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New Potential Serological and Tissue Predictive and Diagnostic Markers in Management of Transplanted Livers

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Backgroud

Liver transplantation is currently a treatment of choice in patients with end-stage liver disease. Life expectancy of patients after transplantation is getting longer and the quality of life is getting better. This is due to more effective and safer therapy, regular check-ups and core-needle biopsies to monitor the condition of the organ. We want patients to be able to live with the same graft as long as possible, and at the same time we are not able to prevent all phenomena that damage it. The most serious and common pathologies include acute cellular rejection, fibrosis, and chronic rejection. Recently, humoral rejection has also been officially recognized as potentially occurring in the liver, which for a long time was considered an immunologically privileged organ. Studies are constantly being carried out on new markers to diagnose, differentiate and predict a worse prognosis of allograft survival. The aim of the paper is to present, based on the latest literature reports, immunohistochemical and serological markers that can potentially be used in the diagnosis of lesions damaging the transplanted liver. Components of complement, apoptosis process exponents and immune checkpoint inhibitors were discussed, with particular emphasis on their role in core-needle biopsies of transplanted livers.

Keywords: Liver transplantation; M30; PDL1; C4d; C3d; Allograft rejection; Fibrosis

Abbreviations: ACR: Acute Cellular Rejection; CR: Chronic Rejection; CK-18: Cytokeratin 18; KC: Kupffer Cells

Introduction

Organ transplantation is the only way to survive for many patients. Thanks to more and more modern surgical techniques and more effective, targeted therapies, life after transplantation is getting longer and its quality is getting better. The liver is one of the most frequently transplanted solid organs in the world, after the kidneys. More livers are transplanted each year (Figure 1). According to poltransplant [1] data, in 2022, 334 livers from deceased donors and 28 liver fragments from living donors were transplanted in Poland. Unfortunately, the number of people waiting for a liver transplant is still very high (in December last year it was 145), and the number of donors is insufficient. Therefore, it is of great importance that patients can live with the same allograft as long as possible. Research is constantly being conducted to search for new diagnostic and predictive markers to help control and treat changes that may cause damage to the organ. The most common causes of allograft loss include acute cellular rejection (ACR), chronic rejection (CR), organ fibrosis and, more recently, officially recognized by the Banff Working Group, humoral rejection (AMR) [2-6]. Herein, we provide an overview of the current knowledge and research on immunohistochemical and serological markers that can potentially be used in the diagnosis of lesions damaging the transplanted liver. Components of complement, apoptosis process exponents and immune checkpoint inhibitors were discussed. Core needle biopsies remain the gold standard in the diagnosis of liver transplant diseases. Most hospitals perform protocol biopsies, which is why in this study we focused mainly on markers that can be determined by immunohistochemistry and thus be used in everyday practice.

Role of Comliment Components: C4d, C3d and C1q

The complement system is a series of proteins that are activated in a cascade by classical, alternative or lectin pathways. It plays an important role in our body, maintaining its immunity

and complementing the role of antibodies. It is classified as non-specific immunity. Complement proteins are produced by monocytes and hepatocytes and are initially inactive. It is only after the appearance of foreign antigens that they are activated. In transplanted organs, the assessment of complement components is studied in the context of humoral rejection. In the literature, the most data relate to the use of C4d, C3d and C1q [7-10]. For years, the liver has been considered an immunologically privileged organ, which is why research on AMR was conducted mainly on the kidneys and hearts. However, it has been officially recognized for some time that the liver can also be damaged by the immune mechanism for various reasons, such as relapse of AIH or insufficient immunosuppression. The Banff working group [2] therefore created criteria in which it is specified what characteristics are necessary to recognize AMR. Among them, diffuse C4d deposition of microvasculature in ABO-compatibile tissues is listed. O'Leary et al. [10] proved that sinusoidal C4d staining pattern was also related to allograft injury in proximity to non-HLA autoantibody binding. On the other hand, Kovandova et al. [7] suggested a higher occurrence of acute AMR in recipients with preformed complement-binding DSA to HLA Class I antigens and chronic AMR associated with de novo-produced antibodies against HLA Class II antigens. Correlation was also found between de novo-formed C1q + and C3d+-binding antibodies to HLA Class II antigens and the development of chronic AMR. Lee H et al. [11] proved that C1q+/C3d+ de novo DSA was associated with more C4d deposition in allograft tissue which may be considered as a potential new marker in AMR diagnosis. Additionally, Couchonnal et al. [12] revealed tha C3d-binding DSA and high MFI (>10,000) were associated with significant poorer long-term graft survival. These studies, although still scarce, not only prove that AMR occurs in the liver, but also emphasize the possibility of using complement components in the diagnosis of humoral rejection and the prediction of graft damage. Antibodies against components C4d, C3d and C1q are available and can be determined by immunohistochemistry, so they are new, promising markers that can potentially be used in daily liver biopsy diagnostics.

