Prevalence, associated causes, and explanatory variables of non-adherence of generic imatinib in chronic myeloid leukemia

Prevalencia, causas asociadas y variables explicativas de la no adherencia del imatinib genérico en pacientes con leucemia mieloide crónica

Jorge Estrada-Acevedo[1*]; Juliana Madrigal-Cadavid[2]; Alejandra Rendon-Montoya[2]; Carlos Alberto Gómez-Mercado[1]; Erika Alejandra Giraldo-Gallo[1]; Dorys Cardona-Arango[1]; Angela María Segura-Cardona[1]

* joestradaa@uces.edu.co

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Abstract

Introduction: Imatinib has become the standard first-line therapy CML in chronic accelerated and blastic phases and has demonstrated hematologic, cytogenetic, and molecular response rates of over 90%. The non-adherence represents one of the main reasons for not achieving therapeutic success, increased disease progression, risk of resistance, and higher mortality rates. Although drug adherence to imatinib has been analyzed in several studies, its prevalence and associated causes are widely variable. **Objective:** To determine the prevalence of non-adherence of generic imatinib in chronic myeloid leukemia, associated causes, the proportion of patients who improve this non-compliance, and its explanatory variables. **Methods:** A retrospective observational cross-sectional analytical study was performed on patients with Chronic Myeloid Leukemia regarding treatment with imatinib generic brand, dispensed by a health institution between August 2018 and December 2022. Drug adherence status was defined as the dependent variable and sociodemographic, clinical, and pharmacological variables as independent variables. The information was extracted from a database of pharmacotherapeutic follow-ups performed on patients automatically identified through algorithms as non-adherent. Pharmacists contacted the patient to intervene and improve this compliance. Univariate, bivariate, and multivariate analysis was performed. **Results:** A total of 315 patients were analyzed, with a mean age of 52±17 years, median treatment time of 250 days [RIC 97-362], 11% were polymedicated and 16.8% were multimorbid; 30.5% were non-adherent. The associated causes were lack of specialist appointment (39.6%), delay in authorization by the insurer (31.9%) and not having a current medical prescription (5.5%). Of the non-adherent patients, 86% had a history of pharmacological non-adherence and 61% of non-timely claims. After the pharmacist's intervention, 80% improved this inadequate compliance. During the bivariate analysis, the variables age, time on treatment, and having a history of non-adherence were found to be significant, which, in the multivariate model, behaved as risks with statistical significance. When adjusting the model for the other variables, although they continued to behave as risks, only the variable of a history of non-adherence remained statistically significant. **Conclusion:** The prevalence of non-adherence is higher than that reported in the literature, the associated causes are mainly administrative, and the persons at greater risk of presenting this health outcome are those with greater age, less time in treatment, and those with a history of non-adherence to other medications.

Keywords: Medication adherence; Leukemia, Myelogenous, Chronic, BCR-ABL Positive; Risk factors.

[1] Universidad CES, Medellín, Colombia.
[2] helPharma. Medellín, Colombia.

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Editorial Note

This article met the requirements to be published in Salud UIS, and the authors have stated that they have no conflict of interest. However, the editorial committee has concerns due to a possible conflict of interest of the authors and makes it publicly known to its readers.

