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# Treatment Free Remission in Chronic Myeloid Leukemia; A Practical Option

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**Abstract**

Chronic myeloid leukemia (CML) is a type of blood malignancy. Unlike some other diseases and cancers, the treatment for CML typically spans many years. Patients achieving and sustaining a deep molecular response may be candidates for treatment stoppage. This concept also known as treatment free remission (TFR) is a new concept in CML management and of late has become a major goal. TFR has also taken the center stage owing to its implications in reducing health and financial burden being imposed by the disease. Numerous clinical trials have made an attempt to study as to which patients are the best candidates for treatment free remission and what percentage of such patients either stay in remission stage or face relapse. Findings of the trials suggest around 45-60% of patients being able to achieve TFR whereas the relapse mostly occurred in first six months of treatment stoppage. Nevertheless, almost all patients who were re-initiated on Tyrosine kinase inhibitors (TKIs) showed molecular response. Certain clinical and molecular biomarkers are thought to be linked to increase probability of TFR. In this review we attempt to discuss both clinical and molecular markers associated with TFR in CML.

**Key Words:** Chronic myeloid leukemia, Treatment free remission, relapse, Tyrosine kinase inhibitors.

## Introduction

CML is a hematological disorder and remains a model in cancer's customized therapy.[1] Approximately 1-2% of adults out of every 100,000 develop CML.[2-4] Translocation between chromosome 9 and 22 involving fusion of gene BCR-ABL1 is the hallmark of CML (Figure 1). Clinically marked by Philadelphia chromosome and BCR-ABL1 gene, CML remains a leading form of blood cancers.[2-4]

Introduction of tyrosine kinase inhibitors opened a new chapter in the management of TFR and subsequently paved the way for possibilities into TFR. The progression of CML starts from a chronic stage and going through accelerated phase moves into blast phase.[5]

BCR ABL1 gene leading to the oncoprotein has become a major target for leukemic cells and was the basis for inception of TKIs, which markedly improved the survival and prognosis of the disease.[6,7] The overall survival of patients taking TKIs started being matched to those without the disease.[8-10] The high therapeutic response of TKIs has shifted the focus from achieving molecular response to eventually stopping the therapy.[11] Earlier on TFR was deemed suitable for patients taking interferon, however now more evidence is also building to practice TFR for patients taking TKIs.[12]

Patients receiving TKIs often attain sustained molecular responses, which not only enhance their quality of life but also reduce the risk of progression from the chronic phase to the accelerated and blast phases.[13-15]

According to ELN society, DMR is either defined as when patient's blood doesn't have detectable BCR-ABL1 mRNA transcripts using quantitative polymerase chain reaction (qRT-PCR) or having two series of qualitative PCRs with less than 104 detection.[16] On the other hand, International scale defines deep molecular response MR4 pointing to >4.0-log reduction, MR4.[5] implying to >4.5-log reduction and subsequently MR5 indicating >5.0-log reduction.[17] Owing to the great disease and healthcare burden, stopping TKI therapy will go a long way in improving quality of life and reducing financial burden on the patients and caregivers.[18] In this review, we aim to discuss the possibilities of achieving TFR in light of the trials and also

look at the possible predictors and factors playing important role in achieving TFR.

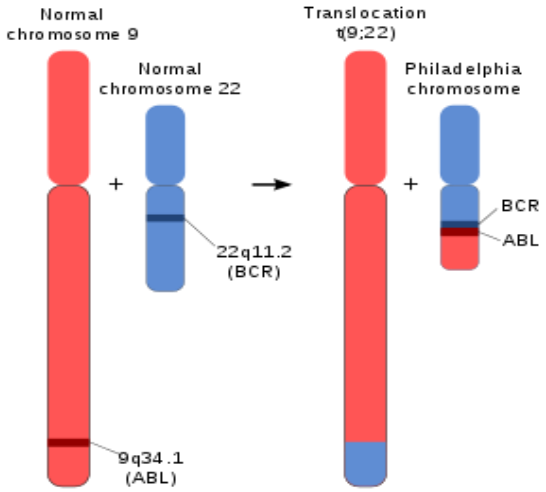


**Figure 1. Chromosomal Translocation resulting in Fusion of BCR-ABL1 gene. (source Cancer.gov/publications)**

CML results from malignant transformation of pluripotent-stem cells causing granulocyte overproduction. CML, initially asymptomatic gradually progresses with time leading towards accelerated and blast crisis. Loss of appetite, weight loss and feeling of discomfort are common symptoms earlier on. During blast phases the signs get more profound like splenomegaly, bruising, bleeding and fever.

