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Cost Sharing and Adherence to Tyrosine Kinase Inhibitors for Patients With Chronic Myeloid Leukemia

Stacie B. Dusetzina, Aaron N. Winn, Gregory A. Abel, Haiden A. Huskamp, and Nancy L. Keating

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Stacie B. Dusetzina, School of Medicine and Lineberger Comprehensive Cancer Center and Cecil G. Sheps Center for Health Services Research; Stacie B. Dusetzina and Aaron N. Winn, Gillings School of Global Public Health; University of North Carolina at Chapel Hill, Chapel Hill, NC; Gregory A. Abel, Dana-Farber Cancer Institute; Haiden A. Huskamp and Nancy L. Keating, Harvard Medical School; and Nancy L. Keating, Brigham and Women's Hospital, Boston, MA.

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Corresponding author: Stacie B. Dusetzina, PhD, Division of General Medicine and Clinical Epidemiology, University of North Carolina at Chapel Hill, 5034 Old Clinic Building, CB #7110, Chapel Hill, NC 27599; e-mail: dusetzina@unc.edu.

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ABSTRACT

Purpose
The introduction of imatinib, a tyrosine kinase inhibitor (TKI), has greatly increased survival for patients with chronic myeloid leukemia (CML). Conversely, nonadherence to imatinib and other TKIs undoubtedly results in disease progression and treatment resistance. We examined trends in imatinib expenditures from 2002 to 2011 and assessed the association between copayment requirements for imatinib and TKI adherence.

Patients and Methods
We used MarketScan health plan claims from 2002 to 2011 to identify adults (age 18 to 64 years) with CML who initiated imatinib therapy between January 1, 2002, and June 30, 2011, and had insurance coverage for at least 3 months before through 6 months after initiation (N = 1,541). Primary outcomes were TKI discontinuation and nonadherence. The primary independent variable was out-of-pocket cost for a 30-day supply of imatinib. By using a propensity-score weighted sample, we estimated the risk of discontinuation and nonadherence for patients with higher (top quartile) versus lower copayments.

Results
Monthly copayments for imatinib averaged $108; median copayments were $30 (range, $0 to $4,792). Mean total monthly expenditures for imatinib nearly doubled between 2002 and 2011, from $2,798 to $4,892. Approximately 17% of patients with higher copayments and 10% with lower copayments discontinued TKIs during the first 180 days following initiation (adjusted risk ratio [aRR], 1.70; 95% CI, 1.30 to 2.22). Similarly, patients with higher copayments were 42% more likely to be nonadherent (aRR, 1.42; 95% CI, 1.19 to 1.69).

Conclusion
Patients with higher copayments are more likely to discontinue or be nonadherent to TKIs. Given the importance of these therapies for patients with CML, our data suggest a critical need to reduce patient costs for these therapies.

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INTRODUCTION

Tyrosine kinase inhibitors (TKIs) are considered by some to be the most successful class of targeted therapies developed in cancer, exceeding all survival expectations.[1] Before the first TKI, imatinib (Gleevec, Novartis, East Hanover, NJ), median survival for patients with chronic myeloid leukemia (CML) was approximately 5 to 6 years. Now, patients with CML who receive and adhere to TKI therapy may live nearly full life spans.[2] TKIs are oral medications taken daily. Despite significant clinical benefits, at least 30% of patients are nonadherent to TKIs.[3,4] Patients who are nonadherent not only receive fewer benefits of therapy, but poor adherence can also result in treatment failure because resistant CML clones can more easily emerge.[5,6]

Recently, much attention has focused on the high cost of TKIs and whether these costs inhibit patient use.[1] When imatinib was introduced in 2001, it was one of the highest priced drugs available, costing roughly $30,000 per year of treatment. By 2012, imatinib's cost had tripled to $92,000,[1] and second-generation TKIs such as nilotinib (2010) and dasatinib (2010) cost roughly $100,000 or more annually. These estimates are based on average wholesale prices, however, and do not provide a clear picture of actual prices paid by consumers for their medications because patients may be sheltered from high and increasing costs by insurance coverage. Indeed, out-of-pocket spending for patients receiving imatinib is not well understood.

