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A population-based analysis of immunosuppression therapy after organ transplantation

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Abstract

Aims In this analysis we investigated the dynamics of original and generic immunosuppressive therapies prescribed to patients after organ transplantation, which are highly sensitive to generic drug conversion.

Methods For the analysis pseudonymised data (years 2017 to 2021) were pooled from the Bavarian Association of Statutory Health Insurance Physicians (Kassenärztliche Vereinigung Bayerns, KVB), covering outpatient contract medical care in Bavaria, and from BARMER Health Insurance, covering inpatient and outpatient care across Germany. The population comprised patients with confirmed transplantation plus outpatient follow-up care.

Results 76.7% (10,287 of 13,424) transplant outpatients from KVB and 76.0% (11,781 of 15,492) patients from BARMER received any immunosuppressive drug. Kidneys were the most common target organ. The most common drugs used were calcineurin inhibitors (KVB 80.2%; BARMER 78.3%), glucocorticoids (KVB 72.6%; BARMER 78.7%), and mycophenolic acid (KVB 64.5%; BARMER 58.7%). In both cohorts, methylprednisolone and tacrolimus use increased over time, while ciclosporin use declined.

Patent-protected everolimus and belatacept had the highest cost per patient. However, taking into account the number of recipients, tacrolimus had the highest cost implications for the healthcare system per year (total: KVB €134 million; BARMER €139 million), followed by mycophenolic acid and everolimus. There was a reduction in the use of originator packs for prednisolone, prednisone, methylprednisolone, mycophenolic acid, tacrolimus, and azathioprine in both cohorts and over time. Generic drug use increased from 15.2% of prescribed drug packs in the first quarter of 2017 to 22.7% in the fourth quarter of 2021 in KVB, and from 16.8 to 24.8% in the BARMER dataset.

Conclusions This population-based analysis of immunosuppressive therapy after organ transplantation in Germany found an increase in the use of generic immunosuppressive drugs between 2017 and 2021, although the increase was lower than expected.

Keywords Immunosuppression, Organ transplantation, Bavaria, Germany, Cost, Prescription

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Background & aim

Patients who undergo organ transplantation require lifelong immunosuppression to reduce the risk of graft rejection. Multiple immunosuppressive agents across several different drug classes are available for use as maintenance treatment, and a variety of regimens is used, generally incorporating two or three drugs [1–3]. The main immunosuppressive drug classes are corticosteroids (e.g. methylprednisolone), calcineurin inhibitors (ciclosporin, tacrolimus), antiproliferatives/antimetabolites (mycophenolic acid, azathioprine), mammalian target of rapamycin (mTOR) inhibitors (everolimus, sirolimus), and costimulation blocker (belatacept) [1–3]. The choice of regimen is determined by the organ being transplanted and by patient and donor characteristics. However, there is evidence that the preferred regimens/agents used for various organ transplants tend to differ between centres and over time [4–8].

The cost of long-term immunosuppressive therapy places a burden on patients and/or healthcare systems, and prescription of generic drugs instead of branded products may help reduce costs [9, 10]. Guidance is available about how to safely undertake generic substitution [11], and a transition towards the use of generic immunosuppressive drugs in the post-transplant setting has been seen in some countries [7, 9, 10]. The current characteristics of immunosuppression provision for patients after transplantation in Germany is largely unknown. Information regarding the drug groups used and the role of generic agents has not been reported. In addition, little is known about the treatment costs for patients. Since 2017, insured patients have been entitled to receive formal hospital discharge management with a written plan for follow-up care, to support their transition to external care (in accordance with Sect. 39 Paragraph 1a SGB V of GKV-Versorgungsstärkungsgesetz). It is not yet known to what extent this has affected the prescription of generic immunosuppressive medications, particularly in light of the cost-effectiveness requirement of Sect. 12 SGB V and § 4 Paragraph 2 of the frame contract. It appears, that the initial prescription of originator versus generic drugs in hospitals in Germany still determines the long-term selection of specific immunosuppressive brands.

The aim of this study was to investigate immunosuppressive therapies prescribed to patients after organ transplantation in Germany using real-world population-based data.

Methods

Design

This was a database analysis with a serial snap-shot for the years 2017 to 2021 and an analysis defined post-hoc (after the establishment of the database and start of data collection). The analyses were performed on the database from the Bavarian Association of Statutory Health Insurance (SHI) Physicians (Kassenärztliche Vereinigung Bayerns; KVB) and from BARMER Health Insurance. KVB is the statutory organization responsible for ambulatory patients treated by SHI-authorized physicians in Bavaria. Pseudonymised patient-level administrative data for SHI outpatients are available from approximately 28,000 office-based physicians, including diagnostic and therapeutic claims information. BARMER Health Insurance is the second largest health insurance company in Germany, covering inpatient and outpatient care for more than 10% of the population across the country (including Bavaria). Anonymised administrative data, including diagnoses and therapies, are recorded for use in scientific research. Data from KVB [12–14] and BARMER [15–17] have been used in multiple studies across different therapeutic areas.

