Perspective

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What is the best treatment option for granulomatosis with polyangiitis?

Granulomatosis with polyangiitis is a systemic necrotizing vasculitis that affects small- and medium-size blood vessels. It is often associated with antineutrophil cytoplasmic antibodies. The main manifestations involve the upper and/or lower respiratory tract and kidneys. Limited forms of granulomatosis with polyangiitis predominantly affect the upper respiratory tract, whereas generalized forms include renal manifestations, alveolar hemorrhage and altered general condition. The combination of immunosuppressant drugs and corticosteroids has converted this typically fatal illness into one in which 80% of patients achieve remission. However, despite considerable therapeutic progress over the last decades, relapses remain frequent (50% at 5 years), and maintenance treatment is now the main therapeutic challenge.

Keywords: ANCA • characteristics • granulomatosis with polyangiitis • treatment

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Clinical aspects

Since 1931, when granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis, was first described by German pathologists Heinz Klinger and Friedrich Wegener, and the 1980s when antineutrophil cytoplasmic antibodies (ANCA) were identified, considerable progress has been made with regard to the diagnosis, treatment and pathophysiology of this disease. It is a systemic, necrotizing vasculitis associated with the presence of ANCA with a cytoplasmic staining pattern directed against proteinase 3 (PR3). GPA is characterized by granulomatous and necrotizing inflammatory lesions located mainly in the upper and lower respiratory tracts, and is often associated with pauci-immune glomerulonephritis, which may be rapidly progressive.

GPA is a rare disease with a prevalence in France estimated at 22 per million inhabitants in 2000 [1]. The incidence has been evaluated between 7 and 12 new cases per million inhabitants per year, although this has probably risen in the last few decades [2]. In Europe, GPA seems to be more frequent in the Nordic countries. There are newer data from UK (2005), from Germany (2006) and Australia (2004) with considerably higher and increasing prevalence rates (65–95 cases per one million), reflecting the better outcome of patients with GPA during the last two decades [3–5]. The annual incidence is about 10 cases per million inhabitants in northern Europe. The age at diagnosis is between 45 and 60 years. Men and women are affected with similar frequency. Rare cases of GPA may occur in black subjects, as well as in children.

According to the 2012 revised Chapel Hill criteria [6], GPA is defined as a necrotizing granulomatous inflammation of the upper and lower respiratory tracts, with necrotizing vasculitis of small- and medium-size vessels, in other words, the capillaries, veins, arterioles and arteries. Necrotizing glomerulonephritis is common but is not essential for the classification. This classification specifies that the granulomatous inflammation does not necessarily need to be histologically proven and can be predicted by noninvasive studies. In some patients, the combination of suggestive clinical characteristics and the presence of cytoplasmic-staining ANCA and/or

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anti-PR3 may be sufficient for making the diagnosis of GPA and initiating treatment [7,8]. It is preferable to have histological evidence however, especially as renal histology is a prognostic factor that determines the therapeutic approach, particularly for the administration of plasma exchange.

According to the criteria of the American College of Rheumatology (ACR; 1990) [9], GPA is defined by the presence of at least two of the following criteria: sinus involvement; lung x-ray showing nodules, a fixed pulmonary infiltrate or cavities; urinary sediment with hematuria or red cell casts; and histological granulomas within an artery or in the perivascular area of an artery or arteriole. The sensitivity and specificity of the ACR criteria are 88.2 and 92.0%.

The exact cause of GPA has yet to be identified and is probably not unique. Environmental factors, such as dust inhalation, or exposure to silica, are most likely involved, but these are only seen in 10% of patients with GPA. It has been suggested that infectious agents may play a role in triggering the disease, particularly through a mechanism of molecular mimicry. Nasal carriage of *Staphylococcus aureus* could be a factor for flares of the disease [10]. Some familial cases reporting the occurrence of GPA cases among siblings have been published. The role of genetic factors in the occurrence of GPA was recently demonstrated in a genome-wide association study of 1683 cases of GPA and 489 of microscopic polyangiitis [11]. The cases of vasculitis with anti-PR3 ANCA were associated with the HLA-DP, SERPINA1 (gene encoding for α1-antitrypsin) and PRTN3 (gene encoding for proteinase 3) genes, while the cases of vasculitis with antimyeloperoxidase ANCA shared a different gene pool, in association with the HLA-DQ gene.

