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Long-term immunosuppression after liver transplantation in real-life clinical practice: modifications and survival of therapy

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Abstract

Background. *High long-term survival rates have been achieved in liver transplant recipients. However, personalised approaches are still needed for selecting and managing the initial immunosuppressive therapy regimen throughout the entire period of graft function.*

Objective. *To evaluate the outcomes of various immunosuppressive therapy regimens in liver recipients over a period of up to 20 years.*

Material and methods. *A retrospective cohort study was conducted using data from 173 patients who underwent 176 liver transplants between December 2004 and December 2021. The following immunosuppressive drugs were used: tacrolimus, steroids, mycophenolates, and everolimus, as monotherapy and in various combinations. Modifications to the initial*

regimen were studied in each patient over time, and the frequency with which various regimens were used at 1, 3, 5 and 10 years after transplantation was analyzed. Clinical observations were divided into two groups depending on whether steroids and/or mycophenolates were present (group 2, n=95) or absent (group 1, n=81) in the initial immunosuppression regimen.

Results. *The median follow-up duration was 79.5 (58;120) (6-220) months, the total duration was 1355 patient-years. The initial immunosuppression regimen included: tacrolimus (100% of patients), mycophenolates (48% of patients), steroids (39% of patients), everolimus (8% of patients). Tacrolimus monotherapy was initially prescribed to 38% of patients. The regimens prescribed at discharge were modified at various times in 77 (44%) patients, in the 1st group in 14 (17.3%), in the 2nd group in 63 (66.3%), ($p<0.05$). The 10-year survival rate of the initial immunosuppression regimen was 89% in the 1st group, 33% in the 2nd group ($p<0.05$). Rejection was observed in 21.1% of cases in group 2 and 6.2% (n=5) in group 1 ($p=0.004$). Immune or unspecified graft dysfunction as a cause of death or retransplantation was significantly less common in group 1 than in group 2: 1 (1.2%) and 7 (7.4%), respectively ($p=0.039$). The average SCF level after 5 years in patients receiving tacrolimus monotherapy was 69.7±14.1 ml/min/1.73m^2, while in the combination therapy group it was 62.4±20.7 ml/min/1.73m^2 ($p>0.05$). SCF ≥ 60 ml/min/1.73m^2 was recorded in 76.9% and 48.3% of patients, respectively ($p<0.01$).*

Conclusion. *Tacrolimus monotherapy or its combination with everolimus is considered optimal for a selective group of adult liver transplant recipients. With careful selection, strict clinical and drug monitoring, these regimens are characterized by the best survival of therapy, minimal*

risk of rejection, rare development of late graft dysfunction, favorable safety profile in terms of side effects, in particular, nephrotoxicity.

Keywords: liver transplantation, immunosuppression, tacrolimus, everolimus, rejection of liver transplants, tacrolimus-induced kidney damage

Conflict of interest The authors declare no conflict of interest.

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A, azathioprine
AIH, autoimmune hepatitis
AILD, autoimmune liver disease
ALP, alkaline phosphatase
ALT, alanine aminotransferase
AST, aspartate aminotransferase
CKD, chronic kidney disease
CP, liver cirrhosis
$LC_{alc.}$, alcoholic liver cirrhosis
E, everolimus
GFR, glomerular filtration rate
GGT, gamma-glutamyl transpeptidase
HBV, hepatitis B virus
HCC, hepatocellular carcinoma
HCV, hepatitis C virus
HDV, hepatitis virus D
INR, International Normalized Ratio
IST, immunosuppressive therapy
LGD, late graft dysfunction
LT, liver transplantation
M, mycophenolates (mycophenolic acid derivatives)
OR, odds ratio
PBC, primary biliary cholangitis
PSC, primary sclerosing cholangitis
RCT, randomized clinical trial
S, steroids (glucocorticosteroid hormones)
T, tacrolimus
ULN, upper limit of normal

Introduction

Thanks to the effectiveness of modern immunosuppressive therapy (IST), the global transplant community has achieved impressive long-term results in liver transplantation (LT). According to international registries and leading Russian centers, 1-, 5-, and 10-year recipient survival rates make 85–90%, 75–80%, and 70%, respectively [1–7]. Basic and clinical research and 60 years of international experience in this field have made a rejection a rare cause of graft loss, reducing its significance as a critical endpoint in clinical trials and practice [8, 9]. Problems associated with the adverse effects of long-term IST, leading to increased morbidity and mortality, have come to the fore [10, 11]. Lifelong immunosuppression is the cornerstone of post-transplant care, but there is surprisingly little evidence on optimal practice after the first year. In a well-known large meta-analysis by M. Rodríguez-Perálvarez (2017), only a small proportion (2.3%) of the cited randomized clinical trials (RCTs) related to immunosuppression studied its composition and modifications occurring 1 year or more after LT [12]. As the long-term period in actual life is prolonged, most patients experience changes not only in the decrease of the dose-dependent exposure to a particular drug, but also in the IST composition [13, 14].

However, none of the known and currently used protocols can be considered consistent, perfect, or universal. Current clinical guidelines, consensus agreements, and clinical trials do not provide a definitive comparative assessment of the long-term use of various IST regimens, leaving a wide choice to the transplant center or treating physician [15]. Recommendations and publications on this topic are often contradictory [16–23].

The objective was to evaluate the results of administration, modification, and survival of various immunosuppressive therapy regimens in liver transplant recipients for up to 20 years.

Material and methods

This is a retrospective, single-center, longitudinal-cross-sectional study. The study was approved by the local Ethics Committee (Minutes No. 14 dated October 12, 2023, issued by the National Ethics Committee Meeting of the Moscow Regional Research and Clinical Institute n.a. M.F. Vladimirskiy). The retrospective analysis included data from 173 patients who underwent 176 liver transplants between December 2004 and December 2021. Clinical and laboratory parameters, IST prescriptions, their changes, and outcomes up to December 2024 were recorded in personal electronic outpatient records, which were used to create a common electronic database.

Inclusion criteria:

- the recipient is 18 years and older;
- liver transplantation from a deceased or living related donor;
- known medical history, laboratory and clinical data from the perioperative period;
- patient's discharge from hospital after LT having a functioning graft;
- availability of clinical and laboratory data until December 2024 or until death/retransplantation/withdrawal from the study.