Diagnosis of CML can be simple, consisting of documenting, persistent leukocytosis, the detection of Philadelphia chromosome, through cytogenetic testing or through FISH technique.[18] Amplification of the region surrounding splice area between ABL and BCR is carried out through RT-PCR(reverse transcription polymerase chain reaction). PCR is either qualitative where it reveals about the presence of BCR ABL fusion or quantitative telling about the quantity of the transcript.[6]

Foundation therapies in CML include Tyrosine kinase inhibitors at first place. Till date there are five TKIs available in the market, including Imatinib, Nilotinib, Dasatinib, Bosutinib and Ponatinib. Imatinib still remains the first line TKI in CML treatment .[13]

## Treatment Free Remission in CML

The concept of operational cure was coined by Prof. John Goldman, where patients can have a close to normal life while they are on TKIs.[19] This further led to the concept of TFR which is one step ahead of the concept of operational cure. According to the concept of TFR, patients achieving a deep molecular response may stop their therapy and lead a normal life.[20] Though TKIs are considered safe and tolerable, still there is a significant population which undergoes side effects and adverse events which greatly affects their compliance and treatment goals.[21] New or second generation TKIs are considered to be more powerful resulting in a more severe side effect profile. Trials suggest around 30-35% of patients taking TKIs experience some sort of side effects, impacting their daily work routines.[22, 23] Patients in the age group of 18-40 have a more profound side effect profile.[24]

During a multi-center survey including 329 patients, 34% patients consented to discontinue TKI, largely because of the low quality of life with TKIs, whereas another 39% were willing to carry on with the treatment fearing a relapse risk.[25] The same survey findings found that younger population was more into being willing to stop treatments whereas pregnant women can't take TKIs.[25]

## Clinical Trials on Treatment Free Remission

Trials and studies done on TFR require patients to be on TKIs and showing a sustained molecular response for a good period of time. One of the limitations with TFR trials is that they are non- randomized, except HOVON, in which the subjects were randomized into two cohorts after a sustained MR4.5 spanning two years. One arm had patients continuing with TKI while the other arm had patients discontinuing TKI.[26] Incidence in group first was 17% whereas in the other case was 67%. Another downside of these TFR trials may be them being observational which may increase bias in some cases.[27] Relatively lower subjects in TFR trials may yield some false positive results. Nevertheless, there are few large TFR trials like EURO-SKI which involved more than one hundred centers covering 11 countries and around 750 patients.[28]

STIM trial included patients taking imatinib for three years and having undetectable BCR-ABL1 transcripts for two straight years. After 77th month follow-up of stopping TKI, the survival rate at 6th month was 43% whereas at 60th month it was 38%.[29] Most of the relapses took place during 6 months of stopping imatinib.

Another TKI stop trial- D-STOP studied TFR in those CML subjects who were able to maintain molecular response

patients defined as BCR- ABL1 less than 0.0069% for a period of 2 years after treatment with any TKI combined with dasatinib. Amongst the patients receiving TKI plus dasatinib therapy, 83% stopped

dasatinib. After sixteen months follow-up, the estimated likelihood of TFR was 63% at 12th month. Patients encountering relapse were reinitiated on dasatinib and were able to achieve molecular response within six months. Figure 2 explains as to when and which type of patients can initiate TFR.

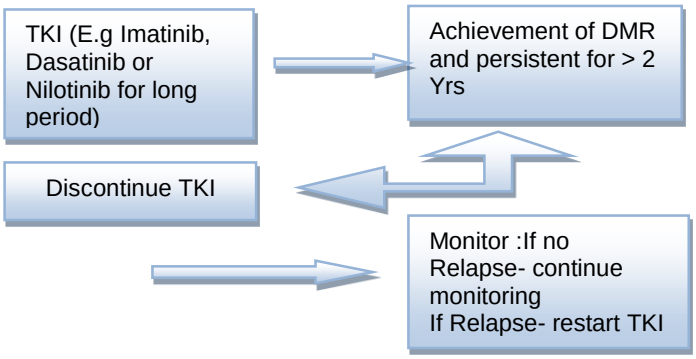


Figure 2. Concept of TFR. Patients achieving a sustained molecular response can attempt TFR. They are then monitored for relapse; in case of relapse TKIs are re-initiated.

