



Brief report

[Translated article] Authorization of off-label drugs in a tertiary hospital: 5-year perspective

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A B S T R A C T

Introduction: The off-label use of drugs requires scientific support to balance risk/benefit, being limited to exceptional cases in which there are no therapeutic alternatives.

Methods: Retrospective descriptive study of the reports of the Pharmacy and Therapeutics Committee between 2018 and 2022 in a third level hospital; analyzing the requests, drugs, final opinion, reasons, level of evidence and economic impact.

Results: A total of 124 reports were analyzed, highlighting oncohematological (41.9%) and autoimmune (27.4%) diseases as main indications. Oncology (37.1%) and Pediatrics (18.5%) were the main applicants, with 87.9% for antineoplastic and immunomodulatory drugs. A total of 74.2% of the applications were approved due to lack of alternatives and solid evidence (phase II-III trials), while 25.8% were denied due to the availability of therapeutic options or insufficient evidence. In terms of cost, 53% of oncohematological drugs cost between €10,000–50,000/treatment and 62.1% of non-oncohematological drugs cost between €1,000–10,000/year. Approval of the rejected treatments would have generated an additional expenditure of €2,272,603.

Conclusion: An increase of up to four times in the evaluation of off-label use drugs was evidenced, with a high approval rate.

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Autorización de medicamentos de uso off-label en un hospital de tercer nivel: perspectiva de 5 años

R E S U M E N

Introducción: el uso off-label de medicamentos requiere respaldo científico para equilibrar el balance riesgo/beneficio, limitándose a casos excepcionales en los que no existen alternativas terapéuticas.

Métodos: estudio descriptivo retrospectivo de los informes de la Comisión de Farmacia y Terapéutica, entre 2018 y 2022, en un hospital de tercer nivel. Se analizaron las solicitudes, los medicamentos, el dictamen final y los motivos, el nivel de evidencia y el impacto económico.

Resultados: se analizaron 124 informes, destacando enfermedades oncohematológicas (41,9%) y autoinmunes (27,4%) como principales indicaciones. Oncología (37,1%) y Pediatría (18,5%) fueron los principales solicitantes, con un 87,9% de medicamentos antineoplásicos e inmunomoduladores. El 74,2% de las solicitudes fueron aprobadas por falta de alternativas y evidencia sólida (ensayos fase II-III), mientras que el 25,8% fueron denegadas por disponibilidad de opciones terapéuticas o evidencia insuficiente. En cuanto al coste, el 53% de los fármacos oncohematológicos tenían un precio comprendido entre 10.000 y 50.000 €/tratamiento, y el 62,1% de los no oncohematológicos entre 1.000 y 10.000 €/año. La aprobación de los tratamientos rechazados habría generado un gasto adicional de 2.272.603 €.

Palabras clave:

Uso off-label

Comisión de farmacia y terapéutica

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Conclusión: se evidenció un aumento de hasta 4 veces en la evaluación de medicamentos de uso off-label, con una alta tasa de aprobación.

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Introduction

Off-label drugs are those used in populations, at dosages or for indications other than those specified in the Summary of Product Characteristics. The latter is the most common form of off-label use.^{1,2} This clinical practice is considered a therapeutic alternative that must be supported by scientific evidence demonstrating a favourable benefit/risk ratio^{3,4}. One cause of off-label use is the underrepresentation or exclusion of certain minorities, such as paediatric, geriatric, or pregnant patients, in clinical trials (CTs)⁵. Moreover, there are delays in publishing CT results and in authorisation by regulatory agencies¹. Laboratories are also less likely to apply for authorisation for new indications due to the low cost of drugs already marketed for these indications or the small target patient population^{1,3}. Finally, terminal situations may prompt the off-label prescription of a drug⁵.

Consequently, off-label use is most prevalent in paediatrics, psychiatry, and oncohaematology⁶. The paediatric population is underrepresented in CTs due to high costs, limited results, and ethical implications⁷. The inclusion of psychiatric patients in CTs is limited due to ethical issues^{6,8}. Oncohaematological patients often exhaust standard treatment lines. However, due to the severity of their condition, they have easier access to drugs with clinical benefit, even if they have not been approved⁴.

