

CASE REPORT

Ruxolitinib for treatment of polycythemia vera and myelofibrosis in patients after liver transplantation

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Abstract

Although ruxolitinib contributes to immunomodulation and can lead to severe infections, it seems a feasible treatment strategy for patients with polycythemia vera and myelofibrosis after liver transplantation.

KEYWORDS

liver transplantation, myelofibrosis, polycythemia vera, ruxolitinib

1 | INTRODUCTION

Ruxolitinib (Jakavi[®]), an inhibitor of Janus kinase 1 and 2, enables efficient therapy of myeloproliferative disease such as polycythemia vera (PV) and myelofibrosis (MF) by reducing spleen size and constitutional symptoms. However, ruxolitinib is a potent immunomodulator and thus might contribute to the high risk of infectious complications due to long-term immunosuppression after liver transplantation.¹ Clinical information on outcomes and risks of ruxolitinib therapy after liver transplantation is limited, although myeloproliferative neoplasms after liver transplantation have been described in some cases.^{2,3} Compared with the general population, solid organ transplant recipients have an elevated risk for

myeloid neoplasms, with a 7.2-fold increase for polycythemia vera.⁴ The incidence of polycythemia vera is about 12 cases/100,000 person-years at all ages, while it is only 5 cases/100,000 person-years for ages 50–64. However, risk of death is not significantly increased following the diagnosis of polycythemia vera after solid organ transplantation.⁴

Here, we report on two patients who developed progressive myeloproliferative disease after liver transplantation and therefore were treated with ruxolitinib.

2 | PATIENT 1

Ten years after liver transplantation for acute liver failure of unknown origin, a 49-year-old female patient

on mycophenolic acid (3 × 360 mg/day) and tacrolimus (1.5 mg/day) developed JAK2 V617F positive polycythemia vera. CBC at diagnosis was leukocytes, 5.1 G/L (ref. range: 3.9–10.2); erythrocytes, 6.74 T/L (ref. range: 3.9–5.2); hemoglobin, 16.8 g/dl (ref. range: 12–15.4); HKT, 50.1% (ref. range: 35.5–45.5); platelets, 306 G/L (ref. range: 150–370); and LDH: 310 U/L (ref. range: 250). The patient had a DIPPS Score of 1 at the time of diagnosis. PV was at first treated with acetylsalicylic acid and intermittent phlebotomy. After 3 years, the patient's platelet counts and hemoglobin levels dropped, and a second bone marrow biopsy confirmed progression to post-PV myelofibrosis. However, being afraid of potential side effects, our patient refused therapy with ruxolitinib and therefore was continued on acetylsalicylic acid alone. Two months later, urinary outflow obstruction was diagnosed by ultrasound and a surgical pyeloplasty was advised. Again, the patient was afraid of complications and refused surgery, accepting the increased risk to develop urinary tract infections.

Subsequently, her health tremendously deteriorated further: Her enlarged spleen reached a size of 22 cm in length in MRI and she became increasingly weaker so that she was barely able to walk. MPN-TSS score was then 60 (out of 100). Finally, she agreed to start treatment with 10 mg bid ruxolitinib. Within the next 6 months her general health rapidly improved, she gained 22 pounds in weight, spleen size decreased to 17 cm, and platelet counts normalized. Intermittent facial edema and eye redness were the only side effects attributed to ruxolitinib. CBC after treatment initiation with ruxolitinib steadily improved to leukocytes, 5.75 G/L (Ref. range: 3.9–10.2); erythrocytes, 5.4 T/L (Ref. range: 3.9–5.2); hemoglobin, 13.0 g/dl (ref. range: 12–15.4); HKT, 41% (ref. range: 35.5–45.5); and platelets: 203 G/L (ref. range: 150–370). MPN-TSS score improved to 37 (out of 100). However, the patient developed bacterial pneumonia, treated successfully with a course of piperacillin/tazobactam for 7 days, and two episodes of cystitis responding well to oral fosfomycin. Despite the infections, ruxolitinib was continued without interruption, and the patient made a rapid recovery after each infection.

