Araştırma Makalesi
Research Article

Side Effects of Immunosuppressive Treatments in Primary Glomerulonephritis

İMMÜNOSÜPRESİF TEDAVİLERİN YAN ETKİLERİ

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ABSTRACT

Background: It is imperative to closely monitor patients for adverse effects of immunosuppressive (IS) agents, widely used in treating glomerulonephritis (GN). Our study aimed to investigate the occurrence of any drug-related adverse events in patients with primary GN, explicitly focusing on IS.

Methods: The present study analyzed 162 adult GN patients treated with IS drugs. The study scrutinized the demographic and clinical profiles of the patients, laboratory findings, and any side effects associated with IS drugs. We further investigated the patients for frequency and nature of infections, musculoskeletal and gastrointestinal symptoms, thromboembolism, new-onset diabetes, avascular necrosis, neuropsychiatric side effects, and premalignant conditions.

Results: The study comprised a diverse group of patients with a male majority of 51.9% and a mean age of 37.2±12.9 years. The patients were under clinical observation for an average of 69.6±40.1 months, and during the treatment, 71% experienced at least one adverse effect. After evaluating the data, we did not find a significant correlation between the GN type and the presence of side effects. Research demonstrates that patients receiving corticosteroids (CS) exhibit a higher incidence of myopathy than those receiving other IS therapies (p=0.001). Hypoalbuminemia (OR: 2.05; 95% CI: 1.82–2.28; p =0.001) and steroid treatment (OR: 1.04; 95% CI: 1.01–1.06; p = 0.009) are significantly associated with increased risk of adverse outcomes.
Conclusion: In cases of GN, it is not unusual for patients to encounter adversities associated with IS treatment, primarily when there is a comorbidity of hypoalbuminemia and CS exposure. The probability of these side effects occurring may increase under such circumstances.

Main Points:

- Patients diagnosed with GN should undergo meticulous monitoring to detect any potential adverse effects that may arise from the administration of IS agents
- The probability of experiencing side effects is higher when hypoalbuminemia and CS exposure are present.
- The present study suggests no discernible correlation between the type of GN and side effects

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ÖZ

Amaç: Glomerülonefrit (GN) tedavisinde yaygın olarak kullanılan immünosupresif (IS) ajanların yan etkileri açısından hastaların yakından izlenmesi gerekmektedir. Çalışmamız, özellikle IS'ye odaklanarak, primer GN'li hastalarda ilaca sekonder görülen yan etkileri araştırmayı amaçladı.

Yöntemler: Bu çalışmaya IS ajanlarla tedavi edilen 162 yetişkin GN hastası dahil edildi. Çalışmada hastaların demografik ve klinik özellikleri, laboratuvar bulguları ve IS ilaçlarla ilişkili yan etkiler incelendi. Hastalar; enfeksiyonların sıklığı ve natürü, muskuloskeletal ve gastrointestinal semptomlar, tromboembolizm, yeni başlayan diyabet, avasküler nekroz, nöropsikiyatrik yan etkiler ve premalign durumlar açısından da araştırıldı.
Bulgular: Hastaların %51,9'u erkekti ve yaş ortalaması 37,2±12,9 yıldı. Hastalar ortalama 69,6±40,1 ay süreyle klinik gözlem altında tutuldu ve tedavi sırasında %71'inde en az bir yan etki görüldü. Veriler incelendiğinde GN tipi ile yan etki varlığı arasında anlamlı bir korelasyon saptanmadı. Kortikosteroid (KS) alan hastaların, diğer IS tedavilere göre daha yüksek miyopati insidansı sergilediği gösterildi (p=0,001). Hipoalbüminemi (OR: 2,05; %95 GA: 1,82–2,28; p =0,001) ve steroid tedavisi (OR: 1,04; %95 GA: 1,01–1,06; p = 0,009), yan etki riskinin artmasıyla anlamlı şekilde ilişkili bulundu.
Sonuç: GN vakalarında, özellikle hipoalbüminemi ve KS maruziyetinin eşlik ettiği durumlarda, hastaların IS tedavisiyle ilişkili yan etkilerle karşılaşma olasılığı artabilir.

