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A nationwide evaluation of off-label drug utilization in Turkey

Emine Nur ÖZDAMAR[1], Ahmet AKICI[1,*], Ali ALKAN[2], Banu BAYAR[2], Hakkı GÜRSÖZ[2]

[1]Department of Medical Pharmacology, Faculty of Medicine, Marmara University, İstanbul, Turkey

[2]Ministry of Health Turkish Medicines and Medical Devices Agency, Ankara, Turkey

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Background/aim: Off-label drug use (OLDU) is under the control of the Turkish Medicines and Medical Devices Agency (TMMDA) in Turkey. It was aimed to investigate demographic and medical features of patients with OLDU applications in Turkey.

Materials and methods: A total of 4426 electronic OLDU application records of the TMMDA were evaluated retrospectively. Information regarding patients' demographic characteristics, diagnoses, requested drugs, institutions, and specialties of the physicians were evaluated.

Results: OLDU applications were mostly made by rheumatologists (21.5%) and 95.2% of them were approved by the TMMDA. The mean age of the patients was 35 years and 54.4% of them were female. Off-label drugs were mostly prescribed for patients aged 18–64 years (62.1%) and were most frequently prescribed by physicians from university medical centers (81.0%). Systemic lupus erythematosus (10.1%) was the most common diagnosis. Mycophenolate (16.1%) and rituximab (10.1%) were the most frequently prescribed off-label drugs. There were differences regarding some characteristics of patients and their physicians among most frequently prescribed off-label drugs ($P < 0.05$).

Conclusion: It is noteworthy that OLDU applications showed demographical and institutional differences. It is expected that this study will provide important contributions to physicians working in the relevant area with respect to treatment alternatives of diseases with treatment challenges.

Key words: Off-label drug use, systemic lupus erythematosus, mycophenolate, rituximab

1. Introduction

Candidate drugs are tested on many issues, particularly for safety and effectiveness, with detailed preclinical and clinical trials before getting licensed. Drugs with enough convincing data in their claimed area are then licensed by the regulatory authorities for the relevant indication and population. Due to the various requirements in the process of drug development, such clinical trials are mostly performed on "standard people/patients" with certain features. Therefore, the license information concerning the appropriate use of the drugs in special populations such as children, the elderly, and patients with conditions such as cancer or mental disorders is generally not enough (1). This situation results in off-label drug use (OLDU) that covers the use of drugs outside the terms of product license with regard to age, dosage, route of administration, indications, and contraindications (2).

OLDU is a common practice throughout the world with rates reported to be between 18% and 36% in adults (3–6) and 3%–87% in pediatric patients (7–15). Moreover, the incidence of OLDU may vary depending on several factors such as the healthcare facility and the disease profile (11). Various studies have shown that OLDU is related to adverse drug reactions (2,16). In addition, it has been reported that a majority of OLDU applications possess little or no scientific support (17).

OLDU is legal in many countries (1,2,18), and in Turkey, it is under the control of the Ministry of Health (MoH) Turkish Medicines and Medical Devices Agency (TMMDA). Physicians are required to apply to the TMMDA on behalf of patients for off-label prescribing. Like international common definitions (2), OLDU is defined as "the use of licensed drugs out of the registered indications" in the "Off-Label Drug Use Guideline" published by the TMMDA (http://www.titck.gov.tr/Mevzuat/). In the guideline, it is pointed out that the TMMDA will not allow OLDU for approved indications and diseases that can be treated with standard doses of drugs and physicians are informed about OLDU application procedures and the forms that they have to fill out. It is also stated that in the

* Correspondence: aakici@marmara.edu.tr

case of determination of OLDU without permission given by the TMMDA, legal action will be initiated against the physician. The TMMDA evaluates OLDU applications with scientific advisory committees according to the provisions specified in the guideline. In the case of the approval of OLDU applications by the TMMDA, the cost of the licensed drugs will be reimbursed by the Social Security Institution and unlicensed drugs will be imported by the Turkish Pharmacists' Association.