18 months later, the patient developed leukocytosis of 25.8 G/L (ref. range 3.6–10.5 G/L) and erythrocytosis of 6.8 T/L (ref. range 3.85–5.2 G/L). A CT scan of the chest revealed mild residual changes after pneumonia in her basal lung sections, but a meticulous workup did not provide any evidence to support infection (CRP = 0.6 mg/L, ref. range: 0–3 mg/L). Thus, the leukocytosis and the erythrocytosis was attributed to the hematologic malignancy rather than infection. Consequently, the dose of ruxolitinib was increased to 15 mg bid. Blood counts and general health improved immediately once more, so that ruxolitinib has been continued at the higher dose. Since then, the patient

experienced five further episodes of cystitis, which rapidly responded to oral antibiotic treatment. During the entire post-transplant observation period, her immunosuppressive regimen remained unchanged, because the patient was afraid of transplant rejection. Overall, the patient was followed until today for 33 months after initiation of ruxolitinib.

3 | PATIENT 2

This young female patient had to undergo three liver transplantations because of recurrent thrombotic events. The first transplantation was performed due to Budd-Chiari syndrome at the age of 19 years. The second transplantation was needed to treat focal nodular hyperplasia with partial thrombosis of the liver veins at the age of 38. A third transplantation was needed shortly thereafter owing to acute occlusion of the portocaval anastomosis. Myeloproliferative disease was suspected but was not confirmed over the next 16 years, although clinical and lab investigations were done repeatedly. Likewise, an underlying coagulopathy was not detected. In order to prevent further thrombotic complications, she received phenprocoumon (target range: INR of 2.5–3). Despite her history with recurrent thromboses the patient continued smoking (14 py, 30 cig/day).

Her initial immunosuppressive medication after liver transplantation comprised ciclosporin and prednisone, which was changed to tacrolimus (Prograf) and mycophenolate at age 25, and switched again to daily sirolimus 1 mg and prednisolone 2.5 mg at the age of 28, because she developed calcineurin inhibitor (CNIs)-induced kidney injury.

At the age of 44, a kidney tumor in the right kidney combined with thrombosis of the inferior vena cava (VCI) was identified during a routine follow-up MRI. The kidney tumor was removed and was classified as moderately differentiated renal cell carcinoma (pT1a, L0, V0, R0, Pn0). A radiologic attempt to recanalize the VCI closure failed and phenprocoumon was continued (target range: INR of 2.5–3).

Six months later, hemoglobin steadily increased to 19.8 g/dl (Ref. range 12–15.4 g/dl). At this time leukocytes were 10.9 G/L (ref. range: 3.9–10.2), erythrocytes >8.9 T/L (ref. range: 3.9–5.2), HKT 58% (ref. range 35.5–45), and platelets 180 G/L (ref. range: 150–370). LDH was increased to 519 U/L (ref. range: 250). The erythropoietin level was decreased to 2 mIU/ml (ref. range 4.3–29.0). Now, JAK2 V617F positive polycythemia vera was confirmed for the first time by genetic testing and bone marrow biopsy. Molecular studies identified an ETV6 deletion, and next generation sequencing also showed JAK2

V617F mutation and DNMT3A S770L mutation in 70% and 40% of cells, respectively. Bone marrow histology revealed moderate reticulin fiber fibrosis and collagen fiber fibrosis (M2).

As a first therapeutic step, her high hematocrit was lowered by phlebotomies. Next, ruxolitinib 15 mg bid was initiated. Progressive pancytopenia developed so that the dose was reduced to 10 mg once daily. At this lower dosage, the patient still had reduced hemoglobin and platelet counts, which however remained stable. Her splenomegaly declined from 20 to 14 cm in diameter measured by ultrasound and the patient reported a good clinical recovery and stable general well-being. Finally, ruxolitinib was given in two divided daily doses of 5 mg, which further improved tolerability. Immunosuppression was continued with daily 1 mg sirolimus and 2.5 mg prednisolone. Thus far, this patient has not suffered from any infectious complications. CBC after treatment initiation improved to leukocytes 6.02 G/L (ref. range: 3.9–10.2), erythrocytes 5.1 T/L (ref. range: 3.9–5.2), hemoglobin 13.2 g/dl (ref. range: 12–15.4), HKT 40% (ref. range: 35.5–45.5), and platelets 100 G/L (Ref. range: 150–370). The patient has been followed on ruxolitinib treatment since 19 months so far.