Ana noktalar:
• GN tanılı hastalar, IS ajanlardan kaynaklanabilecek olası yan etkileri tespit etmek için dikkatli bir şekilde izlenmelidir.
• Hipoalbuminemi ve kortikosteroide maruziyet, yan etki görülme olasılığını artırır.
• Bu çalışmada, GN tipi ile yan etkiler arasında anlamlı bir ilişki olmadığı görülmüştür.

Anahtar Kelimeler: Glomerülonefrit, yan etkiler, enfeksiyonlar, immünosupresif tedaviler

Glomerular inflammation can cause glomerulonephritis (GN), which is one of the essential causes of kidney failure, presented with hematuria, different amounts of proteinuria, leukocyturia, hypertension, and other organ involvements (such as purpura, arthritis, pulmonary hemorrhage). Patients who do not receive treatment are at a higher risk of developing protein malnutrition, acute kidney failure, hyperlipidemia, accelerated atherosclerosis, venous or arterial thrombosis, pulmonary embolism, and infection(1). As clinicians, we aim to provide treatment regimens that minimize complications and prevent disease progression with the lowest IS drug exposure.

The current immunosuppression strategies may not provide sufficient relief, particularly in recurring or treatment-resistant GN. Nonspecific drugs, though useful, may cause unintended toxicity and compliance issues. In cases where drugs with narrow therapeutic windows are utilized, it is essential to balance the potential risks and benefits. Decreasing drug doses to minimize the risk of infections may result in disease reactivation, while increasing immunosuppressants to address relapse may heighten the risk of infections. Infectious agents can also trigger disease recurrence. The current challenge is to adjust the drug dose and duration to limit conditions and other adverse events without recurrence. Our study aimed

to offer valuable information regarding the potential adverse effects of IS therapy in patients diagnosed with primary GN.

METHODS

We conducted a study involving 162 patients with primary GN, specifically primary membranous nephropathy (PMN), focal segmental glomerulosclerosis (FSGS), membranoproliferative glomerulonephritis (MPGN), minimal change disease (MCD), and immunoglobulin A nephropathy (IgAN), confirmed by kidney biopsy. Exclusion criteria for this study included the following: (1) absence of a 12-month follow-up, (2) presence of diabetes mellitus (DM), (3) presence of another autoimmune disease, (4) missing data, and (5) presence of malignancy or viral hepatitis.

Reviewing their medical records, we collected the patients' demographic, clinical, and laboratory data. Throughout the patient's follow-up, we documented the occurrence and nature of any infections they encountered, including upper and lower respiratory infections, gastrointestinal (GI), urinary tract, skin, and soft tissue infections, as well as viral infections like herpes simplex and varicella-zoster virus. The patient's blood, urine, tissue culture results, and parenteral antibiotherapy requirements were investigated. We examined patients' files for myopathy, GI side effects (nausea, vomiting, diarrhea, abdominal pain, dyspeptic complaints, GI bleeding, high transaminase level, hyperbilirubinemia), and malignancy. The diagnosis of avascular necrosis (AVN) was verified by magnetic resonance imaging (MRI). The presence of neuropsychiatric events such as depression, psychosis, delirium, confusion, severe headache, and seizures observed after the initiation of IS medication was investigated. Assessment of kidney function was performed by estimating the glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration formula. The urinary protein-to-creatinine ratios were also utilized in the study to measure the level of proteinuria in patients. In addition, the study evaluated the use of preferred IS drugs and the duration of treatment. Starting in 2012, patients were treated according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, ensuring they received the most appropriate and effective treatment for their kidney disease(2). Mortality has been verified via the death notification system.

This study has obtained ethical approval from the Non-invasive Clinical Ethics Committee of Istanbul University Faculty of Medicine, with decision number 2023-2265277. The ethical principles of the Declaration of Helsinki have conducted all the procedures in this study.

Statistical analysis

Data entry and analysis were executed utilizing SPSS 21, a robust statistical software. The normality assessment was conducted using the Kolmogorov-Smirnov test. Mean ± standard deviation (SD) was used to represent continuous variables, while nominal and ordinal data were presented as percentages. To compare continuous variables between two independent groups, the Mann-Whitney U test was utilized, whereas Fisher's exact test was employed for categorical variables. A logistic regression analysis was carried out to determine the predictive factors influencing side effects. The statistical significance was set at a two-tailed P value of 0.05 or lower.

