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The role of complement activation in autoimmune liver disease

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ABSTRACT

Introduction: The complement system, an essential part of the innate immune system, is involved in various autoimmune diseases. Activation of the complement system by autoantibodies results in immune activation and tissue damage. At the moment little is known about the role of the complement system in autoimmune liver disease, including primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH). Since inhibition of the complement system is currently being tested in several autoimmune diseases as a therapeutic option, its role in autoimmune liver disease requires further clarification.

Methods: A review of the literature was performed on studies investigating complement activation in PBC, PSC and AIH. Since data on AIH were lacking immunohistochemical staining for IgG, C1q, C3d, C4d and C5b9 was performed on liver tissue of nine AIH patients, two healthy controls and one positive control (acute liver failure caused by paracetamol intoxication).

Results: Immunohistochemical analysis in AIH revealed increased production of C3 and C4 by hepatocytes. Despite a strong staining for IgG in the immune infiltrate in AIH, C3d, C4d and C5b9 deposition was only present in one AIH patient and the deposition was restricted to the interface between portal tracts and liver parenchyma. No deposition was found in all other AIH patients or healthy controls.

Literature review showed raised plasma C3 and C4 levels in AIH, PBC and PSC patients compared to healthy controls. For PBC and PSC no complement depositions at the bile ducts were reported.

Conclusion and discussion: Although complement is involved in various autoimmune diseases, the role of complement in autoimmune liver disease seems limited. Therefore it is unlikely that complement inhibition will become a novel treatment option for these diseases.

1. Introduction

The complement system is an essential part of the innate immune system and well known for its role in the immune response against infections [1]. It is also involved in instructing the adaptive immune response and several physiological processes such as clearance of immune complexes and apoptotic cells, neovascularization, nerve pruning and tissue regeneration. Unfortunately the powerful immune effector mechanisms of complement can also be directed against the host tissue in the setting of autoimmunity or transplantation and contribute to tissue damage. Examples of autoimmune diseases where complement is involved in tissue damage are rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and ANCA associated vasculitis (AAV) [2–5]. With the successful introduction of C5 inhibitor Eculizumab for atypical hemolytic uremic syndrome and paroxysmal nocturnal hemoglobinuria, it became clear that the complement system can be targeted in vivo [6,7]. This spurred the development of a wide array of complement inhibitors blocking several steps in the complement cascade [8]. Complement inhibition was thought to be particularly effective in autoimmune diseases. The use of complement blocking therapeutics will

Abbreviations: AIH, autoimmune hepatitis; AMA, antimitochondrial antibodies; ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibodies; IVIG, intravenous immunoglobulins; MAC, membrane attack complex; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; SLE, systemic lupus erythematosus; SMA, smooth muscle antibodies; UDCA, ursodeoxycholic acid

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also lead to a better understanding of the relative contribution of complement activation in the various disease processes. However, even if complement is involved in a disease process complement inhibitory treatment will always be initiated after the onset of clinically overt symptoms, which may render it less successful than earlier treatment. It is clear that complement plays an important, yet complex, role in autoimmune diseases.

While complement is important in several autoimmune diseases, little is known about the role of complement in autoimmune liver disease.

1.1. Complement system and the liver

The complement system is a highly preserved part of the innate immune system. The complement cascade can be activated through three pathways: the classical pathway, the alternative pathway and the lectin pathway. C1q is the first protein of the classical pathway and can recognise immunoglobulins bound to an antigen [9]. After binding of C1q, C3 and C4 become activated finally resulting in formation of the membrane attack complex (MAC) consisting of C5b9. The complement system can also be activated by the lectin pathway after binding of microbial surface molecules to mannose binding lectin (MBL). In the alternative pathway a C3 tick-over leads to conversion of C3 and C5 without conversion of C4. The MAC, by damage to the cell membrane, can cause lysis of cells and tissue damage. Moreover, opsonization by binding of C3b facilitates phagocytosis by macrophages. Complement activation fragments C5a and C3a are anaphylatoxins and can recruit additional immune cells to the location of complement activation. C5 can also stimulate hepatocyte proliferation after liver damage and promote liver regeneration [10]. The role of complement in liver regeneration and transplantation has been reviewed recently [10].

