Abstract
Antibody-mediated rejection (AMR) caused by donor-specific anti-human leukocyte antigen antibodies (DSA) is widely accepted to be a risk factor for decreased graft survival after kidney transplantation. This entity also plays a pathogenic role in other solid organ transplants as it appears to be an increasingly common cause of heart graft dysfunction and an emerging issue in lung transplantation. In contrast, the liver appears relatively resistant to DSA-mediated injury. This “immune-tolerance” liver property has been sustained by a low rate of liver graft loss in patients with preformed DSA and by the intrinsic liver characteristics that favor the absorption and elimination of DSA; however, alloantibody-mediated adverse consequences are increasingly being recognized, and several cases of acute AMR after ABO-compatible liver transplant (LT) have been reported. Furthermore, the availability of new solid-phase assays, allowing the detection of low titers of DSA and the refinement of objective diagnostic criteria for AMR in solid organ transplants and particularly in LT, have improved the recognition and management of this entity. A cost-effective strategy of DSA monitoring, avoidance of class II human leukocyte antigen mismatching, judicious immunosuppression attached to a higher level of clinical suspicion of AMR, particularly in cases unresponsive to conventional anti-rejection therapy, can allow a rational approach to this threat.

Key words: Donor-specific anti-human leukocyte antigen antibodies; Liver transplantation; Rejection; Acute antibody-mediated rejection; C4d; Solid-phase immunoassays; Human leukocyte antigen single antigen bead

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INTRODUCTION

Although human leukocyte antigen (HLA) antibodies (Abs) have been more extensively studied in kidney transplantation, they can be detected after any solid organ transplantation. As with renal transplantation, the presence of anti-HLA Abs in heart and lung transplants is associated with a worse graft survival[1]. The impact of donor-specific anti-HLA antibodies (DSA) on short- and long-term liver transplant (LT) outcome is not clearly defined. In LT, the presence of preformed DSA is well recognized, although in most cases, DSA disappear a few months after liver transplantation. In the setting of DSA persistence and evidence of complement activation after LT, no significant clinical impact in the first year post-transplantation has been described[2]; however, recent reports indicate that some LT recipients who develop de novo DSA result in lower graft survival and patient survival[3-7]. Thus, there is a need to investigate and quantify the potential adverse impact of DSA on LT outcomes. The present review addresses the current knowledge on this issue with a particular focus on LT.

IMPORTANCE OF ANTIBODY-MEDIATED REJECTION IN SOLID ORGAN TRANSPLANTATION

The detrimental effects of DSA on renal transplantation outcomes have been recognized since 1969[8], and since then, strong evidence has indicated longer kidney allograft survival among patients without DSA. In this setting, the incidence of hyperacute rejection caused by pre-existing DSA has been nearly eliminated by performing a complement-dependent cytotoxic cross-match prior to kidney transplantation; however, acute and chronic antibody-mediated rejection (AMR) plays an increasingly critical role in kidney allograft loss and is considered among the most important barrier that limits long-term outcomes[9-14]. In 2003, at the National Institutes of Health conference, acute AMR in renal transplantation was defined as an acute rejection with graft dysfunction, histological evidence of acute tissue injury and C4d deposition in the presence of DSA[15].

The negative impact of alloantibodies directed against donor HLA antigens was subsequently widely demonstrated and accepted not only in kidney but also in heart transplant, and recent evidence also endorses this notion in pancreatic and lung transplantation[16-24]. For instance, whereas the incidence and mortality of cardiac acute cellular rejection (ACR) have decreased in recent years as a result of advances in immunosuppression, the incidence of AMR appears to be increasing[25]. Furthermore, AMR also seems to be an increasingly common cause of graft dysfunction and cardiac allograft vasculopathy[26,27]. In fact, the presence of DSA in these types of solid organ transplant may contraindicate the transplant due to the increased risk of acute rejection and lower graft survival[28-30]. Moreover, in these patients the development of de novo DSA after transplantation has also been associated with an increased risk of rejection and lower survival[22,24,31,32]. As a consequence of the above-mentioned problems, different strategies-from prevention, DSA monitoring, and selection of adequate immunosuppressive regimens to therapeutic approaches-have been adopted to minimize the deleterious effects of AMR. In the next sections we will focus on these factors.

