

Immunosuppressive regimens following kidney transplantation in five European countries: The observational RECORD study

Arnol, Miha; Naumovic, Radomir; Dimitrov, Emil P.; Rački, Sanjin; Bucsa, Cristina A.; Covic, Adrian; Mitić, Igor; Vavic, Neven; Radovanović, Radmila M. Velickovic; Zibar, Lada; ...

Source / Izvornik: **Transplantation Reports, 2020, 5, 1 - 11**

Journal article, Published version

Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

<https://doi.org/10.1016/j.tpr.2020.100061>

Permanent link / Trajna poveznica: <https://um.nsk.hr/um:nbn:hr:184:569900>

Rights / Prava: [Attribution-NonCommercial-NoDerivatives 4.0 International/Imenovanje-Nekomercijalno-Bez prerada 4.0 međunarodna](#)

Download date / Datum preuzimanja: **2024-11-09**



Repository / Repozitorij:

[Repository of the University of Rijeka, Faculty of Medicine - FMRI Repository](#)





ELSEVIER

Contents lists available at ScienceDirect

Transplantation Reports

journal homepage: www.elsevier.com/locate/tpr

Immunosuppressive regimens following kidney transplantation in five European countries: The observational RECORD study

Miha Arnol^{a,b}, Radomir Naumovic^{c,d}, Emil P. Dimitrov^e, Sanjin Racki^f, Cristina A. Bucsa^g, Adrian Covic^h, Igor Mitic^{i,j}, Neven Vavic^k, Radmila M. Velickovic Radovanovic^{l,m}, Lada Zibar^{n,o}, Sanja Bizilj^p, Vanja Erculj^q, Tatjana Supanc Missoni^r, Katarina T. Stupica^s, Mladen Knotek^{t,*}

^a Department of Nephrology, University Medical Center Ljubljana, Ljubljana, Slovenia

^b Medical Faculty, University of Ljubljana, Ljubljana, Slovenia

^c Clinic of Nephrology, Clinical Center of Serbia, Belgrade, Serbia

^d School of Medicine, University of Belgrade, Belgrade, Serbia

^e Department of Nephrology and Transplantation, Medical University of Sofia, Sofia, Bulgaria

^f Department of Nephrology and Dialysis, Clinical Hospital Center Rijeka, Rijeka, Croatia

^g Center of Urology, Dialysis and Kidney Transplantation, Fundeni Clinical Institute, Bucharest, Romania

^h Department of Nephrology, Dialysis and Renal Transplantation, CI Parhon Clinic Hospital, Iasi, Romania

ⁱ Clinic of Nephrology and Clinical Immunology, Clinical Center of Vojvodina, Novi Sad, Serbia

^j Medical Faculty, University of Novi Sad, Novi Sad, Serbia

^k Center for Transplantation of Solid Organs, Military Medical Academy, Belgrade, Serbia

^l Clinic of Nephrology, Clinical Center of Niš, Niš, Serbia

^m Faculty of Medicine, University of Niš, Niš, Serbia

ⁿ Department of Dialysis, Clinical Hospital Center Osijek, Osijek, Croatia

^o Faculty of Medicine, University Josip Juraj Strossmayer Osijek, Osijek, Croatia

^p Astellas Pharma, D. O. O., Ljubljana, Slovenia

^q Rho Sigma, Ljubljana, Slovenia

^r Formerly Astellas D. O. O., Zagreb, Croatia

^s Formerly Astellas Pharma, D. O. O., Ljubljana, Slovenia

^t Division of Nephrology, University Hospital Merkur, Zagreb, Croatia

ARTICLE INFO

Keywords:

Clinician education
Immunosuppressive drugs – toxicities
Immunosuppression – general
Kidney/renal transplantation

ABSTRACTS

Objective: To examine current immunosuppressive regimens administered to kidney transplant recipients (KTRs) in South-eastern Europe.

Methods: This was a 12-month, multicenter, non-interventional, prospective, observational study of immunosuppressive regimens in adult *de novo* and maintenance KTRs. The primary endpoint was to identify the number, type, dosage and trough concentrations (C_0) of immunosuppressive medications.

Results: Data were available for 1774 KTRs from five countries (Bulgaria [$n = 109$], Croatia [$n = 339$], Romania [$n = 647$], Serbia [$n = 434$] and Slovenia [$n = 245$]). The most common immunosuppressive regimen in all countries was a triple therapy regimen (*de novo* KTRs, 67.9 – 100% at baseline and 67.3 – 100% at end of study; maintenance KTRs, 48.8 – 90.7% and 43.2 – 90.1%, respectively). The most frequent regimen in *de novo* KTRs comprised tacrolimus, mycophenolate mofetil (MMF) or mycophenolate sodium (MPS), and corticosteroids. In maintenance KTRs, the most frequent regimen was tacrolimus or cyclosporine, and MMF or MPS, with or without corticosteroids. A C_0 of <5 ng/mL was recorded in 40.2% of immediate-release and 48.7% of prolonged-release tacrolimus patients; 79.5% of patients taking cyclosporine had a C_0 of <75 ng/mL. Infections were the most common adverse event (358/597, 60.0%), mainly urinary tract infections (208/358, 58.1%).

Conclusions: Triple therapy—comprising a calcineurin inhibitor (CNI; tacrolimus or cyclosporine), anti-proliferative drugs (MMF or MPS) and corticosteroids—was the most common immunosuppressive regimen used

Abbreviations: AE, adverse event; AZA, azathioprine; CNI, calcineurin inhibitor; CTCAE, common terminology criteria for adverse events; C_0 , trough concentrations; eCRF, electronic case report form; ESKD, end-stage kidney disease; IR, immediate-release; KDIGO, Kidney Disease: Improving Global Outcomes; KTRs, kidney transplant recipients; MedDRA, Medical Dictionary for Regulatory Activities; MMF, mycophenolate mofetil; MPS, mycophenolate sodium; mTORi, mammalian target of rapamycin inhibitor; NA, not available; PR, prolonged-release; SD, standard deviation; UTI, urinary tract infection

* Corresponding author.

E-mail address: mladen.knotek@kb-merkur.hr (M. Knotek).

<https://doi.org/10.1016/j.tpr.2020.100061>

Received 10 October 2019; Received in revised form 26 June 2020; Accepted 11 July 2020

Available online 13 July 2020

2451-9596/© 2020 Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

in KTRs in South-eastern Europe. Individual CNI C_0 were below the target range in a substantial proportion of KTRs, highlighting the need to maintain therapeutic drug monitoring of immunosuppressive therapy in this patient population.

1. Introduction

Kidney transplantation has become standard clinical practice for patients with end-stage kidney disease (ESKD) [1]. Advances in transplant procedures and the introduction of immunosuppressive therapies have resulted in improvements in both post-transplant graft and patient survival [2]. Kidney transplant recipients (KTRs) have benefitted from improved one-year survival rates (>90%) [3]; however, despite these improvements and longer life expectancies, the focus of long-term patient management has shifted towards managing the adverse effects of immunosuppression, recurrence of the primary kidney disease, malignancy, and chronic diseases including diabetes, hypertension, dyslipidemia, obesity, and cardiovascular disease. It is therefore important to focus on improving long-term transplant and patient outcomes by optimizing post-transplant care, as well as immunosuppressive regimens [4].

The mainstay of post-transplant immunosuppression consists of triple therapy with a calcineurin inhibitor (CNI) (tacrolimus or cyclosporine), plus an antiproliferative agent (mycophenolate mofetil [MMF]/mycophenolate sodium [MPS], azathioprine [AZA], sirolimus, everolimus), and corticosteroids (prednisone) [1]. The introduction of new immunosuppressive agents has expanded therapy options, but has also made the long-term clinical management of kidney transplant recipients increasingly complex, with clinical practice (immunosuppressive protocols) differing between transplant centers in different countries [1]. It is important for clinicians to be familiar with all management options in order to determine the most effective combination of agents to treat individual patients. Randomized controlled trials have led to many improvements in transplant medicine; however, they do not accurately reflect transplant medicine in real-world clinical practice. There is a need to better understand real-world data sets by conducting observational studies of registries to provide a better representation of clinical practice, and help identify the most appropriate post-transplant immunosuppressive regimen for KTRs [5].

As there are limited data regarding the immunosuppressive regimens used for kidney transplant recipients in routine clinical practice in South-eastern Europe, this study was undertaken to identify the immunosuppressive regimens currently used in kidney transplant recipients (*de novo* and maintenance), including the doses and trough concentrations (C_0) of immunosuppressive medications used in this region.

2. Materials and methods

2.1. Study design and patients

This was a prospective, 12-month, multicenter, non-interventional, observational study (RECORD), conducted between March 2013 and October 2016 in five South-eastern European countries (one center in Bulgaria, three in Croatia, four in Romania, four in Serbia, and one in Slovenia). Independent ethics committees in each participating country approved the protocol, and the study was conducted in accordance with the Declaration of Helsinki (Revised Edinburgh 2000) and International Conference on Harmonisation guidelines. Patients were informed that they could withdraw from the study at any time.

