Reviewer 1:

SPECIFIC COMMENTS TO AUTHORS

1. This manuscript describes the hepatotoxicity of targeted therapy of myeloproliferative neoplasms (MPN) from the aspects of mechanism, treatment and prevention, which has practical clinical significance. However, the main content discusses the hepatotoxicity of targeted therapy of chronic myeloid leukemia (CML), which is only a classification of MPN. The title is inappropriate.

RESPONSE: Thank you for this suggestion. Our manuscript also discusses cases of liver toxicity induced by treatment options prescribed in polycythemia vera, essential thrombocythemia and myelofibrosis. To ensure that the title is accurate, we have included more data on the aforementioned entities, particularly data derived from randomized controlled clinical trials. It is indeed true that publications on DILI in Philadelphia-negative MPNs are relatively scarce.

In the 5-year follow-up of the phase 3 DASISION (Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients) trial which compared the two aforementioned pharmacological agents, DILI was a rare event, and therapy discontinuation was only required in the subgroup who received 400 mg of imatinib daily due to increases in ALT or AST concentrations (n=1 each out of 258 individuals) and in one cases for toxic hepatitis (n=1), however, no subjects (n=0 out of 258 individuals) discontinued treatment with 100 mg of daily dasatinib due to DILI [43].

In the ENESTnd trial which compared the daily administration of 400 mg nilotinib (n=277 patients) and 300 mg nilotinib (n=279 patients) to each other and to 400 mg imatinib (n=280 patients) for the management of newly diagnosed CML, the investigators pointed out multiple cases of liver toxicity. Elevations in total bilirubin (n=171, 62% vs n=149, 53% vs n=27, 10%), ALT (n=203, 73% vs n=186, 66% vs n=57, 20%) and AST (n=134, 48% vs n=112, 40% vs n=65, 23%) concentrations were more likely to occurs in the 400 mg nilotinib and 300 mg nilotinib versus 400 imatinib group, respectively, whereas an increase in alkaline phosphatase (n=76, 27% vs n=59, 21% vs n=92, 33%) values was more common in patients who received imatinib. However, grade 3/4 adverse events were rare and occurred predominantly in individuals who were prescribed nilotinib 400 mg or 300 mg vs imatinib 400 mg; All grades elevations occurred in total bilirubin (n=21, 8% vs n=10, 4% vs n=1, <1%), ALT (n=25, 9% vs n=11,

4% vs n=7, <2%) and AST (n=8, 3% vs n=4, 1% vs n=3, 1%) values, respectively, whereas a grade 3/4 increase in alkaline phosphatase only occurred in 1 case (<1%) of imatinib-treated patients [44].

The NOVEL trial evaluated the safety and efficacy of nilotinib in 85 subjects suffering from imatinib intolerant/resistant-CML. Their findings revealed that non-hematological adverse events occurring in correlation with the use of nilotinib manifested as elevations in ALT (n=18, 21.2%), bilirubin (n=12, 14.1%) and/or AST (n=7, 8.2%) values, respectively, however grade 3/4 were rare and only 2 and 1 patients, respectively, experienced grade 3/4 rises in AST (2.4%) and/or ALT (1.2%) concentrations. In NOVEL, one patient with imatinib-induced liver toxicity required a switch of therapy to nilotinib with subsequent resolution of DILI. Serious adverse events related to DILI manifested as jaundice and chronic hepatitis [45].

In the BYOND trial which explored the benefits of 500 mg once daily of bosutinib for CML individuals (n=163 subjects) who exhibited resistance and/or intolerance to other TKIs, DILI manifested only as elevations in AST (all grades n=32, 19.6%) and/or ALT concentrations (all grades n=42, 25.8%). However, grade 3/4 increases in ALT (n=23, 14.1%) and/or AST (n=7; 4.3%) were not common [46].

In the clinical trial which evaluated the benefits of bosutinib prescription in 119 CML subjects who failed to achieve satisfactory responses to imatinib and dasatinib and/or nilotinib, an increase in AST/ALT values was noted in 16% of cases (13% classified as therapy-related), with only 6% of grade 3 adverse events and none serious/grade 4 side effects being noted. Elevations in these biochemical markers manifested early after drug initiation (approximately 81 days) and lasted for about 29 days. DILI was successfully managed with dose interruptions, reductions and/or use of hepatoprotective agents in 6, 5 and 1 case(s) of CML, respectively. Grade 3/4 DILI was more likely to be seen in CML individuals who received imatinib in the first 6 months following CML diagnosis and in subjects who exhibited elevated basophil counts [47].

Data from the CML registry in Belgium suggest that ponatinib-induced DILI cases are rare. In the 33 CML subjects who received ponatinib, liver toxicity was rare and occurred in <10% of treated individuals: hepatocellular injury, hepatitis and cholestasis were noted in 1 case each [48].

In the PEARL study which evaluated the safety and efficacy of ponatinib in CML subjects who experienced failure to 2 or more TKIs, grade 1/2 non-hematological adverse events (including DILI) were highlighted in 19 (40%) of the 48 CML individuals enrolled. No liver-related grade 3/4 side events were noticed by the investigators [49].

Asciminib is a recently introduced TKI for the management of CML, including T315I-mutated cases. This pharmacological agent inhibits the BCR-ABL1 protein in an allosteric manner, leading to an inactive conformation of its target. In a phase 1 trial of asciminib in heavily pretreated CML individuals, this novel medication lead to elevation in ALT (n=16, 10.7%; grade 3/4 n=4, 2.7%), AST (n=15, 10%; grade 3/4 n=3, 2%) or gamma-glutamyltransferase (n=12, 8%; grade 3/4 n=3, 2%) concentrations, however, grade 3/4 liver-related adverse events occurred in <3% of asciminib-treated subjects [50].

In the STAMP trial that investigated 40 mg of asciminib twice daily versus 500 mg of bosutinib once daily in individuals diagnosed with CML with ≥2 previous TKI therapies, DILI was more frequently noticed in the bosutinib group, i.e., 27.6% (n=21) and 21.1% (n=16) of subjects experienced elevations in ALT and AST concentrations, respectively, versus 3.8% (n=6) each in the asciminib group. Grade 3/4 adverse effects were more likely to present in bosutinib-prescribed subjects (14.5%, n=11 for ALT; 6.6% n=5 for AST) versus asciminib-treated subjects (3.8%, n=6 for ALT and AST each). Treatment discontinuation was required in bosutinib-prescribed CML cases due to significant increases in ALT concentrations [51].

Ruxolitinib seems a safe option in terms of liver toxicity. Based on the findings of a double-blind, placebo controlled trial assessing ruxolitinib in the management of MF classified as intermediate-2 or high-risk, DILI was not mentioned amongst the most common adverse (experienced by at least 10% of the 155 enrolled subjects) caused by the aforementioned pharmacological agent [52].

Ruxolitinib was associated with an increase in ALT concentrations in around 6% of MF patients and with high-grade elevations in only 1% of the individuals enrolled in the JUMP trial [53].

In the RuxoBeat trial which investigated the benefits of ruxolitinib therapy in newly-diagnosed PV, 7 of 28 treated subjects (25%) experienced changes in biochemical markers, including DILI, however, only 3 cases of grade 3 adverse events were reported

out of which 2 consisted of elevations in AST/ALT concentrations and required reduction of the prescribed dose. However, no patient necessitated interruption of ruxolitinib [54].