Resumen

Introduccion: El imatinib se ha convertido en el tratamiento estándar de primera línea de la LMC en las fases crónica acelerada y blástica y ha demostrado tasas de respuesta hematológica, citogenética y molecular superiores al 90%. La falta de adherencia representa una de las principales razones para no alcanzar el éxito terapéutico, el aumento de la progresión de la enfermedad, el riesgo de resistencia y las mayores tasas de mortalidad. Aunque la adherencia al tratamiento con imatinib se ha analizado en varios estudios, su prevalencia y las causas asociadas son muy variables. **Objetivo:** determinar la prevalencia de la no adherencia al imatinib genérico en leucemia mieloide crónica, causas asociadas, proporción de pacientes que mejoran y sus variables explicativas. **Métodos:** se realizó un estudio observacional, retrospectivo, transversal analítico, en pacientes con leucemia mieloide crónica en tratamiento con imatinib de marca genérica, dispensados por una institución de salud entre agosto de 2018 y diciembre de 2022. Se definió el estado de adherencia al medicamento como variable dependiente y las variables sociodemográficas, clínicas y farmacológicas como variables independientes. La información se extrajo de una base de datos de seguimientos farmacoterapéuticos realizados a pacientes identificados automáticamente mediante algoritmos como no adherentes. Los farmacéuticos contactaron al paciente para intervenir y mejorar la adherencia. Se realizó análisis univariado, bivariado y multivariado. **Resultados:** se analizaron 315 pacientes, con una edad media de 52 ± 17 años y una mediana de tiempo de tratamiento de 250 días [RIC 97-362], el 11 % eran polimedicados y el 16,8 % multimórbidos. El 30,5 % eran no adherentes. Las causas asociadas a la no adherencia fueron la falta de cita con el especialista (39,6 %), el retraso en la autorización por parte de la aseguradora (31,9 %) y no disponer de prescripción médica vigente (5,5 %). De los pacientes no adherentes, el 86 % tenía antecedentes de falta de adherencia farmacológica y el 61 % de reclamaciones fuera de plazo. Tras la intervención del farmacéutico, el 80 % mejoró este cumplimiento inadecuado. En el análisis bivariado se encontraron significativas las variables edad, tiempo en tratamiento y tener antecedentes de no adherencia, que en el modelo multivariado se comportaron como riesgos con significancia estadística. Al ajustar el modelo para las demás variables, aunque siguieron comportándose como riesgos, sólo la variable de antecedentes de falta de adherencia se mantuvo estadísticamente significativa. **Conclusión:** la prevalencia de no adherencia es superior a la reportada en la literatura, las causas asociadas son principalmente administrativas y las personas con mayor riesgo de presentar este resultado de salud son aquellas con mayor edad, menor tiempo en tratamiento y con antecedentes de no adherencia a otros medicamentos.

Palabras clave: Cumplimiento de la Medicación; Leucemia mielógena crónica BCR-ABL Positiva; Factores de riesgo.

Nota Editorial

Este artículo cumplió los requisitos para ser publicado en Salud UIS, y los autores han manifestado que no tienen conflicto de interés. Sin embargo, el comité editorial tiene preocupaciones por posible conflicto de interés de los autores y lo deja manifiesta de manera pública a sus lectores.

Introduction

Chronic myeloid leukemia (CML) is a hematological disorder, mainly associated (in more than 95% of cases) with a reciprocal translocation between chromosomes 9 and 22, known as the Philadelphia chromosome, which gives rise to the formation of the BCR/ABL1 hybrid gene responsible for the pathogenesis of the disease due to its increased tyrosine kinase activity, which generates excessive production of leukocytes, accumulation of myeloid cells and precursors[1,2]. It represents 15% of hematologic neoplasms in adults[3], with an annual incidence of 1.5 cases per 100,000 individuals[4] with a median age of 67 years[5] and with a ratio of 2.2 males per 1.4 females[4].

The introduction of tyrosine kinase inhibitors (TKIs) in 2006 revolutionized the treatment of CML, increasing the 5-year survival rate from 22% to 80%[6–8], markedly improving quality of life[9] and dramatically changing its prognosis to the point where treatment can discontinue when the patient achieves a deep and stable molecular response over time[10]. Imatinib has become the standard first-line therapy CML in chronic[11], accelerated, and blastic phases[12]; it has demonstrated hematologic, cytogenetic, and molecular response rates of over 90%[4]; a response that in turn has been strongly associated with adherence to drug treatment[12,13].

The fact of not having adequate pharmacological adherence, defined as the period elapsed from the beginning to the premature discontinuation of treatment[14,15] by the decision of the patient or for reasons beyond the patient's control[15–17]; represents one of the main reasons for not achieving therapeutic success[18,19], increased disease progression, risk of resistance and higher mortality rates[4,20,21].

Although drug adherence to imatinib has been analyzed in several studies, its prevalence and associated causes are widely variable[3,4,12,14,16,22] because sociodemographic, economic, and pharmacological factors have been dynamic and interrelated[22]; however, the main are adverse effects, untimely access to treatment, lack of knowledge of the therapy and the disease by the patient[3,4,12,22–26].

