بسم الله الرحمن الرحيم

GRANULOMATOSIS WITH POLYANGIITIS (GPA) AND MICROSCOPIC POLYANGIITIS (MPA)

management of relapsing & resistant disease

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INTRODUCTION:

A therapeutic strategy combining glucocorticoids(GC) and cyclophosphamide or rituximab to induce remission has dramatically improved survival of AAV in t the past decades.

Despite this improvement, maintaining remission in patients with

Relapse occurs in Granulomatosis with polyangiitis (GPA)or Microscopic polyangiitis remains (MPA) challenging.

Relapse occurs 13.7%–44% of cases at 18–36 months depending on the duration of follow-up, patient characteristics and maintenance treatment .

DEFINITION:

Treatment-resistant granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) is diagnosed if one or both of the following are present despite optimal immunosuppressive therapy for an adequate period (usually six months, or three months in a patient who is dialysis dependent):

- A progressive decline in kidney function (increase in serum creatinine) plus persistence of an active urine sediment (dysmorphic hematuria with or without red cell casts) that is judged to be due to active vasculitis or a kidney biopsy showing active glomerulonephritis

- Persistence or new appearance of extrarenal manifestations of active vasculitis

A clinical relapse is defined by the presence of both of the following:

- The recurrence of signs or symptoms of active vasculitis in any organ system after remission is achieved:

• An active urine sediment (dysmorphic [glomerular] hematuria with or without red cell casts), which may be accompanied by a rise in serum creatinine

• Hemoptysis or pulmonary hemorrhage or new or expanding pulmonary nodules in the absence of evidence of infection

• Iritis or uveitis, mononeuritis multiplex, rhinitis, sinusitis, any of several types of skin lesions, or necrotizing vasculitis on biopsy of any tissue

- Such signs or symptoms are judged to be due to active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) and not to another cause.

French Vasculitis Study Group Relapse Score (FRS)

The FRS can be used at diagnosis to assess the relapse risk in patients with GPA or MPA.

identified three factors

- ❑ PR3-ANCA
- ❑ age ≤75 years
- ❑ estimated glomerular filtration rate ≥30 mL/min/1.73 m2

associated with a higher risk of relapse of AAV.

These factors were combined to form a score, ranging from 0 to 3 points (1 point for each factor) that predicts the risk of relapse in AAV

MANAGEMENT:

The first step in the management of the patient suspected of being treatment resistant is to exclude alternative diagnoses.

Exclusion of alternative diagnoses:

- Permanent tissue damage due to previous inflammatory injury
- Nonadherence to therapy
- Inadequate initial immunosuppression
- Medication toxicity
- Infection
- Incorrect original diagnosis

APPROACH BASED ON PRIOR THERAPY:

Patients resistant to induction with cyclophosphamide:

For patients whose disease is resistant to initial induction therapy with cyclophosphamide, we suggest treatment with rituximab
The rituximab dosing is the same as is used for induction immunosuppression therapy.

Patients resistant to induction with rituximab:

For patients whose disease is resistant to initial induction therapy with rituximab, we suggest treatment with cyclophosphamide.
Although there are limited data to support this approach , it is our experience that some patients who are refractory to initial treatment with rituximab may achieve remission with

Patients resistant to induction with cyclophosphamide and rituximab:

For patients who have been treated with both rituximab and cyclophosphamide for at least three to six months but continue to have active disease, we suggest treatment with mycophenolate mofetil (MMF) rather than other therapies.

Concurrent therapy with both cyclophosphamide and rituximab is a reasonable alternative in patients with life-threatening illness. However, this combination clearly raises serious concerns for risk of infection

Another option for such patients with refractory disease may include obinutuzumab (another anti-CD20 antibody), which was used effectively in a small case series of three patients who had a hypersensitivity to rituximab .These approaches are based upon our clinical experience given the lack of high quality supportive evidence.

The target dose of MMF is generally between 1.5 and 3 grams daily, in divided doses.

Another regimen that may be used is derived from the International Mycophenolate MofetilProtocol to Reduce Outbreaks of Vasculitides (IMPROVE) study, in which patients start with MMF 2000 mg per day followed by a reduction to 1500 and 1000 mg per day after 12 and 18 months, respectively .