Accepted definitions

Immunosuppressant regimen is a single drug or a combination of immunosuppressants taken continuously. Within a fixed regimen, the

dose of each drug can be adjusted. Substitution, discontinuation, or addition of any drug constitutes ***a change (modification) of the regimen***. The following drugs were used: tacrolimus (T), mycophenolates (M), glucocorticosteroid hormones (S), everolimus (E), and azathioprine (A) received both as monotherapy of T or E, and various combinations of TMS, TM, TS, TE, TA, TAS.

The initial regimen selected and recommended to the patient at hospital discharge after LT was determined primarily by the etiology of the underlying disease, as well as perioperative characteristics, the graft and renal function, drug tolerance, and the timing of the surgery. Subsequent modifications to the IST regimen were personalized based on graft function, time since LT, drug monitoring data, liver graft biopsy results, drug tolerance, and the severity of side effects, as well as the occurrence of surgical, oncological, nephrological, and cardiovascular events.

IST survival was defined as the proportion of patients (in %) continuing to use the initial regimen at checkpoints of 1, 3, 5, and 10 years after LT. This is an integral characteristic of the regimen, reflecting its stability or adaptability, efficacy, safety, tolerability, and overall acceptability for both patients and physicians. IST survival in a given patient was defined as the time from the start of its use to its modification. Assessing survival is undoubtedly important for determining the place of a particular regimen in real-world clinical practice.

***Late liver transplant dysfunction (*LGD)** is a functional disorder that is manifested by at least one of the following symptoms and occurs more than 3 months after LT [24]:

- alanine aminotransferase (ALT), aspartate aminotransferase (AST) and(or) gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP) > 1.5 of the upper limit of normal (ULN);
- increased total bilirubin > 2 ULN;
- increase in international normalized ratio (INR) > 1.6;
- complications of liver cirrhosis (LC) (signs of portal hypertension, ascites, encephalopathy).

Statistical processing and data analysis

The clinical case reports were registered in the specially developed electronic database in the “Microsoft® Excel” format in the Windows 10™ operating system. Data analysis was performed using the Jamovi statistical software package (version 2.3.28.0). Descriptive statistics determined by the type of statistical parameter were used to characterize the study cohort for all statistical parameters. Parameters with a normal distribution are represented by the following values: the sample mean and standard deviation. To describe quantitative parameters with an irregular distribution, the median, 25% and 75% quartiles were used. To assess the normality of quantitative data distribution, the Shapiro-Wilk test, skewness and kurtosis measures were used. When describing qualitative parameters or quantitative characteristics that take only a very small number of values, frequency y and percentage were used. Statistical comparison of the mean values of quantitative continuous variables between two independent groups was performed using Student's t-test (for normally distributed variables). To compare independent populations in cases where there was no evidence of normal data distribution or when comparing by the ordinal value, the Mann–Whitney U test and the Kruskal–Wallis test were used. Differences in variables were considered statistically significant at $p<0.05$. Nominal data were compared using the

Pearson χ^2 test and Fisher's exact test. The odds ratio (OR) was used as a quantitative measure of effect when comparing relative values.

Results

General characteristics of clinical cases

The study cohort included 72 men (41%) and 104 women (59%). Eleven recipients (6.3%) underwent LT from a living related donor, 165 (93.7%) from a deceased donor diagnosed with brain death. The age of the donors was 40.3±12.2 years. The mean patient age at the time of LT was 47.2±11.2 years. Among the indications for LT, the most common were viral LC (34%), autoimmune liver diseases (AILD) (30%), and hepatocellular carcinoma (HCC) (13%) (Fig. 1).

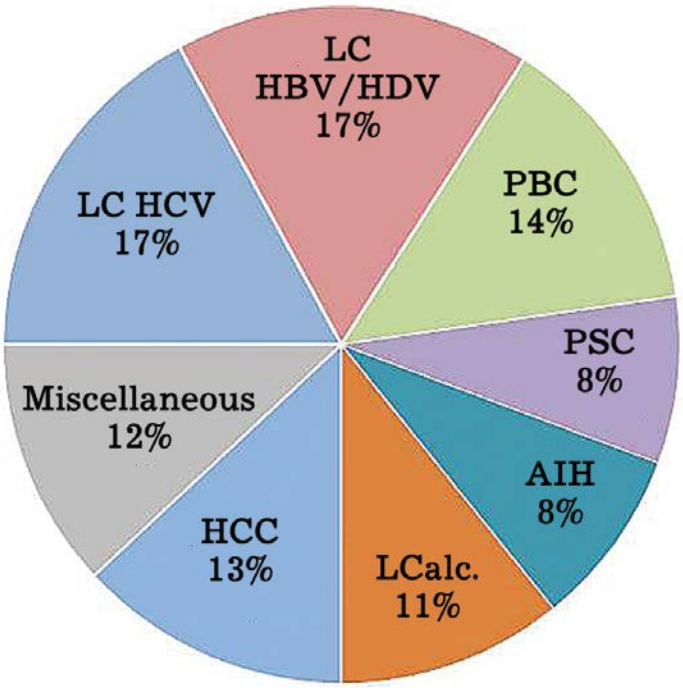

Fig. 1. Indications for liver transplantation. PBC, primary biliary cholangitis; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; AIH, autoimmune hepatitis; PSC, primary sclerosing cholangitis; $LC_{alc.}$, alcoholic liver cirrhosis

Choice of initial immunosuppressive therapy

All patients received 500–750 mg of methylprednisolone intraoperatively before the graft reperfusion. In most cases (86%), induction with basiliximab was performed at a dose of 20 mg intraoperatively and on the 4th day after LT. By the time of discharge, various initial regimens were selected for patients; they are shown in Figs. 2 and 3. They included: T (100% of patients), M (48% of patients), S 39% of patients, E (8% of patients). T monotherapy was administered to 38% of patients (see Fig. 2). According to the local protocol, the determining factor in the choice of the initial regimen was the nature the recipient underlying disease. Monotherapy with T was considered preferable and was administered to patients with viral etiology of cirrhosis (68%) and HCC (39%). Almost half of the patients with HCC (48%) at the time of discharge (not earlier than 3 weeks after LT) also received everolimus as part of the TE regimen.

