Drug-induced anti-neutrophil cytoplasmic antibody-associated vasculitis

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Abstract

Objective: In recent years, an increasing number of drugs have been proved to be associated with the induction of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). This article reviews the latest research progress on drug-induced AAV.

Data sources: We conducted a comprehensive and detailed search of the PubMed database. The search terms mainly included drug-induced, ANCA, and vasculitis.

Study selection: We summarized the original articles and reviews on drug-induced AAV in recent years. The extracted information included the definition, epidemiology, associated drugs, pathogenesis, clinical features, diagnosis, treatment, and prognosis of drug-induced AAV. We also focused on the differences between drug-induced AAV and primary vasculitis.

Results: The offending drugs leading to drug-induced AAV are almost from pharmacologic categories and we need to be vigilant when using these drugs. The pathogenesis of drug-induced AAV might be multifactorial. The formation of neutrophil extracellular traps is an important mechanism for the development of drug-induced AAV. The clinical features of drug-induced AAV are similar to those of primary AAV. Understanding the difference between drug-induced AAV and primary AAV is helpful to identify drug-induced AAV. Stopping the offending drug at once after diagnosis may be sufficient for those patients with mild symptoms. Immunosuppressive therapy should only be used in patients with vital organs involvement.

Conclusions: Patients with drug-induced AAV usually have a good prognosis if they stop using the offending drug immediately. Recent advances in research on AAV are expected to help us better understand the pathogenesis of drug-induced AAV.

Keywords: Anti-neutrophil cytoplasmic antibody; Drug-induced; Vasculitis

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of autoimmune diseases characterized by the presence of ANCAs and necrotizing inflammation of small and medium vessels, including microscopic polyangiitis (MPA), granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis.[1,2] Diffuse cytoplasmic staining-ANCA (C-ANCA) and perinuclear staining-ANCA (P-ANCA) are two main fluorescence patterns that can be identified by indirect immunofluorescence reactions. The C-ANCA pattern is almost exclusively associated with antibodies against proteinase 3 (PR3). By contrast, the P-ANCA pattern can be caused by many proteins, mainly including myeloperoxidase (MPO), cathepsin G, elastase, β-glucuronidase, and others.[3] Although there is now increasing evidence to support the pathogenic effects of these antibodies in AAV, the mechanism for ANCA production is not fully understood.[4,5]

In recent years, more and more cases of drug-induced vasculitis (DIV) have attracted people's attention. In previous cases, it has been recognized that almost all pharmacological classes of drugs are potentially associated with the development of DIV.[6] As a large proportion of patients with DIV are characterized by ANCA positive, the detection of ANCAs can serve as a warning of the possibility of DIV. So, in some cases, DIV mainly refers to drug-induced AAV.[7,8] Although both drug-induced lupus disease and drug-induced AAV have been classified as autoimmune syndromes,[8-12] it is often difficult to distinguish them because of their similar clinical and experimental features, even some researchers have the opinion that trying to separate them is partly artificial.[8]

This review aims to summarize the definition, epidemiology, associated drugs, pathogenesis, clinical features, diagnosis, treatment, and prognosis of drug-induced AAV. The differences between drug-induced AAV and primary AAV are also the focus of this review.

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Definition

Previously, DIV was poorly understood and empirically defined. Ambiguous and undefined terms such as leukocytoclastic vasculitis, allergic vasculitis, hypersensitivity vasculitis, serum sickness, and so on were often used to describe such diseases.[13] Some researchers regarded DIV as a group of vascular inflammatory diseases, in which a specific drug is identified as a suspected cause of the disease while other types of vasculitis are excluded.[6] Similarly, there is no clear definition of drug-induced AAV. Traditionally, drug-induced AAV has only been understood as a class of DIV characterized by ANCA positive. Based on our understanding of the disease, the 2012 International Chapel Hill Consensus Conference classified drug-induced AAV as vasculitis associated with probable etiology.[14] This increased our awareness of this subset of vasculitis.

