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The side effects of immunosuppressive use in patients receiving Kidney transplants

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Abstract: It is known that advanced chronic kidney disease in the patient leads to the need for transplantation, and, consequently, to the use of immunosuppressants, which are drugs that prevent rejection of the transplanted organ. The present work is a literature review and aims to analyze the side effects of immunosuppressants in renal transplant patients. From studies

on the adverse effects of immunosuppressants in patients who have undergone kidney transplantation, it will be analyzed whether it is possible to select a combination of drugs that minimize the risk of graft rejection and protect the transplanted from aggressor agents and above all from the adverse reactions of immunosuppressants on the patient. The present work is a descriptive study carried out through bibliographic consultation, using articles between 2016 and 2021, which had as inclusion the inclusion criteria the Keywords: Kidney disease, Transplantation, Immunosuppressants and Adverse reactions; and exclusion, all that did not address the have. This work did not need to go through the Ethics Committee, because it is a literature review. It was noticed that side effects can be minimized by following the protocol of the use of immunosuppressants and that therapeutic individualization can reduce the damage caused by these medications.

Keywords: Kidney disease. Transplantation. Immunosuppressants. Adverse reactions

1. Introduction

The kidneys are fundamental organs for the maintenance of the human body, as they have several roles in the balance of their homeotase. According to the Brazilian Association of Organ Transplantation ABTO (2021), they are responsible for ensuring excretion and osmorphization by removing products from cellular metabolism and substances that are too much in the human body. In an anatomophysiological way, blood reaches the kidneys through the renal arteries, in the inner part of the kidneys there are small vessels that form small skeins of very thin vessels called glomeruli. In each kidney there are millions of glomeruli that are the real filters of blood. That's where the blood is filtered and its excesses eliminated(ASSIS, 2020).

According to Zats, Seguro and Malnic (2011), the kidneys are vital organs for the maintenance of homeotase of the human body and the progressive decrease in renal function may imply a compromise and regulation of other organs. The main pathologies related to the kidneys are: nephritis, kidney stones, kidney infection, renal obstruction, kidney cancer, renal failure and chronic renal failure. Kidney disease is usually silent, however, in some cases, the individual may exhibit some symptoms. But only when the disease is very advanced, they present more visible symptoms, and may occur loss of appetite, nausea, vomiting, cramps, itching, memory loss, lack of concentration, tremors, insomnia and drowsiness.

For the present study, greater attention will be given to advanced chronic kidney disease that leads to the need for transplantation, and, consequently, to the use of immunosuppressants, which are drugs that prevent rejection of the transplanted organ. The immune system recognizes, defends and protects the body from infections, and, rejects everything that is strange, the transplanted organ is seen by the immune system as something strange not belonging to "your organism". In Brazil, according to Alcalde and Kirszt (2018), the incidence of chronic kidney disease is growing, and the consequences of the disease are severe and the costs of its treatment are very high. The projected figures for patients with the disease and undergoing dialysis and kidney transplantation reach almost 120,000, at a cost of 1.4 billion reais for the country.

2. Methodology

The present work has as a methodology that guide stems from a descriptive study conducted through bibliographical consultation of articles, dissertations and theses that deal with the adverse effects of immunosuppressants in renal transplant patients in the last decade, using articles between 2016 and 2021, using works that are of paramount importance for the construction of the work.

The digital libraries of Scientific Electronic Library Online (SciELO), CAPES Journal Portal, Google Scholar, Digital Library of Theses and Dissertations (BDTD), Science.gov and the Federal Council of Pharmacy were used as research base for its construction. In addition to books and data from government surveys. Using as inclusion criteria the articles that cited the actions of immunosuppressants and their negative effects, excluding those that do not directly reference these drugs. This work did not need to go through the Ethics Committee, because it is a literature review.

3. Results and Discussion

Transplantation, according to Noronha (2018), is a surgical process that consists of transferring cells, tissues or living organs from a donor, whether alive or dead, to a recipient in order to maintain the functional integrity of the transplanted material in the patient who received it. However, the biggest problem that the transplanted person may face is rejection, often being mediated by a cellular or humoral reaction.