Whether complement is involved in a disease process or not is often indirectly deduced based on decreased plasma levels of complement proteins as a consequence of consumption, the presence of activated complement fragments in the circulation or the presence of activated complement fragments in the target tissues on histology [11]. Plasma levels of complement proteins are determined by production and consumption by activation. Production of most complement factors occurs mainly in the liver. In the liver C3 and C4 are produced by hepatocytes. Kupffer cells, the liver resident macrophages, produce C1q [12]. Production of complement proteins can be decreased in liver cirrhosis, as is the case with other proteins like albumin [13]. Systemic inflammation can increase complement protein production by the liver and can thereby cause increased plasma complement levels [14]. Excessive activation can cause decreased plasma levels due to consumption, as seen in SLE [2].

Even if signs of complement activation are present it still needs to be determined whether the complement activation is contributing to inflammation and tissue damage or if the complement activation is beneficial by orchestration waste disposal and tissue regeneration.

1.2. Autoimmune diseases of the liver

The liver is an organ with a unique immunotolerance compared to other organs. It is continuously exposed to bacterial products from the intestines, and without immunotolerance the liver would be constantly inflamed [15]. Another manifestation of the immunotolerant nature of the liver is in the context of transplantation: rejection is less prevalent in liver transplantation than in kidney or heart transplantation patients. Some reports suggest that up to 25% of the liver transplant patients can be weaned from immunosuppression [16]. A transplanted liver can also lead to partial operational tolerance for other transplanted organs, like a simultaneously transplanted kidney [17].

Despite the liver being a tolerogenic organ, autoimmune diseases of the liver do exist. The three main distinctive autoimmune diseases of the liver are autoimmune hepatitis (AIH), primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC).

1.3. Autoimmune hepatitis

Autoimmune hepatitis (AIH) is characterized by a lymphoplasmacytic infiltrate, interface hepatitis, raised total IgG and autoantibodies [18]. It has a predominance in females and can present at all ages [19,20]. Type 1 AIH is the most prevalent and is characterized by smooth muscle antibodies (SMA) and antinuclear antibodies (ANA). Type 2 AIH is characterized by the highly specific liver-kidney-microsome-1 (LKM-1) antibodies and presents more often in childhood [21]. Treatment is the same for both types of AIH and consists of prednisone and azathioprine. As second-line therapy mycophenolate mofetil is frequently used [22]. Treatment leads to a decrease in liver enzymes and IgG and normalization in about 80% of the patients [23], but this can take several years [19]. For the patients not rapidly reaching remission and patients with significant side-effects of treatment with prednisone and azathioprine, there is a clinical need for new therapies and new therapeutic targets.

Due to the presence of autoantibodies and high IgG levels formation of antibody-antigen complexes in the liver can be expected in AIH. These antibody-antigen complexes might then activate complement through the classical pathway leading to the formation of MAC, causing damage to the hepatocytes. At the moment no studies regarding the role of complement in adult AIH patients have been published.

The aim of this study was to assess the complement cascade in AIH patients using immunohistochemistry and perform a literature review on the role of complement in autoimmune liver disease.

2. Methods

2.1. Immunohistochemical analysis in AIH

AIH patients with at least probable type I AIH according to the simplified criteria with available liver biopsy at diagnosis were eligible for inclusion [24]. Two tissue samples of healthy liver parenchyma obtained of liver resections for colorectal metastasis were used as normal control tissue. One tissue sample of acute liver failure after paracetamol intoxication was used as positive control, as due to the excessive liver damage and necrosis the complement system was expected to be activated. All AIH patients gave informed consent for the use of their data and biopsy material. As the tissue of the positive and healthy controls were used anonymously no informed consent was needed.

Formalin fixed, paraffin embedded sections of liver parenchyma were stained using the following antibodies IgG, C1q, C3d, C4d and C5b9. Staining was performed according to laboratory standard procedures. Sections were deparaffined with xylene and subsequently rehydrated with graded alcohol solutions. 0.3% hydroperoxide (H2O2) was used to block endogenous peroxidase activity. After antigen retrieval the tissue was incubated with the primary antibody overnight at room temperature. Rabbit and mouse Envision were used as secondary antibody. Detailed information regarding used antibodies and staining procedure used are given in Appendix A. Visual assessment was used as quantification method and all stained tissue was scored for degree and location of the staining.

2.2. Literature review autoimmune liver disease

Pubmed and Embase were searched using the terms: autoimmune hepatitis, primary sclerosing cholangitis, primary biliary cirrhosis, primary biliary cholangitis, complement, complement system, C4d, C5b9 and combinations of these terms. Titles and abstracts of articles were read. If articles discussed complement activation in autoimmune liver disease the full article was read. Results were summarized in a review.

