

Patient- and physician-reported pain after tyrosine kinase inhibitor discontinuation among patients with chronic myeloid leukemia

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Abstract

For patients with optimally treated chronic myeloid leukemia (CML), discontinuation of tyrosine kinase inhibitor (TKI) therapy can lead to treatment-free remission. In previous trials, TKI discontinuation has been associated with increased musculoskeletal pain in some patients (“withdrawal syndrome”), based on physician-reported adverse events (AE). Patient-reported pain has not been described. The Life After Stopping TKI study was a 14-site prospective, non-randomized clinical trial of TKI discontinuation. We defined increased pain after discontinuation as: (i) a physician-reported pain AE, (ii) a 2-level increase in self-reported musculoskeletal pain (4-level single item), or (iii) initiation of a medication for pain. We plotted the trajectory of patient-reported pain over time using a piecewise mixed-effects ordinal logistic model. Within 3 months of discontinuation, 35 of 172 patients (20.3%) had a physician-reported pain AE, 22 of 172 (12.8%) had an increase in self-reported pain, and 18 of 154 (11.7%) initiated a pain medication. Agreement among these measures was limited; overall, 60 of 172 patients (34.9%) had increased pain. Three patients (1.7%) restarted a TKI because of pain. The model-predicted trajectory showed an increase in pain in the first 3 months followed by a decrease, returning to baseline levels by 6 months and further decreasing after that. This trajectory was similar among patients who did and did not restart TKI, suggesting that resuming a TKI for withdrawal syndrome may be necessary for some, but other approaches to manage pain should be tried so that patients can remain in treatment-free remission when possible.

Introduction

Compared to other treatments for chronic myeloid leukemia (CML), tyrosine kinase inhibitors (TKI) are highly effective¹ and less toxic.^{2,3} However, they are still associated with side effects, particularly fatigue and gastrointestinal symptoms.⁴ Moreover, TKI may be cost-prohibitive for patients, leading to non-adherence.⁵ For select patients who achieve a sustained deep molecular response, TKI discontinuation may lead to treatment-free remission (TFR), effectively a “cure” for CML.⁶ In TKI discontinuation trials, 32-67% of patients sustained TFR.⁷⁻¹⁶ For patients without sustained TFR, restarting TKI therapy was effective in restoring stable remission, including return to deep molecular response. TKI discontinuation is hypothesized to improve patient-reported symptoms and functioning, and

this was recently demonstrated in the US Life After Stopping TKI (LAST) study.^{16,17} However, previous trials found that TKI discontinuation was unexpectedly associated with increased musculoskeletal pain for some patients, which has been called “TKI withdrawal syndrome”. In these previous trials, physician-reported adverse events (AE) related to musculoskeletal pain were reported for anywhere from 10-50% of patients.¹⁸

Uncertainty about the extent of increased musculoskeletal pain associated with TKI discontinuation is compounded by the reliance on physician-reported AE. Studies with patients with solid tumor cancers have documented generally poor-to-moderate agreement between physician and patient reports of pain.¹⁹ A previous study in CML assessed physician-patient agreement on nine symptoms and found 44% agreement for musculos-

keletal pain, with physicians underestimating patient musculoskeletal pain for 42% of patients and overestimating it for 14% of patients.²⁰ To our knowledge, no previous studies have described patient-reported musculoskeletal pain after TKI discontinuation. Herein we describe physician-reported pain-related AE and patient-reported musculoskeletal pain, as well as their overlap, in the context of the LAST study.

Methods

LAST was a 14-site, single-arm, prospective longitudinal TFR study. Eligible patients had chronic-phase CML, were aged ≥ 18 years, and receiving imatinib, dasatinib, nilotinib, or bosutinib for ≥ 3 years with continuous documented BCR-ABL $< 0.01\%$ International Standardized by real-time quantitative polymerase chain reaction (RQ-PCR) for ≥ 2 years. The study was approved by the Institutional Review Board of each participating institution, and all patients provided written informed consent. Additional methodological details are included in the *Online Supplementary Appendix* and have previously been published.²¹

Measures

Physician-reported adverse events

AE were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. We defined pain-related AE as any grade AE that was reported after TKI discontinuation using toxicity group “musculoskeletal and connective tissue disorders”.

