# Persistence with generic imatinib for chronic myeloid leukemia: a matched cohort study

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## Supplementary Material

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**Supplementary Table 1.** Peer-reviewed cohort studies reporting effectiveness and safety of generic imatinib

| Study | Country | F/U* | GI | BI | %MMR or higher† | TKI cessation d/t intolerance | Comments |
|---|---|---|---|---|---|---|---|
| **Razmkhah 2010**[1] | Iran | 28.8/0 | 30 | 0 | 46.7 | NA | |
| **Parikh 2013**[2] | India | 51 | 237 | 671 | NA | NA | Unclear if GI group included switchers |
| **Alwan 2014**[3] | Iraq | ≥9 | 126 | 122 | NA | NA | 17.5% progression to blastic or accelerated phase at 3 months |
| **Eskazan 2014**[4] | Turkey | 8.5/20 | 26 | 36 | 33% in GI and BI | NA | |
| **Saavedra 2014**[5] | Colombia | 6.3/0 | 12 | 0 | NA | 66% of initiators and 62.5% of switchers | No cytogenetic response in initiators |
| **Islamagic 2017**[6] | Bosnia | 36 | 41 | 0 | 48% of initiators; 7% of switchers lost MMR | 22.2% of initiators; NA for switchers | Further 29.6% of initiators switched for resistance |
| **Eskazan 2017**[7] | Turkey | 13 | 43 | 0 | 81.4% | NA | 47 additional patients had BI and GI exposure |
| **Danthala 2017**[8] | India | 46/46 | 144 | 1067 | 40% for BI; 41% for GI | No reported Gr. 3 or higher adverse events | Event-free survival higher with BI; unclear if GI group included switchers |
| **Awidi 2017**[9] | Jordan | 12 | 91 | 0 | 45% of initiators; 88% in switchers | NA | Higher rate of adverse events in switchers vs initiators |
| **Sacha 2017**[10] | Poland | 12 | 726 | 0 | 49.5% of initiators | 13.1% of initiators; 2.4% of switchers | 15.1% of switchers had worsened molecular response |
| **Lejniece 2017**[11] | Latvia | 24 | 25 | 0 | 100% | NA | |
| **Entasoltan 2017**[12] | Algeria | 46 | 355 | 0 | 67% | 8% | |

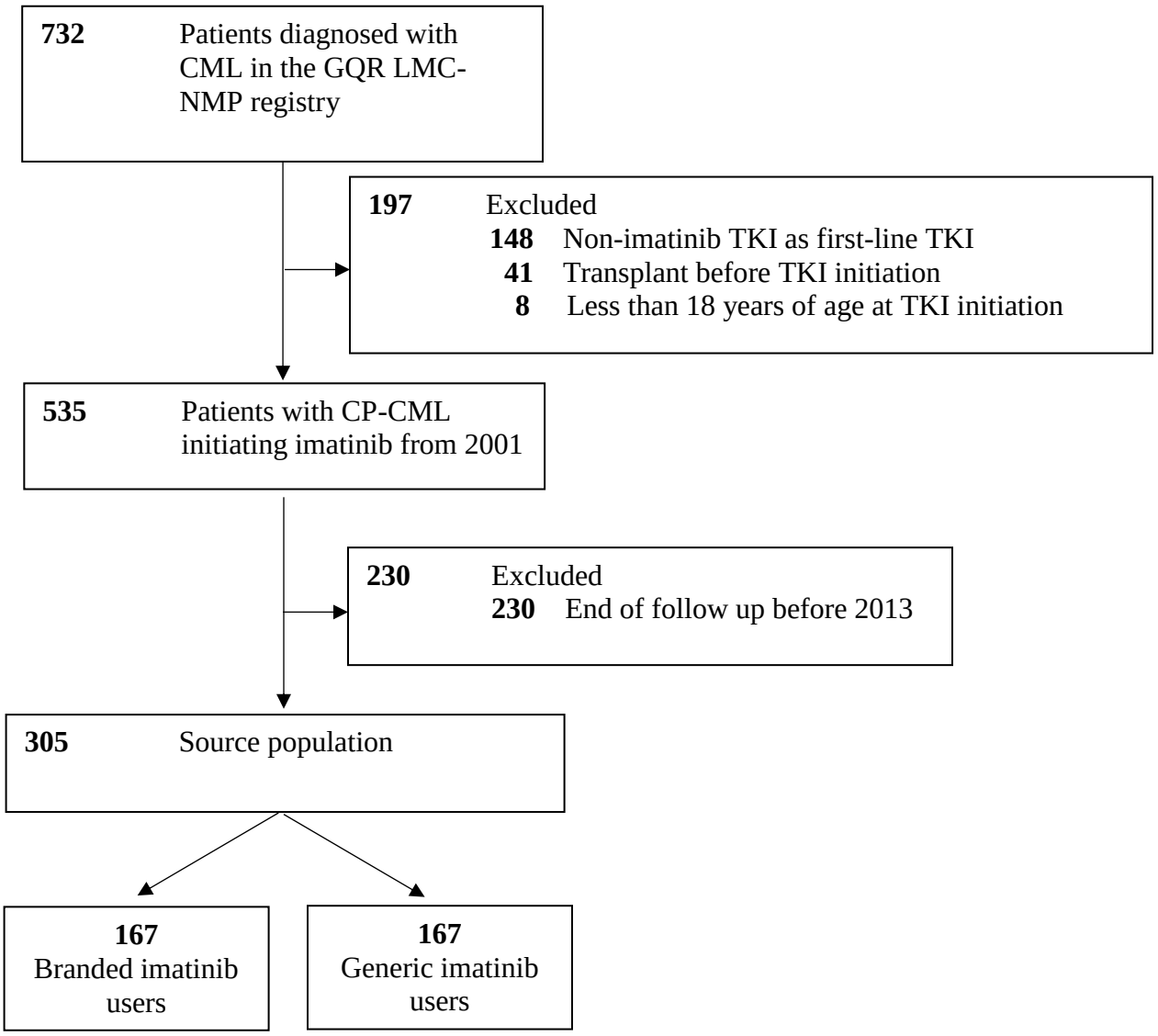
BI, branded imatinib; F/U, follow-up; GI, generic imatinib; MMR, major molecular response; NA. not available; TKI, tyrosine kinase inhibitor
*Generic/branded imatinib follow-up in months
†At the last time point provided