ANTIBODY-MEDIATED REJECTION IN LIVER TRANSPLANTATION

Human liver allografts are highly resistant to acute AMR from preformed human HLA alloantibodies in comparison with kidney allografts[33]. In LT, the presence of preformed DSA is well recognized, although in most cases, DSA disappear a few months after liver transplantation. Several separate mechanisms in isolation or in combination have been postulated to explain this state of "immune privilege" in the LT setting[34,35]; (1) the liver secretes soluble HLA class I molecules that form immune complexes with alloantibodies, which are then cleared by Kupffer cells; (2) Kupffer cell phagocytosis of platelet aggregates and immune-complexes limits complement activation; (3) the limited distribution of HLA class I expression in the microvasculature; (4) the great liver restorative and regenerative capacity before any insult, even mediated by the immune system; and (5) a large endothelial surface that is capable of absorbing circulating Abs. For example, in a rat model, DSA are cleared from the circulation in only 30 min when the serum is perfused through an extracorporeal liver of donor origin[36]. Other possible mechanisms proposed are

Core tip: The role of donor-specific anti-human leukocyte antigen antibodies (DSA) in liver transplant (LT) remains unclear. Alloantibody-mediated adverse consequences are increasingly being recognized, and several cases of acute antibody-mediated rejection after ABO-compatible LT have been reported. There is a need to investigate and quantify the potential adverse impact of DSA on LT outcomes. The present review addresses the current knowledge on this issue.

related to the particular coagulation state in advanced liver diseases (the deficit of coagulation factors and thrombocytopenia-related portal hypertension can help reduce platelet aggregates and hence the formation of vascular thrombosis observed in humoral rejection mediated by DSA) that can facilitate the vascular flow, the hypocomplementemia of liver cirrhosis, and the dual hepatic vasculature that facilities improved flow during injury. This factor may decrease hepatic necrosis from arterial vasospasm and local intrahepatic coagulation that occur as result of DSA.

However, in the last years there have been different reports that highlight a potential deleterious role of preformed HLA Abs in liver graft survival. Kozlowski et al. found that preformed DSA that persists after LT was associated with severe early rejection. Moreover, Krukekemeyer et al. have revealed portal infiltration and proliferation of lymphocytes (CD20) and plasma cells (CD138) as well as the expression of the B cell/plasma cell-activating chemokines MIP-3, CXCL9, CXCL10, CXCL11, and CXCL12 in acute liver allograft rejection. Recently, O’Leary et al. have found AMR to be a contributor to previously unexplained early liver allograft loss through the analysis of 60 patients with idiopathic early allograft loss when strict criteria for AMR diagnosis were fulfilled. The authors concluded that liver allograft recipients with preformed DSA with a high mean fluorescence intensity (MFI) seem to be at risk for clinically significant allograft injury and possibly for loss from AMR, often in combination with ACR. In addition, Musat et al. demonstrated that DSA is present in up to 75% of patients experiencing rejection, and both DSA and C4d staining was present in 54% of the patients diagnosed with ACR, demonstrating a previously unrecognized humoral component to these rejections. Furthermore, in this study 70% of the patients with ductopenia had DSA and 60% of the ductopenia cases had both circulating DSA in association with diffuse portal C4d deposition, supporting a role for AMR in the pathogenesis of interlobular bile duct injury and loss. These results have been corroborated in other studies. Morphometric studies have shown that portal tract microvasculature destruction precedes bile duct loss in the process of liver allograft rejection. Thus, the following chain of events seems to occur: the formation of the DSA-HLA complex on endothelial cells of the portal tract microvasculature triggers complement activation (evidenced by C4d deposition) and destruction of the portal microvasculature/capillaries branching off the communicating artery from which the periludical vascular plexus arises, resulting in ischemic bile duct injury and loss. In fact, the resolution of cholestasis and ductopenia in association with a reduction of C4d deposition only after a decrease in circulating DSA with aggressive therapy specifically directed towards antibody removal further supports this role.