THERAPIES OF UNPROVEN EFFICACY:

❑ Anti-tumor necrosis factor (TNF)-alpha therapy:

Insights into the role of T helper (Th)1 cytokines in the pathogenesis of GPA have led to trials involving therapy with antagonists to TNF-alpha and inhibitors of monocyte function, such as interleukin 10 The best available data on the possible efficacy of these agents for ANCA-associated vasculitis come from a randomized trial of 180 patients with GPA (Wegener's Granulomatosis Etanercept Trial [WGET]) that found that etanercept provided no additive benefit to treatment with methotrexate in maintaining remission. None of the patients enrolled in the WGET trial had resistant disease, and patients with MPA were not included.

In an open-label study, infliximab was added to standard immunosuppressive therapy in 16 patients with acute ANCA-associated vasculitis at first presentation or relapse and in 16 with persistent disease despite multiple immunosuppressive regimens
Fourteen patients in each group (88 percent) achieved remission within a mean of 6.4 weeks,
but serious infections and death were reported in seven and two patients, respectively.
In addition, five patients (three with persistent disease) had a relapse at a mean of 27 weeks.

❑ Abatacept (anti-CTLA-4 Ig) :

In a series of 20 patients with established GPA and active, non-organ-threatening disease, abatacept (a drug that inhibits T cell activation) demonstrated promise as a treatment for relapsing GPA .These patients who received abatacept were also permitted to use glucocorticoids for the initial two months and to continue treatment with azathioprine, MMF or methotrexate. Sixteen patients (80 percent) achieved remission, and 11 of 15 patients treated with prednisone were able to stop glucocorticoid therapy. Abatacept was well tolerated. A randomized, placebo-controlled trial evaluating the use of abatacept for the treatment of relapsing, non-severe GPA is in progress

Intravenous immune globulin:

Intravenous immune globulin has been studied in only a limited fashion in ANCA-associated vasculitis, and none of the available studies provide clear answers regarding potential efficacy.

The best data come from a randomized, placebo-controlled trial of 34 patients with ANCA-associated systemic vasculitis and persistent disease activity despite previous immunosuppressive therapy, Improvement occurred in 6 of 13 who had lung involvement, but no information was provided regarding the presence or response of kidney manifestations of the disease.

❑ Alemtuzumab :

Alemtuzumab is a humanized anti-CD52 monoclonal antibody that depletes lymphocytes. In a report from a single-center cohort of 71 patients with resistant or relapsing GPA and MPA, 60 patients (85 percent) obtained remission with alemtuzumab, although 43 (72 percent) of these patients subsequently relapsed .

The rate of adverse events and death was high, including from infection and autoimmune thyroid disease.
alemtuzumab may be an option for patients with severe refractory GPA or MPA, use of this drug is associated with substantial potential toxicity and requires careful monitoring by clinicians experienced in the use of this agent.

Alemtuzumab when used to treat multiple sclerosis has been associated with anti-glomerular basement membrane (GBM) disease, which may cause confusion if this occurs in patients with GPA and MPA.

❑ Stem cell transplantation :

High-dose myeloablative chemotherapy with stem cell transplantation has been utilized for the treatment of refractory severe vasculitis. There are case reports of successful treatment of vasculitis with kidney involvement, including a few patients with GPA Much more study is required to determine whether there is a role for high-dose chemotherapy with stem cell reconstitution in the management of resistant ANCA-associated systemic vasculitis

RELAPSING DISEASE:

Risk factors for relapse:

- Seropositivity for PR3-ANCA
- Prior history of relapsing disease
- Involvement of the lung prior to remission
- Involvement of the upper respiratory tract prior to remission
- Persistence of elevated ANCA titers, particularly PR3-ANCA, and rising ANCA titers

> The goal of managing relapsing disease is reinduction and maintenance of complete remission, which is the absence of any signs of active disease.

Organ- or life-threatening relapse:

Severe relapses are usually treated with reinstitution of induction therapy followed by maintenance therapy.

Reinduction therapy:

For patients who relapse after successfully achieving remission with a cyclophosphamide-based or a rituximab-based regimen, we suggest readministering induction therapy with rituximab rather than cyclophosphamide.

Data from randomized trials suggest that rituximab is at least as effective for treating disease relapses and may also be associated with less cumulative toxicity compared with cyclophosphamide.

Rituximab is also the preferred agent in women who wish to preserve their potential to conceive a child.

Cyclophosphamide is a reasonable alternative for patients whose relapse is characterized by advanced and progressive crescentic glomerulonephritis or severe pulmonary disease with massive hemorrhage.

However, there are no trial data to guide the choice between cyclophosphamide and rituximab in such patients.

In addition, some experts treat such patients with both cyclophosphamide and rituximab (eg, four weekly infusions of rituximab plus two intravenous pulses of cyclophosphamide)

If patients cannot tolerate cyclophosphamide or rituximab,
we attempt to achieve remission with mycophenolate mofetil (MMF).