In Spain, Royal Decree 1015/2009 sets out the regulations for drugs used in special situations. It states that the use of drugs for purposes other than those authorised is exceptional and restricted to situations in which there are no authorised alternatives available^{2,6}. In accordance with Law 41/2002, the physician must justify their use, inform the patient of the risk/benefit ratio, and obtain their consent⁹. The Pharmacy and Therapeutics Committee (PTC) is responsible for evaluating each request.² The PTC pharmacists prepare a report containing a proposed recommendation based on the patient's clinical situation, scientific evidence, the availability of authorised or unauthorised alternatives, cost, and convenience. The final decision is made by a vote among the other members of the PTC.

The aim of this study was to analyse the cases of off-label use requested from the PTC between 2018 and 2022, how these were resolved, and the level of evidence on which the final decisions were based.

Methods

A retrospective descriptive study of the reports produced by the PTC, focusing on the characteristics of requests, the requested drugs, and the final decision. The following information was collected for each request: total number of requests, year of request, the patient's sex and age, type of therapeutic indication, and the requesting department. The following information was recorded for the requested drugs: ATC classification, type of dispensing, additional monitoring status, orphan medicine, and year of authorisation. Treatment costs were also calculated on an annual basis for both non-oncohaematological drugs and complete oncohaematological drug treatment. The final decision and its justification were both recorded. Approved applications were categorised as follows: a) due to the absence of authorised therapies; or b) due to the absence of both authorised and unauthorised therapies. In the case of rejected applications: a) the availability of alternatives in the

Table 1

Characteristics of requests for off-label drugs evaluated (2018–2022).

	Requested n (%)	Approved n (%)
Total	124 (100)	92 (74.2)
<i>Year of application</i>		
2018	13 (10.5)	6 (46.2)
2019	12 (9.7)	10 (83.3)
2020	16 (12.9)	13 (81.3)
2021	32 (25.8)	23 (71.9)
2022	51 (41.1)	40 (78.4)
<i>Gender</i>		
Female	114 (91.9)	83 (72.8)
Male	10 (8.1)	9 (90.0)
<i>Age</i>		
Average	40	37
0–18 y	31 (25.0)	26 (83.9)
19–30 y	13 (10.5)	10 (76.9)
31–50 y	31 (25.0)	24 (77.4)
51–65 y	31 (25.0)	19 (61.3)
66–80 y	16 (12.9)	13 (81.3)
>80 y	2 (1.6)	0 (0)
<i>Therapeutic indication</i>		
Oncological	52 (41.9)	35 (67.3)
Autoimmune	34 (27.4)	29 (85.3)
Haematological	13 (10.5)	9 (69.2)
Dermatological	9 (7.3)	5 (55.6)
Infectious	7 (5.6)	7 (100)
Neurological	5 (4.0)	3 (60.0)
Cardiovascular	4 (3.2)	4 (100)
<i>Requesting department</i>		
Medical oncology	46 (37.1)	31 (67.4)
Paediatrics	23 (18.5)	19 (82.6)
Dermatology	18 (14.5)	12 (66.7)
Haematology	15 (12.1)	12 (80.0)
Nephrology	11 (8.9)	10 (90.9)
Digestive	2 (1.6)	0 (0)
Infectious diseases	2 (1.6)	2 (100)
Neurology	2 (1.6)	2 (100)
Mental health	2 (1.6)	1 (50.0)
Traumatology	1 (0.8)	1 (100)
Urology	1 (0.8)	1 (100)
Internal medicine	1 (0.8)	1 (100)
Characteristics of the requested medicine		
<i>ATC classification</i>		
L: Antineoplastic and immunomodulating agents	109 (87.9)	78 (71.6)
J: Anti-infectives for systemic use	4 (3.2)	4 (100)
N: Nervous system	3 (2.4)	2 (66.7)
V: Miscellaneous	3 (2.4)	3 (100)
B: Blood and haematopoietic organs	2 (1.6)	2 (100)
M: Musculoskeletal system	2 (1.6)	2 (100)
R: Respiratory system	1 (0.8)	1 (100)
<i>Type of dispensing</i>		
HD	64 (51.6)	43 (67.2)
H	60 (48.4)	49 (81.7)
Additional monitoring	40 (32.3)	24 (60.0)
Orphan drug	16 (12.9)	14 (87.5)
<i>Year of medicine authorisation</i>		
1995–1999	9 (7.3)	9 (100)
2000–2004	13 (10.5)	12 (92.3)
2005–2009	23 (18.5)	19 (82.6)
2010–2014	21 (16.9)	16 (76.2)
2014–2020	56 (45.2)	35 (62.5)
2020–2022	2 (1.6)	1 (50.0)

H, hospital use; HD, hospital diagnostic use.

