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GENERIC IMATINIB IN THE TREATMENT OF CHRONIC MYELOID LEUKEMIA: TWO YEARS' EXPERIENCE IN LATVIA

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Background: **Imatinib is tyrosine kinase inhibitor (TKI) and as a targeted anti-cancer agent has significantly changed chronic myeloid leukemia (CML) prognosis and patient survival. Currently TKI is the main therapy in CML Philadelphia chromosome-positive (Ph-positive) cases. When generics of imatinib appeared in the pharmaceuticals market, reimbursement policies in many countries switched to using generics or encouraged use of generic imatinib to lower the expenses. Cost savings were substantial; however, for doctors and CML patients the efficacy, safety and quality of generic imatinib were an issue of concern.** ***Objective:*** **Since the global number of CML patients, who in the future will have to switch from original imatinib to generic imatinib, is high, the aim of study was to monitor, whether during 24 months of generic imatinib usage patients maintain the achieved major molecular response (MMR) or whether the treatment results are inferior.** ***Methods:*** **We conducted a retrospective study, which included CML patients, who were above 18 years of age and who until May 2013 had used at least for 2 years (24 months) the original imatinib, and following that used at least for 24 months one of the generic imatinib medicines. In 2013, before switching to generic imatinib, all patients had reached MMR in accordance with European LeukemiaNet (ELN) Guidelines. Every three months blood count, BCR-ABL fusion gene (BCR-ABL), biochemical analysis and side effect were monitored.** ***Results:*** **Our study proved that CML patients, who had achieved MMR by original imatinib therapy, retained MMR during 24 months of generic imatinib therapy. Nobody was switched to second line generation TKI. During observation period neither haematological, nor non-hematological toxicity was found.** ***Conclusion:*** **Our study proved that CML patients, who had achieved MMR by original imatinib therapy, retained MMR during 24 months of generic imatinib therapy. This demonstrates that generic imatinib is not inferior to original imatinib. As to expenses, the annual costs of generic imatinib are lower by 96%, which is a significant benefit to health-care financing.**

Key Words: **generic imatinib, BCR-ABL, CML, MMR, Philadelphia chromosome, TKI.**

The last two decades have witnessed fast progress in the treatment of haematological diseases. One of the examples is imatinib (Gleevec, Novartis), which was for the first time used for treating chronic myeloid leukemia (CML) in 1998. Imatinib is tyrosine kinase inhibitor (TKI) and as a targeted anti-cancer agent has significantly changed CML prognosis and patient survival. Currently TKI is the main therapy in CML Philadelphia chromosome-positive (Ph-positive) cases, it is leading to a decline in annual mortality rates from 10–20% to 2% and has improved the estimated 10-years survival from less than 20% to more than 80%, and the number of patients, who have attained treatment-free remission, keeps increasing. Alongside these achievements, the costs of successful CML treatment also increased. When generics of imatinib appeared in the pharmaceuticals market, reimbursement policies in many countries switched to using generics or encouraged use of generic imatinib to lower the expenses. Cost savings were substantial; however, for doctors and CML patients the efficacy, safety and quality of generic imatinib were an issue of concern.

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Abbreviations used: BCR-ABL – BCR-ABL fusion gene; CCyR – complete cytogenical response; CHR – complete haematological response; CML – chronic myeloid leukemia; CP – chronic phase; ELN – European LeukemiaNet; MMR – major molecular response; Ph-positive – Philadelphia chromosome-positive; TKI – tyrosine kinase inhibitor.

The first TKI — imatinib mesylate (imatinib) (Glivec; Novartis, Basel, Switzerland) was registered for use in Europe in 2002. In Latvia imatinib for CML patients was included in the list of medicines reimbursed by the state in 2006 October. Initially imatinib was reimbursed in the presence of following CML indications: children with CML all phases and second line treatment for adult CML chronic phase (CP) patients. From May 2013 the original Glivec was substituted by generic imatinib in the state reimbursement medicines list. Tibaldix and Meaxin were the first generic imatinibs used in Latvia. The registered indications for using the medicines did not coincide with the ones for which the state reimbursed the use of it. However, considering the great difference in prices, the State reimbursement system ignored it, providing that all indications for using imatinib that have ever been registered were applicable also to these medicines. Patients had no choice — the state reimbursement system paid only for generic imatinib. Only one patient with CML CP continued to pay himself for the original drug Gleevec. In this country the purchase price of medicines is reviewed every 3 months, and if the price of a medicine belonging to a certain group changes, then the state reimburses in 100% amount only the cheapest medicine. Thus, not all patients received all the time generic imatinib of the same producer; many received various generic imatinibs in their treatment. Table 1 shows those generic imatinibs that were on the reimbursement list from May 2013 until March 2016, as well their marketing authorisation holder and the state.

