Original vs generic drugs in treatment of chronic myeloid leukaemia

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ABSTRACT

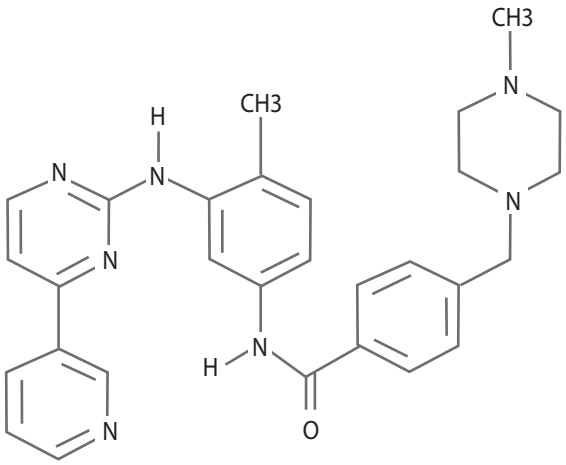
The beginning of the twenty-first century saw a breakthrough in haematology, oncology and general medicine driven by the introduction of imatinib (*Glivec*) to the treatment of chronic myeloid leukaemia. For the first time, a neoplastic disease was successfully treated by a therapy targeting the genetic cause of the disease. At present, targeted therapy based on imatinib is the first one to enter a new stage which is the launch of generic drugs. Poland is the first country in the European Union which, from the beginning of July 2014, introduced generic imatinib. Hence, there is no reliable data on its use except for results from bioequivalence tests. The only data available comes from developing countries where other preparations are used, without reliable bioequivalence studies. However, all generic drugs of imatinib registered in Poland have successfully passed such tests. Undoubtedly, it is necessary to appropriately monitor patients with chronic myeloid leukaemia receiving generic drugs in order to ensure their safety and provide information to other countries where therapy based on generic drugs will be introduced in the following years.

KEY WORDS: chronic myeloid leukaemia, imatinib, the original drug, generic drug, generic imatinib

INTRODUCTION

Chronic myeloid leukaemia (CML) is a myeloproliferative disorder with a relatively low incidence rate (1–2 cases per a 100,000 population per year) [1]. CML accounts for approx. 15% of all adult leukaemias diagnosed globally each year [1, 2]. Leukaemia is the first neoplastic disease whose origins were associated with a specific genetic modification, that is the formation of a Philadelphia chromosome in consequence of a translocation of genetic material between chromosomes 9 and 22 [3]. Following the translocation, the *ABL* gene (located on chromosome 9) is moved, at the molecular level, to the breakpoint cluster region of chromosome 22. As a result, an oncogenic *BCR-ABL1* gene fusion occurs [4]. The gene produces tyrosine kinase which, by activating specific transcription factors, stimulates myeloid cells proliferation, reduces their apoptosis and changes their adhesive properties. Szczylik and colleagues [5] were the first to demonstrate that once the mutated gene is inhibited, the leukaemic cells stop proliferating. However, the antisense oligonucleotides used for that purpose had poor pharmacological properties which made them unfit for clinical application. However, what could not be achieved at the nucleic acid level, was successfully accomplished at the protein level. The protein product of the *BCR-ABL1* gene is an enzyme known as tyrosine kinase (BCR-ABL). A search for an inhibitor of that enzyme was successfully completed by biochemist Nicholas Lydon of Novartis and haematologist Brian Drucker of Oregon Health and Science University in the 1990s. Figure 1 shows the chemical formula of the molecule which was named "imatinib". Imatinib is an organic compound, whose molecular formula is $C_{29}H_{31}N_7O$.

FIGURE 1.
Chemical structure of imatinib



After Novartis introduced imatinib (under trade name "Glivec" and, in the US, "Gleevec") to CML treatment in 2001, the therapeutic results were excellent, starting an era of targeted cancer therapy. Based on imatinib's success, other tyrosine kinase inhibitors (TKI) were registered for CML treatment, including dasa-tinib (trade name "Sprycel") in 2006 and nilotinib (trade name "Tasigna") in 2007. Currently, over 200 similar substances are being studied for effects on various neoplastic disorders.

