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## Effect of Everolimus on the Liver Function of Children Receiving Liver Transplant with Chronic Rejection: An Evidence–Based Case Report

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## Effect of Everolimus on the Liver Function of Children Receiving Liver Transplant with Chronic Rejection: An Evidence–Based Case Report

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### Abstract

**Introduction.** Chronic rejection, a complication after pediatric living donor liver transplantation (LDLT), is challenging to treat as management generally requires retransplantation. However, retransplantation is avoided because of rejection risks, longer operating time, higher mortality, and lower survival rates. Immunosuppressant therapy has potential as an option for nonsurgical treatment. Everolimus, a mammalian target of rapamycin inhibitors (mTOR inhibitors), is a well-known immunosuppressant in treating chronic rejection of LDLT. However, studies in the pediatric field remain minimum.

**Method.** The discussion was based on evidence found from studies found through a systematic literature search. These three studies showed permanent liver function improvement after LDLT on immunosuppressant therapy without Everolimus. Liver function and fibrosis stability improved without mortalities. Differences in Everolimus' efficacy in improving liver function due to the lack of facility to control Everolimus level in the blood resulted in overwhelming infection due to over-immunosuppression of this drug since Everolimus has a narrow therapeutic range.

**Conclusion.** The administration of Everolimus pediatric after living donor liver transplantation reduces ALT and AST levels and improves fibrosis stability.

**Keywords:** everolimus, chronic rejection, living donor liver transplantation liver function improvement, pediatric

### Introduction

Chronic rejection is a complication after receiving liver transplantation from living donors, which is challenging to treat and has a high mortality rate. Such a complication has a poor prognosis and is often unsuccessfully treated. Chronic rejection is a major cause of liver graft failure.<sup>1,2</sup> The incidence of chronic rejection in the pediatric is 2.5-8% globally,<sup>3</sup> while in Indonesia, it is 18%.<sup>4</sup> This incidence is higher than the adult population, only 2-5%.<sup>5</sup>

Chronic rejection requires retransplantation if medical therapy cannot achieve liver function reversibility. Liver function is evaluated from the clinical presentation and levels of alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), Gamma-Glutamyl Transferase (GGT), serum bilirubin, prothrombin time (PT), international normalized ratio (INR), and albumin. Children who have had liver retransplantation can still experience chronic rejection again with an incidence of 90%.<sup>5</sup> Retransplantation is strictly avoided as not only does it not guarantee free from subsequent rejection. Such intervention requires a longer duration and a higher difficulty level than the first one, with a greater mortality risk and lower survival rates.<sup>7,8</sup> To address these problems, research on immunosuppressants in chronic rejection developed as it can provide a nonsurgical treatment. The administration of immunosuppressant agents to reduce graft rejection is expected to be the primary therapy after solid organ transplantation.<sup>9-11</sup>

Everolimus is the immunosuppressant of a mammalian target of rapamycin inhibitors (mTOR inhibitors) class,<sup>9-11</sup> given in chronic rejection and other anti-rejection therapies. It has some advantages, including its non-toxicity to the kidneys (nephrotoxicity),<sup>5</sup> and good effect in treating chronic rejection of LDLT to stop the rejection process or improve their liver function. In contrast to Everolimus, another mTOR inhibitor, namely sirolimus, has greater thrombogenic effects, renal dysfunction, and neurotoxicity.<sup>12</sup>

The use of Everolimus in managing chronic rejection after LDLT in adults is quite common, and its effectiveness has been widely studied.

However, studies focused on the pediatric field remain scarce.<sup>13,14</sup> No guidelines on using Everolimus to treat chronic rejection after LDLT in children, but studies are limited and merely a small-sized sample. A study by Ueno et al.<sup>15</sup> on only two children showed that Everolimus effectively improved LDLT who experienced chronic rejection, as evidenced by improved liver function after drug administration.<sup>15</sup>

The lack of existing studies with promising results provides a strong reason for conducting studies to find more evidence regarding the effectiveness of Everolimus therapy on liver function in children with chronic rejection after living donor liver transplantation. Thus, we reported a case with biliary atresia, underwent LDLT and was treated with Everolimus for chronic rejection. The discussion elaborated on evidence for sharing experience in management.

