Management of Autoimmune Hepatitis

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ABSTRACT

Autoimmune hepatitis (AIH) is a necroinflammatory liver disease of unknown etiology. Although the pathogenetic mechanism of AIH is still unknown, an underlying genetic predisposition and the association of the disease with certain human leukocyte antigens (HLAs) have been suggested. The molecular mimicry has been proposed as a pathogenetic mechanism for AIH.

The diagnosis of AIH is based on a constellation of clinical, serological, and histopathological findings. The International Autoimmune Hepatitis Group (IAIHG) proposed diagnosis criteria in 1993, which were revised in 1999. In 2008, the IAIHG decided to devise a simplified scoring system for wider applicability in routine clinical practice. Based on clinical and serological parameters, AIH cases have been categorized into three subtypes: type-1 AIH, type-2 AIH and type-3 AIH.

The therapeutic guidelines of AIH include immunosuppressive agent with corticosteroid and usually in combination with azathioprine. Starting dose of prednisone monotherapy is 60 mg daily, which should be tapered slowly over a 1 week period to a maintenance dose of < 20 mg daily. The other regimen is used in combination with azathioprine, prednisone dose is started at 30 mg and tapered 10 to 5 mg every week until a maintenance dose of 10 mg is achieved. Azathioprine is given at the dose of 50 mg daily. In the very few patients that do not tolerate or have significant side effects to gold standard therapy, alternative immunosuppressive drugs should be given. Other powerful immunosuppressive drugs and molecular interventions are being developed based on recent insights into pathogenic pathways, emerging pharmacologic agents, and new technologies.

Keywords: autoimmune hepatitis, pathogenesis, diagnosis, management

ABSTRAK

Hepatitis autoimun (HAI) adalah penyakit hati akibat nekroinflamasi sel hati dengan penyebab tidak diketahui. Mekanisme patogenesis HAI secara pasti belum diketahui, diduga HAI berkaitan dengan faktor genetik, HLA tertentu dan proses molekuler mimikri.


Pedoman terapi HAI menggunakan kortikosteroid (prednisone) sebagai obat imunosupresif yang umumnya dikombinasikan dengan azathioprine. Terapi prednisone tunggal dimulai dengan dosis 60 mg/hari dan diturunkan pelan-pelan selama 1 minggu sampai pada dosis pemeliharaan < 20 mg/hari. Regimen lain menggunakan kombinasi prednisone dan azathioprine 50 mg/hari, dengan dosis awal prednisone 30 mg/hari, diturunkan 5 s/d 10 mg/minggu sampai mencapai dosis pemeliharaan 10 mg/hari. Untuk pasien yang peka atau memiliki efek samping terhadap terapi standar emas tersebut, harus diberikan imunosupresif alternatif. Saat ini obat-obat imunosupresif lain dan intervensi molekuler masih dikembangkan berdasarkan perkembangan terbaru jalur patogenesa, farmakologis, dan teknologi.

Kata kunci: hepatitis autoimun, patogenesis, diagnosis, manajemen
INTRODUCTION

The term autoimmune hepatitis (AIH) is used to describe a mostly chronic, but many times, acute and fulminant form of inflammatory liver disease. The disease entity was first described in 1950 by Waldenstrom, as a chronic form of hepatitis in young women. In 1965, it became designated by Mackay et al as “autoimmune hepatitis”. Since then, it has been known by a variety of terms, including active chronic hepatitis, chronic active hepatitis or autoimmune chronic active hepatitis and by other names such as chronic aggressive hepatitis, lupoid hepatitis and plasma cell hepatitis. In 1994, the International Autoimmune Hepatitis Group (IAIHG) designated “autoimmune hepatitis” as the most accurate and suitable term for such condition.1,2,3

AIH is a generally unresolving inflammation of the liver of unknown cause. A working model for its pathogenesis postulates that environmental triggers, failed immune tolerance mechanisms, and genetic predisposition collaborate to induce a T-cell–mediated immune attack upon liver antigens, leading to progressive necroinflammatory and fibrotic process in the liver.4,5,6

The diagnosis of AIH is based on histological abnormalities, characteristic clinical and laboratory findings, abnormal levels of serum globulins, and the presence of one or more characteristic auto-antibodies. Female are affected more frequently than male (sex ratio female : male was 3.6 : 1), and the disease is seen in all ethnic groups and at all ages. The AIH has an incidence of 1 to 2 per 100,000 persons per year and it has a prevalence of 11 to 17 per 100,000 persons per year.7,8,9 There has been no definite data reported on the incidence of AIH in Indonesia.

