the drug efflux pump ABCB1, previously known as P-glycoprotein. CYP3A enzymes and ABCB1 form a cooperative barrier against absorption of xenobiotics. The absorption of drugs by enterocytes and subsequent excretion by ABCB1 can be repeated multiple times along the GI tract. The consequent repeated exposure to CYP3A enzymes increases the probability of the drug being metabolized. ABCB1 keeps intracellular drug concentrations within the linear range of the metabolizing capacity of the CYP3A enzymes [6]. The CYP3A isoenzymes metabolize immunosuppressive drugs by hydroxylation and demethylation. Several studies showed that differences in expression of CYP3A4, CYP3A5 and ABCB1 cause patient-to-patient variability in the absorption and intestinal metabolism of drugs [7,8].

CYP3A4 is the predominant CYP3A isoform in the GI tract, with an increase in the expression from stomach to the jejunum and then a decrease in the ileum [9]. The intestinal expression of CYP3A5 seems to be only relevant in carriers of the *CYP3A5*1* allele (expressers), and is especially present in stomach and ileum [7,8]. Expressers have a faster intestinal tacrolimus metabolism than non-expressers. The ABCB1 expression is equally distributed in stomach, jejunum and ileum [9]. A number of characteristics concerning intestinal absorption and metabolism of the different immunosuppressive drugs are summarized in Table 1.

2.2. Antiproliferative agents

Currently, two mycophenolate compounds are available: mycophenolate mofetil (MMF) and enteric coated mycophenolate sodium (EC-MPS). In both cases, mycophenolic acid (MPA) is the active drug moiety. After oral administration, MMF and EC-MPS are extensively hydrolyzed to MPA by esterases in the stomach, small intestine, blood, liver and other tissues. Uridine diphosphate glucuronosyltransferases metabolize MPA in the liver, and to a lesser extent in the GI tract and the kidneys. The major metabolite is the pharmacologically inactive 7-O-MPA-glucuronide (MPAG), which is excreted into bile. Biliary excretion of MPAG is followed by intestinal deconjugation through colonic bacteria after which MPA can be reabsorbed. This results in an

Table 1
Time to reach the maximum concentration, oral bioavailability, interference of food intake and polymorphism of metabolizing enzymes of the different immunosuppressive agents.

		T_{max}	Oral bioavailability	Interference of food intake	Polymorphisms affecting metabolism
Tacrolimus	Regular	1–2 h [106]	20–25% [107]	Fatty meal decreases exposure with 33% [108]	*CYP3A4*22*[109]
	Prolonged-release	2–3 h [112,113]	20–25%[a] [113]	Food decreases exposure with 25% [112]	*CYP3A5* [110]
	LCP	6 h [114]	26–33% [114]	Food decreases exposure with 55% [115]	*POR*28*[b] [111]
Sirolimus		1.5–2 h [116]	15% [117]	Fatty meal increases exposure with 35% [118]	*CYP3A5* [119]
Everolimus		1–2 h [120]	16% [120]	Fatty meal decreases exposure with 16% [121]	CYP3A4*22 [122]
Cyclosporine (microemulsion)		1.5–2 h [123]	40% [124]	Fatty meal decreases exposure with 15% [124]	CYP3A4*22 [122]
Steroids		1–3 h [125]	90% [125]	No effect on exposure [125]	None
Mycophenolate mofetil		1–2 h [29]	81–87% [10,29]	No effect on exposure [29]	None
Enteric-coated mycophenolate sodium		1.5–2.75 h [29]	72% [28]	No effect on exposure [29]	None
Azathioprine		1–2 h [126]	47% [126]	Unknown	None

LCP: prolonged-release with LifeCyclePharma delivery technology.
[a] Investigated with the regular formulation.
[b] Only in *CYP3A5* expressers.

important enterohepatic recirculation of MPA/MPAG, which is reflected in a second peak in the MPA concentration-time curve 6–12 h after the ingestion of MMF and accounts for 10%–60% of the total MPA exposure [10]. CsA inhibits the biliary excretion of MPAG and therefore also the enterohepatic recirculation [11–13]. Consequently, patients treated with CsA usually require a higher dose of MMF than patients not treated with CsA [14].

After absorption, approximately 90% of the prodrug AZA undergoes conversion to 6-mercaptopurine (6-MP) by sulphydryl-containing compounds that are present in every mammalian cell [15]. In a study with healthy volunteers, AZA was administerd at different locations in the GI tract [16]. The exposure to 6-MP was highest when AZA was administered in the jejunum and lowest when AZA was delivered in the cecum, indicating that the small bowel is important in absorption of AZA.