Patient-reported pain

In order to measure musculoskeletal pain, we used a single item with four response options from the European Organization for Research and Treatment of Cancer (EORTC) QLQ-CML24 that asks about aches or pains in muscles or joints. We assessed how much pain affected daily life using the PROMIS® Pain Interference computerized adaptive test.²²

Pain medications

On the 3-month PRO assessment for those in TFR (off TKI), we asked patients about changes in medications since TKI discontinuation, including whether they had started any new prescription or over-the-counter medications. For any “yes” responses, patients were asked to name the medication. These responses were coded by a physician (EA) to determine whether they were related to pain. We included analgesics, anti-inflammatory medications, and muscle relaxants.

Statistical approach

We summarized the different measures of pain using fre-

quencies and percentages. Patients were classified as having an indicator of increased pain after stopping TKI if they had any of the following within 3 months of stopping: (i) physician-reported pain AE, (ii) a ≥ 2 level increase from their previous assessment in self-reported musculoskeletal pain, or (3) initiation of a medication for pain (while a 1 category change may reflect meaningful change, because of uncertainty around what to consider a meaningful change on this single item, for subsequent analyses we selected the ≥ 2 category increase to be conservative.) Characteristics of patients who did and did not have increased pain within 3 months were compared using Wilcoxon rank sum tests for continuous or ordinal categorical variables and χ^2 tests for categorical variables. Among patients with increased pain within 3 months, we plotted the distribution of responses over time for self-reported musculoskeletal pain and for PROMIS Pain Interference scores. In order to better account for missing data, we also plotted the predicted trajectory of pain using piecewise mixed-effects ordinal logistic (EORTC QLQ-CML24 item on musculoskeletal pain) and a piecewise mixed-effects ordinal logistic regression model (EORTC QLQ-CML24 item on musculoskeletal pain) and a piecewise mixed-effects linear regression model (PROMIS Pain Interference) that allowed the slope to differ before and after the 3-month visit. Random intercepts and slopes were included in models to allow the trajectories to differ among individual patients. For time points after 6 months, we computed the percentage of patients with no or mild pain. We used a 2-tailed significance level of $\alpha = 0.05$ for all assessments. Statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

From 12/2014 to 12/2016, 173 patients from 14 US centers were enrolled, of whom 172 had evaluable data. Median duration of TKI therapy prior to study enrollment was about 7 years (Table 1), similar to other studies.^{8,9,23}

Indicators of increased pain within 3 months after TKI discontinuation

Physician-reported pain-related adverse events

Cumulatively, 35 patients (20.4%) had physician-reported pain-related AE in the first 3 months (Table 2), with most happening within the first month. One month after TKI discontinuation, physicians reported pain-related AE for 26 patients (15.1%). At 2 months, physicians reported pain-related AE for 11 patients (6.4%), and at 3 months it was five patients (2.9%). For most patients, the maximum pain grade was mild (Table 3). While our study focused on increased pain within 3 months, ten additional patients (5.8%) had pain-related AE reported at time points later

Table 1. Baseline patient characteristics overall and by increased pain status (N=172).

	Values	With increased pain N=60	Without increased pain N=112
Age in years Median (range)	61 (22-88)	61 (22-84)	61 (26-88)
Sex, N (%)			
Female	89 (51.7)	37 (61.7)	52 (46.4)
Male	83 (48.3)	23 (38.3)	60 (53.6)
Race, N (%)			
Asian/Pacific Islander	5 (2.9)	1 (1.7)	4 (3.6)
Black/African American	18 (10.5)	8 (13.3)	10 (8.9)
White	145 (84.3)	51 (85.0)	94 (83.9)
Other	3 (1.7)	1 (1.7)	2 (1.8)
Hispanic/Latino ethnicity, N (%)	7 (4.1)	1 (1.7)	6 (5.4)
Education, N (%)			
Associate degree or less	83 (48.3)	26 (43.3)	57 (50.9)
Bachelor's degree or more	89 (51.7)	34 (56.7)	55 (49.1)
Health insurance, N (%)			
Private	104 (60.5)	35 (58.3)	69 (61.6)
Public	56 (32.5)	21 (35.0)	35 (31.3)
Other or uninsured	12 (7.0)	4 (6.7)	8 (7.1)
TKI prior to discontinuation, N (%)			
Imatinib	102 (59.3)	36 (60.0)	66 (58.9)
Nilotinib	39 (22.7)	13 (21.7)	26 (23.2)
Dasatinib	27 (15.7)	10 (16.7)	17 (15.2)
Bosutinib	4 (2.3)	1 (1.7)	3 (2.7)
Duration of TKI treatment, months Median (range)	83.0 (36.1-199.1)	83.1 (36.1-199.1)	83.0 (36.8-182.9)
PROMIS Pain interference, mean (SD)	50.7 (10.0)	51.9 (10.4)	50.0 (9.8)
PROMIS Fatigue, mean (SD)	52.9 (9.9)	54.1 (10.0)	52.3 (9.9)
PROMIS Physical function, mean (SD)	47.3 (8.3)	47.1 (7.9)	47.4 (8.6)
PROMIS Depression, mean (SD)	48.8 (8.0)	48.9 (8.1)	48.8 (8.0)
PROMIS Anxiety, mean (SD)	50.4 (10.0)	50.6 (8.3)	50.3 (8.7)
PROMIS Sleep disturbance, mean (SD)	49.7 (8.2)	49.8 (8.0)	49.7 (8.4)
PROMIS Social roles, mean (SD)	51.1 (9.6)	50.5 (9.2)	51.4 (9.8)

