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Quantity and economic value of unused oral anti-cancer and biological disease-modifying anti-rheumatic drugs among outpatient pharmacy patients who discontinue therapy☆

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ABSTRACT

Background: Patients sometimes discontinue the use of expensive oral anti-cancer drug (OACD) or biological disease-modifying anti-rheumatic drug (bDMARD) therapies early, leading to medication waste if the patient has not used all dispensed medication.

Objective: To determine the proportion of patients who have unused OACDs or bDMARDs after therapy discontinuation, and the quantity and economic value of these unused medications. Furthermore, patients' reasons for therapy discontinuation and their disposal method for unused medications were determined.

Methods: In a retrospective follow-up study using a Dutch outpatient pharmacy database, patients (≥18 years) who did not refill an OACD or bDMARD prescription, dispensed between November 2015 and February 2016, within two weeks of the prescription end date were contacted by phone and asked about their unused medication and reasons thereof. The economic value was calculated using Dutch medication prices. Data were descriptively analyzed in STATA13.

Results: The database included 1173 patients, of whom 159 likely had discontinued therapy and were contacted. Of these, 88 patients were excluded (39 refilled, 47 missing, and 2 other). Of the 71 patients who had discontinued therapy, 39 (54.9%) had unused medications, comprising 22 OACD users (mean age 63.0 (SD ± 15.9) years, 50.0% female) and 17 bDMARD users (mean age 50.7 (SD ± 13.5) years, 47.1% female). A total of 59 packages were unused, with a total value of €60,341. Unused OACD packages and bDMARD packages had median values of €179 (IQR €24–2487) and €992 (IQR €681–1093), respectively. Patients primarily discontinued therapy due to adverse or insufficient effects.

Conclusions: This study illustrates that more than half of patients discontinuing OACD or bDMARD therapies have unused medication. This emphasizes the need for waste-reducing interventions.

1. Introduction

Oral anti-cancer drugs (OACDs) and biological disease-modifying anti-rheumatic drugs (bDMARDs) comprise a significant amount of healthcare spending for expensive medications,[1] which is expected to increase more than 20% annually.[2] Both OACDs and bDMARDs have had a substantial impact on the treatment of cancer and inflammatory diseases, significantly improving the quality of life of affected patients.[3–6] However, studies have also shown that at least one-third of patients using OACDs or bDMARDs discontinue therapy early due to a lack of efficacy, adverse events, high out-of-pocket costs and negative beliefs about treatment.[7–12] Discontinuation of therapy may lead to medication waste if the patient has not used all of the dispensed medication.

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Previous studies have assessed the type and quantity of unused medications that are returned to community pharmacies, revealing that they are generally low-cost medications.[13–17] Some countries have adjusted their dispensing policies in an attempt to manage costs by dispensing more expensive therapies, including OACDs and bDMARDs, only from hospital-based outpatient pharmacies, which might partially explain why low-cost medications are typically those returned to community pharmacies. Patients using expensive therapies may be more likely to return those to the outpatient pharmacy during their regular visits. Furthermore, the number of patients using expensive medications within the general population is relatively low[18] and only half of patients are found to return their unused medications to pharmacies.[19] A more efficient strategy to assess the quantity and value of unused expensive medications would therefore be to personally approach patients who have discontinued their expensive therapy. However, currently little is known about the extent of those expensive medications that remain unused. Such findings are only described in terms of wasted costs without prescribing the exact medication quantity that remain unused[7] or are published in a non-peer-reviewed journal.[20] If such information is available, this may provide guidance for the development of waste-minimizing strategies for expensive medications.

This study aimed to determine the proportion of patients who have unused OACDs or bDMARDs after discontinuation of therapy, and the quantity and economic value of these unused medications. Furthermore, patients' reasons for therapy discontinuation and their disposal method for unused medications were determined.