Brazil is the second country in the world, in absolute numbers, in cases of kidney transplants among 35 countries surveyed, only losing to the U.S., as stated by the Ministry of Health (2021). Having the largest public organ, tissue and cell transplant program in the world, responsible for funding 95% of cases in the country, where the most transplanted organ is the kidney.

In the last 5 years the Brazilian Association of Organ Transplants - ABTO (2021) recorded an increase of 5.2% in kidney transplantation, with growth of both: transplantation with deceased donor (5.5%) and with living donor (4.1%). In these years, another relevant aspect was also observed, with attention to the growth rate of living and non-relative and non-spouse donor, which was 4.2% and in the last 10 years it was 7.1%.

However, the Ministry of Health (2021) in 2020 recorded a 37% drop in the number of transplants performed

in January and July 2020 compared to the same period of 2019, this decrease is associated with the atypical event of the covid-19 pandemic.

From January to July 2019, according to DATASUS (2020) 15,827 transplants were performed in the country, as in 2020, 9,952 procedures were performed in the same period, until the beginning of 2021, there were 46,181 patients waiting for organs in the country.

The most transplanted organ in 2020, according to the Ministry of Health (2021), as well as in 2019, was the kidney, there were 2,759 surgeries in 2020, compared to 3,596 in 2019, the drop verified by the Ministry of Health was 23% of this type of transplantation.

CONITEC (2020) states that diagnosis of kidney disease is made through comparations of clinical and laboratory parameters. From the diagnosis in hand, the doctor needs to research the cause of nephropathy, regardless of the patient's age group and the assessment of the degree of functional impairment of the kidney. The most frequently used methods to discover renal function levels include determining serum creatinine level, creatinine and urea clearance, respectively.

According to David Neto (2017) the indication for dialysis treatment or indication of transplantation is made when the estimate of glomerular filtration rate (eTFG) is below 18ml/minute. The Brazilian Society of Nephrology states that transplantation can only occur when glomerular filtration is below 20ml/minute, and that the patient has presented a fall in renal functions in the last 12 months.

After the patient is transplanted, immunosuppressive drugs take action because they are used to prevent acute and chronic rejection. Immunosuppression has the function of inhibiting immune recognition, so that the cells of the body do not reject the organ, thus, the activation of the cellular and humoral allogeneic response can be divided between its phases: the induction phase and the maintenance phase. Subsequently, there may be a need for the treatment of rejections (CONITEC, 2020).

Immunological risks should be measured and evaluated prior to the procedure so that the induction regimen can be defined before transplantation. The definition is based on the demographic characteristics of the donor and recipient and risk factors associated with the higher risk of rejection, including:

1. Low HLA compatibility (Human leukocyte antigen);
2. HLA antigen sensitization events through pregnancies, blood transfusions and prior transplantation;
3. Presence of specific preformed antibodies against donor HLA antigens;
4. Initial graft dysfunction (CONITEC, 2020).

When these characteristics are observed and analyzed, transplantation is defined as lower or higher risk according to the table provided below:

Table 1. Classification of the immunological risk of transplantation

Transplant with lower risk	Transplant at higher risk
Transplant recipients of living or deceased donor;	Transplant recipients of living or deceased donor;
Not sensitized or with a low degree of sensitization;	Sensitized;
No anti-HLA preformed antibodies from the donor;	With anti-HLA preformed antibodies from the donor;
With good HLA compatibility; and/or	With good HLA compatibility; and/or
With immediate renal function.	At risk of initial graft dysfunction.

Source: CONITEC (2020).

According to Assisi (2020), rejections in kidney transplantation are classified as hyperacute, acute and chronic. Hyperacute rejection occurs immediately after anastomosis of the vessels. When surgery is successful the transplanted kidney becomes rosy and begins to excrete urine. However, in case of hyperacute kidney rejection presents irregular and cyanotic staining, excreting very low amount of urine and blood. The mechanisms of these lesions is an antigen-antibody reaction at the level of the endothelium with renal graft failure, and therefore transplantectomy is essential. According to the author, this rejection occurs when there are incompatibilities between the donor and the recipient.