3. Effects of ageing on metabolism of immunosuppressive medication

Ageing is associated with changes in pharmacodynamics and pharmacokinetics. Elderly renal transplant patients have a reduced risk of acute rejection but an increased risk to die from infectious complications. The amount of body fat increases, which results in an increased distribution volume for lipophilic drugs, such as tacrolimus and CsA. Elderly renal transplant patients are at increased risk for drug-drug interactions and adverse effects, including nephrotoxicity.

A prospective study that assessed tacrolimus through levels in several age groups, found that advanced age and CYP 3A5*1 were associated with higher dose and weight adjusted through levels, indicating an age related decline in clearance [17]. A similar effect of age on through levels was observed for CsA. In the nEverOld Trial, pharmacokinetics of MPA was not different between younger and older renal transplant patients [18].

4. Consequence of gastrointestinal abnormalities and diseases on the exposure to immunosuppressive drugs

4.1. Vomiting

In general, vomiting reduces the absorption of immunosuppressive drugs, particularly if drugs have not yet passed the stomach and duodenum. If the pills appear to be complete in the vomit or patients throw up within 0.5 h after ingestion, it is typically recommended to take the full dose again. When absorption of immunosuppressive drugs is insufficient due to ongoing vomiting, it is common practice to administer higher doses of CS intravenously to avoid underimmunosuppression. If complaints persist for >24 h, the CNI is usually administered intravenously. Based on the bioavailability of tacrolimus, a dose conversion ratio of 4:1 (oral:intravenous) is recommended. The aim with continuous intravenous infusion is to attain blood concentrations that are 1.4 times higher than target trough levels applied for regular oral use [19].

CsA can also be administered intravenously with a recommended dose conversion ratio of 3:1 [20]. It has been estimated that the target blood concentration of CsA during continuous intravenous administration has to be 2.55 times higher than the target trough level with oral administration [19].

GI adverse effects of MMF, like vomiting and diarrhea have still been reported during intravenous infusion [21]. Therefore, this drug is often discontinued if patients suffer from vomiting.

AZA can be given intravenously in a reduced dosage accounting for the bioavailability of about 50%. Sirolimus and everolimus are poorly soluble in water and can therefore only be given orally.

In patients who vomit but otherwise have a normal function of the GI tract, some drugs can also be administered rectally. Rectal administration of powder obtained from the oral tacrolimus capsules results in systemic exposure and might represent an alternative for oral administration [22]. Additional research should establish the optimal dose and dosing frequency for rectal administration. In contrast, CsA cannot be administered rectally since it leads to negligible systemic exposure [23]. Finally, CS may also be rectally administered since hydrocortisone as rectal suppository resulted in adequate systemic exposure [24].

4.2. Tube feeding

Direct enteral feeding through a nasogastric tube is required for patients who cannot eat normally, but have an intact GI tract like ventilated patients. Potential issues in these patients are the possibility to crush tablets and the bioequivalence of available alternatives such as sublingual and rectal administration (see above).

A tacrolimus suspension is available for administration via a nasogastric feeding tube. However, the bioavailability of this suspension is reduced due to incomplete solubility or absorption [25]. An alternative might be to administer the drug sublingually, but data on the absorption after sublingual administration are contradictory [22,26].

CsA solution can be administered by a nasogastric feeding tube in the same dose as taken in tablets. Adequate trough levels of CsA were obtained using this way of administration [27].

Sirolimus is available as a solution and everolimus as a dispersible tablet. A study with stable renal allograft patients who were converted from the liquid to tablet formulation of sirolimus, demonstrated near bioequivalence for the two formulations [28].

CS are available in a liquid formulation for administration via a feeding tube, the dose being similar to the dose in tablets.

MMF can be given in a suspension formulation via a feeding tube [29]. However, if the tip of the tube is situated in the duodenum this can result in reduced de-esterification of MMF and decreased exposure to MPA. EC-MPS tablets should not be crushed prior to ingestion to

maintain the integrity of their enteric coating. Therefore, they are not suited for administration via a nasogastric tube.

Finally, AZA cannot be given via a nasogastric feeding tube since the tablet cannot be crushed and a liquid formulation is not available.

