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Review article

Donor-specific antibodies and their impact on antibody-mediated rejection post-liver transplantation: A comprehensive review

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ABSTRACT

Antibody-mediated rejection (AMR) following liver transplantation is a significant clinical challenge, with donor-specific antibodies (DSAs) playing a pivotal role. Understanding the mechanisms and impact of DSAs is crucial for improving transplant outcomes and patient care. This review provides an in-depth analysis of the pathogenesis, diagnosis, and management of AMR in liver transplantation, focusing on the role of DSAs. AMR in liver transplants, though less common than in other organ transplants, presents unique diagnostic and therapeutic challenges. The review explores the latest diagnostic criteria, including serum DSAs, C4d staining, and liver biopsy findings. It delves into the pathogenesis of AMR, emphasizing the role of both preformed and de novo DSAs in causing graft injury and rejection. The review also discusses current therapeutic strategies, such as the use of immunosuppressants, plasmapheresis, intravenous immunoglobulin, and proteasome inhibitors, highlighting their efficacy and limitations. Furthermore, it examines the unique aspects of liver immunology that contribute to the organ's relative resistance to DSA-mediated injury. Emerging research, particularly on gene expression changes in renal allografts during simultaneous liver-kidney transplantation, is also discussed, offering insights into future directions. This review is instrumental for clinicians and researchers in understanding the complexities of AMR in liver transplantation and in developing more effective management strategies.

1. Introduction

Liver transplantation is a life-saving procedure for patients with end-stage liver disease or acute liver failure. Despite advancements in surgical techniques and postoperative care, transplant recipients still face significant challenges, notably antibody-mediated rejection (AMR). AMR in liver transplantation poses a unique set of complexities and implications for patient management and graft survival. Estimates of its incidence vary, with reports indicating it to be between 0.3 % and 2 % [1]. This lower incidence is thought to be due to the liver's unique anatomy and its characteristic as an "immune-privileged" organ, which makes it less susceptible to AMR compared to organs like the heart (10–20 % incidence) and kidney (20–50 % incidence) [2]. AMR occurs when the recipient's immune system produces antibodies against the donor liver, specifically targeting human leukocyte antigens (HLAs) present on the donor organ. These antibodies, known as donor-specific antibodies (DSAs), are key players in the process of AMR, leading to graft injury and potentially graft loss if not promptly and effectively managed [3]. A previous study reported 13 % of liver transplant recipients had DSAs at a median of 51 months post-transplant, and 9 % developed de novo DSAs at a median of 36.5 months after the first screening [4]. Likewise, another study reported that preformed DSAs were found in 4.7 % of patients, while 19.9 % developed de novo DSAs (12.2 % at 1 year, 13.4 % at 5 years, and 19.5 % at 10 years) post-transplant [5]. The liver's unique immunological environment often results in a more tolerogenic response compared to other organs, yet cases of severe AMR, particularly in the presence of high levels or specific subclasses of DSAs, have been documented [6].

DSAs can either be preformed, existing in the recipient's blood before transplantation, or de novo, developing after the transplant. Preformed DSAs are typically detected in patients who have been previously sensitized, such as through blood transfusions, previous transplants, or pregnancies. De novo DSAs, however, arise post-transplantation and are associated with various risk factors, including

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inadequate immunosuppression and immune system activation by infections or graft damage [7]. The development of de novo DSAs is particularly concerning as they have been linked to chronic rejection and long-term graft dysfunction. Diagnosing AMR in liver transplant recipients involves detecting DSAs in conjunction with histopathological examination of liver biopsy samples. Typical findings include C4d deposition, a complement degradation product, in the liver tissue, indicating antibody involvement in the graft injury. However, the diagnosis of AMR remains challenging due to the variable presentation and sometimes indistinct histological features, especially in chronic cases [2].

The aim of this review is to synthesize current knowledge and recent advancements in the understanding of AMR in liver transplantation, with a particular focus on the role and impact of DSAs. We will examine the pathogenesis, clinical presentation, diagnostic criteria, and management strategies for AMR, as well as discuss the challenges and future directions in research and clinical practice. Understanding the intricacies of DSAs and their role in AMR is crucial for the development of targeted therapies and the improvement of graft survival and patient outcomes in liver transplantation.

2. Antibody-mediated rejection: definition and diagnosis

2.1. Definition and clinical presentation of AMR in liver transplantation

AMR is a form of graft rejection that occurs when the recipient's immune system produces antibodies against the donor organ. In liver transplantation, AMR is characterized by the presence of DSAs targeting donor HLAs. Both Class I and Class II (Table 1) HLA mismatches can stimulate the recipient's immune system to produce DSAs, which can bind to the transplanted organ and activate the complement cascade, leading to tissue injury and rejection. HLA Class I molecules are present on nearly all nucleated cells in the body and include HLA-A, HLA-B, and HLA-C. They play a crucial role in the immune response, and mismatches in these antigens can lead to the production of DSAs, potentially resulting in AMR. Meanwhile, HLA Class II molecules are primarily expressed on antigen-presenting cells (such as B cells, dendritic cells, and macrophages) and include HLA-DR, HLA-DQ, and HLA-DP. Class II molecules are particularly important in the context of transplantation as they are highly immunogenic. DSAs against HLA Class II antigens are often associated with a more severe form of AMR and are considered highly relevant in the transplant setting [8,9]. Willuweit et al. [10] investigated the association between DSA after liver transplantation and post-transplant complications. Data from 430 liver transplant recipients were analyzed, with DSA detected in 18.8 % of patients, predominantly HLA class II antibodies. While there was no correlation between DSA mean fluorescence intensity (MFI) levels and complications, the presence of DSA, particularly HLA Class II antibodies, was significantly associated with graft cirrhosis. This suggests that the occurrence of HLA Class II DSA post-LT may indicate a higher risk of graft damage. Next, Liu et al. [11] assessed the impact of DSAs on graft survival following pediatric liver transplantation. Forty-eight recipients were analyzed based on posttransplant serum samples for DSAs. DSAs were detected in 10 patients (20.8 % of cases). One case was positive for HLA class I and HLA class II antibodies, whereas 9 cases were positive for HLA class II antibodies, and the gene loci were HLA-DR and/or DQ. Four of the DSA-positive patients experienced antibody-mediated rejection (AMR). Noteworthily, the specific HLA antigens involved in AMR can vary between individuals, depending on the genetic differences between the donor and recipient [8,9].

