Original Study

# Comparison of Branded and Generic Imatinib Plasma Concentrations in Patients With Chronic Myelogenous Leukemia: Unicentric Study

Alen Ostojic,[1] Dubravka Sertic,[1] Pavle Roncevic,[1] Zinaida Peric,[1,2] Paula Granic,[3] Nikolina Matic,[1] Sandra Basic-Kinda,[1] Ranka Serventi-Seiwerth,[1] Ivo Radman,[1] Renata Zadro,[4,5] Damir Nemet[1,2]

## Abstract

**Imatinib has been the standard of care in chronic myelogenous leukemia for 15 years. Its optimal plasma concentration correlates with optimal disease response. We compared plasma concentrations in patients who switched from branded to generic imatinib. No statistical difference in achieved imatinib plasma concentrations was found, and the treatment response was maintained.**

**Introduction:** For over a decade, imatinib has been the first-line treatment of Philadelphia chromosome-positive chronic myeloid leukemia (CML). Doubts on the bioequivalence and bioavailability of emerging generic compounds have been expressed. Adequate imatinib plasma concentration ([IPC] $\geq$1000 μmol/L) is associated with a better chance of optimal treatment response in patients with CML. In this study, we compared the achieved IPCs between the branded compound and its 2 generic forms. **Patients and Methods:** IPCs were compared in 24 consecutive patients with CML in the first chronic phase who changed from branded to generic imatinib. The median age was 49 years (range, 22-76 years). Fifteen of them were male. Six patients were switched to Neopax, 13 to Imakrebin, and 5 patients received both generics consecutively. All compounds were used in an equivalent dose of 400 mg orally once daily for at least 1 month before plasma concentrations were measured. High-performance liquid chromatography was used to determine imatinib plasma concentration from a specimen collected 21 to 24 hours after the last dose. **Results:** The median IPC achieved with branded imatinib was 1454 μmol/L (range, 485-2707 μmol/L) with 18 patients (75%) having IPC $\geq$ 1000 μmol/L. For Neopax and Imakrebin, median IPCs were 1717 μmol/L (range, 1249-3630 μmol/L) and 1458 μmol/L (range, 707-880 μmol/L), respectively, with 11 of 11 (100%) and 16 of 18 (89%) patients having IPC $\geq$ 1000 μmol/L. No significant difference in measured IPCs between all 3 compounds was found ($P > .257$). **Conclusion:** When taken at equivalent doses, imatinib generics are bioequivalent and comparable in clinical efficacy and have the potential for substantial savings in the treatment cost for CML.

*Clinical Lymphoma, Myeloma & Leukemia,* Vol. 16, No. 8, 472-6 © 2016 Elsevier Inc. All rights reserved.
**Keywords:** Bioavailability, Clinical equivalency, Cost savings, Imatinib mesylate, Therapeutic drug monitoring

## Introduction

Since 2001, imatinib improved the prognosis in patients with chronic myelogenous leukemia (CML)[1] and is the standard of care worldwide. Recently, imatinib generics became available. Some case reports/series[2-6] raised concerns about its efficacy but refer to generics with questionable bioequivalence.[7] To date, there is no evidence that imatinib generics approved in North America and the European Union lack efficacy compared with the branded drug, even when comparing different imatinib crystal forms.[7]

[1]Department of Internal Medicine, Hematology Division, University Hospital Center Zagreb, Zagreb, Croatia
[2]Department of Internal Medicine, University of Zagreb School of Medicine, Zagreb, Croatia
[3]Department of Laboratory Diagnostics, Analytical Toxicology and Pharmacology Division, University Hospital Center Zagreb, Zagreb, Croatia
[4]Department of Laboratory Diagnostics—Hematology and Coagulation Division, University Hospital Center Zagreb, Zagreb, Croatia
[5]Department of Medical Biochemistry and Hematology, Faculty of Pharmacy and Biochemistry, University of Zagreb, Zagreb, Croatia

Submitted: Mar 17, 2016; Revised: Mar 31, 2016; Accepted: Apr 26, 2016; Epub: May 5, 2016

Address for correspondence: Alen Ostojic, MD, Department of Internal Medicine, Division of Hematology, University Hospital Center Zagreb, Kispaticeva 12, 10000 HR Zagreb, Croatia
E-mail contact: aostojic@kbc-zagreb.hr



2152-2650/$ - see frontmatter © 2016 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.clml.2016.04.003