4 | DISCUSSION

Malignancies are the most frequent cause of mortality in adult liver transplant recipients.⁵ Myeloproliferative neoplasms after liver transplantation have been described but seem to be rather rare events³ and underlying hematologic etiologies may become unmasked only several years after liver transplantation in patients with Budd-Chiari syndrome and thrombotic hepatic diseases, as is illustrated in our second patient. Nevertheless, data on treatment of PV and MF are lacking for patients after liver transplantation. Of note, in a cohort of 17 patients with liver transplantation for Budd-Chiari syndrome, 12 patients (71%) had detectable evidence of an underlying myeloproliferative disorder. These patients were treated with warfarin, hydroxyurea, and aspirin.⁶ Treatment of myeloproliferative neoplasms in patients after organ transplantation is hampered by the fact that the alternative use of interferons would probably induce organ rejection. On the other hand, the longtime hydroxyurea promotes the development of secondary malignancies, additive to the risk caused by the long-term immunosuppression for organ transplantation. Both hydroxyurea and interferon are poorly effective in relieving symptoms and the effects on splenomegaly are moderate, while ruxolitinib is effective in controlling the hematocrit, reduction of spleen size, and improving

symptoms.⁷ Since both of our patients had splenomegaly and constitutional symptoms, we preferred a therapy with ruxolitinib.

There are no known direct interactions between immunosuppressive agents used in liver transplant recipients and ruxolitinib. Nevertheless, an increased risk for infectious complications must be assumed given that ruxolitinib, which can be used for the treatment of graft versus host disease, has profound immunomodulatory effects.⁸ In the clinical settings it remains unclear, how to adjust long-term immunosuppression after solid organ transplantation when ruxolitinib must be administered.

The randomized, double-blind and placebo-controlled study COMFORT-I and -II demonstrate that ruxolitinib relieves symptoms and improves survival. Accordingly, in our two patients occurred astonishing improvements in clinical presentation and quality of life after treatment with ruxolitinib was started. However, one of our patients experienced more frequent episodes of cystitis in the context of an anatomic predisposition, and pneumonia as infectious complications under ruxolitinib. In the COMFORT-I study, sepsis (2.6%) and pneumonia (1.9%) were the leading adverse events contributing to death in the ruxolitinib arm.⁹ Of note, it has been shown that ruxolitinib decreases the function of dendritic cells, NK cells and T cells as important players of immune control.^{10,11}

There is no data on how immunosuppression in solid organ recipient should be adjusted in concomitant treatment with ruxolitinib to avoid infectious complications. Given that both ruxolitinib and mycophenolate display strong antiproliferative properties, the increased frequency of infections in patient 1 may be related to this combination. However, the patient declined to at least reduce the dose of mycophenolate.

Our patients were regularly monitored for any infections, and we strongly recommend to follow this strategy when ruxolitinib has to be prescribed after liver transplantation, taking into account published clinical experience is still limited to few patients with rather short observation periods.

Taken together, our patients confirm a positive treatment response of myeloproliferative disease to ruxolitinib, leading to a rapid relief of symptoms and improved quality of life. These clinical observations suggest a favorable balance between risks and benefits in patients after liver transplantation who may need ruxolitinib therapy for severe progressive PV and MF. Thus, we hope that our case series will stimulate more reports on the use of ruxolitinib in solid organ transplantation to establish optimal concomitant immunosuppression regimens and monitoring intervals.

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Informed consent was obtained from both patients.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

LD, PL, and AH provided medical care and collected all data. TJW, CPS, and US helped with preparation of the manuscript. LD wrote the manuscript. All authors read and approved the final manuscript.

ETHICAL APPROVAL

The authors have no ethical conflicts to disclose.

DATA AVAILABILITY STATEMENT

Data sharing not applicable – no new data generated.

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