Gastrointestinal Side Effects of Post-Transplant Therapy

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ABSTRACT

Modern immunosuppressive therapy has produced a real revolution in renal and organ transplantation but it comes with the price of multiple side effects. There are many gastrointestinal (GI) complications that are the consequence of transplant immunosuppressant medication. In fact, for any immunosuppressant therapy, certain standardized precepts and attitudes that aim to reduce the incidence and the impact of the medication side effects must be applied. Many patients undergo renal transplantation and the physicians have to be aware of the advantages and the risks associated. This article reviews the main GI complications that may arise as a consequence of immunosuppressive therapy after solid organ transplantation, focusing on renal and renal/pancreas transplantation, as well as the ways in which the incidence of these complications can be reduced. Management of the post-transplant therapy is mandatory in order to increase not only the grafts' and the patients' survival, but also their quality of life by the occurrence of fewer complications.

Key words: gastrointestinal complications – transplant – renal transplant – immunosuppression.

Abbreviations: Aza: azathioprine; CMV: cytomegalovirus; CsA: cyclosporine A; GI: gastrointestinal; MMF: mycophenolate mofetil; NSAID: non-steroidal anti-inflammatory drugs; Tac: tacrolimus.

INTRODUCTION

Modern immunosuppressive therapy has produced a real revolution in renal and other organ transplantations, generally leading to a dramatic improvement in patients' survival and their quality of life. However, this success comes with a price: multiple side effects of the immunosuppressive drug therapy. Many of these complications occur in the gastrointestinal (GI) tract [1-6].

This article reviews the main GI complications that may arise as a consequence of the immunosuppressive therapy administered after solid organ transplantation, focusing on renal and renal/pancreas transplantation, and the ways in which these complications could be prevented.

As expected, by using such drugs, which decrease the immune defense ability of the body, the most common complications are infections, of which some persistently affect the functionality and integrity of the GI tract. The infections consecutive to immunosuppressive therapy may be bacterial, viral, fungal or parasitic.

CYTOMEGALOVIRUS (CMV) INFECTION

Of all the viruses that may affect the GI tract: adenovirus, syncytial virus, influenza virus, polyoma virus, we will mainly focus on CMV infection because it results in the widest range of GI complications.

The CMV infection affects many transplanted patients, particularly, but not only, in areas where patients often have a latent infection preexisting to the transplantation. It is estimated to be present in up to 100% patients after renal or renal/pancreas transplantation, a significant proportion of these having symptomatic disease [7]. A peculiarity is that CMV infection may be systemic even if symptoms are systemic or localized to a specific region of the digestive tract. Gastrointestinal location of the CMV infection is present in about 50% of these patients, with pancreas recipients at a greater risk. The digestive symptoms of the infection usually occur within the first 6-12 months after transplantation.

It should be noted that CMV can affect any segment of the digestive tract, from the mouth to the anus, so that symptoms can have a very wide range, starting with dysphagia, odynophagia, nausea, vomiting, abdominal pain, GI bleeding and intestinal perforation or bleeding. Frequently, the infection can cause a clinical picture of pancreatitis, especially if the patient has underwent kidney/pancreas transplantation or had preexisting CMV infection. This digestive manifestation of the CMV infection was shown to be more common in patients treated with cyclosporine A (CsA) [8, 9]. If we assess the five or six, commonly used, immunosuppressive medications, we observe that mycophenolate mofetil (MMF) is associated with a higher rate of CMV tissue invasiveness especially in the GI tract [6-8, 10]. Indeed, increased immunosuppression, such as by anti-lymphocyte antibody and conventional MMF therapy is one of the main predisposing factors to CMV infection. Besides this, there are other independent risk factors for CMV infection, such as transplantation from a CMV positive donor to a CMV negative recipient with or without concomitant presence of leukopenia.

There are several studies that discuss the connection of tissue invasiveness of CMV, more or less targeted on the GI tract, in comparison with the treatment with MMF [10-12]. Mycophenolate mofetil treatment and CMV invasiveness were also compared with the equivalent of the classic MMF, i.e. azathioprine (Aza). With regard to Aza therapy, the CMV infection rate is approximately 6.5-7%, while the incidence of GI infections with CMV in case of MMF therapy depend on the dosage (2g-3g per day), reaching up to 12% in the investigated groups [11-13].

