Treat-to-Target in Autoimmune Hepatitis: How Far To Go?

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Abstract

Autoimmune hepatitis is a chronic inflammatory liver disease characterized by good response to immunosuppressive therapy, and the treatment is typically long-term or even life-long. The principle of treat-to-target is characterized by closely monitoring and disease-activity-guided therapeutic adaption. To date, the concept has been successfully applied to many chronic diseases, whereas it is not yet applied to the treatment decision in autoimmune hepatitis. The aim of this review is to summarize the current difficulties of the treatment decisions and the treatment targets in AIH. The treatment of autoimmune hepatitis is discussed from the point of treat-to-target strategy which improves outcomes of patients with chronic diseases. To achieve the treat-to-target in autoimmune hepatitis treatment, accurate evaluation of disease activities and stepwise medication choices are key things to go.

Keywords: Autoimmune hepatitis; Treat-to-target strategy; Disease activity; Therapy; Outcome

Introduction

Over the past 50 years, the therapeutic strategy for some of the common chronic diseases has developed from a symptom-based to a target-based approach, under the influence of evidence that such approaches achieve superior outcomes [1,2]. Autoimmune hepatitis (AIH) is a chronic progressive autoimmune liver disease with unknown etiology, characterized by hyperimmunoglobulinemia, the presence of autoantibodies in serum, interface hepatitis on liver histology [3]. The biochemical features include elevated transaminases and IgG levels, which are the principal indicators of immunosuppressive therapies [4,5]. In general, AIH patients have good responses to immunosuppressive therapy. However, some patients cannot achieve complete remission and some patients develop to cirrhosis, even liver failure and death [6,7].

The major goal of treat-to-target strategy is to improve outcomes. Treat-to-target must have these three things: i) a target, ii) a way to measure if the target has been hit or achieved, iii) available treatment options which make it possible to hit the target. To date, the concept of treat-to-target in AIH treatment decision is still lacking. Accurate evaluation of disease activities and the stepwise medication choices are key points to achieve the treat-to-target in the treatment decision of AIH.

The favorable outcome of treat-to-target strategy

Compared with the traditional treatment, treat-to-target strategy is characterized by closely monitoring, timely therapeutic adaptation based on the disease activity, and emphasizing early strengthened and individualized treatment. The treat-to-target strategy has been defined to improve outcomes for a reduction in the risk of organ damage [8]. It has become a consensus in many chronic diseases such as diabetes, hypertension and dyslipidemia [9-11]. In recent years, treat-to-target strategy is widely applied to autoimmune diseases, especially rheumatoid arthritis (RA) [12].

In 2010, an international task force of rheumatologists recommended that treating RA to target is the core strategy. The aim of treatment was defined as remission with lower disease activity [13]. The way to measure the disease activities and remission includes several evaluation criteria: Disease Activity Score (DAS) 28, Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI) [14]. Regular follow-up (every 1-3 months during active period) with stepwise therapeutic adaptation to reach the desired target within 3 to a maximum of 6 months was recommended, and follow-up examinations ought to be composed of composite measures of disease activities [15].

Abundant evidences showed that targeted therapy significantly improve the outcomes of patients [16-20]. In Grigor’s trial, 111 patients with active RA were randomly assigned to either intensive management or routine care. Patients of the intensive group were monitored closely, had a higher rate of good response and remission, and the mean fall in disease activity score was greater in the intensive group than in the routine group [21]. Besides, in the management of hypertension, targeting suitable values for systolic and diastolic blood pressure reduce the risks for cardiovascular diseases and benefit long-term outcomes [22]. Likewise, in the management of diabetes, targeting specific values for blood-glucose, monitored closely, has been proved to yield major improvements in long-term prognosis [23].

The difficulty of the treatment decisions in AIH

2015 EASL Clinical Practice Guidelines recommend that all patients with active AIH (elevated transaminases >3 normal values and hepatitis activity index (HAI)>4/18) should be treated, which requires induction of remission and prolonged maintenance therapy [3]. The treatment aim is to obtain complete remission and prevent further progression of liver disease. The clinically feasible target is to obtain complete normalization

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of serum transaminases and IgG levels (biochemical remission). Treatment should be continued for at least 3 years and for at least 24 months after biochemical remission and empiric salvage therapy can be introduced to patients refractory to the standard treatment [3,24].

