Utilization of biotechnological drugs in rare diseases requiring use of off-label drugs in children in Turkey

Abstract

Background/aim: Pediatric patients, especially with rare diseases, represents a population which has high tendency towards off-label drug use (OLDU) and needs a careful practice of pharmacotherapy than in adults. We aimed to investigate biotechnological drug use in children with rare diseases requiring OLDU.

Materials and Methods: This retrospective study examined all single-diagnosed OLDU applications (n=5792) for 4992 children (<18-year) in Turkey. Applications of rare diseases were selected, and their descriptive characteristics were examined including demographic features of patients, biotechnological drug utilization status, and disease categories. The off-label status of the drugs at the end of 2020 was also examined.

Results: In total, 77.7% (n=4501) of OLDU applications were made for rare diseases. Biotechnological drug use was higher in rare disease applications than in non-rare diseases (37.9% vs. 19.2%, respectively; $p<0.0001$). Canakinumab was the top applied biotechnological drug (73.2%). Compared to that in small-molecule drugs, the mean age of patients was higher in biotechnological drug-containing applications (8.1±5.3 vs 9.7±4.9, respectively; $p<0.0001$). Biotechnological drug use was higher in non-neoplastic rare diseases (40.3%) than in neoplastic rare diseases (26.4%), ($p<0.0001$). At the end of the year 2020, the approval status of the off-label indications covered in 2016 was significantly higher for rare (24.4%) vs. non-rare (5.2%, $p<0.0001$) diseases and for biotechnological (32.3%) vs. small-molecule (13.9%, $p<0.0001$) drugs. In total, 87.7% of the drugs would have to be still used in the off-label setting at the end of 2020.

Conclusion: It was seen that more than three-quarters of the pediatric OLDU applications are for rare diseases and the need for biotechnological OLDU in this group is almost 2-fold of small-molecule drug use. While further projected findings imply a higher approval tendency towards for rare diseases and biotechnological drugs, there seems to be more room for improvement for pediatric drug use.

Key words: Off label drug use, pediatrics, rare disease, biotechnological drugs, canakinumab

1. Introduction

Rare diseases, despite with differences in its definition, are generally considered to cover diseases affecting no more than 5/10.000 people in the community [1]. Studies show that rare diseases in childhood may cause sequelae in children and pose serious psychological and economic burden on both families and all stakeholders of the health system [1,2]. A major attempt to alleviate this burden is obviously the novel drug development studies for the treatment of rare diseases. However, apart from conductibility of a limited number of studies in children due to ethical reasons, it is known that clinical studies in rare diseases has additional methodological challenges and the pharmaceutical industry does not find it attractive always to direct research and development incentives to this group [3,4]. Although granting extra privileges to clinical trials for rare diseases has been on the agenda of health authorities for a long time, off-label drug use (OLDU) still remains prevalent in diagnoses within the scope of rare diseases [3–5]. Moreover, it is estimated that the high OLDU burden already existing in children may escalate even more in the case of rare diseases [3,6–8].

Data on pediatric usage of biotechnological drugs is very limited [9]. Biotechnological drug is defined as “a human medicinal product whose active ingredients or substances were produced in or purified from a biological source, where the quality, manufacturing process, and audits is demonstrated by means of physicochemical and biological tests” [10]. Biotechnological drugs are among the treatment options in a wide range of conditions, including cancers, rheumatological/immunological diseases, and nephrological diseases and they can also be used in the treatment of many rare diseases in these areas [11,12]. Available literature does not have shown any study about the management of rare diseases via off-label drugs with a particular focus on biotechnological products [1,3]. In fact,

58 biotechnological drug utilization data is needed in rare diseases to overcome therapeutic
59 challenges in these diseases especially in the pediatric population. In this study, we
60 aimed to evaluate the use of biotechnological drugs for the rare disease in children who
61 needed off-label drugs.
62

2. Materials and Methods

2.1.Data collection

In this cross-sectional study, we examined OLDU applications that were conducted between 1 January and 31 December 2016 in Turkey. Applications for OLDU are submitted to Turkish Medicines and Medical Devices Agency (TMMDA) of Ministry of Health to be evaluated and approved [13]. We reviewed single-diagnosed applications for pediatric population (<18 years) submitted by pediatricians, subspecialists of pediatrics, child psychiatry, and pediatric surgeons in 2016 (n=8272). In this dataset, those applications belonging to a patient for the same drug during the study period were determined as a repeated application and excluded (n=2480).