Often, the GI consequences of CMV infection, such as persistent and abundant diarrhea, nausea, vomiting and leukopenia [14] have led to the cessation of the MMF treatment or to the reintroduction of Aza, replacing the MMF [10]. All these digestive and general symptoms are more pronounced if MMF is administered in a crisis situation of acute rejection, when high doses of other immunosuppressant drugs, including steroids, are concomitantly used. Moreover, patients who are in such situations experience pathological manifestations in the upper digestive tract, which quite often require endoscopic evaluation, biopsy and endoscopic treatment [14].

Recent studies have further complicated the controversy over the existence of a link between CMV disease and the MMF dosage [15]. These studies showed that patients who were given maintenance therapy with MMF in the context of a complex immunosuppression with either CyA or tacrolimus (Tac), to which prednisone was added, had persistent epigastric pain. Gastric endoscopy followed by biopsy demonstrated in most cases the existence of CMV either in the gastric mucosa or at the level of intestinal mucosa. More than that, if instead of CyA, Tac was added to the MMF therapy, the risk of CMV infection manifested by epigastric pain was higher.

In principle, any patient who is in the early post-transplant stage or during intensive immunosuppression treatment against rejection, and who has fever, nausea, vomiting, diarrhea and leukopenia with increased liver enzyme levels must be submitted as soon as possible to GI endoscopy and biopsy in order to exclude the existence of CMV gastroenteritis. The inability to identify the presence of the enteric CMV at this stage may indicate a systemic disease with multiple organ damage: lung, liver or even perforation of hollow organs [8].

Even if CMV typically is associated with erosive, ulcerative or erythematous injuries of the digestive tract, the endoscopic aspects do not allow the diagnosis in the absence of histopathological or laboratory confirmation of the biopsy specimen.

The prophylaxis of CMV disease after transplantation has evolved from acyclovir to valganciclovir. The results seemed contradictory when using acyclovir. However, prophylaxis has proved to be efficient in cases where the administration of at least 2 g of acyclovir is given for a period of time up to 6 months [16]. Ganciclovir alone has significant impact on CMV infection post-transplantation, regardless both the immunosuppressive context of the patient and the quality of the donor [17]. More recently, valganciclovir has proved to be efficient. One of the latest randomized studies that compared two series of patients (one series was given a placebo and the other received 2 g of valganciclovir 4 times a day for 90 days) showed a significant reduction in the occurrence of CMV disease within approximately 6 months after the onset of treatment [18]. Ganciclovir and valganciclovir significantly reduce the incidence of CMV disease in transplant recipients, and are currently the principal drugs used for the treatment or prevention of CMV infection.

DIARRHEA

Diarrhea occurs in transplanted patients mainly due to infectious conditions, but it may occur even in the absence of infection. Many studies suggest that side effects on the intestinal tract are more frequent when Tac is administered as compared to CyA [1, 2, 19]. Diarrhea, nausea and vomiting are more common in patients receiving Tac [2, 19]. Dyspepsia and constipation are also common, as well as abdominal pain. Obviously, all of these symptoms depend on the dosage. Generally, dose reduction is followed by the decrease or the disappearance of GI symptoms. When patients have these symptoms under immunosuppression with Tac, they are usually given CyA, which has fewer GI symptoms. Sometimes, patients with severe GI symptoms may require parenteral nutrition to lessen the side effects of anorexia.

Therapy with MMF presents a very high rate of GI incidents, too. One of the possible mechanisms through which MMF causes the mentioned intestinal symptoms, in particular diarrhea, is the inhibition of cell division and induction of apoptosis at the level of the colonic crypts through an immune-mediated mechanism, as well as the loss of villous, normal structure of duodenum [20]. As many GI symptoms have been related with the use of MMF (CellCept), this has been largely replaced by enteric-coated mycophenolic acid (Myfortic), with fewer GI side effects [7].

Obviously, as a consequence of the mentioned symptoms, other strategic attitudes have been selected in order to alter the manner of administration of these immunosuppressant drugs (total dose reduction, or dividing the total dose into two or three smaller doses which resulted in the reduction of the intensity and duration of the side-effects) [10, 11, 21].