Since the TKIs were introduced, insurance plans have implemented many policies to control

prescription drug costs, including raising copayments and increasing use of coinsurance.[7-9] These cost control features may result in significant financial burdens for patients who use TKIs, which may have an impact on patient use and adherence. Previous studies have shown that increased cost sharing reduces the use of and adherence to drugs.[10-14] Research focused specifically on high-cost specialty drugs has found mixed results on whether benefit generosity influences patients' drug use and, if so, the size of its impact.[15-17]

Our objectives were to examine trends in patient out-of-pocket and health plan expenditures for imatinib from 2002 to 2011 and to estimate the association between copayment requirements for imatinib and TKI discontinuation and nonadherence during the first 180 days of treatment for patients newly initiating imatinib therapy.

PATIENTS AND METHODS

Data Source

We used data from the Truven Health MarketScan database from 2002 to 2011. The data came from a selection of large employers, health plans, and government and public organizations and represent the health care experience of employees and their dependents enrolled in commercial health insurance plans sponsored by approximately 100 payers, representing more than 50 million covered lives.[18] The data include monthly enrollment data, inpatient and outpatient medical claims, and outpatient prescription drug claims.

Design and Study Populations

We identified patients with CML diagnoses (International Classification of Diseases, 9th revision [ICD-9] codes 205.1, 205.8, 205.9, 207.8, 208.1, 208.8, and 208.9) who were new imatinib users between January 1, 2002, and June 30, 2011 (N = 4,660). The first observed imatinib dispensing date was considered the index drug date. We excluded patients younger than age 18 years and older than age 64 years (n = 116), and those with acute lymphoid leukemia (ICD-9 codes 204.0, 204.1, and 205.0; n = 941). Finally, we excluded patients who did not have continuous health plan enrollment from 3 months before through 6 months after their index drug date (n = 2,040), those whose first imatinib claim had copayments and coinsurance amounts less than $0 (likely representing fills that were returned or data errors; n = 2), and those with missing demographic information (n = 20). This resulted in 1,541 patients for analysis.

Key Variables

The primary dependent variables of interest were TKI (imatinib, nilotinib, or dasatinib) discontinuation and nonadherence within 180 days of initiation. Although we selected our cohort on the basis of imatinib initiation, our outcome measure included adherence to any TKI used during our study period since patients may have been switched to another TKI (dasatinib or nilotinib) because of intolerance or failure to respond to imatinib. Patients were counted as using a TKI for any day during which they had TKIs available during the study period. We defined discontinuation as a gap in supply of more than 60 days following the exhaustion of drug supply.[19,20] We chose 60 days because treatment breaks are rarely for 60 days or more. We defined adherence by using the proportion of days covered. This measure represents the number of days that a patient had medication available, divided by the number of days in the period (capped at 100%). Patients were considered adherent to TKIs if they had more than 80% of days with TKIs available during the 180-day period after initiating imatinib[20]; otherwise, they were considered nonadherent. We measured discontinuation and nonadherence among all individuals in the sample and separately among patients who did not discontinue.

The primary independent variable was the level of copayment required for a 30-day supply of imatinib. We estimated the copayment requirement as the copayment and coinsurance paid by the patient for the first imatinib prescription filled, standardized to a 30-day supply. We excluded deductible payments from this calculation to avoid overestimating copayment requirements since deductibles represent one-time payments that may not apply to subsequent fills and may primarily affect individuals whose index date is at the start of the calendar year. In addition, we summarized total expenditures for the first imatinib prescription, including patient and health plan expenditures. We used the distribution of copayments required to determine whether patients paid high copayments, defined as copayments at the 75th percentile or greater. Copayment distributions were calculated for each calendar year. All dollars were adjusted for inflation to 2011 dollars by using the medical component of the Consumer Price Index.

