

# Wegener's Granulomatosis

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## Abstract

*Wegener's granulomatosis (WG) is a necrotizing vasculitis associating inflammation of the vessel wall and peri- and extravascular granulomatosis. Its complete form is clinically characterized by ear, nose and throat manifestations, pulmonary involvement and renal involvement. Other systemic manifestations of vasculitis can also be present. WG is a rare disease and its prevalence has been estimated to be 24/1,000,000 inhabitants in the Paris region and 30/1,000,000 inhabitants in the United States. Both sexes are affected. The mean age of occurrence is 45 years. Forms have been described in very elderly subjects and children. WG is a severe disease that is fatal if left untreated. However, currently available treatments can control its evolution and even cure most cases of the disease, although relapses remain frequent.*

## Keywords

necrotizing vasculitis, multisystemic disease, ANCA

## Pathogenesis of the disease

Although better understood at present, the pathogenetic mechanisms of Wegener's granulomatosis (WG) are not completely known (1). The discovery of antineutrophil cytoplasm antibodies (ANCA) showed that pathogenic antibodies could be directly involved in the vasculitic process. Under the effect of an unknown antigen and certain cytokines (anti-tumor necrosis factor-alpha (TNF $\alpha$ ) and interleukin-1b $\beta$ ), neutrophils express cytoplasmic proteinase 3 (PR3) on their surface, leading to the production of anti-PR3 antibodies, followed by leukocyte and monocyte rolling and cell adhesion to the vessel wall via adhesion molecules (selectin, lymphocyte function-

associated antigen 1 (LFA-1), etc.). Under the influence of cytokines and ANCA, diverse factors (reactive oxygen species (ROS)) are released and contribute to the aggression of the vessel wall. ANCA also directly attack the vessels and PR3 participates in these phenomena. Vessel thrombosis ensues. Granuloma formation occurs secondarily and requires the input of lymphocyte subpopulations, whose exact roles are poorly elucidated. In addition, according to the stage of the disease, the respective preponderance of granulomatous and vasculitic elements can vary. Certain forms, often the earliest, are more granulomatous; others, later, are predominantly vasculitic.

### Histopathology

In histological terms, WG consists of ischemic necrosis with a specific "geographical" organization, with the formation of a non-microbial abscess and a polymorphic granuloma containing polymorphonuclear leukocytes, lymphocytes and multinucleated giant cells. The vasculitis affects small-sized vessels, and, more rarely, middle-sized vessels, capillaries and venules. It is often difficult to single out because of the predominance of granulomas. A granuloma containing giant cells is not specific. Histological proof of the diagnosis can be obtained by biopsy of clinically involved sites; however, they should be selected carefully so as to avoid risk for the patient.

### Potential biopsy sites

A lung nodule can be biopsied in a patient presenting with alveolar hemorrhage. Nodule biopsy can reveal a granuloma containing palisading epithelial cells and vasculitis. Capillaritis is seen in the majority of patients with alveolar hemorrhage. Lung biopsy is guided by fiber optic bronchoscopy. Thoracotomy is a highly invasive intervention, whose associated mortality and morbidity are not negligible. The necessity of such an act should be considered, especially for a patient with a highly suggestive clinical picture including ANCA giving a diffuse cytoplasm-labeling pattern (c-ANCA) and of anti-

PR3 specificity, as detected by enzyme-linked immunosorbent assay (ELISA).

A nasal-sinus biopsy is easy to do but requires a good technical approach with numerous samples taken from granulomatous and necrotic zones. However, it is less informative than lung biopsy. Kidney biopsy should imperatively be done as soon as urinary sediment abnormalities, proteinuria and/or even a moderate change of renal function are observed. It should be carefully examined for extracapillary glomerulonephritis and direct signs of vasculitis, with an assessment of the degree of parenchymatous involvement.

Muscle or neuromuscular biopsy is useful and highly contributive to the diagnosis when the patient presents with peripheral neuropathy. Although temporal artery biopsy also yields helpful information for patients with headaches, its systematic use has not been validated.