Table 1
Clinical characteristics of AIH patients.

	Age	Gender	IgG level in g/L	ALT	Initial treatment	Response
1	16	Female	34.1	926	Prednison + AZT	Remission < 12 months
2	24	Female	21.9	668	Prednison + AZT	Remission < 12 months
3	53	Female	19.1	259	Prednison +6TG	Remission < 6 months
4	54	Male	20.5	94	Budesonide	Remission < 6 months
5	54	Male	39	391	Prednison + AZT	Remission < 6 months
6	59	Male	14.3	418	Prednison	Incomplete response
7	59	Female	18.7	48	Budesonide + AZT	Remission < 6 months
8	64	Female	20.1	189	Prednison + AZT	Remission < 6 months
9	68	Male	29.3	1314	Prednison	Remission < 12 months

Used abbreviations: IgG immunoglobulin G; ALT alanine aminotransferase; AZT azathioprine; 6TG 6-thioguanine.

3. Results

3.1. Immunohistochemical analysis in AIH

To provide insight into the possible role of complement activation in type I AIH a immunohistochemical analysis of complement proteins was performed. Nine treatment naïve type 1 AIH liver biopsies were included in this study. Median age at diagnosis was 54 years (range: 16–68 years). Further baseline characteristics can be found in Table 1. IgG staining was present in the infiltrate of all patients with increased intensity in plasma cells. Liver sinusoids were positive for IgG in AIH patients and in healthy controls (Fig. 1).

C1q staining was present in Kupffer cells in the sinusoids, in AIH patients and healthy controls. Intracellular staining of C3 and C4 was detected using antibodies specific to the C3d and C4d fragments of the C3 and C4 proteins. Staining was more intense in patients with AIH compared to healthy controls. In the patient with acute liver failure due to paracetamol intoxication intense C3d and C4d deposition with the same localization as the C5b9 deposition was seen. In patients with AIH C3d and C4d staining did not correspond to C5b9 staining (Fig. 1). C5b9 staining, a marker of complement activation, was only present in 1 of the 9 AIH patients and in none of the healthy controls (Table 2). In this patient the C5b9 staining was present in the extracellular matrix on the interface between infiltrate and hepatocytes (Fig. 2).

