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ORIGINAL ARTICLE

Impact of off-label use regulations on patient care in dermatology – a prospective study of cost-coverage applications filed by tertiary dermatology clinics throughout Germany

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Abstract

Background In dermatology, a medical speciality with a relatively high number of rare diseases, physicians often have to resort to off-label treatment options. To avoid claims, physicians in Germany can file a cost-coverage request (off-label application, OL-A).

Objectives Our aim was to investigate the extent to which the current regulations affect patient care.

Material and methods Prospective cohort study among tertiary dermatology clinics throughout Germany, consecutively including OL-As (05/2019–09/2020) and assessing the follow-up correspondence. We modelled regressions to assess factors associated with cost-coverage decisions and the time needed by health insurers to process the OL-As.

Results Thirteen clinics provided data on 121 OL-As, two of which applied for on-label treatments. Of the remaining 119 OL-As, 70 (58.8%) were immediately approved and 44 (37.0%) rejected. Including cases with one or more appeals, 87 of 119 OL-As (73.1%) were finally approved and 26 (21.9%) rejected. There was an association of the final approval rate with (1) the class of medication/treatment, with approval rates being significantly lower for JAK inhibitors than for biologics (OR 0.16, 95%-CI: 0.03–0.82); (2) German state, with approval rates being lower in eastern than in western states (OR 0.30, 95%-CI 0.12–0.76); and (3) cost of the intervention (no linear trend). However, none of these predictors was significant in our multiple logistic regression models. The median health insurer's processing time (first response) was 29 days (IQR 22–38). Our analyses showed no evidence of an association with the predictors we assessed. In cases approved, the median time from the decision to file an OL-A to the actual initiation of the treatment was 65.5 days (IQR 51–92).

Conclusions Our study points to substantial delays and inequalities in the provision of timely health care for dermatological patients with rare diseases, often involving treatments for which there is no adequate approved therapy.

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Conflicts of interest

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Introduction

Approved treatment options for rare diseases[1] or vulnerable populations, including children,[2–5] pregnant women[6] and elderly patients,[7,8] are often limited. In such cases, health care providers may have to resort to prescribing or administering medicines or medical procedures outside the terms of their marketing authorization, an approach known as 'off-label use'.[9–14] This may be the case, if approved treatment options prove to be insufficiently effective in a given patient, lead to adverse reactions or are contraindicated due to comorbidities. In dermatology, a medical speciality with a relatively high number of rare diseases for which only few authorized treatment options are available, physicians must frequently decide whether to prescribe or administer treatments on an off-label basis,[4,9,15–18] particularly in highly specialized tertiary care centres.

According to a decision by the German Federal Social Court (Bundessozialgericht) from 2002, prescribing or administering off-label medical treatments at the expense of statutory health insurance in Germany (Gesetzliche Krankenversicherung, GKV) is permitted only under specific conditions:[19] (1) the disease in question must be serious (i.e. life-threatening or have a severe and permanent impact on the patient's quality of life), (2) there must be no authorized treatment options for the disease that can be used for the patient in question, and (3) based on the available scientific data, there must be a reasonable prospect that the treatment will be successful. In a subsequent decision, from 2005, the German Federal Constitutional Court (Bundesverfassungsgericht) specified that—in case of a life-threatening disease—a reasonable prospect means that 'there is a not entirely remote prospect of a cure or a noticeable positive effect on the course of the disease' (English translation by the authors).[20]

Given that these three conditions for off-label use of medical treatments are subject to interpretation, physicians can, on a case-by-case basis, file a request for cost coverage (off-label application, OL-A) with a patient's health insurer before initiating an off-label treatment. Physicians who prescribe off-label treatments before such authorization is obtained are liable for the costs of treatment if the health insurer later determines that the conditions for off-label use were not met. Unlike in the United States, there are no 'clinical compendia', which are used as an administrative tool to determine cost coverage for drugs beyond their FDA approval for specific conditions.[21] In an earlier, retrospective analysis[22] of health insurer decisions on OL-As filed between 2010 and 2012 from a single dermatology clinic, we found that health insurers approved around 75% of OL-As that were filed during this period. However, the study also revealed substantial delays in the provision of the patients' medical care.[22]

In February 2013, the Patient Rights Act ('Patientenrechtegesetz') came into effect. It stipulates that health insurers must respond to an OL-A within 3 weeks of its receipt, or within 5 weeks if an expert opinion is obtained from a body known as the Statutory Health Insurance Medical Review Board (Medizinischer Dienst, MD).[23] Although the aim of the legislation was to improve the timeliness of patient care, it remains unclear how and to what extent decisions on OL-As have been affected by it and whether delays in treatment initiation have, in fact, been reduced.

