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MAINTENANCE IMMUNOSUPPRESSION AFTER LIVER TRANSPLANTATION: DATA FROM A LOCAL TRANSPLANT REGISTRY

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The steady annual increase in the number of liver transplants (LT) in Russia, together with the expansion of the liver recipient population, underscores the need for large-scale studies on the actual clinical practice of prescribing and managing immunosuppressive therapy. **Objective:** to analyze the structure of maintenance immunosuppressive therapy (MIT) at various time points after liver transplantation and to assess the evolution of approaches to selecting initial immunosuppressive regimens between 2010 and 2024. **Materials and methods.** This single-center, retrospective registry study included data from 568 consecutive LT performed between 2010 and 2024, using grafts from living-related (72%) and deceased (28%) donors. The MIT composition was evaluated at six time points: at hospital discharge and at 1, 3, 5, 7, and 10 years after transplantation. **Results.** At hospital discharge and at 1, 5, and 10 years after LT, calcineurin inhibitors (CNIs) were prescribed in 99%, 96%, 94%, and 90% of patients, respectively. The use of glucocorticoids (St) decreased over time, accounting for 51%, 17%, 10%, and 14%, respectively. Proliferation signal inhibitors (mTOR inhibitors) were prescribed in 13%, 17%, 14%, and 14% of cases, while antimetabolites (A/M) were used in 6%, 7%, 7%, and 14% of patients, respectively. At intervals ranging from one to ten years after transplantation, CNI monotherapy was used in approximately 70% of recipients. Combination regimens included CNI + St in 7%, CNI + A/M ± St in 8%, CNI + mTOR ± St in 8%, and mTOR ± St in 7% of patients. At discharge and at 5 years after transplantation, mTOR-based regimens were more commonly prescribed in patients who underwent surgery for liver tumors (48% and 57%, respectively), A/M-based regimens in patients with immune-mediated liver diseases (22% and 18%), and CNI monotherapy in recipients with viral cirrhosis (52% and 89%). Immunosuppression regimens changed with a frequency ranging from 9% (in the 5–7 year interval) to 49% (in the interval from discharge to 1 year). Over the period from 2010 to 2024, the most notable trends in initial immunosuppression included a shift from immediate-release to prolonged-release tacrolimus, as well as increased use of mycophenolates and mTOR inhibitors, rising from 2% and 4% in 2010–2015 to 9% and 21% in 2019–2024, respectively. **Conclusion**. The underlying etiology of the disease remains the primary determinant in selecting MIT. The high prevalence of CNI monotherapy from 1 to 10 years post-transplant provides a strong rationale for initiating clinical trials to evaluate the safety and efficacy of minimizing or discontinuing immunosuppressive therapy in liver transplant recipients.

Keywords: liver transplantation, immunosuppressive therapy, tacrolimus, cyclosporine, glucocorticoids, mycophenolic acid, azathioprine, everolimus.

INTRODUCTION

Over the past 20 years, the number of LT performed annually in Russia has steadily increased. For instance, the number of procedures rose from 33 in 2004 to 829 in 2023. This growth in transplant activity has been accompanied by a corresponding rise in the population of LT recipients. According to estimates from the Russian Transplant Society, the number of patients living with a transplanted liver increased fourfold between 2013 and 2023 – from 1,150 to 4,644 individuals [1].

In this context, the accessibility and quality of outpatient care for transplant recipients have become increasingly important. A central and specific challenge is the long-term management of maintenance IST.

To date, no multicenter studies in Russia have comprehensively evaluated current practices in pharmacological immunosuppression. Most available studies focus either on the early postoperative period or on specific subgroups of recipients. Moreover, studies published more than a decade ago were typically based on small patient cohorts with limited follow-up durations and may no longer accurately reflect actual clinical practice.

This report presents an analysis of the composition and changes in maintenance IST from hospital discharge up to 10 years after LT. In addition, it traces the evolution

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of approaches to selecting initial immunosuppressive regimens over the 15-year history of the program at Burnazyan Federal Medical and Biophysical Center, Moscow.

MATERIALS AND METHODS

The data for this analysis were obtained from the Local Scientific Registry of Transplantations at Burnazyan Federal Medical and Biophysical Center. Between May 26, 2010, and December 31, 2024, a total of 568 consecutive LT were performed, including 411 (72%) from living-related donors and 157 (28%) from deceased donors with brain death and preserved circulation at the time of transplantation.

Overall, 549 patients underwent transplantation, comprising 277 (49%) men and 291 (51%) women. Recipient age at the time of transplantation ranged from 18 to 72 years (median [Me], 45 years; interquartile range [IQR], 37–54). The preoperative MELD-Na score ranged from 6 to 42 (median, 16; IQR, 13–21). According to the Child–Pugh classification, 69 patients (12%) were class A, 280 (49%) class B, and 184 (33%) class C; in 35 cases (6%), classification was not applicable.

The most common indications for transplantation were viral-related liver cirrhosis (n = 202; 36%), liver tumors (n = 96; 17%), including hepatocellular carcinoma (n = 87; 15%), cirrhosis due to cholestatic diseases (n = 86; 15%), unresectable hepatic alveolar echinococcosis (n = 49; 9%), and cirrhosis of unknown etiology (n = 43; 8%).

The median duration of static cold ischemia for living-donor transplantation was 0.6 hours (IQR, 0.5–0.7), with a secondary warm ischemia time of 25 minutes (IQR, 21–35). For deceased-donor transplantation, the corresponding values were 8.6 hours (IQR, 7.4–10.0) and 42 minutes (IQR, 34–50), respectively.

At various time points following the primary transplantation, 22 patients underwent one retransplantation, and one patient underwent two retransplantations. In four cases, the primary transplantations had been performed at other institutions. In total, 24 retransplantations were carried out.

Graft loss was defined as either retransplantation or recipient death. All other cases were censored at the date of the last documented follow-up at the Center for Surgery and Transplantology, at which time the recipient was confirmed to be alive with a functioning graft.

As of March 1, 2025, 159 (28%) of the 568 transplanted grafts had been lost, including 8 (1.4%) occurring more than 10 years after transplantation.

Recipient survival at 1, 3, 5, 7, and 10 years was 85% (95% CI, 82–88%), 80% (76–83%), 76% (72–80%), 70% (65–75%), and 64% (57–71%), respectively. Corresponding graft survival rates were 83% (80–86%), 77% (73–81%), 73% (69–77%), 67% (62–72%), and 61% (54–67%).