The analysis was performed in accordance with the German guideline on good practice for secondary data analysis [18]. Ethics committee approval and patient informed consent were not required as pseudonymised data were used for the study. However, approval was obtained from the Upper Insurance Office (Oberversicherungsamt) (20. September 2019) and from data protection officers for KVB (26. February 2021) and BARMER (26. February 2021).

Patient population

The analysis population comprised patients with confirmed transplantation plus outpatient follow-up care by contract physicians. Confirmed cases of transplantation were based on ICD- 10-GM (German modification), and diagnosed in at least two quarters; with the second diagnosis made in one of the three quarters following the index quarter (M2Q criterion).

Patients who underwent transplantation (diagnosis) and met the following criteria were identified: M2Q plus ≥ 1x Gebührenordnungspauschale (GOP)/Zusatzpauschale (ZP); M2Q plus ≥ 2x GOP/ZP; ≥ 1x M2Q with or without GOP/ZP. Next, patients within this population who received immunosuppressant drugs at least once in the year after diagnosis were identified. The index year was the first year in which both the diagnosis (transplantation) and immunosuppressive therapy were documented. Patients who met the diagnostic criteria but did not receive immunosuppressive therapy were excluded from the analysis.

Immunosuppressive therapies were identified based on the PZN list (Pharmazentralnummer; German pharmaceutical registration number), and information on licensed generic and biosimilar drugs from WidO (Wissenschaftliches Institut der Allgemeinen Ortskrankenkasse [AOK]; Scientific Institute of the AOK, Germany).

Table 1 Patient population

	Bavaria, outpatients	Nationwide, in- and outpatients
Patient number, n (%)	10,287 (76.6%)	11,781 (76.0%)
2017	7,064 (77.0%)	8,082 (78.7%)
2018	7,230 (77.0%)	8,113 (78.8%)
2019	7,283 (77.4%)	8,071 (77.9%)
2020	7,293 (77.0%)	7,915 (78.1%)
2021	7,284 (76.0)	7,774 (76.4%)
Data coverage, n (%)		
5 years	4,893 (47.6%)	5,443 (46.2%)
4 years	974 (9.5%)	938 (8.0%)
3 years	1,058 (10.3%)	1,071 (9.1%)
2 years	1,257 (12.2%)	1,446 (12.3%)
1 year	2,105 (20.5%)	2,883 (24.5%)
Age, years (mean)	55.0	57.0
2017	54.5	56.4
2018	54.5	56.8
2019	54.7	57.0
2020	54.9	57.3
2021	55.2	57.4
Female, n (%)	4,077 (39.6%)	5,456 (46.3%)
2017	2,761 (39.1%)	3,731 (46.2%)
2018	2,850 (39.4%)	3,732 (46.0%)
2019	2,878 (39.5%)	3,692 (45.7%)
2020	2,891 (39.6%)	3,626 (45.8%)
2021	2,872 (39.4%)	3,566 (45.9%)

Statistics

Data were summarized, including number and percentage of patients or drug packs. Analyses were performed for the overall study period and by individual year.

Results

Patient and disease characteristics

A total of 13,424 patients who underwent transplantation were identified from the Bavarian outpatient dataset (Table 1). Of these, 10,287 received immunosuppressive therapy (76.6%; Bavarian cohort). Out of 15,492 patients that underwent transplantation in the nationwide in- and outpatient dataset, 11,781 received immunosuppression (76.0%; nationwide cohort).

The mean age was 55.0 years in the Bavarian cohort and 57.0 years in the nationwide cohort with less female patients in the Bavarian (39.6%) than in the nationwide cohort (46.3%). The proportion of patients with a Charlson Comorbidity Index score of ≥ 3 was also lower in the Bavarian than in the nationwide cohort (82.6% versus 89.5%).

When analysed by year (2017 to 2021), the Bavarian and nationwide cohorts were of similar size, with a lower mean age in the Bavarian cohort each year, and a lower proportion of female patients. The characteristics of the total population of transplant patients (with or without immunosuppressive therapy) appeared to be similar to the immunosuppression cohort.

Table 2 Organs transplanted

	ICD- 10	Bavaria, outpatients *N* = 10,061	Nationwide, in- and outpatients *N* = 11,447
Kidney, n (%)	Z 94.0	5,891 (58.6%)	5,861 (51.2%)
Liver, n (%)	Z 94.4	1,381 (13.7%)	1,517 (13.3%)
Heart, n (%)	Z 94.1	666 (6.6%)	643 (5.6%)
Lung, n (%)	Z 94.2	447 (4.4%)	416 (3.6%)
Heart & Lung, n (%)	Z 94.3	19 (0.2%)	4 (0.0%)
Several organs, n (%)	Z 94.0 – Z 94.4	226 (2.2%)	403 (3.5%)
Others, n (%)	Z 94.8 & 9	1,431 (14.2%)	2,603 (22.7%)

Legend: No ICD- 10 code was available for 226 patients in Bavaria and 334 patients in the nationwide BARMER cohort, but they had care positions (GOP's) in the German medical fee schedule according to the Uniform Value Scale (Einheitl Bewertungsmaßstab) twice a year

A substantial proportion of patients had data available throughout years 1 to 5 of the study period (47.6% for Bavaria; 46.2% for the nationwide cohort; Table 1).