Propensity-Score Estimation and Application

We estimated a propensity score by modeling the probability of having higher versus lower copayments as a function of the following control variables measured in the month of the patient's index therapy: patient age, insurance type (preferred provider organization or other), region, and the enrollees' relationship to employee (employee *v* spouse or dependent). We also included two measures of health care use and comorbidity during the 3 months before imatinib initiation: the Klabunde modification of the Charlson score[21] and the number of medication classes used preceding treatment initiation.[22,23] Next, by using the resulting propensity score, we created inverse probability of treatment weights for each patient; equal to $1/p$ (where p is the propensity score) for patients in the higher copay group and $1/(1-p)$ for patients in the lower copay group.[24,25] We stabilized the propensity-score weights by multiplying the inverse probability of treatment weights by the marginal prevalence of the treatment actually received.[26] This method of propensity-score weighting provided an estimate of the treatment effect in the population—in this case, the effect of high copayments among privately insured patients.

Statistical Analysis

First, we described general trends in imatinib copayment requirements and total expenditures over the study period. Next, by using the propensity-score weighted cohort, we estimated the risk of discontinuing therapy and the risk of being nonadherent to therapy for patients with higher versus lower copayments. We used generalized estimating equations with log links and binomial distributions for each of the outcome models. Finally, we estimated the proportion of days of medication used during the 180 days following drug initiation by using a generalized estimating equation with an identity link and normal distribution. Adjusted risks and adjusted risk ratios (aRRs) with 95% CIs were estimated from each model. We used SAS 9.3 (SAS Institute, Cary, NC) for all analyses.

Sensitivity Analyses

To test the robustness of our study findings, we conducted several sensitivity analyses. First, we excluded 97 patients who were hospitalized after imatinib initiation because adherence during hospitalization cannot be detected by using prescription claims. Second, we excluded 74 patients who paid drug deductibles for their first imatinib fill since we excluded these expenditures from our copayment calculations. Third, we included only patients who had at least 6 months of enrollment before their first observed imatinib fill to reduce the likelihood for misclassification of TKI exposure that might arise from using a 3-month clean period. Fourth, we varied our cut point for defining adherence from 80% of the proportion of days covered to 85% and 90% to reflect additional clinically meaningful cut points. Finally, we were unable to accurately distinguish breaks in therapy to address toxicity from imatinib from breaks related to nonadherence; thus, we revised our discontinuation definition from more than 60 days to more than 90 days without TKIs to avoid misclassifying patients as discontinuing during gaps in treatment related to toxicity.

Sensitivity of Propensity-Score Adjusted Estimates to Unobserved Confounders

Because propensity score analyses can adjust only for observed characteristics, we examined the robustness of our findings to potential unobserved confounders.[27,28] To do this, we assumed an unobserved variable exists, such as lack of understanding of one's illness, associated with both type of health plan and/or level of copayment and adherence.[29,30] We then re-estimated the association of copayment level with the outcomes after adjusting for this unmeasured variable under specific assumptions regarding the prevalence of

Table 1. Characteristics of New Imatinib Users, 2002-2011

Characteristic	Before Propensity-Score Weighting			After Propensity-Score Weighting		
	Lower Copayment (n = 1,134)	Higher Copayment (n = 407)	*P*	Lower Copayment	Higher Copayment	*P*
Age, years			.35			.43
Mean	49.0	48.4		48.9	48.5	
SD	11.1	10.8		10.4	12.7	
Female sex, %	44.0	45.7	.55	44.1	45.1	.70
Region, %			.01			.99
Northeast	12.6	8.4		7.4	12.2	
Midwest	29.3	25.3		28.2	28.2	
South	42.2	51.6		44.7	44.4	
West	15.0	13.8		14.7	14.4	
Relationship of patient to employee, %			.30			.16
Employee	66.5	69.3		66.8	70.3	
Spouse or dependent	33.5	30.7		32.2	30.7	
Type of health plan, %			< .001			.82
Preferred provider organization	57.3	67.8		60.1	60.7	
Other	42.7	32.2		39.9	39.3	
Starting dose (mg), %			.90			.98
≤ 400	89.4	89.2		89.2	89.3	
> 400	10.6	10.8		10.8	10.7	
No. of medications in 3 months before the index date			.34			.57
Mean	5.5	5.3		5.3	5.2	
SD	4.0	3.9		3.7	4.4	
Comorbidity score, %			.23			.06
0	94.1	95.3		93.5	95.8	
1+	5.9	4.7		6.5	4.2	