### Case Presentation

A girl of 17 months, weight 7.8 kg, underwent LDLT after a year of being diagnosed with biliary atresia based on a liver biopsy. Liver grafts were sourced from 2-3 segments of the patient's father, with a graft-recipient weight ratio of 3.71%. The operation lasted 10 hours and 5 minutes, with 400 mL bleeding, 29 minutes of cold ischemic time, 54 minutes of warm ischemic time, and 3 hours 24 minutes of anhepatic time. The operation went well, and no significant complications during the surgery. Postoperatively, the patient was maintained stable, with no complications like infection and sepsis. Treatment given referring to the standard protocol of Dr. Cipto Mangunkusumo Hospital (CMGH) are analgesics, antibiotics, and immunosuppressants. Immunosuppressants, i.e., methylprednisolone corticosteroid of 10 mg/kgBW administered intraoperatively, then subsided to 1 mg/kgBW the following day and were gradually reduced according to protocol. In addition, Tacrolimus was given with a dose adjusted according to the target level in the blood of 10-12 ng/mL.

Eleven days after surgery, she experienced jaundice, fever, diarrhea, and greenish stools. A serial abdominal Doppler ultrasonography (USG) showed no abnormalities indicating vascular disorders in the

anastomosis of blood vessels or other anatomical surgical-related disturbances. Further, the liver enzyme levels increased from the eleventh to the fourteenth postoperative day. Serum AST 124-237 U/L, serum ALT 191-366 U/L, and GGT 214-241 U/L. At the time, a percutaneous liver biopsy was performed, denoting mild acute cellular rejection, in the form of mild infiltration of inflammatory cells in the subendothelial area, mild lobular necrosis, without damage to the biliary ducts, and no fatty liver or accumulation of bile. High doses of methylprednisolone ("pulse" dose) were given starting at 10 mg/kg BW for three days and then gradually reducing, according to the immunosuppressant protocol at CMGH. In addition, tacrolimus immunosuppressant was given with a target blood level of 10-12 ng/mL and mycophenolate mofetil (MMF) with a dose of 2x75 mg. The administration was continued without additions, with maintenance doses of methylprednisolone. Still, the patient again experienced late-onset acute cellular rejection in the 8th month, characterized by fever, increased levels of AST, and ALT, along with biopsy results corresponding to late-onset acute cellular rejection. The patient was then given methylprednisolone in addition to two other immunosuppressant regimens. After that, the patient experienced an improvement in symptoms until the 11<sup>th</sup> month.

Eleven months after LDLT, there were complaints of fever, nausea, vomiting, and abdominal circumference increase in the range of 49-54 cm, but the patient did not experience jaundice. Laboratory findings showed that bilirubin level was within the normal range: 0.27 to 0.5 mg/dL, with indirect bilirubin of 0.3 to 0.9 mg/dL and direct bilirubin of less than 0.3 mg/dL. However, liver transaminase enzymes increased, characterized by increased levels of AST and ALT, reaching a peak on the 6<sup>th</sup> and 7<sup>th</sup> days and then slumping in the following days after being given higher doses of immunosuppressants. (Figure 1).

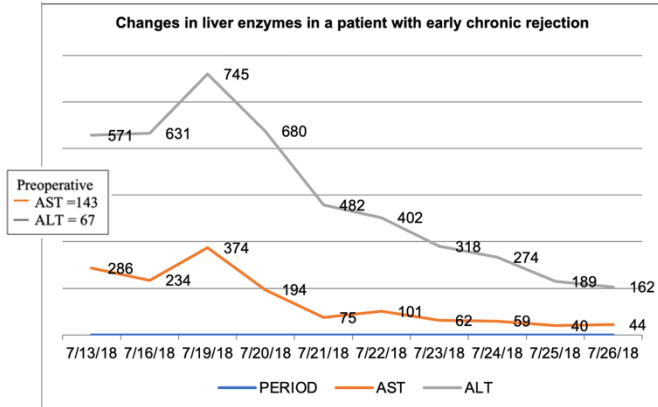


Figure 1. Changes in AST(U/L) and ALT(U/L) levels during early chronic rejection, characterized by increased AST and ALT, form a curve.

Abdominal Doppler ultrasound examination showed normal venous flow in the portal, hepatic, and hepatic arteries. In addition to ultrasound, a computed tomography (CT scan) examination of the abdomen was performed, resulting in good liver parenchymal and vascular images (Figure 2). Percutaneous liver biopsy showed results corresponding to early chronic rejection, showing the bile duct atrophy and biliary duct damage; characterized by irregular nuclei and irregular spacing between nuclei (Figure 3).