The applications were grouped according to their indicated diagnoses as rare and non-rare diseases. Whether the diseases in the applications were rare or not were decided according to the Orphanet database supported by the European Commission [14]. The biotechnological or small-molecule status of the applied drugs was determined, and their distribution was compared according to the groups. In addition, single or multiple drug application status was compared in OLDU applications for rare or non-rare diseases. The age, gender characteristics of the patients, and the distribution of the physician's specialties were compared according to the diagnosis groups.

OLDU applications for rare diseases were further analyzed in detail. The drugs in these applications were grouped according to the "Anatomical Therapeutic Chemical" (ATC) coding system. The first five most common biotechnological and small-molecule active substances were identified. The distribution of the drugs at ATC-1 level was evaluated and the percentage of biotechnological or small- molecule drugs in each sublevel was determined. In addition, ATC-1 level status within biotechnological and small-molecule drugs was evaluated. The most frequently applied biotechnological and

small-molecule drug in off-label setting was determined for each ATC-1 group. The mean age of patients for whom OLDU was applied and their biotechnological and small-molecule drug status was compared for each ATC-1 group.

The distributions of the main diagnosis groups according to "International Statistical Classification of Diseases (ICD)" in rare disease applications were examined according to their status as biotechnological or small-molecule drugs. The most frequently applied biotechnological or small-molecule drugs were examined in each main diagnosis group. The diagnoses were also classified as neoplastic and non-neoplastic and were compared in terms of off-label biotechnological drug use. Single/multiple OLDU applications were compared whether these were made for biotechnological drugs or not. These applications were also evaluated in terms of off-label drugs' pharmaceutical form and route of administration.

As the regulatory approval status of the drugs may alter by time owing to the completion of trials, we also examined the off-label status of the drugs at the end of the year 2020 in order to reflect the progression of the safe and effective use of drugs for children. For this purpose, the approval status of all drugs applied for all off-label indications in 2016 was analyzed as if they were applied at the end of the year 2020. This projection was detailed for rare vs. non-rare diseases and for biotechnological vs. small-molecule drugs.

2.2. Statistical analysis

Statistical analyses were made through SPSS 24.0 software. Categorical variables were expressed as number/percentage and continuous variables were mentioned as mean/standard deviation. The comparisons between categorical and continuous variables were analyzed via chi-square and t-test, respectively. An overall 5% type-I error level was used to infer statistical significance.

2.3. Ethical approval

The data were collected after the study was approved by Ethics Committee of Institute of Health Sciences of Marmara University (Approval No: 11.09.2017/171).

3. Results

3.1. Main findings

A total of 5792 OLDU applications were detected for 4992 children in the study period. It was determined that the applications with rare diseases constituted 77.7% (n=4501) and that these applications were made for 3894 (78.1%) patients. There was no significant difference in terms of age (8.6±5.1 and 8.5±5.0, respectively) and gender (boys, 52.4% and 55.4%; respectively) between children with rare diseases and non-rare diseases in their applications ($p>0.05$). The need for multiple distinct off-label drugs for one patient during the year was similar for rare and non-rare diseases ($p>0.05$). The percentage of biotechnological drug use for rare diseases was significantly higher than that for non-rare diseases (37.9% and 19.2%, respectively), ($p<0.0001$), (Table 1). OLDU applications were made most frequently by pediatric rheumatologists/nephrologists (28.1%) and child neurologists (39.0%) in rare and non-rare diseases, respectively.

3.2. Rare diseases

When the drugs in the applications were examined at the ATC-1 level, the most commonly encountered groups were “L-Antineoplastic and immunomodulating agents” (48.2%), “A-Alimentary tract and metabolism” (12.4%) and “B-Blood and blood-forming organs” (7.4%). When biotechnological drug ratio was examined in each subgroup at ATC-1 level, the highest rate was “H-Systemic hormonal preparations” (63.2%), followed by "L-Antineoplastic and immunomodulating agents" (57.5%) and "B-Blood and blood-forming organs" (27.5%), (Figure 1).