Clinically, AMR can manifest as acute or chronic graft dysfunction (Table 2), and its presentation can range from asymptomatic to severe graft failure. Acute AMR usually presents within days to weeks post-transplantation and is often characterized by a sudden onset of liver function abnormalities, such as elevated liver enzymes and bilirubin levels. Symptoms may include jaundice, fatigue, and general malaise. In contrast, chronic AMR develops over months to years and is typically more insidious. It may present as progressive liver fibrosis and chronic graft dysfunction, often leading to a gradual decline in liver function.

Table 1
Comparison between Class I and Class II HLA in AMR.

Feature	Class I HLA	Class II HLA
Components	HLA-A, HLA-B, HLA-C	HLA-DR, HLA-DQ, HLA-DP
Expression	Widely expressed on almost all nucleated cells, including liver cells	Expressed primarily on antigen-presenting cells; less abundantly expressed in the liver compared to Class I
Role in Transplant	Crucial for T-cell recognition and cytotoxic response	Key in helper T-cell activation and regulation of the immune response
DSA Activation	Direct activation of cytotoxic T cells leading to cell-mediated damage	Activation of helper T cells, promoting B-cell antibody production and inflammatory response
Clinical Implications	Immediate and acute rejection risks; may affect graft survival directly	Associated with chronic rejection and graft dysfunction over time due to persistent immune activation
Management Strategies	Immunosuppressive therapy, monitoring of DSA levels, and potential desensitization protocols	Similar to Class I but with added emphasis on managing chronic inflammation and immune modulation
Impact on AMR	Acute AMR, characterized by rapid onset and potentially reversible with aggressive treatment	Chronic AMR, leading to gradual loss of graft function and harder to reverse
Abundant Expression in Liver	Yes, making it a significant target for immune response in liver transplantation	No, with limited expression primarily in specialized cells, impacting its role in liver transplant immunity

Table 2
Comparison between acute and chronic AMR in liver transplantation.

Category	Acute AMR	Chronic AMR
Definition	A rapid onset of graft dysfunction due to antibody-mediated damage to the liver allograft, occurring typically within days to weeks post-transplantation.	A gradual decline in graft function over months to years post-transplantation, due to ongoing antibody-mediated vascular damage and fibrosis.
Time of Onset	Days to weeks post-transplant.	Months to years post-transplant.
Clinical Features	Sudden deterioration in liver function tests, fever, malaise, jaundice.	Progressive increase in liver enzymes, jaundice, ascites, and evidence of liver fibrosis or cirrhosis.
Histological Findings	Capillaritis, microvascular inflammation, endothelialitis, and necrosis.	Fibrosis, arterial intimal thickening (transplant arteriopathy), chronic ductopenia, and ischemic cholangiopathy.
Diagnostic Criteria	Detection of DSA, complement activation (C4d staining), and acute tissue injury in biopsy.	Detection of DSA, chronic tissue damage in biopsy, including fibrosis and vascular changes without acute inflammation.
Management Strategies	High-dose corticosteroids, plasmapheresis, IVIG, rituximab, and possibly bortezomib or eculizumab for severe cases.	Management is more challenging; may include optimizing immunosuppression, treating complications of cirrhosis, and in some cases, re-transplantation.
Outcomes	If treated promptly, potentially reversible, but may lead to graft loss if severe or not adequately managed.	Generally leads to progressive graft dysfunction, with a higher risk of graft loss and complications related to chronic liver disease.

The clinical presentation of AMR in liver transplants is less defined compared to other organ transplants, such as kidney or heart, due to the liver's unique immunobiology and tolerance. As such, AMR in liver transplantation has historically been under-recognized and under-diagnosed [12].

2.2. Diagnostic criteria of AMR in liver transplantation

The diagnosis of AMR in liver transplantation is complex and relies on a combination of clinical, serological, and histopathological criteria. The presence of DSAs is a key diagnostic criterion for AMR. These antibodies are directed against specific HLA antigens on the donor liver. Testing for DSAs is typically performed using solid-phase assays, such as Luminex-based assays, which can detect even low titers of DSAs. The detection of DSAs, especially when they are complement-binding, is strongly associated with AMR and poor graft outcomes [13]. Next, C4d is a degradation product of the classical complement pathway and serves as a marker for antibody-mediated damage. In liver transplantation, C4d staining in liver biopsy is considered indicative of AMR, especially when correlated with the presence of DSAs. C4d deposition is typically assessed in the portal tract capillaries and sinusoids of the liver graft. However, the sensitivity and specificity of C4d staining in liver AMR are variable, and C4d-negative AMR can occur [14]. Furthermore, histological examination of liver biopsy samples is crucial for diagnosing AMR. Findings suggestive of AMR include evidence of acute tissue injury, such as endothelialitis, portal inflammation, and bile duct injury. In chronic AMR, features may include transplant arteriopathy, fibrosis, and ductopenia (Table 2). However, these findings are not specific to AMR and can be seen in other forms of graft rejection or injury. Therefore, liver biopsy findings must be interpreted in conjunction with clinical data and the presence of DSAs [9].

The diagnosis of AMR in liver transplantation remains a challenge due to the overlap of clinical and histological features with other forms of rejection and liver injury. Additionally, the liver's inherent immunotolerance can mask or modulate the presentation of AMR. As such, a high index of suspicion and a combination of serological, histological, and clinical criteria are essential for accurate diagnosis. Further complicating the diagnosis is the phenomenon of subclinical AMR, where DSAs and histological features of AMR are present without overt clinical symptoms. This condition requires careful monitoring, as it can progress to clinical AMR and impact long-term graft survival. Advances in diagnostic techniques, such as more sensitive assays for DSAs and improved histopathological evaluation, are enhancing the detection and understanding of AMR in liver transplantation. However, there is still a need for standardized diagnostic criteria and better biomarkers to improve the accuracy and timeliness of AMR diagnosis [6,8,14–16].

3. Pathogenesis of antibody-mediated rejection

3.1. Role of donor-specific antibodies in AMR

DSAs are pivotal in the pathogenesis of AMR in liver transplantation. These antibodies target specific antigens, mainly HLAs present on the donor liver cells. The development of DSAs, either pre-existing or de novo, post-transplant is a key factor in the initiation and progression of AMR. DSAs contribute to AMR through various mechanisms, primarily involving the activation of the complement system, direct cellular toxicity, and the recruitment of inflammatory cells. When DSAs bind to their target antigens on the donor organ's cells, they trigger the classical pathway of the complement system (Fig. 1). This activation leads to the sequential activation of complement components, culminating in the formation of the membrane attack complex (MAC). MAC creates pores in the cell membranes, leading to cell lysis and death. Another key feature of complement activation is the generation of split products like C3a and