It is important to distinguish AIH from other forms of chronic hepatitis since a high percentage of cases may respond to anti-inflammatory or immunosuppressive therapy, or both. Although appropriate management can prolong survival, improve the quality of life, and avoid the need for liver transplantation, but there are considerable therapeutic challenges remain in the treatment of this disorder.10 The objective of our review is to focus on the management of AIH.

ETIOLOGY AND PATHOGENESIS

The liver is a unique anatomical and immunological site, in which antigen-rich blood from the gastrointestinal tract is pressed through a network of sinusoids and scanned by antigen presenting cells and lymphocytes. The liver’s lymphocyte population is selectively enriched in natural killer and natural killer T-cells which play critical roles in first line immune defense against invading pathogens, modulation of liver injury and recruitment of circulating lymphocytes. Circulating lymphocytes that come in close contact to antigens are displayed by endothelial cells, Kupffer cells and liver resident dendritic cells in the sinusoids. Circulating lymphocytes can also have direct contact with hepatocytes because the sinusoidal endothelium is fenestrated and lack of basement membrane. This unique anatomy of the liver may facilitate direct or indirect priming of lymphocytes, modulate the immune response to hepatotrophic pathogens and contributes to some of the unique immunological properties of this organ, particularly its capacity to induce antigen-specific tolerance.11

The pathogenetic mechanism of AIH is still unknown, but the most common theory of the mechanism of inflammatory injury in AIH postulates that an environmental agent, either a drug or a virus or another agent seems to trigger a T-cell mediated cascade directed against liver antigens in genetically predisposed individuals. Various mechanisms have recently been identified. The most important and convincing seems to be the model of autoreactive T-cells. Immune reactions against host liver antigens are believed to be the major pathogenic mechanism of AIH.4,5

An underlying genetic predisposition has been suggested because of the fact that patients are predominantly female and the association of the disease with certain human leukocyte antigens (HLAs). HLA genes reside in the major histocompatibility complex (MHC), which is located on the short arm of chromosome 6. The MHC is a genetic system with extensive polymorphism. Although multiple genes are probably involved, HLA genes appear to play the dominant role in predisposition to AIH.4,6

Molecular mimicry has also been proposed as a pathogenetic mechanism for AIH. In molecular mimicry, multiple antigens such as hepatitis C virus, cytomegalovirus, and herpes simplex type 1 virus, with the same or similar epitopes on the recombinant CYP2D6 can activate CD4+ T-cells because of incomplete specificity of T-cell antigen receptors. It has been recognize as the break self-tolerance. Such activation may lead to expansion of liver-infiltrating cytotoxic T-cells that may cause liver injury and develop the antigen-sensitized plasma cells that produce autoantibodies. Humoral cross-reactivity or the cross-reacting antibodies has been described in autoimmune conditions; however, cellular cross-reactivity that includes cross-reacting lymphocytes has been difficult to demonstrate.4,6,12

DIAGNOSTIC CRITERIA

AIH is one of chronic liver diseases resulting from dysregulated immune mechanism which has not yet clearly defined. The diagnosis is based on a constellation of clinical, serological, and histopathological findings.
Clinically, it is more often encountered in female than male. Seropositivity for auto-antibodies is found in most cases. Histologically, the typical findings consist of periporal, portal, and lobular chronic inflammation with prominent plasma cells.9

Based on combination of clinical and laboratory parameter with both positive and negative weight, IAIHG devised a scoring system in 1993.13 The sum of numerical score given to each of these parameters is useful in predicting the definite or possible diagnosis of AIH in a given patient. The system was modified in 1999 and has proven to be useful for both diagnostic and research purposes.14 It is highly sensitive for the diagnosis of AIH with a diagnostic accuracy close to 90%. The negative scores given to biliary marker/findings provide help in excluding AIH for patients with biliary diseases who may have some overlapping features.9