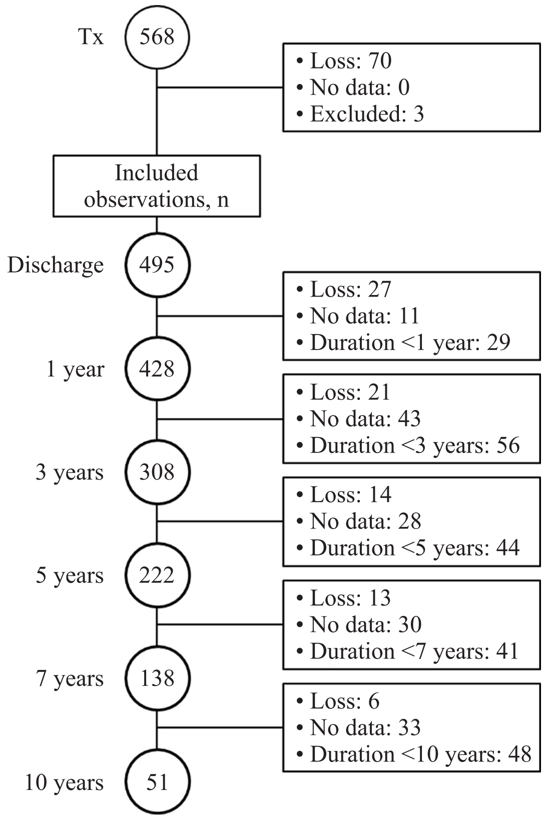

Fig. 1. Study flowchart – distribution of cases by outcomes and time periods after liver transplantation (Tx)

The composition of maintenance IST was evaluated at the time of hospital discharge (approximately 4 weeks after surgery) and at 1, 3, 5, 7, and 10 years after transplantation. At each time point, the number of patients under observation was taken as 100% (Fig. 1). Re-transplants were counted as separate cases. Three cases were excluded from the analysis. In two cases, patients were discharged without IST, as it had been discontinued in the early postoperative period due to sepsis; both patients died within the first year after transplantation. In the third case, the patient independently discontinued tacrolimus monotherapy 3 years after transplantation; the patient remained alive at 5 and 7 years of follow-up but was subsequently lost to follow-up.

IST regimens were categorized according to the classes of agents included in the treatment regimen:

- **Calcineurin inhibitors (CNI):** cyclosporine A (CyA), tacrolimus (Tac), including immediate-release (IR-Tac) and prolonged-release (PR-Tac) formulations;
- **Antimetabolites (A/M):** mycophenolate mofetil (MMF), mycophenolic acid (MPA), azathioprine;
- **mTOR inhibitors:** everolimus, sirolimus;
- **Glucocorticoids (St):** prednisolone, methylprednisolone.

Induction and initial maintenance immunosuppression

In all cases, basiliximab was used for induction therapy at a dose of 20 mg administered intraoperatively and repeated on postoperative day 4. In addition, methylprednisolone was administered prior to graft reperfusion at a dose of 10 mg/kg. From postoperative day 1, methylprednisolone was administered intravenously once daily with stepwise dose reduction: 500 mg → 250 mg → 125 mg → 60 mg when 750–1000 mg had been given intraoperatively, or 250 mg → 125 mg → 60 mg when the intraoperative dose was 500 mg. Beginning on postoperative days 4–5, patients were transitioned to oral methylprednisolone (prednisolone) at an initial dose of 16 (20) mg/day, followed by tapering to 4 (5) mg/day or complete discontinuation by the end of postoperative week 4.

Tac was initiated on postoperative day 3 at a fixed dose of 1 mg, with subsequent dose adjustment to achieve target trough plasma levels of 8–10 ng/mL. When everolimus was included in the initial maintenance immunosuppressive regimen, it was introduced on postoperative days 10–12 at a dose of 3 mg/day, followed by dose titration to maintain target blood levels of 3–8 ng/mL. In such cases, the target Tac concentration was reduced to 3–5 ng/mL.

Antimetabolites (at early stages, exclusively mycophenolates) were added to the CNI + glucocorticoid regimen on postoperative days 10–12 at doses of 720 mg/day for MPA or 1000 mg/day for MMF.

Statistical analysis

Quantitative variables were summarized using the median, interquartile range (IQR), and minimum and maximum values. Qualitative variables were presented as absolute frequencies and percentages. Differences between two independent groups for categorical variables were assessed using the chi-square test. Differences were considered statistically significant at $p < 0.05$. Statistical analyses were performed using the Jamovi software package (version 2.3.21.0; Jamovi Project, Australia).

RESULTS

Maintenance immunosuppressive therapy at various time points after liver transplantation

The frequency of use of different classes of immunosuppressants varied depending on the time elapsed since LT (Fig. 2). CNIs were the predominant component of maintenance therapy throughout the follow-up period. At the time of hospital discharge, 491 recipients (99%) were receiving CNIs, including cyclosporine A in 24 (5%) patients, IR-Tac in 174 (35%), and PR-Tac in 293 (59%). Between 1 and 7 years post-transplant, the proportion of patients receiving CNIs remained high (94–96%), declining to 90% at 10 years post-transplant.

At the end of the inpatient treatment phase, glucocorticoids (St) in combination with other immunosuppressants were included in maintenance regimens in 253 cases (51%). By the end of the first year after transplantation, the proportion of patients receiving St had decreased to 17%; between 3 and 7 years, it remained at 9–10%, and by 10 years post-transplant, it had increased to 14%. The use of proliferation signal inhibitors showed no significant variation over time, ranging from 13% to 17% across all follow-up periods. mTOR inhibitors were most frequently prescribed during the 1–3-year period (16–17%). Antimetabolites (A/M) were used least frequently, with a prescription rate of 6–7% from discharge up to 5 years post-transplant. However, their use increased at later time points, reaching 10% at 7 years and 14% at 10 years after transplantation.