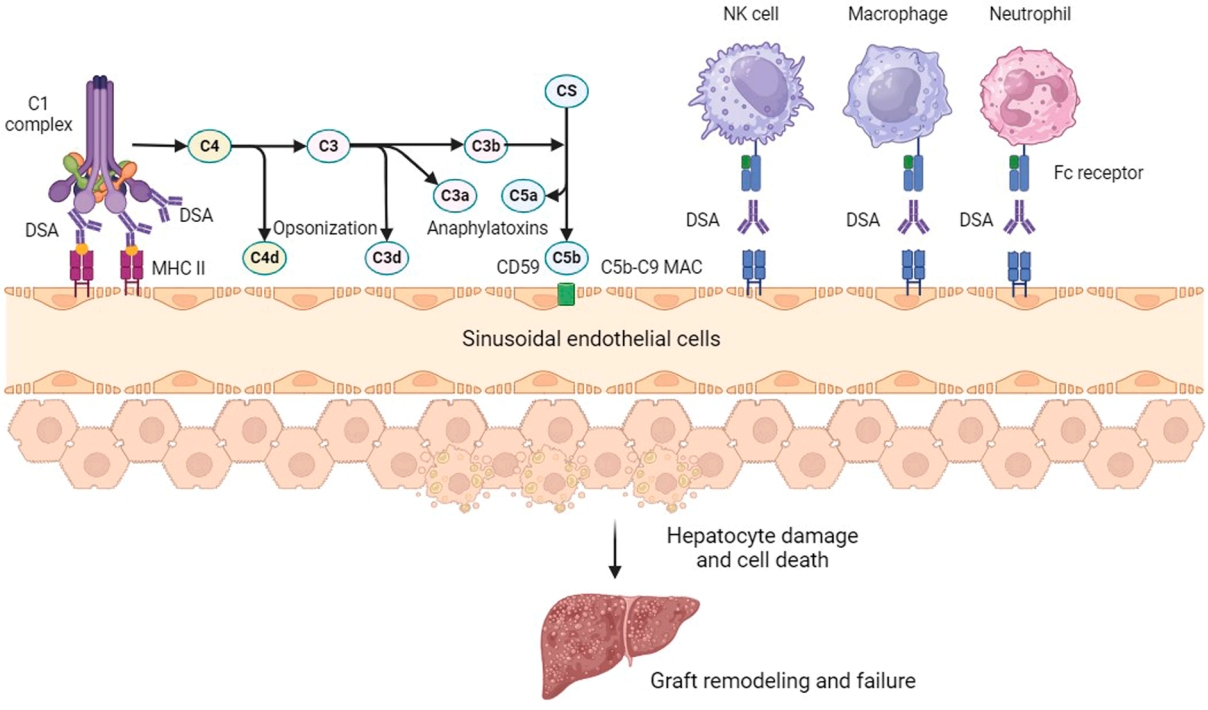

Fig. 1. Pathophysiology of AMR in Liver Transplantation. This diagram illustrates the immunological mechanisms involved in antibody-mediated rejection (AMR) following liver transplantation. Donor-specific antibodies (DSAs) bind to MHC class II molecules on the surface of liver sinusoidal endothelial cells, activating the classical complement pathway. This activation leads to the sequential cleavage and activation of complement components C4, C3, and C5, and the formation of C3 and C5 convertases. The generation of anaphylatoxins (C3a, C5a) and the assembly of the C5b-C9 membrane attack complex (MAC) result in cell lysis and damage. Additionally, the diagram shows the role of natural killer (NK) cells, macrophages, and neutrophils, which engage with the Fc receptors and DSA to contribute to cellular damage, leading to hepatocyte damage and death. Ultimately, these processes can lead to chronic allograft damage and liver failure [34]. (CS = complement system).

C5a, which are potent anaphylatoxins and chemoattractants. C4d, a byproduct of complement activation, binds covalently to endothelial cells in the graft and is used as a diagnostic marker for AMR. The overall result of complement activation is tissue inflammation, endothelial damage, and ultimately, graft injury [3,17–20]. Moreover, DSAs can exert direct effects on the cells of the transplanted organ, independent of complement activation. This can occur through antibody-dependent cellular cytotoxicity (ADCC), where DSAs bind to their target antigens and recruit natural killer (NK) cells, macrophages, and other effector cells. These cells then release cytotoxic substances like perforin and granzymes, leading to targeted cell death. DSAs can also cause apoptosis (programmed cell death) directly upon binding to the cells, disrupting cellular processes and leading to graft injury [3,21–23]. Likewise, the binding of DSAs to the graft endothelium and subsequent complement activation lead to the expression of adhesion molecules and release of chemokines and cytokines. These molecules promote the recruitment and adhesion of various inflammatory cells, including neutrophils, monocytes, and lymphocytes, to the site of the graft. These infiltrating cells can amplify the immune response by releasing more inflammatory mediators and further attacking the graft tissue. This inflammatory milieu can exacerbate endothelial injury, contributing to a cycle of ongoing inflammation and damage [3,24–28]. Together, these mechanisms illustrate how DSAs, once formed against the transplanted organ, can initiate and perpetuate a cascade of immune reactions leading to the damage and potential rejection of the graft.

3.2. Mechanism of DSAs in causing graft injury and rejection

The interaction of DSAs with their specific HLA targets on the endothelial cells of the graft triggers a cascade of immunological reactions. Upon binding to these antigens, DSAs activate the classical complement pathway, leading to the generation of C4d, a split product that becomes covalently bound to the endothelium. This process is associated with endothelial cell activation, upregulation of adhesion molecules, and the release of pro-inflammatory cytokines, contributing to a local inflammatory environment. The activated endothelium facilitates the recruitment and adhesion of leukocytes, including monocytes and NK cells, which further contribute to graft injury through the release of cytotoxic mediators and inflammatory cytokines. This inflammatory response exacerbates endothelial damage, leading to vascular occlusion, ischemia, and ultimately graft dysfunction. Moreover, antibody binding to the graft endothelium can induce apoptosis or ADCC, further contributing to graft injury. In some cases, the direct pathogenic effect of DSAs can lead to thrombosis and ischemia-reperfusion injury, exacerbating the graft damage [12].

Ducreux et al. [29] presented three cases demonstrating varied outcomes of AMR in liver transplantation, depending on complement-fixing donor-specific antibody (C3dDSA) titers. Rejection episodes were associated with the presence of C3dDSA, with successful resolution in cases where C3dDSA titers decreased under treatment, while persistent high titers were linked to continued rejection and the need for re-transplantation. Interestingly, traditional DSA assays showed consistent positive results regardless of outcome, whereas C3dDSA titers fluctuated significantly during treatment and follow-up. Furthermore, Couchonnal et al. [30] investigated anti-HLA DSA in pediatric liver transplant recipients and found a 24 % prevalence of DSA, increasing steadily over time since transplantation, predominantly class II antibodies, with 79.3 % being C3dDSA. DSA presence correlated with time since transplantation and history of fulminant hepatitis, with C3dDSA and high MFI (MFI $>$ 10,000) associated with poorer long-term graft survival. Likewise, O'Leary et al. [31] evaluated the presence of IgG3 and C1q-fixing DSA in liver transplant recipients to assess their association with rejection and mortality. They concluded that patients with IgG3 DSA, both preformed and de novo, had the highest hazard ratio for death compared to those with C1q-fixing or standard DSA, while preformed C1q-fixing class II DSA was strongly correlated with early rejection.

