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Title	Second Treatment-Free Remission Attempt in Patients with Chronic Myeloid Leukemia
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Citation	Clinical Lymphoma Myeloma and Leukemia , 24 (4) : e138 - e141
Issue Date	2023-12-29
DOI	
Self DOI	
URL	<a href="https://ir.lib.hiroshima-u.ac.jp/00056117">https://ir.lib.hiroshima-u.ac.jp/00056117</a>
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Relation	



## **Mini Review Article**

# **Second Treatment-Free Remission Attempt in Patients with Chronic Myeloid Leukemia**

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**Running title:** TFR2 attempt in CML-CP

**Main text:** 1944 words

**Abstract:** 177 words

**References:** 23

**Abstract**

Long-term survival outcomes of patients with chronic myeloid leukemia in the chronic phase (CML-CP) are now similar to those of the general population, following the introduction of ABL1 tyrosine kinase inhibitors (TKIs). Approximately 40–80% of patients with CML successfully achieved treatment-free remission after the first attempt of TKI discontinuation (TFR1), after achieving a durable deep molecular response (DMR). However, the possibility of achieving treatment-free remission after a second attempt of TKI discontinuation (TFR2) remains unclear. Therefore, we reviewed current TFR2 studies to clarify the feasibility of achieving TFR2. We identified five TFR2 clinical trials and two real-world reports. TFR2 attempt may be feasible after re-treatment with imatinib, nilotinib, or dasatinib. Patients who have achieved MR<sup>4.0</sup> or deeper durable molecular remission are eligible to enter the TFR2 phase. Imatinib is well tolerated and can be administered for consolidative treatment before the TFR2 attempt, whereas drug-related adverse effects of nilotinib or dasatinib affect their tolerability and might lead to discontinuation. Late onset relapse (> 1 year or > 2 year) was often reported, thus careful monitoring is needed.

**Key Words:** Treatment free remission (TFR), second attempt TFR (TFR2), imatinib, dasatinib, nilotinib

## Introduction

Long-term survival outcomes of patients with chronic myeloid leukemia in chronic phase (CML-CP) are now similar to those of the general population following the introduction of BCR::ABL1 tyrosine kinase inhibitors (TKIs)<sup>1</sup>. However, new medical issues such as late adverse events (e.g., cardiovascular events and renal dysfunction) have been reported and so were issues such as high-medical costs due to long-term administration. Several clinical trials have confirmed that approximately 40–80%<sup>2,3</sup> of patients with CML who achieved a durable deep molecular response (DMR) following treatment with TKIs successfully achieved treatment-free remission after the first TKI discontinuation (TFR1), without receiving any further treatment<sup>2,4–6</sup>. However, 20–60% of these patients were later reported to have experienced molecular relapse. These patients subsequently successfully achieved DMR following the resumption of TKIs, but it is unclear whether TKI administration must be continued throughout their lifetime.

Recently, the possibility of achieving treatment-free remission after second attempt TKI discontinuation (TFR2)<sup>7</sup> has been investigated by some researchers, and they have confirmed the possibility of second attempt TKI discontinuation, even after the failure of the first attempt. Therefore, in this study, we reviewed current TFR2 studies to investigate the criteria necessary for the successful achievement of TFR2.

## Summary of TFR1 studies

STop Imatinib (STIM) study was a pioneering TKI discontinuation study<sup>4</sup>, according to which, 41% of the patients who achieved a durable DMR (complete molecular response at that time) following imatinib therapy for at least 2 years maintained DMR for one year. The A-STIM study later enrolled 80 patients with the same enrollment criteria as the

STIM study<sup>8</sup>. The study confirmed the possibility of identifying a trigger for resuming imatinib after the loss of major molecular response (MMR). The estimated TFR1 rate was 64% at one year, 64% at two years and 61% at three years. The molecular relapse after this period was defined as the loss of MMR. Imatinib discontinuation can be safely performed in patients with a DMR of at least two years.