2. Methods

2.1. Design and setting

This retrospective follow-up study was conducted in the outpatient pharmacy of the University Medical Center (UMC) Utrecht in the Netherlands from November 2015 until July 2016. The university hospital dispenses medications to approximately 11,000 patients per year, with 900 patients receiving OACDs and 1300 patients receiving bDMARDs. Due to national regulations, OACDs and bDMARDs are predominantly dispensed by hospital-based outpatient pharmacies in the Netherlands.

2.2. Ethics and confidentially

Patient data was handled confidentially and according to the Dutch law ‘Protection of Personal Data’ for medical research. The oral consent of patients was obtained prior to the start of the telephonic survey. The study was approved by the Medical Research and Ethics Committee of the UMC Utrecht (protocol reference number 16–114/C).

2.3. Study population

Patients aged ≥18 years who had received an OACD (a cytostatic, hormone antagonist, immunosuppressant or protein kinase inhibitor) or a bDMARD (an interleukin inhibitor, selective immunosuppressant or tumor necrosis factor alpha inhibitor) from the outpatient pharmacy for at least one week between November 2015 until February 2016, either as a first or repeated supply, were considered eligible for study inclusion. OACDs and bDMARDs that can also be dispensed by the community pharmacy were excluded. A detailed overview of the OACDs and bDMARDs included in the study is presented in Appendix I. Information about eligible patients was extracted from the outpatient pharmacy's database, including patient characteristics (gender, age) and information about their dispensed medications, including the dispensing date, medication name, anatomical therapeutic chemical (ATC) classification,[21] medication strength, administration form, dispensed quantity and prescribed daily dose. Hospital records were consulted to exclude patients that were terminally ill or deceased. Patients were considered to have discontinued therapy if they did not receive a refill of their medication within two weeks from the theoretical end date of their prescription, or if they switched to a different strength of the same medication or to another type of OACD or bDMARD. Patients identified as discontinuers were contacted by phone by the first author. Those who could not be reached in a first attempt were contacted again on a different day in the same or the following week. Patients who could not be reached by phone received a letter explaining the aim of the study and were requested to contact the researcher.

The selection of discontinuers was performed monthly and the supply of OACDs and bDMARDs was assessed over a retrospective period of four months. Patient data was anonymized using an identification code list that was kept in the pharmacy. Only patients identified as discontinuers were decoded and contacted for this study.

2.4. Measurements

Consenting patients were interviewed using a structured closed-ended questionnaire. The questionnaire was developed through discussion by the research group and outcomes of previous conducted studies and pilot-tested in terms of interpretation by interviewing 10 patients using bDMARDs. The questionnaire included questions about whether patients had indeed discontinued therapy, and whether they had unused medications as a result. Patients who indicated they had unused medications were asked about the duration of their therapy, the reason for therapy discontinuation, the number of unused packages (if possible with the number of capsules, tablets or syringes), the number of unused packages that were unopened (i.e. not used at all), the reason for having unused medications and how they had disposed of the unused medications. Only medications dispensed by the hospital-based outpatient pharmacy of the UMC Utrecht were included.

The outcomes of this study included the determination of the proportion of patients who had unused OACDs or bDMARDs after therapy discontinuation. Furthermore, the quantity unused packages among patients who had discontinued therapy, including the economic value and the quantity of unopened packages, was assessed. The economic value was calculated using the Dutch medication prices in 2016,[22] excluding value-added tax, which was corrected for the unused quantity (number of capsules, tablets and syringes). Therefore, unit costs (cost of one tablet/syringe) were multiplied with the reported quantity. If patients were unable to report the unused quantity, these medications were excluded from the cost calculations.

2.5. Analysis

Descriptive analyses were performed. Proportions were expressed as percentages, while averages were expressed as means with standard deviations (SD) or as medians with interquartile ranges (IQR) if non-normally distributed. Outcomes were differentiated between OACDs and bDMARDs. The following co-variates were assessed for patients that had unused medications: patient demographics (gender, age), type of OACD or bDMARD, duration of medication use (< 6 months, 6–12 months and ≥12 months), reasons for discontinuation (adverse effects, condition resolved, no/insufficient effect, therapy changed, other [further specified]) and disposal practices of the unused medications (kept at home [for later use, no time for disposal, other], returned to the pharmacy [community/outpatient], other [further specified]). All analyses were performed in STATA13.