In total, eight immunosuppressive regimens were used: CNI; CNI + St; CNI + A/M; CNI + A/M + St;

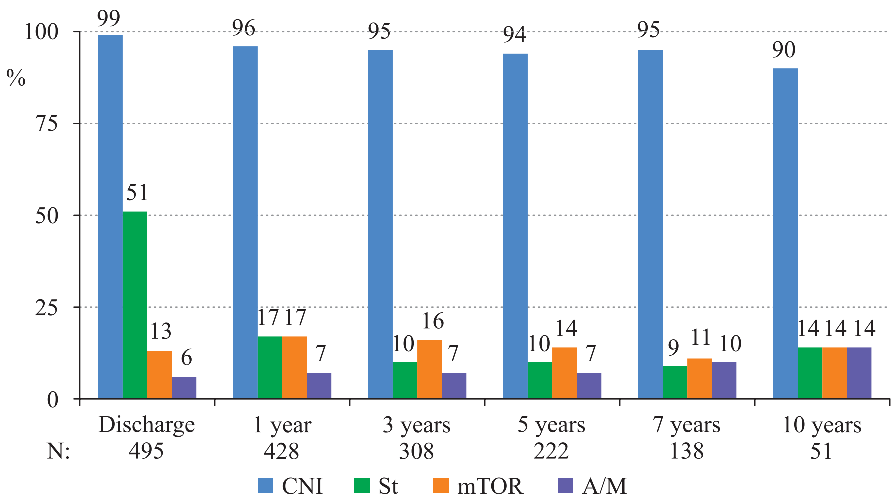

Fig. 2. Immunosuppressants used post-liver transplant. CNI, calcineurin inhibitors; St, glucocorticoids; mTOR, mTOR inhibitors; A/M, antimetabolites

CNI + mTOR; CNI + mTOR + St; mTOR; and mTOR + St. The distribution of maintenance IST according to the number of components in each regimen is presented in Fig. 3a, while Fig. 3b shows the frequency of individual regimens. For clarity, the CNI + A/M and CNI + A/M + St regimens were combined as CNI + A/M ± St, and CNI + mTOR and CNI + mTOR + St as CNI + mTOR ± St.

A key trend during the first three years post-transplant was a marked reduction in the use of two- and three-drug regimens: the proportion of patients receiving two-drug therapy decreased from 52% to 19%, while the use of three-drug regimens declined from 9% to 5%. At the same time, the proportion of patients on monotherapy – primarily CNIs, and less frequently mTOR inhibitors – increased from 39% to 76%.

From discharge through the third year post-transplant, median Tac blood levels gradually decreased from 7.6 to 6.1 ng/mL. From the fifth year onward, levels stabilized at 5.6–5.8 ng/mL. The addition of other agents – A/M, mTOR, and/or St – to maintenance immunosuppressive regimens did not have a significant impact on Tac levels (Fig. 4).

At discharge, Tac levels within the target range of 6–10 ng/mL were observed in 92 patients (50%) receiving monotherapy and in 78 patients (45%) receiving

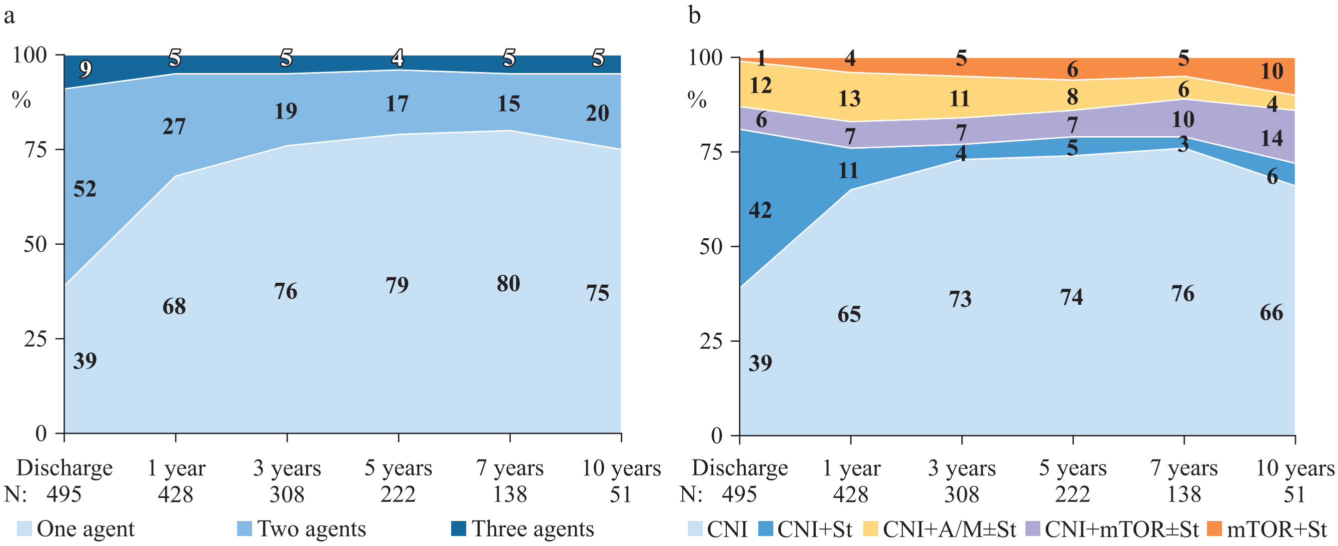

Fig. 3. Structure of maintenance immunosuppression after liver transplantation: (a) number of agents; (b) treatment regimens. CNI, calcineurin inhibitors, St, glucocorticoids; mTOR, mTOR inhibitors; A/M, antimetabolites