Eligible patients provided signed, informed written consent to participate in the study, and were kidney transplant recipients aged ≥ 18 years, who had undergone transplantation either ≤ 90 days before enrollment (*de novo*) and were receiving immunosuppressant therapy, or who were receiving maintenance immunosuppressant therapy according to routine clinical practice >90 days before enrollment.

Eligible patients were included in the study on the basis of availability and/or accessibility of patients at the discretion of the Investigator. Exclusion criteria included multi-organ transplant recipients (e.g. kidney and pancreas, kidney and liver), previous non-kidney transplantation, and patients who were enrolled, or planned to enroll in another clinical study.

2.2. Treatment

Patients were followed for 12 months after inclusion in the study, with *de novo* kidney transplant recipients having up to six planned visits and kidney transplant recipients on maintenance immunosuppression having two planned visits. At each visit, the following data were collected: medical history (first visit only), vital parameters, hematology, biochemistry, current immunosuppressive drugs, trough levels of immunosuppressive drugs, concomitant therapy, biopsy-confirmed rejection and adverse events (AEs). The first (baseline) visit was at the time of study entry and the final visit at 12 months after study entry. In *de novo* patients, additional data capture was performed during routine scheduled follow-up visits according to standard clinical care at the individual center.

2.3. Endpoints

The primary composite endpoint comprised the number, daily dose and C_0 of medications in patients' immunosuppressive regimens throughout the study period. Medications included CNIs (cyclosporine, immediate-release [IR] or prolonged-release [PR] tacrolimus), mammalian target of rapamycin inhibitors (mTORi), antiproliferative agents (AZA, MMF, MPS) and corticosteroids. Blood concentrations of immunosuppressant drugs were measured by center-specific assays. Target C_0 levels were ≥ 5 ng/mL for tacrolimus and ≥ 75 ng/mL for cyclosporine [4,6]. The secondary endpoints were laboratory parameters and vital sign measurements, and the incidence of biopsy-proven rejections, AEs, graft loss and patient death during the 12 months follow-up study period. AEs were assessed in all enrolled patients.

For patients who received Astellas-manufactured tacrolimus (IR: Prograf[®], Astellas Pharma Ltd, Chertsey, UK; PR: Advagraf[®], Astellas Pharma Europe BV, Netherlands), investigators provided a causality assessment for treatment-emergent AEs. No causality assessments were made for generic tacrolimus.

2.4. Safety

AE reporting was based on the Medical Dictionary for Regulatory Activities (MedDRA). AEs were graded according to severity (mild, moderate, severe) using the Common Terminology Criteria of AEs (CTCAE) scale. Assessment of treatment causality was carried out by the Investigator.

2.5. Statistical analysis

All of the analyses in the study were descriptive. The daily dose and trough level data for maintenance and *de novo* patients were summarized separately. Continuous variables were summarized by mean and standard deviation (SD) and categorical variables by number and percentage of patients. Data were summarized using SPSS statistical software (IBM SPSS statistics, version 23.0, IBM Corporation, Armonk, NY, USA).

3. Results

3.1. Patient and donor characteristics

A total of 1774 kidney transplant recipients were enrolled from Bulgaria ($n = 109$), Croatia ($n = 339$), Romania ($n = 647$), Serbia ($n = 434$) and Slovenia ($n = 245$). Patient characteristics for each country are summarized in Table 1. The majority of kidney transplant recipients were male (59.5%). The mean (SD) age of all patients was 46.9 (12.7) years, although patients from Slovenia and Croatia were older. The most frequent causes of ESKD were glomerulonephritis (36.0%) and polycystic kidney disease (10.1%). In Serbia, 54.5% of patients received organs from living-related donors, whereas the majority of patients from Croatia, Bulgaria, Romania and Slovenia received organs from deceased donors.

3.2. Immunosuppressive regimens

3.2.1. De novo regimens

At baseline, the majority of *de novo* patients received triple immunosuppressive regimens, with any others receiving dual therapy (Fig. 1A). At the end of the study, most patients remained on triple therapy (Fig. 1B), with only two *de novo* patients receiving monotherapy.

The most common immunosuppressive treatments in *de novo* patients were tacrolimus (IR or PR), MMF or MPS, and corticosteroids, at both baseline (Fig. 2A) and end of study (Fig. 2B). Approximately 20% of Slovenian patients received cyclosporine and 30% of both Slovenian and Croatian patients were on a corticosteroid-free regimen. There were no major differences in the number or composition of

immunosuppressive regimens between baseline and the end of the study.

3.2.2. Maintenance regimens

Most maintenance patients (>70%) received triple immunosuppressive regimens at baseline (Fig. 3A) and at end of study (Fig. 3B), with the exception of Slovenia, where 47.4% and 48.8% of patients received dual and triple therapy, respectively. Dual therapy was the second choice of maintenance regimen and monotherapy was used in only 1% of maintenance patients.

The most common immunosuppressive therapies in maintenance patients at baseline and the end of the study were CNI (tacrolimus or cyclosporine) and MMF or MPS, with or without corticosteroids (Fig. 4A and Fig. 4B). Tacrolimus (IR or PR) was the most frequently used CNI, except in Slovenia where similar numbers of patients received either tacrolimus or cyclosporine, and approximately half of patients were on a corticosteroid regimen. Corticosteroid use in the other countries was much higher. A similar composition of immunosuppressive regimens was observed at the baseline and at the end of the study.

3.3. Immunosuppressant dosage and C_0

3.3.1. Mean daily dose

In *de novo* patients, at baseline and at the end of study, respectively, the overall mean (SD) daily dose of IR tacrolimus was 5.7 (3.8) mg and 3.7 (2.2) mg (Fig. 5A), of PR tacrolimus was 9.0 (5.1) mg and 4.3 (2.2) mg (Fig. 6A), of MMF was 2000.0 (556.7) mg and 1517.0 (569.1) mg (Fig. 7A), and of MPS was 1312.4 (262.8) mg and 1147.8 (319.1) mg (Fig. 7C). Results for cyclosporine are not presented, as only seven and

Table 1
Baseline demographics and clinical characteristics by country.

	Bulgaria ($n = 109$)*	Croatia ($n = 339$)*	Romania ($n = 647$)*	Serbia ($n = 434$)*	Slovenia ($n = 245$)*	Total ($n = 1774$)*
Patient characteristics						
Male, n (%)	62 (56.9)	200 (59.0)	404 (62.4)	260 (59.9)	130 (53.1)	1056 (59.5)
Age, years	44.7 ± 12.2	54.5 ± 11.3	41.9 ± 11.3	45.5 ± 11.6	53.2 ± 12.2	46.9 ± 12.7
Body weight, kg	71.0 ± 14.6	76.4 ± 15.0	72.5 ± 14.3	73.3 ± 14.6	71.7 ± 13.7	73.3 ± 14.5
BMI, kg/m ²	24.5 ± 5.2	26.3 ± 4.7	24.8 ± 4.1	24.5 ± 3.8	26.4 ± 4.5	25.0 ± 4.3
Cause of end-stage kidney failure, n (%)						
Glomerulonephritis not histologically examined	36 (33.0)	82 (24.2)	358 (55.3)	132 (30.5)	29 (11.8)	637 (36.0)
Polycystic kidney disease	13 (11.9)	53 (15.6)	63 (9.8)	29 (6.7)	20 (8.2)	178 (10.1)
Biopsy-confirmed glomerulonephritis	29 (26.6)	61 (18.0)	28 (4.3)	40 (9.2)	9 (3.7)	167 (9.4)
Diabetic nephropathy	4 (3.7)	32 (9.4)	28 (4.3)	35 (8.1)	10 (4.1)	109 (6.2)
Nephroangiosclerosis	10 (9.2)	22 (6.5)	11 (1.7)	46 (10.6)	9 (3.7)	98 (5.5)
Chronic pyelonephritis	7 (6.4)	35 (10.3)	37 (5.7)	7 (1.6)	2 (0.8)	88 (5.0)
Not specified	10 (9.2)	54 (15.9)	120 (18.6)	144 (33.3)	166 (67.8)	494 (27.9)
Transplant recipient type, n (%)						
<i>De novo</i>	14 (12.8)	55 (16.3)	92 (14.5)	17 (4)	28 (11.6)	206 (11.8)
Maintenance	95 (87.2)	283 (83.7)	543 (85.5)	409 (96)	213 (88.4)	1543 (88.2)
Time from transplantation to Visit 1 (baseline) [†]						
<i>De novo</i> (days)	43 ± 28	31 ± 26	31 ± 24	44 ± 28	34 ± 22	NA
Maintenance (years)	6.3 ± 6.4	5.2 ± 5.2	3.5 ± 3.2	6.1 ± 5.7	7.2 ± 5.9	NA
Duration of study participation, days	349.1 ± 62.6	368.9 ± 94.2	171.5 ± 105.8	377.9 ± 47.5	346.6 ± 95.3	295.2 ± 128.9
Donor characteristics						
Male, n (%)	13 (39.4)	110 (55)	220 (49.1)	160 (45.5)	NA	
Age, years	($n = 14$) 43.4 ± 15.5	($n = 189$) 49.4 ± 14.4	($n = 199$) 44.8 ± 15.3	($n = 281$) 54.9 ± 10.8	NA	
Transplant donor type, n (%)						
Deceased	($n = 109$) 63 (57.8)	($n = 312$) 289 (92.6)	($n = 638$) 380 (59.6)	($n = 433$) 186 (43)	($n = 1$) 1	
Living related	27 (24.8)	20 (6.4)	228 (35.7)	236 (54.5)	0	
Living unrelated	19 (17.4)	3 (1)	30 (4.7)	11 (2.5)	0	

Data in the table are presented as mean ± standard deviation or total number (percentage). * Owing to the non-interventional nature of the study, not all patients had data recorded for each variable by the investigators. [†]For 25 patients, their transplantation date was not captured. [‡]In Slovenia, data on donor type were captured for only one patient. BMI, body mass index; NA, not available.