Similarly, the results of the assessment conducted by Vannnucchi et al. only pointed out minor changes in ALT/AST values following ruxolitinib administration in individuals diagnosed with PV [55].

The EXPAND trial assessed the safety and efficacy of ruxolitinib in individuals with MF and thrombocyte counts between 50000/mmc and 100000/mmc. In this investigation, a total of 5 cases of elevations in bilirubin values were noticed: 1 of the 18 patients who had platelets <75000/mmc but >50000/mmc and 4 of the 20 patients who had platelets <100000/mmc but >75000/mmc. However, of these, only two grade 3 or more increases in bilirubin levels were highlighted, all of which were reported in patients with thrombocyte counts <100000/mmc but >75000/mmc [56].

In a clinical trial which explored the co-administration of ruxolitinib and interferon alpha-2 for management of PV and MF, grade 1/2 liver-related adverse events, i.e., an increase in AST and lactate dehydrogenase (LDH) values were noted in 7 (14%) and 17 (34%) of the 50 patients receiving therapy, with no cases of grade 3-4 side effects occurring in neither subjects with PV nor MF [57].

In the JAKARTA trial which compared fedratinib versus placebo, elevations of liver enzymes were detected in 40-60% of the subjects, however, ≥3 grade elevations in these serum markers were not common. In JAKARTA, 96 subjects were assigned to receive 400 mg of fedratinib daily, 97 to receive 500 mg/day of the same drug, whereas 95 individuals received placebo pills. All grades elevations in ALT (fedratinib 400 mg: 53%; fedratinib 500 mg: 46%; placebo: 17%) and AST (fedratinib 400 mg: 60%; fedratinib 500 mg: 48%; placebo: 29%) concentrations were frequently detected in the fedratinib subgroups versus placebo, whereas bilirubin levels were more likely to increase in the placebo group (fedratinib 400 mg: 31%; fedratinib 500 mg: 28%; placebo: 40%) [58]. However, grade 3-4 increases in ALT values were only noted in 3% of the fedratinib 400 mg and 500 mg subgroups each versus 0% in placebo, grade 3-4 increases in AST values were only noted in 2% of the fedratinib 400 mg and 500 mg subgroups each versus 1% in placebo, whereas grade 3-4 elevations in bilirubin concentrations occurred in 2% of the

placebo and fedratinib 400 mg subgroups and in 1% of the fedratinib 500 mg subgroup, respectively [58].

Momelotinib therapy in MF was also associated with cases of liver toxicity, i.e., grade 3-4 increases in ALT concentrations in 4% of patients and in AST and ALP concentrations in 2% of patients each [59]. Grade 1-2 increases in AST (21%), ALT (19%) and bilirubin (13%) concentrations were also detected [59]. In an integrated assessment of momelotinib based on data derived from phase 3 randomized clinical trials, Verstovsek et al. also highlighted that of the 725 individuals with MF who received the drug, 9 subjects (1.2%) experienced notable elevations in ALT values which required dose interruption/reduction or momelotinib discontinuation [60]. When momelotinib was tested for PV and/or ET, the investigators did not report cases of liver toxicity in either cohort [61].

Ropeg interferons are relatively safer drugs than previously used interferons in terms of liver toxicity. When pegylated interferon alfa-2a was tested in the management of PV (n=40) and ET (n=39), grade 3 increases in liver function tests were reported in 5% (n=2) and 8% (n=3) of the PV and ET subgroups, respectively. No grade 4 side effects were reported [62]. In a trial exploring the safety and benefits of pegylated interferon alpha-2b in PV and ET, elevations in liver enzymes were among the most frequent non-hematological side effects. In total, 2 subjects required pegylated interferon alpha-2b discontinuation due to elevations in AST and ALT values [63].

2. The page 7 of the manuscript states that "Normalization of liver enzymes' values after discontinuation of the drug supports the diagnosis of DILI", which is a crude exclusion method. It is important to highlight the necessity of liver biopsy and genetic testing for hereditary diseases, as and when required.

RESPONSE: Thank you for this comment. The diagnosis of DILI has been extensively discussed in the revised version of the paper.

Its pathogenesis is complex and not fully understood and can vary greatly between different individuals and based on the drugs that cause liver injury, explaining the wide range of phenotypic traits in terms of clinical presentation and severity [17]. DILI is the result of a combination of genetic, non-hereditary, and environmental variables, and is typically attributed to an allergic immune response [18].

The potential multiple clinical presentations and the lack of specific biomarkers or biochemical tests makes the diagnosis often difficult and delayed. Consequently, DILI must always be taken into account in patients who are prescribed medications and exhibit unexplained liver injury [17, 19]. Moreover, DILI represents the leading cause for drug withdrawal from the marketplace and can lead to changes in drug costs and challenges regarding medication availability [20].

The pathophysiology of DILI is a complex, multistep process that involves both direct injury and different inflammatory responses, induced by either the drug itself, by its metabolites or by the immune system. It implies a combination of various host-related, environmental and drug-related factors. If ALF does not occur, patients usually fully recover after an episode of DILI if the responsible medication is halted [12, 18, 21].

Among the main pathophysiological processes involved in the pathogenesis of DILI, one must highlight oxidative stress, interference with bile acids' transportation, alteration of mitochondrial biogenesis and triggering of innate immune responses, necrosis or even apoptosis [15, 18].

Liver toxicity can be categorized as direct, indirect or idiosyncratic based on the underlying mechanism of action of the chemical compound that leads to DILI:

Direct hepatotoxicity is caused by agents which cause direct harm to the liver. This type of injury is common, predictable, dose-dependent, and has a short latency period (1 to 5 days). It causes elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations, induces minimal or no symptoms, is associated with normal total bilirubin levels and usually disappears once the drug is stopped or the dose is lowered [22, 23].

Indirect hepatotoxicity represents "a condition caused by the medication's actions rather than from its inherent hepatotoxic effects or immunogenicity". This best translates to "what the drug does rather than what the drug is" and can either mean induction of a new liver condition or an exacerbation of a preexisting condition, e.g., induction of immune-mediated hepatitis, reactivation of viral hepatitis or progression of fatty liver disease [12, 22].

Idiosyncratic hepatotoxicity is caused by agents that have no direct hepatotoxic effect. It is an unpredictable condition, less common (<1 of every 10,000 exposed individuals), it is

not dose-related, has a longer latency period (up to several weeks) and a more variable clinical presentation [12, 22, 24].

A rapid diagnosis of DILI is crucial since one of the primary treatment interventions for hepatotoxicity is drug withdrawal. Moreover, establishing a DILI diagnosis can aid in the prevention of further adverse reactions through regulatory decisions, such as prescription warnings or even the removal of pharmaceuticals from the market [12, 13, 25].

In most cases, diagnosis of DILI is one of exclusion, since there is no specific test available for this entity. One must eliminate other causes of liver injury, e.g., infectious hepatitis, acute alcoholic hepatitis or ischaemic hepatitis. Suspicion of DILI arises from the discovery of alterations in usually ordered liver tests, i.e., AST, ALT, total and direct bilirubin levels, serum albumin, alkaline phosphatase (ALP) or international normalized ratio [13].

