Risk of hepatitis B reactivation in patients with myeloproliferative neoplasms treated with ruxolitinib

Adeniyi Abraham Adesola, Matei-Alexandru Cozma, Yong-Feng Chen, Bahadar Singh Srichawla, Mihnea-Alexandru Găman

Abstract

Classical Philadelphia-negative myeloproliferative neoplasms (MPNs), i.e., polycythemia vera, essential thrombocythemia, and primary/secondary myelofibrosis, are clonal disorders of the hematopoietic stem cell in which an uncontrolled proliferation of terminally differentiated myeloid cells occurs. MPNs are characterized by mutations in driver genes, the JAK2V617F point mutation being the most commonly detected genetic alteration in these hematological malignancies. Thus, JAK inhibition has emerged as a potential therapeutic strategy in MPNs, with ruxolitinib being the first JAK inhibitor developed, approved, and prescribed in the management of these blood cancers. However, the use of ruxolitinib has been associated with a potential risk of infection, including opportunistic infections and reactivation of hepatitis B. Here, we briefly describe the association between ruxolitinib treatment in MPNs and hepatitis B reactivation.
**Key Words:** Ruxolitinib; Myeloproliferative neoplasms; Hepatitis B; Polycythemia vera; Myelofibrosis; JAK inhibitor

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**Core Tip:** The JAK inhibitor ruxolitinib has been approved for the treatment of classical Philadelphia-negative myeloproliferative neoplasms (MPNs), *i.e.*, polycythemia vera, essential thrombocythemia and primary/secondary myelofibrosis. However, its use has been associated with a potential risk of opportunistic infections, including hepatitis B reactivation. Herein, we briefly overview the association between ruxolitinib treatment in MPNs and hepatitis B reactivation.

**Citation:** Adesola AA, Cozma MA, Chen YF, Srichawla BS, Găman MA. Risk of hepatitis B reactivation in patients with myeloproliferative neoplasms treated with ruxolitinib. *World J Hepatol* 2023; 15(11): 1188-1195


**DOI:** [https://dx.doi.org/10.4254/wjh.v15.i11.1188](https://dx.doi.org/10.4254/wjh.v15.i11.1188)

### INTRODUCTION

**Introduction to hepatitis B virus reactivation**

Hepatitis B virus (HBV) infection is the most common chronic viral infection in the world. It affects more than 350 million people worldwide as chronic carriers, and more than 2 billion (30% of the world’s population) people show evidence of past exposure. Additionally, HBV infection has accounted for roughly half of total liver cancer mortality in 2010[1,2]. Once contacted, the virus cannot be eliminated, even with proper and rapid antiviral treatment, but the infection is self-limiting in more than 95% of immunocompetent adults. These patients are now known as carriers ‘anti-HBc positive’. They do not require specific management or monitoring unless immunosuppression is suspected[3].

If HBV persists for more than 6 mo in the body, the affected individual is considered to have chronic hepatitis B. Its incidence depends on the time of exposure: 95% of newborns, 20%-30% of children aged 1 to 5 years, and less than 5% of adults[3]. The reason for this dormant state of HBV is the presence of covalently closed circular viral DNA (cccDNA) that penetrates and persists indefinitely in hepatocyte DNA[2-4]. This cccDNA acts as a template for future viral components in the case of HBV reactivation (HBVr). Viral transmission has been greatly slowed recently by the advent of a safe and effective vaccine, available since 1981 and introduced in 2011 in routine vaccination schedules in more than 180 countries [1,5].

### DEFINITION, EPIDEMIOLOGY AND MANIFESTATIONS OF HBVR

The number of cases of HBVr after treatment with immunosuppressive agents is increasing worldwide, mostly attributed to an increase in the prevalence of positive HBV serology and, at the same time, an increase in the number of clinical indications for potent immunosuppression, including solid malignancies, inflammatory bowel disease, autoimmune disorders, blood cancers, *e.g.* myeloproliferative neoplasms (MPNs), and rheumatic diseases[3].