TKI: tyrosine kinase inhibitor; SD: standard deviation.

than 3 months, for a total of 45 patients (26%) who had a pain-related AE after TKI discontinuation.

Patient-reported pain

We previously reported that for patients in the LAST study, baseline pain interference scores were the same as the average in the US general population (score of 50).¹³ Regarding musculoskeletal pain specifically, the majority of patients (77.8%) reported some musculoskeletal pain before TKI discontinuation. At baseline, 38 patients (22.2%) reported no musculoskeletal pain, 60 patients (35.1%) reported a little bit, 43 patients (25.2%) reported quite a bit, and 30 patients (17.5%) reported very much (1 missing re-

sponse at baseline). Within the first 3 months after TKI discontinuation, the worst musculoskeletal pain rating reported by patients was “a little bit” for 43 patients (25%), “quite a bit” for 64 patients (37.2%), and “very much” for 57 patients (33.1%). Eight patients (4.7%) consistently reported no musculoskeletal pain between baseline and 3 months, while 62% of patients reported a ≥ 1 category increase in musculoskeletal pain, and 13% reported a ≥ 2 category increase in pain (Table 2).

Initiation of medications for pain

At 3 months, of the 154 patients who reported on changes in medications, 18 patients (11.7%) reported adding a

medication for pain, including eight (5.2%) who started an over-the-counter medication and 11 (7.1%) who started a prescription medication; one patient reported starting both over-the-counter and prescription medications for pain.

Agreement among indicators of increased pain

Agreement between physician-reported pain-related AE and patient-reported pain varied depending on the threshold considered for increase in patient-reported pain (Table 2; *Online Supplementary Table S1*). There was slightly better agreement between patients and physicians regarding the presence of increased pain using a ≥ 1 level increase (14%) compared to considering a ≥ 2 level increase (4%); however, there was also worse agreement regarding the absence of increased pain (31% agreement for a ≥ 1 level increase vs. 71% for a ≥ 2 level increase), resulting in a better overall agreement for a ≥ 2 level increase (75%) compared to a ≥ 1 level increase (45%). The cross-tabulation of AE grade and patient-reported increase in musculoskeletal pain is shown in Table 3. Although phys-

icians and patients reported the symptoms using different methodologies and scales, Table 3 suggests that physicians' ratings reflect under-reporting (values in the upper right cells) more than over-reporting (values in the lower left cells).

Using the ≥ 2 level increase in patient-reported pain, 45 patients (26%) had a single indicator of increased pain (AE, increase on PRO measure, or reported new medication), and 15 patients (9%) had more than one indicator of increased pain, for a total of 60 patients (35%) who had strong evidence of increased pain within 3 months after TKI discontinuation.

Characteristics of patients experiencing increased pain after stopping tyrosine kinase inhibitors

There were no statistically significant differences in baseline characteristics of patients who did and did not have increased pain within 3 months (Table 1), including age or the particular TKI the patient had been taking prior to discontinuation. Of the 60 patients with evidence of increased pain within 3 months, at 4 years of follow-up, 40

Table 2. Pain within 3 months of tyrosine kinase inhibitor discontinuation.