4.3. Gastroparesis

Gastroparesis is a syndrome characterized by delayed gastric emptying in the absence of mechanical obstruction. Diabetes mellitus and previous surgery are common causes of gastroparesis, but it is idiopathic in a considerable number of cases [30]. The time course of gastric emptying can affect the absorption of several immunosuppressive agents. The bioavailability of CsA is markedly impaired by gastroparesis [31]. Although the rate of tacrolimus absorption, reflected by the time to achieve maximum blood concentration, is delayed by gastroparesis, total absorption and exposure are unaffected [32]. The effect on exposure to other immunosuppressive agents has not been studied.

Tacrolimus has a prokinetic effect on the GI tract via motilin receptors. In contrast, CsA does appear to slow gastric emptying of solids [33]. Tacrolimus is therefore the CNI of choice in patients with gastroparesis [34]. Since mTOR inhibitors also have prokinetic properties, they might be an alternative to tacrolimus [35]. AZA, mycophenolate and CS do not affect gastric emptying [33,35].

4.4. Intestinal resection

Absorption of CNIs, mTOR inhibitors and CS particularly takes place in the upper GI tract (duodenum and proximal jejunum) and the effect on blood concentrations is most pronounced if this part of the tract has been resected [36]. Consequently, the absorption capacity is diminished after intestinal resection, but the pattern of the concentration-time curve of CNI is similar to that in subjects with a normal GI tract [37]. After a jejunoileal bypass, therapeutic blood concentrations can be achieved with an elevated dose of a CNI [38].

There are no data about the effect of intestinal resection on the absorption of mTOR inhibitors.

As discussed previously, mycophenolate undergoes enterohepatic recirculation, which contributes approximately 40% to the area under the concentration time curve [29]. Consequently, ileostomy can severely reduce the blood concentration of MPA [39].

The exposure to oral CS has reported to be normal in patients who underwent intestinal resection, although concomitant hypoalbuminemia seems to reduce the exposure to CS [40]. The effect of intestinal resection on the absorption of AZA is unknown.

In all patients with intestinal resection, more intensive pharmacokinetic monitoring of immunosuppressive drugs is recommended. Before transplantation, pharmacokinetic measurements after a single or multiple test doses can be performed to provide an estimation of an appropriate starting dose after transplantation. An alternative approach might be to use belatacept instead of a CNI since the intravenous dosing schedule (once every 2–4 weeks) warrants adequate exposure.

4.5. Bariatric surgery

A frequently performed bariatric operation is the Roux-en-Y gastric bypass that results in an intended decreased stomach capacity and a bypass of the duodenum and first part of the jejunum. Limited data are available about the absorption of immunosuppressive drugs in patients with a Roux-en-Y gastric bypass. A study in two renal transplant patients after gastric bypass surgery using tacrolimus or MPA demonstrated that the AUC: dose ratio was significantly lower in both patients after bariatric surgery than in controls without gastric bypass [41]. Proposed mechanisms include an increase in stomach pH, decreased gastric mixing capacity, reduced exposure of hydrophobic drugs to bile acids, and a decrease in absorptive area [42]. Sleeve gastrectomy is another effective surgical intervention to lose weight in obese patients. One pilot cross-over study assessed pharmacokinetics of immunosuppressive medication in patients with a sleeve gastrectomy. This study concluded that no specific drug changes are necessary and standard therapeutic drug monitoring is recommended [43].

4.6. Diarrhea

Diarrhea, defined as >3 loose stools per day, is the result of inflammation, infection or malabsorption amongst other causes. Diarrhea leads to an enhanced exposure to tacrolimus which can be explained by two mechanisms. Firstly, the oral bioavailability of tacrolimus is increased due to diminished activity of the CYP3A system and/or ABCB1 in damaged enterocytes [44]. Secondly, a higher amount of tacrolimus may be delivered to the colon due to a shortened ileal transit time. In the colon, a lower metabolic activity of CYP3A could result in increased absorption [45]. Therefore, it is recommended to monitor tacrolimus levels intensively during and shortly after an episode of diarrhea. Although CsA, mTOR inhibitors and CS are also substrates for CYP3A isoenzymes and ABCB1, increased exposure during diarrhea has not been described for these drugs. This suggests that the intestinal metabolism contributes lesser to total drug clearance for these drugs than in the case of tacrolimus [46]. There are no reports about the effect of diarrhea on AZA and mycophenolate exposure.