Epidemiology

Due to the lack of relevant studies, there is no clear epidemiological data to help us calculate the incidence of drug-induced AAV. According to the available prospective and cross-sectional studies, Balavoine *et al*[15] summarized that the prevalence of propylthiouracil (PTU)-induced AAV ranged from 4% to 64%, with a median prevalence of 30%, while the prevalence of methimazole (MMI)-induced AAV ranged from 0% to 16%, with a median prevalence of 6%.

Associated Drugs

So far, the associated drugs leading to drug-induced AAV are almost from all pharmacologic categories, mainly including anti-thyroid drugs[16-19] and the tumor necrosis factor (TNF) inhibitor.[20-23] Moreover, the following drugs are also showed a possible association with the occurrence of drug-induced AAV: cephotaxime,[24] minocycline,[25] nitrofurantoin,[26] trimethoprim-sulfamethoxazole,[27] vancomycin,[28] isoniazid,[29] rifampicin,[30] D-penicillamine,[31] sulfasalazine,[32] clozapine,[33] thioridazine,[34] allopurinol,[35] atorvastatin,[36] cocaine/levamisol,[37,38] denosumab,[39] hydralazine,[40] isotretinoin,[41] and phenytoin.[42] But most articles are confined to case reports [Table 1].

Since 1946, anti-thyroid drugs (ATD) have been gradually used,[43,44] especially in Graves' patients.[45] ATD are simple molecules in the group of thioamides. According to the different molecular structures of ATD, they can be divided into two major categories: derivatives of thiouracil (PTU and benzylthiouracil [BTU]) and methyl-mercaptoimidazole (MMI and carbimazole [CMZ]).[45,46] However, many side effects began to be seen soon after people started taking ATD. Besides granulocytosis and acute liver injury,[47] several cases of ATD-induced AAV have also been described subsequently and most of them were PTU-induced AAV.[48,49] So far, there were more than 200 cases of ATD-induced AAV have been reported. Approximately 90% of the ATD-induced AAV were related to PTU, while cases induced by MMI, CMZ, and BTU were relatively rare.[17-19] Studies have shown that ANCA production is related to the duration of ATD,[50,51] those patients taking PTU for more than 18 months should pay more attention to serum ANCA and it is not recommended to take PTU for more than 3 years. However, when PTU-induced AAV occurs, conversion from PTU to MMI is still not recommended, as it has been reported that this will lead to the recurrence of drug-induced AAV.[52]

In the past few years, biologics agents are increasingly used in rheumatic diseases. Puzzlingly, more and more biologics-induced autoimmune diseases have been gradually reported, including a wide range of organ-specific autoimmune diseases and systemic diseases.[53] Anti-TNF-α drugs are a class of biologics agents that widely used in rheumatoid arthritis, ankylosing spondylitis, and other autoimmune diseases. Studies have shown that repeated use of these drugs causes about 10% of patients to develop autoantibodies, such as anti-nuclear antibodies (ANA), anti-cardiolipin antibodies and anti-dsDNA.[54] Although uncommon, some patients were also found to develop AAV after receiving anti-TNF-α drugs.[20-23]

Cocaine is one of the most common and widely used drugs. It stimulates people by increasing dopamine levels and inhibiting its reuptake. Levamisole is an immunomodulator and anthelmintic drug widely used as an adulterant of cocaine.[37,38] Levamisole adulterates cocaine mainly because they have similar properties and levamisole enhances the effects of cocaine.[55,56] According to previous data, at least 66% of cocaine samples contained levamisole.[57] Levamisole was banned from the US market in 1999 because of serious side effects. Severe rash and neutropenia are the most common complications of levamisole. In the last decade, levamisole has gained renewed attention as an adulterant in cocaine. A series of

Table 1: Medications associated with drug-induced AAV.