NOTE. Out-of-pocket payments are calculated based on copayment and coinsurance paid for the initial imatinib fill, standardized to a 30-day supply. Patients are characterized as having higher copayments if they have out-of-pocket costs that are above the 75th percentile of imatinib costs for the calendar year versus lower copayments (all others).
Abbreviation: SD, standard deviation.

the confounder in the lower- and higher-copayment groups and the confounder's relationship with adherence.

RESULTS

Characteristics of the 1,541 patients newly initiating imatinib are provided in Table 1. The mean age was 48.8 years (standard deviation [SD], 11.0), and 44% were female. Before propensity-score weighting, patients with relatively lower imatinib copayment requirements were similar on most measured characteristics to those with higher (≥ 75th percentile) copayment requirements, although patients with higher copayment requirements were less likely to reside in the Northeast (8.4% *v* 12.6%) and more likely to have a preferred provider organization health plan (67.8% *v* 57.3%). After propensity score adjustment, there were no differences (Table 1).

Copayment requirements for imatinib were largely drug copayments rather than coinsurance. Only 6.4% of our sample paid any coinsurance for imatinib versus 88.5% paying any copayments. Among those with coinsurance requirements, the mean spending on a 30-day supply of imatinib was $286 (SD, $470; median, $50; interquartile range [IQR], $327). Costs varied substantially among individuals in our sample, with 6.4% of the sample paying more than $500 for a 30-day supply of imatinib.

Patient and Health Plan Spending on Imatinib

Over the study period, the mean copayment required for a 30-day supply of imatinib was $108 (SD, $301). Mean copayments varied widely, with patients in the lowest 25th percentile paying $17 and those in the upper 75th percentile paying $53. Importantly, the median copayment required across all years was approximately $30 per fill, but copayments ranged from $0 to $4,792. Over time, monthly copayments increased from an average of $55 in 2002 to $145 in 2010 (Fig 1A).

Total imatinib expenditures, including both health plan expenditures and patient copayments, increased substantially over the study period. The mean monthly total expenditures nearly doubled between 2002 and 2011, from $2,798 to $4,892 (Fig 1B). Median total imatinib expenditures over the study period similarly increased from $2,846 (IQR, $100) in 2002 to $4,954 (IQR, $156) in 2011.

Association Between Cost-Sharing Level and Discontinuation

Among new users of imatinib, approximately 10% of patients with relatively lower copayment requirements and 17% of patients with higher copayments discontinued therapy during the first 180 days following treatment initiation (Table 2). There was a 70% increase in the risk of discontinuing TKIs among patients with higher copayment requirements (upper 75th percentile; aRR, 1.70; 95% CI, 1.30 to 2.22). Similarly, approximately 21% of patients with lower copayments were nonadherent to their TKI therapy (< 80% of days with drug available) versus 30% of patients with higher copayments. Patients with higher copayments were 42% more likely to be nonadherent to their TKI therapy (aRR, 1.42; 95% CI, 1.19 to 1.69).