Assisi (2020), indicates that acute rejection occurs in days or even after months or years of immunosuppressive use. May involve cellular, humoral mechanisms or both. Acute cellular rejection may occur more frequently after months of transplantation, because of cytotoxic lymphocytes, leading to increased creatinine and progressive renal failure. Acute humoral rejection is due to antibodies and is manifested by vasculitis with fibrinoid necrosis, neutrophil infiltration and thrombosis, leading to external necrosis in the renal parenchyma.

According to the Classification of Assisi (2020), chronic rejection represents a progression that occurred in acute rejection. Presenting vascular alterations, characterized by intimal fibrosis more frequently in the cortical arteries. There is also interstitial inflammatory infiltrate of lymphocytes, with progressive increase in creatinine level over a period of 4 to 6 months, advancing to a chronic insufficiency.

In order to avoid rejection, the immunosuppression strategy is used, and they are divided into two phases: induction of immunosuppression and maintenance, and rejection treatment may be necessary.

For patients with preformed anti-HLA antibodies from the donor, desensitization therapies are additionally described, as this offers a higher risk. Immunosuppression induction is used in biological agents that instill t lymphocyte activity. Immunosuppression maintenance therapy is characterized by its long-term use, using a combination of immunosuppressive drugs in order to prevent rejection, preserving renal function and minimizing adverse effects, being used before transplantation or even 24 hours after

surgery (CONITEC, 2020 p.18-19).

According to the clinical protocol and therapeutic guidelines renal transplants posted by the Ministry of Health (2008), the immunosuppressive drugs indicated for the treatment of rejection are: Cyclosporine, Azathioprine, Tacrolimus, Mycophenolato, Mofetil, Sodium Mycophenolae, Sirolimus, Everolimus, Monoclonal Antibody Murino Anti CD3 (OKT3), Basiliximab, Daclizumab, Antilymphocytic Globulin, Antitychonite Globulin, Methylprednisolone, Prednisone 1.

The doses, according to the Ministry of Health (2021), of immunosuppressive drugs are very variable and can be used in combination, and their indication takes into account the type of rejection, the type of donor and its immunological compatibility with the recipient, the post-transplant time, the immunological events that have occurred and the adverse effects of the drugs in use, as well as potential drug interactions with other drugs that may be required.

However, when using these drugs, the transplanted patient needs to sign a term of clarification and responsibility about the adverse effects of the aforementioned drugs, and, above all, the risks related to their use for the preventive or therapeutic treatment of renal transplantation rejection.

The Brazilian Association of Organ Transplants (2021), states that Drugs classified as category C, are drugs that do not have adequate studies in women, and in animal experiments have emerged some side effects on the fetus, although the benefit may justify the potential risk during pregnancy. Drugs such as cyclosporine, mycophenolate (mofetile or sodium), sirolimus, everolimus and tacrolimus are included in this category. Medicines classified as category D, as is the case of azathioprine, where there is concrete evidence of risks in human fetuses, but their indication is to use only in case of life-threatening or in case of serious diseases for which safer drugs cannot be used, or if these drugs are not effective. The increased risk of infections of various etiologies and neoplasms, mainly arise with the associated use since medications (ABTO, 2021).

Immunosuppressive therapy, according to Manfro and Gonçalves (2020), has shown significant advances in recent decades. Abandoning the classical protocol with the junction of prednisone and azathioprine, and adding to this traditional duo cyclosporine in the early 1980s and, later, several drugs that today were incorporated into clinical practices such as:

> Tacrolimus, mycophenolates (esodium mofetil) and rapamycins (sirolimus and everolimis). Biological agents were improved – antithymocyte globoline – and others, using monoclonal antibody production technology, were created: monoclonal anti-CD3 antibodies (OKT3) and interleukin-2 anti-receptor antibodies (basiliximab daclizumab). Additionally, with belatecept, the era of clinical use of fusion proteins was inaugurated. In this case, blocking co-stimulator signals essential for the activation of T cells (MANFRO and GONÇALVES, 2020 p.3).