### Prevalence

WG is a rare disease, whose prevalence is estimated to be 24/1,000,000 inhabitants in the metropolitan Paris region and 30/100,000 inhabitants in the United States. It affects both sexes. Although the mean age at the time of occurrence is 45 years, some cases have been described in very elderly subjects and children. The principal clinical manifestations are summarized in Table I (2-5)

| Characteristic   | Hoffman <i>et al.</i> (3) 1992 | Anderson <i>et al.</i> (2) 1992 | Matteson <i>et al.</i> (5) 1996 | Reinhold-Keller <i>et al.</i> (4) 2000 |
|--|--------------------------------|---------------------------------|---------------------------------|--|
| Number of patients   | 158                            | 265                             | 77                              | 155                                    |
| M/F ratio  | 50/50                          | 55/45                           | 64/36                           | 49/51                                  |
| Age (yr)   | 41                             | 50                              | 45                              | 48                                     |
| Year of diagnosis  | 1966-90                        | 1975-85                         | 1978-87                         | 1966-93                                |
| Years of follow-up (mean)  | 8                              | NR <sup>a</sup>                 | 7.1                             | 7                                      |
| c-ANCA positivity (%) <sup>b</sup>   | 88                             | NR                              | NR                              | 84                                     |
| Involvement <sup>c</sup> (% at time of diagnosis/% at any time during disease evolution) |                                |                                 |                                 |  |
| Ear, nose, throat  | 73/92                          | 75/NR                           | NR/NR                           | 93/99                                  |
| Kidney   | 18/77                          | 60/NR                           | NR/73                           | 54/70                                  |
| Lung   | 45/85                          | 63/NR                           | NR/53                           | 55/66                                  |
| Eye  | 15/52                          | 14/NR                           | NR/NR                           | 40/61                                  |
| Heart  | NR/8                           | NR/NR                           | NR/14                           | 13/25                                  |
| Peripheral nerve   | NR/15                          | NR/NR                           | NR <sup>d</sup>                 | 21/40                                  |
| Central nervous system   | NR/8                           | NR/NR                           | NR <sup>d</sup>                 | 6/11                                   |
| Gastrointestinal tract   | NR/NR                          | NR/NR                           | NR/19                           | 3/6                                    |
| Skin   | 13/46                          | 25/NR                           | NR/NR                           | 21/33                                  |
| Arthralgias  | 32/67                          | 20/NR                           | NR/NR                           | 61/77                                  |
| Localized involvement (% of patients diagnosed)  | NR                             | 22                              | NR                              | 15                                     |
| Patients on cyclophosphamide (%)   | 89                             | 29 <sup>e</sup>                 | 60                              | 92                                     |
| Prednisone (mg/d) <sup>f</sup>   |                                |                                 |                                 |  |
| Initially  | 70                             | NR                              | NR                              | 70                                     |
| After 3 months   | 30                             | NR                              | NR                              | 10                                     |
| Infections (%)   | 46                             | NR                              | NR                              | 26                                     |
| Mean survival (yr) NR 8.5 NR 21.7g   | NR                             | 8.5                             | NR                              | 21.7 <sup>g</sup>                      |
| Death rate (%)   | 20                             | 56                              | 36                              | 14                                     |
| Deaths due to WG or its treatment (%)  | 13                             | NR                              | NR                              | 12                                     |
| Deaths due to infection (%)  | 3                              | 12                              | 10                              | 3                                      |

**Table I. Characteristics of WG described in different series reported in the literature.**

<sup>a</sup>NR: not reported.

<sup>b</sup>Antineutrophil cytoplasm antibodies directed against proteinase 3 and giving a diffuse cytoplasm-labeling pattern.

<sup>c</sup>Anderson *et al.* reported only information collected at the time of diagnosis.

<sup>d</sup>Peripheral and central nervous systems.

<sup>e</sup>During the first 3 months.

<sup>f</sup>Dose based on a body weight of 70 kg.

<sup>g</sup>Survival estimated using the Kaplan–Meier method.

### **Ear, nose and throat (ENT) manifestations**

ENT signs are often those that reveal the disease. They can persist for several months and remain unrecognized until other manifestations arise. Long-lasting sinusitis or rhinitis is common. Computed tomography (CT) scan, which can show bone destruction, is necessary for the diagnosis and evaluation of the lesions. Sinusitis, nose bleeds and deafness have also been described. Subglottic stenosis is less common. Finally, the orbital region can be affected with an initial clinical picture of inflammatory pseudotumor and unilateral exophthalmia.

### **Pulmonary manifestations (6)**

Pulmonary symptoms are non-specific: cough, dyspnea, thoracic pain, hemoptysis. Chest radiographs and CT scans show uni- or bilateral, isolated or multiple nodules, cavitated in half of the patients, and often with a thick wall. They can be numerous but, generally, are fewer than 10. Their occurrence parallels the progression of the disease. Uni- or bilateral pulmonary infiltrates can also be seen. A pleural effusion can be associated. Fiber optic bronchoscopy can detect stenoses caused by granulomatosis. They are often difficult to treat. Pseudotumoral pulmonary masses can also be found.

