Journal of
AIDS & Clinical Research
ISSN: 2155-6113

Zhang et al., J AIDS Clin Res 2017, 8:11
DOI: 10.4172/2155-6113.1000743

Review Article Open Access

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

Hongxia Zhang[1], Liping Guo[1], Wei Wei[2], Bangmao Wang[1] and Lu Zhou[1]*

[1]Department of Gastroenterology and Hepatology, Tianjin Medical University General Hospital, Tianjin Medical University, Tianjin, P.R. China
[2]Department of Rheumatology and Immunology, Tianjin Medical University General Hospital, Tianjin Medical University, Tianjin, P.R. China

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 for their disease activity scores every month, of which a score of more than 2.4 received an escalation of their oral treatment according to a protocol. Participants of the routine group were reviewed every 3 months, with no formal composite measure of disease activities used in clinical decision. At the 18 monthd assessment, patients in the intensive group 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

***Corresponding author:** Lu Zhou, Department of Gastroenterology and Hepatology, Tianjin Medical University General Hospital, Tianjin Medical University, Tianjin 300052, P.R. China, Tel: 0086-22-60362608; E-mail: lzhou01@tmu.edu.cn

Received November 03, 2017; **Accepted** November 09, 2017; **Published** November 16, 2017

Citation: Zhang H, Guo L, Wei W, Wang B, Zhou L (2017) Treat-to-Target in Autoimmune Hepatitis: How Far To Go? J AIDS Clin Res 8: 743. doi: 10.4172/2155-6113.1000743

of serum transaminases and IgG levels (biochemical remission). Treatment should be continued for at least three 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 overwhelms 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, rosettes 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 METAVIR 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 periportal 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 periportal and portal lesions into a single category [36]. The French METAVIR 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 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 85% respectively [50].

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 azathioprine 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.

Acknowledgement

The work was supported by National Natural Science Foundation (Grant no. 81470834).

References

1. Eeg-Olofsson K, Cederholm J, Nilsson PM, Gudbjornsdottir S, Eliasson B (2007) Glycemic and risk factor control in type 1 diabetes: Results from 13,612 patients in a national diabetes register. Diabetes Care 30: 496-502.
2. van Vollenhoven RF, Mosca M, Bertsias G, Isenberg D, Kuhn A, et al. (2014) Treat-to-target in systemic lupus erythematosus: Recommendations from an international task force. Ann Rheum Dis 73: 958-967.
3. European Association for the Study of the Liver (2015) EASL clinical practice guidelines: Autoimmune hepatitis. J Hepatol 63: 971-1004.
4. Cook GC, Mulligan R, Sherlock S (1971) Controlled prospective trial of corticosteroid therapy in active chronic hepatitis. Q J Med 40: 159-185.
5. Lamers MM, van Oijen MG, Pronk M, Drenth JP (2010) Treatment options for autoimmune hepatitis: A systematic review of randomized controlled trials. J Hepatol 53: 191-198.
6. Manns MP, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, et al. (2010) Diagnosis and management of autoimmune hepatitis. Hepatology 51: 2193-2213.
7. Feld JJ, Dinh H, Arenovich T, Marcus VA, Wanless IR, et al. (2005) Autoimmune hepatitis: Effect of symptoms and cirrhosis on natural history and outcome. Hepatology 42: 53-62.
8. Smolen JS (2012) Treat-to-target: Rationale and strategies. Clin Exp Rheumatol 30: S2-S6.
9. Egan BM, Lackland DT, Cutler NE (2003) Awareness, knowledge and attitudes of older americans about high blood pressure: Implications for health care policy, education and research. Arch Intern Med 163: 681-687.
10. Rachmani R, Slavacheski I, Berla M, Frommer-Shapira R, Ravid M (2005) Treatment of high-risk patients with diabetes: motivation and teaching intervention: A randomized, prospective 8 year follow-up study. J Am Soc Nephrol 16: S22-S26.
11. Atar D, Birkeland KI, Uhlig T (2010) 'Treat to target': Moving targets from hypertension, hyperlipidaemia and diabetes to rheumatoid arthritis. Ann Rheum Dis 69: 629-630.
12. Pincus T, Castrejón I, Bergman MJ, Yazici Y (2012) Treat-to-target: Not as simple as it appears. Clin Exp Rheumatol 30: S10-S20.
13. Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, et al. (2010) Treating rheumatoid arthritis to target: Recommendations of an international task force. Ann Rheum Dis 69: 631-637.
14. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, et al. (2012) 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res 64: 625-639.
15. Singh JA, Saag KG, Bridges SL, Jr., Akl EA, et al. (2016) 2015 American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol 68: 1-26.
16. Cohen G, Gossec L, Dougados M, Cantagrel A, Goupille P, et al. (2007) Radiological damage in patients with rheumatoid arthritis on sustained remission. Ann Rheum Dis 66: 358-363.
17. Rantalaiho V, Kautiainen H, Korpela M, Hannonen P, Kaipiainen-Seppänen O, et al. (2014) Targeted treatment with a combination of traditional DMARDs produces excellent clinical and radiographic long-term outcomes in early rheumatoid arthritis regardless of initial infliximab. The 5 year follow-up results of a randomised clinical trial, the NEO-RACo trial. Ann Rheum Dis 73: 1954-1961.
18. Rantalaiho V, Kautiainen H, Korpela M, Puolakka K, Blåfield H, et al. (2014) Physician's adherence to tight control treatment strategy and combination

DMARD therapy are additively important for reaching remission and maintaining working ability in early rheumatoid arthritis: A sub-analysis of the FIN-RACo trial. Ann Rheum Dis 73: 788-790.