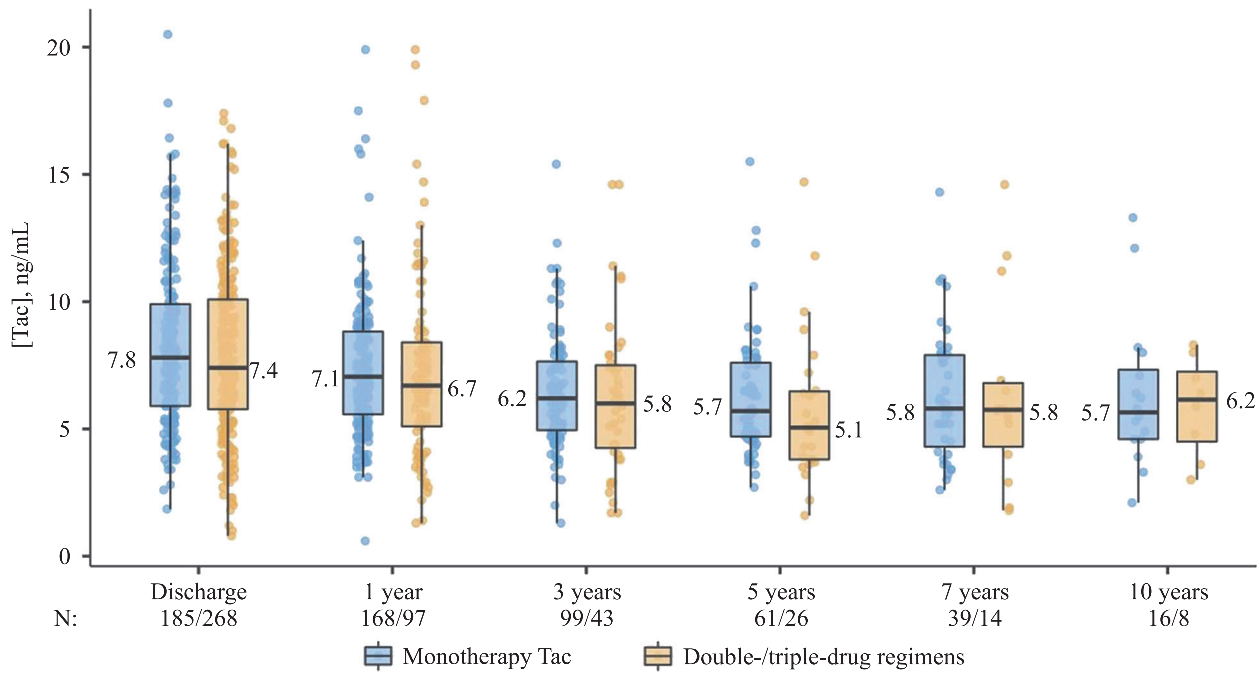

Fig. 4. Tacrolimus trough levels on monotherapy (*blue*) and double-/triple-drug (*yellow*) immunosuppression

two- or three-drug regimens. Higher concentrations were recorded in 44 (24%) and 69 (26%) patients, respectively, while lower concentrations were observed in 49 (26%) and 78 (29%).

Over the follow-up period from 1 to 10 years, Tac levels exceeding 6 ng/mL were observed, on average, in 23% of patients receiving monotherapy (Fig. 5a) and in 20% of those on combination IST (Fig. 5b).

At various time points after discharge, modifications of maintenance IST regimens occurred with a frequency ranging from 9% to 49% (Table). In total, 288 discontinuations and 130 additions of immunosuppressive agents were performed. Glucocorticoids were discontinued most frequently (n = 201; 48%), whereas the mTOR inhibitor everolimus was the most commonly added agent (n = 54; 13%).

The individual trajectories of maintenance immunosuppression for all patients included in the analysis are presented in Fig. 6. The etiology of the underlying liver disease was a key determinant of maintenance IST strategy. Tac monotherapy was the preferred regimen in patients with viral-related cirrhosis (Fig. 7a): more than half of recipients were receiving it at discharge, and by one year after transplantation, approximately 80% were maintained on this regimen.

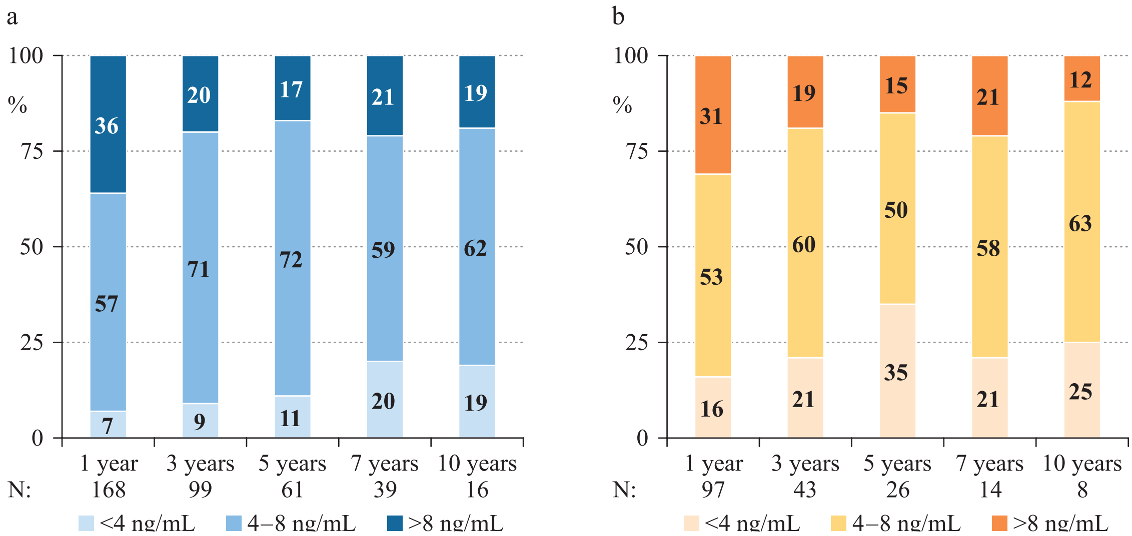

Fig. 5. Liver recipients with tacrolimus trough levels within, above and below the target range (4–8 ng/mL): (a) monotherapy, (b) double- and triple-drug regimens

