The Three Year Follow-up of CML Patients Treated with First-line Generic and First-line Branded Imatinib in Bosnia and Herzegovina

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ABSTRACT

Imatinib mesylate, a selective BCR-ABL tyrosine kinase inhibitor, has been well established as the standard of care for chronic myeloid leukaemia patients. In this study, we compared clinical outcomes of patients who received first-line Glivec (Group 1) with patients who received first-line generic imatinib (Group 2) in Bosnia and Herzegovina with three years follow-up of therapy. At 24 months of therapy, the achievement of complete cytogenetic response and major molecular response were comparable between the studied groups (CCyR was 69% vs. 70%, respectively; MMR was 54% vs. 48%, respectively). After comparing the reasons for the switch to nilotinib, we found that treatment failure was higher in patients treated with generic imatinib (30% vs. 8%, respectively) and side effects were similar in both patient groups (22% vs. 19%, respectively). In general, patients on first-line generic imatinib had higher rates of treatment failure compared to patients treated with first-line branded imatinib.

Keywords: Generic imatinib, Glivec, Clinical outcomes, CML

ÖZET

Bosna Hersek'te İlk-basamak Jenerik ve İlk-basamak Preparat Imatinib ile Tedavi Edilmiş CML Hastalarının Üç Yıllık Takbi

Selektif BCR-ABL tirozin kinaz inhibitörü olan İmatinib Mesilat, Kronik miyeloid lösemi hastalarının tedavisinde iyi bir standart olarak saptanmıştır. Bu çalışmada, Bosna Hersek'teki İlk-basamak Glivec (Grup 1) alan hastalarla ilk-basamak jenerik imatinib (Grup 2) alan hastaların klinik sonuçlarını üç yıllık tedavi takibi ile karşılaştırdık. 24 aylık tedavide, tam sitogenetik cevap ve majör moleküler cevabın başarısı, incelenen gruplar arasında karşılaştırılabilir düzeydeydi (sırasıyla, CCyR %69'a karşı %70; MMR, sırasıyla %54'e karşı %48 idi). Nilotinib'e geçiş nedenlerini karşılaştırdıktan sonra, jenerik imatinib ile tedavi edilen hastalarda tedavi başarısızlığının daha yüksek olmakla beraber (sırasıyla %30 ve %8), yan etkiler her iki hasta grubunda benzerdi (sırasıyla, %22'ye karşı %19). Genel olarak, ilk-basamak jenerik imatinib verilen hastalarda başarısızlık oranlarını, ilk-basamak preparat imatinib ile tedavi edilen hastalara kıyasla daha yüksek saptadık.

Anahtar Kelimeler: Jenerik imatinib, Glivec, Klinik sonuçlar, CML

INTRODUCTION

Imatinib mesylate is the first tyrosine kinase inhibitor (TKI) targeting the constitutively active BCR-ABL1 fusion protein responsible for the pathogenesis of chronic myeloid leukaemia.[1,2] The International Randomized Study of Interferon and STI571 (also known as IRIS) was the first clinical trial to show the superiority of imatinib (Glivec, Novartis, Switzerland) compared with interferon and low-dose cytarabine.[3,4] Since 2011, imatinib has been available as both branded (Glivec) and generic therapy. Low cost generic alternatives of imatinib are an integral part of cost effective healthcare strategies for developing countries. However, the efficacy and tolerability of imatinib generics as an alternative therapy have been contradictory.[5] The use of generics has been associated with different clinical outcomes. Studies conducted in Egypt, Morocco, Columbia and Iraq highlighted the increased toxicity of generic imatinib in comparison to the branded imatinib.[6-10] However, studies from Turkey, Canada, India, Bosnia and Herzegovina, and Iran showed that generic therapy is well tolerated in CML patients and that adverse effects are manageable with supportive care.[11-15] In this study, we compared clinical outcomes of patients who received first-line Glivec (Group 1) to patients who received first-line generic imatinib (Group 2) in Bosnia and Herzegovina after three years of therapy.