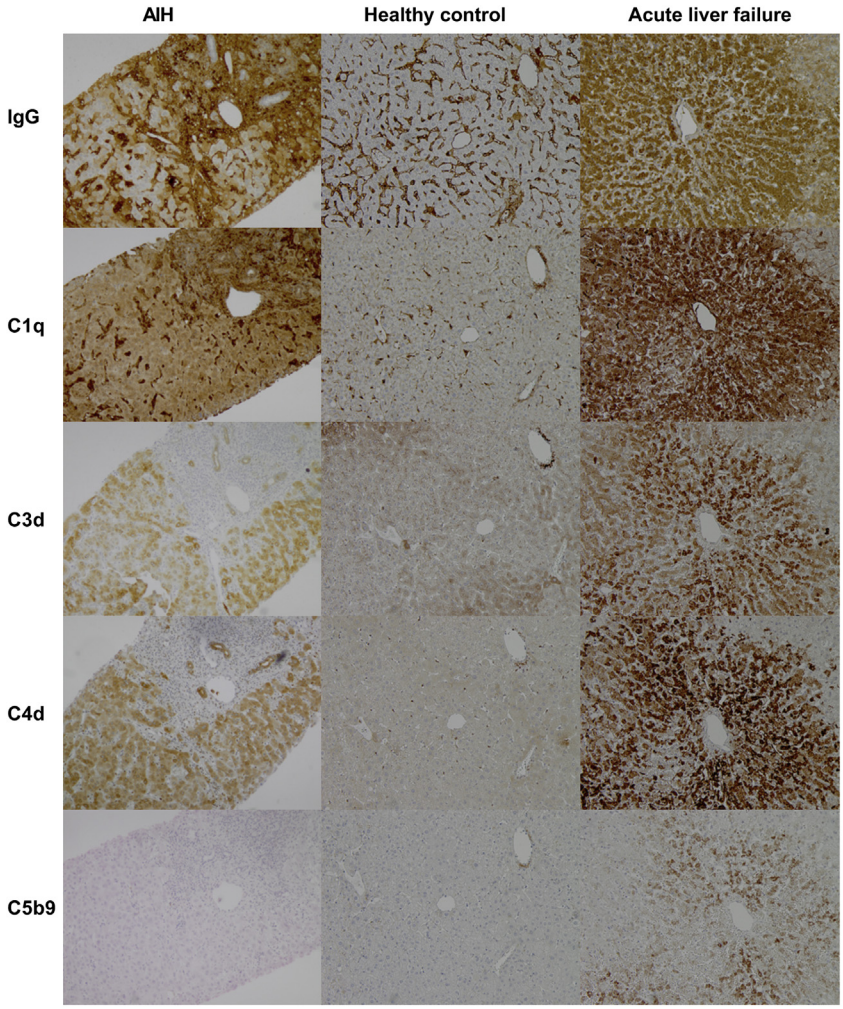

Fig. 1. Results of complement cascade in AIH, healthy control and acute liver failure. Staining for IgG, C1q, C3d, C4d and C5b9 are shown.

Table 2
Results of immunohistochemical stainings.

	Patient	1	2	3	4	5	6	7	8	9	HC	HC	ALF
IgG	Infiltrate	+	+	+	+	+	+	+	+	+	NA	NA	NA
	Sinusoids	+	+	+	+	+	−	+	+	+	+	+	−
C1q	Kupffer cells	+	+	+	+	+	+	+	+	+	+	+	+ −
	Deposition	−	−	+	−	−	−	−	−	−	−	−	+ +
C3d	Hepatocytes	+	+	+	+ −	+	+	+	+	+	−	−	−
	Deposition	−	−	+	−	−	−	−	−	−	−	−	+ +
C4d	Hepatocytes	+	+	+	+ −	+	+	+	+ −	+	−	−	−
	Deposition	−	−	+	−	−	−	−	−	−	−	−	+ +
C5b9	Deposition	−	NA[a]	+	−	−	−	+ −[b]	−	−	−	−	+ +

Used abbreviations: HC healthy control; ALF acute liver failure; NA not applicable.
[a] For this staining not enough tissue was available for reliable evaluation.
[b] Traces of C5b9 were present in the immune infiltrate.

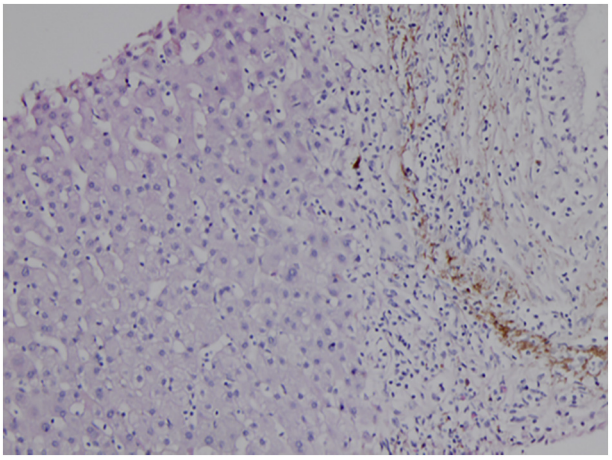

Fig. 2. C5b9 deposition in an AIH patient.

3.2. Literature review AIH

Current literature regarding the role of complement in AIH is very limited. C3 levels were elevated in an AIH mouse model and in plasma of AIH patients compared to healthy humans and mice controls respectively [25]. One report mentioned that on immunohistochemistry C4d deposition was present in 83% of the patients with paediatric AIH. Depositions were reported to be present in the immune infiltrate and extended to the periportal sinusoids in some patients. The same frequency of C4d deposition was found in patients with hepatitis B [26]. Little to no C5b9 deposition was seen in another study in paediatric AIH [27]. No reports discussing the role of complement in adult AIH patients were found in the literature review.

3.3. Literature review on PBC

Primary biliary cholangitis (PBC) is an autoimmune disease of the liver which targets the intralobular bile ducts. The incidence is higher in women (1.9 per 100.000) than in man (0.3 per 100.000) [28]. The disease is characterized by anti-mitochondrial antibodies (AMA) (present in > 90% of the patients) and high serum IgM [29]. Pyruvate dehydrogenase complex (PDC)-E2 subunit, a protein normally expressed in the mitochondria but which can be present on cholangiocytes, is the main target of the antimitochondrial antibodies in PBC [30]. Continuous bile duct inflammation leads to ductopenia (bile duct loss), cholestasis and development of fibrosis and liver cirrhosis.