19. Bouguen G, Levesque BG, Feagan BG, Kavanaugh A, Peyrin-Biroulet L, et al. (2015) Treat to target: A proposed new paradigm for the management of Crohn's disease. Clin Gastroenterol Hepatol 13: 1042-1050.
20. Alba P, Gobbi C, Babini AM (2014) Treat to target in systemic lupus erythematosus. Rev Fac Cien Med Univ Nac Cordoba 71: 5-6.
21. Grigor C1, Capell H, Stirling A, McMahon AD, Lock P, et al. (2004) Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): A single-blind randomised controlled trial. Lancet 364: 263-269.
22. Swales JD (1994) Pharmacological treatment of hypertension. Lancet 344: 380-385.
23. Eastman RC, Keen H (1997) The impact of cardiovascular disease on people with diabetes: The potential for prevention. Lancet 350: SI29-S32.
24. Sahebjam F, Vierling JM (2015) Autoimmune hepatitis. Front Med 9: 187-219.
25. Dhaliwal HK, Hoeroldt BS, Dube AK, McFarlane E, Underwood JC, et al. (2015) Long-term prognostic significance of persisting histological activity despite biochemical remission in autoimmune hepatitis. Am J Gastroenterol 110: 993-999.
26. Czaja AJ (2010) Difficult treatment decisions in autoimmune hepatitis. World J Gastroenterol 16: 934-947.
27. Czaja AJ (2002) Treatment strategies in autoimmune hepatitis. Clin Liver Dis 6: 799-824.
28. Al-Chalabi T, Heneghan MA (2007) Remission in autoimmune hepatitis: What is it and can it ever be achieved? Am J Gastroenterol 102: 1013-1015.
29. Liberal R, Mieli-Vergani G, Vergani D (2016) Contemporary issues and future directions in autoimmune hepatitis. Expert Rev Gastroenterol Hepatol, pp: 1-12.
30. Thanos L, Zormpala A, Papaioannou G, Malagari K, Brountzos E, et al. (2005) Safety and efficacy of percutaneous CT-guided liver biopsy using an 18-gauge automated needle. Eur J Intern Med 16: 571-574.
31. Ishak K1, Baptista A, Bianchi L, Callea F, De Groote J, et al. (1995) Histological grading and staging of chronic hepatitis. J Hepatol 22: 696-699.
32. Czaja AJ, Carpenter HA (1997) Histological findings in chronic hepatitis C with autoimmune features. Hepatology 26: 459-466.
33. Hennes EM, Zeniya M, Czaja AJ, Pares A, Dalekos GN, et al. (2008) Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology 48: 169-76.
34. de Boer YS, van Nieuwkerk CM, Witte BI, Mulder CJ, Bouma G, et al. (2015) Assessment of the histopathological key features in autoimmune hepatitis. Histopathology 66: 351-362.
35. Knodell RG, Ishak KG, Black WC, Chen TS, Craig R, et al. (1981) Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. Hepatology 1: 431-435.
36. Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ (1994) Classification of chronic hepatitis: Diagnosis, grading and staging. Hepatology 19: 1513-1520.
37. Bedoss P (1994) Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C: The French METAVIR cooperative study group. Hepatology 20: 15-20.
38. Liberal R, Grant CR, Longhi MS, Mieli-Vergani G, Vergani D (2014) Diagnostic criteria of autoimmune hepatitis. Autoimmun Rev 13: 435-440.
39. Czaja AJ, Davis GL, Ludwig J, Taswell HF (1984) Complete resolution of inflammatory activity following corticosteroid treatment of HBsAg-negative chronic active hepatitis. Hepatology 4: 622-627.
40. Czaja AJ, Menon KV, Carpenter HA (2002) Sustained remission after corticosteroid therapy for type 1 autoimmune hepatitis: A retrospective analysis. Hepatology 35: 890-897.
41. Miyake Y, Iwasaki Y, Terada R, Takagi S, Okamaoto R, et al. (2005) Persistent normalization of serum alanine aminotransferase levels improves the prognosis of type 1 autoimmune hepatitis. J Hepatol 43: 951-957.
42. Czaja AJ (2009) Rapidity of treatment response and outcome in type 1 autoimmune hepatitis. J Hepatol 51: 161-167.
43. Wang Q, Qiu D, Ma X (2011) Early normalisation of aminotransferase predicts complete biochemical remission in autoimmune hepatitis patients. Aliment Pharmacol Ther 34: 107-109.
44. Suzuki Y, Ikeda K, Hirakawa M, Kawamura Y, Yatsuji H, et al. (2010) Association of HLA-DR14 with the treatment response in Japanese patients with autoimmune hepatitis. Dig Dis Sci 55: 2070-2076.