RESULTS

The data of 162 patients with primary GN (84 male, mean age 37.2±12.9 years) who used IS agents were analyzed. The distribution of patients included in the study was as follows: 34.5% (n=56) PMN, 17.3% (n=28) FSGS, 27.2% (n=44) IgAN, 15.4% (n=25) MPGN, 5.6% (n=9) MCD. At least one side effect due to IS drugs was detected in 71.1% (n=115) patients. The study found that a significant percentage of patients with PMN, FSGS, IgAN, and MPGN experienced adverse effects secondary to drugs. All patients with MCD reported adverse effects. Presented in Table 1 are the demographic characteristics and laboratory findings of the patients.

Table.1 Demographic, clinical and laboratory characteristics of patients with primary glomerulonephritis

Age,(years)*	37.2 (±12.94)
Gender (male), n (%)	84 (51.9)
Body mass index *	26.3 (±4.62)
Smoker, n (%)	34 (30.9)
Follow-up duration,(months)*	69.6 (±40.1)
Distribution of diagnosis, n (%)	
Membranous GN	56 (34.6)
FSGS	28 (17.3)
IgAN	44 (27.2)
MPGN	25 (15.4)
MCD	9 (5.6)
Baseline sistolic blood pressure, mmHg*	131 (±23.66)
Baseline diastolic blood pressure, mmHg*	83 (±14.72)
Baseline laboratory test results*	
Leukocyte /mm^3	9549 (±4252.2)
Creatinine (mg/dL)	1.13 (±0.95)
eGFR	87.9 (±34.25)
Albumin (g/dL)	2.92 (±0.89)
Total protein (g/dL)	5.45 (±1.23)
Spot urine protein creatinine ratio	5.92 (±6.22)
Antihypertensive agents, n (%)	
ACE inhibitors	119 (73.5)
ARB	108 (66.7)
CCB	54 (33.3)
Diuretics	63 (38.9)
Beta blockers	8 (4.9)
Distribution of immunosuppressive agents used, n (%)	
Steroid	143 (88.3)
Cyclophosphamide	8 (4.9)
Rituximab	4 (2.5)
Azathioprine	35 (21.6)
Mycophenalate mofetil	51 (31.5)
Cyclosporine	58 (35.8)
Tacrolimus	10 (6.2)
Duration of steroid use*	27.9 ± 27.8
Number of exacerbations*	0.9 (±0.99)
*mean (±SD)	

The study observed that many patients experienced upper respiratory tract infections (URTIs) as a side effect. The incidence of URTIs varied among different types of kidney diseases, with the highest rate observed in patients with IgAN. URTI was observed in 42.8% (n=12) of patients with FSGS, 30.3% (n=17) of PMN, 47.7% (n=21) of patients

with IgAN, 28% (n=7) of patients with MPGN, 33.3% (n=3) of patients with MCD. Viral agents caused one-fifth of these URTIs. During follow-up, it was observed that 28.6% of patients with PMN, 46.4% with FSGS, and 30.2% with IgAN were diagnosed with lower respiratory tract infections (LRTI). Notably, Mycobacterium tuberculosis was identified in the sputum culture of one patient, while atypical mycobacteria were detected in bronchoalveolar lavage fluid in another.

Urinary tract infection (UTI) was detected in 19.8% (n=32) patients once, in 4.9% (n=8) patients twice, in 1.9% (n=3) patients three times, and in 0.6% (n=1) patients nine times. Escherichia coli (n=23) was the most common bacteria detected in the patient's urine cultures. Klebsiella pneumonia (n=3), enterococcus spp (n=1), chlamydia trachomatis (n=1), ureaplasma urealyticum (n=1), and candida spp (n=1) were also detected.

Soft tissue infection was observed in five patients with PMN, three with FSGS and IgAN, and two with MPGN; this risk was independent of diagnosis. Morganella morganii (n=1) and listeria monocytogenes (n=1) were identified in tissue culture.