3. Results

Over a period of four months, 605 patients received OACDs and 568 patients received bDMARDs from the outpatient pharmacy. After excluding patients who received a refill, were terminally ill or deceased, 90 patients using OACDs and 69 patients using bDMARDs were identified as likely discontinuers of these therapies and were contacted by

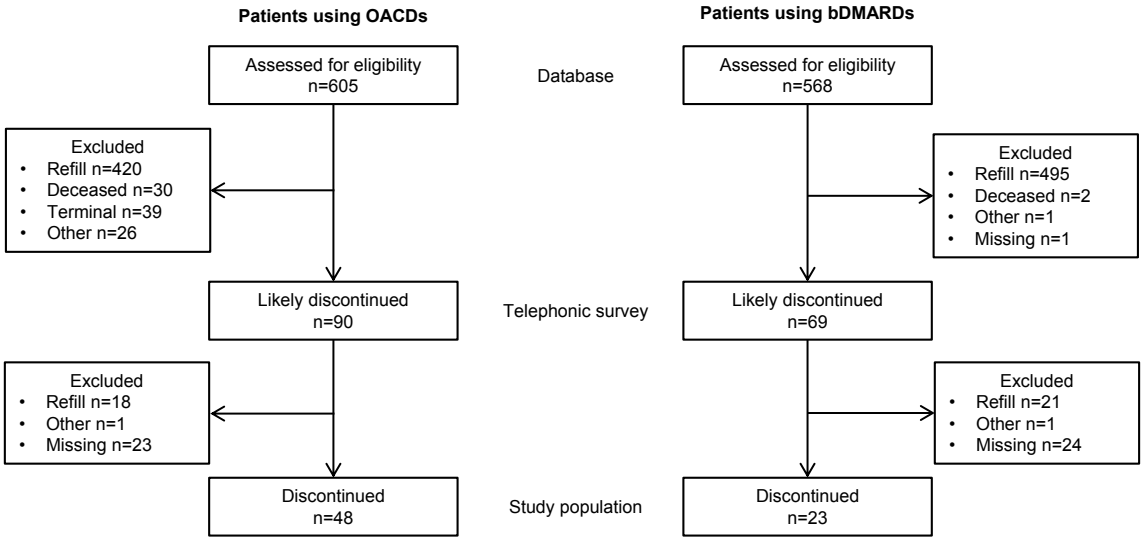

Fig. 1. Procedure for the identification of patients who discontinued therapy. Patients categorized as "other" were excluded due to other reasons (e.g. went to another hospital) and those categorized as "missing" could not be contacted.

phone. Of these, 23 (25.6%) and 24 (34.8%) patients, respectively could not be contacted, and some patients reported that they were still using the medication and had received a refill during the identification procedure, while others could not be contacted. A total of 71 patients confirmed that they had discontinued therapy and were included in this study, of whom 48 patients discontinued an OACD therapy (mean age 62.6 (SD ± 13.0) years, 52.1% female) and 23 patients discontinued a bDMARD therapy (mean age 50.3 (SD ± 12.0) years, 43.5% female). Information about patient inclusion is depicted in Fig. 1.

3.1. Proportion of patients with unused medication

Of the 71 patients who had discontinued therapy, 39 (54.9%) reported that they had unused medication. Five patients (7.0%) were unable to remember the precise quantity of unused medication. Specifically, 48 patients discontinued OACD therapy, of whom 22 patients (45.8%) had unused medication (mean age 63.0 (SD ± 15.9) years, 50.0% female). Twenty-three patients discontinued bDMARD therapy, of whom 17 patients (72.0%) had unused medication (mean age 50.7 (SD ± 13.5) years, 47.1% female).