Drug classification	Specific drugs
Anti-thyroid drugs	Benzylthiouracil, Carbimazole, Methimazole, Propylthiouracil
Biological agents	Adalimumab, Etanercept, Infliximab, Golimumab
Antibiotics	Cefotaxime, Minocycline, Nitrofurantoin, Trimethoprim-sulfamethoxazole, Vancomycin
Anti-tuberculosis drugs	Isoniazid, Rifampicin
DMARDs	D-Penicillamine, Sulfasalazine
Psychoactive agents	Clozapine, Thioridazine
Miscellaneous drugs	Allopurinol, Atorvastatin, Cocaine/Levamisol, Denosumab, Hydralazine, Isotretinoin, Phenytoin

AAV: ANCA-associated vasculitis; ANCA: Anti-neutrophil cytoplasmic antibody; DMARDs: Disease-modifying anti-rheumatic drugs.

adverse side effects of levamisole-adulterated cocaine is known as cocaine/levamisole-associated autoimmune syndrome (CLAAS).[55] Neutropenia and vasculitis are also the most common clinical manifestations of CLAAS.[55,56] The positive serum ANCA in some patients with CLAAS makes people realize that the formation of ANCAs may be the cause of the development of CLAAS.[37,38] Due to the high prevalence of levamisole in cocaine, it is difficult to distinguish whether the development of CLAAS is because of the synergistic effect of levamisole and cocaine or the result of levamisole alone.

Pathogenesis

Etiology of AAV mainly includes genetic factors, epigenetic factors, and environmental factors.[5] Drug as an environmental factor can trigger the development of AAV. Primary AAV and drug-induced AAV share a partial pathway in pathogenesis. To date, the pathogenesis of drug-induced AAV is still poorly understood. Here we summarize the role of genetic and epigenetic factors in AAV and the correlation between drug-induced AAV and neutrophil extracellular traps (NETs) [Figure 1].

Genome-wide association studies identified several genes associated with AAV susceptibility. Major histocompatibility complex class II genes have the strongest association with AAV.[58,59] Genetic factors were associated with ANCA specificity rather than with the clinical manifestation. PR3-ANCA was associated with human leukocyte antigen (HLA)-DP and MPO-ANCA was associated with HLA-DQ.[58] The pathogenesis of these genes in AAV remains to be further studied.

Epigenetic modifications that induce gene silencing mainly includes histone H3 lysine 27 trimethylation (H3K27me3) and DNA methylation.[60,61] The decrease of H3K27me3 is associated with the abnormal expression of MPO and PR3 in patients with AAV.[60] DNA methylation is associated with MPO and PRTN3 the gene that encodes PR3 expression. Hypomethylation of MPO and PRTN3 was seen in patients with active AAV and DNA methylation generally increased in remission.[61] Some drugs, such as hydrazine, inhibit DNA methylation and induce self-reactivity in T cells.[62,63] Activated T cells further induce B cells and plasma cells produce autoantibodies. These studies indicated that the abnormal epigenetic modification is associated with the inappropriate expression of PR3 and MPO in patients with AAV.

As an important part of innate immunity, NETs are extracellular structures composed of granule proteins and chromatin that kill bacteria.[64,65] The formation of NETs is strictly regulated and disordered regulation of NETs is an important cause of ANCA production.[66,67] Infectious factors stimulated neutrophils to form NETs, which are mainly degraded by serum endonuclease DNase I.[68] In patients with MPA, DNase I activity is reduced and NET