Several studies correlated imatinib plasma concentrations (IPCs) with adequate treatment response.[8-10] The recommended therapeutic IPC is between 1000 μmol/L and 3000 μmol/L. Small intra-patient variations, greater inter-patient variation, proportional dose-exposure relationship, and therapeutic concentration interval are basic imatinib properties, making it suitable for therapeutic drug monitoring.[11] The standard operating protocol at our institution does not require regular screening IPC monitoring except in cases of unmet optimal treatment goal at respective time points according to European Leukemia Net criteria.[12]

After the branded imatinib patent expired in March 2013 (before Croatia was admitted to the European Union), Neopax (later on marketed as Meaxin, Krka) and Imakrebin (Alvogen) became available on the Croatian market as the first 2 generics. According to the Croatian Institute for Health Insurance reimbursement policy, generics were instituted as the first line of treatment in newly diagnosed and those already using branded imatinib (Glivec, Novartis AG). Motivated by controversies on the efficacy of imatinib generics, we conducted a trial measuring IPCs in patients changing from branded to a generic drug. The results of the comparison of IPCs achieved with branded and generic imatinib are presented here as a unicentric experience.

## Patients and Methods

### *Study Design*

The IPC was measured in 24 consecutive patients with CML in their first chronic phase running out their last branded imatinib prescription. Their prescriptions were refilled with one of the available generics by our institution pharmacy. Afterward, branded imatinib was changed to one of the available generics or both consecutively. IPCs were measured every time the change in prescription was made. All drugs were used in an equivalent dose of 400 mg orally daily for at least 1 month before IPCs were measured. Patients were interviewed for adherence to regular imatinib use. During the study, no relevant changes in other chronic therapy were recorded.

### *Blood Sampling and Analytical Methods*

High-performance liquid chromatography was used to determine the IPC from a peripheral blood specimen collected 21 to 24 hours after the last dose. The test was performed without delay or pooling the samples. Imatinib was extracted from plasma with methanol. Clozapine was used as an internal standard. The sample was fractionated on a column (MN EC Nucleosil 100-5-C-18 EC 250 × 4.6 mm) with a mobile system consisting of ammonium acetate buffer, methanol, and acetonitrile (40:40:20). The flow rate was 0.75 mL/min. Quantitation was performed by measurement of ultraviolet detector at the wavelength of 265 nm.

The bcr-abl1 level in peripheral blood was quantified after at least 1 month of the use of a different drug compound. A quantitative real-time polymerase chain reaction was performed using a commercial Ipsogen BCR-ABL1 Mbcr kit (Qiagen). Reporting was done on an international scale, according to European Leukemia Net standards.[13]

**Table 1** Patient Demographics and Adherence Characteristics

| Parameter | Glivec/All Patients | Neopax | Imakrebin | *P* |
|---|---|---|---|---|
| **Patients While on Corresponding Imatinib** | | | | |
| Total | | | | |
| n (%) | 24 (100) | 11 (46) | 18 (75) | |
| Gender | | | | |
| Male, n (%) | 15 (63) | 6 (55) | 11 (61) | .935 |
| Age | | | | |
| Median, years (range) | 49 (22-76) | 49 (22-76) | 55 (30-72) | .698 |
| Adherence | | | | |
| Optimal n (%) | 19 (79) | 11 (100) | 17 (94) | .166 |
| Suboptimal n (%) | 5 (21) | 0 (0) | 1 (6) | |
| **Parameter** | **Glivec to Neopax** | **Glivec to Imakrebin** | **Glivec to Neopax then to Imakrebin** | ***P*** |
| **Patients Grouped According to Consecutive Generic Use** | | | | |
| Total | | | | |
| n (%) | 6 (25) | 13 (54) | 5 (21) | |
| Gender | | | | |
| Male, n (%) | 4 (67) | 9 (69) | 2 (40) | .546 |
| Age | | | | |
| Median, years (range) | 51 (30-67) | 47 (22-76) | 57 (36-72) | .701 |
| Adherence | | | | .059 |
| Optimal n (%) | 6 (100) | 8 (62) | 5 (100) | |
| Suboptimal n (%) | 0 (0) | 5 (39) | 0 (0) | |

Download English Version:

https://daneshyari.com/en/article/2754228

Download Persian Version:

https://daneshyari.com/article/2754228

Daneshyari.com