In order to fill this gap in the literature, we prospectively collected and analysed OL-As filed by tertiary dermatological clinics throughout Germany and, in doing so, aimed to identify (a) the frequency of specific combinations of treatments and indications in the OL-As, (b) the amount of time required by the physicians to prepare an OL-A, (c) the rate of positive coverage decisions by health insurers and (d) the duration of the entire OL-A process and parts of it.

Material and methods

Study design and ethics

This was a prospective cohort study conducted among tertiary dermatology clinics in Germany. We aimed to include and analyse each OL-A filed by the participating centres with any statutory health insurer in Germany between May 2019 and September 2020, including any follow-up correspondence with the insurer. The study protocol was approved by the institutional ethics committee of Charité—Universitätsmedizin Berlin (EA2/112/18) and, where required, by the ethics boards of the collaborating centres. Participation of the centres and of the patients in the study was voluntary, and all patients provided written informed consent.

Participating centres and inclusion criteria

We announced the study at various events relevant to dermatologists (e.g. conferences of the German Dermatological Society and of the Commission for Quality Assurance in Dermatology in 2019) and repeatedly invited each of the 38 tertiary dermatology clinics in Germany to participate. Office-based dermatologists were invited to participate; however, due to the administrative effort needed to file an OL-A, off-label use is not as relevant for this sector, and no records from office-based dermatologists were received.

We asked participating centres to include all OL-As filed during the observation period, irrespective of the patient's disease, age, gender, comorbidities or type of health insurer. We excluded OL-As only in cases where cost coverage had already been approved for a limited time period by the health insurers previously (follow-up OL-As).

Data sources and variables

For each OL-A in our sample, we collected all follow-up correspondence between the physician and the health insurer (e.g. the health insurer's coverage decision on the OL-A and any appeals by the physician against negative coverage decisions). The participating centres sent the documents *via* fax to Charité—Universitätsmedizin Berlin, where these were pseudonymized for further analysis. Two independent researchers (AP and RNW) abstracted the following information from each OL-A and any related follow-up correspondence: (1) the patient's disease and the off-label treatment for whose costs the OL-A had been filed, (2) the patient's age, gender, place of residence, comorbidities and health insurer, (3) the health insurer's initial coverage decision and, where appropriate, any subsequent decisions, and (4) the date specified on the OL-A and each follow-up document.

Additionally, we obtained the following information for each OL-A by surveying the physician who filed it: (1) the time required to prepare the OL-A, (2) the date of the decision to file an OL-A, (3) the date on which the relevant off-label treatment was initiated after coverage had been approved by the insurer.

An explanation of our assessment of the conformity of each OL-A with the three conditions for off-label use stipulated in German court rulings and our calculations of the costs of the treatments, as well as detailed definitions of the variables used in our subsequent analysis are given in Online Appendix S1 (Table S1).

Efforts to address sources of bias

To reduce the risk of selection bias, we designed and conducted this study as a prospective investigation in which patients were included in a consecutive manner. We regularly sent the participating centres information to remind them about the inclusion criteria and to motivate them to include OL-As for each patient for whom coverage was sought during the recruitment period and who was willing to participate in this study. In order to increase the completeness of follow-up, we sent physicians case-specific emails reminding them to send us any follow-up correspondence with the health insurers. A final reminder to provide us with missing information was distributed 8 months after recruitment was completed.

Study size and statistical methods

As this was an exploratory study, the sample size was based on feasibility considerations. We aimed to include 70 to 140 OL-As with complete follow-up correspondence. We conducted all data analyses with Stata (Stata Statistical Software, Release 14, StataCorp LP). We used absolute and relative frequencies or means (SD)/median (quartiles) to describe the data, depending on their type and distribution. To test hypotheses, we used chi-squared tests or Kruskal–Wallis equality-of-populations rank test. We used multiple logistic regression to identify predictors of positive coverage decisions and multiple linear regression to identify predictors of the time needed by health insurers to process OL-As. When developing the regression models, we used forward selection to identify relevant predictors. The rule for including individual variables in the regression was $P < 0.2$. We selected the following variables for the regression models *a priori*: disease group, intervention class, health insurer group, patient's age, patient's place of residence, centre that filed the OL-A, costs of the treatment and conformity of the OL-A with the three regulatory conditions. We excluded missing cases in a listwise fashion for each model. The level for statistical significance was set at $P < 0.05$.

