Severe side effects while Living with TKI

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Introduction

- First hematologic and non-hematologic adverse events should be considered separately
- What are the Off-target effects of TKI
- Severe adverse drug reactions i.e., pulmonary arterial hypertension or pleural effusion
- TKI-Associated Cardiovascular Toxicity
- Side effects that impair quality of life
- Side effects increase with phase or the evolution of the disease

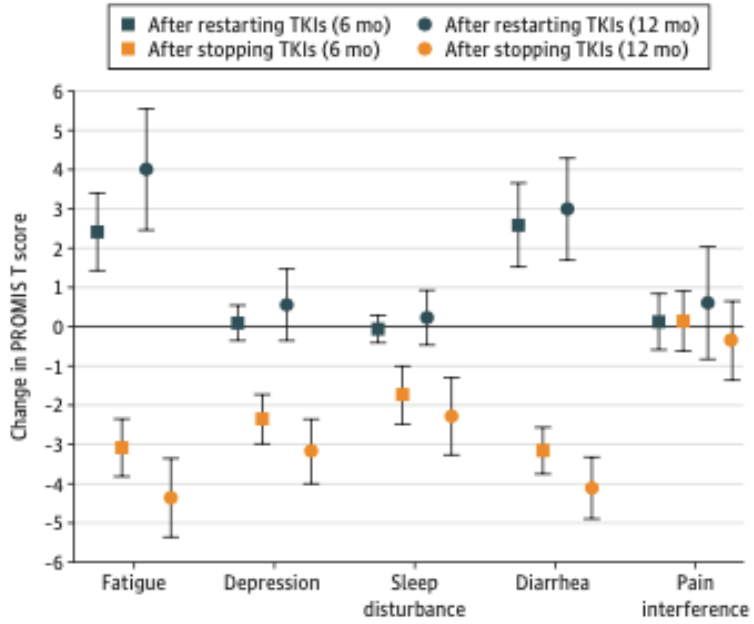
What are the most common side effects?

Those who impair daily the quality of life

- **Fatigue**
- **Cramps**
- **Fluid retention and periorbital oedema**
- **Cutaneous problems**
- **Diarrhea**
- **Nausea vomiting**
- **Hyperglycemia occurs mainly with nilotinib.**

that affect tolerability and life quality

Figure 3. Mean Changes in Patient-Reported Outcomes After Tyrosine Kinase Inhibitor (TKI) Discontinuation and TKI Restart at 6 and 12 Months



Vertical lines indicate 95% CIs. PROMIS indicates Patient-Reported Outcomes Measurement Information System.

Atallah E et al. JAMA Oncol. 2021 ;7(1):42-50.

How severe is severe adverse event?

All of those which concern the major organs

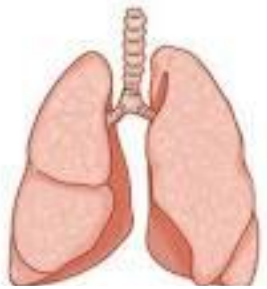
All Vascular Adverse events are severe
ischaemic heart disease (IHD),
ischaemic cerebrovascular events (ICVE)
peripheral arterial occlusive disease (PAOD) (ponatinib or nilotinib)

Pleural effusion is primarily associated with dasatinib, with a 5-year cumulative incidence of 37%.

Pulmonary arterial hypertension

Hepatitis and Hepatotoxicity may occur with any TKI, but particularly with bosutinib and nilotinib,

* “complications” that require a treatment change



Contraindication

- Previous or concomitant arteriovascular disease : contraindication to nilotinib and ponatinib

- Respiratory failure and previous or concomitant pleuro-pulmonary disease : contraindications to dasatinib.

When should a patient talk to their doctor about side effects?

- All the time
- At each consultation
- When the Treament is modified
- By writting on his personnal book
- When a new drug is introduced for other disease
- By drug drug interaction