When the distribution of biotechnological and small-molecule drugs in the applications was analyzed at the ATC-1 level, it was found that both biotechnological and small-molecule drugs more commonly belong to the “L-Antineoplastic and

142 immunomodulating agents" group (73.2% and 33.0%, respectively). Canakinumab and
143 mycophenolate were the most common biotechnological (20.8%) and small-molecule
144 (29.6%) drugs in this group. The mean age of the patients using biotechnological drugs
145 (9.7±4.9 years) was significantly higher than that using small-molecule drugs ((8.1±5.3
146 years; p<0.0001). This age difference between biotechnological and small-molecule
147 drugs was preserved in patients using "A-Alimentary tract and metabolism"
148 (p<0.0001), "J-Anti-infectives for systemic use" (p=0.008), and "M-Musculoskeletal
149 system" drugs at ATC-1 level (p=0.025), (Table 2).

150 The most common five biotechnological drugs used off-label were canakinumab
151 (15.3%), rituximab (13.3%), eculizumab (11.2%), somatropin (10.0%), and anakinra
152 (7.9%). In small-molecule drugs, this ranking included mycophenolate (9.8%),
153 sapropterin (6.9%), iloprost (5.1%), sirolimus (4.0%), and tacrolimus (3.5%).
154 "Endocrine, nutritional and metabolic diseases" main ICD group were the most
155 commonly indications for both biotechnological (33.9%) and small-molecule drugs
156 (27.2%). The most commonly encountered biotechnological and small-molecule drug
157 in this diagnosis group was canakinumab (31.7%) and sapropterin (25.1%),
158 respectively (Table 3).

159 It was detected that 17.5% of the rare disease were neoplastic in nature. The use of
160 biotechnological drugs was significantly lower in neoplastic diseases (26.4%) than that
161 in non-neoplastic ones (40.3%), (p<0.0001). In rare diseases requiring multiple OLDU
162 applications, biotechnological drug utilization (31.1%) was significantly lower
163 compared to that in the diseases which needed only a single off-label drug (40.0%),
164 (p<0.0001), (Figure 2a and Figure 2b).

165 Analysis of off-label drug administration routes showed that the drugs were
166 administered with injectable forms (49.1%), followed by enteral (47.1%) and other

administration routes (3.8%). In almost all biotechnological drug applications, the route of administration was injection (99.6%), whereas the injectable forms constitute 18.2% of small-molecule drugs.

3.3. Projected off-label status

We identified that 20.1% (n=1163) of the off-label indications covered in 2016 would have been approved as of the 1 January 2021. This projection was significantly more pronounced for rare diseases (24.4%) vs. non-rare diseases (5.2%, $p<0.0001$) and for biotechnological drugs (32.3%) vs. small-molecule drugs (13.9%, $p<0.0001$). In terms of the all drugs applied for off-label use in 2016 (n=353), twelve drugs (3.4%) had been approved for those particular indications until 2021 whereas 33 drugs (9.3%) were partially approved for certain indications. The rest (87.3%) was observed to be used in the off-label setting until the end of year 2020.

4. Discussion

This was the first study that focused off-label biotechnological drug use in children at national level, where important findings were obtained that may help to manage rare diseases. Pediatric population requires additional care in drug use and frequently needs OLDU [3]. The management of rare diseases in this group, which already has limited drug use data, is a special area with unique balances. Despite the incentives for clinical trials in rare diseases, the number of drugs approved for use in these diseases still remains low [15,16]. Considering that 95% of rare diseases do not have approved treatment, it is often expected to refer to OLDU in rare diseases in children [15,17]. This was supported by our finding that more than three quarters of OLDU applications in children were rare diseases. Although rare diseases are thought to affect a restricted population, 8% of the society were reported be faced with a congenital or acquired rare disease [2,18]. Around 8000 rare diseases have been described worldwide, 70% of which had a pediatric onset [15,17]. Considering the population of children in Turkey [19], rare diseases (n=3894) that need to be referred to the health authority to be managed by off-label drugs can be said to affect 17 out of every 100,000 children.