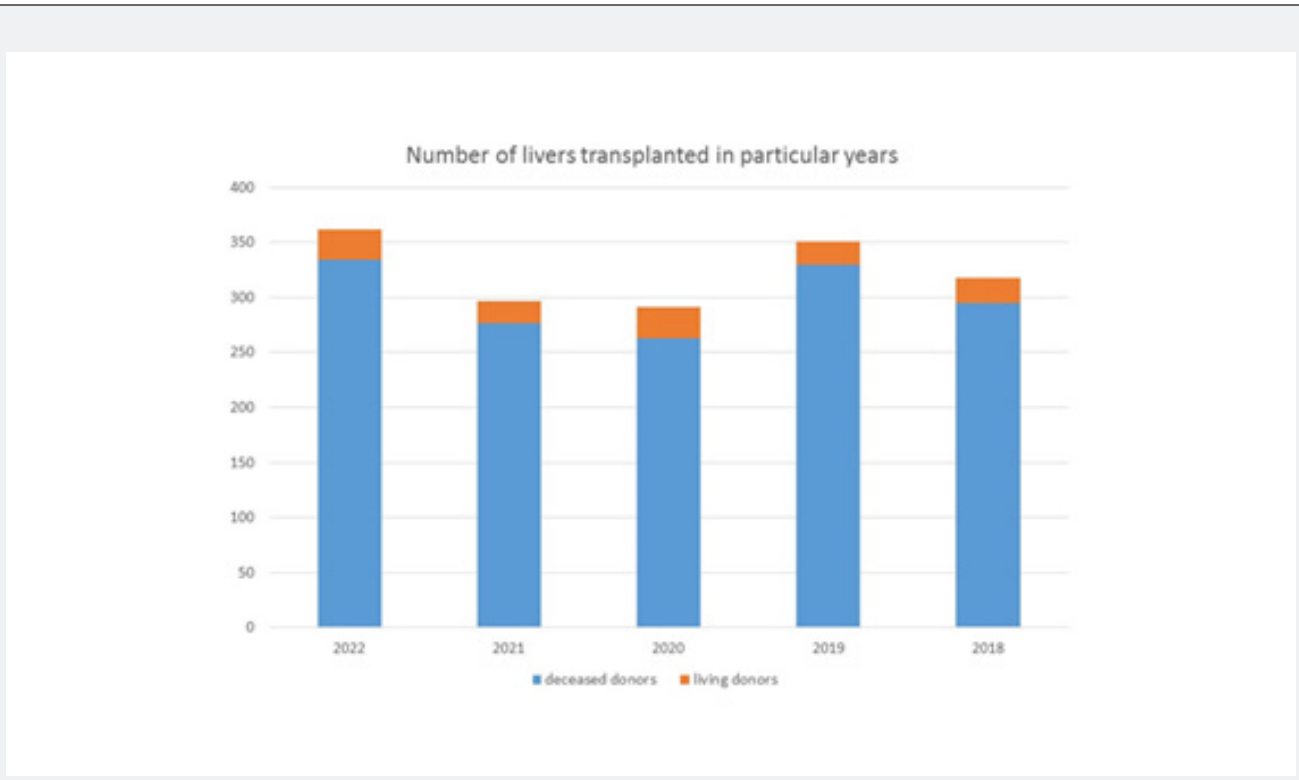

Figure 1: The graph shows the number of livers transplanted from deceased donors and organ fragments from living donors over 5 years (from 2018 to 2022).