However, clinicians often confront with difficulties in making decisions: when to start corticosteroid therapy, whether the treatment is effective and what the treatment target for a particular patient is. Clinically, the normalization of serum transaminases and IgG levels is considered as the treatment target (biochemical remission). However, those are not always consistent with histological remission [25]. Exploring new reliable noninvasive biomarkers is overwhelming to finely monitor disease activities and progressive fibrosis. In addition, the stepwise therapeutic adaptation for refractory AIH patients is still under investigation, especially for patients who are not tolerant to standard treatment or incomplete response.

Czaja reviewed the difficult treatment decisions in AIH and provided some bases for making sound therapeutic judgments, emphasizing that the established therapies should be further improved [26]. Similar with many other chronic diseases, the concept of treat-to-target strategy should be performed in the management of AIH for better outcomes of patients. In conclusion, the difficulties in the treatment decisions of AIH are due to the variations of clinical phenotypes, the blur of treatment end points, the limited monitoring indicators of disease activities and the lack of stepwise choices of medications [27-29].

The treatment targets in AIH

The histological target: The target of treatment in AIH patients is to achieve histological remission. Liver biopsy is recognized as the golden standard to assess the histology activity index (HAI) [30]. EASL Clinical Practice Guidelines recommend all patients with active AIH (HAI ≥ 4/18) should be treated and the treatment should be maintained long enough to reach histological remission [3].

The Ishak system is the most widely used scoring system to evaluate the HAI. It provides consecutive scores for well-defined lesions within 4 separate categories, including piecemeal necrosis, confluent necrosis, focal (spotty) lytic necrosis, apoptosis, focal inflammation and portal inflammation [31]. The Ishak system is funded based on viral hepatitis, mainly describing the intensities of inflammatory activities and structural progression of the liver diseases. However, in the histology of AIH, interface hepatitis, plasma cells infiltration, rosette and emperipolesis are typical histological features [32,33]. A recent study suggests that emperipolesis and rosette formation are superior histological predictors of AIH than classic hallmark features, such as interface hepatitis and plasma cells infiltration [34]. Although the Ishak system is the one recommended by EASL Clinical Practice Guidelines, to accurately describe the histological activities, a scoring system specific to AIH might be needed.

Other systems for grading and staging the lesions of chronic hepatitis include Knodell system, Scheuer system, and French META VIR system. Each of them has their merits and limitation. The Knodell system is the first scoring system for histopathological evaluation of liver. The scoring system is composed of three categories for necroinflammation and one for fibrosis. It gives greater weight to perportal and bridging necrosis, but did not separately score the inflammatory activities and cirrhosis [35]. The Scheuer system gives the portal and lobular components of activity equal weight, and groups the perportal and portal lesions into a single category [36]. The French META VIR system, combined ratings for focal lobular necrosis, portal inflammation, piecemeal necrosis, and bridging necrosis, was also used in some literatures nowadays [37].

The histological scoring system is the golden standard to evaluate the disease activities and define the target of histological remission or activation. We recognize that chronic hepatitis shares many histological features with AIH, but current scoring systems are mainly funded based on viral hepatitis, which gives greater weight to the necroinflammation rather than the immune activities [31]. Histochemical and immunohistochemical analysis may provide more immunological information to AIH patients in the future.

The serological target: The clinical treatment target in patients with AIH is to obtain normalization of transaminases and IgG [3,38]. Early studies found the improvement of serum aminotransferase levels to be less than twice the UNL in conjunction with normalization of serum bilirubin and γ-globulin abnormalities is achievable in most patients, which can be the clinical standard for evaluating the primary treatment end point [39,40]. Researchers found complete biochemical remission on adequate immunosuppressive treatment can improve the prognosis of AIH [41].

Moreover, the rapidity of biochemical responses in AIH patients is also associated with the outcomes. Czaja retrospectively analyzed 146 patients with AIH. He found patients who responded within 12 months had lower frequencies of progression to cirrhosis and requirement for liver transplantation than patients who responded more than 36 months [42]. Wang et al retrospectively evaluated 115 patients with AIH, including 81 patients whose aminotransferase levels had normalized within 3 months (Group 1) and 34 patients whose levels remained abnormal (Group 2). The 2 years remission rate was 86% for Group 1 vs. 27% for Group 2 and normalization of serum aminotransferase within 3 months of starting treatment has predictive value for complete biochemical remission at 2 years [43]. Furthermore, Czaja reported that patients aged ≥ 60 years responded more rapidly to treatment than patients aged <40 years, and they were characterized by a high frequency of HLA DRB1*04, therefore age and HLA status may relate to the rapidity of response [42,44]. Taken together, the rapidity of achieving the treatment target has some prognostic significance.