Most of the studies investigating OLDU in the literature are specific to particular age groups, healthcare facilities, and indication (3–17). Therefore, there is a need for pharmacoepidemiological studies assessing OLDU more thoroughly from a nationwide perspective. The aim of the present study was to investigate demographic features and medical conditions of patients who have submitted OLDU applications to the health authority in Turkey.

2. Materials and methods

This retrospective study was carried out to investigate the OLDU applications coming from all provinces of Turkey in 2011. Among these applications, electronic records in the TMMDA computer database were evaluated. OLDU applications that resulted in 'approval' or 'rejection' between 1 January 2011 and 31 December 2011 were analyzed in the TMMDA database, following approval by the Ethics Committee of Marmara University Medical School and permission from the TMMDA.

Parameters such as patients' demographic characteristics, diagnoses, requested drugs, institutions, and specialties of the physicians that submitted the application (but not identity information of patients or physicians) were obtained from the OLDU application records in the TMMDA database. In this study, for ethical reasons, the patients' identification information was not used explicitly, but encoded identification numbers of the patients were obtained. In order to eliminate the possibility that an application was assessed more than once for the same drug for the same patient, encoded identification numbers were compared one by one with the drugs used. Duplications were avoided by noting the first encountered application in the registration system for the patient relating to the same drug.

Diagnoses were classified according to the International Classification of Disease (ICD-10). Drugs were grouped by the anatomic, therapeutic, and chemical (ATC) classification system. The most common reasons for rejections in applications of OLDU were identified. At level 1, ATC classification of the off-label prescribed drugs by age categories were determined**.** The results of applications for OLDU were compared by some characteristics of patients, their physicians, and the drugs (status of licensing, administration route, common subgroups, etc.). Distributions of applications for OLDU by physicians' specialties and by months were identified. The most frequent drugs were analyzed for the five most frequent diagnoses in OLDU applications. Patients' age, sex, and their physicians' affiliations were compared among the three most common prescribed off-label drugs.

Statistical analyses were carried out by SPSS 11.5. The chi-square test was used for the statistical analyses. The comparisons were considered as statistically significant at $P < 0.05$.

3. Results

In this study, 4426 OLDU applications that had been 'approved' or 'rejected' within the given time period (1 January 2011 to 31 December 2011) were analyzed. Of these applications, 4214 (95.2%) were approved by the TMMDA. The most common reason for rejection was "standard treatment options had not been tried before the OLDU application was sent" (Table 1). When the distribution of OLDU applications was analyzed by calendar month, OLDU applications were highest between March and September 2011 with a peak in April (13.6%) and May (13.5%) (Figure 1).

Table 1. Distribution of the reasons for rejection of applications for off-label drug use (OLDU).

The common reasons for rejection	n	%
Standard treatment options had not been tried before the OLDU application was sent.	64	27.4
Patient was not completely evaluated in terms of the other treatment options.	26	11.1
There was no need to take additional approval from the MoH for the use of the drug in the relevant indication.	18	7.7
There were not sufficient scientific data regarding the use of the drug in the relevant diagnosis.	14	6.0
There were not sufficient data on efficacy and safety regarding the use of the drug in the relevant diagnosis.	14	6.0
Patient who had previously received OLDU approval submitted an application for a repeat too early.	11	4.7
Others	87	37.1
Total	234	100.0