Cytokeratin 18 (marker of apoptosis) and its Relation to Post Transplant Liver Injury

Cytokeratin 18 (CK18) which is an intermediate filament protein, belongs to the cytokeratin acidic type I group (CK9-CK12) and is primarily expressed in single-layered epithelial tissues of such organs as liver, kidney, breast, prostate or gastrointestinal tract [13-15]. It was also shown to play a role in apoptosis. M30 is used as a non-invasive test for the detection of apoptosis [16] of epithelially derived cells. To date, several studies have been conducted on the role of M30 in livers, however, very little applies to transplanted organs. In a few studies conducted [17-19]

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elevated serum M30 levels have been proven to reflect the degree of liver dysfunction. Waidmann et al. [20] in his study conducted on three hundred and thirty-one patients, additionally stated that epithelial cell death reflected by M65EpiDeath serum levels is an indicator for the severity of cirrhosis. The study by Reis et al. [21] is one of the very few that has analyzed the usefulness of the M30 in the diagnosis of ACR. Researchers have proven that the antibody can be useful in differentiating rejection from HCV reinfection. In their analysis, they compared tissue and serological expression of M30 in different groups of patients. In both ACR and HCV reinfection, M30 was elevated but more so in viral infection. On the other hand, the latest study conducted by Macía et al. [22] proved that an increase in serum concentrations of K18 fragments (M30) was observed in the two cases with HCV recurrence however, it was not seen in ACR patients. Data on the utility of M30 in differentiating between HCV infection and ACR are inconclusive, therefore we believe that further studies should be carried out on larger groups of patients, as it would be very useful to validate a new marker to differentiate between infections and ACR. Lim et al. [23] who studied the effect of immunosuppressive drugs on fibrosis and apoptosis proved that immunosuppressive drug regimens employed after liver transplantation enhance hepatocyte cell death and may thus contribute to the increased liver fibrosis. It seems that M30 may be potentially useful in the everyday diagnosis of protocol biopsies when it comes to predicting organ fibrosis. Nevertheless, further studies in larger groups of patients are necessary.

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors are the proteins which are expressed on different types of immune system cells, such as T cells and they help to keep immune responses from being too strong. Examples of checkpoint proteins found on T cells include PD-1/PD-L1 and CTLA-4/B7-1/B7-2. PD1 is predominantly expressed on activated peripheral T cells and B cells, as well as on APCs [24,25]. Moreover, it is constitutively expressed by a variety of parenchymal cells, including liver. In the liver, PDL1 is expressed by sinusoidal endothelial cells (LSECs), Kupffer Cells (KC), stellate cells and hepatocytes [26] therefore, it can be particularly interesting and useful in the diagnosis of transplanted livers. Especially, that there are targeted therapies commercially available which are less toxic than conventional immunosuppression and could potentially be used in transplant patients. The fear of their use is the possibility of patients developing ACR. DeLeon et al [27] and Friend et al [28]. suggested a link between PDL1 and ACR, however, the studied groups were very small. Lipson et al. [29] presented a case report of A 57-year-old woman who underwent kidney transplantation and developed cutaneous squamous-cell carcinoma because of the applied therapy. Thus, she was administered anti-PD-1 drugs and unfortunately, she had ACR and finally has lost her graft. Based on the observation, authors speculated that PD-1 pathway agonists could be useful in the prevention of allograft rejection. Munker et al. [30] also described 14 cases of liver transplant patients treated with immune checkpoint inhibitors, all developed ACR. The available literature reports are based on small groups of patients and mostly concern the consequences of the treatment used. Little is known about the effect of PDL1 expression in biopsies of transplant patients who receive conventional immunosuppression. PDL1 may be a promising new marker predictive of ACR, and patients with elevated PDL1 expression should be monitored particularly closely. Further research in this direction is necessary.

Conclusion

Liver transplantation is currently the only effective treatment for patients with liver failure. The waiting list of donors is getting longer, and recipients are missing, which is why it is so important to keep the graft in the best condition for as long as possible. Core-needle biopsy of the liver remains the gold standard in the diagnosis of transplant patients. In the above review, based on the latest available literature reports, we presented potential diagnostic and predictive markers that may be useful in everyday practice and in the management of patients after liver transplantation.

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