To these findings, administration of methylprednisolone, tacrolimus, and MMF was continued with dose-adjustments to the previous regimen. Methylprednisolone was given in pulsed doses and then gradually reduced. Tacrolimus is also adjusted according to the target blood level (target blood level of 6-8 ng/mL), and MMF was given 2x125 mg. Following administration, a clinical improvement was achieved; jaundice was subsided, improved appetite, decreased

abdominal circumference. Such a thriving condition was maintained in the 11<sup>th</sup> to 24<sup>th</sup> months.

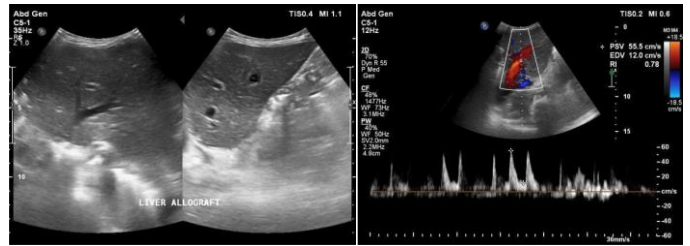


Figure 2. Doppler ultrasound of the patient's abdomen showing normal parenchymal and vascularity.

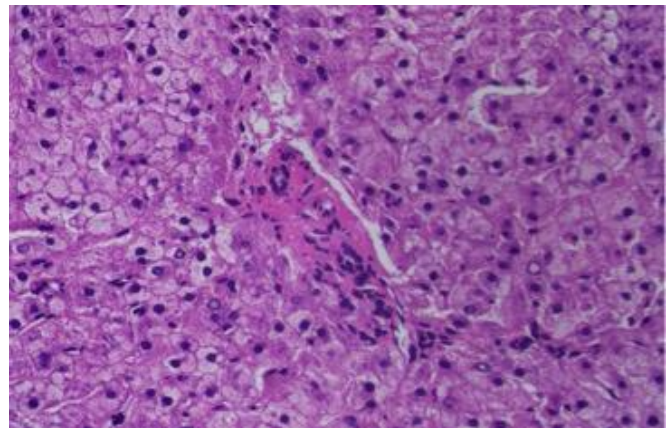


Figure 3. Histopathological image of the patient showing results corresponding to early chronic rejection with bile duct atrophy and biliary duct damage; characterized by irregular nuclei and irregular spacing between nuclei.

In 24 months after LDLT, the condition worsened. The liver biopsy showed late chronic rejection. In this second episode of chronic rejection, Everolimus was given after a standard immunosuppressant had failed; even though this drug was relatively new and not a gold standard use, only several previous promising studies. The new drug, which did not have facilities to measure blood levels at that time, was administered with an initial dose of 2x2 mg. All in all, the patient received four regimens of immunosuppressants.

Everolimus was administered with poor liver function, as seen from the high blood levels of AST and ALT, namely 336 U/L and 280 U/L, respectively (Figure 4).

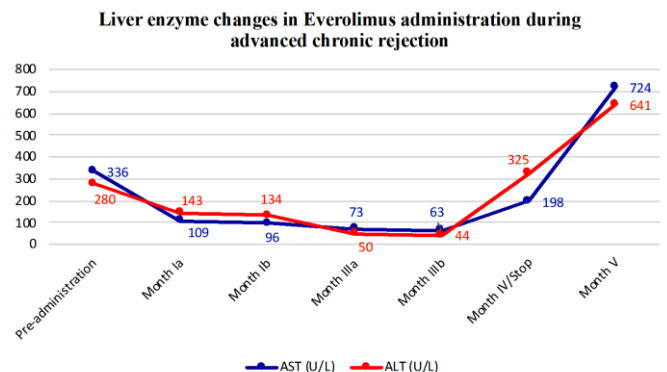


Figure 4. Diagram demonstrated that liver enzyme changes in AST and ALT were affected by administration and discontinuation of Everolimus during advanced chronic rejection. The additional letters "a" and "b" after the month number indicate that administration is still in the one-month period after the living donor liver transplant, but on a different day.