Physician-reported pain-related AE	Patient-reported increased muscle/joint pain (1+) (N=172)		Patient-reported increased muscle/joint pain (2+) (N=172)		Added medication for pain (N=154)		Patient-reported increased muscle/joint pain (2+) or added medication for pain (N=172)	
	No	Yes	No	Yes	No	Yes	No	Yes
No, N (%)	54 (31.4)	83 (48.3)	122 (70.9)	15 (8.7)	108 (70.1)	14 (9.1)	112 (65.1)	25 (14.5)
Yes, N (%)	11 (6.4)	24 (14.0)	28 (16.3)	7 (4.1)	28 (18.2)	4 (2.6)	24 (14.0)	11 (6.4)
Total, N (%)	65 (37.8)	107 (62.2)	150 (87.2)	22 (12.8)	136 (88.3)	18 (11.7)	136 (79.1)	36 (20.9)

Note: 18 patients were missing data on medication, 14 of whom because they had restarted a tyrosine kinase inhibitor (TKI). AE: adverse events.

Table 3. Agreement between patient- and physician-reported musculoskeletal pain in first 3 months after tyrosine kinase inhibitor discontinuation (N=172).

Maximum grade of physician-reported pain-related AE	Increase in patient-reported muscle/joint pain after TKI discontinuation				
	No increase ^a	+1	+2	+3	Total
None, N (%)	54 (31.6)	68 (39.8)	14 (8.8)	1 (0.6)	137 (79.7)
Mild, N (%)	7 (4.1)	14 (8.2)	4 (2.3)	0	25 (14.5)
Moderate, N (%)	2 (1.2)	3 (1.8)	2 (1.2)	1 (0.6)	8 (4.7)
Severe, N (%)	1 (0.6)	0	0	0	1 (0.6)
Missing, N (%)	1 (0.6)	0	0	0	1 (0.6)
Total, N (%)	65 (37.8)	85 (49.7)	20 (11.7)	2 (1.2)	172 (100.0)

^aNo increase includes patients with no change as well as those with decreased pain. TKI: tyrosine kinase inhibitor; AE: adverse events.

(66.7%) had molecular relapse-free survival and 37 (61.7%) had sustained TFR, similar to the rates for patients who did not have increased pain within 3 months (64.0% molecular relapse-free survival and 60.4% TFR, *Online Supplementary Figure S1*).

Trajectories of pain after stopping tyrosine kinase inhibitors

Self-reported musculoskeletal pain

Figure 1 displays the distribution of self-reported musculoskeletal pain over time by TFR, among patients who had an indicator of increased pain after TKI discontinuation.

The black line represents the best estimated pain trajectory for patients who experienced an increase in pain after TKI discontinuation. Both the observed (blue) line and the model-adjusted (black) line (which accounts for missing data) show an average increase in pain in the first 3 months that then decreases over time, returning to the baseline level by 6 months and further decreasing after that. Importantly, by 12 months, half of patients on TKI as well as more than half of patients off TKI reported little-to-no musculoskeletal pain (Figure 2). By 24 months this had increased to about three-quarters of patients who reported little-to-no pain.