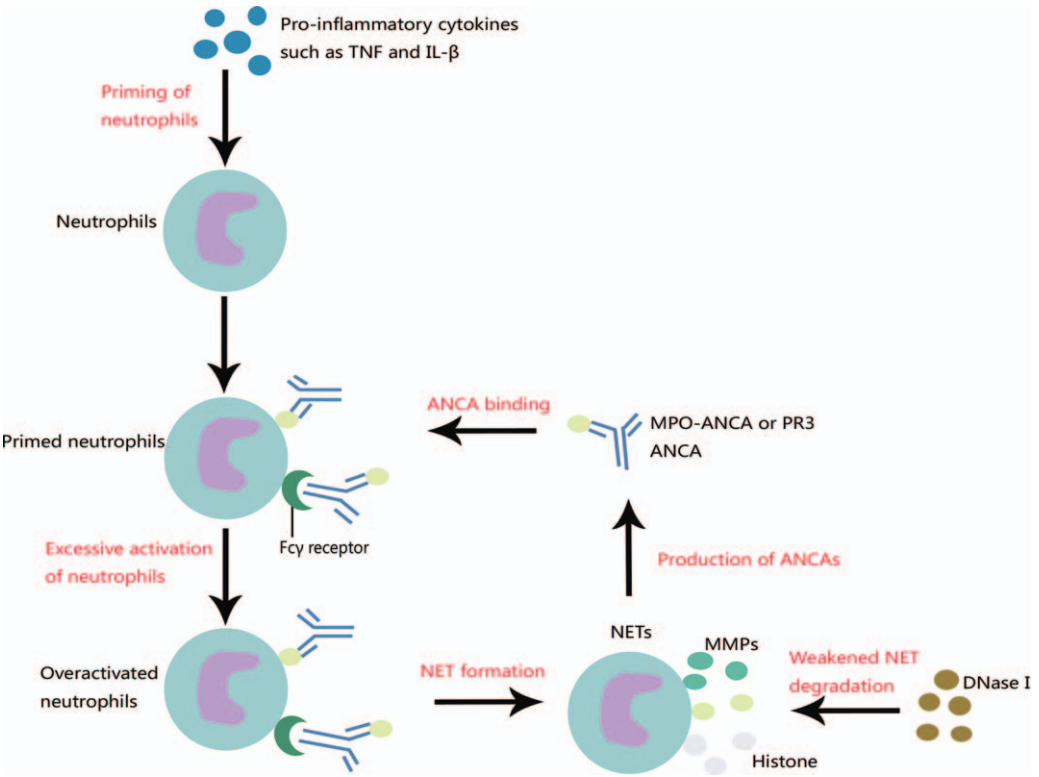

Figure 1: The role of NET formation in the development of drug-induced AAV. In some patients with drug-induced AAV DNase I activity is reduced and NET degradation is weakened. The persistence of NETs results in the generation of ANCAs. Pro-inflammatory cytokines such as IL-1β and TNF prime neutrophils then ANCAs binds to the primed neutrophils. This binding leads to the excessive activation of these neutrophils and eventually to the formation of NETs. Histones and MMPs in NETs can damage vascular endothelial cells. AAV: ANCA-associated vasculitis; ANCA: Anti-neutrophil cytoplasmic antibody; IL: Interleukin; MMPs: Matrix metalloproteinases; MPO: Myeloperoxidase; NET: Neutrophil extracellular trap; PR3: Proteinase 3; TNF: Tumor necrosis factor.

degradation is weakened. The persistence of NETs can destroy the tolerance to MPO and generate MPO-ANCA.[66] Pro-inflammatory cytokines such as interleukin-1β and TNF prime neutrophils, then primed neutrophils express ANCA specific antigens. ANCAs binds to these antigens and the Fc region of ANCAs binds to the Fcγ receptor on neutrophils. This binding leads to the excessive activation of these neutrophils and eventually to the formation of NETs.[69-71] Histones and matrix metalloproteinases in NETs can damage vascular endothelial cells.[72,73] In conclusion, the formation of NETs and ANCAs forms a vicious circle in the pathogenesis of AAV.

In healthy conditions, Semaphorin 4D (SEMA4D) receptors on neutrophils interact with plexin B2 ligands on endothelial cells to negatively regulate neutrophils activation. While in patients with AAV, SEMA4D is proteolytically cleaved from the surface of neutrophils. Alterations in SEMA4D-plexin B2 interactions can lead to the formation of NETs.[74,75] These studies further illustrate the important role of NET formation in the pathogenesis of AAV.

PTU induces abnormal NETs that are difficult to digest by DNase I. It is speculated that the metabolites of PTU may mask the DNase I recognition sites.[76] Both cocaine and levamisole induce NET formation and also augment the release of B-cell activating factor.[77] In addition, hydralazine can also significantly induce the formation of NETs.[63] As mentioned above, NETs induced by these drugs lead to the formation of ANCAs.