Constitutional signs (fever, asthenia, weight loss) are frequent (50%) but nonspecific.

Ear, nose and throat (ENT) signs are present in 70 to 100% of cases at diagnosis. These can include crusting rhinorrhea, sinusitis, chronic otitis media or damage of the facial cartilage with deformities causing saddle-nose (resulting in a scooped out or depressed appearance of the nose), and/or perforation of the nasal septum, the palate or the pinna of the ear [12]. Nasal-sinus involvement is the most common manifestation of GPA, the most common hallmark of the disease, and may be the only sign in the localized forms. Nasal obstruction with hyposmia or anosmia is often the first symptom.

Lung involvement affects 50 to 90% of patients. It is characterized by alveolar hemorrhage of variable severity (small quantity or more massive, leading to acute respiratory failure), and/or parenchymatous nodules, either single or multiple (rarely more than 10), which are removed in half of the cases. Tracheal and subglottic stenosis, sometimes associated with endobronchial locations, are found in approximately 16% of cases but are rarely hallmarks of GPA [13,14].

The most typical renal involvement is focal segmental necrotizing glomerulonephritis associated with extracapillary proliferation with pauci-immune crescent formation (i.e., without immunoglobulin or complement deposition by immunofluorescence). It is observed in 40 to 100% of cases according to the series and the specialty of the clinicians managing these patients (nephrologists, rheumatologists, internists). It usually leads to microscopic hematuria and proteinuria. There may be involvement of the interlobular arteries, veins and peritubular capillaries. It is the renal damage that negatively impacts the prognosis of this disease. The initial glomerular filtration rate is significantly and independently linked to mortality [15]. The kidney biopsy puncture is done for both the diagnosis and the prognosis (the number of normal glomeruli on biopsy is an important prognostic factor) [16]. Urogenital manifestations are much rarer and have only been described in men. They can be both a hallmark of the disease or occur during relapse. These manifestations can include prostatitis, orchitis, epididymitis, renal pseudotumor, ureteral stenosis or penis ulceration [17].

Involvement of the peripheral nervous system affects about one-third of patients. It is characterized by mononeuritis multiplex or, less commonly, by sensorimotor neuropathy. Involvement of the central nervous system is much rarer (6 to 13%) [18] and may be caused by granulomatous deposits, intracerebral vascular lesions or an extension of sinus lesions. Pachymeningitis is the most suggestive manifestation. Cases of granulomatous infiltration of the pituitary stalk responsible for panhypopituitarism have also been reported.

Muco-cutaneous lesions, mainly vascular purpura to the lower limbs, are reported in 10 to 50% of cases; they can be ulcerating, necrotic and widespread. There may be subcutaneous nodules, pyoderma gangrenosum, raspberry-red gingivitis and intraoral and/or genital ulcerations.

Ocular involvement occurs fairly frequently (14 to 60%), usually in the form of necrotizing nodular episcleritis. Scleritis, corneal ulcerations and retinal vasculitis also occur [19]. Involvement of the eye socket in GPA is rarer but can be suggestive of the disease, especially when it presents as a granulomatous retro-orbital pseudotumor or as dacryoadenitis [20,21]. It can be either a primary form or occur secondary to sinus inflammation, and it typically manifests as inflammatory exophthalmia, which may or may not be associated with ophthalmoplegia.

Cardiac involvement is rare in GPA (<10%). It may be the result of the vasculitis or granulomatous effects,

and can occur as pericarditis, myocarditis or conduction disorders [13,22,23]. The clinical presentation is very heterogeneous, ranging from subclinical manifestations to end-stage heart failure.

Gastrointestinal involvement is rare (5 to 11%) and is characterized by ulcerative lesions, often multiple, as well as intestinal perforation [24,25].