There are, although very similar, several definitions of HBVr, proposed by several medical associations from around the globe. All of them take into account both virological and serological criteria and describe HBVr as either an exacerbation of chronic hepatitis B or a reactivation of past hepatitis B infection. The most used definition is the one proposed by the American Association for the Study of Liver Diseases, last updated in 2020, which defines HBVr according to the virological status of the patient[4,6-8].

For HBsAg-positive patients with or without detectable HBV DNA: (1) At least 2 Log (or 100-fold) increase in HBV DNA compared to the baseline level; (2) HBV DNA at least 3 Log (or 1000) IU/mL in patients with previously undetectable HBV DNA; or (3) HBV DNA at least 4 Log (or 10000) IU/mL if the baseline level is unavailable[4,6-8].

For patients with HBsAg negative and HBV DNA negative: (1) HBV DNA becomes detectable; or (2) reverse HBsAg seroconversion (reappearance of HBsAg)[4,6-8].

The natural history of HBVr depends, among others, on the underlying disease requiring immunosuppressives, host immunity and the immunosuppressive agents used. Evolution can be classified into multiple stages[4,6-8].

After the initiation of immunosuppressive therapy, viral replication resumes, leading to a gradual increase in serum HBV DNA levels. The patient is still asymptomatic and, in general, HBVr-related hepatitis, described as an increase in alanine transaminase (ALT) or aspartate transaminase (AST) to 3 times upper limit of normal (ULN), does not develop[4,6-8].

**HBVr-related hepatitis**

ALT or AST increases to ≥ 3 times ULN (in some cases between 5-10 times ULN). Although most patients may remain asymptomatic, a small number might experience constitutional symptoms, such as pain in the right upper quadrant and jaundice. In rare cases, hepatic injury could further progress and cause liver failure, fulminant hepatitis or even death[4,6-
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8].

**Spontaneous or antiviral-induced resolution**
Normalization of serum ALT and AST levels, due to completion of immunosuppressive therapy, due to antiviral therapy, or due to host immunological mechanisms[4,6-8].

**Acute liver failure/persistent liver injury**
Found in a small number of individuals who continue to have a progressive decline in liver function, it is characterized by increased levels of bilirubin, prolonged prothrombin time, and, in very rare cases, even signs and symptoms of acute liver failure and hepatic decompensation (ascites and encephalopathy)[4,6-8].

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**MECHANISMS OF HBVR**

As previously mentioned, after entering the hepatocytes, the viral genome is converted into plasmid-like cccDNA which can persist in liver cells in a latent state, serving as a reservoir for HBVr, in spite of active anti-HBV immune response. Compared to the hepatitis C virus (HCV) infection, complete eradication of both HBV cccDNA and integrated DNA is impossible with current antiviral treatment with nucleos(t)ide analogs. Thus, these cells constitute a reservoir of persistent HBV. Although HBVr can occur in a variety of settings, immunosuppressive therapies are the most commonly reported. A detailed description of the HBVr induction mechanisms of immunosuppressive therapies is provided in Table 1[3,4,6-12].

**RISK FACTORS FOR HBVR**

Host-related risk factors for HBVr include male sex, younger age and older age (the elderly are more likely to have HBsAg seroclearance but persistent levels of total HBV DNA and cccDNA in the liver) and have been associated with increased risk of HBVr. Preexisting conditions, for example, cirrhosis or MPNs, also play a role in HBVr. HBVr has been reported in patients with MPNs, lymphomas, myeloma, and acute myeloid leukemia. However, it is not yet clear whether this association is attributed to the underlying disease or to the potent immunosuppressants used in the management of these blood cancers[7-9].

Virological factors include HBsAg and HBeAg positivity (adding a 5- to 8-fold risk for HBVr), non-A HBV genotypes, elevated HBV DNA levels before starting immunosuppressive therapy, and co-infection of HBV with other viruses such as HIV and HCV[4,7,8].

Type of immunosuppression: the greatest risk of HBVr is represented by the use of B-cell depleting therapies, used in the therapeutic armamentarium of blood and solid cancers and in the setting of bone marrow or solid organ transplantation[3,4,6-12]. More details are presented in Table 1.