Alveolar hemorrhage is one of the severe manifestations of WG and it can be complicated by a respiratory distress syndrome. The association of pulmonary manifestations and renal insufficiency define the pulmonary–renal syndrome that is suggestive of several vasculitides, including WG.

### **Renal manifestations**

These symptoms consist of rapidly progressive renal insufficiency due to glomerulonephritis with extracapillary crescents.

Immunofluorescence is negative.

Renal involvement can lead to end-stage renal failure. It is extremely important to detect it. Hematuria and proteinuria must be sought at the time of diagnosis and at each follow-up visit. The diagnosis of extracapillary glomerulonephritis can be made only based on a renal biopsy. Undetected or not treated in time, it progresses towards severe renal insufficiency. It is important to initiate treatment rapidly, because a partial or total reversal can be obtained under specific

immunosuppressive therapy (corticosteroids and immunosuppressants).

Renal insufficiency can also have other causes, which cannot be ignored: ureteral stenosis responsible for uni- or bilateral hydronephrosis. In a treated patient, renal insufficiency can also have an iatrogenic origin.

### **Other manifestations**

Other symptoms are the same as those observed in other vasculitides. We would like, nonetheless, to point out the possibility of peripheral neurological manifestations that are not specific to the disease and cutaneous signs reflecting involvement of small-sized vessels. Joint and/or muscle manifestations are also possible.

### **Biological and immunological analyses**

WG is accompanied by an immunological component, c-ANCA, essential to the diagnosis and perhaps to patient monitoring. These antibodies directed against PR3 are present in more than 80% of the systemic forms of the disease and 50% of the localized forms. ANCA detected during the course of WG are highly specific and thus carry a high diagnostic value. Under certain conditions, their presence, in association with a suggestive clinical picture, can suffice for the diagnosis. In contrast, it does not circumvent the need for a renal biopsy, which not only establishes the diagnosis but also provides information on the prognosis of renal involvement by revealing the recent or longstanding status of lesions and the extent of their dissemination.

ANCA are often present before a relapse becomes manifest and their persistence under treatment is a factor predictive of relapse, but their disappearance does not allow the possibility of a relapse to be excluded. Although the ANCA titer can also be used to monitor therapy, it is still too early to use it as a marker to adapt therapy.

### **Evolution and prognosis**

Untreated, WG is always fatal. Under treatment, more than 80% of the patients enter remission. Unfortunately, relapses, regardless of their characteristics, are common, occurring in at least 50% of the patients. Some side effects can be seen under therapy: infectious during the short term, particularly, *Pneumocystis carinii* pneumonia (PCP); and malignant over the long term, with the development of bladder disorders (hemorrhagic cystitis), lymphomas and solid tumors under cyclophosphamide. However, the severity of the disease justifies the use of such potent therapies. Prophylaxis against infections is also justified. Indeed, it is necessary to prevent PCP for which co-trimoxazole is

prescribed (1 tablet/d; 400 mg of sulfamethoxazole). Prophylaxis against other infections, tuberculosis for example, is not mandatory, but should be adapted to each patient's potential risk of infection.

The prognosis of WG is associated with different factors: advanced age and renal insufficiency, for example are indicators of a poor prognosis. On the other hand, ENT involvement is a sign of good prognosis. The prognostic factors might reflect the pathogenetic mechanisms of the disease: a good prognosis for the predominantly granulomatous entity and a poor prognosis for the predominantly vasculitic forms.

### Treatment

Treatment of WG relies on the combination of corticosteroids and immunosuppressants. For the systemic forms, it has been demonstrated (7) that corticosteroids, when they are prescribed alone, cannot obtain and maintain remission. The first cases of prolonged remission and cure were obtained when cyclophosphamide was combined with corticosteroids (3). This combination is now considered the 'gold standard' for WG. Nevertheless, long-term study of WG patients has shown that more than half of them on long-term therapy relapse but that long-term therapy is needed to control the disease. In addition, the total duration of treatment is sometimes difficult to define. One of the consequences of such prolonged therapy is the development of frequent and severe side effects. Hoffman *et al.* (3) demonstrated that the risks of developing bladder cancer, lymphoma and solid tumor were multiplied by 33, 11 and 2.4, respectively.