Hennes et al decided to devise a simplified scoring system for wider applicability in routine clinical practice based on the data of patients with well-established diagnoses. The simplified scoring system assesses only 4 factors (Table 1), i.e. the nature and level of autoantibody production evaluated based on assays of indirect immunofluorescence, serum immunoglobulin (Ig) G concentration, the presence of typical or compatible histological features, and the absence of viral markers.15 The simplified scoring system detects fewer cases of AIH than the original system. It has lower sensitivity (95% vs. 100%), but demonstrates higher specificity (90% vs. 73%) and accuracy (92% vs. 82%). The simplified scoring system is useful in excluding AIH for patients with other conditions and concurrent immune features.16,17

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cut off</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoantibodies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANA or SMA positive</td>
<td>≥ 1: 40</td>
<td>+ 1</td>
</tr>
<tr>
<td>ANA or SMA positive</td>
<td>≥ 1: 80</td>
<td>+ 2</td>
</tr>
<tr>
<td>Anti-LKM1 positive</td>
<td>≥ 1:40</td>
<td>+ 2</td>
</tr>
<tr>
<td>Anti-SLA</td>
<td>Positive</td>
<td>+ 2</td>
</tr>
<tr>
<td>IgG level</td>
<td>&gt; Upper limit of normal</td>
<td>+ 1</td>
</tr>
<tr>
<td></td>
<td>&gt;1.1 upper limit of normal</td>
<td>+ 2</td>
</tr>
<tr>
<td>Liver histology</td>
<td>Compatible with AIH</td>
<td>+ 1</td>
</tr>
<tr>
<td></td>
<td>Typical of AIH</td>
<td>+ 2</td>
</tr>
<tr>
<td>Absence of viral hepatitis</td>
<td>Yes</td>
<td>+2</td>
</tr>
</tbody>
</table>

AIH: autoimmune hepatitis; interpretation of aggregate score ≥ 6 points: probable AIH; ≥ 7 points: definite AIH; ANA: anti-nuclear antibody; SMA: smooth muscle antibody; anti-LKM1: antibodies to liver kidney microsome type 1; anti-SLA: antibodies to soluble liver antigen

Based on clinical and serological parameters, AIH cases have been categorized into three subtypes:9,18

- Type-1 AIH, seen more frequently the pediatric population. It is often associated with severe clinical disease and positive anti-LKM in the serum and the patients are usually negative for ANA or SMA. Type-2 AIH in adults may progress to cirrhosis more frequently than type-1 AIH (82% vs. 43% within 3 years).
- Type-3 AIH is represented in patients with antibodies to soluble liver antigen (SLA) or antibodies against the liver pancreas antigen (LP). The antibodies are designated together as SLA/ LP. Both antibodies, especially the former one, are also found in patients with the classic form of AIH; therefore, patients with type 3 AIH are now considered as the type 1 AIH.

Liver biopsy plays an important role in diagnosis and management of AIH patient. Histologically, portal and periportal chronic inflammation with prominent plasma cells is typically found in liver biopsies. The amount of inflammation and number of plasma cells can be quite variable. In clinically severe cases, the periportal lymphoplasmacytic activity or the interface hepatitis or piece-meal necrosis may be very pronounced. Presence of portal plasma cells in liver biopsies, from patients under therapy-induced remission, was found to be a predictor of relapse following treatment withdrawal. The plasma cells also may indicate persistence of immune response. The presence of interface hepatitis on the follow-up tissue examination justifies the continuation of therapy for an additional 6 month before reconsidering drug withdrawal. Full resolution of liver tests and tissue is an ideal treatment end point, but it may be achievable in only 40% of patients.9,19

**THERAPEUTIC MANAGEMENT**

The principle of therapy for chronic inflammatory liver diseases is the removal of causal agents. For autoimmune liver diseases, however, total removal of causal agents and immune cells is impossible. Therefore, autoimmune liver diseases are presently treated by suppression of the immune response. AIH is characteristically responsive to corticosteroids, which are often used in combination with azathioprine to obtain a steroid-sparing effect.20