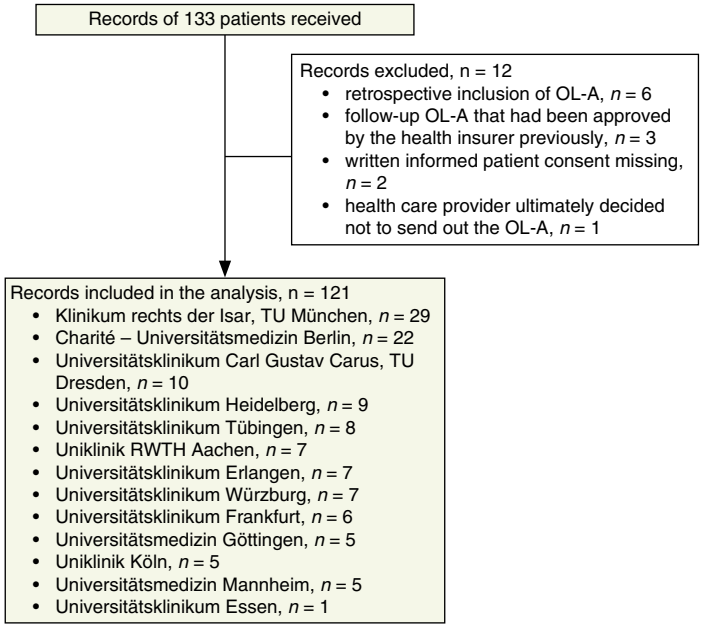

Figure 1 Flow of patients, participating centres and reasons for exclusion. OL-A, Off-label application.

Results

Participating centres, number of included off-label applications (OL-As) and patient characteristics

Overall, 13 tertiary dermatology clinics throughout Germany participated in the study and sent us records from OL-As for 133 patients. Of these records, those for 12 patients were excluded (Fig. 1), yielding an analysis sample of 121 records.

The patients were balanced with regard to gender (54.5% female) and had a mean age of 55.0 years (*SD* = 19.50). The most frequent health insurers were AOK (29.8%), Barmer (19.8%) and Techniker Krankenkasse (10.7%). The majority of the patients had their residence in one of the western German states (71.7%). Detailed patient characteristics are shown in Table 1.

Characteristics of the OL-A

Overall, the OL-As were filed for 72 different combinations of diseases and treatments. The most frequent combinations are shown in Table 2.

The characteristics of the OL-As, including disease groups and classes of treatments, are shown in Table 3. The most frequent disease groups were bullous autoimmune diseases (19.0%), dermato-oncological diseases (17.4%) and chronic inflammatory dermatoses (11.6%). The most frequent classes of treatments were biologics (32.2%) and intravenous immunoglobulins (IVIGs) (30.6%), followed by checkpoint inhibitors (9.9%), further immunomodulatory and antigranulomatous treatments (9.9%), Janus kinase (JAK) (6.6%) and oncologic kinase inhibitors (6.6%). The cost of the treatments ranged from €167.25 to €53776.06 per calendar quarter, with a median of €7887.63.

With respect to the conformity of OL-As with the conditions for off-label use, our analysis indicated that the majority of OL-As specifically addressed all three criteria for off-label use (62.8%). More specifically, the first criterion (severity of the condition) was addressed in 77.7%, the second criterion (no standard treatment options applicable) in 81.8% and the third criterion (reasonable prospect of treatment success) in 89.3% of the OL-As.

The participating physicians reported that they took a median of 60 min to file (i.e. prepare and submit) an OL-A.

