

CASE REPORT

Anticoagulant therapy with fondaparinux in a liver transplant patient with thrombosis and liver fibrosis: a case report

Arturo Cafolla¹  & Giuseppe Gentile²¹Department of Cellular Biotechnologies and Hematology, Thrombosis Centre, Sapienza University of Rome, Rome, Italy²Department of Cellular Biotechnologies and Hematology, Infectious Diseases Unit, Sapienza University of Rome, Rome, Italy**Correspondence**

Arturo Cafolla, Department of Cellular Biotechnologies and Hematology, Thrombosis Centre, Sapienza University of Rome, Via R. Fucini 204- Roma 00137, Italy.
Tel: 00390685795300;
Fax: 00390644241984;
E-mail: cafolla@bce.uniroma1.it

Funding Information

No sources of funding were declared for this study.

Received: 18 December 2015; Revised: 25 July 2016; Accepted: 5 December 2016

Clinical Case Reports 2017; 5(3): 342–345

doi: 10.1002/ccr3.820

Introduction

The treatment of deep vein thrombosis (DVT) is well established, and evidence-based guidelines [1] are regularly updated, whereas the management of vein/artery thrombosis in patients with liver fibrosis and/or cirrhosis has not yet been validated.

The incidence of thrombosis among patients undergoing orthotopic liver transplantation (OLT) is approximately 9%; the majority of events tend to occur within the first 3 months after the transplant [2]. A recent study of liver transplant patients reported a greater incidence of hepatic artery and portal vein thrombosis in patients treated with a reduced dose of immunosuppressive therapy [3]. The hepatic artery thrombosis was observed in 4.6% of 1000 primary liver transplants, and it was one of frequent factors for retransplants [4].

Anticoagulation therapy (AT) with low-molecular weight heparin (LMWH) followed by the administration of a vitamin K antagonist has been reported to be a useful treatment in the management of patients waiting for

Key Clinical Message

The treatment with fondaparinux is the effective and safe anticoagulant therapy in liver transplant patient on immunosuppressive therapy with arterial thrombosis, and it seems able to reduce liver fibrosis. Although this treatment is not generalizable, further prospective large studies need to confirm this case report.

Keywords

Fondaparinux, liver fibrosis, liver transplant patient, thrombosis.

liver transplantation [5]. LMWH appears to be safe and effective in achieving recanalization of the portal vein in patients with cirrhosis [6]. A disadvantage of LMWH in patients with cirrhosis is that the drug efficacy depends on antithrombin. Indeed, antithrombin levels can be significantly reduced in cirrhotic patients. Recently, warfarin anticoagulation was proposed as a treatment for liver fibrosis in patients undergoing liver transplantation for hepatitis C [7].

Since 2003, physicians have been using fondaparinux. Fondaparinux is a synthetic indirect factor Xa inhibitor, which mediates its effects indirectly through antithrombin but, unlike heparin, is selective for factor Xa [8].

Case Report

A 53-year-old woman presented with left renal artery thrombosis in July 2012. The patient, who was seronegative for HCV, HBV, and HIV, underwent liver transplantation for Caroli's syndrome in 2005 and started on immunosuppressive therapy with tacrolimus. Caroli's

syndrome is a combination of Caroli's disease (bouts of cholangitis, hepatolithiasis, and gallbladder stones) with congenital hepatic fibrosis (portal hypertension). Clinical progression and presentation of Caroli's syndrome are highly variable, and symptoms may appear early or late during life [9].

Ultrasound (US)–Doppler, and angio-magnetic resonance imaging (MRI) were performed in October 2006 and showed no sign of a hepatic disorder. Liver function was preserved, and transaminases were within the normal range. These findings were confirmed by subsequent US–Doppler and blood tests, which were regularly performed during the five-year follow-up period (Table 1). In March 2009, after 39 months from the liver transplant, the patient exhibited hypertension related to left renal artery stenosis. The treatment for the stenosis consisted of stenting and drug therapy with dipyridamole (75 mg/day). At this time, the immunosuppressive therapy was adjusted according to the patient's renal function.