**Indication of Treatment**

The absolute indications for treatment are based on the original studies of symptomatic patients. They are: (1) serum aspartate aminotransferase (AST) levels greater than ten-fold upper limit of normal range; (2) serum AST levels that greater than five-fold upper limit of normal in combination with a serum γ-globulin levels that are two-fold the upper limit of normal; (3) histological evidence of bridging or multicinar
necrosis; (4) incapacitating symptoms. These criteria represent a severe end of the disease spectrum, in which untreated patients would have a mortality of 40% within six months and their ten-years survival would only about 27%.21,22

Immunosuppressive therapy with corticosteroids, usually in combination with azathioprine is considered as the gold standard to induce and maintain remission. These two treatment regimens are equally effective in severe AIH (Table 2). Prednisone alone at the dose of 60 mg daily or a lower dose of prednisone (30 mg daily) in conjunction with 50 mg azathioprine is usually used in the United States or it may be administered at dose of 1-2 mg/kg body weight daily, which is widely used in Europe. Prednisone may be tapered down to an individual level sufficient to maintain a remission from 20 mg daily onward. Reduction should be done by 5 mg every week until 10 mg/day are achieved and even further reduction by 2.5 mg/week have been considered up to 5 mg daily. The maintenance regimen is then continued until resolution of the disease, treatment failure, or drug-intolerance.22

The combination regimen is appropriate in patients who will be treated continuously for at least 6 months or who are at increased risk for drug-related complications, including postmenopausal female and individuals with emotional instability, osteoporosis, brittle diabetes, labile hypertension, or obesity. Patients receiving prednisone should undergo eye examinations for cataracts and glaucoma periodically during treatment, and those receiving azathioprine in any dose should be monitored at 6 month intervals for leukopenia and thrombocytopenia.22

Corticosteroid therapy is established as an effective treatment for AIH. It induces clinical, laboratory and histological remission in 80% of patients within 3 years; the 10- and 20-years life expectancies of treated patients exceed 80%; hepatic fibrosis is reduced or prevented in 79% cases; and variceal hemorrhage, death from hepatic failure, and deteriorations warranting liver transplantation occur in less than 5%. These successes are tempered by the development of severe treatment-related side effects in 13% cases; treatment failure in 9%, incomplete response in 13%, and relapse after drug withdrawal in 50%-86%.19 In the very few patients that do not tolerate or have significant side effects to standard therapy, alternative immunosuppressive treatment should be given.

### Table 2. Immunosuppressive treatment regimens for adults in autoimmune hepatitis

<table>
<thead>
<tr>
<th>Msorphy</th>
<th>Combination therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone only*</td>
<td>Prednisone*</td>
</tr>
<tr>
<td>(mg/day)</td>
<td>(mg/day)</td>
</tr>
<tr>
<td>Week-1</td>
<td>60</td>
</tr>
<tr>
<td>Week-2</td>
<td>40</td>
</tr>
<tr>
<td>Week-3</td>
<td>30</td>
</tr>
<tr>
<td>Week-4</td>
<td>30</td>
</tr>
<tr>
<td>Maintenance until endpoint</td>
<td>20 and below</td>
</tr>
</tbody>
</table>

* Prednisolone can be used in place of prednisone in equivalent doses; USA: United States of America; EU: European Union

### Table 3. The endpoints of initial immunosuppressive treatment and courses of action in autoimmune hepatitis

<table>
<thead>
<tr>
<th>Treatment endpoint</th>
<th>Criteria</th>
<th>Courses of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>Disappearance of symptoms, normal serum aminotransferases, bilirubin and γ-globulin levels, normal hepatic tissue or inactive cirrhosis</td>
<td>Gradual withdrawal of prednisone over 6-week period</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serum AST or ALT, total bilirubin, and c-globulin levels determined at 3 week intervals during and for 3 months after drug withdrawal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Repeat laboratory assessments thereafter every 6 months for at least 1 year and then every year life-long</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>Worsening clinical, laboratory and histological features despite compliance with therapy</td>
<td>Prednisone, 60 mg daily, or prednisone, 30 mg daily, and azathioprine, 150 mg daily, for at least 1 month</td>
</tr>
<tr>
<td></td>
<td>Development of jaundice ascites or hepatic encephalopathy</td>
<td>Dose reduction of prednisone by 10 mg and azathioprine by 50 mg for each month of improvement until standard treatment doses are achieved</td>
</tr>
<tr>
<td>Incomplete response</td>
<td>Some or no improvement in clinical, laboratory, and histological features despite compliance with therapy after 2-3 years</td>
<td>Reduction in doses of prednisone by 2.5 mg/month until lowest level possible (≤ 10 mg daily) to prevent worsening of serum AST or ALT abnormalities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Indefinite azathioprine therapy (2 mg/kg daily) as an alternative treatment if corticosteroid intolerance</td>
</tr>
<tr>
<td>Drug toxicity</td>
<td>Development of intolerable cosmetic changes, symptomatic osteopenia, emotional instability, poorly controlled hypertension, brittle diabetes or progressive cytopenia</td>
<td>Reduction in dose or discontinuation of offending drug</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maintenance on tolerated drug in adjusted dose</td>
</tr>
</tbody>
</table>