Approval rates and factors associated with approval

Among the 121 OL-As submitted to the various health insurers, two involved treatments that were actually approved for the disease or had a special authorization according to the Medicinal Products Directive (Arzneimittelrichtlinie, Anhang VI). Of the remaining 119 OL-As, 70 (58.8%) were approved and 44 (37.0%) were initially rejected. In 25 of the 44 cases that were initially rejected, the physicians filed an appeal. Of these 25 cases, 13 were approved after this first appeal and 11 were rejected. A

Table 1 Patient characteristics

Gender	
Female, *n* (%)	66 (54.5)
Male, *n* (%)	55 (45.5)
Age in years (*n* = 121)	
Mean (SD)	55.0 (19.50)
Median (Q1–Q3)	55.0 (42–70)
Range	2–89
Number of concomitant diseases (*n* = 71)	
Mean (SD)	3.0 (2.56)
Median (Q1–Q3)	2.0 (1–4)
Range	0–10
Health insurer/health insurer groups	
Allgemeine Ortskrankenkassen (AOK), *n* (%)	36 (29.8)
Barmer, *n* (%)	24 (19.8)
Techniker Krankenkasse (TK), *n* (%)	13 (10.7)
BKK, *n* (%)	8 (6.6)
IKK, *n* (%)	7 (5.8)
KKH, *n* (%)	7 (5.8)
DAK, *n* (%)	6 (5.0)
DEBEKA, *n* (%)	5 (4.1)
Other, *n* (%)	15 (12.4)
German state	
Western states (excl. Berlin), *n* (%)	86 (71.7)
Baden-Wuerttemberg, *n* (%)	21 (17.5)
Bavaria, *n* (%)	35 (29.2)
Bremen, *n* (%)	0 (0.0)
Hamburg, *n* (%)	0 (0.0)
Hesse, *n* (%)	10 (8.3)
Lower Saxony, *n* (%)	2 (1.7)
North Rhine-Westphalia, *n* (%)	13 (10.8)
Rhineland-Palatinate, *n* (%)	5 (4.2)
Saarland, *n* (%)	0 (0.0)
Schleswig-Holstein, *n* (%)	0 (0.0)
Eastern German states (incl. Berlin), *n* (%)	34 (28.3)
Berlin, *n* (%)	16 (13.3)
Brandenburg, *n* (%)	8 (6.7)
Mecklenburg-Western Pomerania, *n* (%)	0 (0.0)
Saxony, *n* (%)	8 (6.6)
Saxony-Anhalt, *n* (%)	1 (0.8)
Thuringia, *n* (%)	1 (0.8)

Q1, first quartile; Q3, third quartile; SD, standard deviation.

second or third appeal was filed in seven of the 11 rejected cases, of which another four were ultimately approved. Finally, including cases with one or more appeals, 87 of the 119 OL-As (73.1%) were approved and 26 (21.9%) were rejected. In six cases (5.0%), a response was not received from the health insurer or was not available. These data are shown in Table 4.

We found no significant associations between the final approval rate and disease group (with approval rates ranging from 54.5% to 87.5%, $P = 0.709$), health insurer (42.9% to 86.4%, $P = 0.322$), age of the patient (50.0% to 90.9%, $P = 0.464$) or conformity of the OL-A with the three conditions for off-label use (73.2% in cases where one or more of the criteria were not explicitly addressed *vs.* 78.9% in cases where all of the criteria were explicitly addressed, $P = 0.496$). However, there was evidence of an association between the final approval rate and three variables: (1) the class of medication/treatment (37.5% to 100.0%, $P = 0.037$), with approval rates being significantly lower for JAK inhibitors than for biologics (OR 0.16, 95%-CI: 0.03–0.82); (2) residence in a western or eastern state (83.5% *vs.* 60.6%, $P = 0.014$), with approval rates being significantly lower in eastern than in western states (OR 0.30, 95%-CI 0.12–0.76); and (3) cost of the treatment (63.6% to 91.7%, $P = 0.03$), albeit without a linear trend being observable between the cost categories ($P = 0.128$). Lastly, none of the predictors in our two logistic regression models were significant, whether these were selected *a priori* or by means of our forward selection procedure. The detailed findings of associations between the final approval rate and other variables are shown in Online Appendix S2 (Table S2).

Duration of the processes

In 24 cases, the participating physicians initiated treatment without waiting for the health insurer's response. If we exclude these cases, the median time from the physician's decision to file an OL-A to the initiation of the treatment was 65 days for cases approved by the health insurer ($n = 62$). More specifically, the median processing time for the physician (i.e. the time from the decision to file an OL-A to the date it was submitted to the health insurer) was 6 days ($n = 117$), whereas the median time from the date the OL-A was submitted to the health insurer to the health insurer's first response was 29 days ($n = 111$). The median time from the date the OL-A was submitted to the health insurer, and the health insurer's final response (which includes cases with one or more rejections and appeals) was 31 days. These data are shown in Table 5.

