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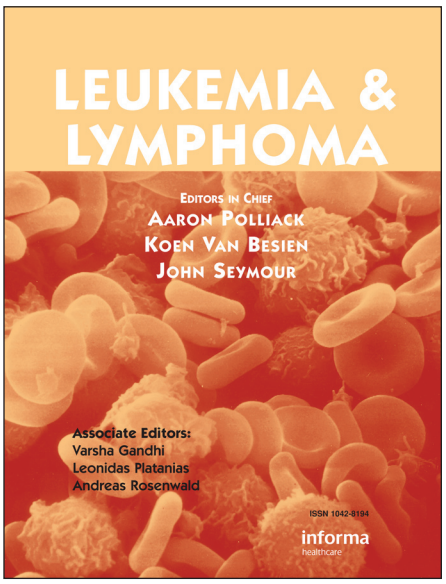

Generic Imatinib: The real-deal or just a deal?

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The importance of generic pharmaceutical agents in increasing access and reducing the cost of medical therapy is widely acknowledged, even in developed countries[1,2]. This is especially relevant in cancer, for developing economies and countries where there is absence of health insurance or a predominantly self-pay system. It is estimated that the use of generic chemotherapy drugs in India, a country which fulfils the above criteria, the annual savings is approximately US $ 843 million[3]. The impact of cost of generics versus innovator molecule of imatinib in the Indian market is illustrated in figure 1. While 55% of the diagnosed patients receive the innovator molecule from the GIPAP (The Glivec® International Patient Assistance Program) and Max foundation at either free or subsidized cost (details of costing not available) the rest of patients purchase the drugs at market rates. For the 45% of patients where the drug is supplied at market rates, the innovator molecule accounts for 1% in units supplied, but are 37.2% of the market share in actual revenue generated per year (Ipsos Research Private Limited - Syndicated Oncology Sales Monitor, India).

The use of generics is invariably associated with controversies on intellectual patent protection, what defines just pricing, quality and efficacy of generic molecules. While these debates have been going on for decades, the recent high profile court rulings with regards to patent protection and generic imatinib that have gone against big pharmaceutical companies have re-ignited these discourses[4]. Overall these court rulings have been welcomed in academic circles[5] and by patient advocacy groups. Big multinational pharmaceutical companies (MNPC) have, as expected, voiced their concerns with these court decisions. The role played by MNPC in drug pricing, in molding and influencing academic and physician opinions and preferences, manipulating legal systems and even governments and drug approval agencies has been widely commented on and is best summarized in an article written by Arnold S. Relman and Marcia Angell for 'The New Republic' in 2002 which is very much relevant even today[6]. In this commentary we will restrict the discussion to addressing the issue of quality and efficacy of generic imatinib.

In this issue of the journal there are two articles which highlight the concern of decreased efficacy and increased toxicity of generic imatinib in comparison to the innovator brand. Saavedra, D et al[7] from Colombia and Alwan, A et al[8] from Iraq describe their experience in 12 and 126 patients with chronic myeloid leukemia (CML) in chronic phase (CML-CP) who received generic imatinib respectively. In the study by Alwan et al, all patients initially received the innovator molecule and were subsequently switched to the generic molecule while a similar switch happened in 8 of the 12 patients in the study by Saveedra et al (the remaining 4 were on generic imatinib from the start). In the study by Alwan et al, patients were on the innovator molecule for a median duration of 4 years (range: 0.5-7) prior to switching to the generic brand. Following switch to a generic brand 17.5% lost complete hematological response (CHR), while in 17.5% there was disease progression in 3 months time. This was also associated with a high proportion of patients developed toxicity though the NCI grade of the toxicity is not given. On

switching back to the innovator molecule in approximately 8% CHR was restored. In the report by Saveedra et al of the 4 patients who received a generic brand from the start only one patient had evidence of response to therapy and all had significant adverse effects. Of the 8 patients who were switched to generic brands there was loss of cytogenetic response (CTG) or rising transcript levels in five within 3 to 4 months of the switch, all patients for these reasons or intolerance to the generic brand were subsequently switched to second generation TKI's. All 8 patients have remained on 2nd generation TKI's and have regained CTG response. Saveedra et al declare that their research was funded by Novartis Pharmaceutical Corporation; Alwan et al declare that they received financial support for editorial assistance from the same company.