AST: aspartate aminotransferase; ALT: alanine aminotransferase
in remission after drug treatment is withdrawn, most patients require long-term maintenance therapy. Albeit there is only scarce evidence for how long maintenance therapy should be given, it has been proposed that patients should be in stable remission for at least 4 years before withdrawal of immunosuppressive therapy can be considered. However, patients who are positive for anti-LKM1 (type 2 AIH) should be treated with life-long immunosuppressive treatment, which can only be stopped in patients with ANA and SMA-positive AIH (type 1 AIH).23

**Non-classical Phenotypes**

The phenotypes that satisfy the definition of AIH but are outside the boundaries of classical disease have acute severe presentations, few or no symptoms (known as asymptomatic AIH), atypical histological findings, absent or variant serological markers, concurrent cholangiographic changes, male gender, and non-Caucasian backgrounds.24

In the acute severe or the fulminant presentation of AIH, corticosteroid therapy is effective in 36-100% patients. The response to corticosteroid therapy should be evident quickly, and the failure of any laboratory test of liver inflammation to improve within 2 weeks in a patient with acute severe disease is a justification for considering liver transplantation.19,24

AIH may be asymptomatic in 25-34% of patients and 25-85% of individuals can be classified as having mild disease by clinical, laboratory and histological findings. Asymptomatic patients are typically men, and they have lower serum AST levels at presentation than symptomatic patients. Histological features are similar between symptomatic and asymptomatic patients, including the occurrence of cirrhosis, and 26-70% of asymptomatic patients become symptomatic during follow-up. Spontaneous resolution is possible, but cirrhosis develops in 49% of untreated patients within 15 years. Until randomized clinical trials are performed comparing treatment against no treatment, the management strategy in patients with mild AIH should lean toward conventional therapy.19,24

The histological hallmark of AIH is interface hepatitis, but other histological findings are compatible with the disease. Centrilobular zone 3 necrosis is probably an early form of AIH that is detected mainly in patients with an acute onset. Concurrent biliary changes, including isolated destructive cholangitis, may also be found in patients with otherwise classical AIH. Fatty changes may also be present at accession or after corticosteroid therapy. These non-classical findings should not alter the diagnosis or the treatment strategy.24

Seronegative patients with AIH constitute an “autoantibody-negative AIH”. They may have escaped detection by testing for the conventional autoantibodies, or their serological signature may be undiscovered or may express conventional autoantibodies later in the course of their disease. Confidence in the diagnosis of autoantibody-negative AIH can be strengthened by applying the comprehensive scoring system of the IAIHG. Once the diagnosis has been made by the exclusion of other conditions that might resemble, corticosteroid treatment should be started with regimes identical to those used in classical AIH. Treatment should not be extended beyond 3 months if there has been no improvement, and the accuracy of the original diagnosis and the legitimacy of the treatment regimen should be reassessed if the disease worsens in spite of compliance with the medication schedule.19,24

The overlap syndromes are important because they are common, occur in 18% of adults with autoimmune liver disease and they can respond poorly to corticosteroid therapy. The variant syndromes should be suspected when patients with AIH manifest clinical, laboratory or histological features of cholestasis or respond poorly to conventional corticosteroid therapy. The serum alkaline phosphatase level is useful in distinguishing classical AIH from its overlap syndromes with primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). Serum alkaline phosphatase levels more than four-fold higher than the upper limit of the normal (ULN) do not occur in classical AIH, and the presence of an abnormality of this degree in a patient with other features of AIH compels a search for underlying PBC or PSC.19,24