Clinical manifestations, such as fatigue, nausea, malaise, right upper quadrant pain, pruritus, and jaundice are non-specific and commonly encountered in a wide variety of acute and chronic liver diseases. Liver imaging (abdominal ultrasonography, magnetic resonance cholangiography or computed tomography) is usually used to exclude the presence of biliary obstruction and focal lesions. Liver biopsy is done in less than half of suspected cases, usually in instances where the evolution of liver injury is not reversed after a suspected medication has been discontinued [22, 26].

There are over 18 different histological aspects of DILI proposed until now all of which associate to different extents inflammation of hepatocytes, bile accumulation, ductopenia, steatohepatitis, macro- and microvesicular fatty depositions in the liver, pigment deposition, fibrosis or vascular congestion and obliteration [12, 19].

DILI can also be classified based on its biochemical pattern based on ALT and ALP levels. A hepatocellular damage pattern is characterized by an increase in ALT greater than 2 to 5 times the upper limit of normal (ULN) and/or an ALT/ALP ratio also greater than 5. A cholestatic damage pattern is characterized by an increase in ALP greater than 3 times the ULN and/or an ALT/ALP ratio less than 2. A mixed hepatocellular/cholestatic pattern is characterized by an increase in ALT greater than 2 to 5 times the ULN and an increase in ALP greater than 3 times the ULN and/or an

ALT/ALP ratio between 2 and 5. These changes are proposed by the "American Association for the Study of Liver Diseases" (AASLD) and are summarized in **Table 1** [18, 27, 28].

Table 1. Biochemical classification of DILI.

	Hepatocellular DILI	Mixed DILI	Cholestatic DILI
AASLD Criteria for diagnosis of DILI	elevation of ALT ≥3 times ULN and ALT/ALP ratio ≥5 times	ALT ≥3 times ULN, ALP ≥2 times ULN and ALT/ALP ratio <5 but >2 times ULN	ALP ≥2 times ULN and ALT/ALP ratio of ≤2 times ULN
R-Value Criteria for different patterns of DILI	R=(ALT/ULN)/(ALP/ULN) > 5	R=(ALT/ULN)/(ALP/ULN) <5 and >2	R=(ALT/ULN)/(ALP/ULN) <2

Legend: ALP - alkaline phosphatase, ULN - upper limit of normal, ALT - Alanine Aminotransferase, AST - aspartate aminotransferase.

Management. While in some patients DILI can spontaneously resolve without the need for active treatment, in most cases, the hallmark of DILI treatment is the withdrawal of the offending drug. Clinical and biochemical alterations are expected to improve over the next several days or weeks. Since patients who develop jaundice are more likely to progress to ALF, these subjects usually require strict monitoring and probably hospitalization, particularly if DILI exhibits a hepatocellular phenotype. Treatment of DILI is usually supportive, with no other specific medications showing any significant use. However, there many agents used for supportive purpose, e.g., corticosteroids (empirically used by many clinicians), cholestyramine (administered to patients with acute liver injury caused by leflunomide), carnitine (an antidote for valproate-induced

liver injury) or N- acetylcysteine (an antidote for acetaminophen toxicity), silymarin, L-arginine, L-ornithine L-aspartate and/or vitamin E [13, 29, 30, 31, 32].

Prognosis. DILI typically resolves after discontinuation of the incriminated drug and/or administration of hepatoprotective agents. However, in rare cases, DILI may progress to ALF, with clinical features such as jaundice, ascites, encephalopathy, coagulopathy and a mortality rate of 60% to 90% without liver transplantation [14, 17].

Different scoring systems for predicting prognosis of DILI have been proposed. The most validated and the one still used by The Food and Drug Administration (FDA) to this day during the drug development process to identify pharmacological agents that can potentially induce severe liver injury is the "Hy's law", developed by Hyman Zimmerman in the 1960s, according to which 10% of the patients who develop jaundice will develop ALF. Other scores for predicting severity in DILI are the Model for End-Stage Liver Disease (MELD) score, King's college criteria (KCC) score and Acute Liver Failure Study Group (ALFSG) index [12, 13, 19].

Older age, higher drug dosages, presence of liver disorders or cardiovascular comorbidities, African American ethnicity and female sex have all been linked to an elevated risk of DILI and to more severe forms, but there is little empiric data available to support that these variables are indeed risk factors for DILI or have an impact on its prognosis [33].

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The relative risk of DILI seems, however, higher with the prescription of 2nd & 3rd generation TKIs compared to 1st generation pharmacological agents (imatinib) [67]. The average duration from drug initiation to DILI development with the use of TKIs was of 2-6 months, whereas with the use of ruxolitinib it was of 1-6 months [68, 69]. In most cases, the diagnosis of DILI was established after the virology panel results for hepatitis B, HIV, CMV or EBV infections came in negative. Autoimmune antibody testing, abdominal ultrasound, liver biopsy and toxicology screening (alcohol, illicit drugs, acetaminophen) were also performed in conjunction with liver function tests to exclude other causes of liver injury [70, 71]. Liver biopsy is usually not preferred to provide diagnostic information regarding liver injury but it is considered for the staging of fibrosis [72]. In some instances, genetic testing for hereditary conditions, such as

hemochromatosis or Wilson's disease, might be required [73]. Pharmacogenomics assessments for mutations/polymorphisms in HLA genes, drug metabolizing enzymes, ABC and/or SLC transporters, might also be required to understand why certain individuals develop DILI [74].

DILI remains a diagnosis of exclusion. The recommended biochemical criteria for DILI are the following [72, 73] :

- ALT values ≥ 5 ULN
- AST values ≥ 3 ULN
- ALP values ≥ 2 ULN
- total bilirubin ≥ 2 ULN

A common tool used for the diagnosis of DILI is the Roussel Uclaf Causality Assessment Method (RUCAM). It is based on 7 factors, including onset of reaction, clinical response after withdrawal or continuation of drug, response to readministration, temporal relationship, risk factors, concomitant drug use and absence of any non-drug etiologies [75].

3. This manuscript describes that the hepatotoxicity of MPN targeted drugs may be related to aspects such as oxidative stress, bile acid metabolism, and immunity, and further elaborating on its related mechanisms may be better.

RESPONSE: Thank you for this excellent suggestion. We have mentioned that oxidative stress, bile acid metabolism and immunity might play a role in DILI in MPNs, however, we did not find any data to support these claims at the moment for the targeted anticancer agents prescribed in MPN patients.

4. If the importance of supplementing the assessment of pre-liver compensatory function in targeted therapy could be added, the manuscript may be more readable.

RESPONSE: Thank you for this excellent suggestion. We have indeed stressed out the importance of liver function tests before drug initiation.

Thus, in patients diagnosed with MPNs who are to be started on potentially hepatotoxicity-inducing targeted agents, we recommend checking liver function tests before therapy initiation, as well as regularly during treatment. Moreover, the

management of each case should be tailored to the comorbidities and concurrent medication of the patient, especially in subjects who suffer from MPNs and exhibit a high burden of cardiometabolic disorders [84]. Thus, DILI can be avoided in some instances.

5. On page 8 of the manuscript, it is mentioned to use a novel score-based method to evaluate the dressing change standard. It would be better if the specific scoring criteria could be further elucidated.

RESPONSE: Thank you very much for this excellent suggestion. The score has been described in detail in the revised manuscript.