In July 2012, after 78 months from the liver transplant, the US–Doppler imaging suggested that the liver had undergone fibrosis. Stiffness was evaluated by Acoustic Radiation Force Impulse (ARFI) and was equal to 16.85 m/sec. The mean value of ARFI measurements in normal individuals was 1.15 ± 0.21 m/sec [10]. In addition, the imaging technique showed a thrombotic event in the left renal artery. The patient's clinical characteristics at the time of this thrombotic event are shown in Table 2.

The patient had no family history of thrombosis. She arrived at the Thrombosis Centre of Hematology and underwent blood tests, which ruled out the presence of inherited conditions such as protein C, protein S, and antithrombin deficiencies or G20210A, G1691A, and JAK2 mutations. The presence of acquired prothrombotic systemic factors was also excluded.

Although the patient did not have any visible varicose esophageal veins and the creatinine clearance was 46 mL/

Table 1. Clinical parameters of the patient during the five years after liver transplantation.

Parameters	2006	2008	2010
Albumin gr/dL	3.6	3.7	4.5
GPT (U/L)	21	20	29
GOT (U/L)	24	21	33
GGT (U/L)	18	15	19
Creatinine (mg/dL)	1.1	1.0	1.0
Tacrolimus (FK506) ng/mL	7.0	6.1	3.6
Fibrosis (Metavir)	F0	F0	F0-1
Portal vein* (mm)	10.4	12.4	11.0
Portal flow [†] (cm/sec)	19.5	13.6	12.6

*Vessel diameter.

[†]Blood speed.

Table 2. Clinical parameters before and after anticoagulant therapy with fondaparinux.

	July 2012 (Before fondaparinux)	July 2013 (After fondaparinux)
Age (years)	53	54
Weight (kg)	68	65
Creatinine clearance (mL/min)	46	64
Factor VIII (%)	178	130
Homocysteinemia ($\mu\text{mol/mL}$)	17	13
Liver stiffness (ARFI)	16.85	5.71
Fibrosis (Metavir)	F4	F0-1
Portal vein* (mm)	8.2	13.4
Portal flow [†] (cm/sec)	14.8	22.7

Reference range: Factor VIII = 65–130%. Homocysteinemia = 8–15 $\mu\text{mol/mL}$.

*Diameter.

[†]Speed.

min, physicians decided to treat the artery thrombosis with 2.5 mg/daily of fondaparinux for 12 months. This treatment is considered off-label, although a large study showed the efficacy and safety of treatment with fondaparinux 2.5 mg/daily in patients with acute coronary syndromes (ACS) which is considered an arterial thrombosis [11].

No pharmacological interference between fondaparinux and the drugs taken by the patient, which included tacrolimus, ursodeoxycholic acid, and a beta-blocker, were noted.

In July 2013, after 12 months from the start of the therapy, the patient underwent abdominal US–Doppler, kidney scintigraphy, and blood tests (Table 2). Imaging techniques and blood tests showed both recanalization of the left renal artery and an increase in the portal vein speed, which was associated with a reduction in liver fibrosis. The authors decided to stop the AT and monitored the patient every 4 months with US–Doppler and biochemical parameters.

In January 2015, the patient was on immunosuppressive therapy with a low dose of tacrolimus in order to obtain a plasmatic concentration of 2.6 ng/mL. At this time, the patient developed two new thrombotic events: one involved the left renal artery, and the other involved the common iliac artery. These two events were diagnosed by abdominal X-ray computed tomography. At the same time, US–Doppler imaging showed that the liver fibrosis was equal to 1.7 m/sec. The extent of fibrosis was evaluated using ARFI.

The patient underwent further therapy with fondaparinux at 2.5 mg/daily, and after 5 months, both thromboses were completely resolved the second time. In addition, US–Doppler imaging showed a reduction in

liver fibrosis to 1.4 m/sec; this value was lower than that observed after the first treatment with fondaparinux.