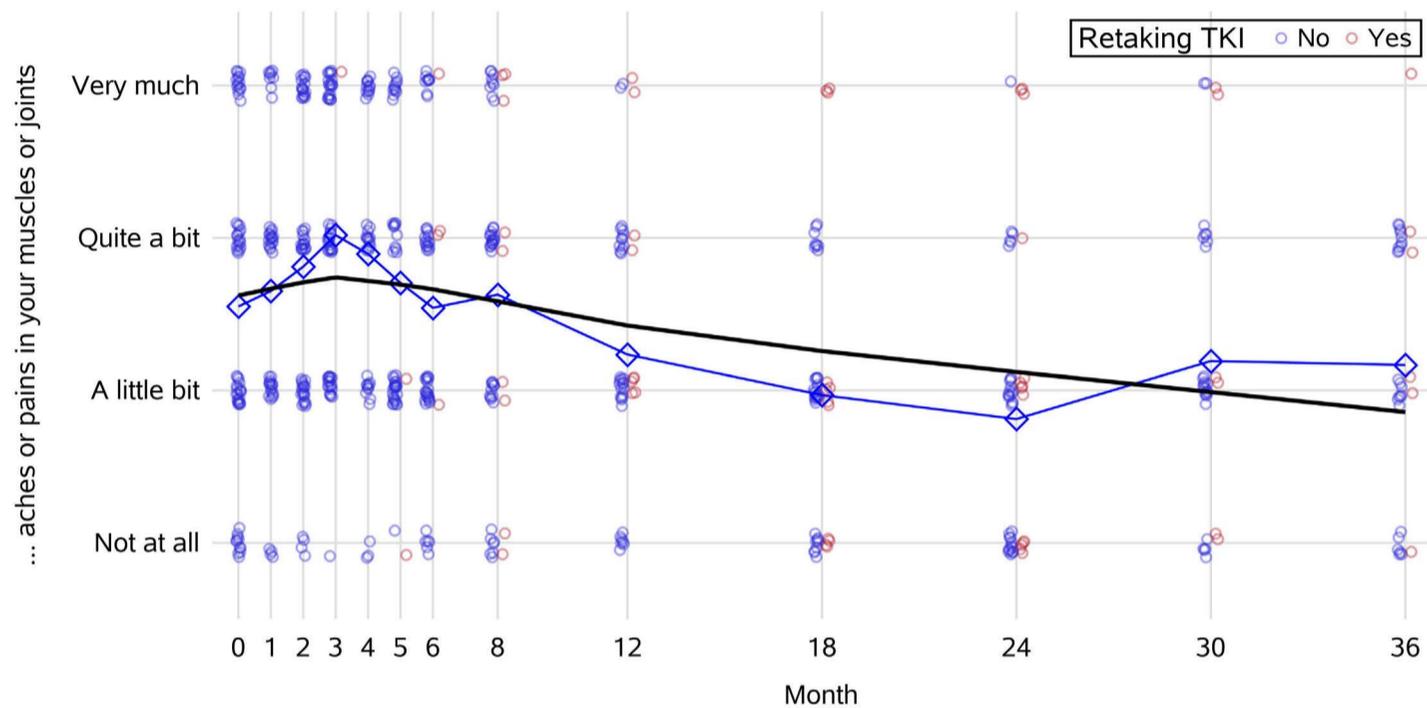


Figure 1. Trajectory of patient-reported musculoskeletal pain among patients with increased pain after tyrosine kinase inhibitor discontinuation (N=60). Note: blue diamonds and line indicate observed average; black line is the predicted trajectory for patients who do not restart a tyrosine kinase inhibitor (TKI) based on a piecewise mixed-effects ordinal logistic regression model.