45. Schiano TD, Azeem S, Bodian CA, Bodenheimer HC, Jr., Merati S, et al. (2005) Importance of specimen size in accurate needle liver biopsy evaluation of patients with chronic hepatitis C. Clin Gastroenterol Hepatol 3: 930-935.
46. Schiano TD, Fiel MI (2011) To B(iopsy) or not to B(iopsy). Clin Gastroenterol Hepatol 9: 3-4.
47. Bjornsson E, Talwalkar J, Treeprasertsuk S, Neuhauser M, Lindor K (2011) Patients with typical laboratory features of autoimmune hepatitis rarely need a liver biopsy for diagnosis. Clin Gastroenterol Hepatol 9: 57-63.
48. Lüth S, Herkel J, Kanzler S, Frenzel C, Galle PR, et al. (2008) Serologic markers compared with liver biopsy for monitoring disease activity in autoimmune hepatitis. J Clin Gastroenterol 42: 926-930.
49. Gronbaek H, Kreutzfeldt M, Kazankov K, Jessen N, Sandahl T, et al. (2016) Single-centre experience of the macrophage activation marker soluble (s) CD163-associations with disease activity and treatment response in patients with autoimmune hepatitis. Aliment Pharmacol Ther 44: 1062-1070.
50. Gutkowski K, Hartleb M, Kacperek-Hartleb T, Kajor M, Mazur W, et al. (2013) Laboratory-based scoring system for prediction of hepatic inflammatory activity in patients with autoimmune hepatitis. Liver Int 33: 1370-1377.
51. Naveau S, Gaudé G, Asnacios A, Agostini H, Abella A, et al. (2009) Diagnostic and prognostic values of non-invasive biomarkers of fibrosis in patients with alcoholic liver disease. Hepatology 49: 97-105.
52. Shah AG, Lydecker A, Murray K, Tetri BN, Contos MJ, et al. (2009) Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 7: 1104-1112.
53. Liu XD, Wu JL, Liang J, Zhang T, Sheng QS (2012) Globulin-platelet model predicts minimal fibrosis and cirrhosis in chronic hepatitis B virus infected patients. World J Gastroenterol 18: 2784-2792.
54. Pan AN, Xu WW, Luo YL, Yu HH, Hu YB, et al. (2017) A novel system for predicting liver histopathology in patients with chronic hepatitis B. Medicine (Baltimore) 96: e6465.
55. Sherman KE, Narkewicz M, Pinto PC (1994) Cyclosporine in the management of corticosteroid-resistant type I autoimmune chronic active hepatitis. J Hepatol 21: 1040-1047.
56. Manns MP, Woynarowski M, Kreisel W, Lurie Y, Rust C, et al. (2010) Budesonide induces remission more effectively than prednisone in a controlled trial of patients with autoimmune hepatitis. Gastroenterology 139: 1198-1206.
57. Burak KW, Swain MG, Santodomingo-Garzon T, Lee SS, Urbanski SJ, et al. (2013) Rituximab for the treatment of patients with autoimmune hepatitis who are refractory or intolerant to standard therapy. Can J Gastroenterol 27: 273-280.
58. Jothimani D, Cramp ME, Cross TJ (2014) Role of mycophenolate mofetil for the treatment of autoimmune hepatitis - An observational study. J Clin Exp Hepatol 4: 221-225.
59. Terziroli Beretta-Piccoli B, Mieli-Vergani G, Vergani D (2017) Autoimmune hepatitis: Standard treatment and systematic review of alternative treatments. World J Gastroenterol 23: 6030-6048.
60. Richardson PD, James PD, Ryder SD (2000) Mycophenolate mofetil for maintenance of remission in autoimmune hepatitis in patients resistant to or intolerant of azathioprine. J Hepatol 33: 371-375.
61. Czaja AJ, Carpenter HA (2005) Empiric therapy of autoimmune hepatitis with mycophenolate mofetil: Comparison with conventional treatment for refractory disease. J Clin Gastroenterol 39: 819-825.
62. Zachou K, Gatselis N, Papadamou G, Rigopoulou EI, Dalekos GN (2011) Mycophenolate for the treatment of autoimmune hepatitis: Prospective assessment of its efficacy and safety for induction and maintenance of remission in a large cohort of treatment-naive patients. J Hepatol 55: 636-646.
63. Czaja AJ (2016) Diagnosis and management of autoimmune hepatitis: Current status and future directions. Gut Liver 10: 177-203.
64. Corrigan M, Hirschfield GM, Oo YH, Adams DH (2015) Autoimmune hepatitis: An approach to disease understanding and management. Br Med Bull 114: 181-191.