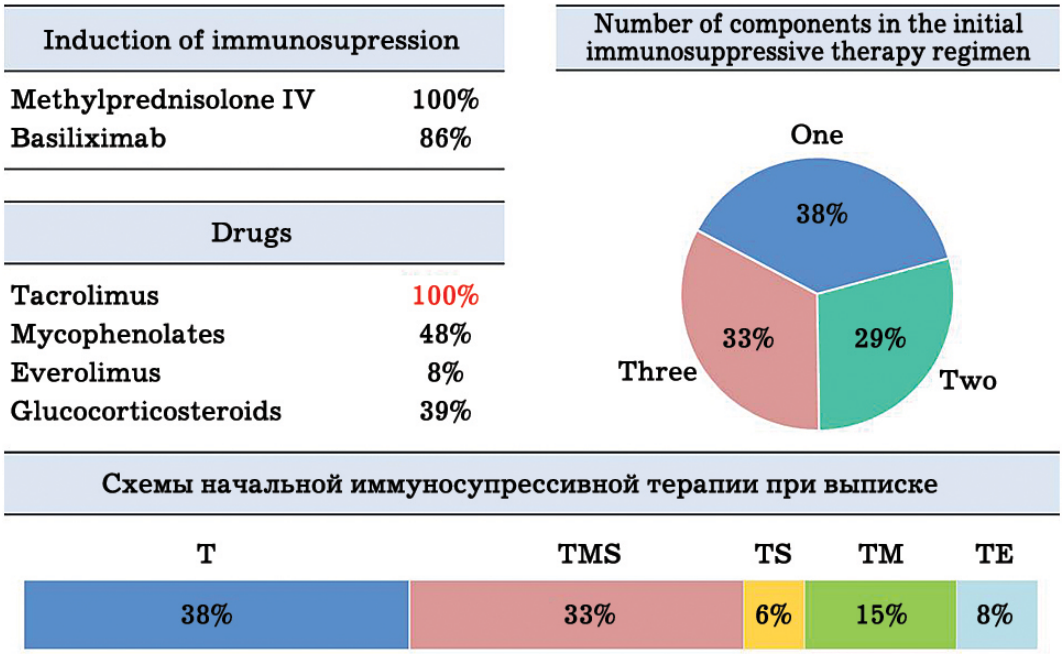

Fig. 2. Components of initial immunosuppressive therapy regimens

The initial regimen of choice for patients with AILD has traditionally been a combined triple IST as TMS (87%) or its derivative TS or TM regimens (11%) (see Fig. 3). The regimens used in patients with AILD included steroids in 90% of cases, whereas in patients with viral cirrhosis, steroids were prescribed only in 12% of cases, and steroids were not used in HCC due to their possible pro-oncogenic effect. Half of the patients with alcoholic cirrhosis (53%) were discharged from the hospital on T monotherapy. For other liver diseases, which include Wilson's disease (4), polycystic disease (4), alveolar echinococcosis (1), focal-nodular hyperplasia (1), congenital fibrosis (2), and cryptogenic cirrhosis (9), the initial IST regimen had no specific peculiarities. However, given the predominantly young age (average 37 years) or unknown etiology of the disease, 15 of 21 patients (71%) were prescribed combined IST regimens, including the use of steroids in 8 patients (38%).

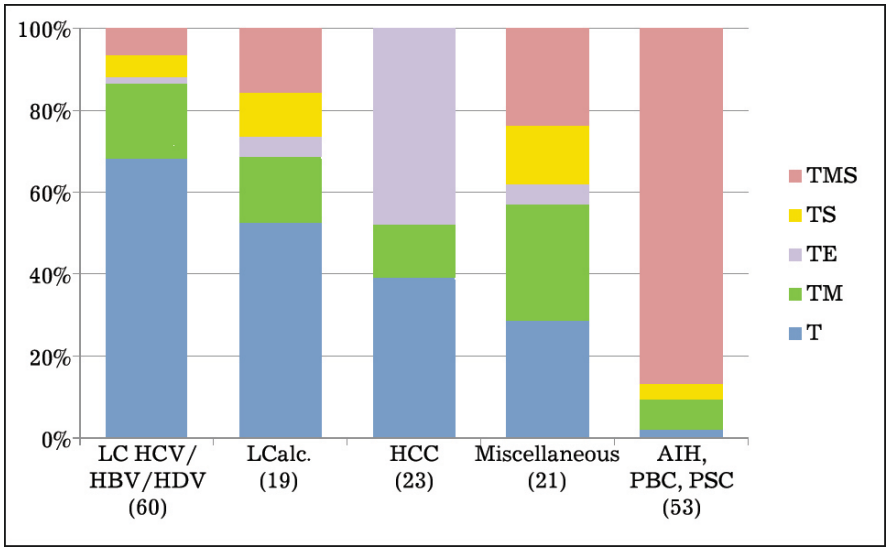

Fig. 3. Initial immunosuppressive therapy regimens with consideration of the etiologic factor that served as an indication for liver transplantation

Modification of IST regimens

At the time of analysis, 99 recipients (56%) maintained their initial regimens. The nature, frequency, and timing of modifications varied significantly across the five groups formed based on the initial IST regimen.

T monotherapy (Fig. 4A). The median follow-up duration for patients discharged after LT on T monotherapy was 76 months (59.5;118) (6–217). Fifty-eight of 67 patients (87%) continued to take it throughout the entire follow-up period. Modifications occurred primarily during the first year after LT. Early changes took place in 7 patients in whom, due to the development of oncological or nephrological complications within 3–6 months, E was added in the IST regimen with a reduction in the T dose. Subsequently, in two of them, T was discontinued with a conversion to E monotherapy, and in one, E was replaced with A. In one patient, T was converted to E at 66 months due to a late HCC relapse. We should emphasize that all modifications were aimed at minimizing IST; in no case additional administration of either steroids or mycophenolates was required to enhance IST or increase the T dose. Two patients completely discontinued T after 9 and 18 years of monotherapy as part of a separate pilot clinical trial conducted at our center.

Three-component TMS regimen (Fig. 4B). This regimen was the most susceptible to diverse and multidirectional modifications throughout the entire follow-up period, the median being 78 months (60;118) (6–220). The initial regimen remained unchanged in 26 (46%) patients. All of them had AILD as an indication for LT. Attempts to discontinue mycophenolates or steroids due to intolerance or the development of side effects in 4 AILD patients were accompanied by the development of LGD (insufficient immunosuppression or, possibly, a disease relapse) or an unspecified rejection, which required a resumption of the initial regimen.