Based on these advances, as Bressan (2016) pointed out, mainly in relation to the individualization of therapy, immunosuppressants can be allocated in a way that allows rational combinations of drugs with high efficacy, acting in the stages of immunological activation inhibiting rejection reactions.

Manfro and Gonçalves (2020), state that the basic premise of the individualization of immunosuppression is that patients are diverse and distinct biologically and present different characteristics, especially in relation to the risks of developing rejections or losing grafts. Thus, treatment with immunosuppressants needs, according to the authors, to understand the susceptibilities of each patient to premeditate the possible side effects of immunosuppressive drugs. Therefore, the above authors mention that the objectives of individualization of immunosuppression serve to:

> a) Maximize success rates: patient survival and grafts;
> b) Decrease side effects and toxicities: immunodeficiencies and non-immune toxicities;
> c) Adapt immunosuppression to the particular comorbidities of each patient (MANFRO And GONÇALVES, 2020 p.3).

For these goals to be met, it is necessary to try to understand the dimensions of side effects that may arise with the use of immunosuppressants. Therefore, the individualization of the medication should meet some requirements, always observing the characteristics of each individual, in order to reduce the side effects of medications in patients and their organs.

Among the most observed side effects, as stated by Manfro and Golçalves (2020), are the risk of diabetes mellitus, dyslipidemia, hypertension, chronic nephropathy of the graft, and other changes such as Hypertrichosis, hirsutism, alopecia, gingival hyperplasia, obesity. Thus, in order to minimize these effects that almost always appear, it is necessary to comply with a protocol in the face of the use of immunosuppressants:

> a) Avoid certain drugs, specifically steroids and calcineurin inhibitors;
> b) Minimize the use of certain drugs, again steroids and calcineurin inhibitors;
> c) Withdrawal of drugs based on the occurrence of para-effects, such as neurotoxicity, diabetes, dyslipidemia, aseptic necrosis, hirsutism, gingival hyperplasia, neurotoxicity, among others (MANFRO And GONÇALVES, 2020 p.3).

According to Souza *et al*. (2016), immunosuppression and its modulation, present a direct relationship not only with some side effects mentioned above, but with the incidence and severity of infectious events that affect the patient, especially in the early stages of the procedure, which

increases the risk of rejection in addition to suffering numerous adverse reactions.

Many factors may interact by modifying the risks of adverse reactions, one of which is associated with the immunosuppression profile employed. The incidence of side effects, such as infection, according to Souza *et al* (2016), is higher in the first months of post-transplant follow-up and is directly related to the dose of immunosuppression used and, above all, its combinations. The additional dose of drug for the treatment of rejection also raises episodes of adverse reactions and consequent infectious episodes.

Immunosuppressants are essential for patient and graft survival, however, it causes numerous reactions as mentioned above, but it is necessary to deal with the risk benefit of its use assertively, combining these drugs so that their adverse effects are minimized. For this, it is necessary that the medical team evaluate the patient individually and to offer a better quality of life and with lower risks.

4. Conclusions

The study on the consequences in the body of the renal transplant patient when taking immunosuppressants sheds light on new possibilities the pharmaceutical industry, which produces such remedies, in an attempt to ensure a better quality of life for the sick who come in the graft the way out for kidney failure and possible cure; seeking above all, alternatives to create new drugs that reduce the negative effects that their use may cause.

In order for the patient not to reject transplantation, it is necessary to administer medicines for long periods, which prevent the body's reactions against "foreign" tissues, to prevent rejection and ensure the proper functioning of the organ. However, in addition to suffering from the adverse effects of its prolonged use, the patient suffers the risk of rejecting the graft after some time.

When transplanted the patient restores function of the kidneys and increases their quality of life and survival time. However, for this to happen, the patient cannot reject the organ, so immunosuppressants are used to reduce these risks. However, its use brings some risks, among them, the development of an infectious condition, neoplasms, bone changes, eye disorders, changes in the nervous system and complications in possible pregnancy of female patients.

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