The most frequent diagnosis codes found in the Bavarian cohort (5,891 out of 10,061; 58.6%) were kidney transplant as the primary intervention, followed by liver (n = 1,381), heart (n = 666), lung (n = 447), and heart & lung (n = 19) transplants (Table 2). A similar pattern was seen in the nationwide cohort, with 5,861 out of 11,477 patients (51.2%) receiving kidney transplants, followed by 1,517 liver, 643 heart, 416 lung, and 4 heart & lung transplants.

Immunosuppression: overall study period

Immunosuppressive drug use and the associated costs are displayed in Table 3. While the data are consistent within each cohort, a quantitative comparison has limitations because of differences in the number of patients involved and the duration of treatment. In the Bavarian cohort, the majority of patients received calcineurin inhibitors (80.2%), glucocorticoids (72.6%), and mycophenolic acid (64.5%). Prednisolone (61.8%) was the most common glucocorticoid used and tacrolimus (61.5%) the most common calcineurin inhibitor. Similarly, in the nationwide cohort, the majority of patients received glucocorticoids (78.7%; prednisolone 58.8%), calcineurin inhibitors (78.3%; tacrolimus 53.1%), and mycophenolic acid (58.7%).

In the Bavarian cohort Belatacept was associated with the highest gross costs per patient (€36,886 per patient) (Table 3), followed by everolimus (€33,971 per patient) and tacrolimus (€1,224 per patient). However, based on the number of patients using it, tacrolimus had the highest cost implications for the healthcare system (total cost 134 million €), followed by mycophenolic acid (52

Table 3 Immunosuppression drugs prescribed (total for 2017–2021)

	Bavaria, outpatients			Nationwide, in- and outpatients		
	N (%)	€/patient	Total costs	*N* (%)	€/patient	Total costs
Glucocorticoids	7,467 (72.6%)	140	1,046,673	9,266 (78.7%)	170	1,577,736
Prednisolone	6,357 (61.8%)	116	739,781	6,922 (58.8%)	132	916,067
Prednisone	1,158 (11.3%)	84	96,987	1,926 (16.3%)	108	208,750
Methylprednisolone	389 (3.8%)	159	62,010	1,328 (11.3%)	216	287,455
Dexamethasone	879 (8.5%)	168	147,404	1,057 (9.0%)	157	165,423
Cloprednol	1 (0.0%)	492	492	2 (0.0%)	20	41
Mycophenolic Acid	6,630 (64.5%)	7,883	52,266,731	6,919 (58.7%)	7,405	51,234,611
mTOR inhibitors	1,454 (14.1%)	26,808	38,979,315	1,834 (15.6%)	26,796	49,143,000
Everolimus	895 (8.7%)	33,971	30,403,614	1,321 (11.2%)	31,946	42,200,100
Sirolimus	586 (5.7%)	14,634	8,575,701	536 (4.5%)	12,953	6,942,900
Calcineurin Inhibitors	8,251 (80.2%)	17,850	147,282,666	9,221 (78.3%)	17,015	156,893,530
Tacrolimus	6,324 (61.5%)	21,224	134,218,122	6,259 (53.1%)	22,228	139,127,575
Ciclosporin	2,233 (21.7%)	5,851	13,064,544	3,359 (28.5%)	5,289	17,765,956
Azathioprine	546 (5.3%)	572	312,414	586 (5.0%)	562	329,254
Belatacept	80 (0.8%)	36,886	2,950,917	170 (1.4%)	29,356	4,990,483

While the data are consistent within each cohort, a quantitative comparison has limitations because of differences in the number of patients involved and the duration of treatment

Legend:mTOR mammalian target of rapamycin

million €) and everolimus (30 million €). Of these drugs, everolimus and belatacept were the only ones with patent protection during the data window considered. In the nationwide cohort, the drugs associated with the highest cost per patient in the nationwide cohort were everolimus having the highest cost per patient (€31,946 per patient), followed by belatacept (€29,356 per patient) and tacrolimus (€22,228 per patient). Tacrolimus had the highest cost implications for the healthcare system (139 million €), followed by mycophenolic acid (51 million €) and everolimus (42 million €).

Immunosuppression: changes over time

With respect to the number of patients using different immunosuppressive agents, there was an increase in the use of prednisolone, methylprednisolone, and tacrolimus in the Bavarian cohort between 2017 and 2021, while ciclosporin use declined (Supplementary Table S1). The same pattern was observed in the nationwide cohort, with the exception of prednisolone use which remained fairly stable over time (Supplementary Table S2).