**Appendix 1. Selection and Matching of Study Cohorts**

Two versions of GI (Apo-Imatinib [Apotex pharmaceuticals) and Teva-imatinib[Teva pharmaceuticals]) were approved for use by Health Canada on 23 April, 2013.[13] In Québec, GI was reimbursed for patients with public drug insurance starting 01 October, 2013. For these patients, pharmacists receiving a prescription for imatinib were allowed to dispense GI unless a "do not substitute" order signed by the physician appeared on the prescription.[14] In the ensuing period, patients with public and private drug insurance alike were gradually required to switch from BI to GI, which meant that the probability of remaining on BI decreased. However, this transition period allowed for the examination of contemporaneous use of BI and GI. Thus, we designed a matched cohort study where every new GI user is matched to a BI user with recorded use on the same calendar date. We first identified from the source population CP-CML patients with a first-ever use of GI from 2013 onward. Patients with prior non-imatinib TKI were not included. From the pool of BI users on the same calendar date we then matched a patient with the closest duration of prior BI use and nearest age at cohort entry. BI users could only be selected once, but GI users were allowed to be included as BI users if they met matching criteria. However, By the end of the study, two more versions of GI were available in Québec: ACT Imatinib (Actavis Pharmaceuticals) and pms-Imatinib (Pharmascience). We made no distinction between GI versions.

**Appendix 2. Baseline Covariates and Clinical Definitions**

Data were obtained for patient age, sex, body mass index (BMI, <25, 25-30, >30 kg/m$^2$, and unknown), ethnicity (white or other), smoking (ever, never, and unknown), and alcohol consumption (yes, no, and unknown). The latter three were self-reported by the patients. The Romano modification of the Charlson comorbidity index was calculated based on comorbidities at any time before cohort entry.[15] Finally, we used information on suboptimal response and drug toxicity (none, hematologic, or non-hematologic) recorded during the relevant treatment period only. The reasons for switch were recorded by the treating physicians. Where resistance was recorded, we extracted further details about the molecular response by quantitative polymerase chain reaction of *BCR-ABL1* copies standardized according to the international scale. Where intolerance was recorded (allowing overlap with resistance), we recorded the identified adverse events. Only adverse events with grade ≥ 3 according to the National Cancer Institute common toxicity criteria were specified, as these were recommended by the European LeukemiaNet to prompt withholding of the TKI.[16]




**Supplementary Figure 1. Study flow chart.**

CP-CML, chronic myeloid leukemia in chronic phase; GQR LMC-NMP, Groupe de recherche en leucémie myéloïde chronique et néoplasies myéloprolifératives; TKI, tyrosine kinase inhibitors

**Supplementary Table 2. Reasons for switching from tyrosine kinase inhibitor**

| Characteristic | Branded imatinib (n = 167) | | Generic imatinib[a] (n = 167) | |
|---|---|---|---|---|
| | No. | % | No. | % |
| **No. of switches** | 17 | 10.2 | 36 | 21.6 |
| **Intolerance[b]** | 9 | 52.9 | 25 | 69.4 |
| **Gr. 3 adverse events** | 5 | 100.0 | 10 | 100.0 |
| Fatigue | 2 | 20.0 | 1 | 10.0 |
| Pain | 2 | 20.0 | 1 | 10.0 |
| Weakness | 0 | 0.0 | 1 | 10.0 |
| Nausea | 0 | 0.0 | 2 | 20.0 |
| Vomiting | 0 | 0.0 | 1 | 10.0 |
| Diarrhea | 0 | 0.0 | 3 | 30.0 |
| Rash | 1 | 10.0 | 1 | 10.0 |
| **Switched to** | | | | |
| Branded imatinib | 0 | 0.0 | 23 | 63.9 |
| Dasatinib | 13 | 76.5 | 10 | 27.8 |
| Nilotinib | 3 | 17.6 | 3 | 8.3 |
| Bosutinib | 1 | 5.9 | 0 | 0.0 |
| **Resistance** | 9 | 52.9 | 12 | 33.3 |
| Failed EMR | 6 | 66.7 | 4 | 33.3 |
| Failed MR2 | 0 | 0.0 | 1 | 8.3 |
| Failed MMR | 1 | 11.1 | 2 | 16.7 |
| Lost MMR | 2 | 22.2 | 1 | 8.3 |
| Other[c] | 0 | 0.0 | 4[†] | 33.3 |

EMR, early molecular response (≤10.0% of *BCR-ABL1* copies); MR2, molecular response to ≤1.0% *BCR-ABL1* copies; MMR, major molecular response (≤0.1% of *BCR-ABL1* copies)

[a]Twenty-nine generic imatinib users were also included as branded imatinib users (from a preceding treatment episode)

[b]Intolerance and resistance were not mutually exclusive

[c]Including loss of MR4, positive nested PCR at 1 year, loss of MR2, and unknown

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