PATIENTS AND METHODS

This was a multicenter retrospective cohort study of BCR-ABL1 positive CML patients (n= 53) in the Federation of Bosnia and Herzegovina between 1 June 2005 and 31 August 2016. Glivec was used from 01 June 2005 until 30 September 2013, when all patients had to switch to generics, which was mandated by the Federal Solidarity Fund that allocates targeted cancer therapies. Patients in Group 1 (n= 26) were treated with first-line Glivec (median follow-up 36 months, range 6-36 months). Group 2 (n= 27) consisted of newly diagnosed CML patients who started treatment with generic imatinib after September 2013. All patients in Group 1 and 2 received the treatment less than 6 months after the diagnosis.[16] The following generic imatinib therapies were used: Anzovip (Zdravlje, Actavis) from 09/2013 to 09/2014, Meaxin (Krka) from 09/2014 to 12/2015, and Plivatinib (Pliva) from 12/2015 to 08/2016 (cutoff date for this analysis). Patient data was collected from the database of the Federal Solidarity Fund, a subsidiary of the Federal Health Insurance Agency. Institutional Review Board Approval was obtained from the Federal Solidarity Fund and Ethical Committee of the University Clinical Centre Sarajevo and the study was conducted in accordance with the Declaration of Helsinki.

Branded and generic imatinib was administered orally at dosage of 400 mg/day. Patients who were switched to nilotinib received orally 400 mg/day. Patient variables that were collected included age, gender, town, date of diagnosis, date of start of therapy, monthly TKI dosage, adverse side effects, progression, lethal outcome, prognostic factors and diagnostic parameters, including cytogenetics and molecular testing. In September 2013, Glivec stopped being available in Bosnia and all CML patients were switched to generic therapy Anzovip. Median duration of each therapy is given in Table 1. Intention to treat principle and cumulative incidence function were used in the analysis of overall survival, the achievement of complete cytogenetic response and major molecular response.

RESULTS

We compared patients on Glivec as first-line therapy (Group 1, n= 26) with patients on first-line generic imatinib (Group 2, n= 27) with the follow-up period of at least three years for each group (Table 1). When we compared Groups 1 and 2 after 36 months of therapy, rate of overall survival was similar (88% vs. 85%, respectively, p> 0.05). At 24 months of therapy, the achievement of complete cytogenetic response and major molecular reponse were comparable between the studied groups (CCyR was 69% vs. 70%, respectively; MMR was 54% vs. 48%, respectively, p> 0.05; Figure 1A).

In Group 1, 27% of patients (7/26) switched to nilotinib (treatment failure in 2 patients and side effects in 5 patients), 54% of patients (14/26) were switched to generics because Glivec was no longer available, and 19% of patients (5/26) stopped therapy (2 patients stopped therapy and 3 patients died). Of the 7 patients who switched to nilotinib,

Table 1. Patient cohort characteristics including gender, median age at diagnosis, and median duration of therapy (months). Among patients who started with Glivec as first-line therapy, 7 patients switched to nilotinib and 1 patient subsequently switched to nilotinib after treatment with generic imatinib as second-line therapy. Among patients treated with generic imatinib as first-line, 14 patients switched to nilotinib.

	1st line Glivec Group 1			1st line Generic Group 2	
Patients	26			27	
	Switched to nilotinib	**Switched to generic**		**Switched to nilotinib**	**Stayed on generic**
	7	14		14	13
		Switched to nilotinib	**Stayed on generic**		
		1	13		
		Female	5		
		Male	9		
Female	9			11	
Male	18			15	
Median age at diagnosis	44	39		59	
Median duration of therapy before switch (months)	23	60		9	14*
		6	60*		

* Median duration of therapy on generic imatinib

71% (5/7) achieved CCyR, 29% (2/7) achieved MMR and none died. Of 19 patients who stayed on imatinib, 68% (13/19) achieved CCyR, 63% (12/19) achieved MMR, and 3/19 (16%) died. Of the 54% (14/26) patients who were switched from branded imatinib to generic imatinib, one patient (7%) lost complete cytogenetic response.