In 2 cases, M in the three-component regimen was replaced by A due to the recurrence of PSC and AIH. The conversion to a two-component TS regimen was implemented in 12 patients with AILD. Stepwise reduction of the regimen to T monotherapy was possible in 13 patients (23%), of whom only 6 (46%) had AILD.

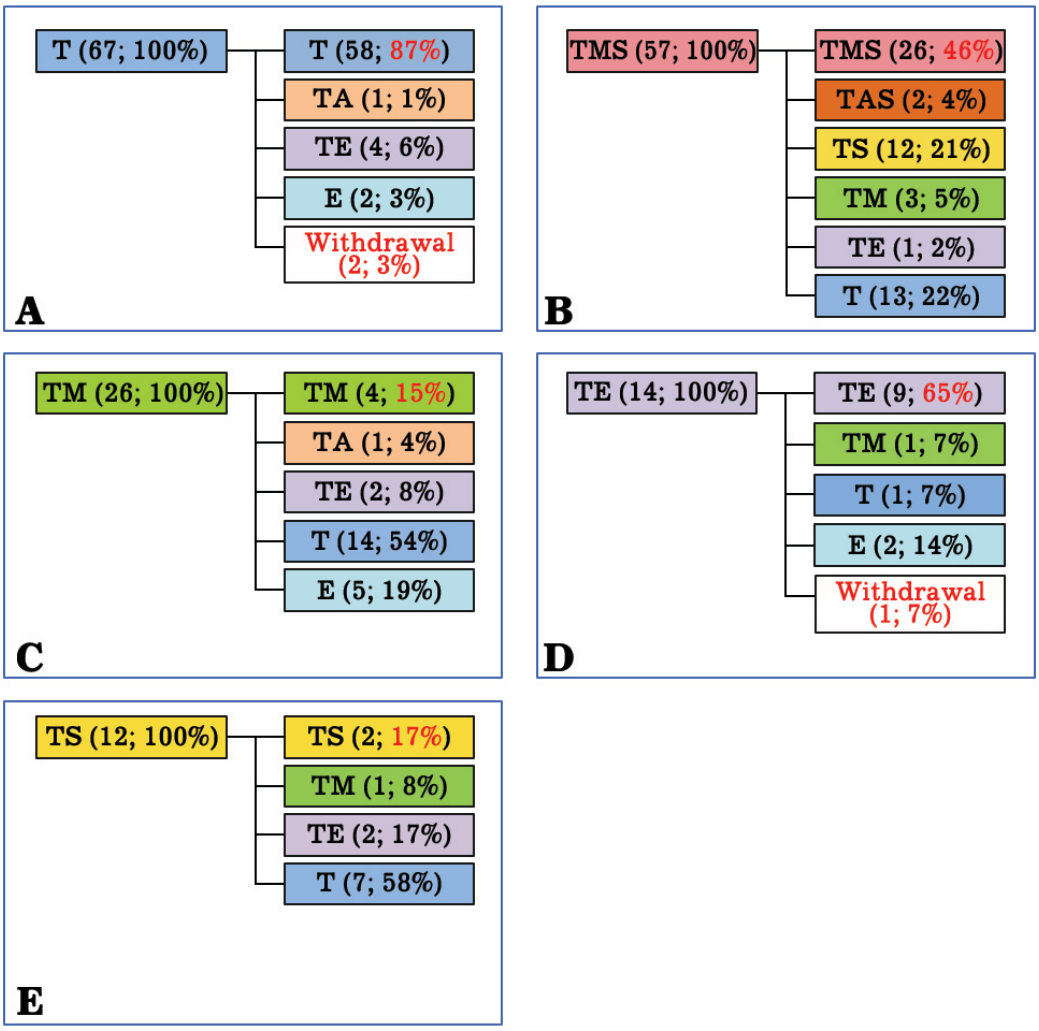

Fig. 4. Modifications of the initial immunosuppression regimen in the groups

Two-component TM regimen (Fig. 4C). This regimen was unchanged in only 4 patients (15%) operated on for AILD. They did not require additional steroids to the IST regimen. In 14 patients (54%)

operated on for alcoholic or viral cirrhosis (n=7), HCC (n=3), polycystic liver disease (n=2), and Wilson's disease (n=2), mycophenolates were subsequently successfully discontinued with a switch to T monotherapy within periods ranging from 1 month to 5 years. Three patients with HCC and one with progressive renal dysfunction underwent early (up to 3 months) conversion to the TE regimen. The conversion to the TE regimen in the long-term due to the development of extrahepatic oncopathology was undertaken in 2 patients at periods of 107 and 134 months, and in another patient for the purpose of nephroprotection after 24 months. Subsequently, in the above-mentioned ongoing clinical study, T was discontinued in 5 patients with the switch to E monotherapy.

Two-component TE regimen (Fig. 4D). The median follow-up duration was 61.5 months (43.5;99.8) (36–125). The regimen was initially administered primarily to 11 (79%) HCC patients and did not require modification in the majority of them, 9 (65%) recipients, during 36–106 months of follow-up. One patient (!) discontinued IST on his own accord 2 years after surgery and continued to be followed-up for extrahepatic HCC relapse (adrenal gland, bones) for more than 10 years having a preserved graft function. In the remaining patients, the changes were minimizing and consisted of discontinuing T (2) or E (2) in the long-term. In 2 of the 3 non-HCC patients, E were discontinued due to the development of side effects and replaced with M in one case. Steroid administration was not required.

Two-component TS regimen (Fig. 4E). In this smallest group, steroids were discontinued in 10 stable patients (83%) after 3–36 months, including three patients with PSC and PBC. Three of these patients subsequently received M or E to minimize the T dose.

During continuous clinical and laboratory monitoring and immunosuppression management in response to the dynamics of the graft

condition and the development of extrahepatic risks and events over the entire study period, the initially prescribed IST regimens were modified in 77 patients (44%), including 14 (17.3%) in Group 1 and 63 (66.3%) in Group 2 ($p<0.05$). We further established significant changes in the IST regimens at the postoperative control periods. As can be seen in the diagram (Fig. 5), clear trends are observed: 1) an increase in the proportion of patients receiving T monotherapy at all control timepoints; 2) a decrease in the proportion of patients receiving mycophenolates and steroids. At 10 years of follow-up, the proportion of patients had decreased from 100 to 93% among those who received T, from 39 to 16% among those who received C, from 47 to 14% among those on M, and the proportion of patients receiving E increased from 8 to 13%. Among patients who survived the 10-year timepoint, the proportion of those receiving T monotherapy was 68%.