The cost per patient for individual agents for the years 2017 to 2021 is summarized in Supplementary Tables S3 and S4. The highest costs per patient were noted for the patent-protected drugs everolimus and belatacept in both cohorts. Relevant changes over time in the Bavarian cohort included an increase in the cost of methylprednisolone (€68 in 2021 vs. €50 in 2017) and cloprednol (€179 vs. €134), and a decrease in the cost of dexamethasone (€103 vs. €112) and mycophenolic acid (€1,459 vs. €2,717). In the nationwide cohort, a similar pattern was observed for methylprednisolone (increase: €84 vs. €73), dexamethasone (decrease: €106 vs. €121) and mycophenolic acid (decrease: €1,413 vs. €2,630). In addition, the cost per patient increased for prednisone (€47 vs. €42) and decreased for sirolimus (€3,883 vs. €4,311).

Immunosuppression: original versus generic packs (overall study period)

In the Bavarian cohort, a high proportion (> 90%) of prescriptions for glucocorticoids (except methylprednisolone and cloprednol) and azathioprine were dispensed as generic packs (Table 4). In contrast, rates of generic packs were 18.4% for mycophenolic acid, and 6.7% for calcineurin inhibitors. Similarly, in the nationwide cohort, a high proportion (> 90%) of glucocorticoids (except cloprednol) were dispensed as generic packs. Rates of generic packs were 21.2% for mycophenolic acid, 8.6% for tacrolimus and 5.4% for ciclosporin. Everolimus, sirolimus and belatacept were only available in originator packs during the observation period.

Immunosuppression: original versus generic (changes over time)

In the Bavarian cohort there was a reduction over time in the use of originator packs for prednisolone, prednisone, methylprednisolone, mycophenolic acid, tacrolimus, and azathioprine (Supplementary Table S5). There was an increase in the number of everolimus and belatacept packs dispensed (only available as originator packs), and a decrease in the use of ciclosporin (both originator and generic) without a shift in the proportion of original vs. generic drugs. In the nationwide cohort (Supplementary Table S6), the same pattern was observed for the drugs mentioned above. Further to these, there was a decline in

Table 4 Immunosuppression according to original vs. generic packs (total 2017–2021)

	Bavaria, outpatients		Nationwide, in- and outpatients	
	Original Packs, *n* (%)	**Generic/Biosimilar, *n* (%)**	**Original Packs, *n* (%)**	**Generic/Biosimilar, *n* (%)**
Glucocorticoids	2,738 (4.5)	58,281 (95.5)	5,833 (6.7)	81,432 (93.3)
Prednisolone	1,848 (3.6)	48,932 (96.4)	3,177 (5.0)	59,752 (95.0)
Prednisone	547 (9.6)	5,163 (90.4)	1,278 (10.6)	10,797 (89.4)
Methylprednisolone	311 (14.1)	1,902 (85.9)	1,347 (14.0)	8,249 (86.0)
Dexamethasone	11 (0.5)	2,284 (99.5)	29 (1.1)	2,634 (98.9)
Cloprednol	11 (100)	0 (0)	2 (100.0)	0 (0.0)
Mycophenolic acid	109,159 (81.6)	24,588 (18.4)	103,477 (78.8)	27,839 (21.2)
mTOR inhibitors	37,805 (100)	0 (0)	49,211 (100.0)	0 (0.0)
Everolimus	27,905 (100)	0 (0)	40,718 (100.0)	0 (0.0)
Sirolimus	9,900 (100)	0 (0)	8,493 (100.0)	0 (0.0)
Calcineurin Inhibitors	325,624 (93.3)	23,278 (6.7)	353,161 (92.4)	28,855 (7.6)
Tacrolimus	237,863 (92.7)	18,759 (7.3)	238,638 (91.4)	22,347 (8.6)
Ciclosporin	87,761 (95.0)	4,619 (5.0)	114,523 (94.6)	6,508 (5.4)
Azathioprine	763 (9.9)	6,982 (90.1)	1,066 (13.1)	7,079 (86.9)
Belatacept	2,688 (100)	0 (0)	4,358 (100.0)	0 (0.0)

Legend: Data are number (%) of packs. *mTOR* mammalian target of rapamycin

the use of dexamethasone (both originator and generic) and sirolimus (only available in an originator pack).

Generic drug use and costs

In both the Bavarian cohort and the nationwide cohort, there was a steady increase in the use of generic drugs over time (Fig. 1, upper panel). In the Bavarian cohort, generic drugs accounted for 15.2% of immunosuppression drug packs prescribed in the first quarter of 2017, increasing to 22.7% in the fourth quarter of 2021. In the nationwide cohort, the percentage increased from 16.8 to 24.8%. When only the initial immunosuppression prescription was considered, there was a more marked increase in the proportion of drugs that were generic, from 15.2% in 2017 to 59.4% in 2021 in the Bavarian KVB cohort, and from 16.7 to 52.3% in the nationwide cohort.

With the increasing use of generic drugs, there was an accompanying shift away from original drugs with an increase in the share of costs of the generic drugs over time (Fig. 1, lower panel). The proportion of generic drug costs increased from 4.6 to 10.9% in the Bavarian cohort and from 4.9 to 10.8% in the nationwide cohort between 2017 and 2021. Thus, although the increase in generic drug use was moderate, the generic cost share increased by more than 2-fold. This appeared to be due to a steeper increase in the cost of generic drugs (e.g. from total €516,988 to €1,319,988 in Bavaria) compared with the cost of originator drugs (patent-protected drugs increased from €1,445,226 to €1,965,732 and originator patent-free drug costs remained stable).