Certainly, no associations between donor-specific HLA alloantibodies with outcomes in liver or simultaneous liver-kidney transplant recipients (SLKT) have been demonstrated in large randomized controlled trials. Nonetheless, a panel of experts gathered in a recent meeting to discuss the different aspects regarding the consequences of DSA in liver transplantation agree that both acute AMR in liver transplantation recipients and an antibody-mediated renal allograft rejection observed in SLKT are two accepted associations on the basis of multiple case-control studies.

Regarding SLKT, "renal allograft protection" by the liver allograft occurs when the recipient harbors isolated preformed class I DSA in low-to-moderate amounts; however, inferior outcomes have been demonstrated when preformed high MFI class II DSA is present. In those cases, both the kidney and liver allografts are at a risk for rejection, especially when class II DSA persists post-transplantation. Patients who undergo SLKT should ideally receive organs without class II antigens against which the recipient has DSA with an MFI > 5000.

Other potential associations described include the following: hyperacute rejection, de novo autoimmune hepatitis, anastomotic biliary strictures, portal venopathy and nodular regenerative hyperplasia.
of 749 LT recipients developed de novo DSA one year after transplantation (most of them against HLA-II, especially HLA-DQ)⁵. De novo DSA resulted in lower graft and patient survival in a multivariate analysis. These findings were confirmed by Fontana et al.⁷² Moreover, 75% of the patients who developed de novo DSA had biliary complications. Furthermore, O’Leary et al.⁷⁹ have shown the clinical relevance of de novo-specific antibodies on rejection and long-term survival. In addition, a higher rate of the novo DSA, especially of HLA-class-II, in pediatric patients with chronic rejection has recently been observed⁸⁰.

**IDIOPATHIC FIBROSIS PROGRESSION**

Evidence has shown that the humoral alloresponse may have a role in interstitial fibrosis and tubular atrophy development after kidney transplantation²³. In LT, graft fibrosis is frequently observed in late biopsies from pediatric patients with a normal or mild hepatic profile, and the severity of fibrosis correlates with the timing from LT to biopsy²⁴-⁷⁷. Miyagawa-Hayashino et al.⁷⁸ are the first to suggest a role of DSA and the humoral response in long-term fibrosis in LT. The LT patients with de novo DSA and normal graft function had a higher grade of fibrosis and inflammation with a C4d-positive biopsy than patients free of DSA. Importantly, this study showed an association between DSA and fibrosis, but the cause-effect was not demonstrated. Although other potential issues could explain the fibrosis such as subclinical biliary obstruction or venous flow, recent publications have confirmed the observations of Miyagawa-Hayashino (Table 1 and Figure 2)⁵⁸,⁷⁹.

**DIAGNOSIS OF DSA-RELATED AMR**

Because of the overwhelming evidence for antibody-

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**Table 1 Association of graft fibrosis and concomitant anti-human leukocyte antigen class II donor-specific anti-human leukocyte antigen antibodies**

<table>
<thead>
<tr>
<th>Ref.</th>
<th>No. of patients</th>
<th>Positive for HLA Abs</th>
<th>Transplant type</th>
<th>Follow-up median (yr)</th>
<th>Time detection DSA</th>
<th>Method detection DSA</th>
<th>MFI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miyagawa-Hayashino et al.⁷⁸</td>
<td>79</td>
<td>32</td>
<td>LD</td>
<td>11</td>
<td>After LT</td>
<td>SAB</td>
<td>&gt; 5000</td>
</tr>
<tr>
<td>Salah et al.⁴⁰</td>
<td>114</td>
<td>5</td>
<td>LD</td>
<td>2</td>
<td>After LT</td>
<td>SAB</td>
<td>&gt; 5000</td>
</tr>
<tr>
<td>O’Leary et al.⁷⁹</td>
<td>507</td>
<td>46</td>
<td>DD</td>
<td>4.5</td>
<td>After LT</td>
<td>SAB</td>
<td>&gt; 5000</td>
</tr>
<tr>
<td>Grabhorn et al.⁷⁷</td>
<td>19</td>
<td>16</td>
<td>LD + DD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iacob et al.⁸⁰</td>
<td>174</td>
<td>34</td>
<td>LD + DD</td>
<td></td>
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HLA: Human leukocyte antigen; DSA: Donor-specific anti-HLA antibodies; SAB: Single-antigen-bead; MFI: Mean fluorescence intensity; LT: Liver transplant.