Bacterial infections

Bacterial infections of the intestinal tract are not uncommon in these patients. The most common species affecting transplanted patients are *Yersinia enterocolitica* and *Clostridium difficile*. Typically, these infections are more frequent if the patient presents a concomitant systemic CMV [22]. Septicemia due to *Yersinia enterocolitica* can occur especially in patients who have iron in excess in their body, diabetes mellitus or chronic liver disease. Very aggressive immunosuppression favors the occurrence of these infections. Clinically, the patients present GI symptoms such as diarrhea and abdominal tenderness, but rarely they have presented erythema nodosum, arthritis, myocarditis, meningitis or acute renal failure. Appropriate antibiotic treatment is effective.

Although the real incidence of *Clostridium difficile* infection in transplanted patients is not known, it was reported in an assessment as being present in 8%-16% of the pediatric renal transplanted patients, approximately 15.5% in combined kidney/pancreas transplanted patients, and around 3.5% in adult patients with renal transplantation [23]. The transplanted patients can be asymptomatic carriers of *Clostridium difficile*, but most often they develop diarrhea, intestinal obstruction, abscesses, or toxic megacolon. The oral treatment with metronidazole and in severe cases with vancomycin is usually effective.

Parasitic infections

Parasitic infections occur in the same context of depression of the immunological defense capability. The most common are the protozoan or metazoan parasites. Microsporidia are intracellular protozoan parasites. Gastrointestinal infection with microsporidia is the most common cause of diarrhea in a different category of immunosuppressed patients, namely in HIV patients. However, such infections have been recorded also in patients with solid organ transplantation who experienced diarrhea and weight loss [24]. It is possible that the microsporidia infection rate could be much higher, but this requires special faecal tests for diagnosis.

Another parasite that causes infection in transplanted patients is the *Strongyloides stercoralis* nematode. It usually produces fever, abdominal pain, abdominal distension, nausea, bloody diarrhea, vomiting. Some patients may experience acute respiratory symptoms due to *Strongyloides stercoralis* migration in lungs. The mortality rate in these cases is very high [25]. This parasitic infection is most common in endemic areas of the West Indies or in Asia. It is remarkable that the rate of infection with this type of parasite significantly decreased when CsA was introduced. Specific examination of faeces is recommended regarding the presence or the absence of this parasite in living donors from those areas. Even if there is only suspicion of an infection with *Strongyloides stercoralis* in a possible kidney donor, it is preferable to initiate the treatment with albendazole until the infection is eradicated. The same treatment can be administered to the transplant recipient [26, 27]. It is worth noting that thiabendazole interferes in the liver with medications containing xanthine, but it does not interefere in its hepatic metabolism with the calcineurin inhibitors.

ULCERS OF THE GI TRACT

Several factors contribute to the occurrence of ulcerations in transplanted patients. Such as, for example, the stress of the surgery, the use of non-steroidal anti-inflammatory drugs (NSAIDs), the use of steroids, the impairment of the existing mechanisms of GI cytoprotection by medications such as Aza or MMF, that slow the intestinal and gastric cell regeneration cycle [28], and the presence of infections. In the case of kidney transplantation there are other ulcer promoter factors such as increased gastric acid secretion during post-renal transplant dialysis, the effect of heparin used during dialysis, the increased histamine and gastrin levels during the post-surgical period [28].

Although, until recently, the role of steroid treatment was clear as a cause of ulceration development, especially gastric ones, currently, at least in transplanted patients, it is controversial. It is clear [28] that patients treated especially with methyl-prednisolone during the crisis of rejection develop a greater rate of gastric and intestinal ulcerations, or of inflammatory lesions at this level in comparison with patients that do not undergo this type of treatment. What is also clear is that the development of peptic ulcers in transplanted patients is actually a multifactorial phenomenon. Although the overall incidence is lower than in other periods of evolution of the post-transplant immunosuppression treatment, these ulcers tend to occur at varying and unpredictable intervals. Moreover, the diagnosis itself is dimmed and complicated because of the fact that steroid administration is actually masking the clinical symptoms of ulcer and of other GI disorders, thereby delaying the diagnosis and the treatment of lesions [5]. In fact, many of the ulcerative lesions in transplanted patients are entirely asymptomatic. In one study, only 39% of patients who were proven to have endoscopic ulcerative lesions presented symptoms [28]. A fact that has not been fully clarified is that in lung transplant patients, especially in those with double lung transplant, giant gastric ulcers (larger than 3 cm) occur. The studies that sought to elucidate the etiology of this very serious and sometimes deadly complication associate this phenomenon with the very high doses of NSAID pain relievers that are taken for at least one week after transplantation together with high doses of steroids against acute rejection and CyA. As a consequence, many transplant centers no longer use NSAIDs in transplanted patients.