A total of 39.1% of patients who discontinued OACD therapy with unused medication had been undergoing treatment for < 6 months, while 17.4% and 30.4% of patients underwent treatment 6–12 months and ≥12 months, respectively (13.1% unknown). A total of 47.1% of patients who discontinued bDMARD therapy with unused medication had been undergoing treatment for 6–12 months, while 23.5% and 23.5% of these patients underwent treatment for < 6 months and ≥12 months, respectively (5.9% unknown).

The primary reason given for OACD therapy discontinuation was adverse effects (50.0%), while insufficient effect was the main reason for patients discontinuing a bDMARD therapy (64.7%, Table 1). For both medication groups, most patients who had discontinued therapy due to adverse effects had been using the medication for less than half a year, whereas all patients who had discontinued due to insufficient effects had been using the medication for more than half a year.

Patients reported that they had unused medication because they discontinued therapy earlier than planned, e.g. their doctor told them to stop taking the medication. Other patients stated that the pharmacist had supplied too much or that they had not started using the medication at all. The majority of patients kept their unused medication at home (63.6% of the OACD users and 52.9% of the bDMARD users) or returned them to the pharmacy (27.3% and 47.1%, respectively), of which half of the patients returned them to the outpatient pharmacy.

Table 1
Patients' reasons for therapy discontinuation, for having unused medication and their method for its disposal.

	Patients with unused OACDs n = 23[a,b] N (%)	Patients with unused bDMARDs n = 17[b] N (%)
Reason for discontinuation		
Adverse effects	10 (43.5)	3 (17.6)
Condition resolved	3 (13.0)	–
Therapy changed	4 (17.4)	3 (17.6)
Insufficient effect	4 (17.4)	11 (64.7)
Other	4 (17.4)	1 (5.9)
Reason for unused medication		
Early discontinuation	19 (82.6)	13 (76.5)
Pharmacy supplied too much	1 (4.3)	2 (11.8)
Other	4 (17.4)	3 (17.6)
Disposal practice		
Kept at home	14 (60.9)	9 (52.9)
For later use	*6 (42.9)*	*3 (33.3)*
No possibility/time for disposal	*5 (35.7)*	*2 (22.2)*
Other	*2 (14.3)*	*4 (44.4)*
Unknown	*2 (14.3)*	–
Returned to pharmacy	6 (26.1)	8 (47.1)
Outpatient pharmacy	*3 (50.0)*	*4 (50.0)*
Community pharmacy	*2 (33.3)*	*3 (37.5)*
Unknown	*1 (16.7)*	*1 (12.5)*
Other	3 (13.0)	–

[a] There were 22 patients, one of whom had two types of unused medications.
[b] More than one answer possible and therefore the sum exceed 100%.

3.2. Quantity and economic value of unused medication

A total of 59 packages were unused, with a total value of €60,341 (Table 2). The majority of the unused packages were unopened (n = 42, 71.2%) and had a total economic value of €48,349. The 22 patients with unused OACDs had, on average, one unused package, which had a median value of €179 (IQR €24–2487). Overall, 17 different types of OACDs were unused, of which 20.0% contained ruxolitinib. The 17 patients with unused bDMARDs had an average of two unused packages, each with a median value of €992 (IQR €681–1093). The majority of unused bDMARDs contained adalimumab (47.1%).

Table 2
The quantity and economic value of unused OACDs and bDMARDs packages among patients who discontinued therapy, including the number of unopened packages.

	Quantity N	Total economic value (€)	Median value per package (€) (IQR)	Median value per patient (€) (IQR)
OACDs and bDMARDs				
Unused packages	59	60,341	826 (179–1093)	1101 (367–2597)
Unopened packages	*42 (71.2%)*	*48,349 (80.1%)*	*1083 (551–1451)*	*2165 (1083–2717)*
OACDs				
Unused packages	31	34,536[a]	179 (24–2487)	367 (48–4235)
Unopened packages	*20 (64.5%)*	*26,044 (75.4%)*	*1800 (24–3580)*	*2602 (112–5401)*
bDMARDs				
Unused packages	28	25,806	992 (681–1093)	1362 (960–2176)
Unopened packages	*22 (78.6%)*	*22,304 (84.4%)*	*1083 (1083–1093)*	*1101 (1093–2165)*

[a] The economic value could only be estimated for 28 packages.