**PREVENTION OF HBVR**

Identifying infected individuals is the first and most important step for HBVr prophylaxis. According to the latest specialty guidelines, HBV infection screening must be performed in all patients who are receiving immunosuppressive treatment. Furthermore, all patients who are HBcAg positive, regardless of the status of HBsAg or the HBV DNA values, must receive prophylactic antiviral treatment. In numerous studies, prophylactic antiviral treatment has been shown to reduce the rate of HBVr, liver failure, and death in these categories of patients. Even if lamivudine was the first and for many years the most used oral antiviral agent for HBVr prophylaxis, YMDD gene mutations cause a high incidence of viral resistance if used for > 6 mo. This is why entecavir or tenofovir are recommended as therapies for HBVr prevention if intended for longer periods of time[4,6-8].

**Duration of antiviral prophylaxis**

In general, the duration of antiviral therapy varies depending on the type of immunosuppressives used. General recommendations include the use of antiviral therapy for at least 6 mo after the last dose of immunosuppressive agents is administered. However, in the case of B cell-depleting therapies (such as rituximab or obinutuzumab), it is recommended that antiviral prophylaxis be continued up to 12 mo after the last dose. Another important step is routine testing for HBV DNA and serum ALT and AST 3-6 mo after discontinuation of immunosuppressives[3,7].

Moreover, particular attention should be given to preventive measures, such as instructing patients to withdraw from alcohol consumption, as well as close monitoring of liver function tests in subjects who are prescribed pharmacological agents with a potentially hepatotoxic effect[13,14]. According to the findings of the Dionysos Study, individuals diagnosed with HBV who consume alcohol experience elevated rates of hepatic fibrosis and death[13].
Table 1 Immunosuppressive agents associated with HBVr