These two articles highlight the concerns with generic imatinib. However, one has to wonder if this is truly reflective of world wide experience with generic imatinib. When one considers a generic molecule the potential differences can arise from the formulation (pills versus syrup versus intravenous preparation), active pharmaceutical ingredient (API) and the excipients used to stabilize or to bulk the final product prior to formulation. In the case of imatinib the formulation is the same for the innovator and the generics (pills). The API in imatinib can be in three polymorphic forms (α,β or γ). The innovator molecule is the β-crystal form while the majority of generics have the α-crystal form. In spite of the initial suggestion and claim that the β-crystal form was superior, the overall consensus is that there is no difference in efficacy, water solubility and absorption of either crystal form[9]. Variation in excipients could potentially alter bioavailability and hence bioequivalence studies are required by agencies such as the US-FDA that are involved in approval and licensing of generic molecules though the theoretical potential impact of these variations in excipients on short and long term toxicity is not addressed by such studies. The Hatch-Waxman Amendments to Federal Food, Drug, and Cosmetic Act Section 505(j) 21 U.S.C-1984 was considered a land mark legislation that facilitated the generic pharmaceutical industry and allowed them to rely on findings of safety and efficacy of innovator drug after expiration of patents and exclusivities. More significantly it did not require them to repeat expensive clinical and pre-clinical trials with the generic molecule. Generic imatinib has been approved by Canada and the European Medicines Agency (EMA) after fulfilling bioequivalence criteria.

There have been numerous anecdotal reports of lack of efficacy of generic imatinib though most of these reports are limited by the small numbers. Of some concern is that a number of these publications have a conflict of interest by being funded in part by the innovator MNPCs. There is also a publication bias in that an article with lack of response in a small subset / cohort being reported is more likely to get published than a similar size subset / cohort where there is appropriate response. However, one should not and cannot discount these reports and the onus should be placed on the generic manufacturers to appropriately address these issues. While MNPC's have come in for significant criticism over pricing and ever greening of patents etc there have not been significant concerns about the quality of

their products. It is also important to recognize and acknowledge that the generic pharmaceutical industry is not in this business for charity. Like MNPC's they are primarily in it for profits and are answerable to the share holders of their companies. The abbreviated new drug approval (ANDA) as a result of the Hatch-Waxman amendment does not require the generic pharmaceutical industry to conduct clinical trials prior to approval. However it would be reasonable to expect them to compulsorily report on Phase IV study data post marketing and have a sample size for such a study to make reasonable comparison with the reported Phase III study of the innovator. Reporting of post marketing data is at present not a requirement by any approval agency in the world. It would have been ideal to have a direct clinical trial in comparison with the innovator molecule however, the costing of the innovator molecule is such that it prevents one from comparing it to cheaper alternatives in a clinical trial setting and serves to protect the innovator from less expensive alternatives[10]. The generic pharmaceutical industry is also driven by profits and they often operate in countries with lower standards and absence of systems in place to approve and monitor the quality of marketed generic drugs. These countries are especially vulnerable to fraudulent practices as has been illustrated by some recent high profile cases[11]. In spite of these concerns the over whelming majority of physicians and academic institutions believe that generic drugs including imatinib are as efficacious as the innovator molecules. In this issue of the journal there is another article by Eskazan, AE et al[12] which also compares the impact of switching patients to generic imatinib. In this report on 145 patients, 65 were continued on the innovator molecule while 76 were switched to a generic brand of imatinib after a median period of 55 months (range: 3-126) and 4 were on generic brands from the time of diagnosis. At a median follow up of 12 months (range: 4-16) post switching to a generic brand there was no significant difference between the two groups in terms of maintenance of response state, achievement of greater depth of response, progression of disease and adverse events. Eskazan et al do not report any conflict of interest. Similar to this report and in response to an article addressing the price of drugs in CML[13] there were 12 responses of which 4 addressed the issue of efficacy (one from Turkey, one from Mexico, two from India) and all of them stated that they did not find any difference in response or toxicity between the generic and the innovator molecule. A more recent article looking at plasma trough levels and response in patients on imatinib did not find any difference between the generic and the innovator molecule[14].

The majority of physicians involved in the treatment of CML in India including the author do not find significant difference between generic and innovator imatinib and numerous articles on this topic have been reported in local Indian journals. In the presence of so many generic brands and absence of genuine scientific comparison the basis of the choice between the generics in India is based on a combination of locally circulated expert opinions, reputation of the company involved, availability of bioequivalence data and personal experience.