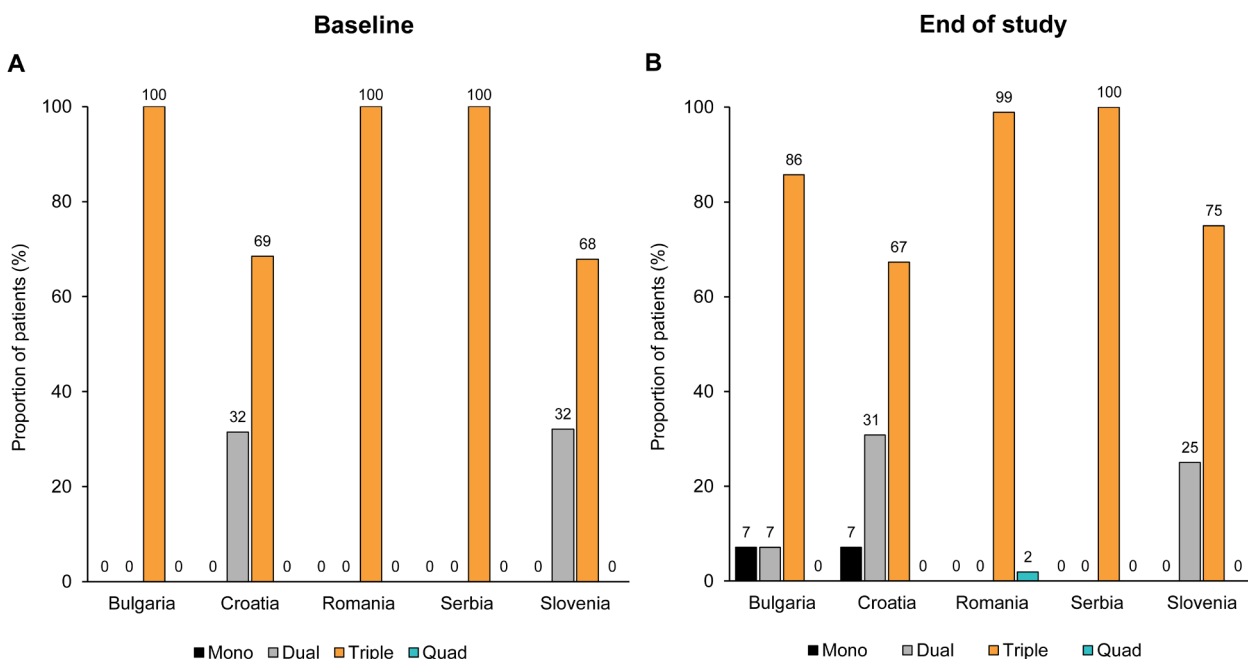


Fig. 1. Post-kidney-transplantation *de novo* immunosuppressive treatments by country at (A) baseline and (B) end of study.

nine *de novo* patients received daily cyclosporine at baseline and at the end of study, respectively. In maintenance patients, at baseline and at the end of study respectively, the overall mean daily dose for IR tacrolimus was 3.6 (2.0) mg and 3.4 (1.8) mg (Fig. 5B), for PR tacrolimus was 3.9 (2.3) mg and 3.6 (2.0) mg (Fig. 6B), for cyclosporine was 113.6 (45.6) mg and 112.2 (44.3) mg (Fig. 8A), for MMF was 1425.0 (507.1) mg and 1379.2 (486.6) mg (Fig. 7B) and for MPS was 1080.1 (325.7) mg and 1041.5 (323.6) mg (Fig. 7D).

The mean daily doses of PR tacrolimus at the end of study in *de novo* patients across all countries were 3.3–5.1 mg and with IR tacrolimus were 2.6 – 4.5 mg. In Croatian *de novo* patients, the mean (SD) daily dose of PR tacrolimus was 3.1 (2.0) mg at baseline and 3.3 (1.6) mg at

the end of the study, whereas in all other countries, the mean baseline doses were higher than the end of study doses. Mean baseline daily doses of MMF in Slovenian and Croatian *de novo* patients were 2214.3 mg and 2282.6 mg, respectively, and were 1625.0 mg to 1692.3 mg in the other countries.

Use of the anti-proliferative agent AZA and the mTORi sirolimus and everolimus was low in all countries. Only 5% of patients received AZA, predominantly in Serbia, while 2 – 16% of patients received mTORi. In patients treated with AZA, daily doses ranged from 25 to 150 mg/d at both baseline and end of study. Mean daily doses for mTORi are presented in Table 2.

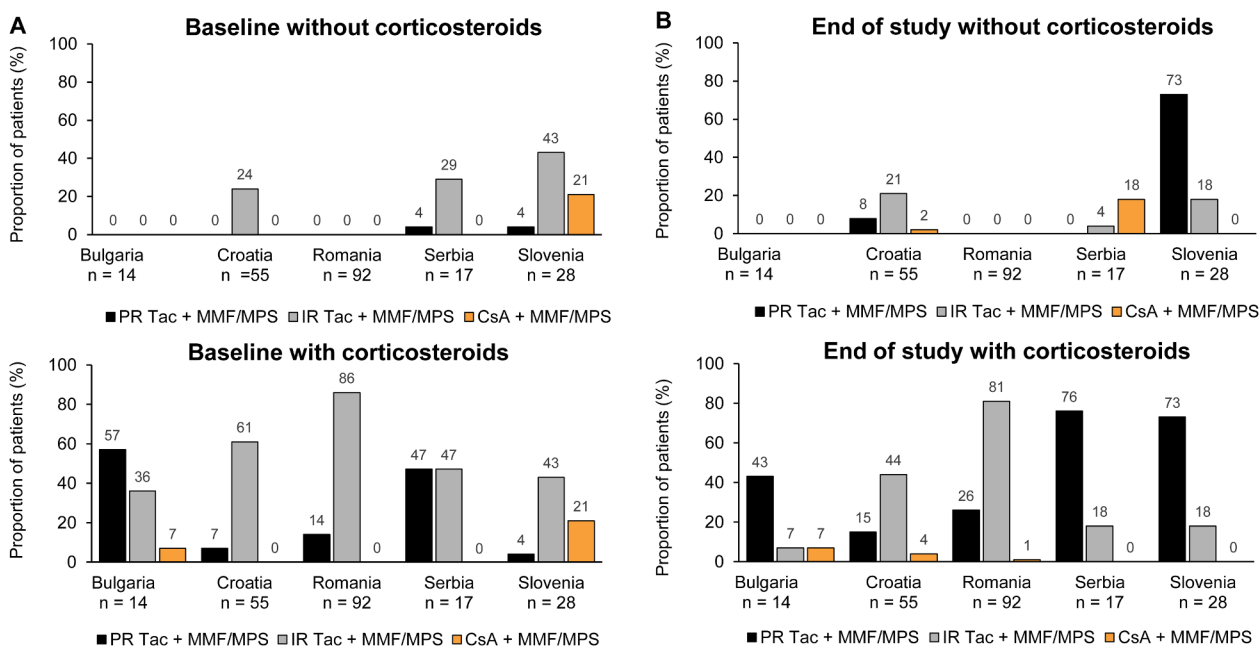


Fig. 2. Post-kidney-transplantation *de novo* immunosuppressive regimens by country at (A) baseline and (B) end of study.

Several immunosuppressive regimens were used in study patients; this figure describes the proportion of patients in each country who received PR Tac + MMF/MPS, IR Tac + MMF/MPS, or CSA + MMF/MPS

CsA, cyclosporine; IR Tac, immediate-release tacrolimus; MMF/MPS, mycophenolate mofetil/mycophenolate sodium; PR Tac, prolonged-release tacrolimus.