Table 2

Outcomes of the requests following evaluation by the Pharmacy and Therapeutics Committee, justifications, and supporting evidence.

	Requested		Approved		Not approved	
	N	%	n	%	n	%
Total	124	100	92	74.2	32	25.8
<i>Reason for approval decision</i>						
a) absence of authorised therapies (although other off-label therapies are available)	29	23.4	29	31.5	–	–
b) absence of authorised and unauthorised therapies	63	50.8	63	68.5	–	–
<i>Reason for rejection decision</i>						
a) availability of alternative in the therapeutic arsenal	20	16.1	–	–	20	62.5
b) lack of evidence supporting a favourable benefit/risk ratio	10	8.1	–	–	10	31.3
c) unfavourable cost/benefit ratio	2	1.6	–	–	2	6.3
<i>Type of evidence supporting the decision</i>						
- Phase III CTs	45	36.3	32	34.8	13	40.6
- Phase II CTs	30	24.2	21	22.8	9	28.1
- Phase I-II CTs	5	4.0	3	3.3	2	6.3
- Phase I CT	1	0.8	1	1.1	0	0.0
- Observational study	8	6.5	7	7.6	1	3.1
- Case series	33	26.6	27	29.3	6	18.8
- Clinical cases	0	0.0	0	0.0	0	0.0
- No evidence	2	1.6	1	1.1	1	3.1

CTs, controlled trials; GVHD, graft-versus-host disease; HPT, haematopoietic precursor transplantation; CIDP, chronic idiopathic demyelinating polyneuropathy; CANDLE, atypical neutrophilic dermatosis-lipodystrophy-elevated temperature syndrome; GIST, gastrointestinal stromal tumour.

therapeutic arsenal (authorised or off-label); b) a lack of evidence to support a favourable benefit/risk ratio; or c) an unfavourable cost/benefit ratio. Finally, the level of evidence that supported the decision was analysed.

Results

A total of 124 reports relating to 50 drugs for 74 different indications were located. The distribution over time was as follows: 13 reports in 2018; 12 in 2019; 16 in 2020; 32 in 2021; and 51 in 2022.

Table 3

Economic impact of off-label drug applications and approval rate.

Oncohaematological treatments				
	Requested		Authorised	
	n	%	n	%
Total	66	53.2	44	47.8
<i>Cost of complete treatment, €</i>				
10–100	0	0.0	0	0.0
100–1000	3	4.5	3	6.8
1000–10,000	8	12.1	5	11.4
10,000–50,000	35	53.0	23	52.3
50,000–100,000	16	24.2	12	29.5
>100,000	4	6.1	0	0.0
Non-haematological cancer treatments				
	Requested		Authorised	
	n	%	n	%
Total	58	46.8	48	52.2
<i>Annual cost, €</i>				
10–100	2	3.4	2	4.2
100–1000	4	6.9	4	8.3
1000–10,000	36	62.1	31	64.6
10,000–50,000	10	17.2	7	14.6
50,000–100,000	5	8.6	4	8.3
>100,000	1	1.7	0	0.0

Table 1 shows the characteristics of the requests and the drugs requested. The most common indications were oncohaematological (41.9%), autoimmune (27.4%), and haematological (10.5%) diseases. The main requesting departments were oncology (37.1%) and paediatrics (18.5%). Most of the drugs (87.9%) belonged to ATC classification group L (antineoplastic and immunomodulating agents).

A total of 92 (74.2%) of the 124 evaluation reports were approved (**Table 2**). Of these, 68.5% were approved due to a lack of authorised alternatives. The remaining 31.5%, however, were approved despite the availability of other off-label therapies. A total of 34.8% of approvals were based on Phase III CTs, followed by case series (29.3%), and Phase II CTs (22.8%).

Of the 32 (25.8%) applications that were not approved, 20 (62.5%) were rejected due to available therapeutic alternatives, 10 (31.3%) due to a lack of evidence supporting a favourable benefit/risk ratio, and 2 (6.3%) due to an unfavourable cost/benefit ratio. Of the applications that were not approved, 40.6% were based on Phase III CTs, 28.1% on Phase II CTs, and 18.8% on case series.