Since CML patients often require lifelong treatment, Lopina et al. have suggested a novel score-based decision algorithm (Table 2) for restarting TKIs after acute imatinib-induced liver injury and for the choice of 2nd generation TKIs [78]. The score takes into account:

- the grade of hepatotoxic reaction
- the grade of response to the use of imatinib, i.e., presence of early molecular response (EMR) to imatinib therapy at 3 months (3-month BCR-ABL1 ≤10% according to the international scale) (not applicable if imatinib treatment was prescribed for <3 months)
- the grade of response to the use of imatinib, i.e., presence of EMR to imatinib therapy at 6 months (6-month BCR-ABL1 <1% according to the international scale) (not applicable if hepatotoxicity developed in <6 months of imatinib therapy)
- the presence of a liver offender (concomitant use of another drug that probably caused drug interactions)
- the presence of viral hepatitis reactivation identified by polymerase chain reaction.

Tabel 2. Novel score for the decision of restarting or withdrawing imatinib in CML [78].

Factors	**Imatinib restart**[#]	**Imatinib withdrawal**
Grade of hepatotoxic reaction		

Grade 1	+	-
Grade 2	+##	-
Grade 3	+/-###	+/-
Grade 4 or presence liver transplantation or imatinib-induced liver cirrhosis or viral hepatitis reactivation	-	+
Presence of EMR to imatinib at 3 months = BCR-ABL1^{IS} ≤10%:		
Yes	+	-
No	-	+
Presence of EMR to imatinib at 6 months = BCR-ABL1^{IS} <1% (if applicable####)		
Yes	+	-
No	-	+
Use of another drug that might cause liver toxicity		
Yes	+	-
No	-	+
Diagnosis of viral hepatitis established by PCR		
Yes	+	-
No	-	+

Legend: + = 1 point/yes, - = 0 points/no; EMR, early molecular response. PCR, polymerase chain reaction; #decide whether to restart imatinib only after resolution of

acute hepatitis and normalization of liver function tests; ##restart imatinib at a reduced or at the same dose. ### restart imatinib if liver toxicity resolves in ≤1 month and there is no sign of recurrence; ####do not take into consideration this factor if liver toxicity develops ≤6 months after imatinib initiation.

The approach to restart imatinib can be based on the score listed above [78] as follows:

- score = 0 points: withdraw the drug and switch to 2nd generationTKIs
- score = 1 point: it is preferred to withdraw imatinib if the patient requires treatment for >6 months
- score ≥ 2 points: restart imatinib after resolution of DILI

6. The conclusion section of the manuscript points out that minor liver injury can be overcome with drug discontinuation and/or dose reductions. This could potentially impact the treatment of primary diseases. It is worth noting the use of hepatoprotective drugs in such cases.

RESPONSE: Thank you very much for this excellent suggestion. We have mentioned these aspects in the revised paper:

Moreover, further research should focus on identifying new hepatoprotective agents that could enable clinicians to overcome DILI and avoid drug cessation or dose reductions/interruptions which aid in the resolution of liver toxicity but might impact the treatment of the hematological malignancy.

Treatment of DILI is usually supportive, with no other specific medications showing any significant use. However, there many agents used for supportive purpose, e.g., corticosteroids (empirically used by many clinicians), cholestyramine (administered to patients with acute liver injury caused by leflunomide), carnitine (an antidote for valproate-induced liver injury) or N- acetylcysteine (an antidote for acetaminophen toxicity), silymarin, L-arginine, L-ornithine L-aspartate and/or vitamin E [13, 29, 30, 31, 32].

7. If the author could further focus on the overview, diagnosis, management, and prevention of DILI, and supplement its clinical classification and prognosis, the manuscript may be better.

RESPONSE: Thank you very much for this excellent suggestion. The overview, diagnosis,

management, and prevention of DILI, along with its clinical classification and prognosis, has been extensively described in the revised manuscript.

DRUG INDUCED LIVER INJURY (DILI): BRIEF OVERVIEW

Because of its central role in metabolism, the liver is susceptible to the deleterious effects of ingested medications (drugs, herbs, and nutritional supplements) that can affect all types of hepatic cells [12, 13]. Drug-induced liver injury (DILI) comprises a range of unexpected reactions that occur after exposure to any type of medication. Even if the majority of cases consist of mild, temporary elevations in liver enzyme markers, DILI can manifest in some patients as acute liver failure (ALF). Thus, DILI may emerge as a significant cause of liver disease and, in some instances, lead to increased mortality rates in subjects who experience it [14, 15, 16].

Its pathogenesis is complex and not fully understood and can vary greatly between different individuals and based on the drugs that cause liver injury, explaining the wide range of phenotypic traits in terms of clinical presentation and severity [17]. DILI is the result of a combination of genetic, non-hereditary, and environmental variables, and is typically attributed to an allergic immune response [18].

The potential multiple clinical presentations and the lack of specific biomarkers or biochemical tests makes the diagnosis often difficult and delayed. Consequently, DILI must always be taken into account in patients who are prescribed medications and exhibit unexplained liver injury [17, 19]. Moreover, DILI represents the leading cause for drug withdrawal from the marketplace and can lead to changes in drug costs and challenges regarding medication availability [20].

The pathophysiology of DILI is a complex, multistep process that involves both direct injury and different inflammatory responses, induced by either the drug itself, by its metabolites or by the immune system. It implies a combination of various host-related, environmental and drug-related factors. If ALF does not occur, patients usually fully recover after an episode of DILI if the responsible medication is halted [12, 18, 21].

Among the main pathophysiological processes involved in the pathogenesis of DILI, one must highlight oxidative stress, interference with bile acids' transportation, alteration of mitochondrial biogenesis and triggering of innate immune responses, necrosis or even apoptosis [15, 18].

Liver toxicity can be categorized as direct, indirect or idiosyncratic based on the underlying mechanism of action of the chemical compound that leads to DILI:

Direct hepatotoxicity is caused by agents which cause direct harm to the liver. This type of injury is common, predictable, dose-dependent, and has a short latency period (1 to 5 days). It causes elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations, induces minimal or no symptoms, is associated with normal total bilirubin levels and usually disappears once the drug is stopped or the dose is lowered [22, 23].

Indirect hepatotoxicity represents "a condition caused by the medication's actions rather than from its inherent hepatotoxic effects or immunogenicity". This best translates to "what the drug does rather than what the drug is" and can either mean induction of a new liver condition or an exacerbation of a preexisting condition, e.g., induction of immune-mediated hepatitis, reactivation of viral hepatitis or progression of fatty liver disease [12, 22].

Idiosyncratic hepatotoxicity is caused by agents that have no direct hepatotoxic effect. It is an unpredictable condition, less common (<1 of every 10,000 exposed individuals), it is not dose-related, has a longer latency period (up to several weeks) and a more variable clinical presentation [12, 22, 24].

A rapid diagnosis of DILI is crucial since one of the primary treatment interventions for hepatotoxicity is drug withdrawal. Moreover, establishing a DILI diagnosis can aid in the prevention of further adverse reactions through regulatory decisions, such as prescription warnings or even the removal of pharmaceuticals from the market [12, 13, 25].

In most cases, diagnosis of DILI is one of exclusion, since there is no specific test available for this entity. One must eliminate other causes of liver injury, e.g., infectious hepatitis, acute alcoholic hepatitis or ischaemic hepatitis. Suspicion of DILI arises from the discovery of alterations in usually ordered liver tests, i.e., AST, ALT, total and direct bilirubin levels, serum albumin, alkaline phosphatase (ALP) or international normalized ratio [13].