4. Discussion

In this study, unused OACDs and bDMARDs among patients discontinuing therapy were assessed. Both therapies significantly contribute to the costs spent on medications. It was found that 55% of these patients had unused medication. These medications were of high economic value, approximately €1100 per patient, and more than two-third of the unused medications included packages that were still unopened. Patients with unused medication had discontinued these therapies primarily due to adverse or insufficient effects. These outcomes emphasize the financial loss that occurs when these medications remain unused and show the need and possibilities for waste-prevention.

Overall, it was estimated that around €7.7 million was spent on OACDs and bDMARDs that were dispensed to the 1173 patients during the inclusion period, of which approximately 0.8% (€60.341 of €7.7 million) was wasted as patients had unused medication due to therapy discontinuation. These findings correspond with those of a previous study estimating the economic value of unused medications among patients discontinuing OACD, bDMARD or growth hormone therapies early, which found that less than 1% of the money spent on these medications was wasted.[20] Both the previous and current studies indicate that only small quantities of OACD and bDMARDs medications dispensed to patients are unused. However, these medications are so expensive that, for the outpatient pharmacy in this study, at least €180,000 is wasted annually when the study results are extrapolated. There are approximately 80 hospital-based outpatient pharmacies in the Netherlands. The outpatient pharmacy that was included in this study covers 5.9% on the national expenditures of OACDs therapies and 1.7% of the expenditures on bDMARDs therapies. When these results are extrapolated to the national level, the yearly value of unused expensive medications will be at least €6 million. Furthermore, it was unable to include all patients who were considered to have discontinued therapy due to a low response rate for this telephonic survey. These findings are therefore likely to be an underestimation of the absolute quantity of unused OACDs and bDMARDs. These outcomes demonstrate that a significant amount of money is wasted when patients discontinue expensive therapies, and that the minimization of unused medication is therefore necessary.

Of the general Dutch population that use prescription medications on a regular basis, one-third has medications that remain unused.[23] In this study, the prevalence of unused medications is lower when compared to the general Dutch population. This is primarily due to the study design, as only patients who had discontinued therapy were specifically asked if a quantity of the OACDs or bDMARDs that was dispensed during the study period remained unused. The number of patients using expensive medications compared to the general population is relatively low. Nevertheless, this suggests that the quantities of medications that remain unused among the general population are also of great concern.

Various interventions can be implemented to reduce the amount of unused medication when patients discontinue therapies, such as dispensing smaller medication amounts or redispensing unopened medication packages. In this study, many patients had unopened packages at home, the number of which would likely be reduced or prevented if patients had received a smaller amount of medication, such as a one-month or a one-package supply. Dispensing smaller amounts will increase the dispensing fee, which is not cost-effective when medications are relatively cheap.[24,25] However, in the case of expensive medications, the dispensing fee is a fraction of their value and dispensing smaller amounts would likely lead to savings. This idea should be evaluated taking into account the patient perspective and their willingness to receive smaller amounts, as shorter refill intervals may be a burden to some patients because of the increased number of pharmacy visits. From a societal perspective and the high costs associated with these therapies, however, asking for such co-operation could be justified. Moreover, not all medications are available in small package amounts. Manufacturers sometimes produce large package sizes that pharmacists are not permitted to split into smaller amounts, and are thereby obliged to supply as large quantities. For the successful implementation of dispensing smaller amounts, a joint initiative may be necessary, involving the prescriber, the pharmacist, the patient, and stakeholders of government and industry.