As with this study, another study conducted in Turkey in 2015 on the use of OLDU in children reported that applications were made more frequently for male patients [8]. Although this may suggest a country-specific difference at first glance, studies in other countries based on drug use in children also reported similar findings, especially in younger children [20,21].

Biotechnological drug use is on an increasing trend across the globe. Similarly, studies focused on new drug development show that the number of biotechnological drugs increases with a rising momentum [22,23]. It is known that many new drugs have been developed in recent years and biotechnological methods have been used in this

process, especially in rare diseases which are a common area of need for alternative treatment [15,23]. In our study, the use of off-label biotechnological drugs in rare diseases is approximately twice that of non-rare diseases, indicating the need for biotechnological drugs in the management of rare diseases in children. Although no enough data has been found on the overall biotechnological drug utilization in children, it has been reported that it is frequently used in immunocompromised conditions and that childhood cancers are one of the areas where biotechnological drug use is most needed [9]. Considering the area covered by these conditions in rare diseases, it can be said that the findings obtained in our study are partially compatible with the literature. On the other hand, it can be stated that when off-label drugs are required in rare diseases, it is important that above one of the three drugs applied is biotechnological in terms of quantitative representation of the need in this area. This high utilization rate and further pharmacoepidemiological study findings are expected to provide the basis for on-label use of biotechnological drugs in rare diseases. Moreover, despite this increasing trend of biotechnological drug use in rare diseases, information on the pharmacokinetics, pharmacodynamics and pharmaceutical application of these drugs is still limited in children -especially those with rare diseases- compared to small-molecule drugs [9]. Besides, the use of biotechnological drugs other than the indications for which they are licensed takes place through extrapolation [24]. Considering their use in rare diseases, it may be suggested that the existing risk management plans of these drugs may be more likely to accompany various uncertainties in rare disease-oriented practice and that additional challenges may arise, indicating the need for additional measures.

Consistent with the results of the previously reported OLDU-focused study in Turkey, we determined that nearly half of the drugs applied for rare diseases belonged

231 to the antineoplastic and immunomodulating agents [7]. This main group was ranked
232 first in both biotechnological and small-molecule drugs for rare disease applications.
233 This may have been due to the procedure related to the application of OLDU in Turkey,
234 rather than the fact that biotechnological drug use in rare diseases brought this main
235 group to the top rank. In fact, the literature findings outside Turkey showed that the
236 mostly encountered off-label used drugs in children indicated other drug groups [6,25].
237 This can be attributed to the diversity of different countries in OLDU-related practices.
238 For instance, drugs in antineoplastic and immunomodulating agents group can be used
239 after meeting more rigorous clinical requirements than do other drugs due to their
240 difficulty in safety, cost, and compliance [9]. The fact that the OLDUs included in our
241 study did not cover “routine use of off-label drugs that do not require additional
242 procedures”, but consisted of OLDUs that are subject to the application to the health
243 authority may have led to this risky drug group being the main group most commonly
244 encountered.

245 Although the definition of orphan drug covers drugs from different groups for
246 different reasons, it is a commonly used concept for many drugs used in the treatment
247 of rare diseases due to its small market share [16]. It is noteworthy that in our study,
248 the most common biotechnological drug was canakinumab, and the small-molecule
249 drug was mycophenolate. In addition, canakinumab was observed to be the most
250 common biotechnological drug in applications containing endocrine, nutritional and
251 metabolic diseases which is the most common diagnostic group. In fact, both these
252 drugs were reported to be at the top in other studies on OLDU in Turkey [7,8,26].
253 Canakinumab, a recombinant human monoclonal antibody, is an interleukin-1 beta
254 inhibiting orphan drug. Systemic juvenile idiopathic arthritis and extremely rare
255 cryopyrin-associated periodic syndromes (CAPS) constitute the main indications of this

drug [27]. Another monoclonal antibody, eculizumab, which was reported to be the most frequently encountered drug in pediatric OLDU practice in Turkey [8], ranked third in our study.