3.3. The impact of both preformed and de novo DSAs on liver allografts

The impact of DSAs on liver allografts varies depending on whether they are preformed or de novo (Table 3). Preformed DSAs are present in the recipient's circulation before transplantation and are typically a result of previous sensitization events, such as blood transfusions, pregnancy, or prior transplantation. These antibodies can immediately bind to the donor antigens upon reperfusion of the graft, leading to hyperacute or acute AMR. Hyperacute rejection, though rare in liver transplantation due to the organ's immunotolerant nature, can lead to immediate graft loss [8,32]. Del Bello et al. [33] investigated the impact of preformed DSAs (pDSAs) on combined liver-kidney transplantation (CLKT) outcomes. They found that patients with pDSAs had lower patient survival rates compared to those without pDSAs. The presence of pDSAs with high MFI (MFI $\geq$ 5000) and having three or more pDSAs were independently associated with increased mortality. While death-censored liver graft survival was similar between groups, kidney graft survival did not significantly differ, although patients with pDSAs had a higher rate of kidney graft rejection. Overall, CLKT with pDSAs was associated with lower patient survival despite generally good outcomes for liver and kidney grafts.

De novo DSAs, on the other hand, develop after transplantation and are often associated with a gradual onset of chronic AMR. These antibodies tend to arise due to insufficient immunosuppression, immune system activation by infections, or graft damage. Chronic AMR is characterized by progressive graft fibrosis, vasculopathy, and ultimately

Table 3
Preformed and de novo DSA in liver transplantation associated AMR.

Category	Preformed DSA	De Novo DSA
Definition	Antibodies present in the recipient against donor antigens before transplantation.	Antibodies that develop against donor antigens after transplantation.
Incidence	Varies widely; less common due to pre-transplant screening and desensitization protocols.	Increasingly recognized due to improved detection methods and longer follow-up periods.
Risk Factors	Previous transplants, blood transfusions, pregnancies.	Acute rejection episodes, non-adherence to immunosuppression, certain immunosuppressive regimens.
Pathophysiology	Immediate binding to donor antigens, activating complement system and causing injury.	Gradual development; may involve B cell activation and differentiation into plasma cells.
Clinical Presentation	Can cause immediate graft dysfunction, hyperacute or acute AMR.	Often insidious, leading to chronic AMR and graft dysfunction over time.
Diagnostic Criteria	Positive crossmatch test before transplant, detection of DSA, graft dysfunction.	Detection of DSA post-transplant, graft dysfunction, histological evidence of AMR.
Management Strategies	Desensitization protocols, plasmapheresis, IVIG, rituximab.	Increased immunosuppression, plasmapheresis, IVIG, rituximab, bortezomib.
Outcomes	Higher risk of graft loss and complications if not adequately managed.	Progressive graft dysfunction, chronic AMR, increased risk of graft loss over time.
Impact on Liver Allograft	Preformed DSA can lead to immediate and severe graft damage, potentially resulting in early graft loss or dysfunction. Effective pre-transplant management is critical to mitigate this risk.	De novo DSA are associated with a more gradual but significant impact on graft function, leading to chronic damage and potentially reduced graft longevity. Their emergence post-transplant requires vigilant monitoring and potentially adjustments in immunosuppressive therapy to prevent or mitigate damage.

graft failure. The development of de novo DSAs is particularly concerning as they have been linked to poorer long-term outcomes and graft survival [7]. The differentiation between preformed and de novo DSAs is important in the management and prognostication of liver transplant recipients. While preformed DSAs necessitate immediate and aggressive intervention to prevent acute graft loss, de novo DSAs require modification of immunosuppressive therapy and close monitoring to prevent chronic rejection and graft failure. Additionally, the subclass of DSAs also plays a crucial role in determining the severity of AMR. For instance, antibodies against HLA Class II antigens are often associated with a more severe form of rejection and worse outcomes compared to those targeting HLA Class I antigens [10,11]. This difference is attributed to the distinct expression patterns and immunogenicity of these HLA classes on liver cells (Table 1) [13].

4. Clinical management of antibody-mediated rejection

The management of AMR in liver transplantation requires a multifaceted approach, involving both the prevention and treatment of acute and chronic rejection episodes. Effective strategies are crucial to mitigate the impact of AMR on graft survival and patient outcomes. Acute AMR typically necessitates rapid and aggressive treatment to prevent immediate graft loss. In contrast, chronic AMR management focuses on preserving graft function and preventing long-term complications [12]. Fig. 2 illustrates the therapeutic algorithm of AMR proposed by Montano-Loza et al. [34].

4.1. Immunosupressants

Immunosuppressants are used to prevent the production of new DSAs and minimize the immune response against the graft. Calcineurin inhibitors (CNIs), such as tacrolimus and cyclosporine, are commonly used in liver transplantation. They reduce T-cell activation and thereby decrease the production of antibodies. In details, CNIs block the phosphatase activity of calcineurin, which is essential for the activation of nuclear factor of activated T-cells (NFAT). NFAT is a transcription factor that increases the production of interleukin-2 (IL-2) and other cytokines, crucial for T-cell proliferation and activation. By inhibiting NFAT activation, CNIs reduce IL-2 production, thereby suppressing T-cell activity and the overall immune response. This mechanism also indirectly leads