Management of the overlap syndromes is empirical and based on the predominant manifestations of the disease. Adults with AIH and features of PBC who have serum alkaline phosphatase levels less than two-fold higher than ULN can be treated with corticosteroids. Adults with higher serum alkaline phosphatase levels and those with florid duct lesions on histological examination are candidates for treatment with corticosteroids and ursodeoxycholic acid. Adults with AIH and PSC are commonly given a trial of prednisone and ursodeoxycholic acid, but in adults with mainly hepatitis features, corticosteroid therapy alone may be beneficial.19

**Alternative Drug Therapies for Sub Optimal Responses**

Treatment options have increased in AIH as new drugs with targeted immunosuppressive actions have been used empirically. None of these treatments has been incorporated into standard management algorithms, but they constitute an evolving armamentarium that promises to improve outcomes by either interrupting critical pathogenic pathways or eliminating intolerances to the current medications.24
The calcineurin inhibitors (cyclosporine and tacrolimus) have been used as frontline and salvage therapies in children and adults with AIH, and multiple small clinical experiences have supported their efficacy and tolerance. The purine antagonists (6-mercaptopurine and mycophenolate mofetil) have also been proven effective in some patients refractory to conventional corticosteroid regimens.\textsuperscript{12,24}

Budesonide is a third generation corticosteroid that has been used empirically as frontline and salvage therapy in AIH. Its high first-pass clearance by the liver and its breakdown to inactive metabolites promised to improve efficacy and safety compared to conventional corticosteroid regimens. Budesonide in combination with azathioprine has been found to be superior to prednisolone and azathioprine in normalizing the serum ALT level and reducing the frequency of steroid-related side effects after 6 months of treatment. Budesonide has not been effective as a salvage therapy in patients with severe disease on long-standing corticosteroid treatment. Moreover, the corticosteroid-induced side effects are still possible, especially in patients who have been treated previously with prednisone or who have cirrhosis.\textsuperscript{24}

Various other drugs (cyclophosphamide, methotrexate, rapamycin, rituximab, intravenous immunoglobulin, deflazacort, and ursodeoxycholic acid) have been proposed for use in AIH, and their number reflects the need for better salvage therapies in the treatment of AIH. Prospective and scientifically rigorous collaborative studies are needed to expand the therapeutic repertoire and comprehensive analyses are required to demonstrate that these incremental improvements in outcome are cost-effective.\textsuperscript{12,24}

**Promising Targeted Molecular and Cellular Therapies**

Cellular and molecular therapies are being developed to preserve adaptive immune defenses, reduce treatment-related complications, ensure prompt onset of action, and allow tight regulation of the duration and intensity of the immunosuppressive effect. These interventions are feasible because of improved understanding on the critical pathogenic pathways of AIH.\textsuperscript{12}

Site-specific molecular inventions, including antigen-blocking synthetic peptides, cytokine manipulations, T-cell vaccination, and oral tolerance regimens, become feasible when the critical pathogenic mechanisms of the disease are clarified, and confident animal models of the human disease are developed. Mesenchymal stem cells from human bone marrow that can differentiate into functional hepatocytes have the potential to rescue individuals from liver failure, reduce reliance on whole organ transplantation, and obviate the complications of whole organ rejection and drug toxicity.\textsuperscript{12,24}

**CONCLUSION**

AIH must be considered in all individuals with acute and chronic hepatitis of undetermined cause. A diagnostic scoring system that was promulgated mainly as a research tool in 1993 had been revised in 1999 to exclude cholestatic syndromes. A simplified diagnostic scoring system was added in 2008 to ease clinical application, and both systems can now be exploited to strengthen the diagnosis in difficult cases.

Optimization of corticosteroid regimens may increase treatment-free intervals, protect against overtreatment, and identify candidates for other therapies. The non-classical manifestations do not alter the management strategy, but they require prompt recognition and confident diagnosis. The new drugs with targeted immunosuppressive actions have been used empirically, and budesonide promises to be more effective and safer than current agents in treatment-naive patients. Other powerful immunosuppressive drugs and molecular interventions are being developed based on recent insights into pathogenic pathways, emerging pharmacologic agents, and new technologies.

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