5. Gastrointestinal side effects of immunosuppressive drugs

Although GI adverse effects of immunosuppressive drugs are commonly reported, delineating the adverse effect profile of each individual drug is hampered by the fact that most patients use a combination of immunosuppressive agents. Moreover, it can be difficult to distinguish side effects from complaints due to the underlying renal disease. In the section below and in Table 2, we summarize the reported GI adverse effects of each agent separately.

5.1. Tacrolimus

A meta-analysis of randomized trials comparing tacrolimus to CsA revealed that GI adverse effects, especially diarrhea, are more common in patients treated with tacrolimus than in those treated with CsA [47]. A cross-sectional study with 543 renal transplant patients who all underwent upper endoscopy because of GI complaints, showed that renal allograft recipients receiving an immunosuppressive regimen consisting of tacrolimus, CS and MMF had a higher frequency of erosive lesions in the upper GI tract (24.4%) as compared to patients treated with CsA-CS-MMF (18.4%) or CsA-CS (15.9%) [48]. However, a difference in the incidence of upper GI complications between patients on tacrolimus and those on CsA is not a uniform finding [49]. Finally, case reports about tacrolimus-induced pancreatitis have been published, possibly related to higher tacrolimus blood levels [50,51].

5.2. Cyclosporine

Gingival hyperplasia is a well-known complication of the use of CsA and might be associated with *ABCB1* polymorphism since the transporter is expressed in the endothelial layers of blood vessels in gingival tissue [52]. Hyperplasia can be aggravated by concomitant use of calcium channel blockers and inflammatory processes due to dental plaque accumulation and other local factors [53]. Appropriate oral hygiene and cessation of the calcium channel blocker are the cornerstones for reducing the severity of gingival overgrowth. If hyperplasia persists, discontinuation of CsA and switch to another immunosuppressive agent should be pursued. Treatment with azithromycin may improve gingival hyperplasia, but increases CsA levels due to inhibition of its metabolism and is thus not routinely recommended [54].

Table 2
GI adverse effects of various immunosuppressive agents.

	Oral ulcers/stomatitis	Gingival hyperplasia	Nausea /vomiting/dyspepsia	Gastroparesis	Pancreatitis	Chronic diarrhea	Constipation
Tacrolimus	+	0	++	0/+	0/+	++	+
Cyclosporine	0	+	+	+	0/+	+	0
mTOR inhibitors	++	0	++	0	0/+	++	++
Corticosteroids	0	0	+	0	+	0	0
Azathioprine	0	0	+	0	+	0	0
Mycophenolate	+	0/+	++	0	0/+	++	+

Undesirable effects are listed using the following categories: ++ very common (≥1/10); + common (≥1/100 to <1/10); 0/+ uncommon (≥1/1000 to <1/100); 0 rare (<1/1000).

CsA slows the gastric emptying of solid foods and therefore patients can suffer from dyspepsia and nausea although these complaints are less frequent than in tacrolimus treated patients (see above).

Moreover, CsA may be able to induce acute pancreatitis. The incidence reported in renal transplant patients treated with CsA is approximately 3% [55].

Diarrhea occurs in CsA treated patients, with a reported incidence between 14 and 47% [56]. The mechanism of CsA-induced diarrhea is unclear [56]. Constipation is also reported and appears to be more frequent in patients treated with CsA than in those treated with tacrolimus [47].

5.3. mTOR inhibitors

A bothersome GI complaint in patients receiving sirolimus is the occurrence of oral aphthous ulcers. It has been suggested that ulceration is caused by a direct toxic effect of sirolimus on the oral mucous membranes [57], but also the antiproliferative effect of sirolimus and the effect on growth factors could play a causal role [58]. The wide variability in the frequency of aphthous ulcers (10–100%) is probably related to various factors like the moment of introduction, the underlying circumstances, and the applied treatment protocols. For example, lack of CS co-administration may increase the incidence of oral ulcers [59]. Chronic fissure of the lips and chronic gingivitis were also reported to be common (20% and 11%, respectively) in patients treated with sirolimus [57]. Although reported less frequently, mouth ulceration has been described in patients treated with everolimus too [60].

The manufacturer reports that the incidence of diarrhea with sirolimus varies from 25% to 42% [61]. Suggested mechanisms are downregulation of the Na+/H+ exchanger 3 expression in apical membranes of the intestines and lipid malabsorption [62,63]. Furthermore, since sirolimus has, like tacrolimus, a macrolide chemical structure, prokinetic effects may contribute to the occurrence of diarrhea [64]. Other reported adverse effects of mTOR inhibitors include abdominal pain, nausea, vomiting, dyspepsia, and notably also constipation.