<table>
<thead>
<tr>
<th>Immunosuppressive therapies with high risk of HBVr</th>
<th>Immunosuppressive therapies with moderate risk of HBVr</th>
<th>Immunosuppressive therapies with low risk of HBVr</th>
</tr>
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<tbody>
<tr>
<td><strong>B-cell depleting therapies</strong>&lt;br&gt;(rituximab and ofatumumab)</td>
<td><strong>Anthracycline derivatives</strong>&lt;br&gt;(doxorubicin and epirubicin)</td>
<td><strong>Methotrexate, azathioprine or 6-mercaptopurine</strong>&lt;br&gt;Commonly utilized in the treatment of IBD, IRD and dermatologic conditions; inhibit local inflammatory response associated with immune-mediated diseases by blocking the localization and traffic of activated lymphocytes</td>
</tr>
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<td><strong>Increased HBVr risk in positive HBsAg and negative HBsAg and anti-HBc subjects by acting against the B-lymphocyte antigen CD20:</strong> The Food and Drug Administration has placed a black box warning for rituximab regarding HBVr in rituximab-treated individuals; used to treat CD20+ blood cancers (lymphomas, CLL) and IRD; B cells play a previously underestimated role in HBV immune control by producing neutralizing antibodies; rituximab associated with &gt; 5x increase in HBVr risk (incidence 3%–5%, overall mortality rate 50%–38%)</td>
<td><strong>High-risk for patients with hepatocellular carcinoma and hepatitis B undergoing TACE; used to treat lymphomas and acute leukemias, breast and ovarian cancer, and sarcoma; HBVr rate = 41% in patients with HBsAg positive</strong></td>
<td><strong>Methotrexate, azathioprine or 6-mercaptopurine</strong>: Commonly utilized in the treatment of IBD, IRD and dermatologic conditions; inhibit local inflammatory response associated with immune-mediated diseases by blocking the localization and traffic of activated lymphocytes</td>
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<td><strong>Prednisone use &gt; 20 mg p.o. daily &gt; 4 wk</strong></td>
<td><strong>Prednisone 10-20 mg p.o. daily &gt; 4 wk</strong></td>
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<td><strong>Corticosteroids</strong></td>
<td><strong>TNF-α inhibitors (infliximab, adalimumab, certolizumab)</strong></td>
<td><strong>Calcineurin inhibitors (cyclosporine or tacrolimus)</strong></td>
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<td><strong>Anti-CD52 monoclonal antibody (alemtuzumab)</strong></td>
<td><strong>Histone deacetylase inhibitors (HDIs)</strong></td>
<td><strong>Calcineurin inhibitors (cyclosporine or tacrolimus)</strong></td>
</tr>
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<td><strong>Intra-articular steroid injections or prednisone &lt; 10 mg p.o. daily</strong></td>
<td><strong>High-risk for patients with hepatocellular carcinoma and hepatitis B undergoing TACE; used to treat lymphomas and acute leukemias, breast and ovarian cancer, and sarcoma; HBVr rate = 41% in patients with HBsAg positive</strong></td>
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<td><strong>Less potent TNF-α inhibitors (etanercept)</strong></td>
<td><strong>Proteasome inhibitors: (Bortezomib)</strong></td>
<td><strong>Methotrexate, azathioprine or 6-mercaptopurine</strong>: Commonly utilized in the treatment of IBD, IRD and dermatologic conditions; inhibit local inflammatory response associated with immune-mediated diseases by blocking the localization and traffic of activated lymphocytes</td>
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<td><strong>Cytokine or integrin inhibitors</strong> (abatacept, ustekinumab, natalizumab, vedolizumab)</td>
<td><strong>Tyrosine kinase inhibitors</strong> (imatinib, nilotinib, dasatinib)</td>
<td><strong>Methotrexate, azathioprine or 6-mercaptopurine</strong>: Commonly utilized in the treatment of IBD, IRD and dermatologic conditions; inhibit local inflammatory response associated with immune-mediated diseases by blocking the localization and traffic of activated lymphocytes</td>
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<td><strong>Moderate risk of HBVr in patients with HBsAg positive (1%–5%) and even lower in patients with HBsAg negative</strong></td>
<td><strong>Standard of treatment for all phases of CML; also used in the treatment of GIST; inhibit various kinase signaling pathways; essential for immune activation and proliferation of lymphocytes, with an important role in immune control of HBV replication; prolymphocytic antiviral therapy and regular monitoring of HBV DNA and liver enzymes are essential; reported HBVr rates of 26%–34.8%</strong></td>
<td><strong>Methotrexate, azathioprine or 6-mercaptopurine</strong>: Commonly utilized in the treatment of IBD, IRD and dermatologic conditions; inhibit local inflammatory response associated with immune-mediated diseases by blocking the localization and traffic of activated lymphocytes</td>
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<td><strong>Moderate risk of HBVr in patients with HBsAg positive (1%–5%) and even lower in patients with HBsAg negative</strong></td>
<td><strong>Used for the treatment of MM and induction therapy for transplant-eligible patients prior to stem cell harvest; target cellular pathways that interfere with the functions of healthy B cells, which are important in HBV immune control</strong></td>
<td><strong>Methotrexate, azathioprine or 6-mercaptopurine</strong>: Commonly utilized in the treatment of IBD, IRD and dermatologic conditions; inhibit local inflammatory response associated with immune-mediated diseases by blocking the localization and traffic of activated lymphocytes</td>
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<td><strong>Histone deacetylase inhibitors (HDIs)</strong></td>
<td><strong>Used in the treatment of T-cell lymphomas; inhibit histone deacetylase, a histone-modifying enzyme that is important for epigenetic regulation of gene expression with possible deacetylation status of silent cccDNA, resulting in active HBV transcription and then HBVr</strong></td>
<td><strong>Methotrexate, azathioprine or 6-mercaptopurine</strong>: Commonly utilized in the treatment of IBD, IRD and dermatologic conditions; inhibit local inflammatory response associated with immune-mediated diseases by blocking the localization and traffic of activated lymphocytes</td>
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<td><strong>Prednisone use &gt; 20 mg p.o. daily &gt; 4 wk</strong></td>