The total number of immunosuppression prescriptions was highest in the first quarter of each year both in the Bavarian and the nationwide cohort (Fig. 2). The relative proportion of generic packs increased in quarters 2 to 4 each year.

For the Bavarian cohort, most immunosuppressants were prescribed in an outpatient setting (by a nephrologist/dialysis center, primary care physician, internist or others), while only 21.6% were prescribed by a hospital outpatient clinic (Fig. 3). Different categories were used to describe prescribers in the nationwide cohort, and it appeared that most prescriptions were made outside of the hospital.

Hospital related prescription is in grey; office based prescription is in blue/green.

Discussion

Immunosuppressive drugs are highly effective, but also very costly for the healthcare system in Germany. This analysis of two large databases of data from the BARMER insurance and the Bavarian Association of Statutory Health Insurance Physicians is the first population-based analysis investigating immunosuppressive therapy after organ transplantation in routine data in Germany. It describes the characteristics of immunosuppression provided for two cohorts, one covering Bavaria and one including patients from nationwide, for the period 2017–2021, including changes over time.

Patient characteristics

The most common primary procedure was a kidney transplant, accounting for >50% of patients in both cohorts, followed by liver and heart transplants. This is consistent with data from other countries that indicate kidney and liver transplants are the most common solid-organ transplants performed [4, 19, 20]. A similar proportion of patients (just over 75%) in the Bavarian

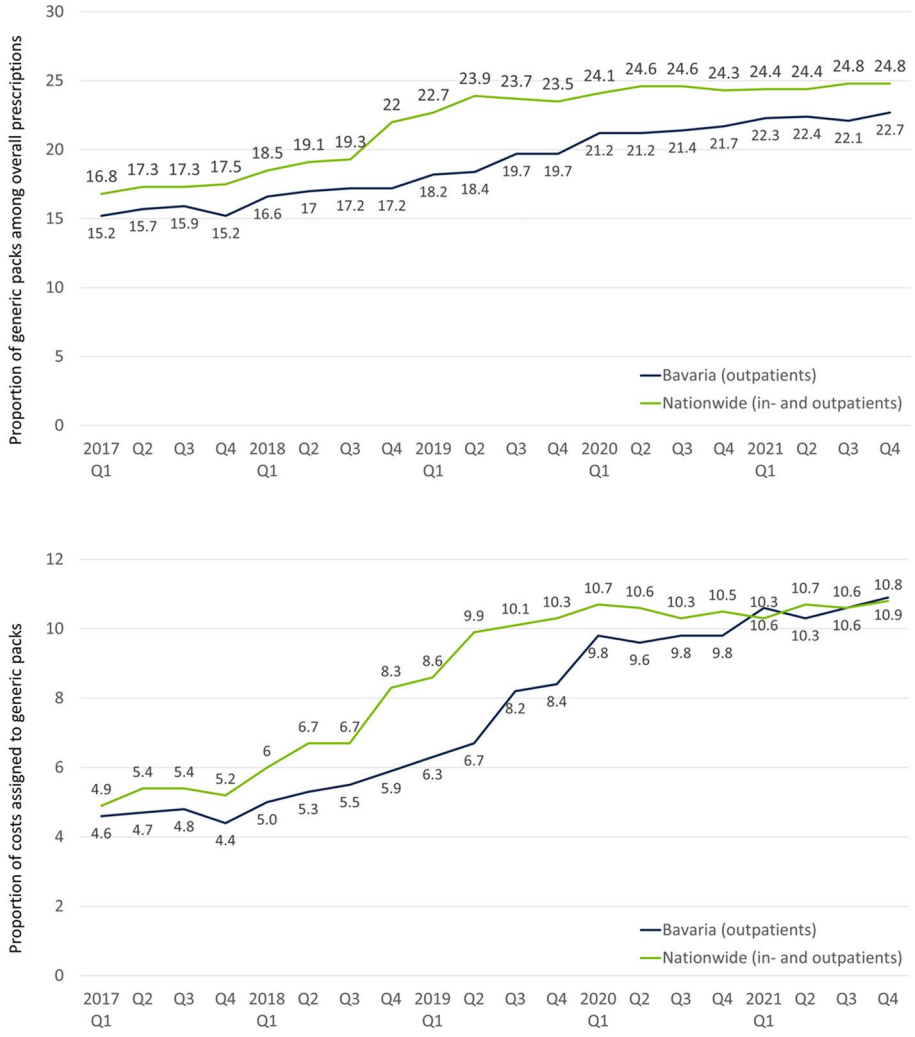

Fig. 1 Generic drug use: percentage of immunosuppression packs (top) and share of drug costs (bottom), 2017–2021

outpatient and nationwide in- and outpatient databases received post-transplant immunosuppressive therapy, and the immunosuppression cohorts that were analysed further were of similar size in each year studied. The main differences between the cohorts were that the nationwide cohort was slightly older and had a higher proportion of female patients than the Bavarian cohort each year. The mean ages of 55 and 57 years were similar to the ages reported for recipients of kidney, liver, and heart transplants in other countries (median 51–57 years) [4, 21]. Approximately 25% of patients who met the diagnostic criteria for transplantation did not receive immunosuppressive therapy and were, by definition, excluded from further analysis. Information on the reasons these patients did not receive immunosuppression was not available. Overall, the general characteristics of the total transplant population were similar to those of the immunosuppression cohort.