5.4. Mycophenolate

Patients using MMF frequently experience nausea, vomiting, heartburn, dyspepsia, anorexia, and especially diarrhea. In three clinical trials where MMF was combined with CsA in renal transplant recipients, the incidence of diarrhea within the first year after transplantation ranged from 15.6% to 32.5% for a 2000 mg daily dose of MMF [65–67]. In patients using the combination of tacrolimus and MMF, the reported incidence of diarrhea is even higher [68]. The mechanisms responsible for GI intolerance and especially diarrhea are still a matter of debate. The symptoms usually resolve after a dose reduction, a temporary interruption, or a complete discontinuation of MMF. The intravenous administration of MMF is associated with a higher incidence of GI adverse events as compared to oral administration and this suggests that systemic exposure to MPA and/or its metabolites contributes to GI adverse effects [69]. However, no relation was demonstrated between diarrhea and the plasma concentration of the reactive acylglucuronide metabolite of MPA [70].

In patients with MMF-associated diarrhea villous atrophy in the duodenum and erosive inflammation in the ileum have been observed [71,72]. It was suggested that local effects of acylglucuronides metabolites, that are excreted with bile in the intestine, might provoke diarrhea [70]. Patients who use CsA and carriers of a biliary transporter polymorphism which reduces the excretion of MPA metabolites, could therefore have less diarrhea [73]. Others suppose that MMF impairs the global enterocyte function through either a higher apoptotic rate or an impaired function of the tight junctions leading to leak-flux diarrhea [74]. Besides, some authors have reported severe oral and colonic ulcerations that were suggested to be attributable to MMF toxicity [75,76]. In some patients the use of MMF has been linked to a Crohn's-like enterocolitis, which responded to discontinuation of the drug [77]. The exact mechanism underlying these ulcerations is unknown, but a direct toxic injury of MPA on the GI mucosa may be involved.

The enteric coated formulation of MPA, EC-MPS, was developed with the perspective to reduce the incidence of GI adverse events. In open-label studies an improvement in GI tolerability after conversion from MMF to EC-MPS was indeed observed [78,79]. EC-MPS might therefore be a useful alternative in some patients who suffer from MMF-related GI symptoms. However, in comparative studies with MMF used in an equipotent dose, the overall incidence and the profile of GI adverse events were similar in patients treated with either MMF or EC-MPS [80,81].

5.5. Azathioprine

In a retrospective review on side effects of AZA, GI complaints were reported in 19 of the 542 patients [82]. Approximately 10% of the patients had nausea and/or vomiting while GI symptoms not otherwise specified were reported in 6% of the patients. There are only two cases described of chronic diarrhea with severe villous atrophy possibly induced by AZA [83,84]. Acute pancreatitis due to AZA is a dreaded complication and was predominantly described in patients with inflammatory bowel disease [85].

In rare cases, a syndrome mimicking serious gastroenteritis may occur after administration of AZA [86].

5.6. Corticosteroids

Adverse effects of CS on the GI system include peptic ulcers, upper GI bleeding, pancreatitis, diverticular perforation, and malakoplakia. A meta-analysis comparing CS therapy for any medical condition to placebo revealed that the use of CS increased the risk of GI bleeding or perforation by 40%, especially in hospitalized patients [87].

CS have been listed as a cause for drug-induced acute pancreatitis [88]. In contrast, experimental studies have shown survival benefit with the use of hydrocortisone in animal models of acute pancreatitis [89]. However, the potential of CS to prevent pancreatitis after endoscopic retrograde cholangiopancreatography could not be demonstrated in clinical trials [90].

Colonic malakoplakia, a chronic granulomatous disease, is linked to the use of CS but also to the use of other immunosuppressive drugs [91].

5.7. Belatacept

Belatacept is a costimulation blocking agent that has to be administered intravenously. In two phase III trials (BENEFIT and BENEFIT-EXT), the incidence of GI side effects, as constipation, diarrhea and nausea was comparable between belatacept and CsA treated patients [92,93]. Several case reports describe development of inflammatory bowel disease during belatacept treatment [94,95].

6. Interaction between drugs targeting the gastrointestinal tract and immunosuppressive drugs

Some commonly given GI targeting drugs can affect the exposure to immunosuppressive drugs. The potential interactions are presented in Table 3 and are described in the following sections.