Only 7.4% of patients required hospitalization for intravenous antibiotic therapy (PMN=4, FSGS=1, IgAN=4, MPGN=3). However, no discernible correlation was observed between the diagnosis and the likelihood of hospitalization. Table 2 lists the common side effects associated with different types of GN.

Table 2. Common side effects according to type of primary glomerulonephritis

	PMN n (%)	IgAN n (%)	FSGS n (%)	MPGN n (%)	MCD n (%)	p value
Any infection	34 (60.7)	32 (72.7)	21 (75)	19 (76)	6 (66.7)	0.532
Hospitalization due to infection	4 (7.1)	4 (9.1)	1 (3.6)	3 (12)	-	0.685
Neuropsychiatric event	8 (14.3)	10 (22.7)	3 (10.7)	5 (20)	1(11.1)	0.643
Secondary diabetes mellitus	7 (12.5)	1 (2.3)	3 (10.7)	4 (16)	2 (22.2)	0.237
Cataract	5 (8.9)	2 (4.5)	1 (3.6)	2 (8)	-	0.736
Avascular necrosis	6 (10.7)	1 (2.3)	2 (7.1)	3 (12)	-	0.396
Myopathy	26 (46.4)	12 (27.9)	13 (46.4)	12 (48)	3 (33.3)	0.309
Gastrointestinal side effect	20 (35.7)	15 (34.1)	8 (28.6)	7 (28)	5 (55.6)	0.608
Venous thromboembolism	-	1 (2.3)	-	1 (4)	-	0.543
Osteoporosis	7 (12.5)	3 (6.8)	3 (10.7)	4 (16)	1 (11.1)	0.820

During IS therapy, premalignant conditions were observed and closely monitored in patients. Throughout the follow-up period, a variety of conditions emerged, including pituitary macroadenoma (n=1), severe dysplasia in the colon (n=1), tubular adenoma (n=1), thyroid papillary microcarcinoma (n=1), basal cell microcarcinoma (n=1), and villous adenoma with moderate dysplasia (n=1).

Patients were closely monitored for the potential development of AVN, a debilitating condition that diminishes their quality of life and restricts their mobility. MRI-confirmed AVN was unrelated to the patient's diagnosis (PMN=6, FSGS=2, IgAN=1, and MPGN=3). No correlation was found between the use of IS and the onset of AVN. Additionally, there was no statistically significant relationship between the CS use duration and AVN development (p=0.665).

One of the critical side effects that reduce drug compliance is GI symptoms. 35.7% (n=20) patients with PMN, 28.6% (n=8) patients with FSGS, 34.1% (n=15) patients with IgAN, and 28% (n=7) patients with MPGN had GI side effects independent of primary diagnosis. GI adverse effects of MMF constitute a significant concern in our cohort, as this adverse event increased 2.2-fold in MMF users (p = 0.017). Although around one-third of patients using CS or cyclosporine (CsA) experienced gastrointestinal complaints, this was not statistically significant. Salmonella (n=2) and Clostridium difficile (n=1) were found in stool samples for diarrhea etiology.

After a comprehensive investigation, we also considered the possibility of cataracts, specifically in patients who have been on CS for a prolonged period at high doses. Nevertheless, in our cohort, we did not find any conclusive connection between drug usage and the formation of cataracts. Furthermore, our results did not indicate any link between the type of GN and the occurrence of cataracts.

In order to identify potentially reversible drug-induced myopathies in our patients, we conducted a thorough inquiry into musculoskeletal complaints. Our findings showed that myopathy was observed in a significant number of patients across several conditions, including 46.4% of those with PMN, 46.4% of those with FSGS, 27.9% of those with IgAN, and 48% of those with MPGN. Of all the patients, approximately 45.8 who were administered CS developed myopathy, demonstrating a statistically significant correlation (OR:15,1; 95% CI: 1.97-116, p=0.001). Table 3 summarizes the drug's observed side effects.