Regarding the economic impact of off-label approval (**Table 3**), most requests for oncohaematological drugs were for between €10,000 and €50,000 per complete treatment (53%). A total of 44 of the 66 applications were approved. Of the 58 applications for non-oncohaematological treatments, 48 were approved, the majority of which ranged in cost from €1000 to €10,000/year (62.1%). A total of 5 applications with a high economic impact, exceeding €100,000, were submitted. Of these, 4 were for oncohaematological treatments. None were authorised. The total budgetary impact of the approved drugs was €2,265,670. It was estimated that the rejected treatments, if approved, would have entailed an additional expenditure of €2,272,603, increasing the total expenditure to €4,538,274.

Table 4 summarises the most frequently requested drugs, their indication, and the final decision. The drugs are listed in descending order by number of applications for their use: rituximab, baricitinib, dupilumab, pazopanib, pembrolizumab, cabozantinib, eculizumab, sorafenib, and vedolizumab.

Discussion

This study reveals a significant increase in the number of evaluations, with requests increasing fourfold. This increase could be due to the incorporation of new drugs¹⁰ and the emergence of new diseases, particularly the 2020 COVID-19 pandemic¹¹. Most of the drugs requested were in ATC classification group L, with indications for oncohaematological and autoimmune diseases, and associated with the medical oncology and paediatrics departments. These results are consistent with those reported in the study by Pérez-Moreno et al.¹, conducted in the same hospital in the period 2009 to 2011. Most of the drug requests for autoimmune diseases were issued by the paediatrics department, reflecting the hospital's role as a reference centre for paediatric autoimmune diseases.

The results show a high authorisation rate of close to 75%, demonstrating that the off-label drug request pathway remains a vital resource even a decade after the publication of RD 1015/2009². Similar results were shown in the study by Pérez-Moreno et al.¹, which could be explained by the complexity of patients in a tertiary hospital. Approval decisions tend to authorise drugs for indications where there are no treatment options or limited alternatives. In contrast, requests with available alternatives or an unfavourable cost–benefit ratio tend to be rejected. On the other hand, it is notable that the approval rate is high even with low-level scientific evidence, probably because there are no alternatives for patients who have exhausted all other therapeutic options. Analysis of the evidence for the rejected applications shows that it was mainly based on Phase II–III CTs. These requests were rejected despite being supported by scientific evidence because therapeutic alternatives with an adequate cost–benefit ratio that had not yet been tested in patients were available.

Table 4

Most frequently requested drugs: indications, final decision, justification, and evidence.