In some cases, waste cannot be prevented, such as when patients develop side effects or with intentional non-adherence. In general, if patients have unused medication packages that are completely unopened, these may still be of good quality and could be redispensed to another patient to reduce medication waste. This could be hypothetically feasible if several requirements are fulfilled.[26,27] Primarily and most importantly, the quality of the medications must be guaranteed by monitoring the patients' storage conditions at home. Previous research has demonstrated that the majority of patients store their OACDs, which require room temperature storage, within the recommended temperature range,[28] indicating that these medications might be suitable for redispensing. With regards to bDMARDs, which require refrigeration, studies report that most patients do not store these correctly at home, making these less suitable for redispensing.[29,30] Furthermore, redispensing should be in compliance with national regulations. In the Netherlands, redispensing is not prohibited by law and may thus be feasible, although this would require adjustments in clinical guidelines of pharmacist organizations as they are currently not allowed to take back medication that has left the pharmacy. However, feasibility of redispensing strongly depends on a country's policy.

When developing waste-reducing interventions, not only patient utilization healthcare patterns such as the amount of medication that is supplied and the number of medications regularly used should be taken into account, but also patient awareness regarding medication waste should be increased, and education about safe disposal of unused medications.[31,32]

The quantity of unused medications among patients discontinuing OACD or bDMARD therapies was explicitly assessed. In clinical practice, it would be useful to be able to predict which patients are likely to

discontinue therapy. Here, it is shown that patients who recently started therapy (< 6 months) discontinued therapies primarily due to adverse effects, while those who were using these medications for a longer period commonly discontinued therapies due to inefficacy. These differences may reflect opportunities to target specific patients for waste-reducing interventions. A management program for patients using OACDs, which consisted of intensive care offered by healthcare providers focusing on the early identification of adverse effects, showed that the amount of medication waste due to therapy discontinuation could be reduced by 30%.[7] Implementing such a program might be valuable for patients beginning therapy. For patients who are in a later stage of therapy, the physician evaluates whether the therapy is effective, and decides if the therapy should be (dis)continued. These decisions are often based on national disease-specific treatment guidelines. To tackle medication waste in the later stages of therapy, patients should only receive the amount of medication needed until the next consultation with their physician. Some countries have implemented guidelines restricting the period for which medications can be prescribed, such as prior authorization in the US and a one-month prescription period for expensive medications in the Netherlands.

4.1. Limitations

The number of patients using OACDs and bDMARDs assessed for discontinuation of therapies was large enough to enable us to satisfactorily determine the outcome measures.

However, some limitations should be noted. It was not possible to include all patients who were considered to have discontinued therapy. In addition, terminally ill and deceased patients were not included and non-adherence among patients was not taken into account. Patients may also have given socially desired answers as they could be embarrassed about having unused expensive medication at home. Therefore, this study might underestimate the absolute quantity and value of unused expensive medications. Furthermore, patients may have incorrectly reported the amount of unused medication due to a recall-bias. However, to minimize this risk the recall period was limited to four months. Lastly, this single-center study may hamper the generalizability of the outcomes to other centers.

5. Conclusions

Both OACD and bDMARD therapies comprise a major part of the costs spent on expensive therapies, and this study shows that more than half of patients who discontinue OACD or bDMARD therapies have unused medications, worth around €1100 per patient. These findings emphasize the need for waste-reducing interventions to save costs.

Declaration of interests

None.

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Appendix I

Table 3
Oral anti-cancer drugs (OACDs) and biological disease-modifying anti-rheumatic drugs (bDMARDs) included in this study.

OACDs	bDMARDs
L01AA Nitrogen mustard analogues	L04AA Selective immunosuppressants
L01AD Alkyl sulfonates	L04AB Tumor necrosis factor alpha inhibitors
L01AX Other alkylating agents	L04AC Interleukin inhibitors
L01BB Purine analogues	
L01BC Pyrimidine analogues	
L01CB Podophyllotoxin derivatives	
L01XB Methylhydrazines	
L01XE Protein kinase inhibitors	
L01XX Other antineoplastic agents	
L02BA Anti-estrogens	
L02 BB Anti-androgens	
L02BG Aromatase inhibitors	
L04AX Other immunosuppressants	

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