Several studies have highlighted a greater risk of deep vein thrombosis in patients with GPA, particularly in the active phase of the disease [26,27]. However, the available data to date do not support the recommendation of systematic preventative anticoagulation in these patients.

At least two different phenotypes can be distinguished in GPA, but there is no consensus as to their definition, with the two forms described as localized and systemic/diffuse/severe [13]. The localized forms manifest primarily through ENT involvement, naturally limited to the upper respiratory tract, but they are recurrent and refractory (known as 'grumbling disease') [28]. These localized forms appear to affect a younger and more female population [29]. The diffuse forms may manifest through renal involvement and/or intra-alveolar hemorrhage, and/or the involvement of at least one vital organ or that of a nonvital organ but in association with constitutional signs (fever, weight loss). They are often more serious initially, but relapse is less common [29]. The transition from a localized form to a diffuse form and vice versa is possible during the course of the disease. Laboratory tests show the presence of ANCA in 90% of the systemic forms, whereas it is only present in 50 to 80% of the localized forms. Besides their clinical differences and variations with regard to their course and laboratory results, these two phenotypes probably have distinct pathophysiological processes. The localized forms are more granulomatous with greater Th1 lymphocyte polarization, as opposed to the diffuse forms that especially present with vascular inflammatory lesions with greater Th2 lymphocyte polarization [30].

Relapses during GPA occur frequently. One-quarter of patients relapse within 2 years of the diagnosis, and over half relapse within 5 years [31]. All forms of GPA can relapse. The clinical manifestations and the organs involved in relapse may differ from those present at the initial GPA diagnosis. The localized forms with an ENT presentation and/or granulomatous manifestations (orbital pseudotumor, pulmonary nodule) relapse more frequently than the systemic forms with renal involvement [29]. There is a sevenfold relative risk of relapse in chronic nasal carriers of *Staphylococcus aureus* [10]. As a result, long-term use of cotrimoxazole (trimethoprim 160 mg – sulfamethoxazole 800 mg) is recommended in patients with GPA. Variations in the ANCA titre, as well as their specificity and their status, do not appear to be predictive of relapse. In contrast, a persistent positive ANCA is predictive of relapse [32]. Renal involvement in GPA is a major prognostic factor that determines both the functional renal prognosis and the life-threatening potential of the disease. The initial glomerular filtration rate is the best prognostic factor. The classification of glomerular damage in ANCA-associated vasculitides can be used to assess the risk of progression toward end-stage kidney failure [33]. Necrosis in a capillary tuft and the number of normal glomeruli are related to renal function at one year. In contrast, the presence of ENT involvement can be a good prognostic factor [34]. The main causes of mortality in the first year following the diagnosis of GPA were infection (32%) and kidney failure (18%) [35]. At 5 years, infections remain the main cause of mortality, while more long-term causes were not identified.

Therapeutic strategies

GPA is a serious disease, with a nearly always fatal outcome in the absence of treatment. Fortunately, with therapeutic approaches that are increasingly standardized and the emergence of new biotherapies, 90% of patients go into remission, and the survival rate is approximately 80% at 10 years.

Treatment is based on a first phase, known as the induction phase, which aims to quickly put the disease into remission, and lasts about 3 to 6 months according to the clinical response. A second phase, known as the maintenance phase, must then consolidate the remission and limit the risk of relapse; it lasts 12 to 24 months [36]. The intensity of the initial therapeutic approach must be adjusted for each patient, and for the type and seriousness of the GPA in order to avoid two pitfalls: excessive treatment associated with a significant risk of side effects, or insufficient treatment with a risk of failure or early relapse. Mild disease can be defined as normal serum creatinine and no red cell casts or proteinuria, and no organ-threatening or life-threatening manifestations, and severe disease as organ-threatening or life-threatening manifestations, including (but not limited to) marked pulmonary hemorrhage or rapidly deteriorating renal function.