Table 1. Generic imatinibs

Generic imatinib	Marketing authorisation holder, state
Tibaldix	Pharma Swiss, the Czech Republic
Meaxin	KRKA, Slovenia
Imatinib Teva	Teva, the Netherlands
Itivas	Briz, Latvia
Imatinib Accord	Accord Healthcare Limited, the UK
Imatinib Sano Swiss	Sano Swiss, Lithuania

Since the global number of CML patients, who in the future will have to switch from original imatinib to generic imatinib, is high, the aim of study was to monitor, whether during 24 months of generic imatinib usage patients maintain the achieved major molecular response (MMR) or whether the treatment results are inferior, to monitor also side effects, frequency of them. If the treatment results are not inferior, to compare the costs of medicines.

MATERIALS AND METHODS

We conducted a retrospective study in Riga East Clinical University Hospital Chemotherapy and Hematology Clinic, which included all CML patients, who were above 18 years of age and who until May 2013 had used at least for 2 years (24 months) the original imatinib, and following that used at least for 24 months one of the generic imatinib medicines. In 2013, before switching to generic imatinib, all patients had reached MMR in accordance with ELN Guidelines [1, 2]. The study design, patients' information and consent forms were approved by the Ethic Commitee of the Riga Stradins University. All patients had agreed to data analysis.

Criteria for including in the study:

- patients > 18 years;
- CP at the moment of diagnosing CML, Ph-positive;
- until switching to using generic medicines, have used at least for 24 months the original medicine (Imatinib, Novartis);
- before switching to generic imatinib MMR was achieved in accordance with ELN recommendation [1].

In addition, data on:

- age at the moment of diagnosing CML;
- age, when the therapy with generic imatinib was started;
- chemotherapy and its duration before switching to generic imatinib were collected.

During 24 months' therapy the following parameters were monitored:

- dynamics of full blood count every three months from start of generic imatinib till 24 months (3; 6; 9; 12; 15; 18; 21; 24) after beginning to use generic imatinib;
- dynamics of BCR-ABL every three months after beginning to use generic imatinib;
- dynamics of commonly used biochemical analysis (creatinine, glomerular filtration rate, bilirubin, ASAT, ALAT) and side effects every three months.

RESULTS AND DISCUSSION

25 patients with CML CP were included in the study, of which 11 were women and 14 were men. At the moment of diagnosing CML patients were from 18 to 84 years old. They started using generic imatinib in the age from 20 to 87 years (Table 2).

Table 2. CML patients' data

Gender/number	Mean age at the time of diagnosis	Mean age of the time of starting generic imatinib
Female, n = 11	54.10	58.38
Male, n = 14	50.33	55.07

All patients included in the study had received at least 24 months of original imatinib therapy, prior to which 8 patients had received treatment with hydroxycarbamidum for mean 7.5 months, and 17 patients for mean 13 months had received treatment with hydroxycarbamidum combined with alpha-interferon.

Patients included in the observational study received a daily dose of 400 mg generic imatinib, and used the medicine regularly. All patients during 24 months retained MMR (Table 3); nobody was switched to second line generation TKI. During the observation period neither haematological, nor non-hematological toxicity was found. 2 patients complained of the generic imatinib 400 mg pill being too large, making it difficult to swallow it. After generic producer was replaced, no more complaints were received.