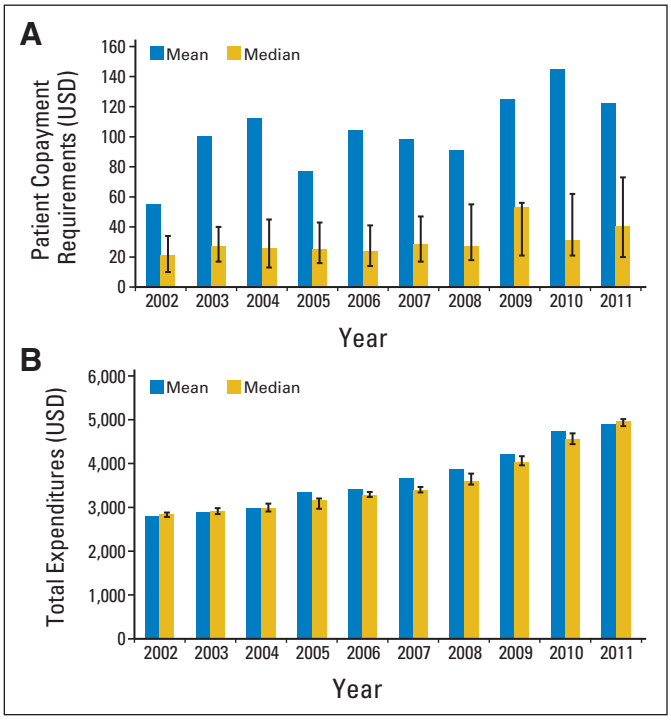

Fig 1. (A) Patient copayment requirements and (B) total expenditures for a 1-month supply of imatinib. USD, US dollars (inflation adjusted to 2011 dollars).

When evaluating the proportion of days covered with their medication supply (Table 3), patients with lower copayments had 87% of days covered versus 82% among patients with higher copayments (adjusted risk difference, −0.05; 95% CI, −0.07 to −0.02). However, we found little difference in the proportion of days covered by copayment level when restricting our analysis to patients who did not discontinue therapy. Among those patients, we found adherence of 93% among those with lower copayments and 92% among those with higher copayments (adjusted risk difference, −0.01; 95% CI, −0.02 to 0.00; $P = .15$).

Sensitivity Analyses

Results from the sensitivity analyses in which we (1) excluded patients who were hospitalized following imatinib initiation, (2) excluded patients who paid drug deductibles, (3) restricted our sample to patients with 6 months of prior enrollment without TKI use, (4) varied our definition of nonadherence to reflect less than 85% and less than 90% of days covered, and (5) redefined discontinuation as more than 90 days of no TKI therapy were consistent with the primary analysis (data not shown).

Sensitivity to Unobserved Confounders

In analyses assessing the sensitivity of our findings to unobserved confounders, we considered a confounder, such as poor understanding of one's disease, and assumed that the prevalence of confounders was twice as high among patients in the higher copayment groups (approximately 20%) than among patients in lower copayment groups (approximately 10%). We also assumed that this confounder was associated with a two-fold increase in risk of discontinuation or nonadherence. Under these assumptions, the risk of discontinuation (risk ratio [RR], 1.56; 95% CI, 1.19 to 2.04) and nonadherence (RR, 1.30; 95% CI, 1.09 to 1.55) remained statistically significant. Lack of understanding would need to be three times as prevalent in the higher versus lower copayment group (ie, 30% *v* 10%) and the association between poor understanding and adherence a three-fold increase for the observed associations to no longer be statistically significant.

DISCUSSION

TKIs are costly to patients and insurance plans, and our results demonstrate that high copayment requirements for drugs are associated with substantially reduced use. Patients with relatively higher cost-sharing requirements were 70% more likely to discontinue therapy and were 42% more likely to have inadequate adherence. Discontinuation and nonadherence to TKIs have severe and costly consequences for patients including CML progression, need for hematopoietic stem-cell transplantation and, potentially, death.[3-5] Even a low level of nonadherence may be dangerous; evidence suggests that 85% adherence is associated with resistant clones and imatinib failure.[6]

Importantly, our analyses may represent the best-case scenario when evaluating the impact of cost sharing on adherence to TKIs, since patients included in our sample represent privately insured patients with relatively generous employer-sponsored insurance (median copayment, $30 per fill) who filled at least one imatinib prescription. Thus, patients with very high copayments that result in primary nonadherence (ie, not filling the first prescription) are not represented in our sample. Yet, even in this setting, we observed a large impact of cost on discontinuation and adherence.