For the induction treatment, it is recommended that GPA be treated with a systemic corticosteroid and immunosuppressant combination. Oral prednisone is recommended at a daily starting dose of 1 mg/kg. For severe or refractory forms, oral corticosteroid therapy is preceded by an intravenous bolus of methylprednisolone at a dosage of 7.5 to 15 mg/kg/day for 1 to 3 consecutive days (depending on the clinical seriousness, the clinician's assessment and the patient's cardiovascular status). After a 3 to 4 week treatment

of oral prednisone (1 mg/kg/day), the corticosteroids are gradually tapered, without going below 15 mg/day before the 4th month. In the absence of an internationally validated tapering regimen, the duration of the tapering in France varies from 18 to 24 months. The addition of an immunosuppressant in the induction phase is essential. For severe or refractory forms, two intravenous immunosuppressive agents can be offered: cyclophosphamide (CYC) or rituximab (RTX). CYC is preferred for use outside of clinical trials (rapidly progressive kidney failure with a serum creatinine >350 µmol/L, intra-alveolar hemorrhage on mechanical ventilation, pulmonary fibrosis). In a French retrospective study, induction therapy with glucocorticoids (GC) alone versus GC plus immunosuppressive drugs was associated with increased mortality [37]. In this cohort, 1, 3 and 5 year survival rates were higher in patients with both GC and cyclophosphamide/rituximab compared with GC alone at 94 versus 73%, 94 versus 64% and 71 versus 51%. Treatment with GC alone was associated with an hazard ratio for death of 2.94. This was consistent with the literature where GC alone carried a 1.7-fold increased risk of death (83 vs 48%) at follow-up. CYC is used at a dose of 600 mg/m^2 (maximum dose of 1.2 g/bolus) every 2 weeks for 1 month (Day +1, Day +15, Day +30), then 700 mg/m^2 every 3 weeks until remission (between 6 and 9 boluses total). The dose will be adjusted for age and kidney function in order to obtain a better tolerability without a decrease in efficacy: 500 mg/m^2 in the presence of kidney failure, and a 500 mg fixed dose every 3 weeks (maximum 6 boluses) if age over 65 years [38]. In a single center retrospective review of 31 consecutive ANCA-associated vasculitis patients aged 60 or more at the time of RTX use for remission induction, RTX was effective for remission induction with a high incidence of infectious complications [39]. There were 3 episodes of bacterial pneumonia, 1 episode of candida pneumonia and 1 episode of disseminated cutaneous zoster. RTX is preferred for use in women of childbearing age or in patients who have already received CYC or have had a relapse after one complete cycle of CYC. In 2010, the RAVE study showed that RTX was as effective as CYC in this indication (i.e., BVAS [Birmingham Vasculitis Activity Score] = 0 at 6 months without corticosteroid therapy, 64% in the RTX arm vs 53% in the CYC arm; $p < 0.001$ for the noninferiority and $p = 0.09$ for the superiority). RTX was even superior in the subgroup of patients with relapse (i.e., BVAS = 0 at 6 months without corticosteroid therapy, 67% in the RTX arm vs 42% in the CYC arm, $p = 0.01$ for the superiority) [40]. In RAVE study, only patients with a serum creatinine <4 mg/dl were included (not patients with RPGN with higher creatinine), also only in these patients, RTX (without additionally CYC) was as effective as CYC in this induction. Furthermore, there were no differences (RTX vs CYC) in the side effects until month 18. RTX is used at a dose of 375 mg/m^2 per week for 4 consecutive weeks. The 18 month follow-up of the patients included in the RAVE study shows the persistence of RTX noninferiority compared with CYC ($p < 0.001$). In the subgroup of patients with relapse, RTX was even superior to CYC at 6 and 12 months follow-up. The superiority of RTX in patients with relapses was no longer evident until month 18 [41]. In another randomized controlled trial (RITUXVAS) 44 patients were enrolled with newly diagnosed GPA or microscopic polyangiitis and renal involvement [42]. The study compared glucocorticoids plus either rituximab (375 mg/m^2/week × 4) with two intravenous cyclophosphamide pulses (n = 33, rituximab group), or intravenous cyclophosphamide for 3–6 months followed by azathioprine (AZA; n = 11, control group). They reported similar remission induction rates and safety between rituximab and cyclophosphamide based regimens for antineutrophil cytoplasm antibody (ANCA)-associated vasculitis at 12 months. The percentage of severe adverse events was not different between the groups (RTX 42%; control 36%), and the rate of mortality was the same (18%).