Currently, the patient continues to be on anticoagulant therapy with fondaparinux. The aim is to reduce the thrombotic risk, as the tacrolimus plasmatic concentration (2.6 ng/mL) was also reduced according to clinical criteria.

Discussion

The management of vein/artery thrombosis in patients with liver fibrosis and/or cirrhosis is not evaluated. A study reported the safety and effectiveness of LMWH in achieving recanalization of the portal vein in patients with cirrhosis [6]. One disadvantage when using LMWH in patients with cirrhosis may be the unpredictable efficacy of this drug, given that LMWH requires antithrombin to exert its anticoagulation function.

A retrospective study reported an incidence of 27 DVTs after liver transplantation (LT) among 304 patients who were followed at a single institution from 2005 to 2012 [2]. Among patients with and without DVT, there was no significant difference in the following preoperative risk factors: age, sex, platelet count, INR value, and the presence of infections and/or cancer. The risk of DVT was related to both the difference in mobility and the perioperative use of factor VII. The risk of developing a DVT after liver transplantation was 9% even with mechanical DVT prophylaxis [2]; the risk is higher in the first 3 months after a liver transplant.

Recently, warfarin anticoagulation was proposed for patients with liver fibrosis undergoing liver transplantation for hepatitis C [7].

Francoz et al. [5] assessed the usefulness of anticoagulation therapy with LMWH followed by administration of a vitamin K antagonist in patients waiting for liver transplantation.

The arterial thrombosis observed in our patient could be considered as late thrombosis, which was not related to the liver transplantation but due to concomitant events, including the change in immunosuppressive therapy and the stent insertion.

Battinelli et al. [12] showed that platelets, when exposed to heparin, tended to release a significantly smaller amount of vascular endothelial growth factor in response to adenosine 5'-diphosphate. The microparticle released from these platelets contained less proangiogenic proteins. In addition, these platelets exhibited decreased angiogenic potential. Fondaparinux showed a similar effect on the platelet angiogenic potential. Moreover, fondaparinux seems to inhibit the generation of thrombin by activated monocytes and monocyte-derived microparticles (MMPs) *via* tissue factor; this inhibition is known to be

dose-dependent. Monocytes and MMPs play a major role in ACS. Indeed, the efficacy of fondaparinux at a daily dose of 2.5 mg in ACS patients appears to be related to its inhibitory effect on MMPs [13].

In addition, Abe et al. [14] reported that LMWH, such as dalteparin sodium, up-regulates serum hepatic growth factor to prevent proliferation of hepatic stellate cells (HSC) and down-regulates the transforming growth factor levels in rats exposed to carbon tetrachloride for an extended period of time. Therefore, our hypothesis is that fondaparinux could exert antifibrogenic effects by direct inhibition of HSC proliferation. Indeed, these cells play a key role in liver fibrinogenesis which could be inhibited by the reduced amount of thrombin secondary to the administration of both LMWHs and fondaparinux [15].

As is the case for any LMWH, fondaparinux is metabolized by the kidney; therefore, caution is required when administering fondaparinux to patients with impaired kidney function, which is defined by a creatinine clearance below 30 mL/min. Caution is needed because the bleeding risk is increased in these patients.

This report suggests that fondaparinux appears to be effective and safe in the anticoagulant treatment of patients with thrombosis and liver fibrosis. Given that the treatment with fondaparinux is uncommon for liver transplant patients, other unknown factors may have played a role in the resolution of arterial thrombosis and liver fibrosis of our patient. Although this treatment is not generalizable, further prospective studies on a large cohort of patients are needed to confirm this case report.