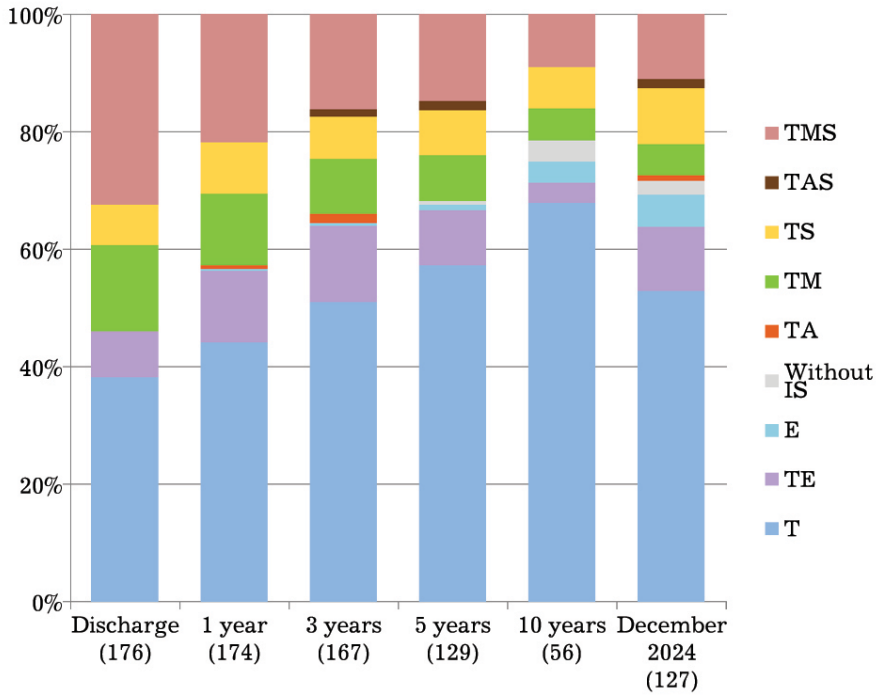

Fig. 5. Frequency of using various immunosuppression regimens depending on the time elapsed after liver transplantation

As of December 2024, in 127 patients the received IST regimens included nine variants. Survival rates varied significantly depending on their initial composition. The initial T and TE regimens demonstrated the best survival rates (Fig. 6).

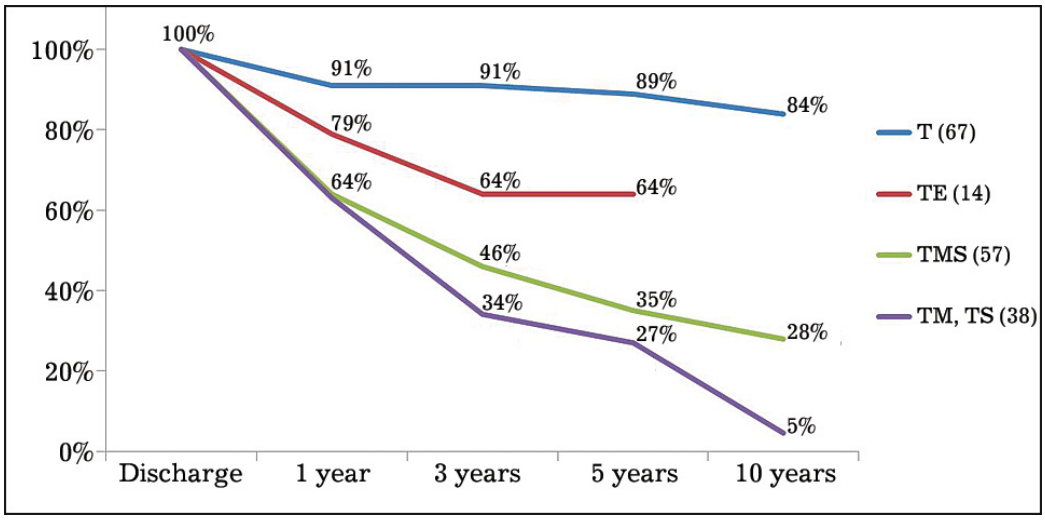

Fig. 6. Estimated survival of initial immunosuppression regimens

For further comparative analysis, all clinical cases were divided into two combined groups depending on the absence/presence of IST C and (or) M in the initial regimen: Group 1 (T, TE) included 81 patients and Group 2 (TMS, TM, TS) included 95 patients.

Characteristics and composition of the constituted groups

Patients in group 1 were statistically significantly older than patients in group 2. The mean age in group 1 was 49.6±10 years, while in group 2 it was 45.2±11.7 years ($p=0.003$) (Table 1). A statistically significant difference in gender was found between the groups: in group 2, men constituted less than a third, i.e. 28.7% (n=27), while in group 1 their proportion was more than half making 55.6% (n=45) ($p<0.001$), that was the medium significance level of the differences ($V=0.275$). No

differences were found in the type of donor (living or deceased) and the donor age.

Table 1. Baseline characteristics of recipients and donors in the combined groups

Parameter	All patients (n=176)	Group 1 (T, TE) (n=81)	Group 2 (TS, TM, TMS) (n=95)	p
Recipient's age at the time of transplantation (years)	47.2±11.2	49.6±10.0	45.2±11.7	p=0.003
Male gender of the recipient, n (%)	72 (40.9%)	45 (55.6%)	27 (28.4%)	p<0.001
Living donor, n (%)	11(6.25%)	6 (7.4%)	5 (5.3%)	p=1.0
Donor age (years)	40.3±12.2	41.2±12.7	39.6±11.8	p=0.42

In women, the initial prescription of regimens using steroids and mycophenolates occurred 3.15 times more often than in men (95% CI [1.68–5.88]). This pattern is obviously due to the predominance of women among patients with AILD, for whom the three-component regimen or its derivatives (TS and TM) were a priority in accordance with clinical guidelines [18]. At the same time, half of the liver transplant recipients, 50.6% (n=41/81), in group 1 had a viral etiology of end-stage liver disease. Patients with HCC in 87% (n=20/23) of cases received an initial immunosuppressive regimen with T or TE (Table 2).