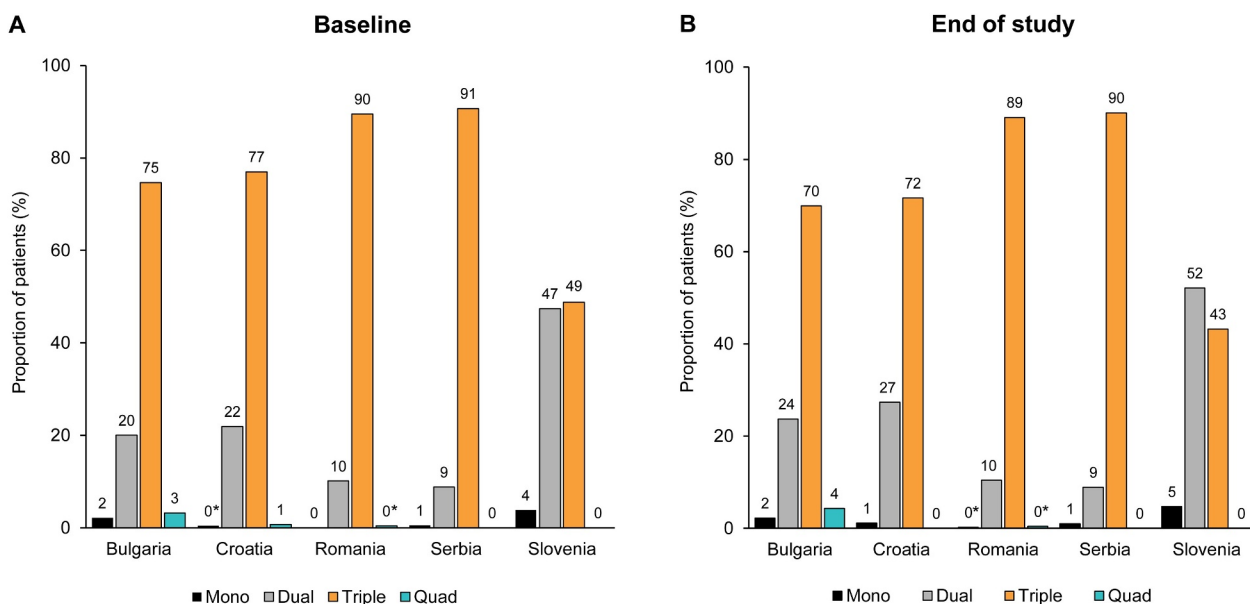


Fig. 3. Post-kidney-transplantation maintenance immunosuppressive treatments by country at (A) baseline and (B) end of study. * Values < 0.5% are cited as 0 due to rounding to one decimal place.

3.3.2. Trough concentrations

In *de novo* patients, the mean (SD) C_0 of tacrolimus at baseline and at the end of the study, respectively, were 9.1 (4.1) ng/mL and 6.9 (2.6) ng/mL for the IR formulation, and 10.8 (4.3) mg/mL and 6.8 (1.9) ng/mL for the PR formulation (Fig. 5C and 4C); in maintenance patients, the mean (SD) C_0 of tacrolimus at baseline and at the end of the study, respectively, were 6.6 (2.6) ng/mL and 6.4 (2.0) ng/mL for the IR formulation, and 6.4 (2.3) ng/mL and 6.2 (2.1) ng/mL for the PR formulation (Fig. 5D and 4D). A C_0 < 5 ng/mL at some point during follow-up was recorded in 40.2% and 48.7% of patients taking IR or PR tacrolimus, respectively.

In maintenance patients, the mean C_0 of cyclosporine increased from baseline to the end of the study (Fig. 8B). Additional analyses revealed that many patients (79.5%) had C_0 of < 75 ng/mL for cyclosporine at some point during follow-up. Mean C_0 of mTORi at baseline and end of study in maintenance patients is presented in Table 2.

3.3.3. Corticosteroids

Eight patients were identified (three in Bulgaria [acute rejection episodes]; five in Croatia [corticosteroid induction therapy]) who were treated with very high daily doses of corticosteroids (up to 500 mg)

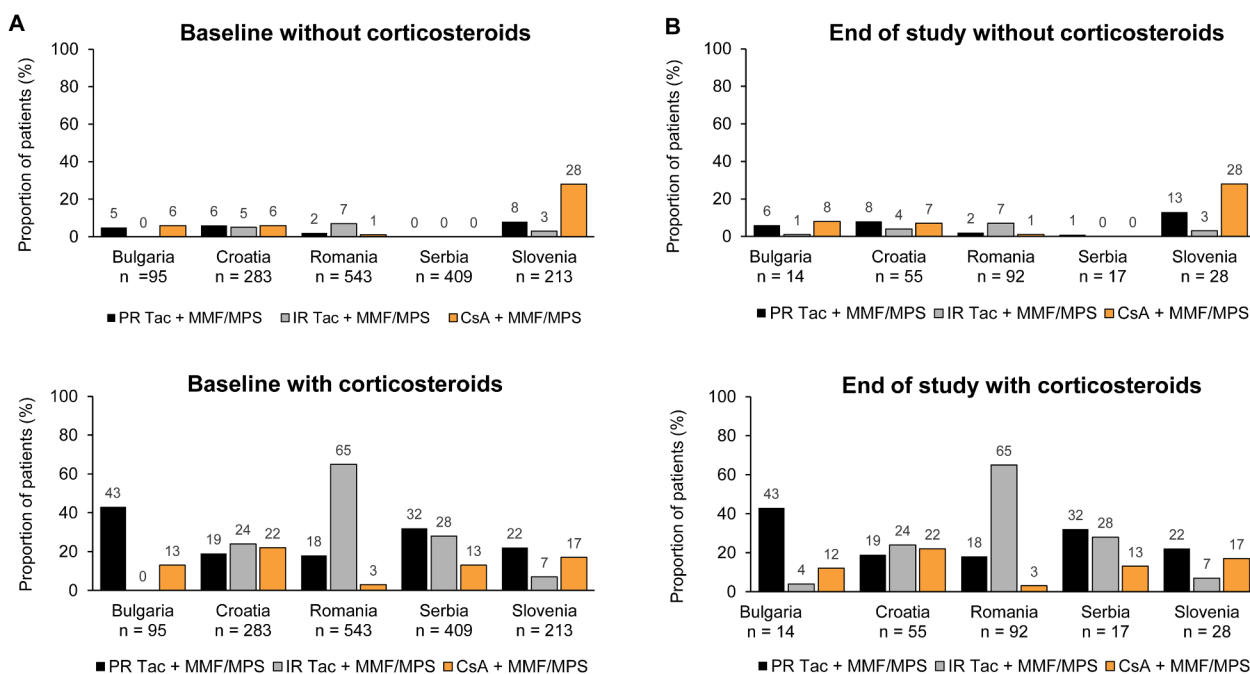


Fig. 4. Post-kidney-transplantation maintenance immunosuppressive regimens by country at (A) baseline and (B) end of study. Several immunosuppressive regimens were used in study patients; this figure describes the proportion of patients in each country who received PR Tac + MMF/MPS, IR Tac + MMF/MPS, or CSA + MMF/MPS. CsA, cyclosporine; IR Tac, immediate-release tacrolimus; MMF/MPS, mycophenolate mofetil/mycophenolate sodium; PR Tac, prolonged-release tacrolimus.

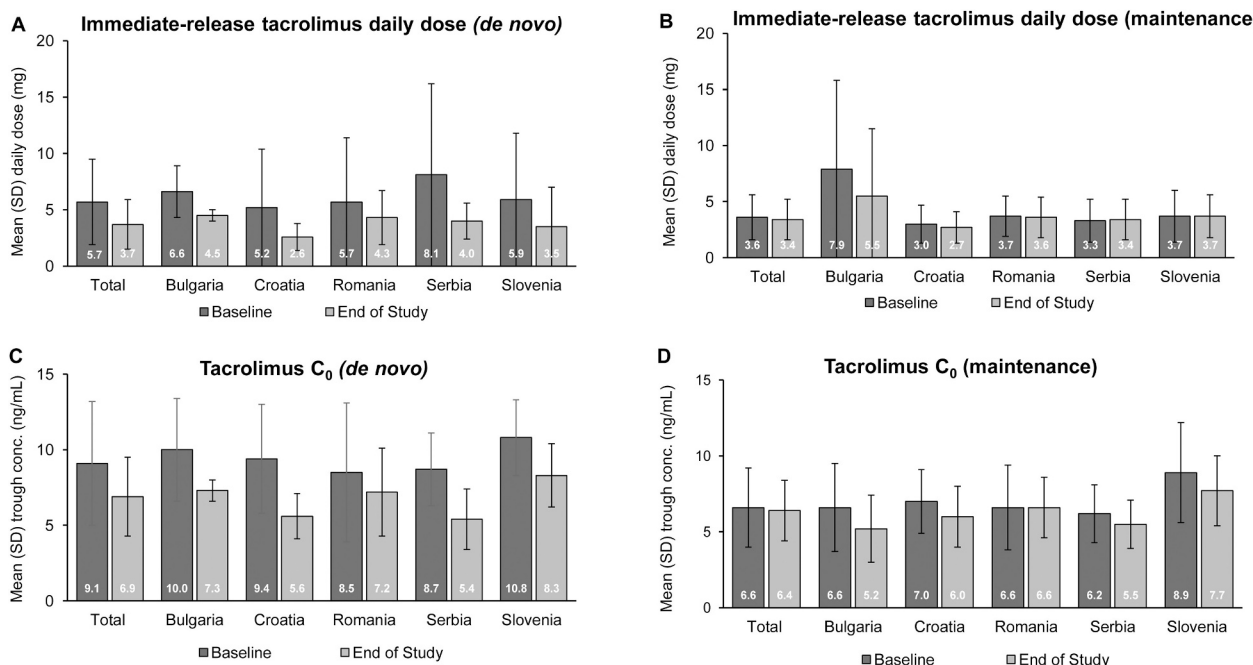


Fig. 5. Baseline and end of study data by country of (A) immediate-release tacrolimus daily dose (*de novo*), (B) immediate-release tacrolimus daily dose (maintenance), (C) immediate-release tacrolimus C₀ (*de novo*), and (D) immediate-release tacrolimus C₀ (maintenance) C₀, trough concentration; SD, standard deviation.

immediately prior to inclusion in the study. Therefore, the median rather than the mean was preferred as the midpoint value of corticosteroid daily doses. In *de novo* patients, median daily doses of corticosteroids ranged from 3.8 – 30 mg at baseline and 3.0 – 10.0 mg at the end of the study; the doses decreased from baseline to the end of the study in 10 of 12 study sites. In maintenance patients, the median daily doses ranged from 2.3 – 7.5 mg at baseline to 2.0 – 6.0 mg at the end of the study; median doses decreased from baseline to the end of the study in three sites.