Immunosuppression drug use

In both the Bavarian and nationwide cohorts, the most common classes of immunosuppressive medication prescribed to transplant patients during the overall study period (2017–2021) were calcineurin inhibitors, glucocorticoids and antiproliferatives, with the most common individual drugs within these classes being tacrolimus alone or in combination with prednisolone and/or mycophenolic acid. The specific regimens/combination of agents prescribed were not evaluated in the current analysis, but regimens based on these drug classes are commonly prescribed for kidney and liver transplant patients [1, 4–8]. In both cohorts, the use of methylprednisolone and tacrolimus increased, while the use of ciclosporin decreased, between 2017 and 2021. A similar temporal trend was found in a multicentre observational study in Italy, which reported an increase in tacrolimus-based regimens at the expense of cyclosporin-based regimens, with the former increasing from 63.0 to 82.2% in

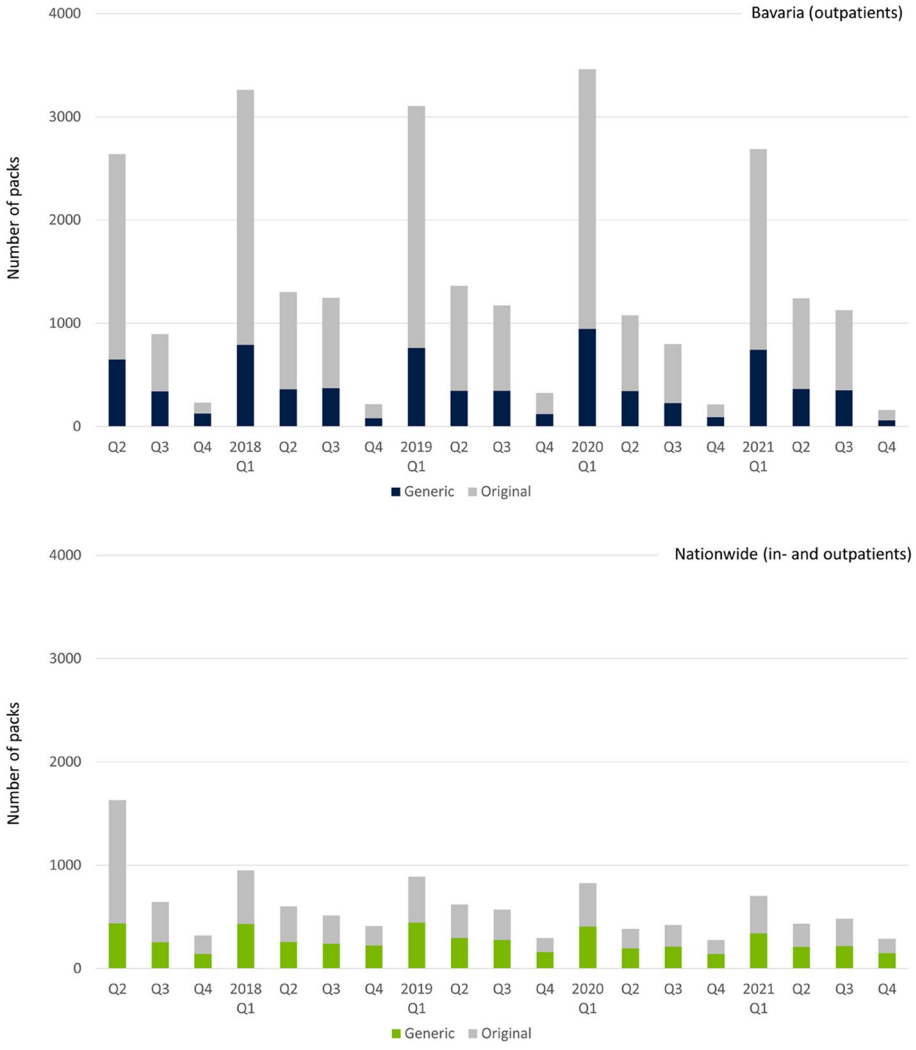

Fig. 2 Number of generic/original immunosuppression drug packs by quarter (2017–2021)

kidney recipients and from 72.7 to 92.9% in liver recipients between 2013 and 2019 [4].

Immunosuppression drug costs

Based on the overall study period, everolimus and belatacept were associated with the highest gross cost per patient for individual drugs, which is unsurprising as they were under patent protection during the study period. However, due to the high number of patients who received tacrolimus, this drug had the highest total cost implication for the healthcare system, followed by mycophenolic acid and everolimus. Substantial changes in the cost of several drugs occurred between 2017 and 2021. In both cohorts, the cost of methylprednisolone increased, and the cost of dexamethasone and mycophenolic acid decreased. Other changes were specific to one or other cohort: the cost of cloprednol increased in the Bavarian cohort only, while the cost of prednisone increased, and the cost of sirolimus decreased, in the nationwide cohort only.