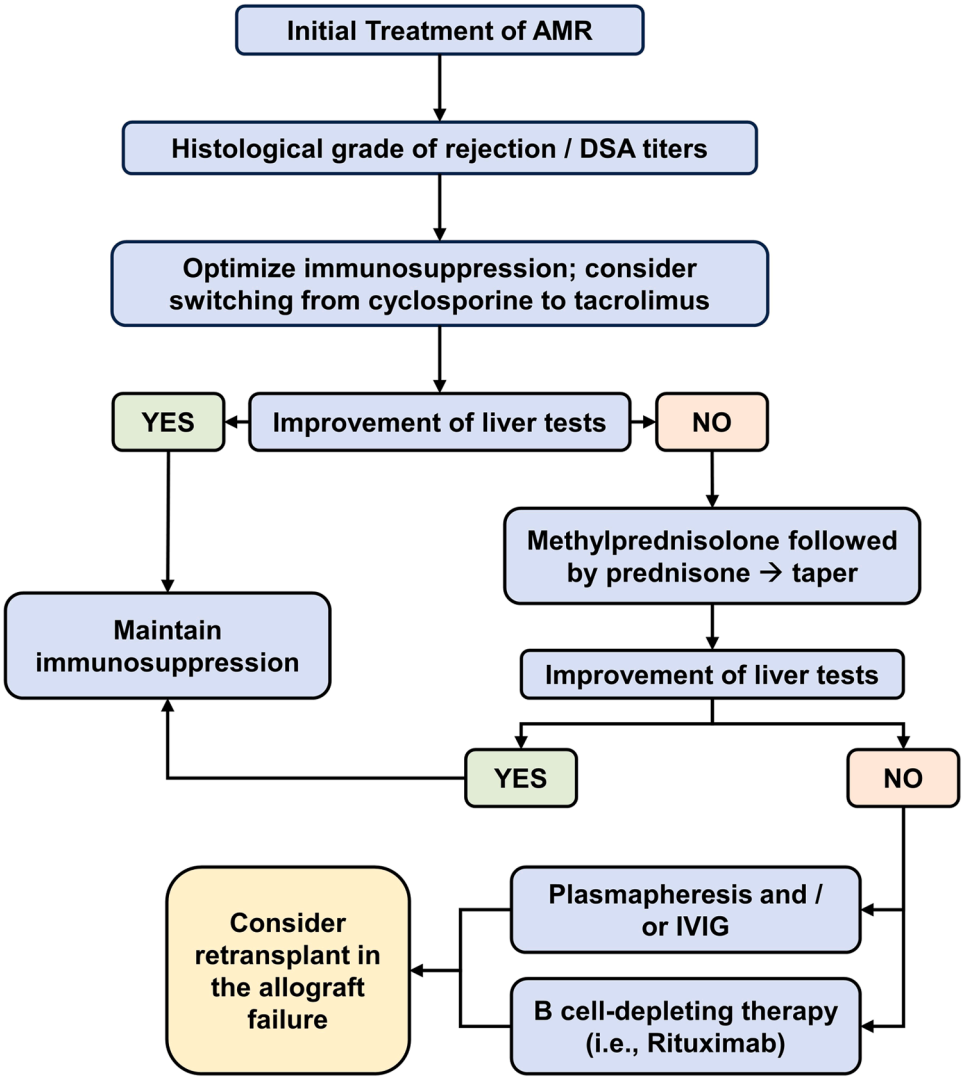

Fig. 2. Management Algorithm for AMR in Liver Transplantation. This flowchart presents a clinical decision-making pathway for the initial treatment of AMR in liver transplant recipients. It begins with the assessment of histological grade of rejection and DSA titers, followed by optimization of immunosuppression, including potential switching from cyclosporine to tacrolimus. Based on the improvement of liver tests, the algorithm guides through maintaining immunosuppression, employing corticosteroid therapy with methylprednisolone and prednisone, and considering advanced treatments such as plasmapheresis, IVIG, or B cell-depleting therapy with Rituximab in the absence of liver test improvement. The final decision point considers retransplantation in the event of allograft failure [34].

to the suppression of antibody production by B cells, as T-cell help is vital for B-cell activation and differentiation into antibody-producing plasma cells [35,36]. Nevertheless, their use must be balanced against the risk of nephrotoxicity and other side effects [37]. For instance, thrombotic microangiopathy (TMA) affects approximately 30 % of solid organ (including liver) transplant recipients and typically manifests in the context of CNI treatment. Broome et al. [38] administered eculizumab, a monoclonal antibody which binds with high affinity to C5, to treat TMA and reported good response, with no recurrent TMA or increase in infectious complications on continued eculizumab plus CNI therapy at greater than 2 years of eculizumab therapy. Bajjoka et al. [39] studied the impact of delayed initiation of CNIs on renal function in liver transplant recipients. They found that delayed CNI initiation with anti-thymocyte globulin was associated with improved renal function and less dependence on dialysis. This study provides insight into the timing and administration of CNIs in liver transplant patients, especially concerning the management of AMR and the prevention of CNI-induced nephrotoxicity. Fukudo et al. [40] investigated the pharmacodynamic properties of tacrolimus and cyclosporine in liver transplant patients, finding that while tacrolimus only partially inhibited calcineurin activity even at high concentrations, cyclosporine almost completely inhibited it. Patients experiencing nephrotoxicity had higher drug concentrations, and those with acute rejection on tacrolimus had lower drug concentrations and higher calcineurin activity, suggesting the importance of pharmacodynamic assessment alongside drug concentration monitoring for individualizing therapy with these medications. Meszaros et al. [41] conducted a retrospective study of liver transplant recipients on CNI-free immunosuppression. The study aimed to assess the impact of avoiding CNIs on de novo donor-specific HLA antibody (dnDSA) development. Their results showed that among liver transplant recipients, 30.1 % of patients on CNI-free immunosuppression developed dnDSA compared to 16 % on CNI maintenance therapy. Moreover, the cumulative incidence of dnDSA 10 years after transplant was higher in the CNI-free group (28 %) compared to the CNI group (20 %). While CNI-free regimen did not impact graft histology, dnDSAs were significantly associated with histological graft abnormalities such as significant allograft fibrosis or rejection. Meszaros et al. [42] evaluated the robustness of Predicted Indirectly ReCognizable HLA Epitopes (PIRCHE-II) score, an algorithm estimating T-cell epitope presence in mismatched HLA, in liver transplant recipients on CNI-free immunosuppression. It finds that higher PIRCHE-II scores are associated with cellular rejection, humoral rejection, and severe portal inflammation, and that both PIRCHE-II score and donor age independently predict liver graft survival in CNI-free patients, suggesting the potential of PIRCHE-II scores as predictive markers for liver allograft survival in this population.

Mycophenolate mofetil (MMF), a noncompetitive inhibitor of inosine monophosphate dehydrogenase, effectively inhibits the proliferation of B and T lymphocytes, thereby reducing the production of antibodies. It is often used in conjunction with CNIs for a synergistic effect [43]. Akamatsu et al. [44] discussed the use of MMF as an immunosuppressant in steroid-resistant rejection after liver transplantation. They reviewed clinical records of patients who underwent living donor liver transplantation (LDLT) and found that MMF was a potent and safe immunosuppressive agent for rescue therapy in patients with acute rejection after LDLT. Stewart et al. [45] conducted a randomized controlled trial of MMF monotherapy in liver transplant patients who developed renal failure associated with calcineurin-inhibitor therapy. While the trial was ultimately stopped due to organ rejection in some patients on monotherapy, this study provides insight into the potential and limitations of MMF in post-transplant immunosuppression, relevant to AMR management. Klupp et al. [46] in their study on MMF use after orthotopic liver transplantation, found that MMF was effective as an adjuvant immunosuppressive agent for rescue and maintenance therapy. Their findings suggest that MMF can be beneficial in managing acute and chronic rejections, including cases that may fall under the spectrum of AMR.