The mean age of the patients that required off-label biotechnological drugs was observed to be higher than that of those requiring small-molecule drugs. This might be attributed to several reasons. The first may be that the diagnosis of diseases requiring biotechnological drugs, such as amyloidosis which is common in OLDU applications, can be diagnosed in older age groups [8,9,28]. Another important reason is that access, application, awareness, cost-effectiveness, reimbursement condition, etc. aspects of the small-molecule drugs can bring up its use before biotechnological drugs [1,29]. Therefore, this age-related condition can be explained by the fact that physicians are likely to apply for biotechnological drugs later for children with rare diseases requiring OLDU.

The status of neoplastic cases in rare diseases is another debatable point of the research. It was reported that 11.1% of rare diseases identified in Orphanet was neoplastic [18]. We found that around one-sixth (17.5%) of rare diseases have neoplastic origin. We further observed that biotechnological drugs were required less frequently for neoplastic rare diseases than non-neoplastic ones. Various studies reported that neoplastic diseases constituted the main indication group that had the highest number of drug development studies and orphan drug approval among rare diseases [4,16,23]. This difference seems to suggest that there may be more alternative drugs for the treatment of neoplastic rare diseases.

The high share of nearly 80% covered by rare diseases in OLDU raises the question of whether the management of rare diseases with OLDU is routine or a mandatory practice arising from seeking treatment. While the method of the study did not allow

for direct answer to this, we observed that one off-label drug was sufficient for at least one year in three out of every four applications in both rare and non-rare diagnoses. This shows the tendency of the situation in the diseases that need OLDU to be partially controlled with a single off-label drug. Accordingly, it can be inferred that management of these diseases could be maintained routinely with OLDU, rather than seeking treatment, at least during the study period, but this was not unique to rare diseases. On the other hand, it was determined that biotechnological drug use in rare diseases requiring multiple applications of OLDU was lower than those requiring application for a single drug. This difference may be related to the tendency of physicians not to replace biotechnological drugs or not to add new biotechnological drugs in the same year in a sensitive therapeutic area like rare diseases. In other words, it can be said that although biotechnological drugs are often used in rare diseases, the physicians tend to insist more on their off-label drug choices. These findings highlight the importance of investigating the use of off-label biotechnological drugs in rare diseases.

Projected approval status of the OLDU showed that one-fifth of this special drug use turned into routine clinical practice between 2016 and 2021. We observed that this possibility was near 5-fold higher in rare diseases and 2.3-fold higher for biotechnological drugs, which seems to be consistent with ongoing efforts in these therapeutic areas [15,16,23]. On the other hand, the fact that only 12.7% were approved or partially approved during 4 years may suggest that there is further room for improvement for pediatric OLDU.

Various research reported that the proportion of parenteral drugs prescribed by routine prescribing procedure in Turkey was between 4-6% [30]. However, in OLDU, which is a non-routine application, this rate was reported to escalate up to 38% [7], with no data on pediatric population. In our study, the distribution of injectable forms found

306 in rare diseases in children increased approximately 10 times of the routine practice,
307 and the share of enteral and injectable pharmaceutical forms was almost equal. This
308 situation can be partly explained by the fact that more than 1/3 of the drugs used in the
309 management of rare diseases with OLDU were biotechnological drugs in our study. We
310 further noticed that near all biotechnological drugs were administered to the patient in
311 injectable forms. In fact, although various studies are under way to deliver
312 biotechnological drugs in different pharmaceutical forms, intravenous and
313 subcutaneous routes are still the most common ways of administration in
314 biotechnological drug [31]. On the other hand, we observed that the proportion of
315 injectable drugs in off-label use of small-molecule drugs in children was approximately
316 five times higher than that of routine use. This suggests that injectable pharmaceutical
317 forms are more common in OLDU setting than in routine practice, even considering
318 only small-molecule drugs.
319 The main limitation of this research was that all of the data accessed were OLDU
320 applications with no other medical records of patients. Such lack of data may
321 underestimate the actual reasons that may have led the physician to apply for OLDU,
322 including prior drug use experiences for this indication, other drug use-related
323 ineffectiveness/adverse effects experience, or comorbid conditions. In addition, the use
324 of the Orphanet database in the classification of rare diseases can be considered as a
325 relative limitation because the rare diseases that do not exist in this database could not
326 be included.
327 In conclusion, the details of particularly biotechnological product-oriented
328 OLDU in pediatric rare diseases were described for the first time in a country-level. It
329 is observed that the majority of OLDU applications made for children consists of rare
330 diseases and that physicians tend to prefer biotechnological drugs more often in these

diseases. While projected findings imply a higher approval tendency towards for rare diseases and biotechnological drugs, the need for improvement still seems to remain for routine safe and effective pediatric drug use. Important findings obtained in the study, especially those specific to biotechnological drugs, are expected to help manage the pharmacotherapy process in this fragile population in a way that would be less likely to require off-label drugs.