Table 3. Common side effects according to immunosupressive agents

	steroid n (%)	**CsA n (%)**	**MMF n (%)**	**AZA n (%)**	**Tacrolimus n (%)**
Any infection	102 (71.3)	43 (74.1)	37 (72.5)	23 (65.7)	7 (70)
Hospitalization due to infection	10 (7)	4 (6.9)	6 (11.8)	2 (5.7)	-
Neuropsychiatric event	23 (16.1)	12 (20.7)	9 (17.6)	9 (25.7)	1 (10)
Secondary diabetes mellitus	14 (9.8)	9 (15.5)	7 (13.7)	3 (8.6)	1 (10)
Cataract	10 (7)	1 (1.7)	5 (9.8)	1 (2.9)	1 (10)
Avascular necrosis	12 (8.4)	6 (10.3)	3 (5.9)	3 (8.6)	-
Myopathy	***65 (45.8)**	28 (48.3)	21 (42)	10 (29.4)	5 (50)
Gastrointestinal side effect	51 (35.7)	22 (37.9)	***24 (47.1)**	12 (34.3)	4 (40)
Venous thromboembolism	2 (1.4)	-	-	-	-
Osteoporosis	18 (12.6)	8 (13.8)	4 (7.8)	5 (14.3)	1 (10)
**between groups p<0.05*					

As our therapeutic drugs can impact glucose metabolism, we closely monitored our patients for the possible development of DM. During the follow-up period, we observed that 13.7% (n=7) of the patients using MMF, 9.8% (n=14) of those using CS, and 15.5% (n=9) of those receiving CsA developed DM. The type of GN did not influence the development of drug-induced DM.

According to this study, patients who present higher levels of proteinuria upon diagnosis may experience side effects more frequently when treated with IS agents (p=0.004). Furthermore, the study revealed hypoalbuminemia (OR: 2.05; 95% CI: 1.82–2.28; p=0.001) and CS treatment (OR: 1.04; 95% CI: 1.01–1.06; p = 0.009) as risk factors for side effects.

DISCUSSION

The incidence rates of various types of primary GN in adults range from 0.2–2.5/100000/year (3). GN is a collection of diverse kidney diseases that accounts for nearly one-fifth of chronic kidney disease cases. Regrettably, GN is also the primary cause of kidney failure among young adults(4). Clinicians can add IS drugs to conservative treatments, taking into account factors such as comorbidity, age, possible drug side effects and interactions, life expectancy, and the patient's kidney reserve. The fundamental objective is to devise a therapeutic plan that adheres to the 'Primum non-nocere' principle, thereby preserving kidney function. Our primary aim is to showcase authentic, real-life data.

Patients diagnosed with nephrotic syndrome are at a heightened risk of developing infections. This is attributed to a decreased serum concentration of immunoglobulin G, insufficient production of specific antibodies, reduced levels of factors B and D in the alternative complement pathway, and the impact of IS therapy(5). In areas with a high prevalence of tuberculosis, it is essential to investigate for latent tuberculosis. M. tuberculosis was found in the sputum culture of a patient who was evaluated for latent tuberculosis before the IS started.

Glucocorticoids (GCs) have been identified as one of the primary causal factors leading to AVN. The risk of developing osteonecrosis is exceptionally high in patients who have been administered high doses of GCs over an extended period. In this study, 8.4% (n=12) of patients who received steroid treatment developed AVN. Patients received GCs at doses outlined in the KDIGO treatment protocols for an average duration of 27.9 ± 27.8 months. In addition, AVN was found to occur at a significantly higher rate in patients receiving CsA compared to other drugs used in maintenance therapy for kidney transplant patients(6). Results from a double-blind, randomized controlled trial indicate no significant difference in AVN or osteoporosis between the MMF recipients and the control group for the chronic graft-host disease(7). After a thorough analysis, we could not establish a correlation between the risk of developing AVN and the use of other drugs. It is possible that the restricted patient count in the cohort and the difficulty in calculating the cumulative drug doses could have contributed to this outcome.

Glucocorticoids have been linked to an increased risk of adverse events, such as the development of gastritis, ulcers, and GI bleeding(8). In our study, we observed that a significant proportion of patients (35.7%, n=51) experienced GI toxicity associated with the use of steroids during the follow-up period. A study conducted on 85 patients who received MMF for psoriasis showed a reduction in the prevalence of GI symptoms such as nausea, diarrhea, and abdominal cramps from 75% at baseline to 20% after a few years of treatment(9). In this study, the risk of this adverse event increased 2.2-fold with MMF. A GI side effect due to CsA occurred in 47% of 478 adult and 51 pediatric patients with liver transplantation during one-year follow-up (10). In our study, 37.9% (n=22) of those using CsA had GI complaints.