High-dose corticosteroids are often the first line of treatment in acute AMR. They are potent anti-inflammatory agents that can suppress the overall immune response. Baradaran et al. [47] described a case series of 8 adult liver transplant recipients who developed AMR, and reviewed literature on AMR in liver transplantation. They developed a stepwise protocol for managing acute, chronic, and recurrent AMR based on their experience and literature data, which included the use of corticosteroids as part of the initial treatment strategy. This underscores the significance of corticosteroids in the early management of AMR in liver transplantation. Yamazaki et al. [48] discussed the standard protocol of combined treatment with an immunosuppressant and a corticosteroid after liver transplantation to improve graft survival. The study highlights the common use of corticosteroids in conjunction with other immunosuppressive agents in the post-transplant period, underscoring their role in managing complications such as transplantation-related TMA (TA-TMA). Tisone et al. [49] investigated the effects of early immunosuppression without the use of corticosteroids on graft outcome and transplant complications. This study is relevant as it explores the potential of managing liver transplant recipients without corticosteroids, providing a comparison to the standard practice which includes corticosteroids. Ramirez et al. [50] assessed the safety and efficacy of a corticosteroid-free immunosuppressive regimen in adult orthotopic liver transplantation (OLT) recipients. This study provides valuable insights into the potential of managing liver transplant recipients without corticosteroids, which is a departure from the traditional use of steroids in post-transplant immunosuppression.

A newer class of drug, belatacept, has shown promise in managing AMR by selectively blocking T-cell activation without the nephrotoxic effects associated with CNIs [51]. Klintmalm et al. [51] reported a case where belatacept was used in treating recurrent late-onset T cell–mediated rejection/antibody-mediated rejection with de novo donor-specific antibodies in a liver transplant patient. The patient, after experiencing multiple rejection episodes and developing de novo donor-specific antibody, began treatment with belatacept 3.5 years after transplantation. This resulted in the normalization of liver tests with no further rejections. A biopsy obtained 6 years after transplantation was normal, appearing without inflammation or residual fibrosis, suggesting that belatacept may be a useful treatment approach in such cases. Klintmalm and Gunby [52] described a successful pregnancy in a liver transplant recipient on belatacept. The patient, who experienced chronic antibody-mediated rejection after her first and second liver transplantations, was started on belatacept after the second transplant with cAMR. Two years later, she became pregnant while continuing belatacept with low doses of tacrolimus, azathioprine, and steroids. Her pregnancy was uneventful, and her child was healthy. This case indicates that belatacept could have a role in specific liver transplant recipients and should be considered. LaMattina et al. [53] discussed the safety of belatacept bridging immunosuppression in hepatitis C-positive liver transplant recipients with renal dysfunction. They reported on seven liver transplant recipients with hepatitis C who received belatacept in the perioperative period due to renal dysfunction. The study suggested that belatacept with mycophenolic acid could be a safe maintenance immunosuppression regimen in this patient group and serve as an effective bridge to calcineurin inhibitor therapy. Klintmalm et al. [54] conducted a Phase II randomized study to evaluate the safety and efficacy of belatacept in de novo adult liver transplant recipients. The study found that while the proportion of patients who met the primary endpoints (composite of acute rejection, graft loss and death by month 6) was higher in the belatacept groups compared to tacrolimus groups, mean calculated glomerular filtration rate (GFR) was higher in belatacept-treated patients at one year. The study was terminated due to an increase in death and graft loss in the belatacept group, highlighting the need for further research. Finally, Hong et al. [55] investigated the efficacy of a chimeric anti-ICAM-1 monoclonal antibody, MD-3, in a rhesus macaque liver transplantation model. While conventional

immunosuppression (i.e., prednisolone, tacrolimus, and an mTOR inhibitor) led to various complications and limited graft survival, short-term therapy with MD-3 significantly prolonged liver allograft survival up to 2 years without the need for maintenance immunosuppressants, suggesting MD-3 as a promising immune-modulating agent for liver transplantation.

4.2. Plasmapheresis

Plasmapheresis is a procedure used to remove DSAs from the circulation, providing immediate reduction in antibody levels. It is particularly useful in acute AMR, often employed as a first-line therapy in conjunction with high-dose corticosteroids. Plasmapheresis is typically followed by other treatments aimed at preventing the re-synthesis of DSAs. Matsuno et al. [56] described cases of ABO-incompatible liver transplantation where patients underwent multiple perioperative plasmapheresis sessions, along with other treatments, to manage the risk of antibody-mediated humoral rejection. This study highlights the critical role of plasmapheresis in managing AMR in complex cases of ABO-incompatible transplantation. Kim et al. [57] detailed the successful use of plasmapheresis in ABO-incompatible living donor liver transplantation (LDLT). In their approach, plasmapheresis was utilized pre- and post-transplantation to maintain low levels of anti-ABO titers, significantly contributing to the prevention of AMR. Choi et al. [58] presented a case of acute AMR under the absence of donor-specific antibody (DSA) after ABO-incompatible LDLT, where plasmapheresis and intravenous immunoglobulin were used as part of the treatment. This case underscores the utility of plasmapheresis in managing AMR, even in the absence of detectable DSAs. Morioka et al. [59] reported on the successful treatment of AMR after adult ABO-incompatible liver transplantation using a combination of therapies, including plasmapheresis. This study demonstrates the effectiveness of plasmapheresis in conjunction with other treatments in resolving AMR.

Anti-HLA and ABO-incompatible DSA represent two distinct entities (Table 4). Among a few studies reporting the use of plasmapheresis to treat anti-HLA DSA, Salazar et al. [60] studied the potential role of therapeutic plasma exchange (TPE) in liver transplant patients with AMR due to anti-HLA DSAs. Eight liver transplant patients with potential AMR and positive anti-HLA DSAs (7 patient had Class II DSAs, including 6 patients with antibodies directed against the DQ antigens, while 4 patients had Class I DSAs) underwent TPE, leading to a rapid reduction in DSA MFI in some cases. Antibodies of Class I and those with lower MFI tended to diminish following two to three TPE sessions, while Class II antibodies targeting DQ antigens with elevated pre-TPE MFI persisted despite repeated TPE sessions performed regularly.