Some studies have shown the specific approach and intervention of this undesirable event through multiple methods, among which the history of medication claims in pharmacy has been considered relatively objective[27–29]. Some experiences show how drug claim rates increase after the detection of inconsistent patients through lists generated by the pharmacy, impacting their correction through the evaluation of the causes and the establishment of resolution measures for each one of them[30–32].

Accordingly, the present study was designed to determine the prevalence of non-adherence, the associated causes, the proportion of patients who improve this inappropriate compliance and its explanatory variables.

Methodology

A retrospective, observational, cross-sectional analytical study was performed. The population were patients attended by a health institution, diagnosed with CML, and on treatment with the generic imatinib, dispensed by a health institution between August 2018 and December 2022.

Dependent variable: Pharmacological adherence status. Patients who do not claim their medication in a timely and systematic according to the periodicity indicated in the medication guideline are considered non-persistent.

Independent variables: Age, gender, type of insurance, schooling, polymedication (5 or more concomitant medications), multimorbidity (3 or more concomitant pathologies), city of residence, daily doses, time on treatment, history of non-adherence.

Other variables to describe: Causes of non-adherence, the origin of the causes (administrative: the patient is not involved; patient: the patient has a direct relationship with the cause), intervening cause, and non-adherence improvement.

The information necessary to carry out the study was extracted from a database with information on outpatient pharmacy claims and pharmacotherapeutic follow-up and notes of pharmacists in the history clinical of a health institution. The institution carries out a standardized process to manage and intervene in the non-timely claiming of the drug. The patient's non-adherence is identified automatically through algorithms that are applied to all medications regardless of their claim frequency. Then, pharmacists call the patients to identify, manage, and intervene in the causes that originated the non-adherence. The group of patients finally contacted constitutes a convenience sample according to the availability of the patients and the number of professionals dedicated to the contact work. A patient with consecutive monthly prescription claims for generic imatinib was considered adherent and the treatment adherence was calculated using the Morisky Green test applied by the pharmacist. A digital capture system was used to collect the information, which offered the advantage of validating and superimposing the data entered during the pharmacist's consultation, thus providing greater accuracy and quality of the data, and allowing interfacing with the Excel program, thus reducing typing errors.

A univariate analysis was performed in which absolute and relative frequencies (simple and cumulative) were used for qualitative variables, and for quantitative variables summary measures such as central tendency (mean), dispersion (range, interquartile range, standard deviation) and position (median and quartiles). We worked with a power of 80%, confidence of 95%, and an alpha error of 5%. The Kolmogorov-Smirnov normality test was performed for quantitative variables. During the bivariate analysis, the t-Student hypothesis test was used to compare dichotomous qualitative variables and quantitative variables that were normally distributed (Mann-Whitney U if the quantitative variable was not normally distributed). For the multivariate analysis, binary multiple logistic regression was used for explanatory purposes, considering those variables that were statistically significant during the bivariate analysis, met the Hosmer-Lemeshow criterion, or

were defined as relevant by the clinical criterion of the subject matter expert. The R Core Team (2021) statistical package was used.

Results

During the observation period, 315 patients with a diagnosis of CML and treatment with first-line therapy generic imatinib were analyzed, with a mean age of 52±17 years, where the youngest was 9, and the oldest was 98 years old. The male-to-female ratio was 1:1, 98.4% were affiliated to the contributory health regime, 72.5% had maximum secondary schooling, 96% had a daily dose of 400 mg or less, which implied one dose per day, the median treatment time was 250 days [RIC 97-362], 11% were polymedicated, and 16.8% were multimorbid (Table 1).

Table 1. Characterization of the population.