Clinical manifestations, such as fatigue, nausea, malaise, right upper quadrant pain, pruritus, and jaundice are non-specific and commonly encountered in a wide variety of

acute and chronic liver diseases. Liver imaging (abdominal ultrasonography, magnetic resonance cholangiography or computed tomography) is usually used to exclude the presence of biliary obstruction and focal lesions. Liver biopsy is done in less than half of suspected cases, usually in instances where the evolution of liver injury is not reversed after a suspected medication has been discontinued [22, 26].

There are over 18 different histological aspects of DILI proposed until now all of which associate to different extents inflammation of hepatocytes, bile accumulation, ductopenia, steatohepatitis, macro- and microvesicular fatty depositions in the liver, pigment deposition, fibrosis or vascular congestion and obliteration [12, 19].

DILI can also be classified based on its biochemical pattern based on ALT and ALP levels. A hepatocellular damage pattern is characterized by an increase in ALT greater than 2 to 5 times the upper limit of normal (ULN) and/or an ALT/ALP ratio also greater than 5. A cholestatic damage pattern is characterized by an increase in ALP greater than 3 times the ULN and/or an ALT/ALP ratio less than 2. A mixed hepatocellular/cholestatic pattern is characterized by an increase in ALT greater than 2 to 5 times the ULN and an increase in ALP greater than 3 times the ULN and/or an ALT/ALP ratio between 2 and 5. These changes are proposed by the "American Association for the Study of Liver Diseases" (AASLD) and are summarized in **Table 1** [18, 27, 28].

Table 1. Biochemical classification of DILI.

	Hepatocellular DILI	Mixed DILI	Cholestatic DILI
AASLD Criteria for diagnosis of DILI	elevation of ALT ≥3 times ULN and ALT/ALP ratio ≥5 times	ALT ≥3 times ULN, ALP ≥2 times ULN and ALT/ALP ratio <5 but >2 times ULN	ALP ≥2 times ULN and ALT/ALP ratio of ≤2 times ULN

R-Value Criteria for different patterns of DILI	R=(ALT/ULN)/(ALP/ULN) > 5	R=(ALT/ULN)/(ALP/ULN) <5 and >2	R=(ALT/ULN)/(ALP/ULN) <2

Legend: ALP - alkaline phosphatase, ULN - upper limit of normal, ALT - Alanine Aminotransferase, AST - aspartate aminotransferase.

Management. While in some patients DILI can spontaneously resolve without the need for active treatment, in most cases, the hallmark of DILI treatment is the withdrawal of the offending drug. Clinical and biochemical alterations are expected to improve over the next several days or weeks. Since patients who develop jaundice are more likely to progress to ALF, these subjects usually require strict monitoring and probably hospitalization, particularly if DILI exhibits a hepatocellular phenotype. Treatment of DILI is usually supportive, with no other specific medications showing any significant use. However, there many agents used for supportive purpose, e.g., corticosteroids (empirically used by many clinicians), cholestyramine (administered to patients with acute liver injury caused by leflunomide), carnitine (an antidote for valproate-induced liver injury) or N- acetylcysteine (an antidote for acetaminophen toxicity), silymarin, L-arginine, L-ornithine L-aspartate and/or vitamin E [13, 29, 30, 31, 32].

Prognosis. DILI typically resolves after discontinuation of the incriminated drug and/or administration of hepatoprotective agents. However, in rare cases, DILI may progress to ALF, with clinical features such as jaundice, ascites, encephalopathy, coagulopathy and a mortality rate of 60% to 90% without liver transplantation [14, 17].

Different scoring systems for predicting prognosis of DILI have been proposed. The most validated and the one still used by The Food and Drug Administration (FDA) to this day during the drug development process to identify pharmacological agents that can potentially induce severe liver injury is the “Hy’s law”, developed by Hyman Zimmerman in the 1960s, according to which 10% of the patients who develop jaundice will develop ALF. Other scores for predicting severity in DILI are the Model for End-

Stage Liver Disease (MELD) score, King's college criteria (KCC) score and Acute Liver Failure Study Group (ALFSG) index [12, 13, 19].

Older age, higher drug dosages, presence of liver disorders or cardiovascular comorbidities, African American ethnicity and female sex have all been linked to an elevated risk of DILI and to more severe forms, but there is little empiric data available to support that these variables are indeed risk factors for DILI or have an impact on its prognosis [33].

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Reviewer 2:
SPECIFIC COMMENTS TO AUTHORS
Very informative review

RESPONSE: Thank you for the positive feedback regarding our manuscript.

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Reviewer 3:

SPECIFIC COMMENTS TO AUTHORS

These authors reviewed the hepatotoxicity of targeted therapy in myeloproliferative neoplasms. Comments:

1. For "abstract": Please remove "slightly" in the sentence "Because of its central role in metabolism, the liver is slightly susceptible to the damaging effects……"

RESPONSE: Thank you for this suggestion. We have removed the term "slightly" as instructed.

2. Please complete this sentence with reference x: "…explaining the wide range of phenotypic traits in terms of clinical presentation and severity (x)."

RESPONSE: Thank you for pointing this out. We have added the reference as instructed.

3. Please format the reference in the same format, especially the paragraph of "Drug induced liver injury (DILI): brief overview."

RESPONSE: Thank you for pointing this out. References have been revised to match the style required by the journal.

4. For "Risk factors for DILI", please give more detailed information of each risk factor, such as why PPI use is a risk factor?

RESPONSE: Thank you for your excellent suggestion. We have given detailed information on each mentioned risk factor as instructed.

Data on risk factors for DILI in patients living with MPNs are scarce, however, several assessments have identified potential risk factors linked with an increased risk of imatinib/TKI-induced hepatotoxicity, namely [64, 65, 66]:

- use of proton pump inhibitors (3.8 fold increased risk): imatinib is both a substrate and an inhibitor of the ABCG2 which is a drug efflux pump expressed on various body tissues, including the liver. Thus, the inhibition of this pump leads to increased drug concentrations in liver cells, thus increasing the risk of hepatotoxicity. Moreover, proton pump inhibitors are hepatotoxic on their own.

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- presence of liver disease or HBV carrier state (8 fold elevated risk): imatinib is metabolized by the liver; therefore, liver impairment or HBV carrier state may increase its plasma levels due to ineffective drug metabolism.
- drug dose >400 mg (2.3 fold increased risk): higher plasma levels of imatinib can enhance the risk of liver toxicity
- body weight of <55 kg (2.2 fold increased risk): the dose of imatinib is chosen based on the phase of the disease and not based on body surface area
- concomitant use of acetaminophen: acetaminophen itself is hepatotoxic
- use of alcohol: alcohol acts as a cytochrome oxidase enzyme inducer, thereby increasing the levels of toxic metabolites
- use of hepatotoxic drugs

5. For the "Diagnosis of DILI ", the authors should discuss patterns of liver injury, such as hepatitic or cholestatic patterns. Any pathologic changes in biopsy specimens?

RESPONSE: Thank you for your excellent suggestion. We have discussed these patterns in detail.

DILI can also be classified based on its biochemical pattern based on ALT and ALP levels. A hepatocellular damage pattern is characterized by an increase in ALT greater than 2 to 5 times the upper limit of normal (ULN) and/or an ALT/ALP ratio also greater than 5. A cholestatic damage pattern is characterized by an increase in ALP greater than 3 times the ULN and/or an ALT/ALP ratio less than 2. A mixed hepatocellular/cholestatic pattern is characterized by an increase in ALT greater than 2 to 5 times the ULN and an increase in ALP greater than 3 times the ULN and/or an ALT/ALP ratio between 2 and 5. These changes are proposed by the "American Association for the Study of Liver Diseases" (AASLD) and are summarized in **Table 1** [18, 27, 28].