Cost of generic drug use

During the study period, everolimus, sirolimus and belatacept were only available in originator packs. Other drugs were off-patent and generic versions as well as originator packs were available. No patents expired during the study period. Most glucocorticoids were dispensed in generic packs (> 90%) in both cohorts. Rates of generic packs for mycophenolic acid, tacrolimus and ciclosporin were lower in the Bavarian cohort than in the nationwide cohort, most noticeably for mycophenolic acid (18.4% vs. 21.2%). Regional variations in the use of generic drugs were also noted in an observational study in Italy [4]. Studies in Italy and the USA have found that variations in the immunosuppressive drugs used in post-transplant patients are often due to differences in the standard practices in place at centres [6, 8], and it is possible this is also

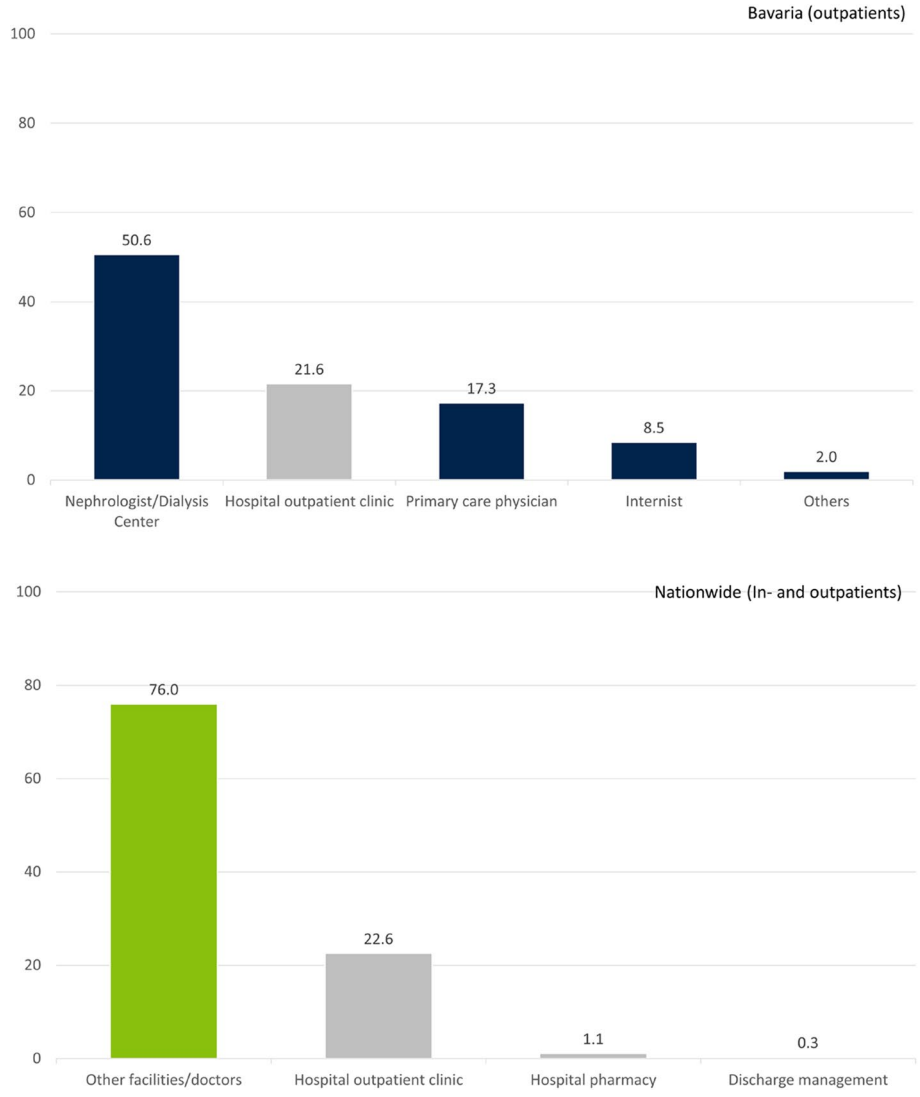

Fig. 3 DDD prescription of immunosuppressants by prescriber (%) for Bavaria (top) and nationwide (bottom)

the case with respect to the use of generic versus originator packs. One Italian study found variation in the use of generic immunosuppressive drugs at both a centre and regional level [9]. This might suggest there could be differences in policies regarding generic drugs at a regional level in Germany. In addition, some university pharmacies work together in purchasing groups to reduce the cost of drugs (https://www2.medizin.uni-greifswald.de/apotheke/genua); this means that some transplant units can obtain originator packs of immunosuppressive drugs at a reduced cost, and so may continue to prescribe that version of the drug rather than a generic version.