Table 2. Nosological comparison of constituted groups

Liver diseases	All patients (n=176)		Group 1 (T, TE) (n=81)		Group 2 (TS, TM, TMS) (n=95)		p
	n	%	n	%	n	%	
Viral LC	60	34	41	51	19	20	0.006
HCC	23	13	20	25	3	3	<0.001
Alcoholic cirrhosis	19	11	10	12	9	9	1.0
AILD: PBC/PSC/AIH	53	30	1	1.2	52	54.7	<0.001
Other nosology	21	12	9	11	12	13	0.664

Statistically significant differences between the groups were observed in the number of patients with AILD, including PSC and PBC ($p<0.001$): only one patient with AILD received T monotherapy from the time of surgery (1.2%), while in the 2nd group, more than half of the patients 54.7% (n=52) had AILD (n=52).

The estimated 10-year survival rate of the initial immunosuppression regimen was 89% in Group 1 and 33% in Group 2 ($p<0.05$) (Fig. 7).

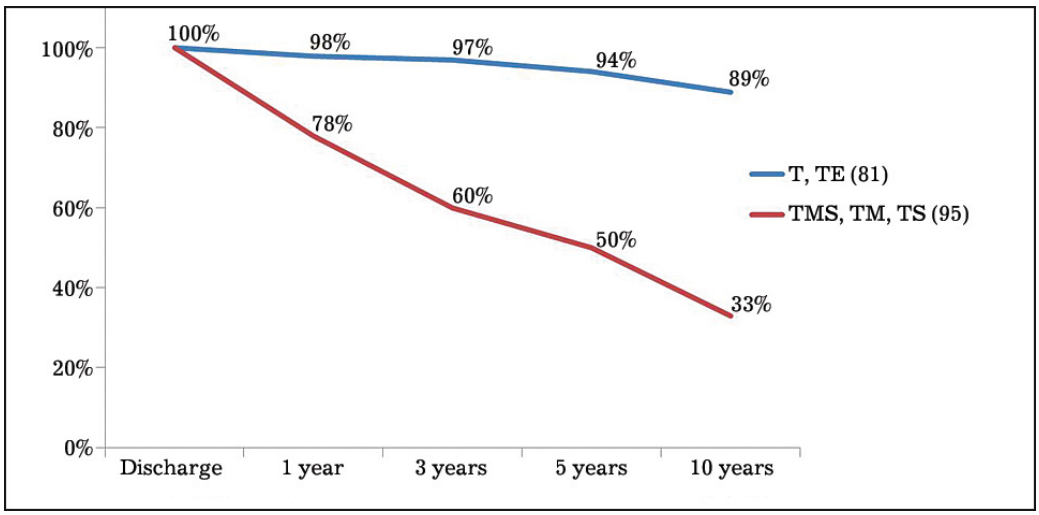

Fig. 7. Estimated survival of initial immunosuppression regimens in the constituted groups ($p<0.05$)

Clinical course of the post-transplant period and outcomes

At the time of database closure, 127 patients were followed-up. They were distributed by time elapsed from LT as follows: 30 (24%) from 3 to 5 years, 59 (46%) from 5 to 10 years, and 38 (30%) over 10 years. The current immunosuppressive regimens are shown in Fig. 5 (right column). Their number is 9, and their composition and frequency of use differed significantly from the initial presentation (left column). It

is noteworthy that currently 70% of patients at various timepoints from LT receive a two component IST with T and E, without using M and S.

Thirty-three patients were lost to follow-up within 6 to 156 months, and 10 died within 12 to 197 months. Retransplantations were performed in six patients within 19 to 144 months, three of which were re-included in follow-up, one patient died in the early postoperative period, and two were lost to follow-up (Table 3). No statistically significant differences in the overall follow-up duration or median follow-up time after LT were found between the constituted groups.

Table 3. Outcomes and duration of follow-up in groups

Parameters	All patients (n=176)	Group 1 (T, TE) (n=81)	Group 2 (TS, TM, TMS) (n=95)	p
Alive, n (%)	127 (72.1%)	60 (74.1%)	67 (70.5%)	0.595
Fatal outcome, n (%)	10 (5.7%)	5 (6.2%)	5 (5.3%)	1.0
Retransplantation, n (%)	6 (3.4%)	1 (1.2%)	5 (5.3%)	0.219
Lost to follow-up, n (%)	33 (18.8%)	15 (18.5%)	18 (18.9%)	0.728
Total follow-up duration (patient-years)	1,355	579	776	–
Follow-up duration, months Me (Q_1;Q_3) (min-max)	79.5 (58;120) (6–220)	73 (57;118) (6–217)	85 (59;137) (6–220)	0.096
Acute rejection, n (%)	25 (14.2%)	5 (6.2%)	20 (21.1%)	0.004
Irreversible LGD as a cause of death or retransplantation, n (%)	8 (4.5%)	1 (1.2%)	7 (7.4%)	0.039
Cancer incidence, n (%)	11 (6.3%)	5 (6.2%)	6 (6.3%)	0.774

Rejection episodes in Group 2 were observed in 21.1% of cases (n=20), while in Group 1, only 5 cases of rejection (6.2%) were recorded. These differences were statistically significant (p=0.004), the level of difference significance was medium (V=0.223). And the odds of developing rejection episodes in Group 2 were 5.67 times higher (95% CI [1.6–20.12]) than in Group 1.

No statistically significant differences were found between the groups in the total frequency of LGD episodes of various etiologies over the entire follow-up period. However, when analyzing data from patients with irreversible LGD of immune and unknown etiology as the cause of death or retransplantation, the number of cases in group 1 was significantly lower than in group 2: 1 (1.2%) versus 7 (7.4%), respectively (p=0.039).

No significant differences were found in the incidence of cancer. In Group 1, these were represented by recurrent HCC (3), ovarian cancer (1), and lymphoma (1). In Group 2, recurrent HCC (1), colorectal cancer (2), prostate cancer (1), breast cancer (1), and esophageal cancer (1) were observed.