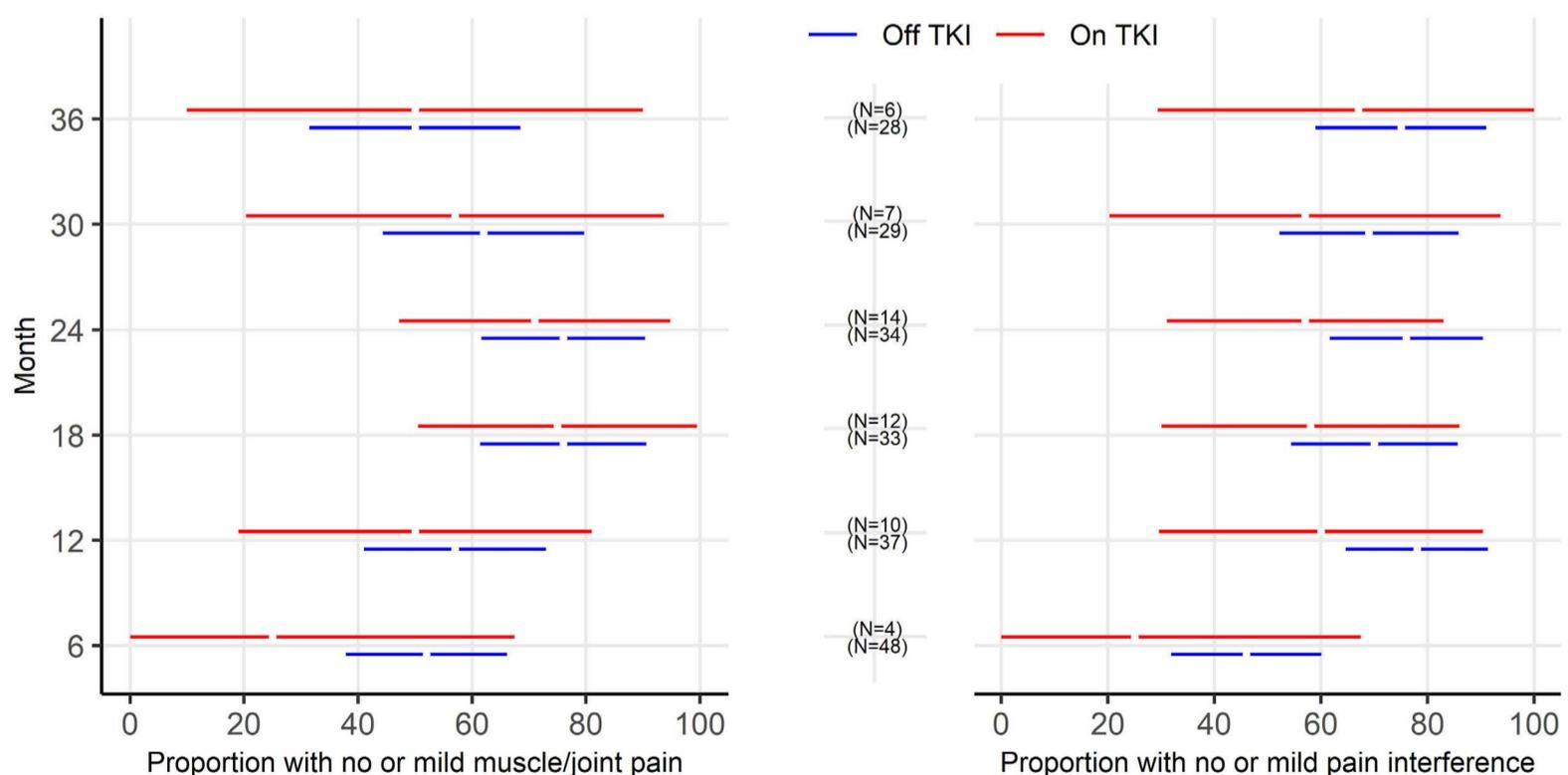


Figure 2. Proportions of patients with well-controlled pain off and on a tyrosine kinase inhibitor over time (N=60). TKI: tyrosine kinase inhibitor.

PROMIS pain interference

Figure 3 displays the distribution of pain interference scores over time by TFR, among patients who had an indicator of increased pain after TKI discontinuation. As with the single musculoskeletal pain item, there was an increase in pain interference after TKI discontinuation that peaked at 3 months and then decreased again. By 12 months, more than half of patients on TKI as well as three-quarters of patients off TKI reported little-to-no pain interference (Figure 2).

Restarting TKI because of pain

Three patients (1.7%) restarted a TKI due to withdrawal syndrome of pain. All three patients had physician-reported pain-related AE by 3 months and none reported starting a new medication for pain. The observed trajectories of patient-reported pain for these patients are shown in Figure 4. All demonstrate an increase in pain or sustained high level of pain after TKI discontinuation, followed by a decrease in patient-reported pain after restarting a TKI. They also show variation in patient-reported pain scores during both periods (on and off TKI). These patients restarted a TKI at 3 months, 7 months, and 12 months.

Discussion

In this large, multi-center trial, 26% of patients had a physician-reported pain-related AE, in line with the 10-50% with physician-reported pain-related AE in previous studies.¹⁸ When including patient-reported indicators of increased pain, 35-72% of patients had increased pain in

the first 3 months after TKI discontinuation. We did not observe differences in pain after TKI discontinuation by type of TKI.

An important question for patients who experience increased pain after TKI discontinuation is whether resumption of a TKI will reduce pain more effectively than remaining off the TKI. Our data provide some insight into this question, because the 60 patients who experienced increased pain within 3 months of discontinuation included patients who did and did not restart a TKI. Almost all who restarted a TKI did so because of disease recurrence. We found that trajectories of musculoskeletal pain and pain interference showed similar patterns of improvement among patients who did and did not restart a TKI. Furthermore, the percentage of patients with well-controlled pain was similar for both groups of patients, suggesting that for patients who have increased pain after TKI discontinuation, pain should decrease again over time. The three patients who resumed a TKI because of increased pain evidenced similar trajectories of pain as the other patients who remained off TKI or restarted because of recurrence. Together, these data suggest that many patients in TFR who experience an increase in pain after stopping TKIs are likely to experience reductions in pain over time without having to restart a TKI. Whereas resuming a TKI may be necessary for some, other approaches to manage pain should be tried so that patients can remain in TFR when possible.