There is no clinical or demographic factor to limit the area for identifying patients at a high risk of having GI ulcers. Therefore, this requires a high degree of clinical suspicion and also a low threshold of endoscopy indication with histology, microbiology and virology harvesting when we suspect this type of pathology [5]. Although there are transplant groups who perform routine digestive endoscopy in the postoperative evolution of transplanted patients (in the 7th and 14th day), even if H2 antagonists or proton pump inhibitors (PPIs) are used, the overall impression is that these maneuvers are aggressive and recommended only in specific cases.

The prophylaxis of these types of ulcers is based on all methods that can reduce acid secretion, or protect the mucous membranes against the effects of gastric acid secretion. These

methods include H2 receptor antagonists, PPIs, surface protection agents or prostaglandins. An effective treatment regimen [30] used to associate misoprostol (analog to E1 prostaglandin) with an antacid and with ranitidine.

In all the efforts to protect transplanted patients against digestive ulcerations, with various combinations of drugs, as mentioned above, this plethora of medication might however greatly complicate the effectiveness of immunosuppression through several mechanisms. Administration of H2 antagonists decreases the efficient levels of CyA. Also, H2 antagonists may result in falsely elevated levels of creatinine by blocking the tubular secretion of creatinine. Routine administration of sucralfate decreases the absorption of CyA. The administration of PPIs and of H2 antagonists, by reducing the gastric acid secretion, may alter the intestinal flora and increase the risk of colonization in an antagonist way with bacteria, parasites and fungi. Currently, most specialists in the field of transplantation use upper GI endoscopy, both for solving gastric or intestinal ulcerations and for managing the complications arising from those ulcerations.

Helicobacter pylori infection

Helicobacter pylori plays an important role in the etiopathogenesis of gastritis and peptic ulcer. Infection with *Helicobacter pylori* is relatively common both in patients on dialysis and in those who have undergone kidney transplantation [30], but gastritis is highlighted only in some of those patients on dialysis and more frequently in patients undergoing kidney transplantation, suggesting that for these patients, there are additional factors that favor the occurrence of gastritis such as steroids and immunosuppressive drugs administration. The rate of digestive tract involvement is much higher if we consider, in addition to gastric lesions, also duodenal lesions, particularly gastritis or duodenitis [32]. Therefore, testing the presence of *Helicobacter pylori* infection is indicated whenever kidney transplanted patients have these specific symptoms.

Fungal infections

As previously mentioned, in immunosuppressed patients, during the treatment for maintaining the transplanted organ, there are multiple risk factors for the emergence of fungal infections such as sustained antibiotic therapy, use of steroids, primary or secondary hyperglycemia, maintainance of catheters for long periods of time, and impaired cellular immunity. Fungal infections occur most frequently in the first two months after transplantation, and the most common is infection with Candida albicans.

Frequently, Candida infection manifests as an esophagitis with or without concomitant oral lesions. Associated risk factors have already been mentioned: broad-spectrum antibiotics, therapy of acute rejection episodes with high doses of steroids and anti-lymphocyte antibodies. Clinically, patients present odynophagia or dysphagia and less common but more serious, they present fever, chest pain, epigastric pain or GI bleeding. Endoscopically, the lesions may appear as superficial erosions to ulcers with white plaques and nodules. The identification of the type of infection is very important because its progression can lead to the necrosis of the ulcerated

lesions with tracheal and esophageal fistulas having a dramatic evolution [32].

The species most commonly responsible for Candida infections are Candida albicans or Candida tropicalis [4]. These fungal infections can occur in conjunction with a systemic CMV infection. Diagnosis is made by fungi cultures or by histopathological examination. Therapy includes topical application of the antifungal preparation (oral nystatin, amphotericin B) and administration of oral or intravenous antifungals. Liposomal formulations of amphotericin B are less nephrotoxic than the common amphotericin but the liposomal preparation is more expensive.

It is obvious that different transplant programs have a different incidence of fungal infections; therefore, prophylaxis may vary from one transplant program to another. For the prophylaxis of fungal infection of the upper digestive tract, nystatin is usually used, which is given orally every 6 hours for a period of 6 months and especially after the initiation of the treatment of acute rejection crisis. Clotrimazole or amphotericin B can also be administered orally, particularly in patients with kidney transplantation, in whom the treatment has the same effectiveness [5].