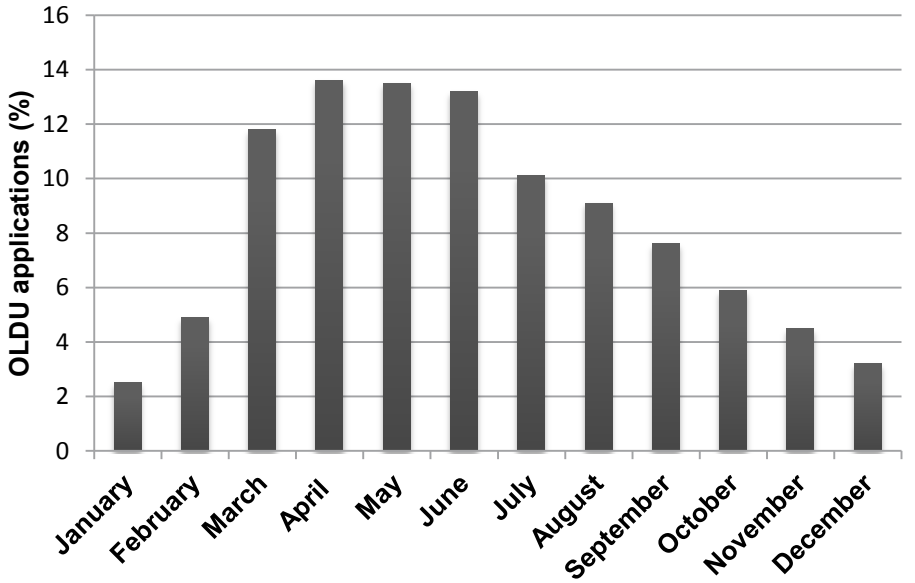

Figure 1. Distribution of applications for off-label drug use (OLDU) by month.

The mean age of the patients was 34.9 ± 21.6 years (62.1% of them aged 18–64 years) and more than half of them were female (54.4%). These patients were followed by the group under 18 years of age (28.2%).

Off-label drugs were mostly prescribed by physicians working in university hospitals (UHs), (81.0%), followed by other healthcare centers (19.0%).

The majority of OLDU applications (96.8%) were made by internal medicine specialists and 3.2% were made by physicians from surgical specialties. Among these specialties, OLDU applications were mostly made by rheumatologists (21.5%), followed by hematologists (8.6%) and neurologists (7.9%), (Figure 2). When physicians' academic titles were evaluated, it was found

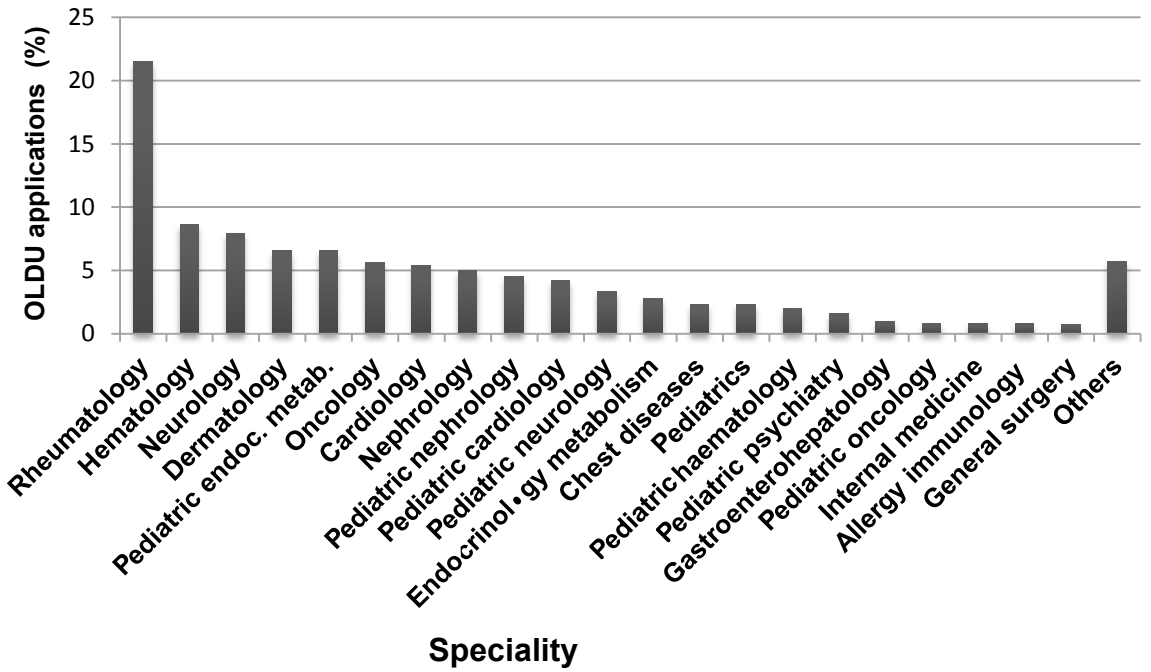

Figure 2. Distribution of off-label drug use (OLDU) applications by physician's specialty.

that specialist physicians (47.8%) most frequently made OLDU applications and this was followed by professors (24.2%) and associate professors (19.2%).