Nonetheless, between 2017 and 2021, the use of generic packs increased for many drugs (including most glucocorticoids, tacrolimus, and azathioprine) in Bavaria as well as in the nationwide cohort. Overall, by the end of 2021, generic packs accounted for >20% of immunosuppressive drug packs in both cohorts. An Italian study also reported increasing use of generic immunosuppressant drugs over time (2013–2019) [9], and the authors suggested that the availability of national as well as regional recommendations on the use of generics in the transplant population may have helped encourage the transition. Guidance on generic substitution of immunosuppressive drugs is available from the European Society for Organ Transplantation [11], and in Germany, regional recommendations are available for Bavaria (www.kbv.de/media/sp/Rahmenvertrag_Entlassmanagement).

The reasons for prescribing generic drugs were not obtained for the current study, but it is likely that cost was a key issue. A US study has shown that generic immunosuppressants have the potential to reduce healthcare costs [10], and an Italian study estimated potential annual cost savings of approximately €2000 per patient per

drug with generic immunosuppressants [9]. The current study found steep increases in the use of generic drugs in recent years in Germany, and an economic evaluation specific to the country is needed to confirm any overall cost benefit.

Implications for the healthcare system

In the current study, the increase in the use of generic immunosuppressive drugs between 2017 and 2021 was lower than expected, which might suggest that outpatients continue to receive the originator or generic drug initially assigned in the hospital and these treatment decisions are rarely challenged by office-based physicians. However, we also found that the increase in generic drug prescriptions was most marked for initial prescriptions, made in transplant centres. It is possible this could in part relate to the introduction of board certification for transplant physicians in Germany between 2018 and 2023 [22], meaning that knowledge about switching to generic immunosuppressive drugs increased amongst transplant physicians (whereas previously it may have been predominantly limited to university centres). This could lead to a continued increase in the overall proportion of generic drug use over time, if most office-based physicians continue with the same prescription.

There could also be some variation depending on the type of transplant performed. In Germany, follow-up for transplant patients is likely to be at university hospital transplant centres for liver, heart and lung transplants, whereas it may occur at nephrology/dialysis centres for kidney transplants. There may be a greater inclination to switch to generics at specialist transplant outpatient clinics than at dialysis centres or general clinics.

Immunosuppressive drugs such as cyclosporine and tacrolimus are narrow therapeutic index drugs. As such a substitution requires caution due to the potential clinical consequences resulting from variations in drug dosage [11]. It is for this reason that patients and their physicians tend to stick to the drug initially prescribed in the hospital setting after transplantation and are reluctant to switch between brands or between original and generic formulations later.

A meta-analysis, however, comparing branded versus generic formulations in solid organ transplantation found no significant differences in acute rejection compared to the originator drugs, although they did not fully meet the bioequivalence criteria established in the US and Europe [23]. Recent studies comparing originator and equivalent formulations of tacrolimus have shown no differences in terms of the incidence of acute rejection, graft failure and adverse events [24, 25]. On this background, the observation of a substantial increase in the proportion of generic drugs amongst drugs prescribed in the 'discharge management' setting based on the national in- and outpatient dataset is encouraging. It is further reasonable to assume that if generic drugs (if available for a given compound) were the default choice in the hospital setting, patients would stick to the generic drug in the longer term, which would certainly translate into further cost savings for the health care system without compromising the quality of care and the prognosis of patients.

Limitations

The observational nature of the study is associated with certain limitations. Information entered into the databases depends on coding of diagnoses, medication and associated descriptors by doctors, and it is possible that some data might have been misclassified. A quarter of transplant patients did not receive immunosuppressive therapy and were excluded from the analysis; the reasons they did not receive documented immunosuppression were not available. The data used for the study are for statutory health insured patients only, and it is possible results would be different for private or non-insured patients. In addition, the data from KVB covered one region covering about 1 out of 7 inhabitants of Germany (Bavaria). However, data from BARMER came from across the country. The data were generally consistent between the two cohorts, suggesting that the results are reasonably representative of clinical practice in Germany. It is possible that some individual centres may have favoured generic drugs whereas other may have preferred to avoid their use; however, a between-centre analysis was not performed as part of the study.

Conclusion

This population-based analysis of immunosuppressive therapy after organ transplantation in Germany found an increase in the use of generic immunosuppressive drugs between 2017 and 2021, although the increase was lower than expected. An increase was most noticeable among initial prescriptions.

Supplementary Information

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Supplementary Material 1.

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Authors' contributions

Substantial contributions to the conception or design of the work (FH, DS, PK, LW, DB); or the acquisition, analysis, or interpretation of data for the work (FH, DS, PK, LW, DB, PB); AND Drafting the work (PB) or reviewing it critically for important intellectual content (FH, DS, PK, LW, DB); AND Final approval of the version to be published (FH, DS, PK, LW, DB, PB); AND Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved (FH, DS, PK, LW, DB, PB).

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Data availability
Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate
Ethics committee approval was not required as pseudonymised data were used for the study. However, approval was obtained from the Upper Insurance Office (Oberversicherungsamt) and from the data protection officers for KVB and BARMER.

Competing interests
The authors declare no competing interests.

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