The role of plasma exchanges in the initial treatment is usually limited to the serious forms of GPA with renal involvement (serum creatinine > 500 µmol/l) or alveolar hemorrhage (in analogy with the treatment of Goodpasture syndrome). They are always prescribed in combination with corticosteroids and an immunosuppressant drug (CYC or RTX), and are given over 6 to 9 sessions. Plasma exchanges at one year, compared with the methylprednisolone bolus, reduce the risk of developing end-stage kidney failure (19 vs 43%), but without significant improvement in overall survival [43]. The on-going, international PEXIVAS study is assessing the efficacy of plasma exchanges in addition to corticosteroids and immunosuppressant drugs for reducing the number of deaths and the progression to end-stage kidney failure [44].

The place of intravenous immunoglobulin (IVIg) in the management of GPA patients is still under debate and no current guidelines exist about the duration, frequency or optimal dose of IVIG [45]. IVIg represent an adjuvant therapy to control disease in patients with some refractory disease. The main reasons for IVIg initiation include patients with ongoing severe infection or recurrent opportunistic infections, treatment-related cytopenia, new onset or relapse of disease in pregnancy, refractory disease to conventional therapy. The main limit is their usually suspensive effect and their high cost [45].

For GPA that is not very severe or is localized or early systemic, methotrexate is used at a dose of 20–25 mg/week ('proof of principle' study – NORAM) [46]. The AGATA study reports the efficacy of abatacept (10 mg/kg IV on Day +1, Day +15, Day +29, then every month) combined with prednisone and an immunosuppressant drug (AZA n = 3, methotrexate [MTX] n = 7 or mycophenolate mofetil [MMF] n = 4) for the treatment of limited and recurrent forms of GPA [47]. Remission (BVAS/WG = 0) was obtained in 16/20 (80%) patients, 11 of whom without prednisone. The efficacy of abatacept appears to be very rapid (remission after a median duration of 1.9 months) and lasting (median remission duration of 14.4 months). At the end of the study, 3 (19%) patients had relapsed after going into remission, and 3 others (19%) did not have a lasting response or worsened on treatment.

The maintenance treatment of GPA lasts between 18 and 24 months after remission is achieved. It combines oral corticosteroids with azathioprine (2 mg/kg/day orally) or methotrexate (20–25 mg/week) [48]. The multicentric prospective randomized controlled MAINRITSAN study showed that a treatment with systematic reinfusions of rituximab at a fixed dose of 500 mg at day 1 (4.5 months after the start of induction therapy), at day 15, and then every 6 months is superior to the 'conventional' maintenance treatment with azathioprine to prevent major relapses. At 28 months, the rates of major relapses were 5% in the 57 rituximab-arm patients versus 29% in the 58 azathioprine-arm patients; p = 0.02 [49]. The rates and types of adverse events were comparable in both arms. RTX had a lower risk of relapse compared with AZA at 28 and 44 months after the start of the maintenance treatment (rate of major relapses at 44 months: 18.2% in the RTX arm vs 51.9% in the AZA arm). The rhythm of RTX administration for maintaining patients in remission is under evaluation (MAINRITSAN 2 study). The study compares the administration of systematic RTX given biannually (Day +1, Day +15, then Month +6, Month +12 and Month +18) versus RTX given according to the changes in the laboratory parameters (ANCA and/or level of $CD19^+$ lymphocytes).

The possibility to use lower doses of RTX has been evaluated. One study evaluated the efficacy of a single dose of RTX (375 mg/m^2) for remission induction and maintenance in 16 patients with ANCA-associated vasculitides [50]. A retreatment for maintenance was possible (a single dose of RTX every 6 to 9 months) in case of rising antibody titers or B-cell return. Remission was achieved in 11 (68%) patients, with a mean time to remission of 9.4 months, and 9 patients had a relapse, with a mean time to relapse of 5.3 months (range, 4 to 24 months). At 24 months, 9/11 (82%) responders were still in remission. In another study, 19 patients with ANCA-associated vasculitides received one single infusion of RTX 375 mg/m^2 [51], and 8 patients received additional immunosuppression at the time of RTX treatment. Complete remission was achieved in 80% of patients at 3 months, with no difference between anti-MPO and anti-PR3-positive patients. Four (21%) patients had a disease relapse, with a median time to relapse of 27 months. The possibility to use lower doses of RTX, which remains an expensive drug not superior to the cyclophosphamide-azathioprine regimen according to the RAVE and RITUXVAS trials, deserves further evaluation.