Most of the OLDU applications included one diagnosis (73.5%); the remaining ones had two or more. When diagnoses were grouped according to the ICD-10 classification, systemic lupus erythematosus (SLE; ICD-10 code: M32; 10.1%) was the most common diagnosis, followed by other pulmonary heart diseases (PHD; I27; 9.5%), multiple sclerosis (MS; G35; 4.8%), congenital malformations of cardiac septa (Q21; 4.5%), and transplanted organ and tissue status (Z94; 4.2%).

When the generic names of the drugs were analyzed, mycophenolate mofetil (MMF; ATC-5 code: L04AA06; 16.1%) was the most frequently prescribed off-label drug, followed by rituximab (L01XC02; 10.1%), iloprost trometamol (B01AC11; 5.7%), immunoglobulin i.v. (J06BA02; 3.9%), dalfampridine (N07XX07; 3.6%), infliximab (L04AB02; 3.2%), bosentan (C02KX01; 2.8%), anakinra (L04AC03; 2.8%), sildenafil citrate (C02KX; 2.3%), and teriparatide (H05AA02; 2.2%). In 13 applications (0.3%), the trade names of the drugs were not specified.

When the ATC-1 group distributions of the off-label prescribed drugs were analyzed, "antineoplastic and immunomodulating drugs" (ATC-1 code: L; 54.3%), were the most commonly prescribed group. When the distributions were analyzed by age categories, as under 18 years, 18–64 years, and 65 years or older, the figures were 34.7%, 64.4%, and 46.5%, respectively. The next most commonly prescribed groups were "nervous system drugs" (N; 15.8%) for the patients under 18 and "cardiovascular system drugs" (C) for both those 18–64 years and 65 years or older (8.3% and 17.4%, respectively) (Table 2).

Of the ATC-2 group distributions of the off-label prescribed drugs, "immunosuppressants" (ATC-2 code: L04; 32.6%) were the most commonly prescribed drugs, followed by "antineoplastic agents" (L01; 18.2%) and "antithrombotic agents" (B01; 6.8%).

Almost all OLDU applications (99.1%) consisted of systemically administered drugs and the oral route (53.9%) was the most common route of administration. This was followed by drugs administered intravenously (27.9%) or subcutaneously (10.3%). One hundred and seven (2.4%) OLDU applications did not include information concerning the pharmaceutical form of the drugs; among the 4319 applications that did, tablets (42.1%) and vials (32.5%) were the most common pharmaceutical forms.

Of the drugs in the OLDU applications, the majority of the drugs had been licensed (78.6%) in Turkey. In

Table 2. Distribution of the ATC-1 classification of the off-label prescribed drugs by age categories.

ATC-1 classification	<18 years of age		18–64 years of age		≥65 years of age		Total	
	n	%	n	%	n	%	n	%
Alimentary tract and metabolism (A)	146	11.7	48	1.7	3	0.7	197	4.5
Blood and blood forming organs (B)	153	12.3	141	5.1	51	11.9	345	7.8
Cardiovascular system (C)	56	4.5	229	8.3	75	17.4	360	8.1
Dermatological (D)	15	1.2	42	1.5	8	1.9	65	1.5
Genitourinary system and sex hormones (G)	20	1.6	11	0.4	2	0.5	33	0.7
Systemic hormonal prep. excluding sex hormones (H)	66	5.3	83	3.0	53	12.3	202	4.6
General antiinfectives for systemic use (J)	65	5.2	163	5.9	22	5.1	250	5.6
Antineoplastic and immunomodulating agents (L)	432	34.7	1771	64.4	200	46.5	2403	54.3
Musculoskeletal system (M)	32	2.6	31	1.1	7	1.6	70	1.6
Nervous system (N)	197	15.8	191	7.0	3	0.7	391	8.8
Antiparasitic products (P)	-	-	2	0.1	2	0.5	4	0.1
Respiratory system (R)	11	0.9	15	0.6	-	-	26	0.6
Sensory organs (S)	-	-	1	0.0	-	-	1	0.0
Various (V)	24	1.9	11	0.4	3	0.7	38	0.9
Others	29	2.3	11	0.4	1	0.2	41	0.9
Total	1246	100.0	2750	100.0	430	100.0	4426	100.0