In our study, we observed that 45.8% (n=65) of the patients using steroids developed myopathy, and a statistically significant relationship was established between the use of CS and the development of myopathy. It was also noted that elderly patients or those with negative nitrogen balance were at an increased risk(11). Further, our findings indicate that myopathy was present in 52.8% (n=28) of the patients whose serum albumin level was less than 2.5 mg/dL. Additionally, the combined use of CsA and statin has been associated with rhabdomyolysis in solid organ transplant patients(12). As per the results of this study, it was observed that a considerable proportion of patients (28 patients out of the total) experienced myopathy attributed to CsA. While MMF is considered a possible treatment option for inflammatory myopathies, it has also been reported to cause myopathy in some cases(13). Our research findings suggest that there is no discernible association between the use of MMF and the onset of myopathy.

Patients undergoing treatment with GCs are at an increased risk of developing both cataracts and glaucoma in a dose-dependent manner(14). Throughout our follow-up period, 7% (n=10) of our patients developed cataracts due to CS.

The administration of steroids has been shown to increase hepatic gluconeogenesis, reduce peripheral tissue use of insulin-dependent glucose, and inhibit insulin activity(15). This study observed secondary DM in 9.8% (n=14) of the patients using GCs. In a meta-analysis, DM treated with insulin occurred in 3% of kidney transplant recipients using CsA (16). Our study showed secondary DM in 15.5% (n=9) of the CsA users. In experimental research, MMF has demonstrated an ability to inhibit the expansion and migration of autoreactive cells, thereby exhibiting a potential anti-diabetogenic effect(17). Our study revealed that secondary DM was observed in a small percentage (13.7%) of patients who received MMF treatment. However, based on our analysis, this result did not reach statistical significance.

A meta-analysis has revealed that individuals with a history of steroid use are at a significantly higher risk for osteoporotic and hip fractures. Specifically, the study found that steroid use can increase the risk of osteoporotic fracture by 1.66 times and hip fracture by 2.25 times (18). In this study, 12.6% (n=18) of the patients using steroids experienced skeletal side effects. CsA monotherapy increased bone mineral density, but combined with GC, it caused bone loss by inhibiting osteoblast differentiation and growth(19). This study found that 13.8% (n=8) of patients experienced osteoporosis while receiving CsA treatment.

In the CureGN cohort, it was observed that the risk of infection was associated with the presence of nephrotic proteinuria and hypoalbuminemia, exposure to CS, and the number of comorbid diseases(20). Additionally, proteinuria at the nephrotic level was identified as a predictive factor for poor prognosis. It may require longer or combined IS therapy, which could lead to a higher frequency of secondary side effects to these drugs. In our study, the side effects of IS were more common in patients with high proteinuria at the first presentation. Each 1 mg/kg/day increase in CS dose resulted in a 2.5-fold increase in the relative risk of adverse events (21). Recent research indicates that exposure to CS is linked to an elevated likelihood of acute care events related to infection (22), and our findings align with the existing literature on this topic.

The limitations of the study are 1) not specifying the cumulative dose of the drugs, 2) retrospective, 3) a small number of patients, 4) short follow-up duration, 5) vaccination status was not available, and 6) lack of a control group.

Considering all these side effects and treatment successes, it is evident that more effective but less toxic IS approaches are needed. Therefore, we should aim to reduce long-term morbidity and mortality without increasing recurrence or adverse events with currently available therapeutic agents.