Prior to introduction of targeted therapy, the prevailing treatment method for younger CML patients was transplantation of hematopoietic stem cells, and elder patients – α interferon or hydroxyurea therapy. Bone marrow transplant was an effective treatment for approx. 60% patients but resulted in early death or severe graft--versus-host disease for approx. 20% patients and a relapse for 20% patients. Alpha interferon therapy improved survival by nearly 2 years, while hydroxyurea therapy most frequently had only a palliative effect. These therapies continue to be used but their application is limited to rare cases where patients are resistant to kinase inhibitors or cannot cope with their adverse effects.

With Glivec patent expiration date approaching, the era of targeted therapy is entering a new phase. Generic imatinib will soon be added to the range of products available for treatment of chronic myeloid leukaemia.

ORIGINATORS VS GENERICS

An original drug (an innovative product) is a new drug introduced to the market for the first time by a company under a registered name. It is patent-protected. Before a drug is admitted to the market, it must undergo a number of chemical, biological, pharmaceutical and pharmaco-toxicological tests as well as clinical studies including multi-centre and randomised trials, to demonstrate its efficacy in treatment and its quality and safety [6]. Glivec is an example of an original drug.

According to the definition given by Directive 2004/27/EC of the European Parliament and the Council of the European Union, a generic medicinal product is a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies [6]. By definition, a generic drug (imitative drug) is a product manufactured under a different name by a different company (sometimes a company directly related to the originator's manufacturer) after the patent for the innovative drug expires (or after other exclusive rights expire). This is how a large

number of generics have been introduced. There is no data to question the merits of this practice.

A patent protection is granted to the original product's first manufacturer to enable it to recover the costs of developing an innovative drug and make profit. The period in which the manufacturer enjoys protection is not indefinite; it lasts 20 years from patent registration and may be extended by a couple of years under special circumstances. The patent protection is time-limited to improve availability of products to patients. This enables alternative manufacturers, contented with smaller profits and determining prices under competitive conditions, to access the market. There is no reason why the originator's manufacturer which has already collected its premium for innovation could not compete with manufacturers of generic drugs on similar terms.

Glivec, the original imatinib in beta crystalline form, was approved by the Food and Drug Administration in the USA and by the European Medicines Agency in Europe in May 2001 with an indication for, *inter alia*, CML treatment.

The polymorphic form of the existing types of generic imatinib is different from that of the original drug. There is no data suggesting that a change in the crystalline structure of imatinib affects its clinical efficacy [7]. Bioavailability studies have proven that there are no differences in solubility and absorption rate from the digestive system between the α form of imatinib used in generic drugs and the original beta form of imatinib. In Poland, the new polymorphic form (α) of imatinib, different from its original beta form, is made by, *inter alia*, the Pharmaceutical Research Institute of Warsaw. In 2010, the Institute was awarded for developing the method of manufacturing this form of the molecule in the *Polish Product of the Future* competition.

There are three registration procedures under which a medicinal product may be placed on the Polish market: the centralised, international and national procedure. The centralised registration procedure covers all European countries and is governed by the European Medicines Agency (the EMA) of London. The international procedure which covers the EU member states is divided into the Mutual Recognition Procedure (MPR) and the Decentralised Procedure (DCP). MPR applies to products which have been granted a marketing authorisation in one of the EU member states and are sought to be registered in other countries. DCP is a newer procedure which applies to medicinal products that have not been authorised in the EU yet. The final stage of both procedures is the national procedure. In Poland, the national registrations are handled by the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products of Warsaw. The requirements relating to registration documents are the same in each of the procedures to ensure appropriate quality, safety and efficacy of medicinal products. Of all the generic imatinib products which have been granted a marketing authorisation in Poland, 4 have been registered under the centralised procedure and 20 under the international procedure (data as at 31 August 2014). In each case, regardless of the procedure applied, the generic imatinib has been demonstrated to have the same bioavailability as the original drug. According to the decision issued at the national, international and pan-European level, generic imatinib drugs are equivalent to the innovative originator. Table 1 lists brands of generic imatinib authorised in Poland under the said procedures as well as the names of authorisation holders.