### Corticosteroids

The initial dose is 1 mg/kg/day. It is sometimes preceded by one or several pulses of methylprednisolone (15 mg/kg/d). After the first 3–4 weeks of treatment, the corticosteroid dose can be tapered, but therapeutic preferences vary for each treating physician. Hoffman *et al.* (3) proposed rapidly passing to corticotherapy on alternating days in an attempt to lower the risk of side effects. Disease control essentially relies on cyclophosphamide. In France, tradition, in conjunction with the results of controlled trials, has led to treating patients continuously with relatively high doses of prednisone. The European Systemic Vasculitis Trial Group (EUVAS) recommends doses intermediate to those used in American and French studies. Objectively, the clinical results have been comparable, regardless of the method applied to taper steroids, but the iatrogenic risk has prompted us to lower the steroid dose as much as possible. It is also desirable, at the end of the first month of therapy, to sharply decrease the

corticosteroid dose and to try to attain a half-dose within 3–6 months.

### Cyclophosphamide

Consensus on the modalities of cyclophosphamide use has not yet been reached. The oral formulation is prescribed at 2 mg/kg/day (3) and can be adapted to the therapeutic response, the occurrence of side effects and the patient's age.

The duration of treatment varies from one country to another: 18 months in France and United States (3), 3–9 months in the United Kingdom (8). Indeed, the duration of treatment is partly conditioned by the choice of maintenance therapy. Cyclophosphamide pulses, 0.5–0.7 g/m<sup>2</sup> given every 3–4 weeks, have also been tried by some authors (9, 10), with comparable results obtained in all studies. Indeed, the data demonstrated that these two intravenous doses gave the same results as those obtained with the oral formulation. Nevertheless, the number of relapses is high when this treatment is prolonged. The most optimistic results were similar, but they usually were obtained with patients having a variety of different types of vasculitides associated with ANCA, notably including microscopic polyangiitis, which responds more favorably to cyclophosphamide pulses than WG.

In our experience, pulse therapy is effective and can obtain remission, but does not seem capable of maintaining it. The therapeutic strategy that remains to be devised must therefore concentrate on treatment(s) to maintain remission.

### Other immunosuppressants – New drugs

Azathioprine is frequently prescribed as maintenance therapy and appears to be effective and well tolerated. It induces fewer side effects than cyclophosphamide over the long term. The initial therapeutic dose is 2–3 mg/kg/day. This dose has to be adapted to the patient, as described above cyclophosphamide.

Methotrexate is also prescribed as maintenance therapy and for some WG relapses (11). The weekly dose is 0.3 mg/kg. Its efficacy is inferior to that of cyclophosphamide but good results have been obtained and this drug is the currently being evaluated in prospective trials (NIH, EUVAS). Methotrexate is also responsible for adverse events: hepatic toxicity, hypersensitivity pneumonia, transient medullary hypoplasia, etc. Other medications have been tested but require further investigation. Cyclosporine (cyclosporin A) appears to be effective in some patients, but has not been validated as first-line therapy and its efficacy/toxicity ratio does not justify its initial use. New drugs (mycophenolate mofetil, deoxyspergualine) have been tested in limited

numbers of patients. They were always prescribed as maintenance therapy or in patients who had relapsed or suffered from disease refractory to corticosteroids and cyclophosphamide. The initial results have been promising. Their use, however, cannot be generalized for the time being.

For patients with WG refractory to all treatments, EUVAS has proposed the administration of antithymoglobulins ("Solution" protocol) and TNF inhibitors can also be tried. Other authors have prescribed intensive chemotherapy followed by autologous bone-marrow transplantation. Analysis of the results will be conducted once sufficient follow-up has been obtained.

#### *Immunoglobulins*

Intravenous immunoglobulins have essentially been given to patients with ANCA-associated vasculitides who relapsed. They have also been tested in untreated patients. The results obtained indicated a real efficacy of this therapy, which also led to a lowering of the ANCA titer. Nevertheless, some patients relapsed and this treatment needs to be evaluated with prospective trials. This therapy is, on the whole, well tolerated. Immunoglobulins are administered intravenously at a dose of 2 g/kg each month. The dose is infused over 2 days, but we recommend extending it to 4 days for patients suffering from renal insufficiency.

#### *Plasma exchanges*

No indication has been found to support using plasma exchanges as first-line therapy for WG.

#### **Conclusion**

WG is a severe, chronic disease that often relapses. Nonetheless, its prognosis has been improved by the application of prolonged, adapted therapy and survival at 5 years exceeds 80% in some series. One of the major therapeutic problems is the occurrence of treatment-related side effects, whose severity and frequency are often associated with prolongation of the treatment, which remains hard to avoid.

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