Table 3. BCR-ABL (%) results during treatment with generic imatinib

Patient Nr	0 months*	3 months	6 months	12 months	24 months
1	0.0013	0.0046	0.0097	0.0018	0.00096
2	0.01	0.0013	0.00056	0.00031	0.0002
3	0.0049	0.00061	0.0029	0.0011	0.0002
4	0.0019	0.0019	0.00044	0.00001	0.00001
5	0.011	0.0084	0.0012	0.006	0.002
6	0.0018	0.001	0.00067	0.00075	0.0003
7	0.01	0.009	0.0096	0.0034	0.0023
8	0.0012	0.0098	0.0021	0.0067	0.00069
9	0.01	0.006	0.00096	0.0003	0.0012
10	0.011	0.003	0.0011	0.0073	0.00087
11	0.0012	0.0037	0.0032	0.0014	0.00033
12	0.0013	0.0026	0.005	0.0013	0.0014
13	0.01	0.0062	0.0035	0.0075	0.00013
14	0.0013	0.0035	0.0016	0.009	0.0042
15	0.0012	0.0017	0.0062	0.0009	0.0001
16	0.007	0.0028	0.0022	0.00073	0.0001
17	0.0077	0.0071	0.00021	0.00001	0.00001
18	0.002	0.007	0.007	0.008	0.00023
19	0.0012	0.0022	0.00034	0.0001	0.0001
20	0.0015	0.00057	0.0013	0.0034	0.0042
21	0.0084	0.012	0.0001	0.0022	0.0048
22	0.00089	0.00077	0.0023	0.00088	0.0006
23	0.0042	0.0089	0.009	0.0089	0.0003
24	0.0052	0.0043	0.0011	0.00043	0.00022
25	0.0073	0.0013	0.0024	0.0031	0.0006

Note: *BCR-ABL results before switching to generic imatinib; and after 3, 6, 12 and 24 months.

We determined the average level of MMR among all patients in each control period. Fig. 1 shows the tendency of MMR changing for each control period during 24 months. The obtained data reflect the level of MMR, after switching to generic imatinib, is below 0.01%. Fig. 2 shows each patient's MMR level at 0; 12 and 24 months.

Since the appearance of the first TKI imatinib generic medicines there have been doubts and concerns about their efficacy, safety and quality. Many patients had been using the original imatinib for years, so they also were doubtful. In the medical press a number of publications express this concern; however, they comprise only very general data that could support or reject this opinion [3–7].

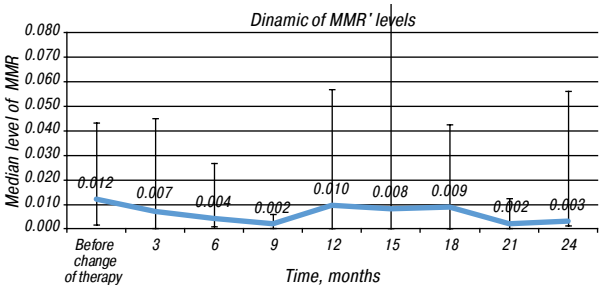

Fig. 1. Tendency of MMR changing during 24 months period.

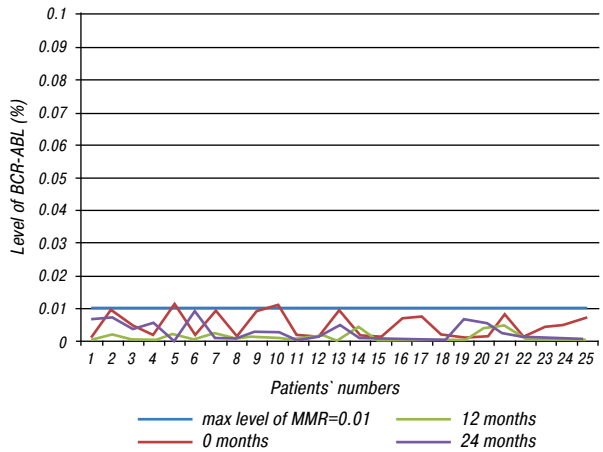

Fig. 2. Patient's BCR-ABL levels during observation period.