comparisons of the approval or rejection status of the OLDU applications in relation to the licensing status of the drugs, for physicians' branches statistically significant differences were found ($P < 0.05$). This was due to a higher rate of rejection (6.0%) for the unlicensed drugs and applications made by surgeons. Among the top three diagnoses in OLDU applications, the "other-pulmonary heart diseases (I27)" indication had more rejections than SLE and MS. Among the top three prescribed OLDU drugs, MMF was more highly approved than rituximab and iloprost trometamol (Table 3).

The top three prescribed drugs (MMF, rituximab, and iloprost trometamol) were almost 1/3 of all OLDU drugs. There were statistically significant differences among these agents based on characteristics of patients' age and sex and also their physicians' affiliations. MMF was most prescribed to females (71.0%) among the three drugs. Iloprost trometamol was more prescribed to children (53.1%) than the other drugs. It was also found that the drug with the most OLDU applications from surgery and "nonuniversity healthcare centers" was iloprost trometamol (Table 4).

For the OLDU applications, the most commonly declared duration of therapy was in the range of 31–90 days (57.0%).

The top five diagnoses were further examined according to the ICD-10 classification. The applications were mostly from UHs for all five common indications (SLE, "other

Table 3. Comparison of the results of applications for off-label drug use (OLDU) based on some characteristics of the drugs, patients and their physicians.

n		Approval		Rejection		Statistics (chi-square)
		%	n	%	n	
Licensing status in Turkey	Licensed (n = 3468)	3314	95.6	154	4.4	P < 0.05
	Unlicensed (n = 945)	888	94.0	57	6.0	
Route of administration	Local (n = 42)	41	97.6	1	2.4	P > 0.05
	Systemic (n = 4384)	4173	95.2	211	4.8	
Patient's sex	Male (n = 2017)	1917	95.0	100	5.0	P > 0.05
	Female (n = 2409)	2297	95.4	112	52.8	
	Total (n = 4426)	4214	95.2	212	4.8	
Patient's age group	<18 years (n = 1246)	1195	95.9	51	4.1	P > 0.05
	18–64 years (n = 2750)	2610	94.9	140	5.1	
	≥65 years (n = 430)	409	95.1	21	4.9	
Physician's branch	Internal medicine (n = 4282)	4085	95.4	197	4.6	P < 0.05
	Surgery (n = 144)	129	89.6	15	10.4	
Physician's working place	University (n = 3586)	3413	95.2	173	4.8	P > 0.05
	Others (n = 840)	801	95.4	39	4.6	
Top three diagnoses	Systemic lupus erythematosus (M32) (n = 436)	428	98.2	8	1.8	P < 0.05
	Other pulmonary heart diseases (I27) (n = 230)	201	87.4	29	12.6	
	Multiple sclerosis (G35) (n = 195)	192	98.5	3	1.5	
	Total (n = 861)	821	95.3	40	4.7	
Top three drugs	Mycophenolate mofetil (L04AA06) (n = 607)	606	99.8	1	0.2	P < 0.05
	Rituximab (L01XC02) (n = 445)	413	92.8	32	7.2	
	Iloprost trometamol (B01AC11) (n = 254)	229	90.2	25	9.8	
	Total (n = 1306)	1248	95.6	58	4.4	

Table 4. Comparison of the top three off-label drugs based on some characteristics of patients and their physicians.