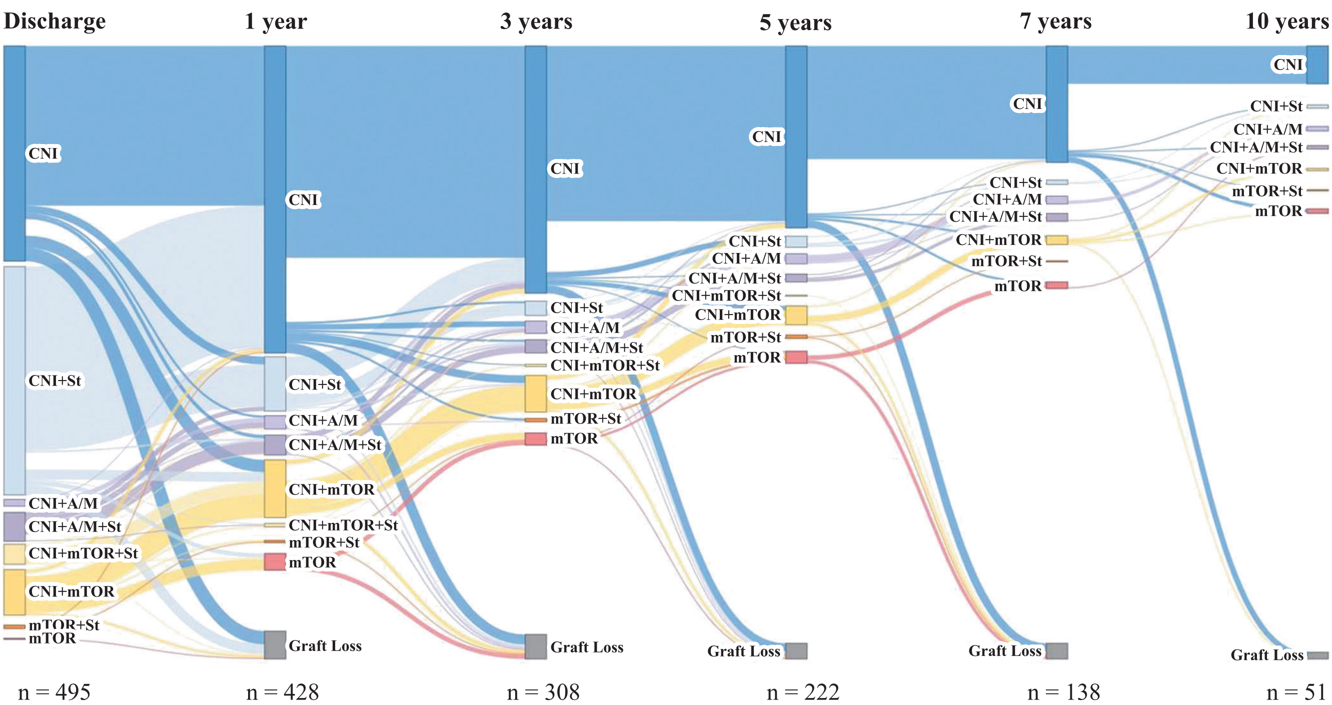

Fig. 6. Individual trajectories of maintenance immunosuppression after liver transplantation

Table

Changes in maintenance immunosuppressive therapy after liver transplantation

Parameter		Discharge – 1 year	1–3 years	3–5 years	5–7 years	7–10 years
Number of immunosuppressive regimens available for modification, n		428	308	222	138	51
Number of modified immunosuppressive regimens, n (%)		209 (49)	70 (23)	33 (15)	13 (9)	11 (22)
Number of additions and cancellations, n (%)		237	90	53	17	21
CNI	*addition*	1 (<1)	–	–	–	1 (5)
	cancellation	16 (7)	8 (9)	13 (25)	2 (12)	5 (24)
A/M	*addition*	9 (4)	11 (12)	4 (8)	3 (18)	3 (14)
	cancellation	6 (2)	9 (10)	5 (9)	2 (12)	–
mTOR	*addition*	26 (11)	13 (14)	7 (13)	4 (23)	4 (19)
	cancellation	6 (2)	5 (6)	7 (13)	1 (5)	2 (9)
St	*addition*	13 (6)	11 (12)	12 (23)	3 (18)	5 (24)
	cancellation	160 (68)	33 (37)	5 (9)	2 (12)	1 (5)

Note. CNI, calcineurin inhibitors; St, glucocorticoids; mTOR, mTOR inhibitors; A/M, antimetabolites.

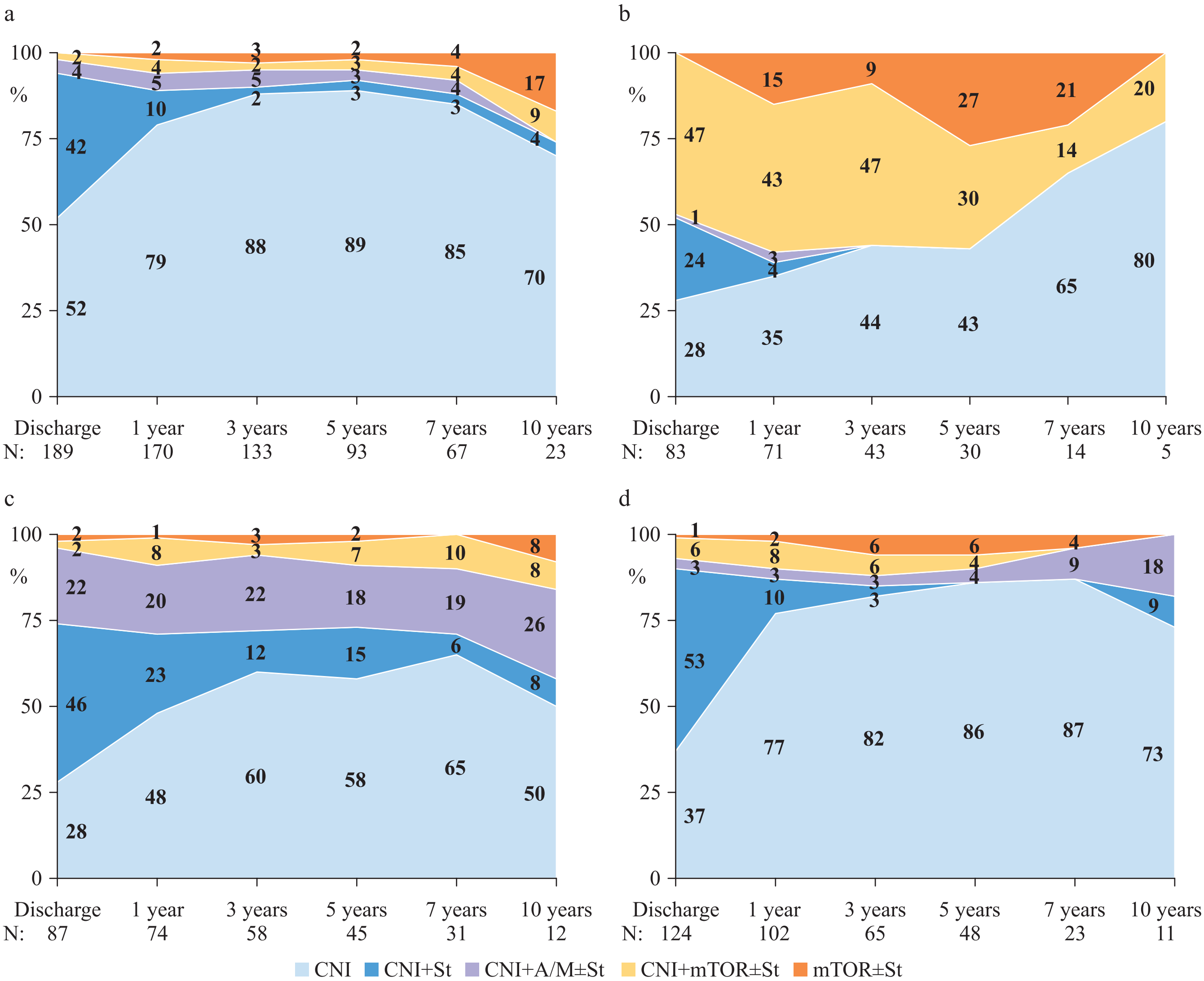

Fig. 7. Maintenance immunosuppressive therapy after liver transplantation for (a) viral cirrhosis, (b) tumors, (c) immune-mediated cirrhosis (AIG, PBC, PSC), (d) parasitic liver disease, cryptogenic and alcoholic cirrhosis, Wilson's disease, and other etiologies

A similar approach was applied in patients undergoing transplantation for unresectable alveolar echinococcosis, cirrhosis of unknown etiology, alcoholic cirrhosis, Wilson's disease, and other indications (Fig. 7d).