4.3. Intravenous immunoglobulin (IVIG)

IVIG is used both in the treatment of acute AMR and as a maintenance therapy in chronic AMR. It provides passive immunity and has immunomodulatory effects, such as neutralizing circulating DSAs, inhibiting complement activation, and modulating B-cell function. The use of IVIG is often combined with plasmapheresis to enhance the removal of DSAs and provide immunomodulation [14]. Baradaran et al. [47] described a case series of 8 adult liver transplant recipients who developed AMR. The treatment strategies for acute, chronic, and recurrent AMR were evaluated, including the use of IVIG, which played a significant role in the initial treatment strategy alongside corticosteroids and plasma exchange. A case study of AMR under the absence of DSA after ABO-incompatible liver transplantation also described the use of IVIG alongside plasmapheresis and steroid pulse therapy. The study illustrated how IVIG can be an integral part of the treatment regimen for AMR, even in complex cases where DSAs are not detectable [58].

Table 4
Comparison between anti-HLA and ABO-incompatible DSA.

Feature	Anti-HLA DSA	ABO-incompatible DSA
Origin	Response to mismatched human leukocyte antigen.	Response to blood group antigens not present in the recipient.
Mechanism	T cell-mediated response to foreign HLA.	Antibody-mediated against ABO blood group antigens.
Impact	Can lead to acute and chronic rejection.	Mainly affects early post-transplant period; manageable with desensitization.
Management	Immunosuppression, monitoring, desensitization protocols.	Pre-transplant plasmapheresis, IVIG, immunosuppression.

4.4. Proteasome inhibitors and others

Bortezomib, a proteasome inhibitor, has emerged as a therapeutic option in AMR, particularly for cases resistant to conventional therapies. Bortezomib leads to plasma cell apoptosis, reducing the production of DSAs. Its use has been associated with improved graft function and a reduction in DSA levels in liver transplant recipients with AMR [12]. Paterno et al. [12] reviewed three cases of AMR in ABO-compatible liver transplant recipients characterized by severe acute rejection resistant to steroids and antithymocyte globulin, histologic evidence of plasma cell infiltrates, C4d positivity, and high serum anti-HLA donor-specific antibodies. All three patients were treated with bortezomib, a proteasome inhibitor effective in depleting plasma cells. After treatment, all patients had improved or normal liver function tests, resolution of C4d deposition, and a significant decline in their HLA donor-specific antibodies. This suggests the effectiveness of bortezomib in treating AMR in liver transplant recipients. Lee et al. [61] reported on the use of bortezomib to treat acute humoral rejection (AHR) after liver transplantation. Patients with AHR who were treated with steroid pulses, rituximab, and plasmapheresis, and then additionally with bortezomib, showed significant improvement and survival, compared to those who did not receive bortezomib. This indicates the potential of bortezomib as an effective strategy for treating AHR after liver transplantation.

Rituximab, a monoclonal antibody against CD20 on B cells, is used in some cases of AMR. By depleting B cells, rituximab reduces the production of new DSAs. It is often used in combination with other therapies, such as plasmapheresis and IVIG, particularly in cases of refractory AMR or when there is a high risk of severe AMR due to the presence of high levels of DSAs [62]. Baradaran et al. [47] underscored the use of rituximab as a crucial component of treatment of AMR in adult liver transplant recipients. Rituximab, alongside corticosteroids, plasma exchange, and IVIG, was started as early as possible if no improvement in liver enzymes/bilirubin was observed during the initial treatment strategy. A nationwide French study performed by Dumortier et al. [63] aimed to investigate the treatment outcomes of liver transplant recipients with AMR who received B-cell targeting agents. The study included 44 patients treated from 2008 to 2020, with AMR classified as acute or chronic. The main treatment combination was plasma exchange/rituximab/IVIG. Patient and graft survival rates at 1, 5, and 10 years post-treatment were 77 %, 55.9 %, and 55.9 %, and 69.5 %, 47.0 %, and 47.0 %, respectively, with initial total bilirubin levels significantly associated with patient and graft survival. Additionally, DSA became undetectable in a subset of patients after treatment.

On a whole, treatment decisions are based on several factors, including the severity of rejection, the levels and specificities of DSAs, the patient's overall health, and the risk of adverse effects from therapies. Monitoring of DSA levels and graft function is essential during and after treatment to assess the response to therapy and adjust the treatment plan as needed.

5. Special considerations in liver transplantation

AMR in liver transplantation exhibits distinct characteristics compared to other solid organ transplants, such as kidney or heart transplants. These differences are largely attributed to the liver's unique

immunological properties and its role in the body. AMR is less common and often less severe in liver transplants than in kidney or heart transplants. This reduced incidence and severity are partly due to the liver's intrinsic immunotolerant nature, which enables it to better resist immunologic attack. Consequently, AMR in liver transplant recipients is often more manageable and less likely to lead to immediate graft loss [12]. Next, the diagnosis of AMR in liver transplantation is more complex due to the liver's immunological profile. Classic diagnostic markers of AMR, such as C4d deposition, are not as consistently present in liver transplants as they are in kidney or heart transplants. Additionally, the clinical presentation of liver AMR can be more subtle and less specific, often overlapping with other post-transplant complications [14]. Furthermore, liver transplant recipients often respond differently to treatments for AMR. For instance, the liver's ability to regenerate and repair itself can sometimes compensate for the damage caused by AMR, allowing for a better prognosis even after an AMR episode. This regenerative capacity is not seen in organs like the kidney or heart.

The liver's unique immunological characteristics also play a significant role in its resistance to DSA-mediated injury. The liver is exposed to various antigens from the gut through the portal circulation, necessitating a high level of immune tolerance to prevent constant immune activation. This natural tolerogenic environment of the liver extends to transplanted organs, making it less susceptible to aggressive immune responses, including those mediated by DSAs. The liver also has a remarkable ability to regenerate and repair itself, which contributes to its resilience against immunological and other forms of injury. This regenerative property is a significant factor in the liver's ability to withstand episodes of AMR, as it can often recover from damage that would be irreversible in other organs. Additionally, the liver's unique dual blood supply, receiving blood from both the hepatic artery and the portal vein, contributes to its distinct microenvironment. This dual supply may dilute the concentration of harmful antibodies and immune cells, reducing the impact of an immune attack. Additionally, the liver's microenvironment, rich in immunomodulatory cells like Kupffer cells and regulatory T cells, contributes to its overall immune tolerance. Next, the expression of HLAs in the liver is different from other organs. The lower and more variable expression of HLA molecules, especially HLA class II, on hepatocytes compared to cells in other organs, reduces the likelihood of antibody binding and subsequent immune activation. Moreover, the liver can release soluble HLA molecules into the circulation, which may act as decoys to bind circulating DSAs, thereby reducing the likelihood of these antibodies binding to and damaging the liver graft. At last, liver endothelial cells exhibit unique characteristics that may contribute to the organ's resistance to antibody-mediated damage. These cells have a higher capacity for regeneration and repair, and their response to injury is different from endothelial cells in other organs [64–68].