Our analyses showed no evidence of an association between the processing time needed by the insurer to send a first response and: the disease group ($P = 0.499$), class of the medication/treatment ($P = 0.853$), insurer ($P = 0.248$), age of the patient ($P = 0.859$), patient residence in an eastern or western German state ($P = 0.330$), cost of the intervention ($P = 0.921$) or conformity of the OL-A with the three conditions for off-label use ($P = 0.072$). Similarly, the linear regression model using a set of *a priori* predictors of the processing time did not produce significant results. The detailed findings of associations between the time to the first response and other variables are shown in Online Appendix S2 (Table S3).

Discussion

Our study is the first to prospectively examine the processing times and approval rates of applications for reimbursement of off-label treatments in Germany and, based on this, the

Table 2 Most frequent combinations of diseases and treatments in the included off-label applications (OL-As)

Disease – treatment combinations		Frequency	
Disease	**Treatment**	***n***	**%**
Cicatricial mucous membrane pemphigoid	IVIGs	5	4.1
Pemphigus vulgaris or foliaceus	IVIGs	5	4.1
Cheilitis granulomatosa/Orofacial granulomatosis/MRS	Adalimumab/infliximab	4	3.3
Livedoid vasculopathy	IVIGs	4	3.3
Malignant melanoma stage IIC	Nivolumab	4	3.3
Pyoderma gangrenosum	Adalimumab/infliximab	4	3.3
Scleromyxedema/Lichen myxedematosus	IVIGs	4	3.3
Alopecia areata	Tofacitinib	3	2.5
Cheilitis granulomatosa/Orofacial granulomatosis/MRS	Clofazimine	3	2.5
Hidradenitis suppurativa	Infliximab	3	2.5
Cicatricial mucous membrane pemphigoid	Mycofenolate mofetil	3	2.5
Bullous pemphigoid	IVIGs	3	2.5
Merkel cell carcinoma stage I-IIIB	Avelumab	3	2.5
Necrobiosis lipoidica	Dimethylfumarate	3	2.5
Pyoderma gangraenosum	IVIGs	3	2.5
Wasp/bee venom allergy	Omalizumab	3	2.5

IVIGs, intravenous immunoglobulins; MRS, Melkersson–Rosenthal syndrome.

implications of the current regulatory situation for the health care provided to dermatology patients.

The regulatory situation for off-label use in Europe differs according to the national legal frameworks:[1] Whereas some countries rely on policy tools designed specifically to address this matter, others leave decisions on off-label prescribing more to the discretion of individual prescribers and insurers. However, even among those countries in the former category, the regulations are not harmonized: in France and Hungary, for example, prescribers or their organizations have to apply for permission for off-label prescribing, whereas in the Netherlands, off-label use is allowed if it is included in protocols or standards issued by professional bodies.

The fact that, despite the considerable amount of time that participation required, 13 tertiary dermatology clinics throughout the country took part in the study reflects the high clinical and policy relevance of the topic in dermatology. We found that off-label applications (OL-As) were filed for a broad range of dermatological conditions and interventions. This made it impossible to draw meaningful comparisons of approval rates for specific disease–treatment combinations, but at the same time reflects the relatively large number of diseases in dermatology for which only a few authorized treatment options are available, as well as the diverse nature of cases seen by tertiary dermatology clinics in Germany.

Overall, almost three-quarters of the OL-As filed during our 17-month observation period were approved, albeit in part only after one or more rejections by health insurers followed by appeals. In the case of successful applications, the median time from the physician's decision to file an OL-A to the initiation of the treatment was more than 2 months. This included the time that physicians needed to prepare the OL-A, insurers needed to reach a decision and respond, and physicians then needed to schedule an appointment with the patient to start the off-label treatment. This interval was shorter than the interval we identified in our previous, retrospective, single-centre analysis of cases filed before 2012.[22] Nevertheless, considering the impact of disease on the patient's quality of life and the risk of disease progression, it still implies a substantial delay in patient care. In fact, in around a fifth of the cases included in our study, the physicians did not wait for the health insurer's response and initiated treatments immediately even though this put them at risk of being liable to the insurer for the cost of treatment. We did not ask the physicians for their reasons for doing so; however, their decision may indicate that initiating a treatment was urgently needed in these cases to prevent disease progression in these patients.

The Patient Rights Act ('Patientenrechtegesetz'), which came into effect in February 2013, stipulates that health insurers must respond to an OL-A within a maximum of 35 days.[23] In our study, the median time between the date of the request and the first response from the health insurer was 29 days. Considering that the third quartile was 38 days, a substantial part of the sample probably experienced delays in the processing of their OL-As by the health insurer.