Some drugs such as minocycline and clozapine did not significantly induce NET formation or impair NET degradation.[63] This may suggest that some unknown mechanisms are also involved in the pathogenesis of drug-induced AAV.

Difference Between Drug-induced AAV and Primary AAV

The clinical manifestations of drug-induced AAV are similar to those of primary AAV. It is difficult to distinguish drug-induced AAV from primary AAV based on clinical manifestations. In addition, there are no unique clinicopathological or laboratory markers that can distinguish drug-induced AAV from primary AAV.[6] The clinical manifestations and severity of AAV induced by different drugs may vary greatly, and it is very difficult to generalize about all types of drug-induced AAV.

ATD-induced AAV is the most common drug-induced AAV, so we mainly summarize the difference between ATD-induced AAV and primary AAV, which may provide useful information for us to identify drug-induced AAV and primary AAV. According to some previous retrospective studies comparing ATD-induced AAV with primary AAV, we can summarize the following contents [Table 2].

In clinical manifestations, ATD-induced AAV mainly occurs in young women, while primary AAV usually occurs in the elderly, with a similar probability between men and women. This difference is related to thyroid disease mainly involving young women.[10,78-80] ATD-induced AAV more frequently has skin damage, and primary AAV is more characterized by high fever (>38.5°C), weight loss (>2 kg a month), and the involvement of kidney, lung, gastrointestinal tract, and the nervous system. There is no significant difference in the involvement of eye, ear, nose, throat, cardiovascular, and joint pain.[10,79,80] As long as the offending drug is stopped in time, the severity of ATD-induced AAV is usually milder than that of primary AAV. The prognosis of ATD-induced AAV is also generally better than that of primary AAV.[10,78-80]

Table 2: Difference between ATD-induced AAV and primary AAV.

Characteristic	ATD-induced AAV	Primary AAV
Age and sex	Mainly young and female	Elderly
Skin damage	More frequently	Relatively rare
High fever (>38.5°C) and weight loss (>2 kg a month)	Relatively rare	More frequently
Involvement of kidney, lung, gastrointestinal tract, and the nervous system	Relatively rare	More frequently
Levels of creatinine, urinary protein, and CRP	Lower	Higher
Serum positive ANA	More frequently	Relatively rare
Presence of antibodies to histones and β2-glycoprotein 1	Can be seen	Relatively rare
Epitope(s) of MPO-ANCA	Restricted	Relatively broad
Target antigen(s) of ANCA	Multiple target antigens including MPO, PR3, cathepsin G, lactoferrin, neutrophil elastase, and azurocidin	Usually single target antigen such as MPO or PR3
Disease severity	Generally mild	Relatively serious
Prognosis	Generally good	Relatively poor

ATD: Anti-thyroid drugs; AAV: ANCA-associated vasculitis; CRP: C-reactive protein; ANA: Anti-nuclear antibody; MPO: Myeloperoxidase; ANCA: anti-neutrophil cytoplasmic antibody; PR3: Proteinase 3.

In laboratory tests, ATD-induced AAV is also slightly different from primary AAV. First, compared with primary AAV, ATD-induced AAV showed lower levels of creatinine, urinary protein, and C-reactive protein. This is consistent with the observed milder clinical manifestations of ATD-induced AAV.[10,78-80] Second, the ANA positive rate of ATD-induced AAV is significantly higher than that of primary AAV.[10,79,80] Third, ATD-induced AAV can also be detected in the presence of antibodies to β2-glycoprotein 1 and histones, which are relatively rare in primary AAV.[8,10] In addition, the epitopes of anti-MPO antibodies in ATD-induced AAV can be more limited than in primary AAV.[81] This is consistent with our observation that almost all patients with ATD-induced AAV presented positive MPO-ANCA instead of PR3-ANCA.[10,78-80] Lastly, ANCAs typically recognize many target antigens in ATD-induced AAV including lactoferrin, cathepsin G, azurocidin, and neutrophil elastase. In contrast, ANCAs generally recognize only one target antigen, MPO or PR3, in primary AAV.[48,82,83]