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Table 1. Biochemical classification of DILI.

	Hepatocellular DILI	Mixed DILI	Cholestatic DILI
AASLD Criteria for diagnosis of DILI	elevation of ALT ≥3 times ULN and ALT/ALP ratio ≥5 times	ALT ≥3 times ULN, ALP ≥2 times ULN and ALT/ALP ratio <5 but >2 times ULN	ALP ≥2 times ULN and ALT/ALP ratio of ≤2 times ULN
R-Value Criteria for different patterns of DILI	R=(ALT/ULN)/(ALP/ULN) > 5	R=(ALT/ULN)/(ALP/ULN) <5 and >2	R=(ALT/ULN)/(ALP/ULN) <2

Legend: ALP - alkaline phosphatase, ULN - upper limit of normal, ALT - Alanine Aminotransferase, AST - aspartate aminotransferase.

6. The authors need to discuss outcomes of these liver injuries.

RESPONSE: Thank you for your excellent suggestion. We have discussed the management of DILI, as well as how DILI induced by drugs used in MPN management was managed (drug discontinuation, dose reduction/interruption etc.)

Management. While in some patients DILI can spontaneously resolve without the need for active treatment, in most cases, the hallmark of DILI treatment is the withdrawal of the offending drug. Clinical and biochemical alterations are expected to improve over the next several days or weeks. Since patients who develop jaundice are more likely to progress to ALF, these subjects usually require strict monitoring and probably hospitalization, particularly if DILI exhibits a hepatocellular phenotype. Treatment of

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DILI is usually supportive, with no other specific medications showing any significant use. However, there many agents used for supportive purpose, e.g., corticosteroids (empirically used by many clinicians), cholestyramine (administered to patients with acute liver injury caused by leflunomide), carnitine (an antidote for valproate-induced liver injury) or N- acetylcysteine (an antidote for acetaminophen toxicity), silymarin, L-arginine, L-ornithine L-aspartate and/or vitamin E [13, 29, 30, 31, 32].

Prognosis. DILI typically resolves after discontinuation of the incriminated drug and/or administration of hepatoprotective agents. However, in rare cases, DILI may progress to ALF, with clinical features such as jaundice, ascites, encephalopathy, coagulopathy and a mortality rate of 60% to 90% without liver transplantation [14, 17].

Different scoring systems for predicting prognosis of DILI have been proposed. The most validated and the one still used by The Food and Drug Administration (FDA) to this day during the drug development process to identify pharmacological agents that can potentially induce severe liver injury is the “Hy’s law”, developed by Hyman Zimmerman in the 1960s, according to which 10% of the patients who develop jaundice will develop ALF. Other scores for predicting severity in DILI are the Model for End-Stage Liver Disease (MELD) score, King’s college criteria (KCC) score and Acute Liver Failure Study Group (ALFSG) index [12, 13, 19].

Older age, higher drug dosages, presence of liver disorders or cardiovascular comorbidities, African American ethnicity and female sex have all been linked to an elevated risk of DILI and to more severe forms, but there is little empiric data available to support that these variables are indeed risk factors for DILI or have an impact on its prognosis [33].

In the 5-year follow-up of the phase 3 DASISION (Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients) trial which compared the two aforementioned pharmacological agents, DILI was a rare event, and therapy discontinuation was only required in the subgroup who received 400 mg of imatinib

daily due to increases in ALT or AST concentrations (n=1 each out of 258 individuals) and in one cases for toxic hepatitis (n=1), however, no subjects (n=0 out of 258 individuals) discontinued treatment with 100 mg of daily dasatinib due to DILI [43].

In the ENESTnd trial which compared the daily administration of 400 mg nilotinib (n=277 patients) and 300 mg nilotinib (n=279 patients) to each other and to 400 mg imatinib (n=280 patients) for the management of newly diagnosed CML, the investigators pointed out multiple cases of liver toxicity. Elevations in total bilirubin (n=171, 62% vs n=149, 53% vs n=27, 10%), ALT (n=203, 73% vs n=186, 66% vs n=57, 20%) and AST (n=134, 48% vs n=112, 40% vs n=65, 23%) concentrations were more likely to occurs in the 400 mg nilotinib and 300 mg nilotinib versus 400 imatinib group, respectively, whereas an increase in alkaline phosphatase (n=76, 27% vs n=59, 21% vs n=92, 33%) values was more common in patients who received imatinib. However, grade 3/4 adverse events were rare and occurred predominantly in individuals who were prescribed nilotinib 400 mg or 300 mg vs imatinib 400 mg; All grades elevations occurred in total bilirubin (n=21, 8% vs n=10, 4% vs n=1, <1%), ALT (n=25, 9% vs n=11, 4% vs n=7, <2%) and AST (n=8, 3% vs n=4, 1% vs n=3, 1%) values, respectively, whereas a grade 3/4 increase in alkaline phosphatase only occurred in 1 case (<1%) of imatinib-treated patients [44].

The NOVEL trial evaluated the safety and efficacy of nilotinib in 85 subjects suffering from imatinib intolerant/resistant-CML. Their findings revealed that non-hematological adverse events occurring in correlation with the use of nilotinib manifested as elevations in ALT (n=18, 21.2%), bilirubin (n=12, 14.1%) and/or AST (n=7, 8.2%) values, respectively, however grade 3/4 were rare and only 2 and 1 patients, respectively, experienced grade 3/4 rises in AST (2.4%) and/or ALT (1.2%) concentrations. In NOVEL, one patient with imatinib-induced liver toxicity required a switch of therapy to nilotinib with subsequent resolution of DILI. Serious adverse events related to DILI manifested as jaundice and chronic hepatitis [45].

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In the BYOND trial which explored the benefits of 500 mg once daily of bosutinib for CML individuals (n=163 subjects) who exhibited resistance and/or intolerance to other TKIs, DILI manifested only as elevations in AST (all grades n=32, 19.6%) and/or ALT concentrations (all grades n=42, 25.8%). However, grade 3/4 increases in ALT (n=23, 14.1%) and/or AST (n=7; 4.3%) were not common [46].

In the clinical trial which evaluated the benefits of bosutinib prescription in 119 CML subjects who failed to achieve satisfactory responses to imatinib and dasatinib and/or nilotinib, an increase in AST/ALT values was noted in 16% of cases (13% classified as therapy-related), with only 6% of grade 3 adverse events and none serious/grade 4 side effects being noted. Elevations in these biochemical markers manifested early after drug initiation (approximately 81 days) and lasted for about 29 days. DILI was successfully managed with dose interruptions, reductions and/or use of hepatoprotective agents in 6, 5 and 1 case(s) of CML, respectively. Grade 3/4 DILI was more likely to be seen in CML individuals who received imatinib in the first 6 months following CML diagnosis and in subjects who exhibited elevated basophil counts [47].

Data from the CML registry in Belgium suggest that ponatinib-induced DILI cases are rare. In the 33 CML subjects who received ponatinib, liver toxicity was rare and occurred in <10% of treated individuals: hepatocellular injury, hepatitis and cholestasis were noted in 1 case each [48].