The monitoring of disease activities in AIH

The measurement of the disease activities for timely therapeutic adaption is pivotal for treat-to-target. Liver biopsy is not suitable for regular monitoring due to the invasiveness and unavoidable sampling error [30,45,46]. In clinical practice, levels of transaminases and IgG were indices to measure the disease activities [47]. Luth et al. compared serological parameters (ALT, AST, IgG, γ-globulin) with corresponding liver histology. They discovered that all serum parameters were significantly related with histology activity, and the presence of both elevated ALT and IgG were significantly associated with high inflammatory activity (99% sensitivity) [48]. However, histological improvement usually lags behind clinical and laboratory improvement by 3-8 months [27]. Czaja et al. found about half of the patients with normal serum parameters still showed residual histologic activity, and normalized serum parameters identified patients at lower risk of fibrosis progression [40].

Recently, new biomarkers and non-invasive inflammatory scoring systems have been studied to assess disease activities of AIH. Soluble CD163, a specific marker of macrophage activation, was markedly elevated in the acute phase of AIH serum [49]. Gutkowski et al. reported that 9 variables including albumin, IgG, prothrombin index, total bilirubin, ALT, AST, ALP, γ-GGT and CRP were significantly correlated with HAI. He proposed a new noninvasive inflammatory score system for patients with AIH based on AST, albumin, total bilirubin and CRP.
of which the sensitivity and specificity for recognizing patients with significant inflammatory activities were 100% and 83% respectively [30].

Similar to other chronic liver diseases, of which several noninvasive models based on demographic and biochemical parameters have been developed to evaluate the severity of inflammation and fibrosis [51-54]. More reliable evaluating systems of disease activities need to be further explored in AIH.

The stepwise medication choice in the treat-to-target strategy

The disease-activity-guided therapeutic choice is vital in the treat-to-target strategy. For instance, 2015 American College of Rheumatology (ACR) recommends that the medication choice strategy for RA is determined by the course, high-risk conditions and disease activities, in which the disease activity is the major consideration. Regardless of disease activities, disease modifying antirheumatic drug (DMARDs) monotherapy (MTX preferred) is the priority. If the disease activity remains moderate or high despite DMARDs monotherapy, a combination of DMARDs or biological agents is needed. If the disease flares or the disease activity remains moderate to high despite combination DMARDs or biological agents, short-term and low dose glucocorticoid therapy should also be added [15]. Overall, the medication choice for RA includes three steps mainly based on the disease activity which should be evaluated every one to three months, and therefore timely step up the therapy for patients who can’t reach the target.

For the treatment of AIH, EASL Clinical Practice Guidelines recommend that prednisone (0.5-1 mg/kg/day) as initial therapy followed by the addition of azathioprine (1-2 mg/kg) after two weeks is the first line treatment [3]. Steroid which may have a more rapid action than immunosuppressive agents is usually administered during the induction-remission phase. For patients who do not respond or are intolerant to standard treatment, second-line drugs including budesonide, mycophenolate mofetil, the calcineurin inhibitors (cyclosporine and tacrolimus) and biologicals (rituximab and infliximab) have been used as alternative choice in AIH [55-59]. Mycophenolate mofetil is the most widely used second-line drug. It has been proved to be safe and effective particularly to patients intolerant to azathoprine or even to those with cirrhosis, but has the side effect of being teratogenic [60-62].

Overall, the evidence of second-line drugs in AIH treatment is mainly based on small, retrospective case series [59,63]. The available evidence does not allow a recommendation as to which of the possible second-line drugs should be preferred [36]. The experience of stepwise medication choices for patients with incomplete response still lacks robust evidence [64].

Summary and Future Perspectives

AIH still remains a major therapeutic challenge, because it is a relatively rare disease and is highly individualized. The treat-to-target strategy which improves outcomes of patients has been successfully used in many chronic diseases such as hypertension, diabetes and RA, and it provides new perspectives in the management of AIH. The treatment target of AIH is to minimize the hepatic inflammation, hence reducing the risk of progressive fibrosis and development of cirrhosis. We have the conclusion that achieving clinical and biochemical remission in the early stage and controlling the disease activity as far as possible is benefit to the prognosis. Currently, the way to monitor disease activities is still limited and the disease-activity-guided therapeutic adaption still lacks robust evidence.

In the future, we would like to personalize each patient's individual treatment plan based on a comprehensive assessment of the disease activity, and to adjust the treatment plan. Quantitative scoring systems evaluating histological inflammatory activity and fibrosis degree are likely to gain a wider use in the clinical practice. Such tailored treatment and monitoring plan will hopefully result a further improvement in prognosis and reduction of cirrhosis in patients with AIH.

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