n		Mycophenolate mofetil (L04AA06) (n = 607)		Rituximab (L01XC02) (n = 445)		Iloprost trometamol (B01AC11) (n = 254)		Statistics (chi-square)
		%	n	%	n	%	n	
Patient's sex	Male	176	29.0	211	47.4	100	39.4	P < 0.05
	Female	431	71.0	234	52.6	154	60.6	
Patient's age group	<18 years	55	9.1	41	9.2	135	53.1	P < 0.05
	18–64 years	522	86.0	338	76.0	100	39.4	
	≥65 years	30	4.9	66	14.8	19	7.5	
Physician's branch	Internal medicine	605	99.7	441	99.1	229	90.2	P < 0.05
	Surgery	2	0.3	4	0.9	25	9.8	
Physician's working place	University	519	85.5	382	85.8	147	57.9	P < 0.05
	Other healthcare center	88	14.5	63	14.2	107	42.1	

PHD", MS, "congenital malformations of cardiac septa", and "transplanted organ and tissue status" at 91.7%, 66.1%, 75.6%, 56.7%, and 75.0%, respectively).

Of the 445 OLDU applications with SLE diagnosis, 438 (98.4%) applications were approved. Most of the patients (86.1%) were female and they were mostly between 18 and 64 years old (89.7%). The most frequent applicants were rheumatologists (77.1%). The majority of the off-label drugs prescribed for SLE were licensed in Turkey (98.9%). MMF (78.9%) was the most frequently prescribed off-label drug for SLE (Table 5).

Of the 419 OLDU applications with "other PHD" diagnosis, 390 (93.1%) applications were approved. Most of the patients (59.7%) were female and they were mostly under 18 (40.6%). Most of the applicants were pediatric cardiologists (42.7%). The majority of the off-label drugs prescribed for other PHD were licensed in Turkey (98.6%). Iloprost trometamol (59.9%) was the most frequently prescribed off-label drug for other PHD diagnoses (Table 5).

Of the 213 OLDU applications with MS diagnosis, 210 (98.6%) applications were approved. Most of the patients (67.6%) were female and they were mostly between 18 and 64 years old (92.5%). The most frequent applicants were neurologists (97.2%). The majority (81.2%) of off-label drugs prescribed for MS were unlicensed in Turkey. Dalfampridine (75.1%), was the most frequently prescribed off-label drug for MS (Table 5).

Of the 201 OLDU applications with a diagnosis of "congenital malformations of cardiac septa", 199 (99.0%) applications were approved. Most of the patients (59.2%) were female and they were mostly under 18 years (59.7%). Most of the applicants were pediatric cardiologists (63.7%). The majority (99.0%) of the off-label drugs prescribed for this diagnosis were licensed in Turkey. Iloprost trometamol (73.6%) was the most frequently prescribed off-label drug (Table 5).

Of the 184 OLDU applications with "transplanted organ and tissue status" diagnosis, 172 (93.5%) applications were approved. Most of the patients (60.3%) were male and they were mostly between 18 and 64 years old (73.9%). The most frequent applicants were nephrologists (25.0%). The majority of the off-label drugs prescribed for this diagnosis were found to be licensed in Turkey (92.8%). MMF (16.8%) was the most frequently prescribed off-label drug (Table 5).

4. Discussion

Evaluation of OLDU can provide insights and assistance for the healthcare providers who are making the regulations and in addition can raise the awareness of physicians about disorders, their treatment challenges, and the potential treatment alternatives. We have conducted a detailed analysis of the OLDU applications without any restrictions regarding age group, healthcare facility, or diagnosis. Except for earlier studies that evaluated OLDU in the specific fields of neonatology, oncology, and endocrinology, this is the first study to investigate the extent of OLDU at a national level in Turkey (15,19,20).

The present study showed that the most common reason for the rejection of OLDU applications was "standard treatment options had not been tried before the OLDU application was sent" (Table 1). Similar reasons were also reported in a recent study that assessed endocrinological OLDU applications in Turkey (20). In addition, the proportion of rejection of OLDU application was higher

Table 5. Distribution of the most frequent drugs prescribed for the five most frequent diagnoses in off-label drug use (OLDU) applications.