Unusual side effects

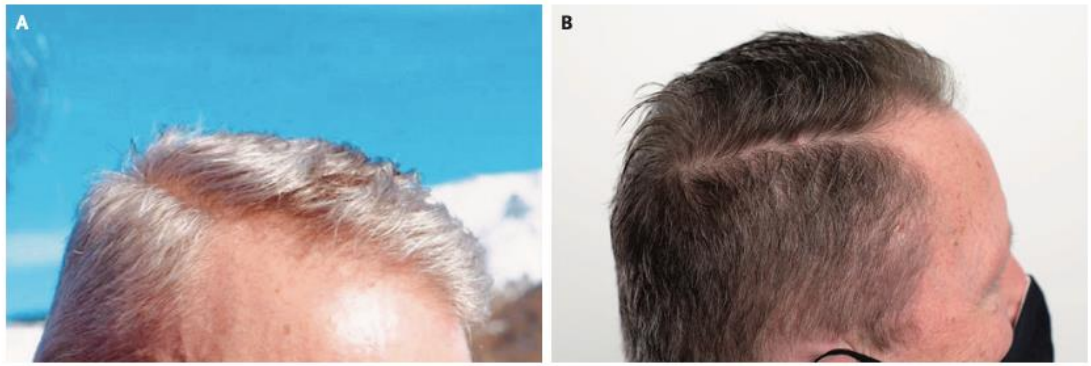
- Histological features of acute hepatitis after imatinib mesylate treatment, C James, H Trouette, G Marit, P Cony-Makhoul, FX Mahon. Leukemia 17, 978–979 (2003)
- Dasatinib and lymphocytosis:
- Kim DH, Kamel-Reid S, Chang H, Sutherland R, Jung CW, Kim HJ et al. Natural killer or natural killer/T cell lineage large granular lymphocytosis asso- ciated with dasatinib therapy for Philadelphia chromosome positive leukemia. Haematologica 2009; 94: 135–139.
- Elevations of serum lipase, sometimes with clinical manifestations of pancreatitis, have been reported after treatment with nilotinib and bosutinib but in true life it is not a problem
- Pulmonary arterial hypertension (PAH) has been reported with the use of dasatinib94–97 at an estimated incidence of 0.45%
- Conjunctival haemorrhage has been reported in 11% of patients, in the absence of cytopenias or bleeding diathesis.

Hair Repigmentation Induced by TKI

The NEW ENGLAND JOURNAL of MEDICINE

IMAGES IN CLINICAL MEDICINE

Hair Repigmentation Induced by Nilotinib



A 51-YEAR-OLD MAN WITH CHRONIC MYELOID LEUKEMIA VISITED THE ONcology clinic for routine follow-up. Treatment with nilotinib, a tyrosine kinase inhibitor, had been initiated 18 months earlier. During that time, the patient had noticed, much to his delight, the gradual repigmentation of his gray hair (Panel A, photo obtained approximately 1 year before the initiation of nilotinib) to its original color. During the same period, he had not started any other new medications and had used no hair-coloring products. On physical examination, his previously gray hair was noted to have become brown (Panel B). No other changes in his hair, skin, or mucosal pigmentation were observed. Molecular testing showed a deep molecular response. A diagnosis of medication-induced hair repigmentation due to the use of a tyrosine kinase inhibitor was made. Given the response of the leukemia to treatment with nilotinib, it was continued, and the patient's hair remained brown.

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This article was published on August 6, 2022, at NEJM.org.

DOI: 10.1056/NEJMicm2119953

August 11, 2022

N Engl J Med 2022; 387:e12

Imatinib Mesylate and Gray Hair

To the Editor: The impressive effects of the tyrosine kinase inhibitor STI571 (imatinib mesylate) in chronic myeloid leukemia were confirmed in the large trial by Kantarjian et al. (Feb. 28 issue).[1] We would like to report a new side effect of the drug.

Between December 1999 and June 2001, we treated 133 patients with chronic myeloid leukemia with imatinib mesylate according to Novartis Pharma protocols.[1,2] Among these 133 patients, 5 men and 4 women (median age, 63.4 years; range, 53 to 75) with gray hair before treatment had progressive repigmentation of the hair (on the head in 8 patients and on the body and head in 1) during treatment. The median time between the end of interferon alfa therapy and the start of treatment with imatinib mesylate was 5.7 months (range, 0.5 to 42). Hair repigmentation occurred after a median of 5 months (range, 2 to 14) of treatment with imatinib mesylate.

How imatinib mesylate might induce hair repigmentation is a mystery. We would be interested to know whether other groups have observed this peculiar side effect.

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Editor's note: Dr. Mahon received research funding from Novartis Pharma for a project about resistance to imatinib mesylate.

1. Kantarjian H, Sawyers C, Hochhaus A, et al. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. N Engl J Med 2002;346:645-52.
2. Talpaz M, Silver RT, Druker BJ, et al. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. Blood 2002;99:1928-37.

Adverse Events : TKI Withdrawal syndrome ?

Musculosceletal pain
Joint pain
Arthralgia
Other

Longer treatment duration and history of osteoarticular symptoms predispose to tyrosine kinase inhibitor withdrawal syndrome

Musculoskeletal pain in CML patients after discontinuation of imatinib:
a tyrosine kinase inhibitor withdrawal syndrome?
J. Richter et al. J Clin Oncol. 2014 Sep 1;32

Tyrosine kinase inhibitor withdrawal syndro
Response to Richter et al.
Ph. Rousselot et al. J Clin Oncol. 2014 Sep