Few studies investigating TFR after the discontinuation of second-generation TKIs (dasatinib or nilotinib) have been reported. The Dasatinib Discontinuation trial (DADI) trial<sup>9</sup>, enrolled 63 patients with CML-CP receiving second-line dasatinib, and the Stop Tasigna Trial (STAT2)<sup>10</sup> enrolled 78 patients receiving second-line nilotinib. The duration of the consolidation phase in the DADI trial was only one year (two years were required in imatinib discontinuation studies), considering the strength of the second generation TKIs. TFR was achieved in 49% (DADI)<sup>9</sup> and 67.9% (STAT2)<sup>10</sup> patients at one year. 58 CML-CP patients who had participated in the first-line DADI trial achieved a DMR following first-line dasatinib treatment for at least 2 years, and 190 CML-CP patients enrolled in the ENESTfreedom trial, achieved a DMR with first-line nilotinib treatment for at least two years. Both studies required consolidation treatment for an additional year, and 55.2% (first-line DADI)<sup>5</sup> and 51.6% (ENESTfreedom)<sup>6</sup> of patients experienced TFR. Second generation TKIs could also be safely discontinued in CML-CP patients who achieved a DMR following treatment with second generation TKIs for at least two years followed by one year of consolidation treatment. The European Stop Tyrosine Kinase Inhibitor (EURO-SKI) trial<sup>2</sup> was the largest trial that enrolled 758 patients with CML-CP whose DMR was maintained for one year while being treated with any TKI, and the TFR rate was 56% at one year. Hence, one of the treatment goals for patients with CML-CP was the achievement of TFR.

In recent years, European LeukemiaNET, 2020, demonstrated that TKI discontinuation in patients with CML-CP is feasible with a minimum of total 5-year TKI treatment (at least four years for second generation TKIs), and at least two year-durable DMR<sup>11</sup>.

### **Mechanisms for successful achievement of TFR**

To date, the mechanisms underlying successful achievement of TFR remain unknown.

Serial *BCR::ABL1* transcriptional detection methods using reverse transcriptase quantitative polymerase chain reaction (RT-qPCR) possess the ability of detecting residual CML leukemic stem cells, even in patients who achieve TFR<sup>12</sup>. These results indicate that the leukemic cells persist, however, in a quiescent phase, because of which they do not cause relapse after discontinuation of TKIs. Given that CML leukemic stem cells exist in patients who have achieved TFR, the host immune systems mediated cancer immunosurveillance could possibly prevent CML relapse<sup>13</sup>.

Natural killer (NK) cells are the major components of the innate immune response against pathogens or cancers, and they reportedly play a significant role in regulating leukemic cells in patients suffering from CML. In the IMMUNOSTIM, EURO-SKI and DADI studies, higher levels of NK cells in the patient's body prior to the discontinuation of imatinib or dasatinib were observed to be significantly associated with the successful maintenance of TFR<sup>2,9,14</sup>, along with the T-cell immune responses, which are also associated with successful achievement of TFR. Treatment with interferon enables the discontinuation of imatinib via induction of cytotoxic T-cell response<sup>15</sup>. CML-CP patients with elevated levels of peripheral blood CD8+ T cells have better TFR rates<sup>16</sup>. The first-line DADI trial demonstrated that depleted levels of CD4+T cells at the time of dasatinib discontinuation were associated with a better TFR rate. Regulatory T cells (Tregs) play

a significant role in preventing excessive immune responses, whereas myeloid- derived suppressor cells (MDSCs) recruit and expand the Tregs. The number of Tregs, which is significantly higher in patients with CML-CP at diagnosis, is reduced following treatment with imatinib or dasatinib, which also reduces the MDSCs in patients with CML, leading to the successful maintenance of TFR<sup>17</sup>. These results indicate the involvement of NK cells or T cell immune responses in the prevention of CML relapse following TKI discontinuation. The mechanisms have not been fully elucidated and controversial results also exist.