Table 2. Association Between Copayment Levels, Discontinuation, and Adherence During the First 180 Days After Imatinib Initiation

Copayment Level Based on the Distribution of Out-of-Pocket Spending	Discontinuation				Nonadherence			
	Unadjusted Proportion (%)	Adjusted Proportion (%)	aRR	95% CI	Unadjusted Proportion (%)	Adjusted Proportion (%)	aRR	95% CI
Lower copayment	10	10	1.00 (reference)		21	21	1.00 (reference)	
Higher copayment (top quartile)	16	17	1.70	1.30 to 2.22	30	30	1.42	1.19 to 1.69

NOTE. Discontinuation is defined as having a gap of more than 60 days after the exhaustion of available therapy. Nonadherence is defined as having < 80% of days with tyrosine kinase inhibitors available during the 180-day period after imatinib initiation. Propensity-score weighting was used to adjust for all covariates.
Abbreviation: aRR, adjusted risk ratio.

Table 3. Association Between Copayment Level and Proportion of Days Covered During the First 180 Days After Imatinib Initiation

Copayment Level Based on the Distribution of Out-of-Pocket Spending	Days Covered Among All Initiators				Days Covered Among Continuers			
	Unadjusted Proportion (%)	Adjusted Proportion (%)	aRD (%)	95% CI	Unadjusted Proportion (%)	Adjusted Proportion (%)	aRD (%)	95% CI
Lower copayments	87	87	0.0 (reference)		93	93	0.0 (reference)	
Higher copayments (top quartile)	82	82	−5	−8 to 3	91	92	−1	−3 to 0

NOTE. Proportion of days covered is a number between 0 and 100. Propensity-score weighting was used to adjust for all covariates.
Abbreviation: aRD, adjusted risk difference.

In 2010, the U.S. Government Accountability Office reported that, under Medicare Part D, individuals not receiving low-income subsidies pay on average $525 per month for imatinib.[31] In fact, 99.6% of Medicare Part D stand-alone prescription drug plans and Medicare Advantage prescription drug plans charge coinsurance rather than a copayment for imatinib, with an average coinsurance of 29.8% per fill (calculated by the authors on the basis of 2011 Medicare Part D formulary data).[32] The high costs of these treatments has a direct impact on patients since their out-of-pocket costs are tied to the negotiated price of the drug. Given recent price increases for imatinib,[1] out-of-pocket costs for this drug are likely to increase further among all patients facing coinsurance requirements for the TKIs. Imatinib is expected to lose patent protection in 2014, but the prices of the other TKIs will remain high. Although our findings from commercially insured individuals may not generalize to Medicare beneficiaries, it is likely that Medicare beneficiaries with CML (who comprise more than half of patients with CML, with a median age at diagnosis of 64 years)[33] would be at greater risk for cost-related discontinuation, since their copayment requirements are typically higher than those observed in our cohort.

Traditionally, systemic anticancer therapies have been injected or infused in hospital or physician's office–based settings. Thus, health care providers are better able to ensure that patients receive their full course of chemotherapy. The TKIs and a growing number of biologic therapies are oral medications obtained by the patient from the pharmacy, and receipt of therapy depends on patient medication-taking behaviors. Numerous studies have documented barriers to optimal medication adherence, including forgetfulness, active decisions to omit doses, cognitive impairment or psychological problems, treatment of asymptomatic disease, polypharmacy, adverse effects, and high out-of-pocket costs.[29,34] The TKIs are some of the most effective biologic therapies available, but we nevertheless identified substantial nonadherence associated with higher out-of-pocket costs. It is likely that nonadherence related to out-of-pocket expenses may be even more pronounced for other expensive biologic anticancer therapies patients perceive as less effective.

Proposed changes in financing oral anticancer therapies, including providing oral anticancer treatments at coverage levels similar to those of infused treatments and limits on total out-of-pocket spending, may further influence patient cost sharing. However, it is unclear to what extent these benefits will be offset by higher premiums, deductible payments, and coverage restrictions (including increased copayments and/or coinsurance) following implementation of the Affordable Care Act.