Drug	Number of applications	Year of application	Indications	Final decision	Justification for decision	Type of evidence
Rituximab	8	2020	Membranous nephropathy	Authorised	No available therapies and no other alternatives	Phase III CT
		2020	Nephrotic syndrome secondary to MCD	Authorised	No available therapies and no other alternatives	Observational studies
		2021	Nephrotic syndrome secondary to GVHD	Authorised	No available therapies and no other alternatives	Observational studies
		2021	Pauci-immune glomerulonephritis	Authorised	No available therapies, with alternatives for off-label use	Case series
		2021	CIDP	Authorised	No available therapies, with alternatives for off-label use	Case series
		2022	Autoimmune encephalitis	Authorised	No available therapies and no other alternatives	Observational studies
Baricitinib	5	2020	CANDLE	Authorised	No available therapies, with alternatives for off-label use	Case series
		2021			No therapies available and no other alternatives	
		2021	COVID-19 infection	Authorised	No therapies available and no other alternatives	Phase I-II CT
		2022	Vitiligo	Not authorised	Alternative available in the therapeutic arsenal	Phase III CT
Dupilumab	5	2021	Prurigo nodularis	Not authorised	Lack of evidence to support a favourable benefit/risk ratio	Case series
		2021	Chronic urticaria	Not authorised	Lack of evidence to support a favourable benefit/risk ratio	Case series
		2022	Persistent pruritic recessive dystrophic epidermolysis bullosa	Authorised	No available therapies and no other alternatives	Case series
		2022	Not authorised	Alternative available in the therapeutic arsenal		
Pazopanib	5	2019	Pancreatic cancer	Authorised	No available therapies and no other alternatives	Phase II CT
		2021	Metastatic papillary thyroid carcinoma	Authorised	No available therapies and no other alternatives	Phase II CT
		2022	GIST	Authorised	No therapies available, with alternatives for off-label use	Phase II CT
		2022	Solitary fibrous tumour	Not authorised	Alternative available in the therapeutic arsenal	Phase II CT
Pembrolizumab	5	2019	Sarcomatoid non-small-cell lung carcinoma	Authorised	No available therapies and no other alternatives	Phase III CT
		2019	Cervical cancer	Authorised	No available therapies and no other alternatives	Phase II CT
		2022	Cutaneous squamous cell carcinoma	Authorised	No therapies available, with alternatives for off-label use	Phase III CT
		2022		Not authorised	Alternative available in the therapeutic arsenal	
Cabozantinib	4	2018	Hepatocellular carcinoma	Not authorised	Alternative available in the therapeutic arsenal	Phase III CT
		2021	Metastatic papillary thyroid carcinoma	Authorised	No available therapies and no other alternatives	Phase III CT
		2021	Osteosarcoma	Not authorised	Alternative available in the therapeutic arsenal	Phase II CT
		2021	Ewing's sarcoma	Authorised	No available therapies and no other alternatives	Phase II CT
Eculizumab	4	2020	C3 glomerulopathy	Authorised	No available therapies and no other alternatives	Observational studies
		2022	Endothelial damage following HPT	Authorised	No available therapies and no other alternatives	Case series
		2022	IgA nephropathy	Authorised	No available therapies and no other alternatives	Case series
		2022	Antibody-mediated acute rejection	Authorised	No available therapies and no other alternatives	Case series
Sorafenib	4	2018	Osteosarcoma	Authorised	No available therapies and no other alternatives	Phase II CT
		2021	Desmoid tumour	Not authorised	Alternative available in the therapeutic arsenal	Phase III CT
		2022		Authorised	No available therapies and no other alternatives	
Vedolizumab	3	2018 2019 2021	GVHD of the digestive tract following HPT Phase II CT	Authorised	No available therapies and no other alternatives	Phase II CT Case series

CTs, controlled trials; GVHD, graft-versus-host disease; HPT, haematopoietic precursor transplantation; CIDP, chronic idiopathic demyelinating polyneuropathy; CANDLE, atypical neutrophilic dermatosis-lipodystrophy-elevated temperature syndrome; GIST, gastrointestinal stromal tumour.

Another aspect to highlight is the cost of the drugs. Lower-cost treatments have a higher approval rate, whereas none of the treatments exceeding €100,000 were approved. As might be expected, even greater priority is given to the level of evidence and the availability of alternatives in these cases. Most authorised oncohaematological drugs have an average cost of €10,000 to €50,000 per treatment. This range is consistent with the range reported by González-Morcillo et al.¹². They analysed the cost-effectiveness of off-label drugs, mainly in the area of oncohaematology, and identified an average cost of €16,288 per application. In contrast, non-oncohaematological drugs have significantly lower average costs, ranging from €1000 to €10,000 per year.

Although there were more requests for oncohaematological drugs than for non-oncohaematological drugs, the authorisation rate was significantly higher for the latter (66% vs 82%, respectively). This difference could be linked to the higher costs associated with oncohaematological treatments, for which greater scientific support is required.

In terms of budgetary impact, approving 92 of the 124 requests resulted in savings of €2.2 million. Thus, drug evaluation and selection policies in hospital management minimise patient exposure to treatments with limited scientific support, while optimising available resources by prioritising the most efficient options.

Ethical responsibilities

All authors have accepted their responsibilities as defined by the International Committee of Medical Journal Editors (ICMJE).

Declaration of authorship

Lupe Rodríguez-de Francisco drafted the manuscript; Ángela María Villalba-Moreno and Eva Rocío Alfaro-Lara critically reviewed the intellectual content of the manuscript and approved the final version to be submitted; Lupe Rodríguez-de Francisco submitted the manuscript.

CRediT authorship contribution statement

Lupe Rodríguez-de Francisco: Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Ángela María Villalba-Moreno:** Validation, Supervision, Conceptualization. **Eva Rocío Alfaro-Lara:** Validation, Supervision, Conceptualization.

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Conflicts of interest

None declared.

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