What is a fact, not solved yet, is that the optimal duration of prophylactic antifungal therapy is not standardized.

DIVERTICULAR DISEASE

Diverticular disease has been diagnosed in 42% of the patients with terminal renal failure [33]. When this disease becomes complicated, perforation, abscess, phlegmon or fistula may appear. Usually, if these occur after renal transplantation, the percent is significantly lower [35]. The study mentioned above, as well as our personal experience highlights, as a possible presentation of complicated diverticular disease, asymptomatic pneumoperitoneum or generalized peritonitis. It is accepted that patients with a polycystic kidney have a higher percentage of intestinal diverticular disease with a higher incidence of complications [35, 36]. To date, there are no known factors that favor the occurrence of these complications. A study of Vanderbild University on over 1000 patients failed to identify the risk factors that impose their framing in a special category that would require a pre-transplant screening [37]. There are transplant centers that, in the context of the association of diverticular disease to polycystic kidney disease, because of the higher rate of post-transplantation complications, indicate pre-transplant preventive segmental colectomies at the diverticular segment. Based on the above mentioned data, it is recommended in practice to abandon pre-transplant screening for diverticulosis even in patients over 50 years old. The screening will be done selectively only to certain candidates for transplant, especially in those patients who have polycystic kidney and who have had a history of complicated diverticulitis.

PERFORATIONS IN THE INTESTINAL TRACT

Perforation may occur in any part of the GI tract but it is most common in the colon, and could be fatal in about

a third of cases [38]. Most often, perforations are due to a combination of a diverticular disease and impairment of the GI tract integrity consecutive to NSAID treatment, steroids or other immunosuppressive agents [39].

There are two moments of manifestation of the GI perforations in patients with renal transplant: either in a relatively short time after transplant, or later [38]. The patients with perforations in the early period after transplantation are those who usually have had kidney failure treated by dialysis and an immunosuppression more aggressive, particularly with high doses of corticosteroids. The perforations occurring in the early post-transplant period are usually associated with pre-existing disorders such as colonic diverticulosis or CMV colitis.

Late post-transplantation perforations (sometimes years after transplantation) are usually attributed to the presence of diverticulosis or to malignant lesions such as lymphoma. Obviously, as in all the complications that we described so far, there may be other factors. Thus, steroids are considered as potential causal factors for spontaneous colonic perforation both in the normal population and in transplanted patients [40]. A recent report of the MMF study group showed a higher incidence of this complication in patients treated with this drug [41]. Fungal infections such as Mucormycosis cause a higher percentage of gastric perforation in transplanted patients [42]. In recent years, the emergence of broad-spectrum antibiotics with increased efficiency, the adapted and more effective ways of diagnosing these infections, the complex imaging techniques, the aggressive and early surgical or medical approach as well as the modulation of corticotherapy have led to the decrease in incidence and severity of colonic perforations.

DISEASES OF THE BILIARY TRACT

Transplanted patients have a higher risk of biliary complications than the general population. Cholecystectomy after transplantation is usually performed in emergency conditions and it presents a high mortality rate [43]. In a study of heart, lung or lung-heart transplanted patients, 37% were diagnosed with biliary disorders which consisted of gallbladder wall thickening, sludge in the gallbladder with distended bile ducts, gallbladder hydrops, or bile duct stones [43], with high mortality rates following surgery. The etiology of the pancreato-biliary disorders after transplantation is multifactorial; therapy with CyA is associated with a higher incidence of gallstones [44] due to cholestasis and reduced bile transit. Also, common bile duct lithiasis occurs more frequently in kidney transplanted patients who use a CyA-prednisone combination as compared with patients treated with Aza-prednisone [45].

Recent recommendations for the management of biliary disease in transplanted patients include their elective treatment before the transplant, and thorough monitoring post-transplant by ultrasound of all patients who might present such complications.