Conflict of interest:

The authors declare that they have no conflict of interest.

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Table 1. Patient and drug characteristics of OLDU applications based on rare disease status of the diagnoses.

		Indication for off-label drug use	
		Rare disease	**Non-rare disease**
Mean age, years (±SD)*		8.6±5.1	8.5±5.0
Gender*	Boys	2041 (52.4)	608 (55.4)
	Girls	1853 (47.6)	490 (44.6)
OLDU applications for	Single drug	3412 (75.8)	961 (74.4)
	Multiple drugs	1089 (24.2)	330 (25.6)
Class of drug§	Small-molecule	2797 (62.1)	1043 (80.8)
	Biotechnological	1704 (37.9)	248 (19.2)
Total OLDU applications, n (%)		4501 (77.7)	1291 (22.3)

OLDU, off-label drug use. *Age and gender data were based on the number of patients (n=4992); §p<0.0001

Table 2. Distribution of ATC-1 groups based on the biotechnological and small-molecule status of drugs in rare disease applications.

ATC-1 code	Biotechnological drugs			Small-molecule drugs		
	n, (%)	Mean age ± SD	Most frequent drug, (%)	n, (%)	Mean age ± SD	Most frequent drug, (%)
A	103, (6.0)	9.1±3.7#	Elosulfase alfa, (89.3)	454, (16.2)	5.0±4.5	Sapropterin, (42.5)
B	92, (5.4)	8.8±5.2	Coagulation factor VIIa, (32.6)	242, (8.7)	9.2±4.9	Iloprost, (59.1)
C	-	-	-	219, (7.8)	8.2±5.3	Bosentan, (33.8)
D	-	-	-	73, (2.6)	4.5±3.3	Isotretinoin, (95.9)
G	-	-	-	161, (5.8)	8.6±5.4	Sildenafil, (54.0)
H	172, (10.1)	9.3±4.3	Somatropin, (99.4)	100, (3.6)	9.2±5.2	Hydrocortisone, (28.0)
J	60, (3.5)	8.6±5.7#	Intravenous immunoglobulin, (86.7)	216, (7.7)	6.4±5.2	Valganciclovir, (37.5)
L	1248, (73.2)	9.8±5.0	Canakinumab, (20.8)	923, (33.0)	10.0±4.9	Mycophenolate, (29.6)
M	12, (0.7)	12.6±5.0#	Denosumab, (100,0)	128, (4.6)	8.8±3.8	Ataluren, (35.2)
N	-	-	-	68, (2.4)	9.2±4.9	Trihexyphenidyl, (22.1)
P	-	-	-	16, (0.6)	1.9±3.6	Pyrimethamine, (100.0)
R	13, (0.8)	9.3±5.9	Omalizumab, (53.8)	52, (1.9)	7.9±5.1	Mannitol, (51.9)
S	-	-	-	3, (0.1)	11.3±9.1	Dexamethasone, (66.7)
V	-	-	-	126, (4.5)	6.6±5.5	Calcium folinate, (52.4)
Others*	4, (0.2)	10.5±4.8	-	16, (0.6)	7.5±6.0	-
Total	1704, (100.0)	9.7±4.9#	Canakinumab, (15.3)	2797, (100.0)	8.1±5.3	Mycophenolate, (9.8)

*A, Alimentary tract and metabolism; B, Blood and blood forming organs; C, Cardiovascular system; D, Dermatological; G, Genito urinary system and sex hormones; H, Systemic hormonal preparations, excl. sex hormones and insulins; J, Anti-infectives for systemic use; L, Antineoplastic and immunomodulating agents; M, Musculoskeletal system; N, Nervous system; P, Antiparasitic products, insecticides and repellents; R, Respiratory system; S, Sensory organs; V, Various; *, Applications that have no defined ATC code).* * *Applications for drugs with no ATC code.* # *$p<0.05$ biotechnological vs. conventional drugs group.*

449 **Table 3.** Distribution of main diagnosis groups based on their biotechnological or
450 small-molecule drug status.