Everolimus administration provided clinical and liver function improvement. At the time, the administration did not monitor blood



levels. No measurement facilities. Following administration, liver function improved for a month or the 25th month after LDLT. AST and ALT decreased to 109 U/L and 143 U/L, respectively (month Ia or the first month after living donor liver transplantation at the first examination stage). Then within a few days in the same month (still within one month after the living donor liver transplant), the AST and ALT levels dropped again to 96 U/L and 134 U/L, respectively (month Ib or the second examination stage in the first post-living donor liver transplantation. At three months of Everolimus administration or at the 27<sup>th</sup> month after living donor liver transplantation (month IIIa), there was a further decrease in AST and ALT levels in the blood to 73 U/L and 450 U/L, respectively. The effect of Everolimus administration became more pronounced five days later (month IIIb), with an even further decrease in AST and ALT levels to 63 U/L and 44 U/L, respectively.

AST and ALT levels increased again at the 28<sup>th</sup> month LDLT or four months after Everolimus stopped due to gastroenteritis characterized by fever and diarrhea, a kind of adverse reaction to immunosuppressants. At that time, the liver function decreased with an increase in AST of 198 U/L and ALT of 325 U/L (month IV). Everolimus was again administered.

At 29 months, the patient underwent a percutaneous liver biopsy due to worsening liver function with AST of 724U/L and ALT of 641U/L (month V) and histopathologically showed advanced chronic rejection. The patient's illness did not improve, and she experienced several episodes of hospitalization with symptoms of nausea and vomiting with worsening liver function (increased liver enzymes, AST-ALT). She experienced recurrent infections, i.e., pneumonia, due to low immunity due to using four immunosuppressant regimens. Finally, she died 32 months after liver transplantation from a living donor due to chronic rejection of liver failure, accompanied by pneumonia and sepsis. (Figure 5).

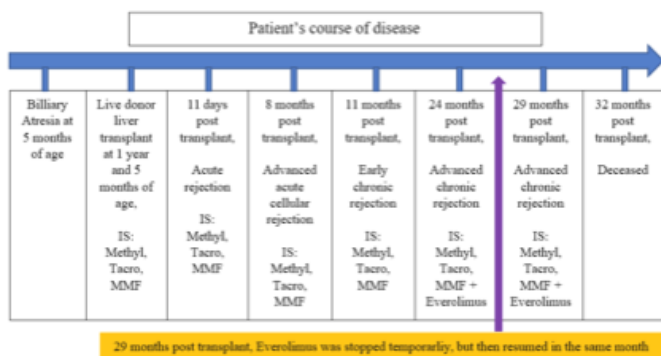


Figure 5. Timeline of disease progression, treatment particularly the administration of immunosuppressant. IS = immunosuppressant; MMF = mycophenolate mofetil; methyl = methylprednisolone; tacro = tacrolimus

Figure 5 shows the course of the patient's disease, starting from the diagnosis of biliary atresia, liver transplantation, and death. After the living donor liver transplantation, standard drugs were given to prevent rejection in the form of methylprednisolone and tacrolimus. MMF was added after episodes of acute rejection, and when chronic rejection occurred, Everolimus, a new therapy for chronic rejection in pediatric patients, was added.

For this case, we proceeded literature search, looking for quality evidence on Everolimus administration for chronic rejection in pediatric LDLT on some databases, i.e., PubMed, EBSCOHost, Scopus, ScienceDirect, and ClinicalKey, with particular reference to liver function improvement. Out of 207 articles, three were eligible for enrollment and were analyzed.

## Discussion

Rejection remains a complication that is at risk in LDLT procedures. The prevalence of acute rejection is 15-25%, while chronic rejection is 10-30%.<sup>1,30</sup> Both types of rejection pose a threat to the successful output of LDLT, and both require immunosuppressant therapy. However, unlike acute rejection, which responds well to treatment and does not affect long-term outcomes and recipient survival, chronic rejection often results in retransplantation and recipient death, even with standard immunosuppressant therapy. This was also the case for the following patient, even though the initial pre-LDLT conditions for both the donor and the recipient and the indications were up to standard.

Living donor liver transplantation in patients is carried out according to indication, namely biliary atresia, without any other comorbidities. The donor's condition before surgery was good, representing an ideal condition for LDLT. The LDLT procedure was carried out smoothly until postoperatively when the patient was in stable condition for up to 11 days after the procedure.