### **Studies on TFR2 Attempt**

#### **RE-STIM study**

RE-STIM study was the first TFR2 study. 70 CML-CP patients who failed a first TKI discontinuation and later achieved DMR (MR<sup>4.5</sup>) following TKI resumption were included in the study<sup>7</sup>. TKIs that were discontinued in the first discontinuation attempt included imatinib in 60 patients, dasatinib in 5 patients and nilotinib in 5 patients. The median time from the resumption of TKIs to the second TKI discontinuation attempt was 32 months. The median duration of DMR (MR<sup>4.5</sup>) before the second TKI discontinuation attempt was 25 months. TKIs at the second discontinuation attempt were imatinib in 50 patients, dasatinib in 7 patients, and nilotinib in 13 patients. Molecular relapse was defined as loss of MMR (similar with first attempt), and TFR at 1 year was 48%, at 2 years was 42%, and at 3 years was 35%. Late onset relapse (> 1 year) was often observed in the RE-STIM study, although most molecular relapses were observed during the first year following TKI discontinuation. Almost all patients who had relapsed re-gained MMR within a median of 4.6 months after resuming TKI

(42/44 patients had received TKIs following molecular relapse, and two patients had also nearly achieved MMR even in a short follow-up time < 3 months). Nonetheless, second attempt TKI discontinuation was considered feasible in patients who after failing the first attempt had obtained a sustained second DMR.

### **Nilo Post-STIM study**

31 patients with CML-CP who relapsed after an imatinib discontinuation attempt in the EUROSKI (n = 16), STIM2 (n = 9) and A-STIM (n = 6) studies were enrolled in the Nilo Post=STIM study<sup>18</sup>. The enrolled patients received nilotinib at a dose of 600 mg daily for two years. Patients who achieved a durable MR<sup>4.5</sup> for at least 12 months were further enrolled for the second TFR attempt. Seven patients developed adverse events, including two arterial occlusive events leading to nilotinib discontinuation, and one patient opted out of the study. Finally, 23 patients (74%) completed nilotinib treatment for 24 months, and 22 (96%) maintained their molecular response for at least 12 months. 22 patients discontinued nilotinib and 12 patients lost MMR. Eight months (range: 2–42 months) was the median time to molecular relapse. The TFR rates at 1, 2, 3, and 4 years following nilotinib discontinuation were 68.2%, 59.1%, 54.2%, and 42.1% respectively.

### **TRAD study**

59 patients who relapsed after imatinib discontinuation were enrolled in the TRAD study. Among these 59 patients, 55 were initiated on dasatinib therapy at a dose of 100 mg daily. 49/55 (89.1%) achieved MR<sup>4.5</sup> or a deeper response with a median time of 2.74 months<sup>18</sup>. Six patients discontinued dasatinib due to adverse events (sepsis, n =



1; pleural effusion, n = 3; pulmonary arterial hypertension, n = 1; and acute coronary syndrome, n = 1). The remaining 49 patients achieved MR<sup>4.5</sup> or deeper response and 35/49 (71.4%) patients, after receiving consolidative treatment for 12 months, discontinued dasatinib for the TFR2 attempt. Nine patients-maintained MMR, making the TFR2 rate as 25.7% (9/35). Late onset relapse (> 1 year) was not observed in the TRAD study.

### **A-STIM trial**

128 patients were enrolled in the A-STIM trial. 76 (61%) patients received imatinib, and 52 (39%) were on second-generation (2G) TKIs at the time of discontinuation. The median duration of DMR (MR<sup>4.0</sup>) before TKIs discontinuation was 4 years. TFR1 rates were 56.5% at 1 year, 53% at 3 years, 51.1% at 5 years, and 45.6% at 7 years, respectively. Then, of the 65 patients resumed a TKI after TFR1 attempt failure, and 32 (49.2%) underwent a TFR2 attempt. 16 patients received imatinib and 16 were 2G TKIs before TFR2 attempt. The median duration of DMR (MR<sup>4.0</sup>) before TFR2 attempt was 2.3 years. TFR2 rates were 46.8% at 1 year, 35.8% at 3 years, and 31.3% at 5 years, respectively. Late molecular relapse rate (<2 years) was 14.3%<sup>19</sup>.