Diagnosis

Early diagnosis of drug-induced AAV and cessation of the offending drug immediately are crucial to the prognosis of drug-induced AAV. Currently, there is no clear definition of the diagnostic criteria of drug-induced AAV, which is still an exclusive diagnosis. The difference between drug-induced AAV and primary AAV mentioned above can help us to identify drug-induced AAV. Furthermore, we suggest

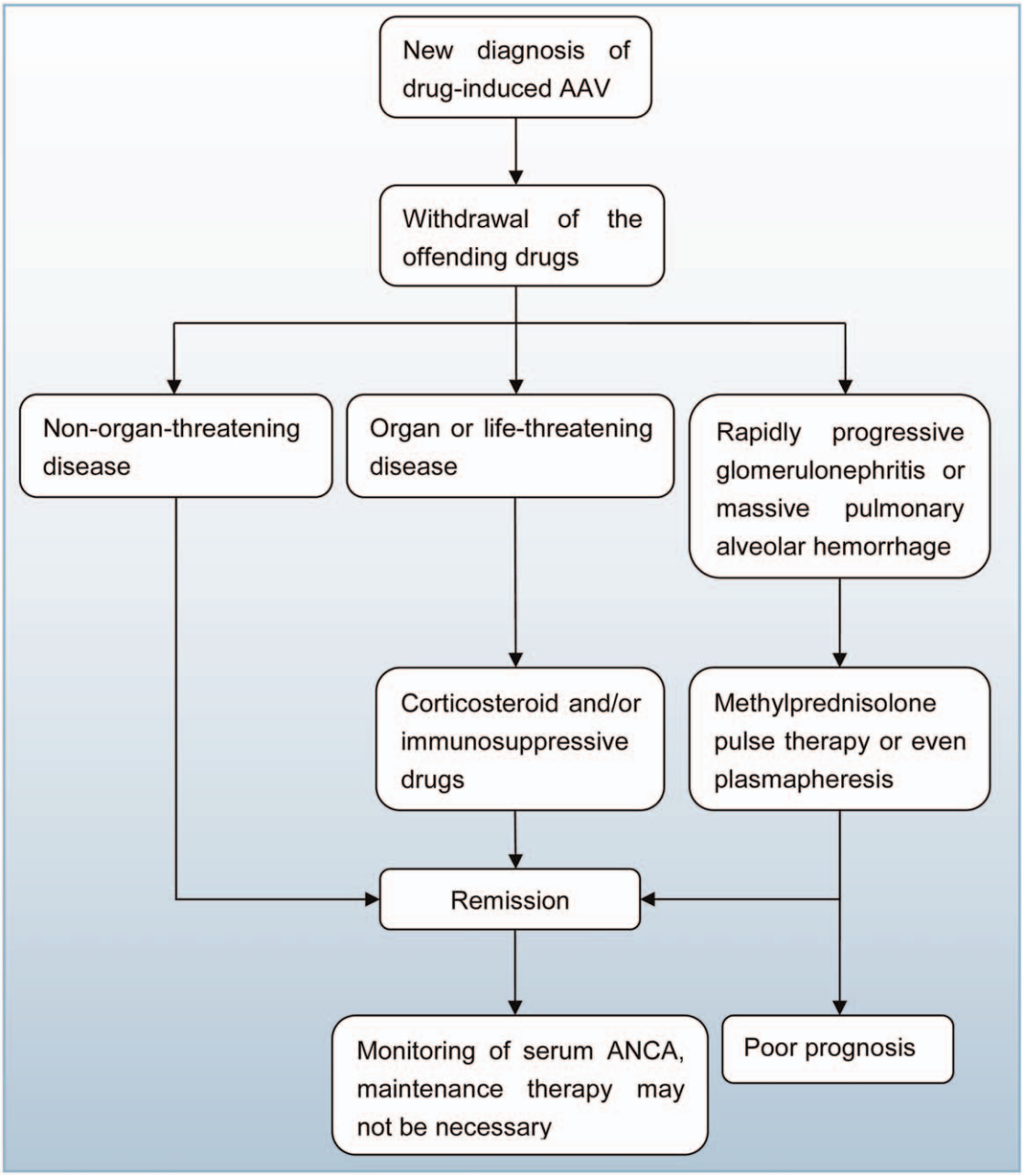

Figure 2: Treatment strategy for patients with drug-induced AAV. AAV: ANCA-associated vasculitis; ANCA: Anti-neutrophil cytoplasmic antibody.

that the diagnosis of drug-induced AAV should be considered when the following conditions are met: (1) Patients should first meet the 2012 Chapel Hill Consensus Conference definition for AAV. (2) The clinical symptoms are related to the use of the offending drug and relieved with discontinuation. (3) Serum ANCA is positive. (4) Excluding diseases with similar characteristics, in particular infections, malignancies, and other types of vasculitis.[6]

If the diagnosis remains difficult, tissue biopsy is strongly encouraged to confirm the definitive diagnosis.[6]

Treatment

To date, there is no standard treatment strategy for drug-induced AAV. Corticosteroid and immunosuppressants used to treat primary AAV may not be appropriate for most patients with drug-induced AAV. The treatment strategy for drug-induced AAV should vary from patient to patient depending on the severity of the disease [Figure 2].[6] For those with mild symptoms including arthralgia, fever, weight loss, and without organ involvement, stopping the offending drug at once after diagnosis may be sufficient to induce disease remission. Active management is reserved for patients with more severe conditions. Prednisone at 1 mg/kg for 1 to 2 months with gradually reduced dose is required for those with severe and active organ involvement. For patients with important organs involved, immunosuppressive agents (especially cyclophosphamide) may be necessary. Furthermore, patients with massive pulmonary alveolar hemorrhage or rapidly progressive glomerulonephritis should be treated with intravenous injections of 7 to 15 mg/kg of methylprednisolone per day for 3 consecutive days or even plasmapheresis.[84-86]

