Autoimmune hepatitis

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Autoimmune hepatitis (AIH) is a chronic inflammatory disease of the liver that impacts people of all ages but affects mainly women. AIH is a relatively rare disease, and its incidence is still rising. (1) The disease is characterised by an increased total level of immunoglobulin (IgG), typical liver histology with the presence of interface hepatitis, portal infiltrate with plasma cells and/or the presence of (a combination of) specific antibodies such as antinuclear autoantibodies (ANA), anti-smooth muscle antibodies (SMA) and disease-specific soluble liver antigen/liver pancreas antibodies (anti-SLA/LP). Histological confirmation of the disease is mandatory prior to therapeutic intervention. In addition, exclusion of other chronic liver diseases needs to be part of the initial diagnostic work-up. Symptoms are not always present or are nonspecific. Symptoms may include intestinal complaints such as abdominal pain, jaundice, and nausea but also extraintestinal complaints including arthralgia, fatigue, and weight loss. (2) The burden of symptoms, including fatigue and depression symptoms, may also have a substantial negative impact on both physical and mental quality of life. (3) Cirrhosis is already present in ~1/3 of patients at diagnosis, irrespective of the presence of symptoms. Timely diagnosis of the disease is crucial, as untreated AIH has a low 10-year survival rate of 10%. (4)

Endpoint	Definition
Complete biochemical response	Normalization of serum transaminases and IgG below the ULN. Should be achieved no later than 6 months after initiation of treatment.
Insufficient response	Lack of complete biochemical response. Should be determined no later than 6 months after initiation of treatment.
Non-response	<50% decrease of serum transaminases within 4 weeks after initiation of treatment.
Remission	Hepatitis Activity Index <4/18.
Intolerance to treatment	Any adverse event possibly related to treatment as assessed by the treating physician leading to potential discontinuation of the drug.

MANAGEMENT OF AIH

Treatment goals

The ultimate goals of AIH treatment are to prevent the progression of liver disease, reduce long-term mortality and improve quality of life with minimal side effects.

Endpoints

In 1993, the International Autoimmune Hepatitis Group (IAIHG) provided guidance in relation to characterizing AIH by proposing a diagnostic scoring system, which was later revised in 1999 to improve specificity. We introduced five standardised response criteria and endpoints in the treatment phase of AIH. (5)

Standard treatment

Standard treatment consists of a combination of predniso(lo)ne, followed by the addition of azathioprine to induce and maintain remission. (2) The European Association for the Study of the Liver (EASL) Clinical Practice Guideline recommends starting treatment with 0.5-1.0 mg/kg predniso(lo)ne and adding azathioprine at 1-1.5 mg/kg after 2 weeks. (2) Most side effects of azathioprine are gastrointestinal complaints (e.g. nausea and vomiting), but in some cases, it may cause neutropenia or pancreatitis, which warrants discontinuation. Steroids are related to an increased risk of diabetes, cataracts, osteoporosis, hypertension, cushingoid appearance, weight gain, depression, and mood disturbances. Steroid-related side effects occur in 80% of patients after two years of treatment, even in patients with low doses of steroids. (6) Therefore, steroid-free monotherapy with azathioprine is the goal of maintenance treatment. (2)

Alternative options

Although treatment is adequate in a substantial proportion of patients, approximately 20% of patients experience adverse events in which azathioprine has to be discontinued in the first year. (7) Different studies have suggested that achieving a biochemical response is frequently below 70%.

Mycophenolate mofetil (MMF) is the most commonly used second-line treatment in patients who are not tolerant or nonresponsive to azathioprine, starting at a dose of 500 mg twice daily and increasing to 1000 mg twice daily. (2) MMF is a prodrug of mycophenolic acid that inhibits the activity of inosine-5'-monophosphate dehydrogenase, leading to selective suppression of both T- and B-cell lymphocyte proliferation. MMF has proven to be effective and safe as a first-line and second-line treatment in uncontrolled (mostly retrospective) studies, with remission rates up to 88%. (2)

The relative efficacy and tolerability of MMF as a first-line treatment in AIH patients compared to azathioprine was recently established through a randomised, open-label, multicenter trial compared the standard treatment (azathioprine in combination with prednisolone) with MMF in combination with prednisolone in newly diagnosed AIH patients. In this 24-week trial, the percentage of patients achieving biochemical remission after 24 weeks of treatment was significantly higher in the MMF group than in the azathioprine group (56.4% vs. 29.0%). A quarter of the patients in the azathioprine group discontinued treatment due to intolerance or (severe) side effects (nausea and vomiting) (7)

Treatment withdrawal

Treatment for AIH is considered to be life-long process, since relapses after withdrawal of treatment occur in the majority of patients. Treatment withdrawal may be considered in patients who show a complete biochemical response for at least 2 years. (8) Liver biopsy before withdrawal is recommended by the guidelines, as histological resolution of disease typically lags behind reaching the biochemical endpoint (9) but is considered optional according to the EASL Clinical Practice Guideline. In

patients with histological disease activity (Histological Activity Index (HAI) >3) or cirrhosis, treatment should not be discontinued. (2)

Talking points

- Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease affecting mainly women.
- AIH is characterized by increased immunoglobulin levels, specific antibodies, and typical liver histology
- AIH treatment should aim the attainment of complete biochemical, clinical, and histological remission of the disease
- First-line treatment includes predniso(lo)ne with azathioprine or mycophenolate mofetil, with steroid-free monotherapy as the goal.
- The majority of patients should receive long-term, often life-long, immunosuppressive therapy

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