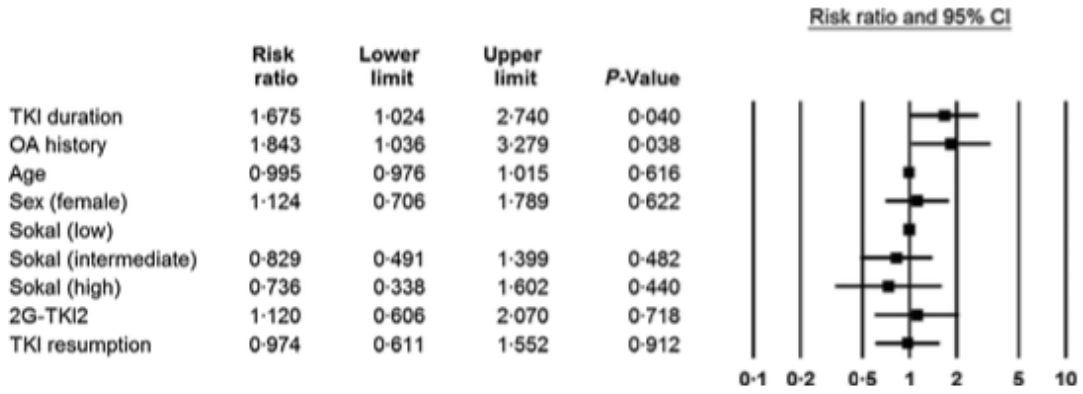


Fig 1. Multivariate analysis of the covariates that could affect TKI withdrawal syndrome prevalence. Multivariate analysis was performed using covariates selected on the basis of the univariate analysis results and their clinical relevance. The trial effect was also taken into account because of the differences observed between the STIM2 and EURO-SKI patients. The forest plot confissrmed that TKI treatment duration and OA history are independent risk factors for withdrawal syndrome. 2G-TKI, treatment with second-generation TKI; OA, osteoarticular; TKI: tyrosine kinase inhibitor

Why there are no guidelines on dose reductions and side effects management?

REVIEW

European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia

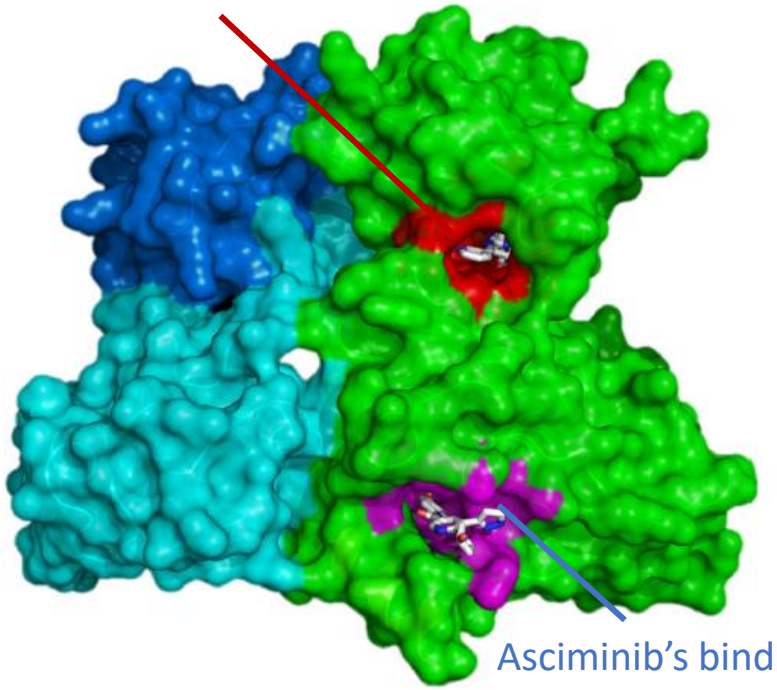
Steegmann JL et *al.* Leukemia (2016) **30**, 1648–1671

ELN European LeukemiaNet

Asciminib inhibits the BCR::ABL1 oncoprotein by specifically targeting the ABL myristoyl pocket

BCR::ABL1 binding sites

Binding site of available TKIs (ATP binding site)



Asciminib's binding site (myristoyl pocket)

In some patients, off-target effects with TKIs may result in significant long-term safety issues

To the best of our Knowledge no off target effect have been observed with asciminib

**data from multiple studies, testing cell panels and concentration ranges varied across studies*

Figures adapted from: Wylie et al (2017). Nature; 543(7647):733-7.

The Five rules of the European Leukemia Net recommendations

- 1 Suboptimal management of AEs must not compromise the main Purpose of CML treatment : the antileukemic effect
- 2 Most patients will have AEs, usually early, mostly mild to moderate, and which will resolve spontaneously
- 3 Reduction or interruption of treatment must only be done if optimal management of the AE cannot be accomplished in other ways,
- 4 Attention must be given to comorbidities and drug interactions, and to new events unrelated to TKIs that are inevitable during such a prolonged treatment.
- 5 some TKI-related AEs have emerged which were not predicted or detected in earlier studies, maybe because of suboptimal attention to or absence from the preclinical data