Variable		%	p-value
Age range (years)	46 - 65 years	44.4%	0.07866*
	19 - 45 years	29.5%	
	>65 years	22.9%	
	<18 years	3.2%	
Gender	Male	52.4%	0.4308
	Female	47.6%	
Health Regime	Contributory	98.4%	1
	Subsidized	1.6%	
Schooling	Basic Primary	15.6%	0.9979
	Basic Secondary	56.9%	
	Professional Technician	11.9%	
	Professional	12.5%	
	Technological	3.1%	
Polymedicated	Yes	10.8%	0.399
	No	89.2%	
Multimorbid	Yes	16.8%	0.6593
	No	83.2%	
Range time in treatment	6 months or less	38.1%	0.0002*
	6 - 12 months	35.9%	
	12 - 18 months	14.9%	
	24 months or more	9.5%	
	18 - 24 months	1.6%	
History of non-adherence	With record	86.0%	0.00132*
	No record	14.0%	

It could be observed that 30.5% were non-adherent in the imatinib claim, the main cause of non-adherence was the lack of specialist appointment for drug formulation (39.6%), followed by the delay in the authorization of the drug by the health insurer (31.9%) and finally, not having the medical formula at the time of dispensing (5.5%) Figure 1. Of the causes detected by the pharmacist, 94.8% were intervened, of which 42.7% were directed to the medical staff, 35.4% to the health insurer's authorization platform and 21.9% to the patient. After the intervention performed, 80% of the patients improved this inadequate compliance (reaching a timely claim every 28±2 days and systematic as a function of time).

During the bivariate or inferential analysis, it was detected that the variables age (p-value: 0.00073), time on treatment (p-value < 0.00000) and having a history of non-adherence (p-value: 0.00133), presented a statistically significant association, which were included in the multivariate model, where it was shown that the crude measures of strength of association (OR) behaved as risks of non-adherence and continued to be statistically significant. When adjusting the model for the other variables, they continued to behave as risks of non-adherence (Table 2). The multiple logistic regression model for explanatory purposes aims to obtain the value contributed by each individual variable on the dependent variable, adjusting for the effect of the other covariates.

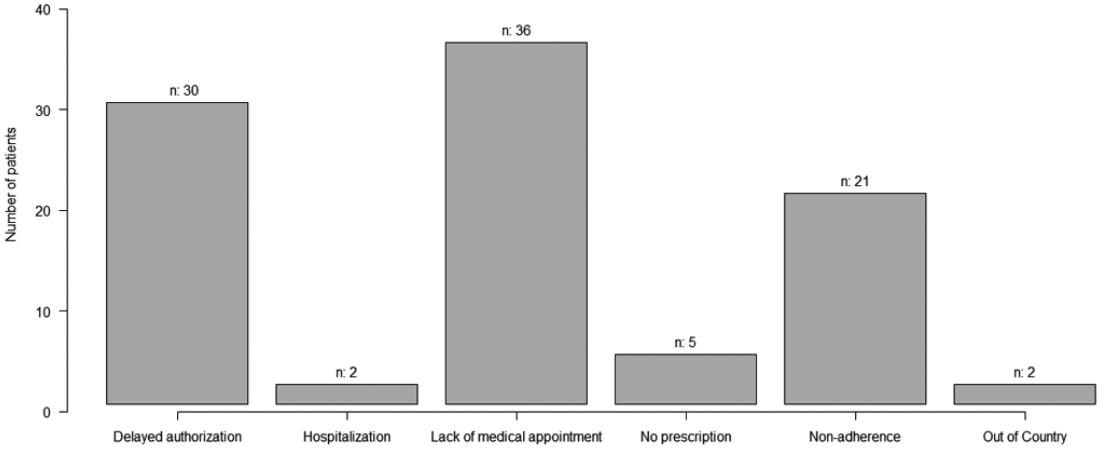

Figure 1. Description of the causes associated with pharmacological non-adherence.

Table 2. Relationship between pharmacological non-adherence and associated individual variables.

Variable	Crude OR* [95% CI]	p-value	Adjusted OR** [95% CI]	p-value
Age range (years)				
≥65 years	4.14 [1.03-16.9]	0.04202	3.49 [0.81-15.1]	0.08799
46 - 65 years	2.11 [0.56-7.95]	0.25601	1.97 [0.49-7.86]	0.32728
19 - 45 years	1.91 [0.49-7.32]	0.33492	1.61 [0.39-6.60]	0.49486
≤18 years	1		1	
Time in treatment				
≤6 months	3.82 [1.60-9.15]	0.002435	2.91 [1.16-7.22]	0.02115
6 - 12 months	1.51 [0.65-3.42]	0.325660	1.19 [0.49-2.80]	0.69133
12 - 18 months	0.87 [0.34-2.18]	0.765257	0.69 [0.26-1.82]	0.46505
18 - 24 months	0.51 [0.06-3.51]	0.493727	0.52 [0.06-3.76]	0.51654
≥24 months	1		1	
History of non-adherence				
With record	2.97 [1.55-5.72]	0.00102	2.52 [1.26-5.05]	0.00866
No record	1		1	

*Simple binary logistic regression for explanatory purposes; **Binary multiple logistic regression for explanatory purposes.