In the PEARL study which evaluated the safety and efficacy of ponatinib in CML subjects who experienced failure to 2 or more TKIs, grade 1/2 non-hematological adverse events (including DILI) were highlighted in 19 (40%) of the 48 CML individuals enrolled. No liver-related grade 3/4 side events were noticed by the investigators [49].

Asciminib is a recently introduced TKI for the management of CML, including T315I-mutated cases. This pharmacological agent inhibits the BCR-ABL1 protein in an allosteric manner, leading to an inactive conformation of its target. In a phase 1 trial of asciminib in heavily pretreated CML individuals, this novel medication lead to elevation

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in ALT (n=16, 10.7%; grade 3/4 n=4, 2.7%), AST (n=15, 10%; grade 3/4 n=3, 2%) or gamma-glutamyltransferase (n=12, 8%; grade 3/4 n=3, 2%) concentrations, however, grade 3/4 liver-related adverse events occurred in <3% of asciminib-treated subjects [50].

In the STAMP trial that investigated 40 mg of asciminib twice daily versus 500 mg of bosutinib once daily in individuals diagnosed with CML with ≥2 previous TKI therapies, DILI was more frequently noticed in the bosutinib group, i.e., 27.6% (n=21) and 21.1% (n=16) of subjects experienced elevations in ALT and AST concentrations, respectively, versus 3.8% (n=6) each in the asciminib group. Grade 3/4 adverse effects were more likely to present in bosutinib-prescribed subjects (14.5%, n=11 for ALT; 6.6% n=5 for AST) versus asciminib-treated subjects (3.8%, n=6 for ALT and AST each). Treatment discontinuation was required in bosutinib-prescribed CML cases due to significant increases in ALT concentrations [51].

Ruxolitinib seems a safe option in terms of liver toxicity. Based on the findings of a double-blind, placebo controlled trial assessing ruxolitinib in the management of MF classified as intermediate-2 or high-risk, DILI was not mentioned amongst the most common adverse (experienced by at least 10% of the 155 enrolled subjects) caused by the aforementioned pharmacological agent [52].

Ruxolitinib was associated with an increase in ALT concentrations in around 6% of MF patients and with high-grade elevations in only 1% of the individuals enrolled in the JUMP trial [53].

In the RuxoBeat trial which investigated the benefits of ruxolitinib therapy in newly-diagnosed PV, 7 of 28 treated subjects (25%) experienced changes in biochemical markers, including DILI, however, only 3 cases of grade 3 adverse events were reported out of which 2 consisted of elevations in AST/ALT concentrations and required reduction of the prescribed dose. However, no patient necessitated interruption of ruxolitinib [54].

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Similarly, the results of the assessment conducted by Vannnucchi et al. only pointed out minor changes in ALT/AST values following ruxolitinib administration in individuals diagnosed with PV [55].

The EXPAND trial assessed the safety and efficacy of ruxolitinib in individuals with MF and thrombocyte counts between 50000/mmc and 100000/mmc. In this investigation, a total of 5 cases of elevations in bilirubin values were noticed: 1 of the 18 patients who had platelets <75000/mmc but >50000/mmc and 4 of the 20 patients who had platelets <100000/mmc but >75000/mmc. However, of these, only two grade 3 or more increases in bilirubin levels were highlighted, all of which were reported in patients with thrombocyte counts <100000/mmc but >75000/mmc [56].

In a clinical trial which explored the co-administration of ruxolitinib and interferon alpha-2 for management of PV and MF, grade 1/2 liver-related adverse events, i.e., an increase in AST and lactate dehydrogenase (LDH) values were noted in 7 (14%) and 17 (34%) of the 50 patients receiving therapy, with no cases of grade 3-4 side effects occurring in neither subjects with PV nor MF [57].

In the JAKARTA trial which compared fedratinib versus placebo, elevations of liver enzymes were detected in 40-60% of the subjects, however, ≥3 grade elevations in these serum markers were not common. In JAKARTA, 96 subjects were assigned to receive 400 mg of fedratinib daily, 97 to receive 500 mg/day of the same drug, whereas 95 individuals received placebo pills. All grades elevations in ALT (fedratinib 400 mg: 53%; fedratinib 500 mg: 46%; placebo: 17%) and AST (fedratinib 400 mg: 60%; fedratinib 500 mg: 48%; placebo: 29%) concentrations were frequently detected in the fedratinib subgroups versus placebo, whereas bilirubin levels were more likely to increase in the placebo group (fedratinib 400 mg: 31%; fedratinib 500 mg: 28%; placebo: 40%) [58]. However, grade 3-4 increases in ALT values were only noted in 3% of the fedratinib 400 mg and 500 mg subgroups each versus 0% in placebo, grade 3-4 increases in AST values were only noted in 2% of the fedratinib 400 mg and 500 mg subgroups each versus 1% in

placebo, whereas grade 3-4 elevations in bilirubin concentrations occurred in 2% of the placebo and fedratinib 400 mg subgroups and in 1% of the fedratinib 500 mg subgroup, respectively [58].

Momelotinib therapy in MF was also associated with cases of liver toxicity, i.e., grade 3-4 increases in ALT concentrations in 4% of patients and in AST and ALP concentrations in 2% of patients each [59]. Grade 1-2 increases in AST (21%), ALT (19%) and bilirubin (13%) concentrations were also detected [59]. In an integrated assessment of momelotinib based on data derived from phase 3 randomized clinical trials, Verstovsek et al. also highlighted that of the 725 individuals with MF who received the drug, 9 subjects (1.2%) experienced notable elevations in ALT values which required dose interruption/reduction or momelotinib discontinuation [60]. When momelotinib was tested for PV and/or ET, the investigators did not report cases of liver toxicity in either cohort [61].

Ropeg interferons are relatively safer drugs than previously used interferons in terms of liver toxicity. When pegylated interferon alfa-2a was tested in the management of PV (n=40) and ET (n=39), grade 3 increases in liver function tests were reported in 5% (n=2) and 8% (n=3) of the PV and ET subgroups, respectively. No grade 4 side effects were reported [62]. In a trial exploring the safety and benefits of pegylated interferon alpha-2b in PV and ET, elevations in liver enzymes were among the most frequent non-hematological side effects. In total, 2 subjects required pegylated interferon alpha-2b discontinuation due to elevations in AST and ALT values [63].

Management of DILI in MPNs. In the majority of cases, discontinuation of the drug in individuals with clinically established hepatotoxicity and/or administration of hepatoprotective agents have been found to normalize liver enzymes in a few weeks. In cases of severe liver injury, resolution has been achieved by treatment with high-dose steroids for a few weeks. For example, imatinib therapy can be resumed with dose

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reductions or with the use of low doses of steroids if hepatotoxicity occurs [76]. The European LeukemiaNet (ELN) has established guidelines for management of TKI-induced liver injury [77] (Figure 1).