3.4. Laboratory parameters and vital signs

Most clinical and laboratory parameters collected throughout the course of this study were within normal range, and there were no clinically relevant changes from baseline to the end of the study in the observed cohort (Table 3). Changes in mean creatinine and estimated glomerular filtration rate (eGFR) from baseline to end of study in all countries are presented in Table 4.

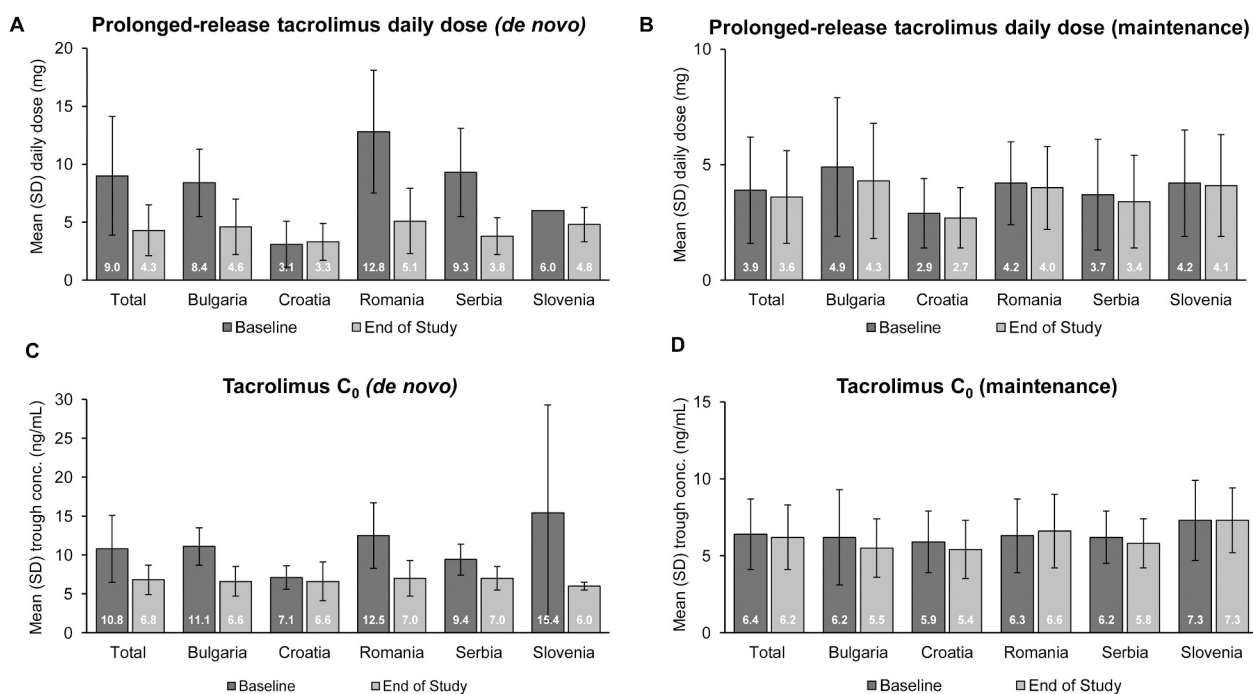


Fig. 6. Baseline and end of study data by country of (A) prolonged-release tacrolimus daily dose (*de novo*), (B) prolonged-release tacrolimus daily dose (maintenance), (C) prolonged-release tacrolimus C₀ (*de novo*), and (D) prolonged-release tacrolimus C₀ (maintenance) C₀, trough concentration; SD, standard deviation.

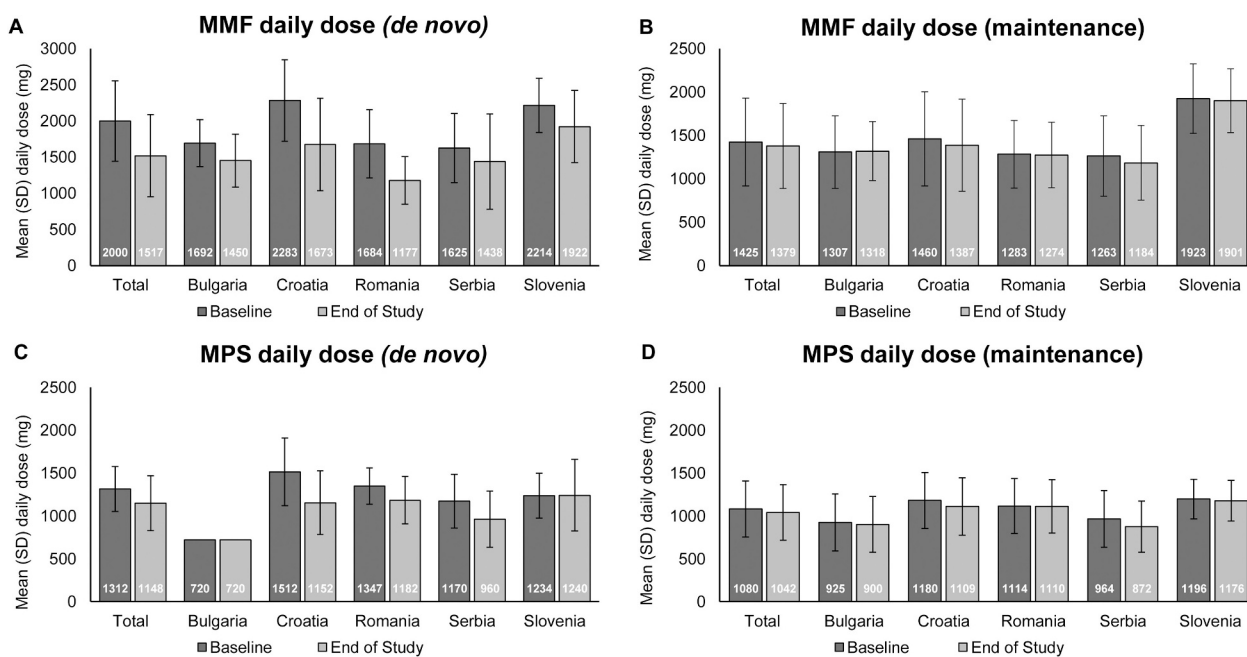


Fig. 7. Baseline and end of study data by country of (A) MMF daily dose (*de novo*), (B) MMF daily dose (maintenance), (C) MPS daily dose (*de novo*), and (D) MPS daily dose (maintenance) MMF, mycophenolate mofetil; MPS, mycophenolate sodium, SD, standard deviation.

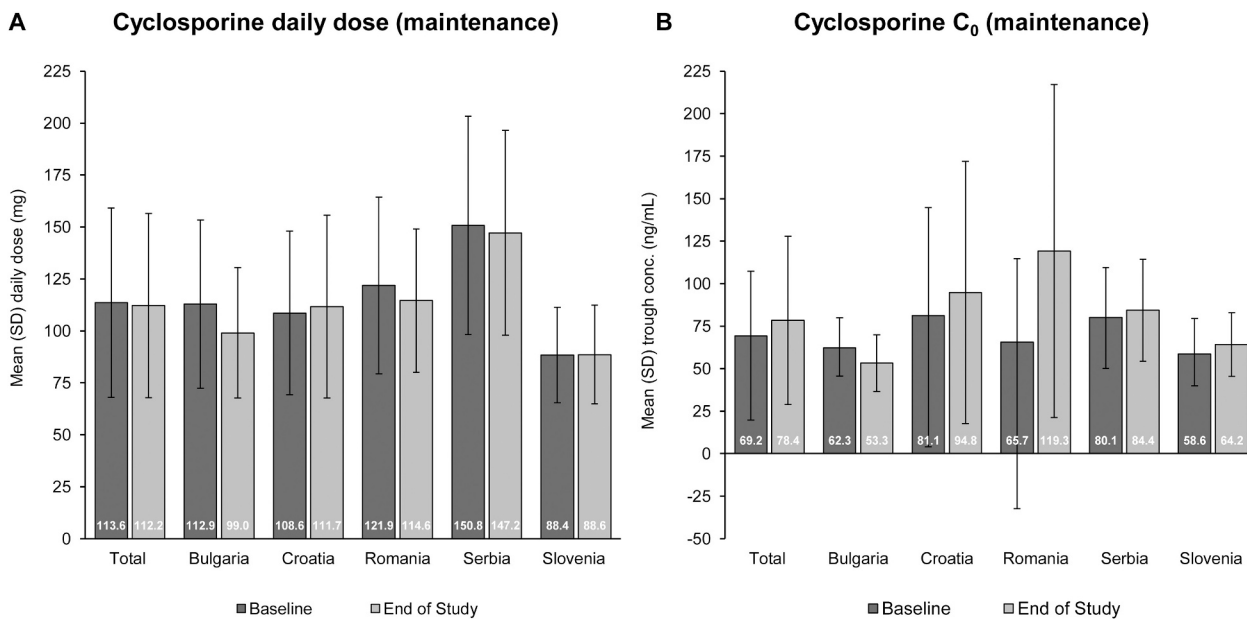


Fig. 8. Baseline and end of study data by country of (A) cyclosporine daily dose (maintenance), and (B) cyclosporine C₀ (maintenance) C₀, trough concentration; SD, standard deviation.