Eleven days after the procedure, the condition was worsening, marked by clinical deterioration in the form of fever, nausea, vomiting, increased abdominal circumference, jaundice, and increased AST and ALT. Other supporting examinations, including Doppler ultrasound and CT scan, were also carried out to rule out vascular abnormalities, particularly hepatic artery thrombosis after living donor liver transplantation, as much as 4-25%.<sup>30</sup> These tests ruled out the vascular abnormalities. The percutaneous liver biopsy, a gold standard diagnostic, showed acute rejection. Such a rejection, the recipient's body's rejection of the donor, is caused by antigen-antibody (humoral), cell-mediated mechanisms, or a combination.<sup>5,12,16,17</sup> Patients are treated with standard immunosuppressants, such as mycophenolate mofetil (MMF), methylprednisolone, and tacrolimus, which have been set as a gold standard for post-LDLT. When the diagnosis of acute rejection is instituted, methylprednisolone is given in a pulsed dose. The administration of immunosuppressants is expected to stop the rate of humoral and cell-mediated processes.<sup>5,9-11,17</sup> Clinical improvement is noted but needs to be more persistent. The patient repeatedly experienced repeated acute rejection phases until the peak at the 8th month after administration of immunosuppressants, when the patient experienced worsening instead improvement.

Administration of immunosuppressants, i.e., methylprednisolone, MMF, and tacrolimus, did not prevent the patient's condition from worsening. The worsening experienced by the patient was noted clinically as fever, nausea, vomiting, increased abdominal circumference, and worsening of AST and ALT levels. These symptoms, coupled with a history of recurrent acute rejection and unresponsiveness to standard immunosuppressants, raise the suspicion of chronic rejection. Clinical symptoms, signs, and supporting examinations enforce chronic rejection after living donor liver transplantation. According to Choudary et al.,<sup>18</sup> the diagnosis of chronic rejection is not based on a specific clinical mechanism; there is not even a clear acute-chronic boundary, unlike the acute and chronic boundaries in other disease conditions in general. Studies showed that the diagnosis of chronic rejection is based on the progressive worsening of graft function, which is then proven by supporting data, the gold standard of which is histopathological findings. This is in line with the opinion of Wiesnerr et al.,<sup>1</sup> which emphasizes the diagnosis of "progressive" loss of biliary ducts and septum and the presence of branch blood vessel abnormalities, manifesting in the worsening of liver enzymes.

Changes in the biliary ducts and blood vessel branches are then grouped according to the Comprehensive Update of the Banff Working Group

on Liver Pathology<sup>19</sup> into early and late-onset chronic rejection. Based on these diagnostic criteria, the patient's chronic rejection at the outset was classified as early chronic rejection, characterized by histopathological findings in the form of atrophy of the bile ducts and damage to the bile ducts characterized by irregular nuclei and irregular spacing between nuclei.

Although the diagnostic criteria for chronic rejection have been classified in such a way, the existing studies have yet to be able to explain in detail the pathophysiology of chronic rejection. Previous studies suggest chronic rejection involves multifactorial immune mechanisms linked together between antigen-antibody mechanisms, angiopathy, and cell-mediated pathways. In addition, the condition of repeated acute rejection also predisposes to chronic rejection.<sup>1,5,17,18,22,23</sup> With the diagnosis of early chronic rejection, the patient then receives additional therapy from the existing standard immunosuppressants, namely Everolimus, which is considered promising in rejection therapy to prevent graft failure, which could result in retransplantation or died.

Everolimus, a class of immunosuppressant mTOR inhibitors, acts by inhibiting B cell proliferation and NK cell activators, thereby inhibiting the progression of multifactor immune mechanisms in patients with chronic rejection.<sup>9-10</sup> In addition, Everolimus inhibits liver fibrosis. According to the Comprehensive Update of the Banff Working Group on Liver Pathology, liver fibrosis manifests chronic rejection changes.<sup>10,19,22</sup> In addition to the advantages associated with direct rejection, Everolimus has the advantage of better safety for the recipient's kidney function than other drugs. However, this is different from the subject of discussion in this report.<sup>10</sup> Fibrosis which is part of the progression of patients with chronic rejection can be recognized by high levels of AST and ALT in the blood, which are indicators of hepatocellular damage.<sup>19,31</sup>

The study by Hiwatashi et al.<sup>25</sup> described a patient who experienced worsening liver function after LDLT on corticosteroid therapy without Everolimus. After the Everolimus combination was given, liver function improved. Administering Everolimus has a temporary positive effect. The clinical improvements were noted, and transaminase enzymes, which were temporary for up to three months of administration of the drug until finally, the AST and ALT levels worsened again after Everolimus and other immunosuppressants were discontinued in the fourth month due to immunosuppressant adverse reaction, i.e., gastroenteritis. After the gastrointestinal infection resolved, immunosuppressants were given again, including Everolimus. The clinical condition worsened with ever-increasing AST-ALT, in which, finally, the patient was re-biopsied with the finding showing an advanced chronic rejection. The patient later died due to liver failure and infection, which worsened, resulting in pneumonia and sepsis.