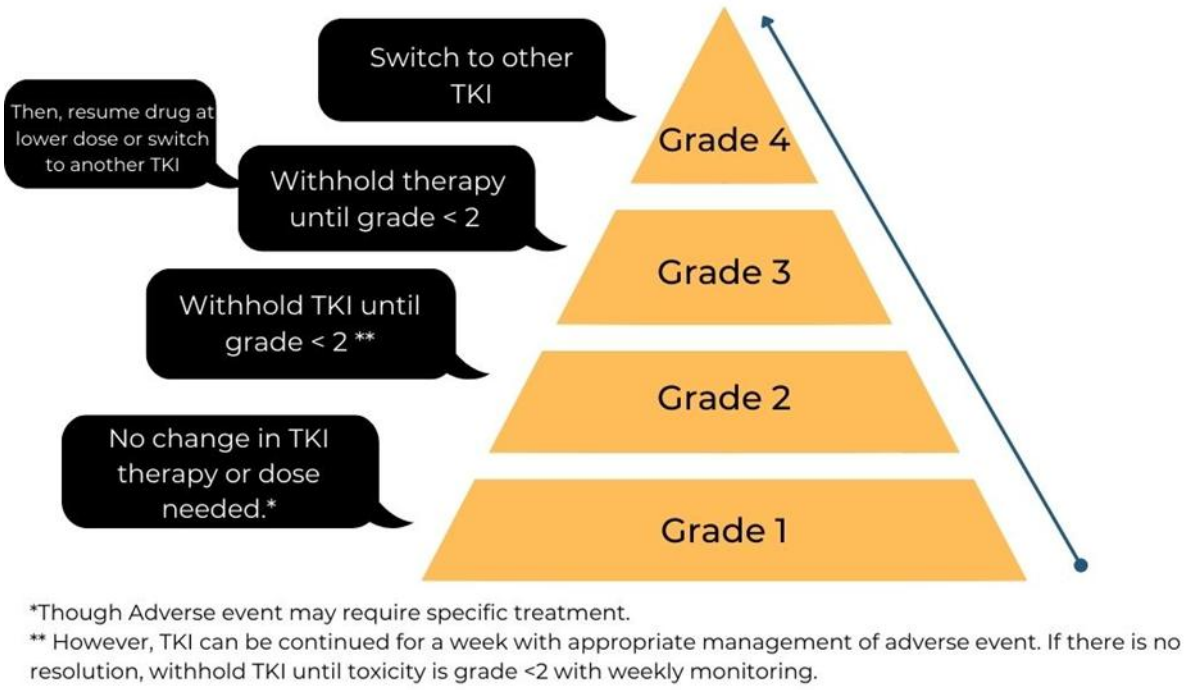

Figure 1. Management of TKI-induced hepatotoxicity according to European LeukemiaNet recommendations.

Since CML patients often require lifelong treatment, Lopina et al. have suggested a novel score-based decision algorithm (Table 2) for restarting TKIs after acute imatinib-induced liver injury and for the choice of 2nd generation TKIs [78]. The score takes into account:

- the grade of hepatotoxic reaction
- the grade of response to the use of imatinib, i.e., presence of early molecular response (EMR) to imatinib therapy at 3 months (3-month BCR-ABL1 ≤10%

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according to the international scale) (not applicable if imatinib treatment was prescribed for <3 months)

- the grade of response to the use of imatinib, i.e., presence of EMR to imatinib therapy at 6 months (6-month BCR-ABL1 <1% according to the international scale) (not applicable if hepatotoxicity developed in <6 months of imatinib therapy)
- the presence of a liver offender (concomitant use of another drug that probably caused drug interactions)
- the presence of viral hepatitis reactivation identified by polymerase chain reaction.

Tabel 2. Novel score for the decision of restarting or withdrawing imatinib in CML [78].

Factors	Imatinib restart[#]	Imatinib withdrawal
Grade of hepatotoxic reaction		
Grade 1	+	-
Grade 2	+[##]	-
Grade 3	+/-[###]	+/-
Grade 4 or presence liver transplantation or imatinib-induced liver cirrhosis or viral hepatitis reactivation	-	+
Presence of EMR to imatinib at 3 months = BCR-ABL1[IS] ≤10%:		
Yes	+	-
No	-	+

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Presence of EMR to imatinib at 6 months = BCR-ABL1^{IS} <1% (if applicable$^{\#\#\#\#}$)		
Yes	+	-
No	-	+
Use of another drug that might cause liver toxicity		
Yes	+	-
No	-	+
Diagnosis of viral hepatitis established by PCR		
Yes	+	-
No	-	+

Legend: + = 1 point/yes, - = 0 points/no; EMR, early molecular response. PCR, polymerase chain reaction; #decide whether to restart imatinib only after resolution of acute hepatitis and normalization of liver function tests; ##restart imatinib at a reduced or at the same dose. ### restart imatinib if liver toxicity resolves in ≤1 month and there is no sign of recurrence; ####do not take into consideration this factor if liver toxicity develops ≤6 months after imatinib initiation.

The approach to restart imatinib can be based on the score listed above [78] as follows:

- score = 0 points: withdraw the drug and switch to 2nd generationTKIs
- score = 1 point: it is preferred to withdraw imatinib if the patient requires treatment for >6 months

- score ≥ 2 points: restart imatinib after resolution of DILI

The choice of a 2nd generation TKI is based on the presence of comorbidities and/or of BCR-ABL1 kinase domain mutations [78].

Other cases of DILI in CML patients require special considerations. For example, reactivation of hepatitis B infection often undergoes spontaneous resolution but treatment with antiviral agents (tenofovir and entecavir) is sometimes needed. Moreover, liver transplantation has been found to be successful in imatinib-induced fulminant liver failure [70].

In patients who develop hepatotoxicity while on ruxolitinib, abrupt drug discontinuation is to be avoided as it can lead to potentially fatal withdrawal symptoms. Therefore, dose reduction is done over time. Douglas et al. recommend liver biopsy for adaptive management in patients with evidence of hepatocellular damage potentially caused by the use of ruxolitinib [79].

Prevention of DILI in MPNs. The relatively limited number of particular treatments and antidotes that are presently available restricts the medical therapy of acute DILI. The primary therapeutic strategy for DILI remains stopping the alleged harmful substance [80]. When N-acetyl cysteine (NAC) is given within 4 to 16 hours after an acute acetaminophen overdose, hepatotoxicity is effectively avoided. NAC is less helpful for acute liver failure caused by non-acetaminophen drugs [81]. First-line prevention measures include avoiding the use of some potentially hepatotoxic medications in patients with underlying chronic liver disease or who have been identified as having a genetic or other risk factor for developing DILI. Other measures include monitoring ALT, AST and other liver-associated enzymes (ALP, bilirubin etc.) to detect hepatotoxicity for particular medications early on. In some developed countries, limiting the availability of potentially dangerous amounts of acetaminophen through regulations has proven

effective in reducing overdoses [82]. Better labeling and patient education are still required in countries with unlimited access, nonetheless, to prevent both purposeful and inadvertent overdoses. The significance of the gut microbiota in preventing DILI will probably continue to be understood, allowing for the development of new therapeutic strategies. Its ability to guard against acetaminophen-induced and other types of acute DILI is currently being investigated [83]. Thus, in patients diagnosed with MPNs who are to be started on potentially hepatotoxicity-inducing targeted agents, we recommend checking liver function tests before therapy initiation, as well as regularly during treatment. Moreover, the management of each case should be tailored to the comorbidities and concurrent medication of the patient, especially in subjects who suffer from MPNs and exhibit a high burden of cardiometabolic disorders [84]. Thus, DILI can be avoided in some instances. Moreover, further research should focus on identifying new hepatoprotective agents that could enable clinicians to overcome DILI and avoid drug cessation or dose reductions/interruptions which aid in the resolution of liver toxicity but might impact the treatment of the hematological malignancy.