TABLE 1.
Brands of generic imatinib authorised in Poland (data as at 22 May 2014).

Brands of generic drugs	Medicinal products marketing approval procedure	Competent body
Imatinib Accord	central	Accord Healthcare Ltd.; Great Britain
Imatinib Actavis	central	Actavis Group PTC ehf.; Iceland
Imatinib medac	central	medac Gesellschaft für klinische Spezialpräparate mbH; Germany
Imatinib Teva	central	Teva Pharma B.V.; Netherlands
Egitinid	international	Egis Pharmaceuticals PLC; Hungary
Imakrebin	international	Alvogen IPCo S.a.r.l.; Luxemburg
Imatenil	international	Biofarm Sp. z o.o.; Poland
Imatinib Apotex	international	Apotex Europe B.V.; Netherlands

Imatinib BioOrganics	international	BioOrganics BV; Netherlands
Imatinib Generics	international	Generics [UK] Ltd.; Great Britain
Imatinib Genthon	international	Genthon BV; Netherlands
Imatinib Glenmark	international	Glenmark Pharmaceuticals s.r.o.; Czech Republic
Imatinib Kiron	international	Kiron Pharmaceutica BV; Netherlands
Imatinib Polfa	international	Polfa S.A.; Poland
Imatinib Synthon	international	Synthon B.V; Netherlands
Imatinib Teva Pharmaceuticals	international	Teva Pharmaceuticals Polska Sp. z o.o.; Poland
Imatinib Zentiva	international	Zentiva, k.s.; Czech Republic
Imavec	international	Helm AG; Germany
Leutipol	international	Zakłady Farmaceutyczne Polpharma S.A.; Poland
Leuzek	international	Nobilus Ent dr inż. Tomasz Koźluk; Poland
Meaxin	international	Krka, d.d., Novo mesto; Slovenia
Nibix	international	Adamed Sp. z o.o.; Poland
Telux	international	Glenmark Pharmaceuticals s.r.o.; Czech Republic
Tibaldix	international	PharmaSwiss Ceska Republika s.r.o.; Czech Republic

REIMBURSEMENT OF ORIGINAL AND GENERIC DRUGS

Registration of a drug and its reimbursement are two separate issues. A decision to grant reimbursement for a drug and its terms is taken by the authority managing the health insurance system in a given country (in Poland – the Ministry of Health and the National Health Fund). An application for reimbursement is submitted by the authorisation holder, i.e. the pharmaceutical company selling a given drug. The decision whether to grant reimbursement or not depends on a number of factors such as funds available in the insurance system, efficacy of the original drug, organisational issues and local practice.

Results from studies into efficacy of TKI therapy in CML patients vary by evaluation of response rates and overall survival. Although it may not always seem obvious, the differences in long-term survival rates among CML patients receiving TKI may be related to varying drug availability attributable to financial affairs. In countries like Switzerland where imatinib is available for practically all patients, more than 80% of CML patients experience a 10-year survival period. In contrast, in the US where many people have no medical insurance or only a minimum-coverage insurance and patient co-payment is required, a 5-year survival rate is achieved for approx. 60% of patients [8].

Another issue is that in regular medical practice doctors can hardly achieve the same level of efficacy as in studies carried out for registration purposes. The reason is that studies are performed on selected patients who meet criteria for inclusion and exclusion while in daily practice doctors must provide treatment to all patients suffering from a given disease. It is noted in the relevant literature on the subject that very high prices of new inhibitors cannot be explained by a high level of expenses incurred by manufacturers on pre-clinical studies and clinical trials [8]. Nevertheless, differences in availability of life-saving medication driven by financial issues are a serious concern.