Table I gives a detailed overview of some of the major TFR trials conducted till date and it depicts the TFR rate to be somewhere between 40- 60% in most of the trials. Also it gives an idea of the minimum molecular response required to initiate TFR. Moreover, the type of TKI used in that particular trial is also given.

## Mechanisms Underlying TFR

Research is still ongoing to find the exact mechanism behind successful TFR. It is thought that leukemic stem cell's biology, immune system and microenvironment may play a vital role.[38] One mechanism explains the role of immune cells as being responsible for maintaining a deep molecular response as before TKIs, interferons were given to CML patients, which played a role in immune system's activation.[39,40] Various trials further established the immune system's role in the management of CML after discontinuation of TKI by pointing to low NK cells as factors for relapse in patients.[41-43]

There are more proposed mechanisms to TFR and one suggests the idea of latency that refers to the interval between the events when BCR–ABL is formed and until CML is diagnosed. It varies and may be between 2 to 40 years. After the incidence of Nagasaki and Hiroshima atomic bombs, the occurrence of CML rose within 2 to 4 years time.[44,45] The more biomarkers we know related to TFR, the more confidently we may discontinue the therapy.

## Factors Important in Success or Failure of TFR

### TKI treatment duration

One important aspect of initiating a TFR is the duration for which TKIs have been administered. The trials done on TFR had criteria of TKI usage for 2 to 3 years. As the years of TKI use increased, the chances of TFR success also went up. In one of the TFR trials (STIM), the duration of imatinib treatment was 50 months.[46] Similarly, in few other studies- (KID and EURO-SKI), it was observed that the patients obtaining a MR4 at first year and having a sustained TFR took TKI for around 5.5 years.[47]

Results from the TRAD trial were also in line with the other studies, where the cutoff was 8.7 years. The Successful TFR rate for patients above 8.7 year treatment was around 80% and for those less than 8.7 years was 28%, which

**Table I: Characteristics of Trials Discontinuing TKI.**

| Trial | N | TKI duration (Yr) | TKI Type | DMR duration (Yr) | Median follow up (M) | TFR Rate |
|---|---|---|---|---|---|---|
| STIM[29,30] | 100 | 3 | Imatinib | UMRD>2 | 77 | 43 and 38% at 2 and 5 yrs |
| TWISTER[31] | 40 | 3 | Imatinib | UMRD>2 | 43 | 47% at 2 yrs |
| ASTIM[32] | 80 | 3 | Imatinib | $MR^4$>2 | 31 | 64% at 2 yrs and 61% at 3 Yrs. |
| HOVON[33] | 15 | 2 | Imatinib | $MR^{4.5}$>2 | 36 | 33% at 2 yrs |
| ISAV[34] | 108 | 2 | Imatinib | UMRD>1 | 21.6 | 48% at 3 Yrs |
| KID[35] | 90 | 2 | Imatinib | $MR^{4.5}$>2 | 26.6 | 62.2% AT Yr 1 and 58.5 at Yr 2. |
| UERO-SKI [36] | 755 | 3 | Imatinib,Nilotinib and Dasatinib | $MR^4$>1 | 27 | 61% at Half yr and 50% at 2 Yr |
| D-STOP[37] | 54 | 3 | Dasatinib | DMR>2 | 16 | 62.9% at 1 yr |

strongly advocates for TKI duration as a key deciding factor in TFR's success.[48]

## Deep Molecular Response

Along with TKI duration, another factor that determines the success of TFR is the level and duration for which molecular response is attained. We define UMRD when the BCR-ABL transcripts are absent from the blood or bone marrow.[49] It was observed that after TKI stoppage, there were more cases of relapse in the case of prolonged molecular response patients.[50-52] Studies also point to the fact that sustained and prolonged molecular response and UMRD strongly link to a successful TFR. In EURO-SKI it was revealed that longer molecular response' duration before stopping TKI resulted in better TFR probability. A Japanese trial STAT2 showed that at 36 months, the TFR rate was higher in those patients with no residual disease as compared to those with molecular residual disease (77 vs. 49% respectively).[53]

## BCR ABL Transcript Type and Detection

The hallmark of CML is BCR-ABL1 gene which codes for tyrosine kinase. We also know in the breakpoint region of BCR-ABL, there is quite variability. Chromosome 22 breakpoints are concentrated in the 5.8 kb section having exons e12 to e16 also called as the M-BCR (major-breakpoint cluster region).[54] In most of the cases, Breakpoint areas occur either between exons e13-e14 & e14-e15. Although, similarly, there is variability in the breakpoints of ABL gene, but due to the splicing cases, transcribed mRNA has either an e13a2 or e14a2. The both transcripts differ in length by 25 amino acids (75 BP).[55]