**Figure 2 Idiopathic fibrosis progression.** Hypothetical chain of events. DSA: Donor-specific anti-HLA antibodies; LT: Liver transplant.
mediated injury to kidney allografts, a consensus conference was held in 2003 to define the diagnostic criteria for antibody-mediated rejection in solid organ transplantation\textsuperscript{[15]}. This group developed diagnostic criteria for AMR after kidney, heart or lung transplantation. Accordingly, the diagnosis of AMR requires clinical evidence of graft dysfunction, histologic evidence of tissue injury, immunopathologic evidence of an antibody response [complement component 4d (C4d) or immunoglobulin deposition] and serologic evidence of anti-HLA or anti-donor antibody at the time of biopsy. In the setting of liver transplantation there are stringent criteria for the diagnosis of acute AMR that include the following (Table 2)\textsuperscript{[34,38]}: (1) the presence of DSA in the serum; (2) histopathologic evidence of diffuse microvascular endothelial cell injury and microvasculitis; (3) strong and diffuse C4d positivity in the tissue; and (4) reasonable exclusion of other causes of injury that might result in similar findings.

Pre-transplantation cross-matching of the recipient’s serum and the donor’s lymphocytes has become a requirement of kidney transplant programs throughout the world on the basis of the known deleterious effects on kidney allografts of antibody-mediated graft injury\textsuperscript{[81]}. In the setting of LT, there is a need to develop a cost-effective DSA monitoring algorithm, but a panel of experts has recently recommended a DSA monitoring schedule that includes testing all liver allograft recipients in the pre-transplant setting, and afterwards retesting all positive patients 1-2 wk post-transplantation to determine persistence\textsuperscript{[34]}. There have been notable technological advances in the available assays to determine DSA. Earlier cell-based assays for DSA detection (i.e., cytotoxic crossmatch) had several limitations in terms of sensitivity and specificity and the ability to differentiate between IgG from IgM Abs and between HLA from non-HLA Abs. Flow cytometry cross-matching is another cell-based assay that relies on the detection of Abs binding to the surface of donor

Table 2 Diagnostic criteria of acute antibody-mediated rejection in liver transplantation

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Details</th>
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<tbody>
<tr>
<td>The presence of DSA in serum</td>
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<tr>
<td>Histopathologic evidence of diffuse microvascular endothelial cell injury and microvasculitis</td>
<td></td>
</tr>
<tr>
<td>Strong and diffuse C4d positivity in tissue\textsuperscript{1}</td>
<td></td>
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<tr>
<td>Reasonable exclusion of other causes of injury that might result in similar findings</td>
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\textsuperscript{1}Diffuse portal microvascular positivity in formalin-fixed, paraffin-embedded samples (although detection of C4d is more sensitive in fresh tissue) is emerging as most strongly correlated with donor-specific anti-HLA antibodies-induced injury. DSA: Donor-specific anti-HLA antibodies.
lymphocytes and is more sensitive than cytotoxic crossmatch. The first solid-phase immunoassay (SPI) used to test anti-HLA Abs was based on an enzyme-linked immune assay (ELISA), but recently SPI is being replaced by single-antigen-bead (SAB) assays. Acquired by Luminex®, this technology offers a new approach in the detection and quantification of post-transplantation anti-HLA Abs, which can be present in any solid transplant. This immunoassay allows the detection of low titters of HLA Abs that were undetectable by former assays, specifically and semiquantitatively. The fluorescence signals detected are expressed as MFI or molecules of equivalent soluble fluorochrome (MESF). The isolated finding of HLA DSA is not specific for AMR because it has been found in 60% of LT recipients without rejection. Certainly, most patients with preformed low-to-moderate levels of isolated class I DSA in the absence of recurrent liver disease appear to have few, if any, short- or long-term consequences. Moreover, the significance of DSA late after liver transplantation without allograft dysfunction is uncertain. As an isolated finding it does not represent an indication for intervention, although the long-term outcomes of such patients are thus far unknown.