Table 2

Mean daily dose and trough levels of mTORi in maintenance patients from baseline to end of study.

	Mean (SD) daily dose, mg/day		Mean (SD) C ₀ , ng/mL	
	Baseline	End of study	Baseline	End of study
Sirrolimus	1.5 (0.9)	1.5 (0.6)	6.5 (2.3)	6.9 (3.3)
n	52	49	32	32
Everolimus	2.0 (1.1)	1.7 (0.8)	4.9 (2.0)	5.5 (2.7)
n	53	62	38	42

C₀, trough concentration; mTORi, mammalian target of rapamycin inhibitor.

3.5. Adverse events and deaths

A total of 597 AEs were reported in this study: 164 in Bulgaria, 253 in Croatia, 91 in Romania, 79 in Serbia and 10 in Slovenia. Overall, AEs were reported in 328 (18.5%) patients: 60/109 patients (55.1%) in Bulgaria, 141/339 patients (41.6%) in Croatia, 67/647 patients (10.4%) in Romania, 52/434 patients (12.0%) in Serbia, and 8/245 patients (3.3%) in Slovenia. Most AEs were considered to be mild (44.2%) or moderate (41.7%) in severity. AEs with a frequency of ≥ 1% are listed in Table 5. The most common AEs were infections, which accounted for 60% of AEs (358 events); most commonly, urinary tract infections (UTI, 210 events) and respiratory infections (33 events).

Table 3
Clinical and laboratory data at baseline and mean change at end of study.

	Mean (SD) at baseline	Mean (SD) change from baseline to end of study
Systolic pressure (mmHg)	131.6 (15.8)	+0.7 (16.8)
n	1745	1625
Diastolic pressure (mmHg)	81.2 (9.9)	-1.2 (11.5)
n	1743	1625
Hemoglobin (g/L)	129.7 (19.9)	2.8 (15.7)
n	1756	1713
Leukocytes (x10 ⁹ /L)	7.8 (2.8)	-0.2 (2.4)
n	1756	1704
CRP (mg/L)	4.7 (11.7)	0.5 (17.3)
n	1034	742
Glucose (mmol/L)	5.5 (1.8)	0 (1.6)
n	1676	1583
AST (μkat/L)	0.4 (0.2)	0 (0.2)
n	1496	1226
ALT (μkat/L)	0.5 (0.7)	-0.1 (0.8)
n	1389	1111
ALP (μkat/L)	1.5 (0.9)	0 (0.7)
n	1188	839
GGT (μkat/L)	0.6 (0.8)	0 (0.6)
n	1146	867
Bilirubin (μkat/L)	10.1 (5.6)	0.5 (4)
n	1200	1020
Total cholesterol (mmol)	5.2 (1.3)	0 (1.4)
n	1315	1101
LDL cholesterol (mmol)	2.9 (1.0)	0.1 (0.8)
n	886	520
HDL cholesterol (mmol)	1.5 (0.6)	-0.1 (0.5)
n	887	522
Triglycerides (mmol)	1.8 (1.0)	-0.1 (0.9)
n	1317	1101

ALT, alanine transaminase; ALP, alkaline phosphatase; AST, aspartate transaminase; CRP, C-reactive protein; GGT, gamma glutamyltransferase; LDL, low density lipoprotein; HDL, high density lipoprotein; SD, standard deviation.

Among the total of 597 AEs, 453 occurred in patients taking Astellas-manufactured tacrolimus (IR or PR), of which 139 AEs were considered as possibly/probably related to treatment. These included 78 infections, five rejections, and 56 other AEs; most commonly urinary tract infections ($n = 41$). No new safety signals associated with tacrolimus (IR or PR) were identified.

Overall, 16 (0.9%) patients died during the study (six patients in Croatia, four in Bulgaria, three in Slovenia, and three in Serbia). Deaths resulted from an AE in 10 patients: infection ($n = 6$, one death in Croatia considered possibly related to PR tacrolimus, MPS, and corticosteroids, and one death in Croatia possibly related to IR tacrolimus, MMF, and corticosteroids), cardiovascular events ($n = 2$) and cancer ($n = 2$, one death in Croatia considered possibly related to therapy with IR tacrolimus, MMF, and corticosteroids). The exact cause of death was not reported for six patients.

3.6. Graft loss and biopsy-proven acute rejection

Nine (0.5%) patients experienced graft loss during the study; six (1.8%) patients in Croatia, two (1.8%) in Bulgaria, and one (0.2%) in Serbia. Two graft losses in Croatia were considered possibly related to immunosuppressive treatment: chronic graft rejection and immunoglobulin A nephropathy that lead to graft loss were considered possibly related to corticosteroid therapy in one patient; in another patient, BK virus associated nephropathy considered possibly related to IR tacrolimus, corticosteroid, and MMF triple therapy resulted in graft loss.

Overall, there were 18 biopsy-proven graft rejections in 14 (0.8%) patients (Table 6); half of these patients were *de novo* and half were maintenance. Eight (2.4%) patients in Croatia experienced 12 acute graft rejection episodes (five patients had one event each, two patients had two events each, one patient had three events) and three (2.8%)

Table 4
Creatinine and eGFR by country: Change from baseline to end of study.

	Creatinine (μmol/L)		eGFR (mL/min)	
	Mean (SD) at baseline	Mean (SD) change at end of study	Mean (SD) at baseline	Mean (SD) change at end of study
Bulgaria				
<i>De novo</i>	123.8 (43.7)	13.6 (96.9)	61.6 (23.3)	0.5 (17.7)
n	14	14	14	14
Maintenance	117.2 (46.2)	3.7 (31.8)	58.5 (18.7)	0 (12.9)
n	95	94	95	94
Croatia				
<i>De novo</i>	340.0 (317.4)	-170.4 (320.3)	36.8 (21.5)	13 (17.6)
n	55	52	38	33
Maintenance	127.2 (54.6)	10 (49.7)	53.8 (20.8)	-1.3 (12.4)
n	281	275	192	183
Romania				
<i>De novo</i>	124.8 (40.5)	-13.7 (37.5)	59.1 (19.8)	9.8 (19.3)
n	92	88	86	82
Maintenance	119.2 (42.4)	0.6 (25.8)	64.0 (21.3)	-0.8 (16.3)
n	542	535	540	523
Serbia				
<i>De novo</i>	150.5 (55.5)	-14.5 (41.3)	47.1 (15.8; $n = 13$)	10 (16.8)
n	17	17	13	13
Maintenance	148.8 (70.1)	16.4 (53.4)	53.4 (23.1)	-3.2 (17)
n	408	406	392	381
Slovenia				
<i>De novo</i>	119.8 (40.7)	-5.5 (27.9)	55.5 (17.1)	5.2 (11.2)
n	27	27	27	27
Maintenance	120.5 (67.5)	15.2 (67.9)	58.2 (22.0)	-2.3 (11.6)
n	210	206	210	205

eGFR, estimated glomerular filtration rate; SD, standard deviation.

patients in Bulgaria experienced one acute graft rejection episode each. Chronic antibody-mediated rejection was experienced by one (0.3%) patient in Croatia and one (0.2%) patient in Serbia, and one (0.3%) patient in Croatia had a rejection episode without biopsy confirmation as to whether it was acute or chronic. Possible associations with treatment are presented in Table 6.

Table 5
Adverse events with a frequency of $\geq 1\%$.

Adverse event, n (%)	Total ($n = 597$)
Urinary tract infection	210 (35.2)
Respiratory infection	33 (5.5)
Acute graft rejection	14 (2.3)
Cytomegalovirus infection	12 (2.0)
Pneumonia	11 (1.8)
Diarrhea	10 (1.7)
Leukopenia	10 (1.7)
Diabetes mellitus	9 (1.5)
Graft loss	9 (1.5)
Hyperglycemia	9 (1.5)
BK virus infection	7 (1.2)
Acute renal failure	6 (1.0)
Anemia	6 (1.0)
Death	6 (1.0)
Elevated creatinine	6 (1.0)
Skin cancer	6 (1.0)

Table 6
Biopsy-proven graft rejections.