Renal function in recipients during long-term monotherapy with tacrolimus and combination immunosuppressive therapy

This section of the analysis includes data from 97 patients who were followed for at least 5 years, of whom 56 (57%) were women. The mean age of the study group at the time of LT was 48±9.65 years. The glomerular filtration rate (GFR) was calculated using the CKD-EPI 2021 formula. Patients were distributed by the stages of chronic kidney disease (CKD) in accordance with the KDIGO 2024 recommendations. In the overall cohort of patients at 5 years, CKD stage C1 was registered in 10 patients (10%), stage C2 in 48 (49%), stage C3A in 31 (33%), stage C3B in 6 (6%), stage C5 in 2 (2%). During the 5 years after LT, 39 people (group 1) continuously received T monotherapy, and 58 people (group 2) continuously received combination immunosuppressive therapy (TMS, TM, TS, TE) continuously or with intra-group modifications.

Contrary to our assumptions and the common notion of “excessive nephrotoxicity of tacrolimus monotherapy”, the mean level of GFR after

5 years was 69.7±14.1 mL/min/1.73 m^2 in the 1st group, and 62.4±20.7 ml/min/1.73 m^2 in the 2nd group ($p>0.05$). In the 1st group, GFR≥60 ml/min/1.73 m^2 was recorded in 76.9% of patients (n=30) versus 48.3% (n=28) in the 2nd group ($p<0.01$).

Discussion

All IST regimens used were prescribed and modified at different periods in accordance with the recommendations that were current at that time, original publications, or protocols of large RCTs, a brief overview of which is provided below.

The advent of calcineurin inhibitors, first cyclosporine and then T, dramatically reduced the risk of rejection and ensured long-term survival of transplants and patients. Currently, T-based immunosuppression is the undisputed standard of treatment [17, 24, 25]. Since the drug has a narrow therapeutic interval, trough T concentrations in the blood are recommended to be carefully monitored and maintained at 6–10 ng /ml during the first month after LT, 4–8 ng/mL during the first year, and about 4 ng /ml thereafter [17, 18, 25]. The relationship between T dosage and its blood levels varies greatly among patients, as well as within the same patient over time [26–28]. The main determinants of individual variability are polymorphisms in the CYP3A genes, non-adherence to treatment, drug interactions, hypoalbuminemia, and anemia [17, 18]. Achieving stable concentrations within the target range is of paramount importance, especially early after LT [27–29]. Additional calculations related to exposure (i.e., cumulative T exposure) may be useful for dose adjustment [30]. Reduction of T adverse effects is achieved by minimizing and maintaining lower than recommended concentrations and combining with other immunosuppressants that are less effective but have an improved safety profile.

Although optimal T levels when using combination regimens have not been established, they may be slightly lower than the range recommended for monotherapy, primarily to preserve renal function (e.g., 4–7 ng/mL for the first month, then 3–5 ng/mL). After the first post-transplant year, most patients can maintain T levels at 4–6 ng/mL with monotherapy or lower if T is combined with other immunosuppressants [16, 18, 20].

In Russian and international practice, basiliximab and corticosteroids are most commonly used for induction of LT, while C, M, and mTOR inhibitor E are used for maintenance IST. Corticosteroids are an integral part of initial immunosuppression with a gradual reduction until discontinuation during the first 3–6 months after LT, with the exception of patients with AILD [3, 18, 22, 31]. According to the latest OPTN/SRTR report (2025), the majority of recipients who underwent LT in the USA were discharged on the traditional combination of T, M, and S (66.6%); the rest used T and mycophenolate mofetil M (18.7%), T and S (4.4%), or other, including T-monotherapy (10.3%) [4].

On the other hand, excellent short-term and long-term results have been obtained previously in a number of studies using T monotherapy “from day one” [32–34]. In these classic studies, in the context of minimizing immunosuppression T monotherapy has traditionally been the main goal.

In our opinion, corticosteroid-free immunosuppression should be considered as preferable for patients with diabetes, especially those undergoing LT for metabolic-associated fatty liver disease, which is becoming a growing indication for LT worldwide [35]. Corticosteroid-free protocols are believed to increase the risk of rejection, although this is not usually associated with a significant risk of graft loss. In turn, the

exclusion of corticosteroids reduces the risk of metabolic disorders, diabetes and arterial hypertension, osteoporosis, and infections.

The use of basiliximab as an induction agent allows for the avoidance of S administration and the delayed administration of T (up to the 7th day after surgery) [36, 37]. The main advantage of basiliximab in clinical practice is the better preservation of perioperative renal function with delayed administration of T. The combination of a reduced dose of T and one of the mycophenolic acid derivatives is the most frequently prescribed immunosuppression protocol in LT and has been shown to improve renal function without pro-oncogenic or adverse metabolic effects [38]. However, administration of M is often associated with diarrhea, bone marrow suppression, and an increased risk of infections, especially cytomegalovirus, which limits its use.

Everolimus is a protein kinase inhibitor. mTOR has immunosuppressive and antiproliferative properties and is a more potent immunosuppressant than M, which facilitates the safe use of lower T concentrations [39]. Complete withdrawal of T with conversion to E monotherapy after the 4th postoperative month is associated with relatively low rates of T-cell rejection, which may be particularly beneficial for patients with renal failure and those operated on for HCC [19, 39–41]. Earlier introduction of E has raised some concerns regarding wound complications, although several RCTs have demonstrated a favorable risk-benefit balance for patients requiring early aggressive T minimization [42, 43]. The use of mTOR inhibitors as adjuvant therapy for patients with HCC is attractive and widespread, but it has not been proven whether this strategy provides oncological benefits [44, 45]. Universal administration of E to all patients with HCC may not be justified, but it should be considered as an option for patients with a high risk of tumor recurrence [46, 47].

Throughout the entire period of graft function, the composition of the IST regimen and its cumulative load (quantity and doses of drugs) can be modified, either by strengthening (escalating) in case of rejection or by weakening (minimizing) for various indications: oncological, nephrological, etc. Immunosuppression is a crucial component of post-LT treatment; however, optimal practice in the mid- and late stages after LT has not been sufficiently studied and covered in the literature.