More than 20% of OL-As were rejected by the health insurers. Initiating the treatment without waiting for the health insurer's response would pose a significant risk for health care providers, who are liable for the treatment costs in such cases. Despite this risk, the common practice among the physicians in our sample was heterogeneous, with physicians initiating treatments without waiting for the insurer's response in a fifth of all cases.

Table 3 Characteristics of the off-label applications, including disease groups and classes of treatment

Variable	
Disease groups	
Bullous autoimmune dermatoses, *n* (%)	23 (19.0)
Dermato-oncological diseases, *n* (%)	21 (17.4)
Chronic inflammatory dermatoses, *n* (%)	14 (11.6)
Connective tissue diseases and associated disorders, *n* (%)	13 (10.7)
Granulomatous dermatoses, *n* (%)	13 (10.7)
Pyoderma gangraenosum, *n* (%)	8 (6.6)
Vasculopathy and vasculitis, *n* (%)	8 (6.6)
Hidradenitis suppurativa, *n* (%)	5 (4.1)
Others, *n* (%)	16 (13.2)
Classes of medication/treatment	
Biologics, *n* (%)	39 (32.2)
IVIGs, *n* (%)	37 (30.6)
Checkpoint inhibitors, *n* (%)	12 (9.9)
Other immunomodulatory and antigranulomatous treatments, *n* (%)	12 (9.9)
JAK inhibitors, *n* (%)	8 (6.6)
Oncologic kinase inhibitors, *n* (%)	7 (5.8)
Others, *n* (%)	6 (5.0)
Cost of the interventions per calendar quarter in euros (*n* = 120)	
Mean (SD)	10 760.37 (9017.09)
Median (Q1–Q3)	7887.63 (3246.30–17 703.53)
Range	167.25–53 776.06
Conformity of the OL-A with conditions for off-label use	
Crit. 1 ('Condition is serious') 'addressed, *n* (%)	94 (77.7)
Crit. 2 ('No standard treatment options applicable') addressed, *n* (%)	99 (81.8)
Crit. 3 ('Prospect of success') addressed, *n* (%)	108 (89.3)
All criteria addressed, *n* (%)	74 (61.2)
Time required to prepare the OL-A in minutes (*n* = 117)	
Mean (SD)	54.8 (26.57)
Median (Q1–Q3)	60.0 (35–60)
Range	15–210

IVIGs, intravenous immunoglobulins; JAK, janus kinase; Q1, first quartile; Q3, third quartile; SD, standard deviation.

We also found heterogeneity among the health insurers with regard to final approval rates, which ranged from 42.9% to 86.4%; however, given the large number of health insurers in Germany, and consequently, the relatively low number of cases for each group of insurers in our study, these differences were not statistically significant. The difference we identified between western and eastern states, however, with significantly lower approval rates seen in the east compared with the west, is indeed relevant and indicates that there might be structural or health inequalities at the state level in Germany. Given the persisting socioeconomic differences between eastern and western states in

Table 4 Approval rates at various stages of the application process and overall

Approval rates	
Initial OL-A, *n* (%)†	**119 (100.0)**
Approval of initial OL-A, *n* (%)	70 (58.8)
Rejection of initial application, *n* (%)	44 (37.0)
Response not received from insurer or not available, *n* (%)	5 (4.2)
Appeal against first rejection, *n* (%)	**25 (100.0)**
Approval after first appeal, *n* (%)	13 (52.0)
Rejection after first appeal, *n* (%)	11 (44.0)
Response not received from insurer or not available, *n* (%)	1 (4.0)
Appeal against second or third rejection, *n* (%)	**7 (100.0)**
Approval after >1 appeal, *n* (%)	4 (57.1)
Rejection after >1 appeal, *n* (%)	2 (28.6)
Response not received from insurer or not available, *n* (%)	1 (14.3)
Final approval rate, *n* (%)†	**119 (100.0)**
Approval, *n* (%)	87 (73.1)
Rejection, *n* (%)	26 (21.9)
Response not received from insurer or not available, *n* (%)	6 (5.0)

†The total number of 119 initial OL-A does not include two cases in which the physicians applied for coverage of interventions that were actually approved for the disease in question or had a special authorization according to the Medicinal Products Directive (Arzneimittelrichtlinie, Anhang VI).