Regarding Group 2, 52% (14/27) of patients switched to nilotinib due to treatment failure (n= 8) and side effects (n= 6), while 48% (13/27) of patients stayed on generics. Of patients who switched to nilotinib, 43% (6/14) achieved CCyR and 15% (2/14) achieved MMR. Of the patients who stayed on generic imatinib, 100% (13/13) achieved CCyR and 85% (11/13) achieved MMR.

More patients in our study stayed on Glivec as compared to generic imatinib (73% vs. 48%, respectively; Figure 1B). When we analysed the reasons for the switch to nilotinib, we found that treatment failure was higher in patients treated with generic imatinib (30% vs. 8%, respectively; Figure 1C) and side effects were similar in both patients groups (22% vs. 19%, respectively; Figure 1C).

DISCUSSION

Imatinib mesylate a selective BCR-ABL tyrosine kinase inhibitor (TKI), has been well established as the standard of care for chronic myeloid leukaemia (CML) patients.[3] After the patent expired in 2013 in the EU and 2016 in USA, generics of imatinib have been approved in many countries as the alternative, low-cost forms for the treatment of CML patients. Studies have shown no difference in water solubility, and absorption between generic and branded imatinib.[17] Three forms of imatinib are identified (α-, β- and γ-crystalline forms), of which the β polymorph is more thermodynamically stable.[18] The branded imatinib is in the β-crystal form, while the majority of generics have the α-form.[19] Studies have shown that the α-crystal form is not inferior in terms of pharmacologic properties and effectiveness.[5]

Using intention to treat principle, our results at three years suggest that there was no significant difference in the overall survival and achievement of CCyR between first-line Glivec and first-line generic imatinib. At 24 months of therapy, the achievement of complete cytogenetic response in