The first large population-based study by Bittermann T, Lewis JD, Goldberg DS (2022) analyzing late post-LT IST regimens in 11,326 adult liver transplant recipients operated in the United States between 2007 and 2016 using the OPTN/SRTR and Medicare databases highlighted the heterogeneity of treatment practices across transplant centers, particularly in the first year after LT [13]. Several key recipient factors, such as race/ethnicity and liver disease etiology, influence treatment choice. The TM combination was found to be associated with improved long-term patient and graft survival compared with TM monotherapy, with this effect increasing with increasing age. These results are consistent with existing data supporting a similar strategy in other specific situations (e.g., renal dysfunction) [16, 17, 20]. In real-life settings, 51.9% and 68.6% of patients received T monotherapy at 1 year and 5 years, respectively. At 5 years post-LT, factors associated with decreased monotherapy use included female gender, AILD, and increasing creatinine levels. The conclusion of this publication suggested that long-term TM combination therapy may have key advantages over T monotherapy, particularly among elderly recipients, due to improved renal function resulting from minimizing tacrolimus exposure. Furthermore, such minimization has been shown to reduce the risk of developing malignancies after transplantation, which may explain why T monotherapy was used less frequently in recipients with HCC [22].

Interestingly, similar long-term benefits of using the TM regimen have been noted in earlier studies [14, 48].

A recent large retrospective population-based Italian study, CESIT (2024), highlights the change in post-LT therapeutic regimens over time towards the preferential use of T in combination with M or E rather than as monotherapy. Furthermore, an association was found between T monotherapy and increased mortality in a cohort of non-HCC cirrhotic patients. These data highlight the importance of implementing personalized approaches to immunosuppression aimed at minimizing the adverse effects of T [49].

In the study by S. H. Kim et al. [50]. In the T monotherapy group, a more significant decrease in the SCF index was observed already during the first 12 months after LT compared with the TM group, indicating that T monotherapy is immunologically effective, but is associated with a greater decrease in GFR than that in TM combination therapy due to the maintenance of higher T concentrations in the blood. However, in another South Korean single-center study Immunosuppressive regimens of 160 recipients who survived 20 years after living donor LT included T monotherapy in 92 recipients (57.9%) and TM dual therapy in 25 (15.7%) [51].

Our study, using local registry data, compared the efficacy and safety of a combined immunosuppressive therapy group (T, TE) and a combination therapy (TMS, TM, TS). Patients receiving T or TE therapy had statistically significantly lower rates of acute and chronic rejection and persistent PDT compared to those receiving combination regimens including C and M. We are inclined to explain this by the different nosological and age-gender composition of the groups, bearing in mind the statistically significant predominance of women, young patients, and patients with AILD and unspecified disease in the second group, which determined their high immunological alloreactivity [51]. An unexpected

result of our study was the detection of good long-term preservation of renal function in the T monotherapy subgroup. We are inclined to explain these results by the strict selection of patients who were prescribed and maintained T monotherapy, taking into account the above-mentioned selection criteria. The most important of these are the absence of pre-existing chronic renal pathology, complete resolution of preoperative and perioperative acute kidney injury, and a SCF level ≥ 60 mL/min/1.73 m^2 at discharge. This may also be associated with our practice of maintaining the drug concentration in the blood at a minimally sufficient level with regular outpatient monitoring and observation at the transplant center. Thus, IST regimens based on T and E, due to their high efficacy and relatively favorable side effect profile, i.e., clinical safety, demonstrated the best survival of therapy.

Conclusion

Our study provides a basis for understanding the historical and current practice of immunosuppressive therapy, its outcomes, and prospects. Tacrolimus monotherapy or its combination with everolimus for specific indications (oncology, nephroprotection), administered from the time of surgery, have been recognized as optimal immunosuppressive therapy regimens for a strictly selective group of liver transplant recipients. These regimens are collectively characterized by the best long-term survival rate of 89% over 10 years, a minimal risk of acute and chronic rejection, a relatively rare development of late graft dysfunction of immune or unknown origin, and a favorable long-term safety profile with respect to side effects and nephrotoxicity, particularly for periods of up to 20 years. The use of steroids and mycophenolates as adjuvants should be strictly personalized, taking into account the comorbidity and immunological, cardiometabolic, oncological, and nephrological risk

profile of the recipient. We believe that this approach creates the preconditions for the development of protocols for personalized minimization and possible weaning from immunosuppression in the context of further clinical trials.

The use of tacrolimus-based immunosuppressive therapy with steroids and/or mycophenolates should be limited to patients with autoimmune liver diseases and increased immunological risk (young age, female gender), as well as for those with underlying renal impairment. The higher incidence of rejection, persistent dysfunction, liver disease recurrence, and drug-related complications in this group necessitates frequent (66.3%) regimen modifications. Analysis of our own experience and comprehension of the data obtained in this study on modifying immunosuppressive regimens, coupled with an assessment of the clinical course and long-term (up to 20 years) post-transplant outcomes, served as the basis for the development of a new concept for managing immunosuppressive therapy, which has been adopted as a basis for our center's current practice and is reflected in the conclusions.

Based on the described study we can make the following conclusions

1. Initial monotherapy with Tacrolimus has been defined as optimal for a strictly selected group of recipients. It is indicated for patients undergoing surgery for viral and alcoholic liver cirrhosis, regardless of the presence or absence of viremia and hepatocellular carcinoma. If renal dysfunction persists (glomerular filtration rate $\leq$ 60 mL/min/1.73 m^2), mycophenolate or everolimus should be administered at discharge, with the tacrolimus dose adjusted accordingly.

2. A three-component immunosuppressive regimen (tacrolimus, mycophenolates, steroids) is prescribed to all patients with a confirmed

diagnosis of autoimmune liver disease and with an unknown etiology of the liver disease. After more than one year, in the absence of dysfunction and rejection, the regimen may be reduced to a two-component regimen. Discontinuation of steroids or conversion to tacrolimus monotherapy is undesirable.

3. An initial three-component immunosuppressive regimen is also preferred in patients with increased immunological risk (age under 40 years, female gender, baseline and perioperative renal impairment) with other diagnoses. After 3–6 months, in the absence of dysfunction and rejection, complete discontinuation of steroids is advisable, followed by a conversion to tacrolimus monotherapy in the absence of renal dysfunction (glomerular filtration rate $\geq$ 60 mL/min/1.73 m^2).

4. For all patients with hepatocellular carcinoma, everolimus should be introduced into the immunosuppressive regimen no earlier than three weeks after transplantation. Until then, a tacrolimus-mycophenolate regimen may be used to minimize tacrolimus exposure (target blood level no more than 6 ng/mL).

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