6.1. Prokinetic agents

Prokinetic agents like metoclopramide can increase the bioavailability of CNIs, mTOR inhibitors and CS by accelerated gastric emptying while metabolic capacity is less in the distal intestine. This phenomenon has especially been described for the combination of metoclopramide and CNIs [96]. Moreover, domperidone and ondansetron are substrates for ABCB1 and are metabolized by CYP3A4. Interactions with CNIs, mTOR inhibitors and CS might thus occur, but they have not been reported.

6.2. Antacids

The concomitant use of antacids containing aluminum and magnesium hydroxides reduces the exposure to MPA as a consequence of diminished absorption [97]. It is most likely explained by chelation, although an increase of the gastric pH with decline of elution and hydrolysis of mycophenolate might be an alternative explanation.

6.3. Proton pump inhibitors

Combined treatment with MMF and proton pump inhibitors (PPIs) reduces the exposure to MPA due to a decreased de-esterification of MMF [98,99]. This could result in undesired under-immunosuppression. A higher rate of acute rejection in renal transplant patients receiving PPIs next to MMF was observed in African Americans, but not in other populations [100]. The pharmacokinetics of EC-MPS is not affected by PPI co-administration as metabolism does not depend on the gastric pH [101].

PPIs are metabolized by cytochrome P450 enzymes, most notably by CYP2C19 but also by CYP3A4. Reduced activity of the CYP2C19 enzyme leads to an increased reliance on CYP3A4 for PPI metabolism. In this situation, an interaction with tacrolimus, resulting in increased tacrolimus levels has been described. Since the extent of metabolism by CYP2C19 versus CYP3A4 differs for the various PPIs, the risk for this type of interaction also varies per PPI [102].

6.4. H2 antagonists

Although H2 antagonists suppress gastric acid secretion, their effect on gastric pH is less than that of PPIs and there is no impact on the exposure to MPA [99]. Of note, it should be taken into account that serum creatinine usually rises after starting with cimetidine due to inhibition of the tubular secretion of creatinine, without a change in the glomerular filtration rate.

6.5. Helicobacter pylori eradication regimens

Triple therapy based on a PPI combined with clarithromycin and amoxicillin and/or metronidazole is the established first-line therapy for Helicobacter pylori eradication [103]. An interaction of clarithromycin with CNI, mTOR inhibitors or CS can occur via inhibition of CYP3A and ABCB1. Therefore, an alternative eradication regimen should be considered in transplant patients using these drugs, although intensified therapeutic drug monitoring is also an option. A disadvantage of the alternative eradication regimen consisting of PPI, levofloxacin and amoxicilline is the rising rates of levofloxacin resistance [103]. Moreover, concomitant use of metronidazole reduced the exposure to MPA with approximately 19% in healthy subjects [104]. This interaction is caused by disruption of the enterohepatic recirculation of MPA [29].

6.6. Loperamide and laxatives

Loperamide and most laxatives do not have clinically relevant interactions with immunosuppressive drugs. In rats, it was established that CsA increased the brain concentration of loperamide by inhibiting ABCB1 in the blood brain barrier [105]. However, such an effect has never been described for the intestinal ABCB1. The only laxatives showing an interaction with immunosuppressive drugs are magnesium containing ones, which reduce the bioavailability of MPA.

7. Conclusion

Most immunosuppressive agents are metabolized to a substantial extent in the GI tract. GI disorders can therefore affect the exposure to these agents. Knowledge on the involvement of transport proteins and metabolizing enzymes will help to better understand the consequences of GI tract disease and disturbances on immunosuppressive therapy. On the other hand, immunosuppressive agents can have adverse effects on the GI tract that affect quality of life, and can even have impact on patient or allograft survival. For physicians who prescribe immunosuppressive drugs to organ transplant recipients it is important to realize this reciprocal interaction.

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Table 3
Interactions between commonly used GI targeting drugs and immunosuppressive agents.

	Prokinetics	Antacids	Proton pump inhibitors	H2 antagonists	Hp eradication	Antidiarrheals	Laxatives
Tacrolimus	±	−	±	−	+	−	−
Cyclosporine	±	−	−	−	+	−	−
mTOR inhibitors	−	−	−	−	+	−	−
Corticosteroids	−	−	−	−	−	−	−
Azathioprine	−	−		−	−	−	−
Mycophenolate	−	+	±	−	+	−	±

Interactions are symbolized as follows: +: proven interaction; ±: possible interaction; −: interaction not reported.
Hp: Helicobacter pylori.

Declaration of interest

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