In previous studies, correlations between clinician-reported symptomatic AE and PRO measures have been shown to be moderate at best.¹⁹ In the LAST study, we also found moderate agreement. Over 60% of LAST patients reported any increase in musculoskeletal pain in the first

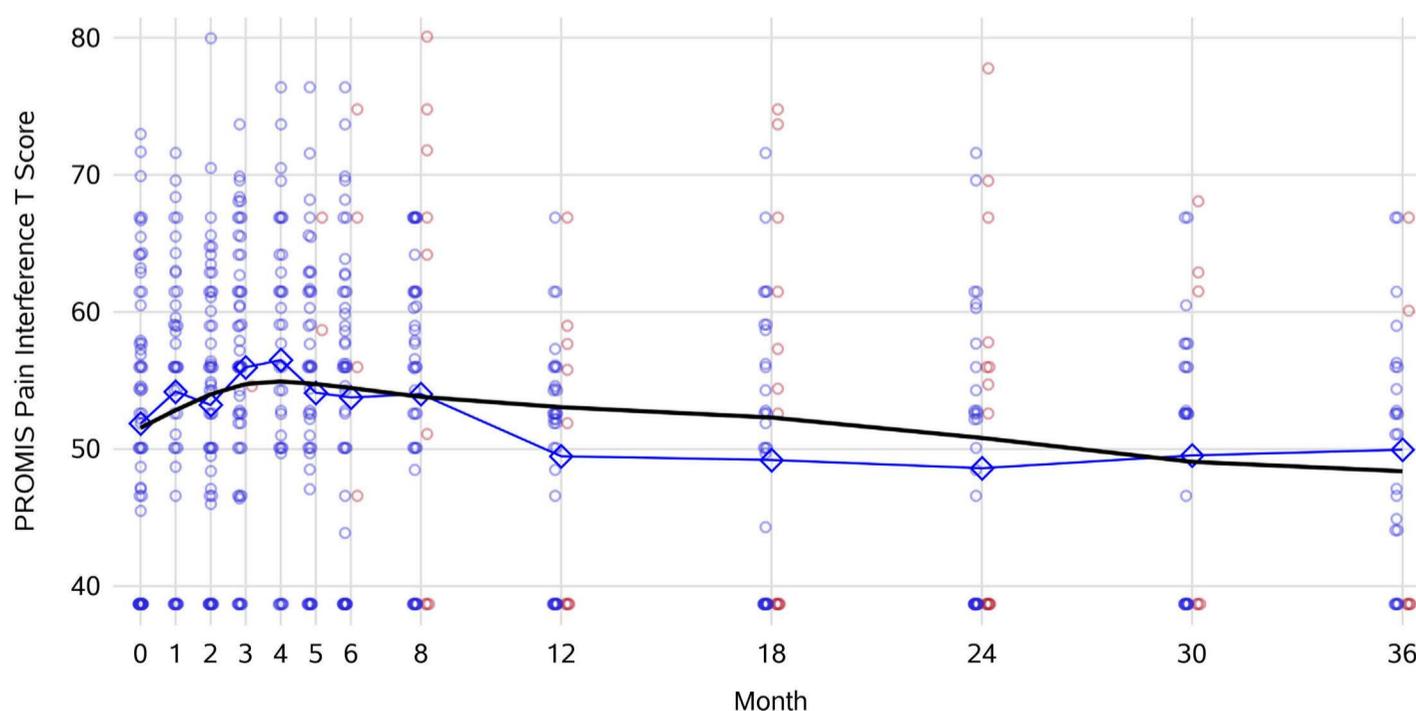


Figure 3. Trajectory of patient-reported pain interference among patients with increased pain after tyrosine kinase inhibitor discontinuation (N=60). Note: blue diamonds and line indicate observed average; black line is the predicted trajectory for patients who do not restart tyrosine kinase inhibitor (TKI) based on a piecewise mixed-effects regression model.