At all post-transplant time points, regimens including everolimus were most frequently prescribed in patients transplanted for hepatocellular carcinoma (HCC) and other liver tumors. This group also had the highest proportion of patients not receiving CNIs (Fig. 7b).

Among patients with immune-mediated liver diseases – autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC) – antimetabolites were included in the IST regimen in approximately 20% of cases at each time point. In this group, the use of CNI monotherapy increased during the first three years after transplantation, from 28% to 60%, and subsequently stabilized at approximately 55% (Fig. 7c).

The Evolution of Approaches to Selecting Initial Maintenance Immunosuppressive Therapy

Over the 15-year period of the program, the structure of indications for LT has undergone notable changes (Fig. 8). Beginning in 2019, a clear and persistent trend emerged toward a reduction in the proportion of patients with viral-related cirrhosis without HCC, accompanied by a concurrent increase in the number of transplantations performed for liver tumors. In addition, recent years have seen an increase in the number of transplantations in patients with alcoholic cirrhosis, while the proportion of procedures performed for cholestatic liver diseases has declined.

When comparing two periods of transplant activity – similar in both duration and number of procedures – a statistically significant, approximately twofold increase was observed over time in the proportion of recipients aged over 60 years with diabetes mellitus and arterial hypertension (Fig. 9).

There was also a slight increase in the proportion of recipients with obesity (body mass index >30 kg/m^2) and impaired renal function (glomerular filtration rate <60 mL/min/1.73 m^2).

These trends, together with accumulated institutional experience, as well as evidence from large international studies and updated clinical guidelines, influenced the approach to selecting maintenance immunosuppressive therapy. During the first five years of the program,

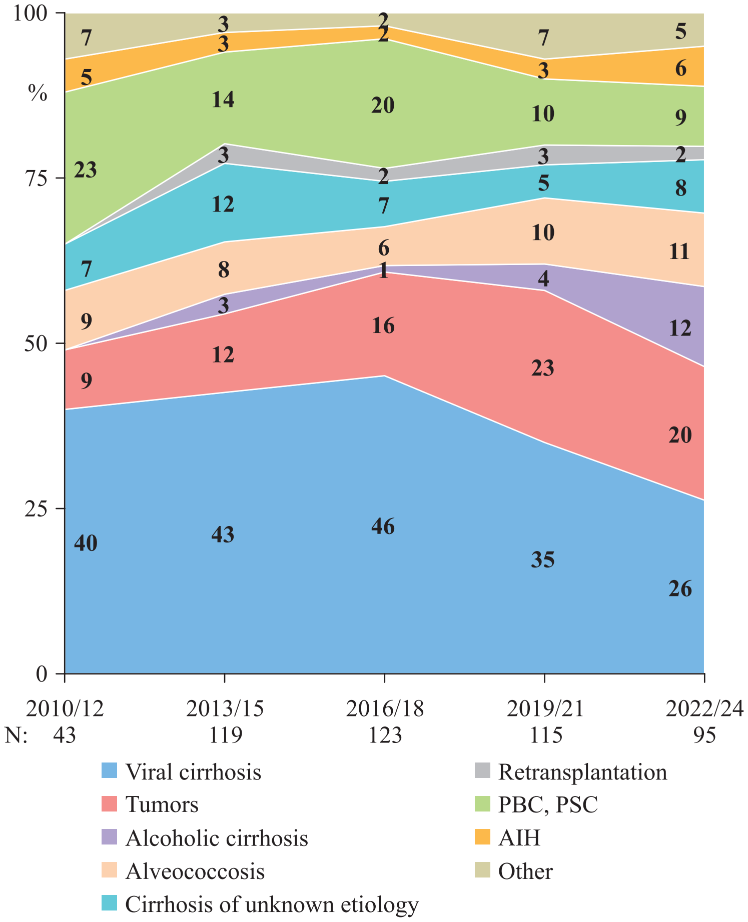

Fig. 8. Changes in the structure of indications for liver transplantation between 2010 and 2024 (discharged patients, N = 495). PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; AIH, autoimmune hepatitis

two-drug regimens (CNI + St) predominated; slightly more than one-quarter of patients received CNI monotherapy, while three-drug combinations were rarely used (Fig. 10).

In 2016–2018, compared with the preceding three-year period, the proportion of patients receiving monotherapy doubled, reaching a peak of 55% over the entire observation period. Thereafter, its use declined to approximately 40%, while the increase in two- and three-drug regimens was largely driven by the more frequent incorporation of everolimus-based regimens (CNI + mTOR and CNI + mTOR + St), particularly in patients undergoing transplantation for HCC.

The most notable change in the selection of immunosuppressants for initial immunosuppressive regimens has been the transition from immediate-release Tac (IR-Tac) to its prolonged-release formulation (PR-Tac). CyA has assumed the role of a "reserve" calcineurin inhibitor, with conversion to CyA in recent years occurring exclusively in cases of serious adverse events (primarily neurological) developed while taking Tac.

The frequency of glucocorticoid use at discharge declined from approximately three-quarters of patients in the early years of the program to one-third in 2016–2018, and has since stabilized at around 50% (Fig. 11).