<td><strong>The mechanism is two-fold: The HBV genome contains a transcription regulatory element responsive to glucocorticoid that is up-regulated by corticosteroids, resulting in increased viral replication; a directly suppressive effect on cytotoxic T cells that are involved in HBV control; risk of HBVr of 10%-15.8% in HBsAg positive individuals</strong></td>
<td><strong>Methotrexate, azathioprine or 6-mercaptopurine</strong>: Commonly utilized in the treatment of IBD, IRD and dermatologic conditions; inhibit local inflammatory response associated with immune-mediated diseases by blocking the localization and traffic of activated lymphocytes</td>
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<td><strong>Calcineurin inhibitors (cyclosporine or tacrolimus)</strong></td>
<td><strong>Suppress T cell function by inhibiting calcineurin required for signal transduction of T cell activation and inhibiting transcription of interleukin required for T cell proliferation</strong></td>
<td><strong>Methotrexate, azathioprine or 6-mercaptopurine</strong>: Commonly utilized in the treatment of IBD, IRD and dermatologic conditions; inhibit local inflammatory response associated with immune-mediated diseases by blocking the localization and traffic of activated lymphocytes</td>
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<td><strong>Immunosuppressive agents with low risk of HBVr</strong></td>
<td><strong>Intra-articular steroid injections or prednisone &lt; 10 mg p.o. daily</strong></td>
<td><strong>Methotrexate, azathioprine or 6-mercaptopurine</strong>: Commonly utilized in the treatment of IBD, IRD and dermatologic conditions; inhibit local inflammatory response associated with immune-mediated diseases by blocking the localization and traffic of activated lymphocytes</td>
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<td><strong>Methotrexate, azathioprine or 6-mercaptopurine</strong></td>
<td><strong>Documented cases of HBVr are rather rare</strong></td>
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<td><strong>Novel therapies</strong></td>
<td><strong>Intra-articular steroid injections or prednisone &lt; 10 mg p.o. daily</strong></td>
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<td><strong>Immune checkpoint inhibitors such as anti-PD-L1 (nivolumab) and anti-CTLA4 (ipilimumab)</strong></td>
<td><strong>BTK inhibitor ibritinib and PI3K delta inhibitor idelalisib</strong></td>
<td><strong>Methotrexate, azathioprine or 6-mercaptopurine</strong>: Commonly utilized in the treatment of IBD, IRD and dermatologic conditions; inhibit local inflammatory response associated with immune-mediated diseases by blocking the localization and traffic of activated lymphocytes</td>
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<td><strong>Ruxolitinib</strong></td>
<td><strong>Mogamulizumab</strong></td>
<td><strong>Methotrexate, azathioprine or 6-mercaptopurine</strong>: Commonly utilized in the treatment of IBD, IRD and dermatologic conditions; inhibit local inflammatory response associated with immune-mediated diseases by blocking the localization and traffic of activated lymphocytes</td>
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<td><strong>Brentuximab</strong></td>
<td><strong>Obinutuzumab</strong></td>
<td><strong>Methotrexate, azathioprine or 6-mercaptopurine</strong>: Commonly utilized in the treatment of IBD, IRD and dermatologic conditions; inhibit local inflammatory response associated with immune-mediated diseases by blocking the localization and traffic of activated lymphocytes</td>
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<td><strong>Hypomethylating agents: Decitabine, azacitidine</strong></td>
<td><strong>Daratumumab</strong></td>
<td><strong>Methotrexate, azathioprine or 6-mercaptopurine</strong>: Commonly utilized in the treatment of IBD, IRD and dermatologic conditions; inhibit local inflammatory response associated with immune-mediated diseases by blocking the localization and traffic of activated lymphocytes</td>
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</table>
Different subtypes of MPNs, subjects with MF had the highest percentage of infectious events, followed by PV and MPN patients experienced one or more episodes of infection within a 12-mo period. The most frequently reported considering prophylactic or preventive interventions for specific infections such as varicella-zoster virus and HBV virus. Therefore, proactive infection surveillance, baseline screening for latent infections, and prophylactic lamivudine. De-escalation of ruxolitinib and the initiation of anti-HBV therapy led to a gradual decline in transaminase levels after the patient discontinued antiviral therapy in patients with chronic HBV infection before starting treatment with ruxolitinib, as such a proactive measure can help prevent HBVr, as observed in their patient. In a case report by Sjoblom et al., a patient with a history of PV received initial treatment with hydroxyurea. However, due to progressive splenomegaly and fatigue, his treatment was changed to pegylated interferon. Furthermore, to more effectively manage his symptoms, ruxolitinib was introduced. The patient experienced HBVr while on ruxolitinib, which was confirmed by abnormal liver function test results, positive viremia, and newly positive surface antigen for hepatitis B (HbsAg). With the initiation of tenofovir disoproxil, the patient's liver function gradually normalized, indicating successful management of HBVr. In another report by Shen et al., a patient with MF and a history of HBV infection experienced HBVr during ruxolitinib treatment. The initial elevation in transaminase levels was mistakenly attributed to drug toxicity. Subsequent detection of high plasma levels of HBV DNA confirmed the reactivation. Ruxolitinib was discontinued and antiviral therapy was started, resulting in a gradual decrease in transaminase levels. Additionally, in another report by Passucci et al., a patient with PMF and previous HBV infection achieved resolution of splenomegaly with ruxolitinib therapy. However, HBVr occurred after the patient discontinued prophylactic lamivudine. De-escalation of ruxolitinib and the initiation of anti-HBV therapy led to a gradual decline in HBV DNA levels without signs of active hepatitis. Kirito et al. highlight the importance of considering prophylactic antiviral therapy in patients with chronic HBV infection before starting treatment with ruxolitinib, as such a proactive measure can help prevent HBVr, as observed in their patient.