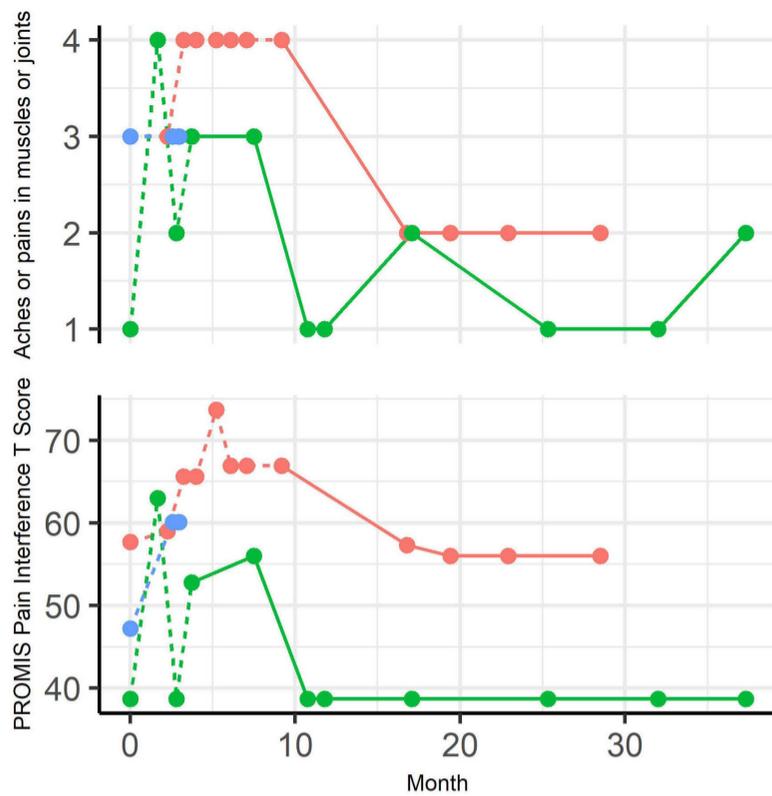


Figure 4. Observed pain ratings for patients who restarted a tyrosine kinase inhibitor for withdrawal syndrome of pain (N=3). Note: dotted lines represent trajectories during treatment-free remission (off tyrosine kinase inhibitor [TKI]) and solid lines represent trajectories after restarting a TKI.

3 months after TKI discontinuation, while 13% of patients reported a 2- or 3-level increase in musculoskeletal pain, and 12% added a medication for pain relief. Using the threshold of a ≥ 2 level increase, there was an overall agreement of 75% between patients and physicians, with the data suggesting physicians reported fewer pain increases and less severe pain increases than patients did. There are a few possible explanations for discrepancies in patient and physician reports. First, patients have direct access to their own pain, whereas physicians have indirect access through observation and conversation with the patient. Second, patient reports and physician AE reports were made on different measurement scales. Third, physicians reported on pain that emerged after TKI discontinuation whereas changes in self-reported pain were based on repeated assessments of pain, reported using a recall period of 7 days.

It is important to consider these findings in the context of previously published findings from the LAST study. The majority of patients reported improvements in fatigue and diarrhea¹⁶ and in social functioning,²⁴ but there were no corresponding improvements in physical function,²⁴ which may seem surprising.²⁵ One hypothesis for this is that while reduced fatigue and diarrhea may be sufficient to improve someone's ability to participate in social roles and activities, it may not be enough to increase their physical function without a concerted effort to increase physical activity. Interventions to increase physical activity have been successful in many other oncologic settings.^{26,27} TKI discontinuation may represent an opportunity to encourage patients to increase their physical activity, taking advantage of the expected improvement in symptoms. This may also serve to mitigate the potential increase in musculoskeletal pain.

LAST patients were representative of the current TKI prescribing patterns in the US, with 59% of patients receiving imatinib.²³ The rate of molecular recurrence in LAST was similar to other studies.²⁴ That said, our sample was drawn from academic medical centers and may not be representative of all patients treated for CML. Self-reported musculoskeletal pain was measured using a single item that might have had limited precision, though the pain trajectory over time was very similar to the multi-item PROMIS Pain Interference assessment. Patients self-reported the changes in prescription and over-the-counter medications at 3 months after TKI discontinuation; we did not verify prescriptions. Finally, this was a group of patients who had been on therapy for nearly 7 years, so they were most likely to have been tolerating their medications well.

Assessing the benefits of TKI discontinuation with regard to musculoskeletal pain is complicated. In the initial few months, the benefit of TKI discontinuation may be masked by the onset of TKI withdrawal syndrome. Our study has demonstrated that musculoskeletal pain improves with time after TKI discontinuation. For patients who experience increased pain, behavioral or cognitive approaches to managing musculoskeletal pain should be considered. In addition, given that TFR is associated with decreased fatigue, increased physical activity to improve musculoskeletal symptoms may be an effective modality to decrease pain. Finally, the use of analgesics and/or anti-inflammatory pain medication may help control pain. Additional studies to elucidate the mechanism of increased joint pain are warranted.

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Contributions

KEF, EA and KPW developed the concept and design of the study; all authors acquired and interpreted data; KEF, LL and KPW performed statistical analysis; KEF, EA, LL and KPW drafted the manuscript; all authors critically revised the manuscript; KEF and EA obtained funding.

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Data-sharing statement

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

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