Patient number	Patient type*	Country	Rejection type	Severity	Possible association with drug
1	<i>De novo</i>	Croatia			
Rejection 1			Acute	Mild	IR tacrolimus, MMF, corticosteroid
Rejection 2			Acute	Mild	IR tacrolimus, MMF, corticosteroid
Rejection 3			Acute	Mild	IR tacrolimus, MMF, corticosteroid
2	Maintenance	Croatia			
Rejection 1			Acute	Severe	Cyclosporine, MMF
Rejection 2			Acute	Severe	Cyclosporine, MMF, corticosteroid
3	<i>De novo</i>	Croatia			
Rejection 1			Acute	Severe	Everolimus, MMF, corticosteroid
Rejection 2			Acute	Severe	Everolimus, MMF, corticosteroid
4	Maintenance	Croatia	Acute	Severe	IR tacrolimus, MMF, corticosteroid
5	Maintenance	Croatia	Acute	Moderate	PR tacrolimus, MPS, corticosteroid
6	Maintenance	Croatia	NA	Severe	PR tacrolimus
7	Maintenance	Croatia	Chronic	Severe	Corticosteroid
8	Maintenance	Croatia	Acute	Severe	None
9	Maintenance	Croatia	Acute	Severe	None
10	<i>De novo</i>	Croatia	Acute	Mild	None
11	<i>De novo</i>	Bulgaria	Acute	Moderate	None
12	<i>De novo</i>	Bulgaria	Acute	Moderate	None
13	<i>De novo</i>	Bulgaria	Acute	Moderate	None
14	<i>De novo</i>	Serbia	Chronic	NA	NA

* *De novo* patients had undergone transplantation ≤ 90 days before enrollment, and maintenance patients had undergone transplantation > 90 days before enrollment. IR, immediate-release; MMF, mycophenolate mofetil; MPS, mycophenolate sodium; NA, not available; PR, prolonged-release.

4. Discussion

Kidney transplantation has become a standard therapeutic option for patients with ESKD, with breakthroughs in transplant procedures and new immunosuppressant therapies providing significant improvements in both graft and patient survival [2]. The RECORD study, one of the largest studies of KTRs to date, documented immunosuppressive protocols used in 1774 *de novo* and maintenance kidney transplant recipients in clinical practice in South-eastern Europe. It is important to note that, given the observational nature of the study, the findings are not necessarily reflective of other patient populations. Nonetheless, they provide valuable key insights into the real-life management of immunosuppressive therapies in KTRs.

Of the 1774 patients included in this study, a high proportion of the study population were male (59.5%), which may reflect the higher incidence of renal disease in males [7]. The majority of patients were maintenance patients (88.2%). Inter-country differences were noted for age, with Croatian and Slovenian patients being approximately 10 years older than the average of the other countries, and the proportion of living donors (Serbia [57%], Bulgaria [42.2%] and Romania [40.4%]). The highest proportion of deceased donors was recorded in Croatia (92.6%). This can probably be attributed to Croatian transplant regulation that supports transplantation as an effective treatment for end-stage kidney disease, as well as high public awareness of the importance of organ donation [8]. The most common reasons for kidney transplantation were chronic glomerulonephritis (36.0%) and polycystic kidney disease (10.1%), which is consistent with previous reports in *de novo* kidney transplant recipients [9–11].

The most common immunosuppressive regimen was triple therapy for both *de novo* and maintenance patients, comprising CNI, anti-proliferative medication and corticosteroid, which is in line with conventional protocols [1,12,13]. A reduction in immunosuppressive regimens to dual (corticosteroid sparing) therapy was particularly evident in Slovenia and Croatia. This reduction may reflect corticosteroid withdrawal practice and/or the older age of patients in these countries which may have driven age-adapted immunosuppression for the purpose of reducing drug toxicities and infections [14]. As 30% of *de novo* patients in Slovenia and Croatia, did not take corticosteroids, this suggests that corticosteroids are withdrawn soon after transplantation in these countries. While this practice is not recommended in the

Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [1], the safety and efficacy of corticosteroid withdrawal has been demonstrated in a recent randomized controlled trial [15].

The type of CNI used across both South-eastern Europe and *de novo* and maintenance patients varied, but was mainly tacrolimus, which is consistent with published evidence showing the net benefits of tacrolimus [1,16]. The exception was Slovenia, where cyclosporine was taken by approximately 50% of maintenance patients. This is probably reflective of the fact that cyclosporine was the major CNI used in maintenance patients in Slovenia until 2012, after which there was a switch to tacrolimus use. In line with KDIGO guidelines [1], mycophenolate was the preferred antiproliferative agent, and AZA was not commonly used. mTORi therapy was generally taken only by maintenance patients, which is consistent with KDIGO guidelines, recommending their introduction once graft function is established and surgical wounds have healed [1].

CNI trough measurements, which were only available for tacrolimus (IR and PR), cyclosporine and mTORi in this study, are important to determine adequate dosing and enable clinicians to balance risk of graft rejection and prevention of immunosuppression-related complications [17]. At the end of the study period, CNI trough concentrations were close to the lowest recommended levels in both *de novo* (IR tacrolimus: 6.9 ng/mL; PR: 6.8 ng/mL) and maintenance kidney transplant recipients (IR tacrolimus: 6.4 ng/mL; PR: 6.2 ng/mL) [4,6]. The decrease in trough concentrations during the study in both groups was consistent with a reduction in daily dose from baseline to end of study.

Mean daily doses of the tacrolimus PR formulation were generally higher in *de novo* than in maintenance patients across all countries; however, in Croatia, PR tacrolimus dose was similar in *de novo* and maintenance patients. This suggests that Croatian centers may administer CNI minimization strategies to *de novo* patients, or, more likely, administer concomitant medications that affect tacrolimus metabolism and increase C_0 levels, such as calcium channel antagonists and fluconazole [18] (which tend to be used within the first several months after transplantation in Croatia).

Daily doses of tacrolimus (IR and PR) in maintenance patients were generally similar across the countries throughout the study, indicating stable and satisfactory immunosuppression. However, in Bulgaria immediate-release tacrolimus daily dose decreased from baseline (7.9 mg/d) to the end of the study (5.5 mg/d), although this might reflect a wide

dose range across a small number of participants.

Overall, tacrolimus daily dose (IR and PR) and trough concentrations were similar in maintenance patients; however, in *de novo* patients, PR tacrolimus doses were higher, which is consistent with current recommendations to initiate PR tacrolimus treatment at a higher dose [19]. Cyclosporine trough concentrations were also close to the lowest recommended levels for immunosuppression (69.2 ng/mL at baseline and 78.4 ng/mL at the end of the study). Differences between trough concentrations of tacrolimus and cyclosporine may be related to the differences in the methods used to measure their levels. Daily doses of MMF were higher in *de novo* versus maintenance patients, with little change from baseline to the end of the study in maintenance patients. Daily doses in Slovenia and Croatia were generally higher, which may have been due to CNI minimization strategies in these countries necessitating use of higher doses of MMF or MPS to achieve adequate levels of immunosuppression. However, the extent to which MMF or MPS immunosuppression compensates for low CNI and the effect of such treatment strategies on graft outcomes and adverse events has not been established.

Adverse events were generally consistent with those expected in kidney transplant recipients receiving immunosuppressive medications [1], with low numbers of AEs recorded in Romanian, Serbian and Slovenian patients, possibly due to a low AE reporting rate and/or low awareness of reporting AEs among these patients. Infections were the most common AEs comprising 358 of a total of 579 AEs. Among patients who received tacrolimus IR or PR, there were 453 AEs of which 139 AEs were considered as possibly/probably related to treatment. However, it should be noted that investigators did not provide causality assessments for 144 AEs among patients receiving generic formulations of tacrolimus.

During this study, the proportion of patients experiencing death, graft loss or biopsy-confirmed rejection (0.9%, 0.5% and 0.8%, respectively) was low. Death and graft loss were generally not considered to be associated with immunosuppressive treatment, while approximately two-thirds of rejection episodes were considered to be treatment-related. However, given that this was a 12-month study, no conclusions can be drawn regarding the long-term efficacy of the different treatment regimens used in kidney transplant recipients in South-eastern Europe.

Study limitations included those inherent to the observational, non-interventional design. Due to the open design of the study and the use of convenience sampling, the possibility of selection bias could not be ruled out. Other limitations included heterogeneity in sample sizes, as well as differences in laboratory methods between centers. For example, the methodology for measuring blood drug concentrations was not standardized between centers. Data from individual countries should therefore be interpreted with caution. In addition, the 12-month observational period may have been too short to capture all changes within the whole sample and to provide meaningful data regarding the efficacy and safety of the different immunosuppressive treatment regimens. Indeed, the comparatively short duration of follow-up in Romania (171.5 days) may have further impacted changes observed in dose, trough concentration or AEs from baseline to the end of the study. Finally, as described above, this observational study is focused solely on transplant recipients in South-eastern Europe, and therefore the conclusions derived from it may not be applicable to patient populations in other regions.