This study has several limitations. First, we could not determine reasons for discontinuation of or nonadherence to TKIs. In sensitivity analyses, results were similar when we redefined discontinuation as more than 90 days without therapy since most patients with severe adverse effects (eg, pleural effusion requiring hospitalization) would likely restart TKI treatment within 90 days. Moreover, we have no reason to assume that adverse effects of TKIs would differ by the generosity of an individual's plan. Second, propensity-score analyses can adjust only for differences in observable characteristics between groups; however, our results were robust to analyses testing the sensitivity of our findings to a potential unobserved confounder. Third, because costs are highly skewed, categorizing spending as being higher or lower than the 75th percentile combined patients with very high and somewhat lower cost sharing into a single category. Although this may weaken estimates of the effect of higher cost-sharing on outcomes, we felt this categorization was most appropriate, given sample size considerations. Finally, when the second-generation TKIs were introduced in 2010, our data were not yet mature enough to assess the potential effects of patient costs on adherence for patients initiating TKIs other than imatinib.

In summary, we found large effects on the discontinuation of and nonadherence to TKIs associated with patient cost-sharing requirements. It is unclear how insurers will respond to recent price increases for imatinib, but the recent tripling of imatinib's price raises questions about the decisions manufacturers make when determining prices.[1] Our findings highlight the potentially harmful effects of high copayment requirements on patients with CML. Given the recent increase in the use of oral medications for cancer treatment and recurrence prevention, it is important to develop rational policies that do not inhibit patient access to highly effective life-extending treatments.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Experts in Chronic Myeloid Leukemia: The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: From the perspective of a large group of CML experts. Blood 121:4439-4442, 2013

2. Gambacorti-Passerini C, Antolini L, Mahon FX, et al: Multicenter independent assessment of outcomes in chronic myeloid leukemia patients treated with imatinib. J Natl Cancer Inst 103:553-561, 2011

3. Noens L, van Lierde MA, De Bock R, et al: Prevalence, determinants, and outcomes of nonadherence to imatinib therapy in patients with chronic myeloid leukemia: The ADAGIO study. Blood 113:5401-5411, 2009

4. Wu EQ, Johnson S, Beaulieu N, et al: Healthcare resource utilization and costs associated with non-adherence to imatinib treatment in chronic myeloid leukemia patients. Curr Med Res Opin 26:61-69, 2010

5. Marin D, Bazeos A, Mahon FX, et al: Adherence is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. J Clin Oncol 28:2381-2388, 2010

6. Ibrahim AR, Eliasson L, Apperley JF, et al: Poor adherence is the main reason for loss of CCyR and imatinib failure for chronic myeloid leukemia patients on long-term therapy. Blood 117:3733-3736, 2011

7. Landon BE, Rosenthal MB, Normand SL, et al: Incentive formularies and changes in prescription drug spending. Am J Manag Care 13:360-369, 2007

8. Smith C, Cowan C, Heffler S, et al: National health spending in 2004: Recent slowdown led by prescription drug spending. Health Aff (Millwood) 25:186-196, 2006

9. Robinson JC: Insurers' strategies for managing the use and cost of biopharmaceuticals. Health Aff (Millwood) 25:1205-1217, 2006

10. Neugut AI, Subar M, Wilde ET, et al: Association between prescription co-payment amount and compliance with adjuvant hormonal therapy in women with early-stage breast cancer. J Clin Oncol 29:2534-2542, 2011

11. Goldman DP, Joyce GF, Escarce JJ, et al: Pharmacy benefits and the use of drugs by the chronically ill. JAMA 291:2344-2350, 2004

12. Goldman DP, Joyce GF, Zheng Y: Prescription drug cost sharing: Associations with medication and medical utilization and spending and health. JAMA 298:61-69, 2007

13. Huskamp HA, Deverka PA, Epstein AM, et al: The effect of incentive-based formularies on prescription-drug utilization and spending. N Engl J Med 349:2224-2232, 2003

14. Huskamp HA, Deverka PA, Epstein AM, et al: Impact of 3-tier formularies on drug treatment of attention-deficit/hyperactivity disorder in children. Arch Gen Psychiatry 62:435-441, 2005

15. Goldman DP, Joyce GF, Lawless G, et al: Benefit design and specialty drug use. Health Aff (Millwood) 25:1319-1331, 2006

16. Karaca-Mandic P, Joyce GF, Goldman DP, et al: Cost sharing, family health care burden, and the use of specialty drugs for rheumatoid arthritis. Health Serv Res 45:1227-1250, 2010