C4d is a component of the complement cascade that is considered a marker of complement regulation. The complement system is a part of the innate immunological response and becomes activated in a variety of immunological events, such as ACR and viral and autoimmune hepatitis. Different C4d staining patterns have been described in liver allografts. Even diffuse endothelial and sinusoidal C4d staining alone cannot be considered specific for the diagnosis of AMR as it has been found in AMR and other common allograft disorders such as ACR, chronic rejection, biliary obstruction and recurrent viral or autoimmune hepatitis. Although there is no consensus, the diffuse portal microvascular positivity in formalin-fixed, paraffin-embedded samples (although detection of C4d is more sensitive in fresh tissue) is emerging to be most strongly correlated with DSA-induced injury. Otherwise, C4d-negative AMR has been identified in renal allografts and likely occurs in the liver, although experts favor the above described conservative approach until more is learned about liver AMR.

Finally, the clinical presentation of liver allograft AMR is nonspecific, and many etiologies, such as ACR, ischemic injury, pharmacological toxicity, infections, initial graft dysfunction, hepatic artery thrombosis, biliary complications, and disease recurrence, can explain increases in aspartate aminotransferase (AST), alanine aminotransferase (ALT), and cholestasis. AMR should be considered as part of the differential diagnosis if DSA are present. These observations have prompted the design of a multicenter study of specific features that could be used to screen patients for acute AMR via routine HE staining.

WHEN MUST AMR BE SUSPECTED?

Acute AMR occurs most commonly during the first several weeks after liver transplantation and consists of an otherwise unexplained liver allograft dysfunction associated with falling platelets and complement levels and increased levels of circulating immune complexes in patients with preformed, persistent DSA. The liver biopsy shows microvascular injury in addition to other characteristics associated with allograft rejection, which is observed in approximately 1% of all early (< 90 d) liver allograft failures. Notwithstanding, acute AMR could explain up to 10% of idiopathic early liver allograft failures in DSA-positive patients.

Therefore, a high suspicion of DSA-induced AMR would theoretically be raised for a liver recipient with high titers of preformed anti-donor HLA class II Abs who presents graft dysfunction in the early posttransplant period (first 90 d) that is otherwise not explained and is associated with falling platelets and complement levels and increased levels of circulating immune complexes. Furthermore, a negative response to conventional antirejection therapy is also associated. SLKT recipients who receive crossmatch-positive organs are also the patients in which a high level of alert must be maintained, especially when the recipient has DSA with an MFI > 5000, however, as stated above, there are other possible clinical presentations where DSA can play a pathogenic effect and thus could indicate the use of a diagnostic approach (i.e., DSA assay, liver biopsy, etc.).

RISK FACTORS FOR DSA-RELATED AMR IN LIVER TRANSPLANT RECIPIENTS

Together with class II HLA mismatching and prior cellular rejection, inadequate immunosuppression (particularly minimization and non-adherence to immunosuppressive medication) is a risk factor for the development of DSA.

Recognized risk factors favoring DSA-mediated liver damage were identified before the use of SAB technology allowed more accurate DSA determinations and included high-titer preformed Abs, the persistence of anti-donor Abs after transplantation, and otherwise unexplained thrombocytopenia and hypocomplementemia. Thereafter, adverse outcomes have been associated with strongly positive flow cytometry cross-matches versus weakly positive cross-matches and strong preformed DSA evaluated for their complement fixing ability with a complement component 1q (C1q) assay. C1q-binding DSA are expected to have the potential to assess cytotoxicity and have been associated with a greater risk of acute rejection and allograft lost in patients undergoing renal and heart transplantation. Thus, in a recently proposed algorithm, a patient with strong DSA and C1q-positive DSA is considered at a higher risk and should be monitored for post-transplant DSA. If
persistent DSA are detected, the patient is monitored as being at a higher risk for AMR.

Furthermore, the effects of DSA can vary depending on cofactors, some of which may promote immunostimulatory/profibriogenic effects and some of which could promote tolerogenic effects. Thus, on the one hand, the up-regulation of DSA targets in allografts of patients with infections or inflammatory-mediated tissue damage as occurs in patients with recurrent hepatitis C chronic infection, as a consequence, appears to be associated with fibrosis progression. On the other hand, HLA class I-restricted regulatory T cell (Treg) epitopes in IgG (also called "Tregitopes") that suppress immune responses to co-administered antigens may be formed as a result of DSA, thereby promoting tolerance.