At the same time, the strategy of early (within 3 months) glucocorticoid withdrawal in patients without immune-mediated liver disease remained unchanged. The timing of steroid discontinuation – whether before or

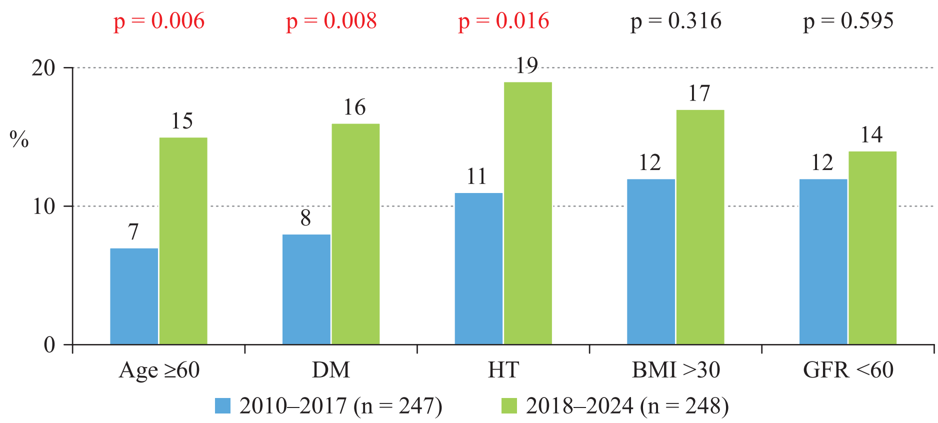

Fig. 9. Proportion of liver recipients at discharge in 2010–2017 *(blue)* and 2018–2024 *(green)* with the following characteristics: over 60 years of age, diabetes mellitus (DM), hypertension (HT), obesity (body mass index (BMI) >30 kg/m^2), and impaired renal function (glomerular filtration rate (GFR) <60 ml/min/m^2)

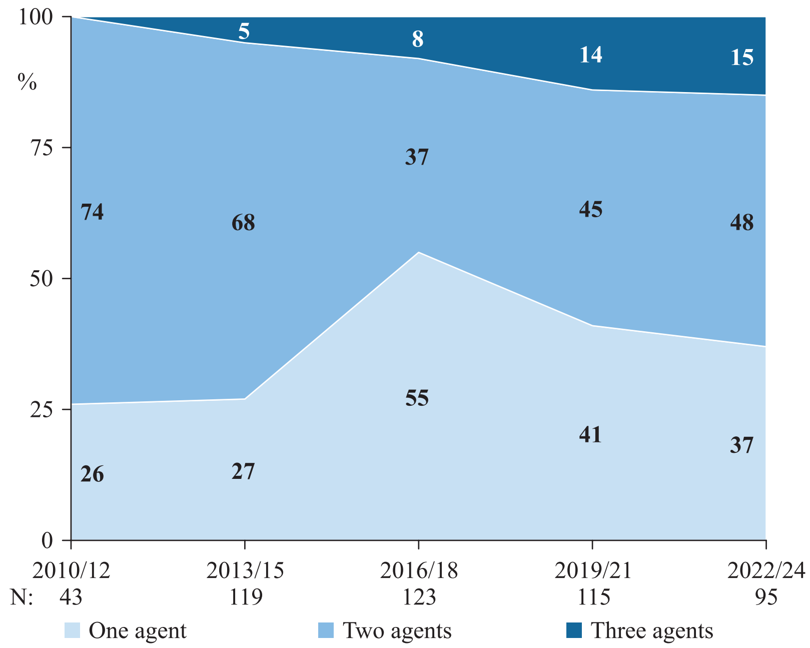

Fig. 10. Single-, dual-, and triple-agent maintenance immunosuppressive regimens at hospital discharge following liver transplantation in 2010–2024

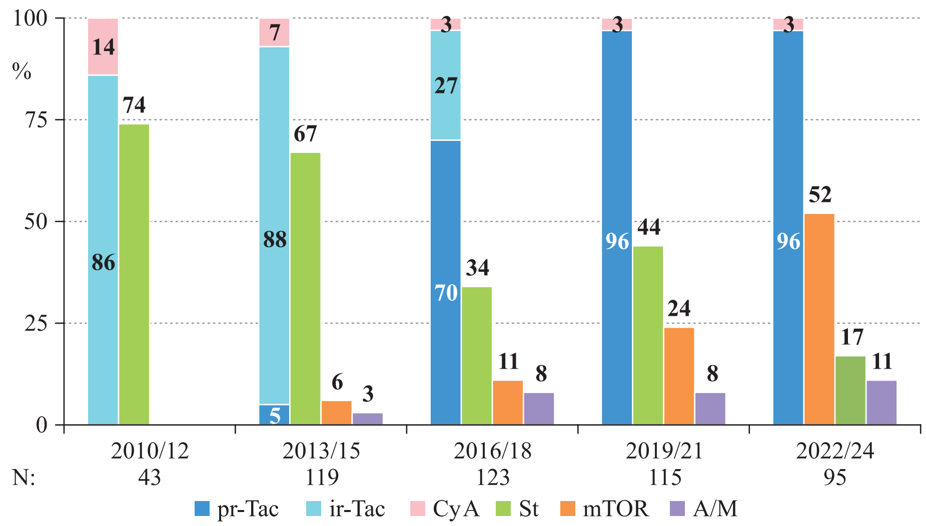

Fig. 11. Frequency of individual immunosuppressants and calcineurin inhibitors at discharge after liver transplantation between 2010 and 2024. pr-Tac, prolonged-release tacrolimus; ir-Tac, immediate-release tacrolimus; CyA, cyclosporine A; St, glucocorticoids; mTOR, mammalian target of rapamycin (mTOR) inhibitors; A/M, antimetabolites

after hospital discharge – was determined by the length of hospitalization and the stability of Tac blood levels.

The practice of prescribing mTOR inhibitors within the first month after transplantation began in 2013. Since 2019, all patients undergoing transplantation for liver tumors, in the absence of contraindications to everolimus, have been discharged on regimens including CNI + mTOR or CNI + mTOR + St. Similar strategies have been employed in recipients with a glomerular filtration rate below <45 mL/min/1.73 m^2. Until 2016, mycophenolates, primarily MPA, were prescribed mainly to patients with cirrhosis secondary to AIH, and later also to those with PSC.

DISCUSSION

It is well established that, compared with other solid organs, the lower risk of liver graft loss due to rejection permits the safe reduction or discontinuation of intensive IST in many cases. Nevertheless, sustained control of the alloimmune response remains essential for maintaining long-term graft function.

The comparable efficacy of different immunosuppressive regimens provides substantial scope for individualized therapy, taking into account recipient comorbidities, risk factors, and treatment-related complications. However, this flexibility often results in considerable variability in treatment regimens [2], not only between transplant centers but also within a single program and even over the course of treatment in an individual patient.

Clinical trials sponsored by major pharmaceutical companies remain a key driver in the evolution of IST. Their high methodological rigor, advanced technical support, and overall reliability are well recognized. However, when translated into routine clinical practice, the reported safety and efficacy of novel regimens often do not fully meet expectations.