Some studies have shown results contrary to this case, in which the administration of Everolimus led to better outcomes than other studies. A case report by Hiwatashi et al. (2018)<sup>25</sup> showed up to 100% success with improved liver function output (ALT <100 IU/L) in both patients, and fibrosis progression stopped. In this study, Everolimus was administered three years after liver living donor liver transplantation when a worsening liver function occurred. Everolimus was combined with tacrolimus and prednisolone with a 5 ng/mL dose. The adverse reaction in this case report was oral ulceration and increased blood cholesterol levels, but there were no signs of infection. These findings are consistent with a retrospective cohort study by Kodama et al. (2020).<sup>15</sup> This study demonstrated a 100% success rate for Everolimus with improved liver function outcomes and no increase in chronic rejection progression. This study also found adverse reaction, which was oral ulceration. Enterocolitis and bacteremia were also found in 1 of 21 patients, indicating a risk of infection with Everolimus administration, as

was the case in the pediatric patient in this case. Likewise, a retrospective cohort study conducted by Dumortier et al.<sup>24</sup> involving seven children with chronic rejection after living donor liver transplantation found a lower success rate than the study previously mentioned. Still, it was more inclined to the success of Everolimus in stopping the chronic rejection process by 57.14%, with four children experiencing complete liver function improvement and stopping the rejection process. In contrast, the other two did not experience significant changes. Further analysis also found that one child had partially increased liver function (14.3%). 50% of children in the study also reported side effects, and 23.3% of Everolimus discontinuation (10% due to adverse reaction).<sup>24</sup> The difference in effects is very hard to compare because, in our reported case, Everolimus administration had to be stopped due to immunosuppression adverse reaction arising from the administration of immunosuppressant agents, leading to an exaggerated infection reaction in the patient.<sup>12,28</sup> Based on a literature review, cases in which discontinuation of Everolimus was done due to side effects can be found.<sup>24</sup> The effects of Everolimus are ideally controlled by keeping blood levels within a narrow therapeutic range, generally at 3-8 ng/mL.<sup>15,32</sup> However, this study did not control Everolimus blood levels because there were no facilities to check Everolimus levels. A study conducted by Ganschow et al.<sup>26</sup> showed that the administration of Everolimus could increase the risk of overimmunosuppression, which makes patients more susceptible to infection. However, the administration of this drug cannot be blamed because it functioned as a savior when standard immunosuppressant medicines failed to treat chronic rejection in the patient. In addition, the range of blood drug levels proposed from other studies has not been based on a gold standard referring to adequate study data. This is because blood level reference data in a global scope has not been supported by studies higher than the third level of evidence, as only cohort studies are available. With a higher level of study, it is hoped that the ideal level of Everolimus in the blood for treating chronic rejection after living donor liver transplantation will be more representative of real-life conditions.

## Conclusion

Administration of Everolimus to pediatric patients after living donor liver transplantation can reduce ALT and AST levels, which indicate improvement in liver function, similar to other previous studies. There is a difference in the effect of the improvement given by Everolimus with previous studies, namely in this study the improvement was only temporary, as the condition worsened until the patient finally died due to liver failure and excessive infection. This difference could occur due to fact that the use of Everolimus in the study at that time was not followed by routine blood level checks of the drug, which was hampered by a lack of facilities. Globally, reference blood levels have not been supported by studies higher than the third level of evidence because currently only limited cohort studies are available

## Disclosure

The authors declare no conflict of interest.

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## Role of authors

Conceptualization DP, ANDP, Data curation DP, ANDP, Formal analysis DP, ANDP, Funding acquisition DP, ANDP, Investigation DP, ANDP, Methodology DP, ANDP, Project administration ANDP, Resources DP, Software DP, Supervision DP, Validation LS,

Visualization DP, ANDP, Writing original draft preparation DP, ANDP, Writing review and editing DP, ANDP.

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