Table 5 Duration of the overall process and various steps within it

Processing times (in days)	
Processing time needed by physician to file application: time from decision to apply for cost coverage of an off-label treatment until date on which OL-A was submitted to insurer (*n* = 117)	
Mean (SD)	13.9 (19.66)
Median (Q1–Q3)	6 (1–19)
Range	0–99
Processing time needed by health insurer to send first response: time from the date on which OL-A was submitted to insurer to the date of insurer's first response letter (*n* = 111)	
Mean (SD)	31.8 (15.10)
Median (Q1–Q3)	29 (22–38)
Range	2–86
Processing time to the final decision: time from date on which OL-A was submitted to insurer to date of insurer's final decision letter, which includes cases with one or more rejections and appeals (*n* = 111)	
Mean (SD)	47.1 (47.49)
Median (Q1–Q3)	31 (23–52)
Range	6–288
Time until initiation of treatment (patient perspective): time from decision to apply for coverage of an intervention until initiation of treatment (*n* = 62)†	
Mean (SD)	86.9 (63.00)
Median (Q1–Q3)	65.5 (51–92)
Range	27–364

†Time until initiation of treatment includes only data from approved OL-As and excludes those in which the treatment was initiated prior to receiving the health insurer's response (*n* = 18).
Q1, first quartile; Q3, third quartile; SD, standard deviation.

Germany, this is a finding that might need to be addressed in future research.

Overall, the results of our study point to substantial delays and inequalities in the provision of timely health care for dermatological patients with rare diseases, often involving treatments for which there is no real alternative. To address this situation, policy makers may wish to revisit current regulations. A shorter-term or perhaps alternative approach in Germany might be to issue a special authorization according to the Medicinal Products Directive (Arzneimittelrichtlinie, Anhang VI), which would allow for less bureaucratic cost coverage of frequently used off-label treatments for some of the most important indications. From our perspective, the framework for off-label use adopted in the Netherlands,[1] which allows off-label prescribing if it complies with standards issued by professional bodies, would also be a viable alternative and involve fewer bureaucratic procedures.

With its prospective design, our study was able to overcome some of the limitations of our previous study on this subject. Nonetheless, when interpreting the present results, there are several important limitations that should be kept in mind. First, the number of OL-As per participating centre included in our study was relatively low and our findings may, therefore, be affected by selection bias. We made several attempts to increase the completeness of the included OL-As, particularly by repeatedly reminding the participating centres of our inclusion criteria and the need to include in a consecutive manner all the OL-As filed by the physicians at each centre. Second, to ensure that we had an adequate number of OL-As per health insurer, we grouped health insurers according to their historical categorization, for example, as company-based (Betriebskrankenkassen, BKK) or guild-based (Innungskrankenkassen, IKK). However, whereas it can be assumed that the regional offices of the larger insurers such as Techniker Krankenkasse and Barmer share, for example, SOPs that would justify such a grouping, this may not be the case with the individual BKK or IKK. Third, we were not able to assess patterns of non-response because we had no information about the total number of patients (1) for whom OL-As were filed during the observation period or (2) who were asked to participate but did not provide consent. In Germany, more than 100 health insurers exist, and it is unclear whether and what type of internal instructions apply for each. Future researchers may wish to supplement process analyses like ours with research on the perspectives of insurance companies, such as systematic assessment of their internal procedures.

Conclusions

Our results reveal that dermatology patients in Germany waited a median of more than 2 months for their off-label treatment to be initiated in cases where their physician's application for cost coverage was approved by the health insurer. In around 20% of cases, the application was rejected by the health insurer, in some cases after one or more formal appeals by the physician. The current legal situation poses a threat to the timely care of dermatological patients with rare diseases. The range of dermatological conditions and off-label treatments in the cost-coverage applications was very broad. This made it impossible to draw meaningful comparisons of approval rates for specific disease–treatment combinations, but at the same time reflects the relatively large number of diseases in dermatology for which only a few authorized treatment options are available, as well as the diverse nature of cases seen by tertiary dermatology clinics in Germany.

Data availability statement

The data that support the findings of this study are available from the corresponding author, RNW, upon reasonable request.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1 Methods specifications.
Table S1. Specification of the main variables and outcomes used in the analysis.

Appendix S2 Results specifications.
Table S2. Univariate associations between the final approval rate and potential predictor variables.
Table S3. Univariate associations between the time to the first response by the health insurer and potential predictor variables.