Previously, studies have revealed that those patients who took imatinib and expressed the e14a2 type of transcript had a better and quick cytogenetic response as compared to those patients with e13a2 type transcript, primarily due to a more profound BCR–ABL tyrosine kinase activity.[56] According to findings of Destiny trial of UK, 15% patients relapsed having e13a2 transcript as compared to 7% patients having 314a2 transcript.[57]

One of the more sensitive ways to detect BCR-ABL1 transcripts is the double-digit PCR technique. The lower the transcript levels are, the greater probability of achieving a successful TFR. The Destiny trial also asserted these aspects, with a few of those trials having patients in MR3 and MR4 at the time of enrollment.[57]

## TKI Resistance

During the STOP-TKI trial, the percentage of patients having an optimal response to TKI (Imatinib) was 65%, and those having resistance was 21.7%. Possibility of relapse at 4th year for patients having previous resistance to therapy was 76.9% and level of TFR was 23%.[37]

Another stop trial -DADI (2015) revealed that patients switching to Dasatinib after Imatinib failure only had a 7.7% remission rate suggesting that once patients face resistance with one TKI, they may not be included in TFR studies.

## Prognostic scoring- Sokal, EUTOS and ELTS score

Classifying the CML patients into either high, intermediate, or low risk patients, the first score based method used was called SOKAL.[58] This score calculates the platelets, blast-cells, patients' age and spleen size.[59] Studies point out to a low SOKAL score as a high probability of having progression-free survival and also a better all cause survival rate.[60, 61] According to STIM trial, chances of having a sustained deep molecular response in patients were higher when the SOKAL and Eutos scores were low as compared to when they were high.

## Re-Initiating TKI and Second Attempt TFR

In various TFR trials, re-starting TKI therapy was subject to the relapse. Nevertheless, the extent of the re-initiating criteria varies among various TKI stop trials. Relapse in STIM trial was defined as positive transcripts of BCR–ABL1 in at least two regular assessments having a ratio of BCR–ABL1 and ABL 10−5 or greater.

TWISTER trial presented with a new definition, which was a loss of molecular response (>0.1% BCR–ABL1IS) and/or 2 repeated samples at any value.[31] A-STIM study had a lesser stringent definition with relapse defined as loss of molecular response at any time during the treatment.

The right time to re-initiate TKI followed by a relapse is an important question. Guidelines suggest re-starting TKI during the first month of relapse and must be followed up for every 3 months. Moreover, data and information is also available on when and how to attempt second TFR (TFR2) by stopping TKI. RE-STIM study reported 70 patients attempting a TFR2 following relapse after first TFR. All of the patients had attained MR4.5 for more than 2 years.

Percentage of patients achieving TFR2 at 1st, 2nd and 3rd year was 48, 42 and 35% respectively. No patient advanced to accelerated and blast phase. The key factor for a second TFR remained the time to relapse during first TFR. Patients retaining DMR in the initial three months of the first TKI stoppage, obtained a TFR2 rate of 72% at 2 years, whereas, for those relapsing in less than 3 months the TFR2 rate was 36%.[62]

## Other Genetic Markers Involved in TFR

More data is surfacing showing CP CML as genetically heterogenic blood cancer. Nevertheless, acute leukemia at the point of diagnosis is more heterogenic genetically. Studies have hinted towards ASXL1 as the most was commonly mutated gene in patients with CP CML, while mutations in other leukemia-associated genes that were selected for screening, including the TET2 and IDH1/2 genes, have rarely been identified. Multiple studies have attempted to find out the genetic factors and their effect on successful TKI discontinuation. Plasma microRNA-215 and microRNA148b's down-regulation has been connected with TKI (imatinib) discontinuation. Analysis of whole exome sequencing discovered CYP1B1, ALPK2, and IRF1 gene variants in patients facing relapse and another variant in PARP9 gene in those patients without relapse. During EURO-SKI sub-analysis, higher probability of relapse was observed in those patients having higher transcript level of ABCG2 efflux transporter.[36]

DADI trial on discontinuation went on to show that at the time of TKI stoppage, lower quantity of CD4+ T cells was linked with a better rate of TFR, and the DADI trial also revealed that patients having a lower CD4/CD8 ratio went on to have a superior rate of TFR.