The problem of localized organ lesions in the course of GPA is to distinguish between signs of active disease requiring systemic therapy and organ lesions which require a localized therapeutic approach. Subglottic stenosis is one of the local symptoms which may occur independently or in association with involvement of other organs. Main usual local procedures include dilations, local corticosteroid injection or application of mitomycin, laser, stenting or tracheal surgery. A Swedish group recently reported a new endoscopic submucosal technique [52] which consists in the incision of the stenosis in its upper part, then the removal of the submucosal fibrous and granulomatous tissue, followed by the reappliance of the mucosa using fibrin sealant and mitomycin. Among 13 patients, patient dyspnea improved in all and quality of life improved in 11. After a mean follow-up of 3.5 years, only 4 patients required only one procedure.

Treatment with cotrimoxazole (sulfamethoxazole/trimethoprim at a dose of 400 mg/80 mg) per day is systematically given for the prevention of relapse of GPA and of *Pneumocystis jirovecii* infections. It has been shown to reduce the incidence of relapses in patients with GPA in remission [53]. Vaccinations should follow the usual immunization schedule, with the contraindication of live vaccines.

Overall, the new therapeutic approaches significantly reduce toxicity and provide better tolerability in the long-term. The treatment regimens are increasingly adapted to the expression of the disease and to its course; relapses remain frequent however, and the maintenance treatment methods warrant better standardization.

Conclusion

The treatment of adult patients with severe GPA includes an induction phase to obtain the remission, then a maintenance phase to maintain the remission. The induction treatment of GPA is based on the combination of glucocorticoids and either cyclophospha-

mide or rituximab. Despite considerable therapeutic progress over the last decades, relapses of GPA remain frequent, and maintenance treatment is now the main therapeutic challenge. Rituximab is an alternative for cyclophosphamide for induction of remission and may be the first choice for relapsing patients and those refractory to cyclophosphamide.

Future perspective

GPA is now a chronic relapsing disorder with >50% rate of relapse within 5 years of initial remission. Effective induction therapy with corticosteroids combined with cyclophosphamide or rituximab transformed the survival of patients with GPA, with 5 year survival rates >80%.

Maintenance therapy to prevent relapses and the occurrence of late complications remains the main therapeutic challenge in this vasculitis. Newer therapies, either alone or in combination, will need to both improve efficacy particularly to maintain long term remission and permit reductions in glucocorticoid and immunosuppressive exposure. Rituximab is a promising therapy for maintenance of remission, but long-term safety should be awaited.

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Executive summary

- Granulomatosis with polyangiitis (GPA) is a multifocal vasculitis characterized by frequent involvement of the upper and lower respiratory tract and kidneys.
- The presence of c-antineutrophil cytoplasmic antibodies with antiproteinase three specificity is observed in more than 90% of patients with GPA.
- Two phenotypes of GPA are recognized: systemic forms, with potentially life-threatening manifestations, and more limited forms (localized or early systemic GPA).
- Chronic nasal carriage of *Staphylococcus aureus* is related to endonasal activity of GPA and relapses; prophylactic treatment with co-trimoxazole is effective in reducing relapse rate.
- The treatment of adult patients with severe antineutrophil cytoplasmic antibodies-associated vasculitides is staged, first with an induction phase to obtain the remission, then a maintenance phase to maintain the remission.
- The induction treatment of GPA is based on the combination of glucocorticoids and either cyclophosphamide or rituximab. Rituximab is an alternative for cyclophosphamide for induction of remission and may be the first choice for relapsing patients and those refractory to cyclophosphamide.

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