Pregnancy in liver transplant recipients represents a unique immunological scenario that can influence the risk of developing DSA and AMR. During pregnancy, the maternal immune system undergoes significant adaptations to tolerate the semi-allogeneic fetus, which involves a complex interplay of immune tolerance mechanisms. The successful progression of pregnancies involves a delicate balance between developing tolerance to the semi-allogeneic fetus and maintaining the capacity to generate protective immunity against infections, which can be transmitted to the fetus and neonate. Preserving humoral immunity during pregnancy may inadvertently generate memory B cells and antibodies specific to the fetus, which could pose risks for subsequent organ transplants. However, despite these challenges, pregnancies can still occur, indicating robust mechanisms at the maternal-fetal interface [69]. These same mechanisms may alter the recipient's immune response to the transplanted liver. On one hand, pregnancy might induce a more tolerant immune state, potentially reducing the risk of AMR. On the other hand, the exposure to paternal antigens through the fetus can lead to the generation of DSAs, especially if these antigens are similar to those present on the transplanted organ. The development of DSAs during or after pregnancy can increase the risk of AMR, leading to graft dysfunction or loss. Moreover, the immunomodulatory effects of pregnancy may mask early signs of AMR, complicating diagnosis and timely intervention. Dumortier et al. [70] conducted a retrospective study aimed to evaluate the impact of pregnancy on the development of DSA and their consequences in young female liver transplant recipients. Among 73 patients studied, the incidence of de novo DSA was 42.5 %, with a majority being anti-class II antibodies, particularly anti-DQ. Pregnancy history and younger age at transplantation were significantly associated with de novo DSA development. Furthermore, patients with de novo DSA, especially those with a history of pregnancy, had a higher risk of antibody-mediated rejection. Thus, while pregnancy after liver transplantation is increasingly common and can be safely managed with careful monitoring, it necessitates vigilant surveillance for the development of DSAs and AMR, to mitigate potential adverse outcomes for both the graft and the recipient.

6. Emerging research and future directions

A notable area of emerging research involves the analysis of gene expression changes in renal allografts exposed to DSAs during simultaneous liver-kidney transplantation. A study highlighted the intriguing phenomenon where simultaneous liver transplantation appears to confer a protective effect on renal allografts against DSA-mediated damage. This study observed a shift in gene expression patterns in the kidney away from pro-inflammatory responses towards tissue preservation in the presence of liver transplantation. This research suggests that the liver may play a role in modulating the immune response against the kidney in the presence of DSAs. The liver's unique immunological properties, such as its tolerogenic environment and ability to produce immunomodulatory factors, could be responsible for this protective effect. This finding opens new avenues for research into how simultaneous liver transplantation could be used to mitigate the effects of DSAs in other organ transplants and improve overall graft survival and function [71,72].

The long-term impact of DSAs and AMR on liver allografts remains a critical area of investigation. Recent studies have focused on understanding how DSAs contribute to chronic graft dysfunction and failure. It is becoming increasingly clear that while the liver may show resistance to acute antibody-mediated damage, chronic exposure to DSAs can lead to progressive graft fibrosis, arteriopathy, and a gradual decline in liver function. Research is being conducted to delineate the mechanisms through which DSAs exert their long-term deleterious effects on the liver. This includes studying the impact of DSAs on hepatic endothelial cells, stellate cells, and the extracellular matrix, all of which play roles in fibrosis development. Additionally, the role of complement activation and the recruitment of inflammatory cells in response to DSA binding are areas of active investigation. Emerging biomarkers are being identified to predict the development of AMR and its long-term impact. These biomarkers could help in early identification and stratification of patients at high risk for AMR, leading to tailored immunosuppressive therapies. The use of advanced molecular techniques, such as transcriptomics and proteomics, is also enhancing the understanding of the molecular pathways involved in DSA-mediated liver injury.

Potential future directions include: First, the identification of specific molecular pathways involved in DSA-mediated liver injury opens the door for the development of targeted therapies. These could include monoclonal antibodies or small molecule inhibitors that specifically block the harmful effects of DSAs on the liver graft. Second, utilizing genetic and molecular profiling of transplant recipients to predict their risk of developing AMR and tailor immunosuppressive therapy accordingly. Third, for patients with pre-existing DSAs, refining desensitization protocols to reduce antibody levels pre-transplant and improve graft outcomes. Fourth, enhanced monitoring of the immune response post-transplant, including regular assessment of DSA levels and graft function, to detect early signs of AMR and intervene promptly. Finally,

further research into the liver's ability to modulate immune responses could provide insights into new strategies to prevent AMR, not only in liver transplants but also in other types of organ transplants.

7. Summary

The current understanding of AMR in liver transplantation has evolved significantly, offering deeper insights into the complexities and challenges it presents. AMR, driven predominantly by DSAs, poses a significant risk to graft survival and patient outcomes. These antibodies target specific antigens on the donor liver, triggering a cascade of immunological reactions that can lead to graft injury and failure. A key aspect of AMR in liver transplantation is its distinctive nature compared to other organ transplants. The liver's unique immunological environment, characterized by a higher degree of tolerance and regenerative capacity, often results in a less severe manifestation of AMR. This intrinsic resistance of the liver to DSA-mediated injury, however, does not negate the potential for significant long-term impacts, particularly in the case of chronic AMR, where ongoing exposure to DSAs can lead to gradual graft dysfunction. The management of AMR involves a combination of strategies, including the optimization of immunosuppressive therapy, the use of plasmapheresis, intravenous immunoglobulin, and, in some resistant cases, proteasome inhibitors like bortezomib. Emerging research, particularly in the realm of gene expression changes in renal allografts during simultaneous liver-kidney transplantation, has provided valuable insights into the liver's potential protective role against AMR. Despite advancements in understanding and managing AMR, several challenges remain. The need for further research is evident, especially in developing more specific diagnostic markers, understanding the long-term impacts of DSAs on liver allografts, and tailoring individualized treatment strategies. Future directions in research and clinical practice should focus on refining desensitization protocols, enhancing immunomonitoring techniques, and exploring novel therapeutic targets to mitigate the effects of DSAs.

Human and animal rights

The authors declare that the work described has not involved experimentation on humans or animals.

Informed consent and patient details

The authors declare that the work described does not involve patients or volunteers.

Author contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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