Maintenance therapy after reinduction :

Relapse can occur while patients are being treated with maintenance therapy or after maintenance therapy has been discontinued.
The choice of drug and the duration of maintenance therapy after reinduction of remission are determined in part by the timing of relapse

Relapse during maintenance therapy :

For patients who exhibit a severe relapse while on the original course of maintenance therapy, we suggest using a different drug for maintenance therapy after reinduction of remission. In such patients, the duration of maintenance therapy may be similar to that suggested for the original course of maintenance therapy (usually 12 to 18 months, but this can vary with the estimated likelihood of relapse).

The usual drugs for maintenance therapy are rituximab, azathioprine, in patients with an estimated glomerular filtration rate (eGFR) above 60 mL/min/1.73 m and no renal vasculitis, methotrexate.

MMF is an alternative agent for patients who do not respond to, cannot tolerate, or have contraindications to these drugs.

Glucocorticoid therapy is part of the maintenance immunosuppression regimen. The median duration of glucocorticoid therapy after the first induction of remission is less than six to eight months. Some experts recommend long-term, low-dose maintenance therapy in patients who have had multiple relapses.

Relapse after maintenance therapy:

For patients who relapse after the discontinuation of the original course of maintenance therapy, we suggest using the same drug for maintenance therapy after remission has been reinduced.
However, the duration should be longer than the initial course (eg, 12 months or longer if the original course of maintenance therapy was 6 to 12 months). For patients who have frequent relapses, lifelong maintenance therapy may be appropriate, similar to that in recipients of organ transplants.

There is some evidence that trimethoprim-sulfamethoxazole is an effective maintenance drug for the prevention of relapses limited to the upper respiratory tract.
However, toxicity is an issue, since in the randomized trial suggesting benefit compared with placebo in this setting, 20 percent of patients treated with trimethoprim-sulfamethoxazole maintenance discontinued therapy due to side effects, most of which are minor (anorexia, nausea, rash) .
In addition, high-dose trimethoprim-sulfamethoxazole cannot be used in patients receiving methotrexate and should be used cautiously in patients with advanced chronic kidney disease.

Non-organ- and non-life-threatening relapse:

Relapse during maintenance therapy :

For patients who develop a non-organ- and non-life-threatening relapse while still receiving maintenance therapy, we suggest increasing the dose of glucocorticoids and, when relevant, increasing the dose of the immunosuppressive agent used for maintenance therapy.

In a patient receiving tapering doses of prednisone and methotrexate, for example, the prednisone dose can temporarily be increased back to 60 mg/day (although lower starting doses may also be adequate), and the methotrexate dose can be increased back to 25 mg once weekly

Relapse after maintenance therapy:

For patients who develop a non-organ- and non-life-threatening relapse after maintenance therapy has been discontinued, we suggest reinstitution of the prior maintenance therapy in combination with a short course of glucocorticoids. However, maintenance therapy should be continued for a longer period of time than was given prior to the relapse (eg, 12 to 18 months if the original course of maintenance therapy was 6 to 12 months).

There are limited data to guide the optimal therapy of patients with a non-organ- and non-life-threatening disease relapse, and our approach is largely based on clinical experience
and observational data. One observational study of 44 patients with their first non-severe relapse found that treatment with a temporary increase in the glucocorticoid dose restored disease remission in most patients (80 percent), but recurrent relapses occurred in the majority of patients by approximately 12 months

Relapses limited to the upper airway :

It may be difficult to distinguish between active disease and infection (and some patients have both) when the manifestations of possible
relapse are limited to the upper respiratory tract, particularly with nasal disease, where ulceration and crusting over granulation tissue can result from both vasculitis and infection.

The therapeutic approach varies with the presumed diagnosis:

- When infection is thought to be the predominant problem, oral antibiotics are often required (eg, trimethoprim-sulfamethoxazole). However, some prefer topical mupirocin ointment for less severe infections. The ointment can be applied directly inside of each nostril or mixed into a saline irrigation solution

Topical antibiotics have the advantage of permitting a long course of therapy without the systemic side effects that may be seen with oral antibiotics.

- When active vasculitis is thought to be the predominant problem and the relapse is limited to the upper respiratory tract, we increase the prednisone dose for at least four weeks

and continue or increase the dose of the drug used for maintenance immunosuppression.

- When possible, we avoid treating for infection and active vasculitis simultaneously since this leads to diagnostic confusion and possibly to overexposure to medication.

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