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FIELD OF VISION

B cell depletion in treating primary biliary cirrhosis: Pros and cons

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Abstract

Primary biliary cirrhosis (PBC) is a progressive autoimmune liver disease of unknown etiology that affects almost exclusively women. Ursodeoxycholic acid (UDCA) is currently the only approved drug by Food and Drug Administration for patients with PBC. Although the precise pathogenesis of PBC remains unclear, it has been postulated that many cell populations, including B cells, are involved in the ongoing inflammatory process, which implicates, not surprisingly, a potential therapeutic target of depleting B cell to treat this disorder. Rituximab is a chimeric anti-CD20 monoclonal antibody that has been approved for the treatment of lymphoma and some autoimmune diseases such as rheumatoid arthritis. Whether it is effective in the treatment of PBC has not been evaluated. Recently, Tsuda *et al*[1] demonstrated that B cell depletion with rituximab significantly reduced the number of anti-mitochondrial antibodies (AMA)-producing B cells, AMA titers, the plasma levels of immunoglobulins (IgA, IgM and IgG) as well as serum alkaline phosphatase, and it was well tolerated by all the treated patients with no serious adverse events. This observation provides a novel treatment option for the patients with PBC who have incomplete response to UDCA.

Key words: Primary biliary cirrhosis; Rituximab; B cell depletion; Anti-mitochondrial antibodies

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INVITED COMMENTARY ON HOT ARTICLES

We read with interest the recently published paper by Tsuda *et al*[1] describing an open-label study of rituximab treatment in six patients with primary biliary cirrhosis (PBC) who had an incomplete response to ursodeoxycholic acid (UDCA). We believe this observation provides a novel treatment option for the patients with PBC who have incomplete response to UDCA and would recommend it to the readers.

PBC is a cholestatic liver disease characterized by serological findings of anti-mitochondrial antibodies (AMA) and pathological non-suppurative destruction of biliary epithelial cells[2,3]. PBC may lead to liver failure or

even death. However, UDCA is the only Food and Drug Administration-approved drug and its efficacy is far from satisfaction in a large proportion of patients[4]. Recent studies have demonstrated that B cells are involved in immune mechanisms of the pathogenesis of non-suppurative cholangitis and the destruction of bile ducts in PBC[5-7]. These findings implicate a potential treatment efficacy of B cell depletion in patients with PBC[8-10].

Rituximab is a mouse-human chimeric anti-CD20 monoclonal antibody designed for B cell depletion in human. Its safety and efficacy as a single therapeutic agent has been demonstrated initially in the treatment of non-Hodgkin B cell lymphoma and chronic lymphocytic leukemia[11,12]. In addition, there were also clinical trials demonstrating that rituximab significantly induced clinical remission in a number of autoimmune diseases such as granulomatosis with polyangiitis, microscopic polyangiitis, and rheumatoid arthritis (RA)[13-15].

In the field of PBC, there were several studies in murine models investigating the treatment effect of B-cell depletion. Dhirapong *et al*[8] reported that B cell-depleted mice developed more aggressive PBC-like liver disease with increased infiltration of inflammatory cells around the damaged bile canaliculi in portal areas. Whereas Moritoki *et al*[16] showed that anti-CD20 therapy had no effect on adult dominant-negative transforming growth factor (TGF)-βRⅡ mice (age range: 20-22 wk to 36-38 wk), and it neither alleviated liver inflammation nor exacerbated colitis. But in younger dominant-negative TGF-βRⅡ mice aged 4-6 wk, anti-CD20 treatment significantly alleviated the liver inflammation and reduced the bile duct damage, suggesting that anti-CD20 treatment might be beneficial for patients with PBC of early disease stage.

Tsuda *et al*[1] used rituximab to treat six patients with PBC who had suboptimal biochemical response to UDCA. After B-cell depletion, they observed a reduction in the number of AMA-producing B cells, AMA titers, the plasma levels of immunoglobulins (IgA, IgM and IgG) as well as serum alkaline phosphatase (ALP) at week 24. As the levels of immunoglobulins, AMA titers and ALP returned to baseline levels at week 36, repeated anti-CD20 treatment was suggested to maintain the treatment effect. The necessity of repeated treatment with rituximab was also demonstrated by recent clinical trials on other autoimmune diseases such as RA and systemic lupus erythematosus, and this treatment strategy did not lead to permanent remission[17-19]. It is noteworthy that there was also study reporting that repeated treatment with rituximab could potentially compromise host protective immune response and might cause severe infection in RA patients[20]. In Tsuda's study on PBC patients[1], two patients (2/6, 33.3%) experienced reactivation of varicella zoster and upper respiratory infection after the first infusion of rituximab. Though it might be arbitrary to ascribe these infections exclusively to rituximab infusion, infections remain the major concern when treating patients with anti-CD20 antibodies. In PBC and other autoimmune diseases, it remains controversial if repeated anti-CD20 treatment is beneficial in terms of safety and efficacy, and if so, when is the optimal time for repeated therapy.

A high titer of serum AMA can be detected in 83%-95% of patients with PBC[21]. Most studies have shown that there is no correlation between the level of serum AMA and the severity of PBC, and AMAs positivity does not predict the patient's response to treatment with UDCA[22-25]. However, there were also some studies suggesting that AMA-positive PBC patients had more severe bile duct destruction than PBC patients with negative AMA[26]. AMAs could induce the caspase activation of the biliary epithelial cells and subsequent cell death and bile duct damage[27]. Tsuda *et al*[1] found that in the PBC patients, together with the number of peripheral B cells, the plasma levels of immunoglobulins and ALP, the level of AMA also decreased after treatment with rituximab and returned to baseline levels 36 wk after cessation of rituximab. They suggested that the depletion of the AMA-secreting plasma cells by rituximab could potentially reduce hyperactive B cell immune response and lead to the amelioration of the bile duct destruction in PBC, even though it is too early to jump to the conclusion that the level of serologic AMAs is a predicting factor for the efficacy of rituximab therapy.

Although B cell is one of the pivotal inflammatory cells in the immunopathogenesis of PBC, its precise role and the adverse events associated with B cell-depletion remain unclear[28]. A study reported that the morbidity of severe side effects of B cell-depletion is low but not insignificant[29]. There were also studies reporting new onset cases of inflammatory bowl disease that may be attributed to the B cell depletion in up to 40% patients with PBC[30,31]. In dominant negative TGF-βRⅡ mice, Moritoki *et al*[16] found that anti-CD20 treatment induced up-regulation of interleukin 6, which could lead to exacerbation of colitis. Paradoxically, in some studies on murine models, B cells might play a protective role in PBC and B cell depletion exacerbated the biliary pathology and caused more aggressive PBC-like liver diseases[8,26,28]. There was also a case report showing that, after rituximab treatment, PBC developed with a high AMAs titer, intrahepatic cholestasis and steatorrhea in a RA patient[32], though it is not exactly understood if PBC was caused by immuno-mechanism underlying RA or by rituximab itself. In Tsuda's study on PBC patients[1], however, there was no evaluation of inflammatory bowel diseases and biliary pathology during follow-up. It should also be noted that, in their study, the number of enrolled patients and the duration of follow-up were not enough and the level of other biochemical parameters and PBC-40 scores remained unaltered. The long-term efficacy and prognosis could be the most important concern of rituximab treatment.

In conclusion, the study by Tsuda *et al*[1] suggests that B cell depletion with rituximab is potentially a promising treatment regimen for the PBC patients who do not have good response to UDCA. B cell depletion merits further investigation in human PBC to illuminate its safety and efficacy.

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