Most newly-diagnosed CML patients in the chronic phase are started on imatinib as the first-line treatment. The majority of such patients successfully continue therapy for months or years. This is particularly true for Poland where there is no possibility, except in small groups of patients taking part in clinical trials, to use the second generation inhibitors (nilotinib and dasatinib) as the first line of treatment. Likewise, there is no possibility to discontinue treatment for patients showing the most favourable prognosis (which should be the case with patients on molecular as part of the so-called non-commercial clinical study). There is no legal framework in Poland under which such trials could take place. If 200 CML patients discontinued imatinib it would gen-

erate savings of PLN 20 million annually provided the price for Glivec remained unchanged. Naturally, once generic imatinib is launched on the market, the price for Glivec will change. There is another observation to be made here. About half of CML patients with molecular remission who discontinue imatinib do not relapse which means they no longer have to take the drug and struggle with its adverse effects. However, the other half of patients must still be able to restart taking the drug [9].

STUDIES INTO EFFICACY OF GENERIC IMATINIB

Till today the trials with evaluation of effectiveness of generic imatinib have been conducted in Iran, Iraq, Morocco [10–13]. The generics registered outside the European Union have been used in these studies. The number of included patients was relatively small, the adopted research methodology was very different, so the definitive conclusions seem to be not clear.

Several more reports are available from the Arab states which describe CML patients receiving generic imatinib [14–17]. Those patients lost their remission after they had been switched from the original drug to an Indian-made generic [14, 15].

The IRIS study was performed on 553 patients receiving the original drug. 97% of them achieved CHR after 18 months of therapy and 87% showed MCyR after 18 months of monitoring [18]. In the ENESTnd study of 283 patients receiving the original imatinib, 22% reached MMR after 12 months of therapy and 53% after 36 months [19, 20]. The overall survival of patients receiving the original drug in the IRIS study was 15,7 years [21]. According to unpublished data from our Department, five years after initiation of Glivec therapy under a drug prescription programme, approx. 70% of patients remained on the programme while 30% were discontinued due to insufficient efficacy or poor tolerance.

Certainly, one needs to definitely consider whether the variability of results can be explained by the different geographical origins of the generic products used. A comparative study was published in one of the last year's issues of the *Advanced Biomedical Research* in which the efficacy and safety level of two generic imatinib products were compared, one of Iranian origin and the other of Indian origin. The study was performed on 43 newly-diagnosed CML patients in two Iranian clinics (Group 1) and 43 Indian patients (Group 2). In total, both group comprised 86 patients (including 51 males; the average age of study participants was 60). The patients received one of the two generic imatinib drugs (Iranian-made or Indian-made) for 6 months (January – June 2011). After that, their haematological and molecular remissions were evaluated. The haematological and molecular response for the group receiving Iranian-made imatinib were, respectively, 86% and 47%, while the rates for the group receiving the Indian-made generic imatinib were 86% and 44%, respectively [22]. Based on the similarity of results in both study groups using two different generic drugs, the safety level of both generic imatinib products can be regarded as comparable. However, those results cannot be directly compared to the results achieved with patients taking the original drug due to the short duration of the study (just 6 months) and the fact that the international standards for evaluation of molecular response were not applied in the study reported above.

SUMMARY

Poland is the first country in the European Union which, on the 1st of July 2014, introduced generic imatinib. There is no reliable data about CML patients in Europe actually using the generic imatinib forms. Given that, and taking into account the patients' mounting concerns, Poland has a special obligation to closely monitor the process of switching patients from the original drug to its generic copy to protect the interest of Polish patients on the one hand and provide more credible data to other countries which will experience a similar process in the future on the other hand. This will not be easy as a number of generic products will be introduced to the market in Poland at the same time, and patients may potentially receive several different generic brands one after another within a short period of time.

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