### **Real world data**

According to the real-world TFR2 data reported by Kim E *et al.*, 21 patients who regained MR<sup>5.0</sup> following resumption of imatinib with durable remission (median 31 months) later discontinued imatinib, following which five of the 21 patients-maintained molecular remission with a median follow-up time of 33 months<sup>20</sup>.

We also reported the real-world TFR2 data. 25 out of a total of 53 patients

relapsed at TFR1 attempt. Subsequently, ten patients who achieved durable MR<sup>4.5</sup> or deeper, discontinued TKIs at TFR2 attempt. Eight patients stopped dasatinib and two patients stopped nilotinib. The median duration of DMR (MR<sup>4.5</sup>) before TFR2 attempt was 34.0 months and four of ten patients-maintained molecular remission with a median of 32.3 months<sup>21</sup>.

### **Predictive factors for successful achievement of TFR2**

The predictive factors for successful achievement of TFR2 are unclear, because few studies investigated TFR2. It has been repeatedly reported that maintaining MR<sup>4.5</sup> at 3 months after discontinuation TKIs is a favorable prognostic factor<sup>7,18,21</sup>. Meanwhile, there are no studies on aspects of immune-related mechanism with respect to TFR2 attempt, and further investigations are needed.

### **Conclusion**

Although the rate of achievement of TFR2 is lower than that of TFR1, TFR2 attempt is feasible after re-treatment with imatinib, nilotinib, and dasatinib. Patients who achieved MR<sup>4.5</sup> or deeper durable molecular remission can enter the TFR2 phase. Optimal duration of the consolidation phase before TFR2 attempt is unclear. Imatinib was well tolerated and could be administered as a consolidative treatment before TFR2 attempt, whereas patient tolerance for nilotinib or dasatinib was lower and could lead to discontinuation due to drug-related adverse events. There is no evidence to support the switch of imatinib to dasatinib or nilotinib for TFR2 attempt<sup>18</sup>. Late molecular relapse was often reported, thus careful monitoring is needed at TFR2 attempt<sup>19</sup>. Asciminib has favorable tolerability profiles and could be a better option to continue the

treatment<sup>22,23</sup>. Patients who received asciminib continued treatment and then achieved MR<sup>4,5</sup> at a higher rate than those who received the 2G TKI.<sup>23</sup> Hence, we are conducting ASSET CML trial to investigate TFR2 after asciminib discontinuation in patients with CML-CP who received asciminib as third or more line treatment after TFR1 attempt failure and achieved durable MR<sup>4,5</sup> at least 24 months. (**JRCTs071230047**).

## **Finding**

This work was partially supported by research grants from the Japan Society for the Promotion of Science Grants-in-Aid for Scientific Research (21K16245 to H.U.), and the Shinnihon Foundation of Advanced Medical Treatment Research (H.U.), Takeda Science Foundation (H.U.), the Medical Research Encouragement Prize of The Japan Medical Association (H.U.), the Japanese society of hematology research grant (H.U.) and Japanese foundation for multidisciplinary treatment of cancer (H.U.).

## **Contributors**

HU, KK and SK made substantial contributions to study conception, design, analysis and data interpretation. HU, KK and SK wrote the manuscript and HU and SK critically reviewed the drafts. All authors approved the final version.

## **Conflict-of-interest disclosure**

SK received honoraria from Bristol-Myers-Squibb, Novartis, Pfizer, and Otsuka Pharmaceuticals and research funding from Bristol-Myers-Squibb, Pfizer and Ohara Pharmaceuticals. The other authors declare no conflicts of interest.

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