Rank	Diagnoses (ICD- 10)	Drugs (ATC code)	Applications, n (%)
1	Systemic lupus erythematosus (M32)	Mycophenolate mofetil (L04AA06)	351 (78.9)
		Rituximab (L01XC02)	69 (15.5)
		Immunoglobulin i.v. (J06BA02)	11 (2.5)
		Others	14 (3.1)
		Total	445 (100.0)
2	Other pulmonary heart diseases (I27)	Iloprost trometamol (B01AC11)	251 (59.9)
		Sildenafil (C02KX)	92 (22.0)
		Bosentan (C02KX01)	65 (15.5)
		Others	11 (2.6)
		Total	419 (100.0)
3	Multiple sclerosis (G35)	Dalfampridine (N07XX07)	160 (75.1)
		Fingolimod (L04AA27)	18 (8.5)
		Natalizumab (L04AA23)	12 (5.6)
		Others	23 (10.8)
		Total	213 (100.0)
4	Congenital malformations of cardiac septa (Q21)	Iloprost trometamol (B01AC11)	148 (73.6)
		Sildenafil (C02KX)	41 (20.4)
		Bosentan (C02KX01)	10 (5.0)
		Others	2 (1.0)
		Total	201 (100.0)
5	Transplanted organ and tissue status (Z94)	Mycophenolate mofetil (L04AA06)	31 (16.8)
		Sirolimus (L04AA10)	26 (14.1)
		Rituximab (L01XC02)	24 (13.0)
		Others	103 (56.1)
		Total	184 (100.0)

in surgery than internal medicine (Table 3).These findings point out the need for physicians' specific attention and focus group educational programs regarding potential causes of refusal of OLDU applications.

"Antineoplastic and immunomodulating drugs" (54.3%) were found as the most common off-label drugs in all age groups (Table 2). On the other hand, oncology and pediatric oncology were ranked as 6th and 18th in the distribution of OLDU applications by physicians' specialties (Figure 2). These findings showed that "antineoplastic and immunomodulating drugs" were mostly preferred by the nononcologist specialists in OLDU applications.

Off-label drug use applications were found to be increased during the spring and summer (Figure 1). These seasonal variations may be related to the increase in the activities of common diagnoses found in this study, such as SLE and MS, which are characterized by attacks and remissions (21,22).

Off-label prescription with respect to age groups is a common practice worldwide, particularly for children and the elderly, who are commonly excluded from the clinical trials necessary to obtain approval by regulatory authorities. Notably, recent studies that have investigated OLDU mainly focused on the pediatric age group (7–15).

On the other hand, a limited number of studies have been published regarding OLDU in the elderly. A study of elderly patients admitted to three wards of a hospital in the United Kingdom found that 84% of the hospitalized elderly patients were prescribed drugs in an off-label or unlicensed way (23). Another study investigating the off-label use of second-generation antipsychotic agents among elderly nursing home residents in the United States reported that 86% of these agents prescribed to the elderly were for off-label indications (24). In our study, off-label drugs were mostly prescribed for patients aged 18 to 64 years (62.1%), followed by the pediatric age group (28.2%). Contrary to the studies in the literature, the elderly constituted a small proportion (9.7%). It is an interesting finding that although drug use is common in the elderly (25,26), we found a lower OLDU rate for this age group in our study. On the other hand, the overbalance of off-label use in young adults and children and the female predominance in the applications could be associated with the nature of the most common diagnoses found in this study, such as SLE, MS, and other PHD (27–29).

UHs are tertiary healthcare centers that have the healthcare service capacity to treat more serious illnesses and embody specific subspecialties. In concordance with this, we found that OLDU applications were most frequently from UHs (81.0%).

When OLDU applications are analyzed according to the diagnoses, applications with the most common five diagnoses, respectively SLE, other PHD, MS, congenital malformations of cardiac septa, and transplanted organ and tissue status, constituted one-third of all applications (33.1%). When the distributions of the first three off-label drugs prescribed for the five most frequent diagnoses were evaluated, it was found that MMF was in first place for SLE and transplanted organ and tissue status, iloprost trometamol for other PHD and congenital malformations of cardiac septa, and dalfampridine for MS (Table 5).