REFERENCES

1. Crew R, J. Radhakrishnan, and G. Appel, Complications of the nephrotic syndrome and their treatment. Clinical nephrology, 2004. 62(4): p. 245-259.
2. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clinical Practice. 2012;120(4):c179-c84.
3. McGrogan A, Franssen CF, de Vries CS. The incidence of primary glomerulonephritis worldwide: a systematic review of the literature. Nephrology Dialysis Transplantation. 2011;26(2):414-30.
4. Floege J, Amann K. Primary glomerulonephritides. The Lancet. 2016;387(10032):2036-48.
5. Anderson DC, York TL, Rose G, Smith CW. Assessment of serum factor B, serum opsonins, granulocyte chemotaxis, and infection in children's nephrotic syndrome. Journal of Infectious Diseases. 1979;140(1):1-11.
6. Abbott KC, Koff J, Bohen EM, Oglesby RJ, Agodoa LY, Lentine KL, et al. Maintenance immunosuppression use and the associated risk of avascular necrosis after kidney transplantation in the United States. Transplantation. 2005;79(3):330-6.
7. Martin PJ, Storer BE, Rowley SD, Flowers ME, Lee SJ, Carpenter PA, et al. Evaluation of mycophenolate mofetil for initial treatment of chronic graft-versus-host disease. Blood. 2009;113(21):5074-82.
8. Messer J, Reitman D, Sacks HS, Smith Jr H, Chalmers TC. Association of adrenocorticosteroid therapy and peptic-ulcer disease. New England Journal of Medicine. 1983;309(1):21-4.
9. Epinette WW, Parker CM, Jones EL, Greist MC. Mycophenolic acid for psoriasis: a review of pharmacology, long-term efficacy, and safety. Journal of the American Academy of Dermatology. 1987;17(6):962-71.
10. FK UM. 506 Liver Study Group: A comparison of tacrolimus (FK 506) and cyclosporine for

immunosuppression in liver transplantation. N Engl J Med. 1994;331(1110):71115.

11. Afifi A. Steroid myopathy. Clinical, histologic, and cytologic observation. Johns Hopkins Medical Journal. 1968;123:158-73.

12. Gumprecht J, Zychma M, Grzeszczak W, Kuźniewicz R, Burak W, Żywiec J, et al. Simvastatin-induced rhabdomyolysis in a CsA-treated renal transplant recipient. Medical Science Monitor. 2003;9(9):CS89-CS91.

13. Galindo M, Cabello A, Joven B, Alonso A, Carreira P, Porta J, et al. Mycophenolate mofetil induced myopathy in a patient with lupus nephritis. The Journal of rheumatology. 2005;32(1):188-90.

14. Skalka HW, Prchal JT. Effect of corticosteroids on cataract formation. Archives of Ophthalmology. 1980;98(10):1773-7.

15. Hirsch IB, Paauw DS. Diabetes management in special situations. Endocrinology and metabolism clinics of North America. 1997;26(3):631-45.

16. Heisel O, Heisel R, Balshaw R, Keown P. New onset diabetes mellitus in patients receiving calcineurin inhibitors: a systematic review and meta-analysis. American Journal of Transplantation. 2004;4(4):583-95.

17. Maksimovic D, Stojkovic MM, STOSIC-GRUJICIC S. Antidiabetogenic Effect of Mycophenolate Mofetil Is Associated with Down-Regulation of Adhesive Interactions and Autoreactive Cell Activation. Annals of the New York Academy of Sciences. 2002;958(1):148-51.

18. Kanis JA, Johansson H, Oden A, Johnell O, De Laet C, Melton III LJ, et al. A meta-analysis of prior corticosteroid use and fracture risk. Journal of bone and mineral research. 2004;19(6):893-9.

19. Yeo H, Beck LH, McDonald JM, Zayzafoon M. Cyclosporin A elicits dose-dependent biphasic effects on osteoblast differentiation and bone formation. Bone. 2007;40(6):1502-16.

20. Glenn DA, Henderson CD, O'Shaughnessy M, Hu Y, Bomback A, Gibson K, et al. Infection-related acute care events among patients with glomerular disease. Clinical journal of the American Society of Nephrology: CJASN. 2020;15(12):1749.

21. Oh GJ, Waldo A, Paez-Cruz F, Gipson PE, Pesenson A, Selewski DT, et al. Steroid-associated side effects in patients with primary proteinuric kidney disease. Kidney international reports. 2019;4(11):1608-16.

22. Glenn DA, Zee J, Mansfield S, O'Shaughnessy MM, Bomback AS, Gibson K, et al. Immunosuppression Exposure and Risk of Infection-Related Acute Care Events in Patients With Glomerular Disease: An Observational Cohort Study. Kidney Medicine. 2022;4(11):100553.