ACUTE PANCREATITIS

Acute pancreatitis is not a very common complication, but it is extremely serious in transplanted patients. The incidence of acute pancreatitis is 3% to 5.7% in patients with orthotopic liver transplantation but the mortality rate is up to 64% [46, 47]. The main causes are intensive biliary handling during transplantation, recent alcohol intake, the preexistence of viral hepatitis, or malignancies simultaneously operated in the area. In patients with renal transplant, acute pancreatitis has a lower incidence, but the mortality rate is much higher [48]. The CMV infection, hypercalcemia, alcohol, gallstones, and immunosuppression are the most frequent precipitating factors. There are studies that have shown a frequency of acute pancreatitis up to 30 times higher in patients with a transplanted heart as compared to patients who received nontransplant cardiac procedures [49]. The incidence of fatal cases in transplanted patients with acute pancreatitis is also higher than in the control series. The association between acute pancreatitis and other GI diseases such as Crohn's disease and Aza treatment has been also reported [50].

Computed tomography is an essential diagnostic tool for the diagnosis of acute pancreatitis. It highlights the degree of inflammation of the pancreas, edema, necrosis, and peripancreatic fluid extension or fluid collections in the peripancreatic areas. The treatment of pancreatitis in transplanted patients includes the removal of the etiologic agent, if known, the cessation of oral feeding and the use of parenteral nutrition, pain treatment and, in selected cases, surgery that may be lifesaving.

SUMMARY

There are many GI complications that are the consequence of post-transplant immunosuppressant medication. However, there are relatively important discrepancies between several very large studies in terms of methodology, events' definition and combination of drugs, which result in a problematic interpretation and, not least, they leave open the possibility that published data do not really reflect the quality and quantity of GI side effects. Due to the emergence of new generations of immunosuppressant drugs, there exists an automatic tendency to consider that these new classes have fewer side effects on the GI tract, which is not entirely true.

In fact, for any immunosuppressant therapy, certain standardized precepts and approaches that aim to reduce the incidence and the impact of the medication side effects should be followed. Antiviral and antifungal medication and ulcer prophylaxis should always be considered when there is a risk of occurrence of the GI side effects. Since most transplanted patients take steroids in high doses, which attenuate the symptoms or sometimes completely mask the clinical aspects, we should always have a high degree of suspicion regarding these cases and make sure that they are more carefully and more frequently monitored. Even if a GI event is only suspected, and even if it has a mild manifestation, it should be investigated aggressively, by endoscopy and biopsy. The inability to identify a progressive pathological GI condition, which is initially asymptomatic, can be life-threatening and might lead, for example, to intestinal perforation. If diarrhea or other GI events occur, it is not necessary to discontinue the immunosuppressive medication, with consecutive disastrous effects on the graft, but to manipulate the dosage, e.g. by the division of the main dose into several smaller doses or even by the reduction of

immunosuppressant dose. If this is efficient, the symptoms will be reduced to acceptable levels. If the patient is taking MMF or Aza, then the administration of these drugs can be temporarily discontinued by a more appropriate handling of other existing immunosuppressive drugs in a particular therapy (CyA, Tac, cortisone) by maintaining adequate immunosuppression to lower the specific toxicity.

Steroid withdrawal after kidney transplantation may be an option to consider, especially because, at present, the first-line very strong immunosuppressive medication such as MMF and rapamycin may allow their withdrawal in patients who develop serious GI complications after their use.

CONCLUSION

As the experience and the diversity of immunosuppressive medication develops, we will be able to improve, by prevention and by early treatment of GI complications, the outcome of the immunosuppressed transplanted patients.

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Efectele secundare gastrointestinale ale terapiei post-transplant

ABSTRACT / REZUMAT

Terapiile imunosupresoare moderne au produs o adevărată revoluție în transplantul renal și transplantul de organe, însă cu prețul unei multitudini de efecte adverse. Există numeroase complicații gastrointestinale care sunt consecința medicației imunosupresoare de transplant. În fapt, pentru fiecare tratament imunosupresor trebuie să fie aplicate anumite precepte si abordări standardizate cu scopul reducerii incidenței și impactului efectelor adverse ale medicației aplicate. Tot mai mulți pacienți primesc un transplant renal, iar medicii trebuie să fie avertizați asupra avantajelor, dar și a riscurilor asociate. Acest referat trece în revistă principalele complicații gastrointestinale care pot apărea ca o consecință a medicației imunosupresoare, precum și căile prin care aceste complicații pot fi reduse. Managementul tratamentului post-transplant este obligatoriu pentru a crește nu doar supraviețuirea grefei și a pacienților, ci și calitatea vieții acestora prin reducerea complicațiilor.