On 1 April 2013 the Indian Supreme Court upheld the decision of the Indian Patent Office to refuse granting patent for Novartis imatinib mesylate (Glivec). The patent application failed to meet the requirements for patentability under the Indian law [8]. And already in 2013 the first report on the experience of using generic imatinib in India, in Mumbai, 2002–2008, was published [9]. It was a retrospective study of 1000 CML CP patients, of which 237 patients used generic imatinib. The study showed that complete cytogenetic response (CCyR) was similar in both the group that used the original and the group using generic imatinib in patients, who were first diagnosed with CML CP. A number of reports on using generic imatinib to treat patients first diagnosed with CML CP patients have been published, for example, Jiang Q with co-authors [10] has published data about 107 first diagnosed CML CP patients, who as the primary therapy received generic imatinib for 3 months, and 54 of which had received it for 6 and more months. After 3 and 6 months their CCyR was assessed, which was, respectively, 98.1% and 100%, CCyR — 35.1% and 71.8%, but MMR was diagnosed in, respectively, 10.4 and 33.3% [10]. The researchers concluded that results revealed excellent early haematological, cytogenetic and molecular response and safety. A similar study was conducted by Demirkan *et al.* [11] about first diagnosed CML CP patients in Izmir (Turkey), of which 14 received generic imatinib and 21 received the original medicine, all patients were able to achieve complete hamatological response (CHR) at the 3rd month, MMR rates at the 6th month were 35.7% and 31.6%, which showed that generic formulation was not inferior to the original imatinib. The study of Algeria CML patients, who started therapy with imatinib, also demonstrated that generic imatinib was effective and safe treatment option [12].

Our study comprised patients, who used generic imatinib after MMR had been achieved by using the original imatinib. Upon switching to generic imatinib all patients retained MMR during 24 months of observation. This demonstrates that generic imatinib is not inferior to original imatinib. There are few similar studies researching the use of generic imatinib following therapy with the original imatinib. One of such studies is the researched published in 2015 about CML patients after the Public Health System in Brazil started reimbursing generic formulation in 2013. Patients with CML, who had achieved MMR with the original imatinib therapy, were studied, patients' daily dose was 400 mg, BCR-ABL was monitored every 3 to 6 months. Of 40 patients, 24 (60%) had no variation on sequential analysis and 13 (32.5%) had one or two variation of BCR-ABL between 0.1% to 1.16%, but re-achieved MMR, 2 patients lost MMR due to compliance issue [7]. The researches noted that generic imatinib was safe and kept the efficacy.

A study that arrives at negative conclusions about generic imatinib is from Iraq, Alwan *et al.* [13] prospectively evaluated the response of patients with CML in CP in one institution. Patients with CHR (n = 126) switched from branded imatinib to an imatinib copy drug. Subsequently, all patients switched back to the branded imatinib. Many patients in this study had a loss of hematologic response and experienced tolerability issues with the imatinib copy drug. Hematologic response and tolerability improved upon retreatment with branded Glivec. There have been many objections to this study, since it lacked standardized control, and no discussion of these data has been published [5, 6].

Ostojic A. *et al.* has published a study on imatinib plasma concentration in the case of original and generic imatinib [14] 24 patients were included in the study, 6 and 13, respectively, had used various generic imatinibs, but 5 patients had used both. The study concluded that median imatinib plasma concentration, when taken at equivalent doses, in imatinib generics was bioequivalent and comparable in clinical efficacy.

All studies have noted substantial savings in the treatment costs [7, 8, 11, 14]. The financial gain in our study is also substantial — comparison of monthly costs of 400 mg per day therapy shows that the first decrease in costs in May 2013 was 86.6%, but currently the monthly costs of generic imatinib is even by 96% lower compared to the costs of original imatinib (Gleevec), thus at present it is 4%. The annual costs of original imatinib therapy (400 mg per day) was 29,835.36 EUR, of generic imatinib — 1,238.4 EUR.

CONCLUSION

Our study proved that CML patients, who had reached MMR by original imatinib therapy, retained MMR during 24 months of generic imatinib therapy.

This demonstrates that generic imatinib is not inferior to original imatinib. As to expenses, the annual costs of generic imatinib are lower by 96%, which is a significant benefit to health-care financing.

CONFLICT OF INTERESTS

The authors declared no conflict of interests.

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