17. Kim YA, Rascati KL, Prasla K, et al: Retrospective evaluation of the impact of copayment increases for specialty medications on adherence and persistence in an integrated health maintenance organization system. Clin Ther 33:598-607, 2011

18. Truven Health Analytics: Comparative Effectiveness Research: Research and Analytics, 2012. http://truvenhealth.com/products/comparative_effectiveness_research.aspx

19. Steiner JF, Prochazka AV: The assessment of refill compliance using pharmacy records: Methods, validity, and applications. J Clin Epidemiol 50:105-116, 1997

20. Hess LM, Raebel MA, Conner DA, et al: Measurement of adherence in pharmacy administrative databases: A proposal for standard definitions and preferred measures. Ann Pharmacother 40:1280-1288, 2006

21. Klabunde CN, Potosky AL, Legler JM, et al: Development of a comorbidity index using physician claims data. J Clin Epidemiol 53:1258-1267, 2000

22. Farley JF, Harley CR, Devine JW: A comparison of comorbidity measurements to predict healthcare expenditures. Am J Manag Care 12:110-119, 2006

23. Schneeweiss S, Seeger JD, Maclure M, et al: Performance of comorbidity scores to control for confounding in epidemiologic studies using claims data. Am J Epidemiol 154:854-864, 2001

24. Sato T, Matsuyama Y: Marginal structural models as a tool for standardization. Epidemiology 14:680-686, 2003

25. Robins JM, Hernán MA, Brumback B: Marginal structural models and causal inference in epidemiology. Epidemiology 11:550-560, 2000

26. Hernán MA, Brumback B, Robins JM: Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. Epidemiology 11:561-570, 2000

27. Lin DY, Psaty BM, Kronmal RA: Assessing the sensitivity of regression results to unmeasured confounders in observational studies. Biometrics 54:948-963, 1998

28. Vanderweele TJ, Arah OA: Bias formulas for sensitivity analysis of unmeasured confounding for general outcomes, treatments, and confounders. Epidemiology 22:42-52, 2011

29. Osterberg L, Blaschke T: Adherence to medication. N Engl J Med 353:487-497, 2005

30. Lacro JP, Dunn LB, Dolder CR, et al: Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: A comprehensive review of recent literature. J Clin Psychiatry 63:892-909, 2002

31. U.S. Government Accountability Office: Medicare Part D: Spending, Beneficiary Cost Sharing, and Cost-Containment Efforts for High-Cost Drugs Eligible for a Specialty Tier. GAO-10-242, Report to the Chairman, Subcommittee on Health, Committee on Ways and Means, House of Representatives, 2010

32. Centers for Medicare & Medicaid Services (CMS): Prescription Drug Plan Formulary, Pharmacy Network, and Pricing Information Files, 2011. www.cms.gov/Research-Statistics-Data-and-Systems/Files-for-Order/NonIdentifiableDataFiles/PrescriptionDrugPlanFormularyPharmacyNetworkandPricingInformationFiles.html

33. Howlader N, Noone AM, Krapcho M, et al (eds): SEER Cancer Statistics Review, 1975-2010. Bethesda, MD, National Cancer Institute, 2013. http://seer.cancer.gov/csr/1975_2010/

34. Gellad WF, Grenard JL, Marcum ZA: A systematic review of barriers to medication adherence in the elderly: Looking beyond cost and regimen complexity. Am J Geriatric Pharmacother 9:11-23, 2011

GLOSSARY TERMS

imatinib: a small molecule compound originally developed for treating chronic myelogenous leukemia and GI stromal tumors. Imatinib (STI571, Gleevec) is a selective tyrosine kinase inhibitor that binds to the ATP-binding pocket and blocks the tyrosine kinase activities of Abl, c-kit, and PDGFR.

Tyrosine kinase inhibitors: Molecules that inhibit the activity of tyrosine kinase receptors. They are small molecules developed to inhibit the binding of ATP to the cytoplasmic region of the receptor (eg, gefitinib), thus further blocking the cascade of reactions that is activated by the pathway.