D-STOP trial proved that subjects having a lower fraction of NK cells at the time of discontinuing dasatinib had long and sustained TFR and it is believed that consolidation treatment with dasatinib may actually contribute to this.[37]

## TFR and Quality of Life

One of the main motivations behind stopping TKI is the factor that by not taking daily TKE treatment, the patients won't be suffering with the side effects and toxic effects of the drug. The most recent study, which looked at life after stopping TKI, was one of the first to discuss patient-reported outcomes. During this trial, patient outcomes were assessed every month for first six months, followed by assessment at 8th and 12th months, and then every 6th month till finishing of this 36-months study.

Analysis of 1883 patient outcomes revealed that stopping TKI was largely associated with a significant reduction in depression, fatigue; sleep related disturbance and diarrhea.

## Guidelines and Clinical Practice

Various trials differ in the context of inclusion and exclusion criteria, TKI discontinuation, and restarting the therapy. However, all important societies have put forward guidelines and recommendations on TFR. These societies include NCCN (national comprehensive cancer network), FCMLSG (French chronic myeloid leukemia study group) and ESMO (European study for medical oncology) etc. Also, these guidelines strongly recommend initiating TFR only where there is facility of molecular testing and where the prerequisites of TFR are well met.[62-65] Table II highlights few of these guidelines.

Important factors to consider while stopping TKI and attempting TFR include; patient consent, molecular response for at least 2 years, patients should be ideally in chronic phase with no disease progression to blast crisis.[66,67] Physicians should take their patients into confidence before stopping TKI and must also let them know of the possible side effects or withdrawal effect-

**Table II: Guidelines for TKI discontinuation in clinical practice.**

| Criteria | FCMLSG | NCCN | ESMO |
|---|---|---|---|
| Age | >18 | >18 | >18 |
| Phase | Only CP | Only CP | Only CP |
| Sokal Test | Not defined | No defined | Not high |
| BCR-ABL mRNA Transcript | e13a2,e14a2 or both e13a2 plus e14a2 | Typical quantifiable transcript | e13a2, e14a2 |
| TKI duration in Yrs | >5 | >3 | >5 |
| DMR Type | $MR^{4.5}$ | $MR^{4}$ | $MR^{4.5}$ |
| DMR Duration | >2 | >2 | >2 |
| Re-Treatment | Loss of MMR | Loss of MMR or <MR4 | Not defined |

most common of which is the muscoskeletal pain occurring in <30% of the patients.[68,69]

Molecular monitoring remains one of the critical factors which makes Physicians reluctant to initiate TFR as most settings outside clinical trial settings often lack this facilit. Guidelines strongly recommend monitoring on monthly basis in the first six months after treatment stoppage, while every three months later on.[70]

## Conclusion

Treatment-free remission (TFR) represents a relatively recent and evolving concept in the management of chronic myeloid leukemia (CML). Data from trials conducted thus far indicate that approximately 40-60% of patients who discontinue tyrosine kinase inhibitor (TKI) therapy can successfully maintain TFR. Also, in the trials most of the relapses took place during first six months, however all patients responded to TKI once the treatment was re-initiated. Prolonged TKI treatment and achieving a deep molecular response for more than 2 years resulted in a successful TFR. Moreover, those having a higher SOKAL level, younger age and resistance to TKI led to TFR failure chances.[71]

During earlier stop trials, disease progression was feared but actually very few cases have been observed.[72, 73] Nevertheless, it must be noted that ISAV trial reported that the patients remaining in TFR have one PCR positive test at minimum and by applying dPCR, it is assumed that the clone may rise by one log in three years' time. The reason for not having a continuous surge in leukemic clone remains unknown and offers a thought provoking question for the next studies.

Making TFR a normal treatment goal, prognosis needs to be better and standard of care needs to improve. One effort at such front can be to use latest treatment options including second and third generation TKIs. Also, we need to have sensitive PCR facilities available at our centers with proper monitoring being ensured. Trials combining the use of TKIs and Interferon yielded better molecular response, however the effect on TFR is yet to be established with researchers hoping this combination to improve TFR rates. The more TFR targeted trials we will have, the better understanding of biology of TFR would be understood and it would be practiced at a larger scale without much fear of relapse and disease progression.

TFR has emerged as a significant milestone in CML management and is a feasible option for a substantial number of CML patients. Upcoming trials on TKI discontinuation and TFR will likely strengthen clinicians' confidence in practicing TFR. Even for those patients who experience a relapse after their initial TFR attempt, there is evidence supporting the possibility of a second TFR attempt, as demonstrated in various trials. [74,75]

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