Individual disease courses are unpredictable and each patient requires careful monitoring. The duration of immunosuppressive therapy in patients with drug-induced AAV remains uncertain. It is generally believed that the duration of immunosuppressive treatment of drug-induced AAV should be shorter than that of primary AAV.[87] Compared with primary AAV, maintenance therapy of drug-induced AAV may not be necessary as long as the offending drug stop being used. Patients with drug-induced AAV usually do not relapse once the offending drug is withdrawn and the disease is in remission.[87]

Prognosis

According to previous studies, the prognosis of drug-induced AAV is generally significantly better than that of primary AAV.[7,84,86,87] Most patients with drug-induced AAV can achieve complete remission after stop using the offending drug without further treatment. A small number of patients with organ involvement can also achieve a good prognosis after immunosuppressive therapy. Very few patients develop end-stage renal disease because of not discontinuation of the offending drug timely.[16,87] In long-term follow-up studies, the incidence of end-stage renal disease and the mortality rate were both lower after discontinuation of the offending drug and no recurrence was observed.[16,87]

Conclusions

The offending drugs leading to drug-induced AAV are almost from every pharmacologic class. Genetic factors, epigenetic factors and the formation of NETs are important mechanisms for the development of drug-induced AAV. Patients treated with drugs that may induce AAV must be closely monitored. ANCA is an effective tool for early diagnosis of drug-induced AAV. Understanding the difference between drug-induced AAV and primary AAV may be helpful in identifying drug-induced AAV. Once diagnosed, the offending drug must be stopped immediately. Most patients can be relieved when they stop using the offending drug. Immunosuppressive therapy should only be used in patients with vital organs involvement to prevent further disease progression. The duration of immunosuppressive therapy in patients with drug-induced AAV should be much shorter than that in primary AAV, and long-term maintenance therapy is generally not required. The prognosis of drug-induced AAV is generally better than that of primary AAV.

Conflicts of interest

None.

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