5. Conclusion

This study demonstrated that, in line with current clinical practice guidelines for kidney transplantation [17], triple therapy with CNI, antiproliferative drugs and corticosteroids was the most common immunosuppressive regimen used in kidney transplant recipients in South-eastern Europe, although the immunosuppressive regimens and the number of medications varied. Individual CNI trough concentrations

were below the target range in some countries, emphasizing the need to maintain monitoring of immunosuppressant target trough concentrations in clinical practice in South-eastern Europe.

CRediT authorship contribution statement

Miha Arnoł: Writing - review & editing, Investigation. **Radomir Naumović:** Writing - review & editing, Investigation. **Emil P. Dimitrov:** Writing - review & editing, Investigation. **Sanjin Racki:** Writing - review & editing, Investigation. **Cristina A. Bucsa:** Writing - review & editing, Investigation. **Adrian Covic:** Writing - review & editing, Investigation. **Igor Mitić:** Writing - review & editing, Investigation. **Neven Vavic:** Writing - review & editing, Investigation. **Radmila M. Velickovic Radovanovic:** Writing - review & editing, Investigation. **Lada Zibar:** Writing - review & editing, Investigation. **Sanja Bizilj:** Writing - review & editing, Conceptualization, Methodology. **Vanja Erculj:** Writing - review & editing, Formal analysis. **Tatjana Supanc Missoni:** Writing - review & editing, Methodology, Conceptualization. **Katarina T. Stupica:** Writing - review & editing, Investigation, Data curation. **Mladen Knotek:** Writing - review & editing, Investigation.

Acknowledgements

The authors thank Lidija Orlić, Stela Živčić-Ćosić, Branka Sladoje-Martinović, Mihaela Gunjača, Dorina Beatrice Tacu, Marija Milinković, Goran Paunović, Branka Mitić, Dejan Čelić, Lada Petrović, Milica Popović, Nemanja Rančić, Katarina Obrenčević, Milorad Radojević and Jean Filipov for their support. Julian Ball, and Amy MacLucas, PhD for Cello Health MedErgy assisted in drafting the initial version of the manuscript under the direction of the authors and provided editorial support throughout its development. Editorial support was funded by Astellas Pharma, Inc.

Disclosures

All authors report non-financial support from Astellas Pharma, during the conduct of the study. Mladen Knotek reports personal fees from Astellas Pharma, during the conduct of the study. Katarina Tepsic Stupica and Tatjana Supanc Missoni are former employees of Astellas Pharma, D.O.O. and Astellas D.O.O. Sanja Bizilj is an employee of Astellas Pharma, D.O.O. This study was sponsored by Astellas Pharma, D.O.O.

Funding

This study was funded by Astellas Pharma, D.O.O., Ljubljana, Slovenia. Medical writing support in the development of this manuscript was provided by Cello Health MedErgy, and funded by Astellas Pharma, Inc.

Data availability statement

Researchers may request access to anonymized participant level data, trial level data and protocols from Astellas sponsored clinical trials at www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing see: <https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx>

References

- [1] Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group, KDIGO clinical practice guideline for the care of kidney transplant recipients, *Am. J. Transplant.* 9 Suppl 3 (2009) S1–S155.
- [2] G. Guerra, G. Ciancio, J.J. Gaynor, A. Zarak, R. Brown, L. Hanson, J. Sageshima, D. Roth, L. Chen, W. Kupin, L. Tueros, P. Ruiz, A.S. Livingstone, G.W. Burke, 3rd Randomized trial of immunosuppressive regimens in renal transplantation, *J. Am.*

- Soc. Nephrol. 22 (2011) 1758–1768.
- [3] A. Gondos, B. Döhler, H. Brenner, G. Opelz, Kidney graft survival in Europe and the United States: strikingly different long-term outcomes, *Transplantation* 95 (2013) 267–274.
- [4] J. Wadström, B.-G. Ericzon, P.F. Halloran, W.O. Bechstein, G. Opelz, D. Serón, J. Grinyó, A. Loupy, D. Kuypers, C. Mariat, M. Clancy, A.G. Jardine, L. Guirado, B. Fellström, J. O'Grady, J. Pirenne, J.G. O'Leary, V. Aluvihare, P. Trunečka, U. Baccharani, J. Neuberger, A. Soto-Gutierrez, E.K. Geissler, M. Metzger, M. Gray, Advancing transplantation: New questions, new possibilities in kidney and liver transplantation, *Transplantation* 101 (2017) S1–S41.
- [5] M.A. Béland, I. Lapointe, R. Noël, I. Côté, E. Wagner, J. Riopel, E. Latulippe, O. Déry, S. Béland, C.N. Magee, I. Houde, S.A. De Serres, Higher calcineurin inhibitor levels predict better kidney graft survival in patients with de novo donor-specific anti-HLA antibodies: a cohort study, *Transpl. Int* 30 (2017) 502–509.
- [6] G. Opelz, Newsletter 1:2014, <https://www.ctstransplant.org/public/newsletters/2014/png/2014-1.html>. (accessed July 24, 2020).
- [7] F. Puoti, A. Ricci, A. Nanni-Costa, W. Ricciardi, W. Malorni, E. Ortona, Organ transplantation and gender differences: a paradigmatic example of intertwining between biological and sociocultural determinants, *Biol. Sex Differ.* 7 (2016) 35.
- [8] Eurotransplant <https://www.eurotransplant.org> (accessed July 2, 2019).
- [9] G. Mourad, M. Glyda, L. Albano, O. Viklický, P. Merville, G. Tydén, M. Mourad, A. Löhms, O. Witzke, M.H.L. Christiaans, M.W. Brown, N. Undre, G. Kazeem, D.R.J. Kuypers, Incidence of posttransplantation diabetes mellitus in de novo kidney transplant recipients receiving prolonged-release tacrolimus-based immunosuppression with 2 different corticosteroid minimization strategies: ADVANCE, a randomized controlled trial, *Transplantation* 101 (2017) 1924–1934.
- [10] O.O. Rummo, M. Carmellini, L. Rostaing, R. Oberbauer, M.H.L. Christiaans, C. Mousson, R.M. Langer, F. Citterio, B. Charpentier, M. Brown, G. Kazeem, F. Lehner, A. study Investigators, ADHERE: randomized controlled trial comparing renal function in de novo kidney transplant recipients receiving prolonged-release tacrolimus plus mycophenolate mofetil or sirolimus, *Transpl. Int.* 30 (2017) 83–95.
- [11] Z. Włodarczyk, J.P. Squifflet, M. Ostrowski, P. Rigotti, S. Stefoni, F. Citterio, Y. Vanrenterghem, B.K. Krämer, D. Abramowicz, F. Oppenheimer, F. Pietruck, G. Russ, C. Karpf, N. Undre, Pharmacokinetics for once- versus twice-daily tacrolimus formulations in de novo kidney transplantation: a randomized, open-label trial, *Am. J. Transplant.* 9 (2009) 2505–2513.
- [12] National Kidney Foundation, New options in maintenance immunosuppression: a clinical update on managing kidney transplant recipients, <https://www.kidney.org/sites/default/files/02-10-7138.pdf> (accessed July 7, 2019).
- [13] A. Muntean, M. Lucan, *Transplantation Immunosuppression in Kidney Transplantation*, 86 (2013) 87–91.
- [14] E.L. Hartmann, Chapter 24: Renal transplantation in the older adult, <https://www.asn-online.org/education/distancelearning/curricula/geriatrics/Chapter24.pdf>. (accessed July 23, 2020).
- [15] O. Thomusch, M. Wiesener, M. Opgenoorth, A. Pascher, R.P. Woitas, O. Witzke, B. Jaenigen, M. Rentsch, H. Wolters, T. Rath, T. Cingöz, U. Benck, B. Banas, C. Hugo, Rabbit-ATG or basiliximab induction for rapid steroid withdrawal after renal transplantation (Harmony): an open-label, multicentre, randomised controlled trial, *Lancet* 388 (2016) 3006–3016.
- [16] H. Ekberg, H. Tedesco-Silva, A. Demirbas, S. Vitko, B. Nashan, A. Gürkan, R. Margreiter, C. Hugo, J.M. Grinyó, U. Frei, Y. Vanrenterghem, P. Daloz, P.F. Halloran, ELITE-Symphony Study, Reduced exposure to calcineurin inhibitors in renal transplantation, *N. Engl. J. Med.* 357 (2007) 2562–2575.
- [17] R. Snanoudj, C. Tinel, C. Legendre, Immunological risks of minimization strategies, *Transpl. Int.* 28 (2015) 901–910.
- [18] T. van Gelder, Drug interactions with tacrolimus, *Drug Saf* 25 (2002) 707–712.
- [19] B-G. Ericzon, E. Varo, P. Trunečka, L. Fischer, M. Colledan, B. Gridelli, A. Valdivieso, J. O'Grady, J. Dickinson, N. Undre, Pharmacokinetics of prolonged-release tacrolimus versus immediate-release tacrolimus in de novo liver transplantation: a randomized phase III substudy, *Clin. Transplant.* 31 (2017).