Discussion

In some studies of adherence to imatinib therapy, correlations between poor adherence, reduced failure-free survival and increased healthcare costs have been identified, and a prevalence of drug non-adherence of approximately 11.3 %[33–39]. In our study, a prevalence of approximately 3 times higher (30.5%) was identified, similar to a study performed by Anderson et al[21], in our case which can be explained by the fact that pharmacists do not spend time identifying patients but are identified through an information system allowing the pharmacist to focus solely and exclusively on the management of these pharmacological risks to ensure adherence to treatment and appropriate use of the drug.

Although the most frequent causes associated with pharmacological non-adherence reported in the literature are related to the patient's situations, such as underdosing, not attending medical appointments, forgetting to take the medication, financial difficulties, low social support, lack of patient knowledge, adverse reactions, in our cohort the most frequent causes were related to situations beyond the patient's control or administrative causes[4,14,19,22,25,40,41]. The most frequent causes were such as lack of an appointment with a specialist to formulate the drug (39.6%), delay in authorization by the health insurer (31.9%), and finally, not having the medical prescription at the time of dispensing (5.5%).

It should be noted that, although the prevalence of non-adherence detected is higher than that reported in the literature, the proportion of patients who improve this inappropriate compliance following intervention by the pharmacist through pharmacotherapeutic follow-up is 80%.

Finally, according to the literature, the sociodemographic variables that most explain pharmacological non-adherence are age, gender, schooling, and monthly income, and the pharmacological variables are mainly the duration of treatment, frequency, dose, polymedication, and comorbidities[4,21,22,25,39,40]. These results were like those identified in our study, where in addition to these variables, having a history of non-adherence was also relevant when evaluating the possibility of pharmacological non-adherence. Some studies suggest that the generic imatinib may have higher adherence rates, associated with the cost of the drug and out-of-pocket costs. However, in the Colombian health system, the health insurer covers this drug and the patient's out-of-pocket cost is relatively low[42].

Since this is a retrospective study, it has some limitations, such as the omission of important measurements or whether the data capture was adequate, as well as the possibility of selection bias or misclassification. However, an attempt was made to control for selection bias by including 100% of the available records and for information bias by excluding variables with a data loss of more than 10%. In addition, potential confounders were controlled by applying adjusted models (multivariate analysis).

Conclusions

The prevalence of non-adherence in patients diagnosed with CML and on treatment with generic imatinib is higher than that reported in the literature, the causes associated with this pharmacological risk are mainly administrative (external to the patient) and the people at greatest risk of presenting this health outcome are those who are older, have been on treatment for less time and have a history of non-adherence to other drugs. It is important to carry out other studies with other methodological designs to identify other causes associated with the non-claiming of medications in a timely.

Authors contribution

JEA, CAGM, EAGG and AMSC contributed to the conception and planning of the study. JEA, JMC and ARM did the data collection, analysis, and interpretation. CAGM, EAGG, DCA and AMSC participated in the orientation of the research. JEA, JMC, ARM and CAGM prepared and drafted the manuscript and EAGG, DCA and AMSC critically revised it. All authors read and approved the final version of the manuscript.

Ethical considerations

According to article 11 of resolution 008430 of 1993 of the Ministry of Health of Colombia, this research is considered as "no risk". The identifying data was suppressed, thus guaranteeing the confidentiality and privacy of the information. The work was endorsed by the research committee of the health institution.

Conflicts of interest

The author reports no conflicts of interest in this work.

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The authors report that they did not use artificial intelligence, language models, machine learning or similar technologies to create or assist with the elaboration or editing of any of the contents of this document.

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