SLE is an autoimmune disease with considerable morbidity and mortality. First-line therapies for patients with SLE consist of hydroxychloroquine, corticosteroids, and nonsteroidal antiinflammatory drugs (30). Even though the pathogenesis of SLE is not fully understood, current experimental evidence suggests that B lymphocytes play an important role in the pathogenesis by producing autoantibodies (31), which supports the potential usefulness of B cell depletion therapy for SLE. Rituximab is a chimeric monoclonal antibody that targets the human CD20 antigen, which is found on the surface of B lymphocytes. Rituximab has been increasingly used off-label for the treatment of certain conditions such as autoimmune diseases, dermatological conditions, and solid organ transplantations (32–34).

Following the first report in 2002 (35), a large number of studies have been carried out on the off-label use of rituximab in patients with SLE. In a study that systematically examined the case reports and observational studies related to the use of rituximab between 2002 and 2007, it was reported that a total of 188 patients were treated with rituximab and 91% of them showed significant improvement of one or more systemic symptoms of SLE (36). Although rituximab has given successful results in the treatment of severe SLE symptoms in case series, two randomized placebo-controlled trials could not show a significant benefit from rituximab in patients with SLE and lupus nephritis (37,38). In Australia, a retrospective study analyzing the off-label use of rituximab in a tertiary care hospital reported that favorable outcomes were obtained in the prevention and treatment of renal transplant rejection and SLE nephritis (39). We found in our study that rituximab is among one of the most commonly prescribed off-label drugs for SLE and transplantation indications in line with the international literature reporting increased off-label use of rituximab.

In this study, MMF was the most frequently preferred drug both for SLE and transplantation indications (Table 5). MMF is an immunosuppressive drug that is approved for the prevention of allograft rejection after kidney, liver, and heart transplantation. MMF shows its activity by suppressing the B and T lymphocyte proliferation and the production of autoantibodies, and it gives successful results in autoimmune diseases such as SLE, RA, and systemic vasculitis (40). On the other hand, there are not enough data concerning the use of MMF for nonrenal manifestations (hematologic, pulmonary, cutaneous, neuropsychiatric, myocardial, etc.) in SLE patients (41).

The diagnosis of other PHD involves primary and secondary pulmonary hypertension (PHT), which are characterized by increased pressure in the pulmonary circulatory system (42). Inhaled iloprost trometamol is a prostacyclin analog that is approved for the treatment of primary (idiopathic or familial) PHT and PHT associated with scleroderma. Particularly in children, the absence of an approved therapy for PHT results in off-label use of inhaled iloprost in this age group (43). In line with this, we found that the patients with the diagnosis of other PHD were mostly under the age of 18 (Tables 4 and 5).

MS is a neurological disorder that affects the optic nerves and spinal cord and is characterized by axonal damage, demyelization, and inflammation. Dalfampridine, a potassium channel blocker, was approved by the FDA in order to improve walking in patients with MS (44). However, dalfampridine is included in the scope of OLDU, because it is unlicensed in Turkey, as seen in this study.

The OLDU application process can be influenced by many factors, such as drug- and disease-centered, patient-related, and the physician's preferences. Indeed, this study

showed that the approval proportions were higher for licensed drugs, drugs requested by internal medicine, and drugs for the treatment of MS and SLE (Table 3). Therefore, before submitting applications to the OLDU process, physicians should be aware of the OLDU status of drugs that are especially related to their specialty.

There are some limitations of our study that need to be mentioned. We could not carry out a comprehensive evaluation regarding the underlying secondary diseases of patients. Furthermore, we could not assess the adverse reactions due to OLDU.

In conclusion, the present study has made a comprehensive evaluation of the OLDU applications that were made to the TMMDA in 2011 and has presented important findings about OLDU. OLDU showed institutional, seasonal, and some demographical differences. It is expected that this study will provide important contributions to physicians working in the relevant area with respect to treatment alternatives of diseases with treatment challenges.

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