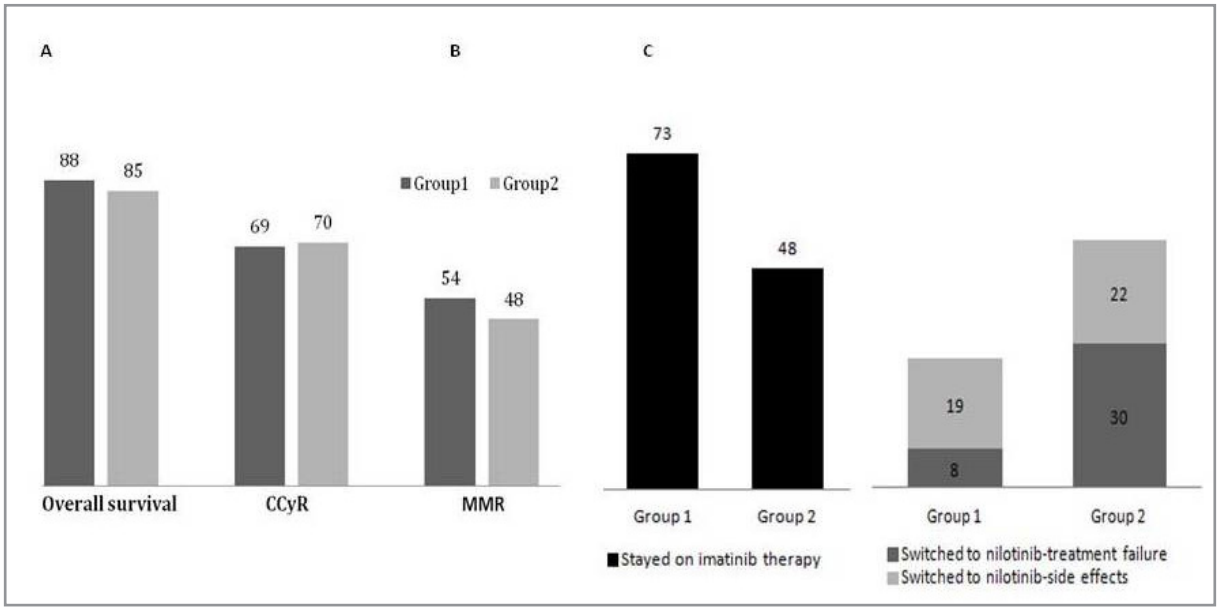

Figure 1. Clinical outcomes of first-line Glivec and first-line generic imatinib patients. **(A)** Percetages of overall survival, complete cytogenetic response (CCyR) and major molecular response (MMR) in newly diagnosed CML patients who were treated with branded imatinib (Glivec, Group 1) or with first-line generic imatinib (Group 2) at three years of therapy. **(B)** Percentages of CML patients treated with imatinib therapy who did not switch to second-generation therapy, nilotinib, in Group 1 (first-line Glivec) and Group 2 (first-line generic). **(C)** Percetages of CML patients who switched to nilotinib because of treatment failure and side effects of branded imatinib (Group 1) and generic imatinib (Group 2). The reason for the switch to nilotinib is marked in light gray (side effects) and dark gray (treatment failure).

patients who were treated with first-line and second-line branded imatinib were 69% vs. 70%, respectively. Major molecular reponse were comparable between the Group 1 and Group 2 of patients (54% vs. 48%, respectively).

Studies on the efficacy of generic imatinib have shown contradictory results.[2,9-14] Several studies highlighted that generic therapy is not well tolerated in CML patients and that adverse effects of therapy are not manageable with supportive care.[2,9,10] In a study by Eskazan et al., 80 CML patients were on second-line generic imatinib therapy, and cumulative MMR rate was 75% (median follow-up under Glivec and generic imatinib was 55 and 12 months, respectively), which is similar to our results (63% of patients in Group 2 achieved MMR).[20] In the same study, MMR response rates for patients on first-line Glivec and patients on second-line generic imatinib were 77% vs 75%, respectively; thus, similar to our results, they did not have significant differences between two study populations.[20]

Several studies stated that there was no difference in response or toxicity between the generic and the branded therapy.[11-14,21] Malkan et al. conducted a study on 120 CML patients, where 104 patients were on Glivec and only 16 patients were on generic imatinib with a follow-up of 36 months. Their results showed that MMR rate at 36 months was 93.9% in patients treated with Glivec, compared to 86.5% in patients treated with front-line generic therapy.[13] The same study found that after 18 months, more patients on generic imatinib were switched to nilotinib, compared to patients on Glivec (5.9% vs. 1%, respectively). It is interesting to note that our study showed higher percentage of patients who switched to nilotinib in both studied groups (52% vs. 27%, respectively). When we analysed the reasons for the switch to nilotinib, we found that treatment failure was higher in patients treated with generic imatinib and side effects were similar in both patient groups.

Median follow-up of patients on generic imatinib in majority of studies was short. In studies conducted by Eskazan et al. and Kang et al., patients were followed for a median period of 12 months after switching from Glivec to a generic, which makes it difficult to estimate long-term outcomes.[12,20]

Fifty-three patients were enrolled in our study, so this study was partially limited by the relatively small patient number. However, this is one of the first comprehensive reports on the long-term effects of first-line generic imatinib on clinical outcomes.

Our results suggest that at three years, there was no significant difference in the overall survival and achievement of CCyR and MMR between first-line Glivec and first-line generic imatinib. However, patients on first-line generic imatinib had higher rates of treatment failure compared to patients treated with first-line Glivec.

Acknowledgments:
We would like thank Esad Kurtovic for patience and assistance.

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