It would have been very useful if we had pharmacokinetic data available in the patients in the two studies in this issue that reported reduced efficacy and

toxicity or if the tablets (manufacturing lot) that were used in these patients were subjected to scientific analysis for content and bioequivalence. Even in the absence of these, the articles reported in this issue highlight the need for greater regulation and oversight of generic molecules being introduced in different health care systems and the need for mechanisms to be put in place to monitor therapy when such changes are made. This is even more relevant in countries where mechanisms of approval and continued monitoring of the quality of the generic drugs being supplied are not well established.

Conflict of interest

Received travel grants from Novartis Pharmaceutical Corporation

Received research grant (research in acute myeloid leukemia) from NATCO pharmaceuticals

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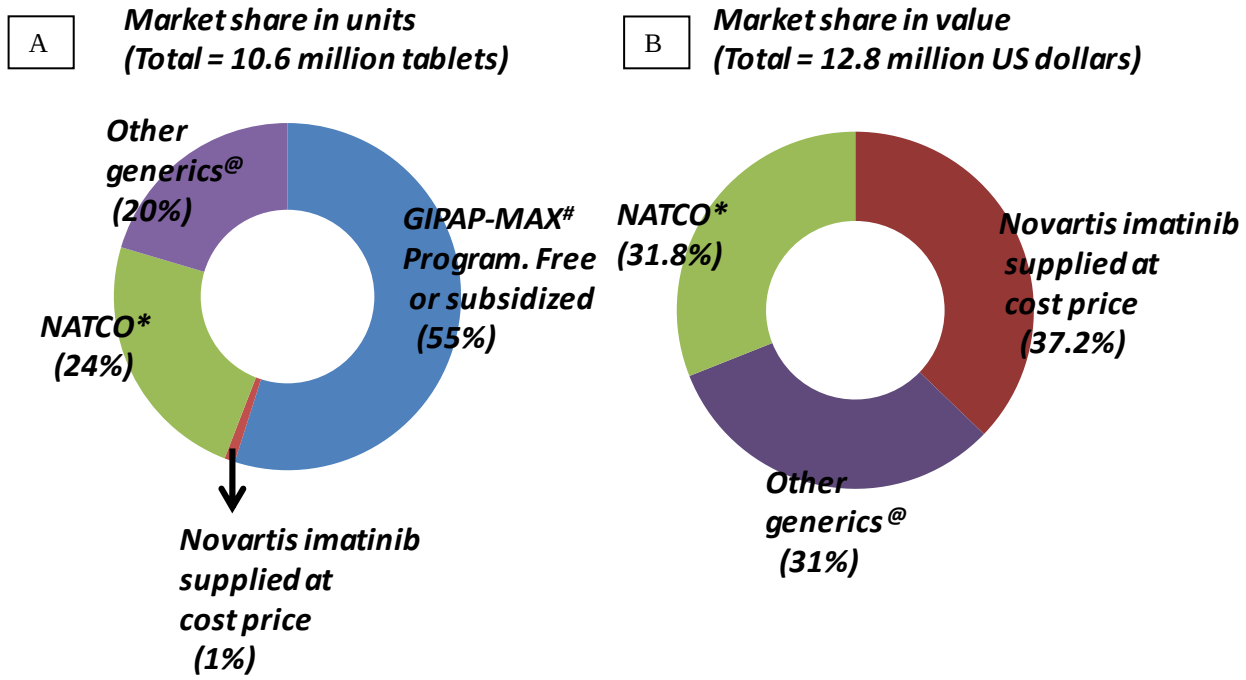
Figure Legends

Figure 1

A) Market share of imatinib units/year (tablets), includes GIPAP-Max program which is supplied either free of cost or at subsidized rates. B) Market share in US dollars/year, excludes GIPAP-Max program and only looks at units sold at market rates



Source: Ipsos Oncology Sales Monitor June 2013
Time Period: June 2013 MAT

GIPAP-MAX foundation - The Glivec® International Patient Assistance Program and MAX foundation

* NATCO - NATCO Pharma Limited, India (manufacturer of Veenat a generic brand of imatinib)

@ Other generics - refers here to 23 other pharmaceutical companies that market generic imatinib in India (all <2% of the market share) .