Treatment with ursodeoxycholic acid (UDCA) can decrease cholestasis, prevent progression to cirrhosis and improve survival [31,32]. Obeticholic acid and bezafibrate can be used as second line therapy in patients with an inadequate response to UDCA [33,34].

The role of complement in PBC has been described in a limited number of studies. The presence of AMA with a target on the cholangiocytes could result in formation of autoantibody-antigen complexes, triggering the classical pathway of the complement system. While in the prototype autoimmune disease SLE often decreased levels of circulating C3 and C4 are detected, in plasma of patients with PBC increased C3 and C4 levels compared to healthy controls were found in all studies [2,35–37]. These increased levels were also present in non-autoimmune forms of hepatitis (alcoholic and viral). A likely explanation is increased production by the liver due to the inflammation, the acute phase reaction. In cirrhotic PBC patients C3 and C4 levels decreased, probably reflecting the reduced protein synthetic capacity of the cirrhotic liver [36].Levels of activated complement fragments including C3a, C4a and C5b9, were not elevated in the plasma of PBC patients compared to healthy women [36].

On immunohistochemistry no C3d and C5b9 deposition was seen at the bile ducts of PBC patients [38]. No evidence of complement activation could be found in the plasma complement protein levels, activated fragments in the plasma or on immunohistochemistry. In conclusion although the disease is characterized by anti-mitochondrial antibodies, the classical complement pathway does not seem to be activated and does not seem to importantly contribute to the damage to cholangiocytes in PBC.

3.4. Literature review on PSC

Primary sclerosing cholangitis (PSC) is a progressive disease with development of strictures in large and small bile ducts. The incidence is estimated to be 0.5 per 100.000. The disease affects males twice as often as females. Co-existent inflammatory bowel disease is present in 70% of the patients [39]. Bile duct strictures cause chronic cholestasis and recurrent cholangitis, which both can lead to fibrosis and liver cirrhosis. Patients have an almost 400 fold increased risk for cholangiocarcinoma compared to the general population [39]. No specific autoantibodies are present in PSC, although antineutrophil cytoplasmic antibodies (ANCA), ANA and SMA can be positive.

At the moment liver transplantation is the only curative treatment option, although UDCA treatment can improve alkaline phosphatase levels in some of the patients [40–42]. Several trials with different medication have been and are being conducted, but at the moment none has been proven effective yet in reducing disease progression and improvement of long-term outcome [43]. There is a great need for new therapeutic options. If complement inhibition, by example eculizumab, could reduce bile duct damage, it might be a therapeutic option preventing progression in PSC.

Only a limited number of studies have been performed on the role of complement in PSC. Plasma C3 levels were elevated in PSC patients compared to healthy controls [44]. Since the same elevation of C3 levels was present in choledocholithiasis patients compared to healthy controls, inflammation could be an explanation for the raised C3 levels

in PSC. No difference was found in C4 levels between PSC and healthy controls [44].

Levels of activated complement fragments, C3d and C4d, were elevated in PSC patients compared to healthy controls and patients with extrahepatic obstructive cholestasis [44]. However, in another study, on immunohistochemistry no C3d and C5b9 depositions could be found in the bile ducts of PSC patients [38].

In conclusion, the available data in PSC patients indicates that if any, the role of the complement system seems limited in this disease.

4. Conclusion and discussion

To our knowledge the present study is the first study to assess the complete complement cascade in adult type I AIH patients and healthy controls. Due to the presence of autoantibodies, plasma cells and IgG, activation of the classical pathway of the complement system seemed probable. C1q staining was present, but restricted to Kupffer cells. C3d and C4d staining was more intense in hepatocytes of AIH patients compared to healthy controls. This could be explained by the increased production of complement in liver due to inflammation, as previously reported [25,35–37,44]. Indeed, C3d and C4d staining was not related to C5b9 staining and the staining was cytoplasmatic, supporting the hypothesis that the positivity is more likely the result of increased synthesis than of deposition. The anti-C4d antibody used in our studies binds to C4d, which is a part of the C4 molecule and not an neoepitope. The antibody detecting C5b9 binds to a neoepitope that is not produced by the liver and is a true marker of complement activation. However, in the current AIH patients C5b9 deposition was only present in one of the nine AIH patients, mostly at the interface. Autoantibodies in most AIH patients did not result in the formation of the membrane attack complex, so that complement does not seem to play a role as the cause of the liver damage in AIH.

IgG staining was positive in the immune infiltrates and in the sinusoids. Staining of sinusoids in AIH and healthy control, could be explained by the Fc-gamma IIb receptor physiologically present on sinusoids in order to bind and take up small IgG immune complexes to promote immunotolerance in the liver [43,44].