**PREVENTION AND MANAGEMENT OF LIVER DSA-RELATED AMR**

As previously mentioned, the advent of new diagnostic technologies, particularly SAB assays, has allowed the assessment of the immunological risk in potential recipients of a particular donor by means of the identification and characterization of HLA Abs. In the kidney transplant setting, a detailed serological follow-up is of critical importance in the decision-making process because it can help determine whether to proceed with the transplantation, desensitize or follow a standard immunosuppressive (IS) therapy. Efficient desensitization protocols have enabled successful transplantations, overcoming immunological barriers in patients including the barrier of a positive complement-dependent cytotoxic cross-match. Anti-humoral therapy is based on two complementary approaches: (1) the removal of harmful Abs from the blood stream through plasmapheresis or immunoadsorption; and (2) the modulation of various components of specific and/or innate immunity using strategies including intravenous immunoglobulin, anti-CD20 antibody (rituximab), antithymocyte globulin (ATG), proteasome inhibitor (bortezomib), anti-CS antibody (eculizumab), or even splenectomy.

In the setting of liver transplantation, the routine assessment of DSA pre-transplantation, with a retest of positive patients 1–2 wk post-transplantation, has been recommended by a panel of experts. This fact is of particular interest when a SLKT is being considered and in the case of anti-donor HLA class II Abs; however, there are several shortcomings with this strategy that need to be solved: (1) only a small percentage of sensitized patients before transplantation will have severe, adverse consequences after transplantation; and (2) the significance of DSA late after liver transplantation without allograft dysfunction is uncertain and, in general, this finding does not merit any intervention. Taking into account these shortcomings, a panel of experts have recently proposed to investigate the design of cost-effective DSA monitoring strategies that allow one to detect the first group of patients and that identifies DSA characteristics late after transplantation that indicate inadequate immunosuppression or an unacceptable risk of chronic allograft injury.

Patients who undergo SLKT should ideally receive organs without class II antigens against which the recipient has DSA with an MFI > 5000; however, if a patient must receive cross-match positive organs after balancing the risks of a DSA-mediated rejection against those related to a protracted waiting list period in terms of progression of the liver disease, postoperative testing to determine antibody persistence and close follow-up are desirable.

Otherwise, the IS regimen and drug exposure can be relevant in terms of prevention of DSA-mediated allograft damage. In the kidney transplantation setting, the selection of an adequate IS can prevent subclinical inflammation and hence fibrosis progression. For instance, in a case-control study, Moreno et al. confirmed the lower prevalence of subclinical inflammation associated with a regimen based on tacrolimus, mycophenolate mofetil, and prednisone than with a regimen based on cyclosporine, mycophenolate mofetil, and prednisone. In addition, lower exposure to tacrolimus between 3 and 12 mo after transplantation was independently associated with higher increases in chronic pathology in patients also treated with mycophenolate mofetil, and prednisone. In the liver transplantation setting, de novo DSA prevention strategies also include a strict adherence to immunosuppression and the use of tacrolimus (rather than cyclosporine).

The treatment of acute AMR in ABO-compatible liver transplants is not clearly determined because of the limited number of cases. Most of the evidence in this field derives from studies in kidney transplantation where different anti-humoral therapies similar those mentioned above have been used. Bortezomib, a proteasome inhibitor effective in depleting plasma cells that in turn are responsible of producing the offending Abs, has been successfully used in three cases of severe AMR in ABO-compatible LT recipients; however, concerns have been raised about the anti-humoral therapies in LT recipients because of their potent immunosuppressive effects that may exacerbate chronic viral hepatitis or increase infectious risks. Thus, experts currently advise that a strategy based on the combination of avoidance/prevention when possible may be the best strategy.

**CONCLUSION**

There has been a recent resurgence of interest in AMR in liver transplantation based on an increasingly number of reports indicating DSA-mediated allograft dysfunction and a better characterization of this entity in terms of diagnostic tools and diagnostic criteria.
Although AMR is a less frequent cause of liver allograft dysfunction, it must be taken into account not only from a diagnostic/therapeutic point of view but also from a preventive standpoint.

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