Ruxolitinib has an immunosuppressive effect, leading to an increased risk of serious infections. The immunosuppressive effect of ruxolitinib is due to its interaction with multiple pathways of the immune system, affecting both adaptive and innate immune responses. This can result in the reactivation of silent infections such as tuberculosis, HBV, and varicella-zoster virus. Therefore, proactive infection surveillance, baseline screening for latent infections, and considering prophylactic or preventive interventions for specific infections such as varicella-zoster virus and HBV virus are crucial. A pilot study conducted by Crodel et al. investigated the frequency of infections in patients with MPNs. The study included multiple centers and relied on patient-reported data. The findings revealed that over 50% of MPN patients experienced one or more episodes of infection within a 12-mo period. The most frequently reported infections were upper respiratory tract infections, herpes virus infections, and gastrointestinal infections. Among the different subtypes of MPNs, subjects with MF had the highest percentage of infectious events, followed by PV and essential thrombocytopenia. Furthermore, Lussana et al. conducted a systematic review and meta-analysis.
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Figure 1

Benefits and risks of ruxolitinib use in terms of opportunistic infections in myeloproliferative neoplasms. MPNs: Myeloproliferative neoplasms; RUX: Ruxolitinib; HBVr: Hepatitis B virus reactivation; NK cells: Natural killer cells.

CONCLUSION

In conclusion, ruxolitinib is an effective medication to manage MPNs such as MF and PV, particularly in intermediate and high-risk cases. By inhibiting JAK1 and JAK2, ruxolitinib helps control excessive blood cell production and reduce splenomegaly. However, its use carries certain risks and considerations. The interaction of ruxolitinib with the immune system can increase the susceptibility to opportunistic infections, highlighting the need for vigilant monitoring and timely...
intervention. Furthermore, there is a potential for HBVr, especially in patients with a history of HBV infection. Close monitoring of liver function and proactive measures, such as prophylactic antiviral therapy, are crucial to managing these risks. In general, ruxolitinib offers therapeutic benefits for MPNs, but careful evaluation of infection risk, regular monitoring, and appropriate interventions are essential to ensure patient safety.

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18637095 DOI: 10.1111/j.1572-0241.2008.01948.x