Complement has an important role in several autoimmune diseases including rheumatoid arthritis, SLE and ANCA associated vasculitis [11]. Although the presence of plasma cells, autoantibodies and IgG are hallmarks of AIH, the data presented here indicate that activation of the classical pathway of the complement system does not seem to be of importance in the pathophysiology of AIH. Despite the fact that in ANCA associated vasculitis, anti-MPO or anti-PR3 antibodies are present, the complement activation is reported to occur mainly through the alternative pathway [5]. If complement is activated through the alternative pathway no IgG, C1q and C4d depositions are expected but C3d and C5b9 depositions in target tissue are expected. In AIH we found increased production of C3 but no depositions of C3d and C5b9, indicating also a limited role for the alternative pathway in the pathophysiology of AIH. Hepatic injury does not seem to be caused by autoantibodies and complement activation. Alternatively autoreactive B-cells producing cytokines or autoreactive T-cells may be the cause of the hepatic injury. Further understanding of the pathophysiological mechanism of liver damage in AIH is important for development of new therapies.

Current therapies for AIH, including prednisolone, azathioprine and mycophenolate mofetil, are targeting T-cells reducing T-cell activation and proliferation [45]. While only around 1% of AIH patients are treatment-refractory, in around 20% of the patients complete remission is not reached within a few years due to partial ineffectiveness or intolerance to the treatment. This, in combination with the long term side-effects of prednisone including osteoporosis and diabetes mellitus, highlights the need for new treatment strategies in AIH.

The field of drugs inhibiting the complement system is rapidly expanding and includes very prominently rheumatic and autoimmune disease [8,11,46]. C5 inhibitor Eculizumab is an effective therapy for some autoimmune diseases and has been approved for atypical hemolytic uremic syndrome and paroxysmal nocturnal hemoglobinuria [6,7]. Studies are being conducted in myasthenia gravis, membranoproliferative glomerular nephritis and neuromyelitis optica to broaden the indications for Eculizumab [8]. For ANCA associated vasculitis a C5a receptor antagonist (CCX168) is being tested in clinical trials [5]. A C3 activation inhibitor is tested for membranous nephropathy [8]. Since in AIH we did not observe evidence to suggest that the autoantibodies activated the complement system in the liver, eculizumab is unlikely to become a new therapy for AIH. Moreover, inhibition of C5 could even be detrimental as it might limit liver regeneration and increase disease severity.

Intravenous immunoglobulins (IVIG) or plasmapheresis can reduce the concentration of auto-antibodies and are effective treatment options in several autoimmune diseases including Guillain-Barré syndrome, immune thrombocytopenia and myasthenia gravis [47–49]. Although autoantibodies are frequently present in autoimmune liver disease, IVIG and plasmapheresis are unlikely to be effective treatment options for these diseases, as the activation of the classical complement pathway is very limited.

B-cell targeted therapies like rituximab could be effective if liver damage is partially caused by cytokines produced by autoreactive B-cells instead of by auto-antibodies. Small case series on the sometimes successful use of rituximab in AIH have been published [50].

Literature review into the role of complement in PBC and PSC showed increased levels of complements proteins in plasma, with inflammation as the most likely explanation. No activation of the classical or alternative complement pathway was present on liver histology. Based on these results the role of the complement system in the biliary damage seen in PSC and PBC seems limited as well, and targeting the complement system is not likely to be an new therapeutic option in these diseases.

In some other liver diseases the complement system does seem to fulfill an important role. For instance, in antibody mediated rejection after liver transplantation C4d deposition on liver biopsy is one of the diagnostic criteria [51]. Polymorphisms in the lectin-pathway of complement activation can increase the risk for infections after liver transplantation [52,53]. In non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) C3d and C5b9 deposition around steatotic hepatocytes were present in up to 50% of the patients [54]. However, even if complement is activated, the causative role of the complement system in the pathophysiology of these diseases still needs to be further investigated since damaged host tissue can also activate complement and complement is important for waste disposal and liver regeneration [10].

In conclusion, although the complement system is involved in various autoimmune diseases and some liver diseases, the role of complement in AIH, PBC and PSC seems limited. Based on this limited role, therapies aiming at complement inhibition, like eculizumab, IVIG and plasmapheresis are unlikely to become new therapeutic options in these diseases.

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Appendix A. supplementary data

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