This discrepancy is typically attributable to several factors [3–5]: highly selective patient recruitment resulting in study populations that are not representative of real-world cohorts; the use of soft (surrogate) endpoints; relatively short follow-up periods that limit assessment of long-term outcomes; and the practical challenges of adhering to strict study protocols in everyday clinical settings. In addition, the potential for bias at the stages of study design, data interpretation, and publication cannot be entirely excluded. In this regard, data from independent research groups and large-scale registry studies are becoming increasingly important from a practical and clinical perspective.

Over the past decade, the principles guiding the initiation and management of IST after LT have remained largely unchanged [6–9]. The introduction of regimens incorporating the mTOR inhibitor everolimus generated considerable expectations; however, their widespread adoption has been limited.

Nevertheless, everolimus-based therapy is strongly recommended for patients with recurrent or *de novo* non-melanoma skin cancer, as well as in combination with reduced (minimal) exposure to CNIs in individuals at high risk of liver tumor recurrence. Furthermore, to mitigate the nephrotoxic effects of CNIs, everolimus – along with mycophenolates and azathioprine – may be used in combination regimens to allow for lower target concentrations of Tac or CyA.

In addition to recipients with oncological risk or impaired renal function, patients undergoing transplantation for immune-mediated liver diseases with a high risk of recurrence require tailored immunosuppressive strategies. In most other cases, Tac monotherapy remains the preferred option for maintenance immunosuppression.

Tac monotherapy – particularly with extended-release formulations – represents an attractive immunosuppressive strategy, as it simplifies the treatment regimen, enhances patient adherence, and avoids adverse effects associated with additional immunosuppressive agents.

With this approach, target Tac levels are typically maintained within the range of 4–8 ng/mL [8]. However, such levels do not always prevent drug-related toxicity and, at the same time, may be insufficient to ensure adequate suppression of the alloimmune response. This may result in prolonged subclinical rejection and an increased risk of graft loss.

Our findings demonstrated no significant differences in Tac levels between monotherapy and two- or three-drug regimens. Over follow-up periods ranging from 1 to 10 years, Tac levels exceeding 6 ng/mL were observed in 23% of patients receiving monotherapy and in 20% of those on combination regimens, suggesting that this pattern is common in routine clinical practice.

In the present study, no comparative analysis of the safety and efficacy of different immunosuppressive regimens was performed. Episodes of acute rejection occurred predominantly within the first months after transplantation, with approximately half arising before hospital discharge. These episodes were rarely associated with severe graft dysfunction, responded to intensification of CNI therapy and/or pulse glucocorticoid treatment, and had a cumulative incidence of no more than 15% over the entire follow-up period. As previously reported [10], rejection led to graft loss in 5 of 500 cases.

Overall, all maintenance IST regimens used – including Tac monotherapy – showed adequate efficacy in preventing acute rejection in both the early and late post-transplant periods.

When interpreting these results, an important feature of the program should be taken into account: the extensive use of living donors. Although current evidence suggests no significant association between the number of A-, B-, and DR-HLA mismatches and the risk of liver allograft rejection [11, 12], the relatively higher degree of histocompatibility in related donor–recipient pairs may represent a key factor enabling the use of less intensive immunosuppressive strategies.

An important, albeit indirect, factor influencing the selection and management of IST is the substitution of original drugs with generic formulations, a practice that began in the 2010s and continues to the present day. There is no objective evidence to suggest that generic formulations of Tac, CyA, everolimus, MPA, or mycophenolate mofetil available in the Russian Federation differ in safety or efficacy from their original counterparts. International data likewise support the feasibility of using generic immunosuppressants in transplant recipients and indicate no adverse impact on graft outcomes [13–15].

However, the current practice of frequent switching between different brand-name formulations of immunosuppressants provided to recipients under preferential programs raises concerns. Such substitutions may be associated with variability in drug blood levels, necessitating additional laboratory and clinical monitoring, which is not always consistently performed. Moreover, in some cases, a patient's daily dose may be composed of formulations from different manufacturers. In such cases, maintaining immunosuppressant levels at the lower end of the therapeutic range, particularly in the setting of monotherapy, appears risky.

A promising direction in the field of post–liver transplantation immunosuppression is the identification of predictors, biomarkers, and inducers of operational immunological tolerance [16, 17]. Despite the growing body of literature on this topic, withdrawal of immunosuppressive therapy in routine clinical practice is still largely based on a trial-and-error approach, with serum biochemical parameters and histological findings remaining the key guidelines [18, 19].

The decision to discontinue immunosuppression or to reduce it to subtherapeutic levels must therefore be preceded by a careful assessment of potential risks and benefits, the balance of which is highly individualized and not always straightforward [20]. To date, published experience on long-term outcomes in LT recipients maintained on minimal immunosuppression or completely free of IST remains very limited.

CONCLUSION

The analysis showed that the etiology of liver disease necessitating transplantation remains a key determinant in selecting maintenance immunosuppressive strategies. In the final years of the 15-year period under review, there has been an increase in the number of transplants performed for HCC, alongside a rise in recipient age. Consequently, there has been a growing prevalence of comorbidities, including hypertension, diabetes mellitus, obesity, and impaired renal function. These trends are likely to persist and will require substantial adjustments not only in immunosuppressive regimens but also in concomitant therapy.

The basic principles of post–LT immunosuppression are defined in national and international professional society guidelines, which are broadly consistent in their recommendations. In routine clinical practice, adherence to these guidelines ensures, in the vast majority of cases, acceptable transplant outcomes by contemporary standards. However, the concept that immunosuppression remains an "art" is still valid.

This "art" lies not merely in the selection of specific drugs or combinations, but in achieving a balance between rational conservatism – avoiding therapeutic inertia – and timely, and when necessary, decisive yet measured modification of therapy in response to evolving risks or complications.

In the current context, where the emergence of fundamentally new immunosuppressants in the near future appears unlikely, the most realistic strategy for improving long-term transplant outcomes lies in systematic, comprehensive, and regular evaluation of recipients, as well as enhanced adherence to prescribed therapy.

Particular importance should be placed on studies aimed at identifying and validating novel approaches for monitoring the adequacy of immunosuppressive therapy and the strength of transplant immunity. These should include expanded panels of biomarkers, histological and instrumental methods, as well as large-scale multicenter retrospective and prospective studies supported by modern medical data analytics.

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The authors declare no conflict of interest.

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