Authorship

AC: designed the study and wrote the report. GG: analyzed the data and revised the manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Pruthi, R. K. 2013. Review of the American College of Chest Physicians 2012 Guidelines for anticoagulation therapy and prevention of thrombosis. *Semin. Hematol.* 50:251–258.
2. Annamalai, A., I. Kim, V. Sundaram and A. Klein. 2014. Incidence and risk factors of deep vein thrombosis after liver transplantation. *Transplant. Proc.* 46:3564–3569.
3. Asrani, S. K., R. H. Wiesner, J. F. Tratter, G. Klintmalm, E. Katz, E. Maller, et al. 2014. De novo sirolimus and reduced dose tacrolimus versus standard dose tacrolimus

- after liver transplantation: the 2000-2003 phase II prospective randomized trial. *Am. J. Transplant.* 14:356–366.
4. Jain, A., A. Shingal, P. Fontes, G. Mazariegos, M. E. deVera, T. Cacciarelli, et al. 2011. One thousand consecutive primary liver transplants under tacrolimus immunosuppression: a 17- to 20-year longitudinal follow-up. *Transplantation* 91:1025–1030.
 5. Francoz, C., J. Belghiti, V. Vilgrain, D. Sommacale, V. Paradis, B. Condat, et al. 2005. Splanchnic vein thrombosis in candidates for liver transplantation: usefulness of screening and anticoagulation. *Gut* 54:691–697.
 6. Amitrano, L., M. A. Guardascione, A. Menchise, R. Martino, M. Scaglione, S. Giovine, et al. 2010. Safety and efficacy of anticoagulation therapy with low-molecular-weight-heparin for portal vein thrombosis in patients with liver cirrhosis. *J. Clin. Gastroenterol.* 44:448–451.
 7. Dharemail, A., E. Tschotzakis, R. Brown, P. Manousou, C. Millson, M. Aldersley, et al. 2015. Warfarin anticoagulation for liver fibrosis in patients transplanted for hepatitis (WAFT-C): results at one year. *J. Hepatol.* 62:S263–S864.
 8. Samama, M. M., and G. T. Gerotziafas. 2003. Evaluation of the pharmacological properties and clinical results of the synthetic pentasaccharide (fondaparinux). *Thromb. Res.* 109:1–11.
 9. Yonem, O., and Y. Bayraktar. 2007. Clinical characteristics of Caroli's syndrome. *World J. Gastroenterol.* 13:1934–1937.
 10. Popescu, A., I. Sporea, R. Sirli, S. Bota, M. Focsa, M. Danila, et al. 2011. The mean values of liver stiffness assessed by Acoustic Radiation Force Impulse elastography in normal subjects. *Med. Ultrason.* 13:33–37.
 11. Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators, Yusuf, S., S. R. Mehta, S. Chrolavicius, R. Afzal, J. Pogue, C. B. Granger, et al. 2006. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N. Engl. J. Med.* 354:1464–1476.
 12. Battinelli, E. M., B. A. Markens, R. A. Kulenthirarajan, K. R. Machlus, R. Flaumenhaft, and J. E. Italiano. 2014. Anticoagulation inhibits tumor cell-mediated release of platelet angiogenic proteins and diminishes platelet angiogenic response. *Blood* 123:101–112.
 13. Ben-Hadj-Khalifa-Kechiche, S., N. Hezard, S. Poitevin, M. G. Remy, B. Florent, T. Mahjoub, et al. 2010. Differential inhibitory effect of fondaparinux on the procoagulant potential of intact monocytes and monocyte-derived microparticles. *J. Thromb. Thrombolysis* 30:412–418.
 14. Abe, W., K. Ikejima, T. Lang, K. Okumura, N. Enomoto, T. Kitamura, et al. 2007. Low molecular weight heparin prevents hepatic fibrinogenesis caused by carbon tetrachloride in the rat. *J. Hepatol.* 46:286–294.
 15. Anstee, Q. M., A. Dhar, and M. R. Thursz. 2011. The role of hypercoagulability in liver fibrogenesis. *Clin. Res. Hepatol. Gastroenterol.* 35:526–533.