Main diagnosis group	Biotechnological drugs		Small-molecule drugs	
	n (%)	Most frequent drug, (%*)	n (%)	Most frequent drug, (%*)
Certain infectious and parasitic diseases	12 (0.7)	Interferon beta-1a, (41.7)	85 (3.0)	Valganciclovir, (44.7)
Neoplasms	208 (12.2)	Bevacizumab, (21.6)	579 (20.7)	Isotretinoin, (11.9)
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	350 (20.5)	Eculizumab, (50.0)	222 (7.9)	Eltrombopag, (26.6)
Endocrine, nutritional and metabolic diseases	578 (33.9)	Canakinumab, (31.7)	761 (27.2)	Sapropterin, (25.1)
Diseases of the nervous system	34 (2.0)	Rituksimab, (41.2)	205 (7.3)	Ataluren, (22.0)
Diseases of the eye and adnexa	2 (0.1)	Rituksimab, (100.0)	14 (0.5)	Idebenone, (35.7)
Diseases of the circulatory system	6 (0.4)	Dornase alfa, (50,0)	431 (15.4)	Iloprost, (32.7)
Diseases of the respiratory system	5 (0.3)	Dornase alfa, (40,0)	2 (0.1)	Pamidronic acid, (50.0)
Diseases of the digestive system	14 (0.8)	Denosumab, (50.0)	22 (0.8)	Mycophenolate, (36.4)
Diseases of the skin and subcutaneous tissue	5 (0.3)	Intravenous immunoglobulin, (20.0)	9 (0.3)	Flutamide, (44.4)
Diseases of the musculoskeletal system and connective tissue	330 (19.4)	Adalimumab, (29.7)	89 (3.2)	Mycophenolate, (69.7)
Diseases of the genitourinary system	127 (7.5)	Rituksimab, (84.3)	249 (8.9)	Mycophenolate, (56.6)
Certain conditions originating in the perinatal period	1 (0.1)	Factor VIII inhibitor bypassing activity, (100.0)	54 (1.9)	Calcium folinate, (29.6)
Congenital malformations, deformations and chromosomal abnormalities	32 (1.9)	Somatropin, (96.9)	75 (2.7)	Sirolimus, (36.0)
Total	1704 (100.0)	Canakinumab, (15.3)	2797 (100.0)	Mycophenolate, (9.8)

451 **Percentage of drugs that are used in the diagnosis group column below.*
452

Figures:

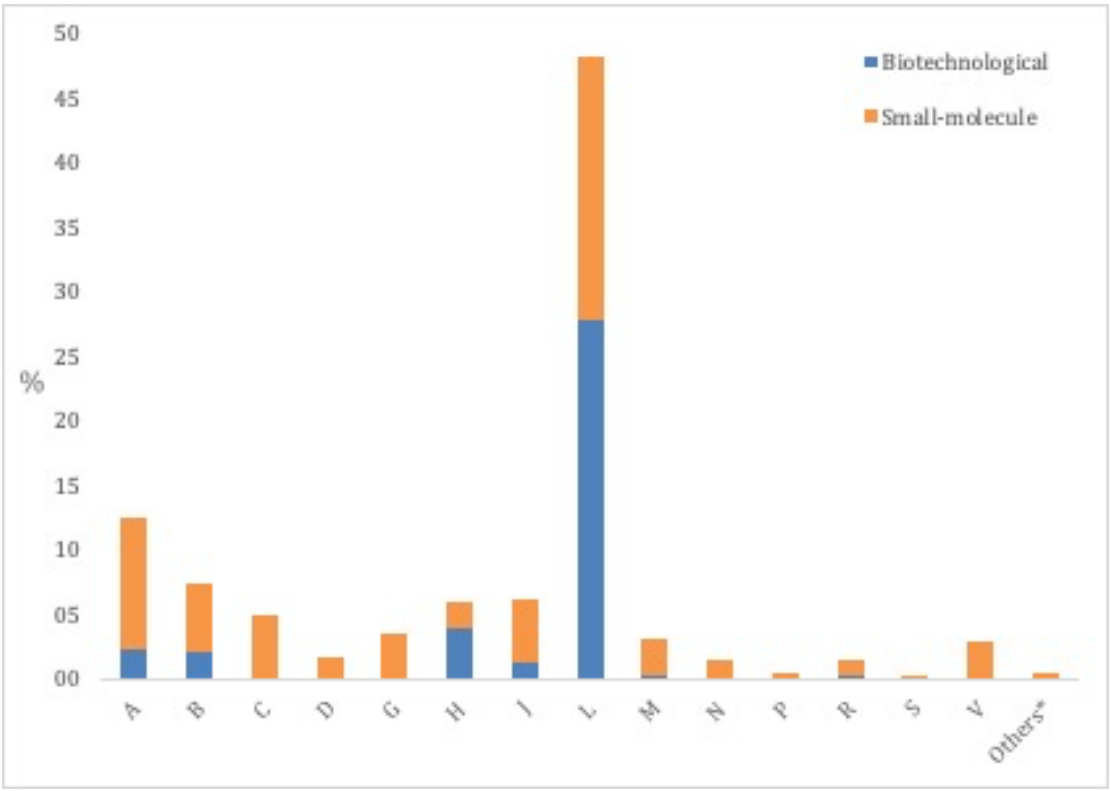

Figure 1. Distribution of the biotechnological and small-molecule drugs by ATC-1 category in rare disease applications *[A, Alimentary tract and metabolism (n=557); B, Blood and blood forming organs (n=334); C, Cardiovascular system (n=219); D, Dermatological (n=73); G, Genito urinary system and sex hormones (n=161); H, Systemic hormonal preparations, excl. sex hormones and insulins (n=272); J, Anti-infectives for systemic use (n=276); L, Antineoplastic and immunomodulating agents (n=2171); M, Musculoskeletal system (n=140); N, Nervous system (n=68); P, Antiparasitic products, insecticides and repellents (n=16); R, Respiratory system (n=65); S, Sensory organs (n=3); V, Various (n=126); *, Applications that have no defined ATC code (n=20)].*

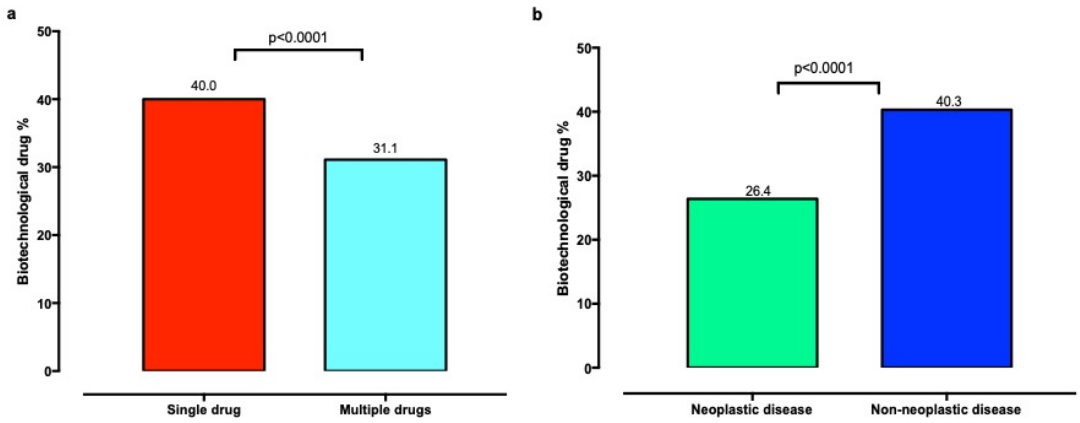

Figure 2. Comparison of biotechnological drug use in terms of a) rare disease requiring single drug vs rare disease requiring multiple drugs and b) neoplastic rare vs. non-neoplastic rare diseases.