The treatment of Wegener's Granulomatosis with immunosuppressive-cytotoxic drugs

By P. J. FROUD (London) and A. H. HENDERSON (Bristol)

Abstract

Previous reports of 18 patients with Wegener's Granulomatosis treated with immunosuppressive and cytotoxic drugs are reviewed, and 4 new cases are reported. The prognosis in these patients is shown to be significantly better than that found in previous series where such drugs were not used.

Introduction

Wegener's Granulomatosis—WG—is generally distinguished from other polyarteritic conditions by the presence of (1) necrotizing granulomata of the upper respiratory tract, with or without bronchopulmonary involvement, together with (2) arteritis of wider distribution, leading to (3) necrotizing glomerulitis (Zeek, 1953; Godman and Churg, 1954; Walton, 1958). Malignant Granuloma (Lethal Midline Granuloma, Granuloma Gangraenescens)—MG—is a separate clinical entity where necrotizing granulomata remain localized in the upper respiratory tract (Stewart, 1933; Spear and Walker, 1956), but it may sometimes progress to typical WG (Mills, 1967). MG can be successfully controlled by local radiotherapy (Ellis, 1955; Howells, 1955), by immunosuppressive-cytotoxic drugs (Ristow and Martin, 1969; Peermohamed and Shafar, 1969), and in some cases by corticosteroids (Malcolmson, 1966; Friedmann and Osborn, 1969), but the prognosis of generalized WG remains poor. Thus the two-year mortality in WG was over 90 per cent in one series of patients treated with high doses of steroids (Hollander and Manning, 1967), and over 94 per cent in an earlier series (Walton, 1958). More recent individual case reports and experience with the patients to be described below, suggest that cytotoxic and immunosuppressive drugs—hereinafter named cytotoxic drugs—may be beneficial in the treatment of WG. However, controlled therapeutic trials are difficult because of the rarity of the disease, and the management of WG remains controversial (Brit. Med. J., 1969). To assess the value of cytotoxic therapy, previously reported cases treated with these drugs have been reviewed, together with four newly described cases, and their prognosis has been compared with that found in two series where cytotoxic drugs were not used (Walton, 1958; Hollander and Manning, 1967).
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Review

Details of all patients with WG treated with cytotoxic drugs are summarized in Tables I and II. Current information about as many as possible of the previously reported cases was obtained by personal inquiry. Four previously unreported cases, described below, provide illustrative examples of the response to cytotoxic drugs.

**TABLE I.**

**Wegener’s granulomatosis with renal involvement treated by cytotoxic drugs.**

<table>
<thead>
<tr>
<th>Case</th>
<th>Reference</th>
<th>Steroids</th>
<th>Cytotoxics</th>
<th>Known survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Fahey, Leonard, Churg and Godman, 1954. (Case 7)*</td>
<td>Yes</td>
<td>Triethylene melamine, nitrogen mustard</td>
<td>Alive at 36 months, but subsequently died, date unknown</td>
</tr>
<tr>
<td>2.</td>
<td>Aungst and Lessmann, 1962.</td>
<td>Yes</td>
<td>Nitrogen mustard, chlorambucil</td>
<td>Dead at 6 months, 26 days after starting cytotoxics</td>
</tr>
<tr>
<td>3.</td>
<td>Kraus, Vortel, Fingerland, Salavec and Krch, 1965. (Case 2)</td>
<td>Yes</td>
<td>Nitrogen mustard analogue</td>
<td>Alive at 60 months</td>
</tr>
<tr>
<td>4.</td>
<td>Bouroncle, Smith and Cappage, 1967.*</td>
<td>No</td>
<td>Azathioprine</td>
<td>Died at 61 months</td>
</tr>
<tr>
<td>5.</td>
<td>Wing and Bulteau, 1967.*</td>
<td>Yes</td>
<td>Chlorambucil</td>
<td>Alive at 36 months</td>
</tr>
<tr>
<td>6.</td>
<td>Hollander and Manning, 1967.*</td>
<td>Yes</td>
<td>Nitrogen mustard, chlorambucil</td>
<td>Alive at 46 months</td>
</tr>
<tr>
<td>7.</td>
<td>Bruno and Fischer, 1967.</td>
<td>Yes</td>
<td>Azathioprine</td>
<td>Dead at 5 months, 5 days after starting cytotoxics</td>
</tr>
<tr>
<td>8.</td>
<td>Norton, Suki and Strunk, 1968. (Case 1)</td>
<td>Yes</td>
<td>Azathioprine</td>
<td>Alive at 43 months</td>
</tr>
<tr>
<td>9.</td>
<td>Norton, Suki and Strunk, 1968. (Case 2)</td>
<td>Yes</td>
<td>Azathioprine</td>
<td>Alive at 17 months</td>
</tr>
<tr>
<td>10.</td>
<td>Toma, 1968. (Case 2)</td>
<td>Yes</td>
<td>Cyclophosphamide (intra-arterial)</td>
<td>Dead at 39 months</td>
</tr>
<tr>
<td>11.</td>
<td>Kaplan, Hayslett and Calabresi, 1968. (Case 1)</td>
<td>Yes</td>
<td>Azathioprine, duazomycin A</td>
<td>Alive at 19 months</td>
</tr>
<tr>
<td>12.</td>
<td>Kaplan, Hayslett and Calabresi, 1968. (Case 2)</td>
<td>Yes</td>
<td>Azathioprine, duazomycin A</td>
<td>Alive at 41 months</td>
</tr>
<tr>
<td>13.</td>
<td>Ristow and Martin 1969. (Case 2)*</td>
<td>Yes</td>
<td>Azathioprine, 6-mercaptopurine</td>
<td>Alive at 24 months</td>
</tr>
<tr>
<td>15.</td>
<td>Froud and Henderson, 1971.</td>
<td>Yes</td>
<td>Azathioprine</td>
<td>Dead at 36 months</td>
</tr>
<tr>
<td>17.</td>
<td>Froud and Henderson, 1971.</td>
<td>Yes</td>
<td>Azathioprine</td>
<td>Alive at 26 months</td>
</tr>
<tr>
<td>18.</td>
<td>Froud and Henderson, 1971.</td>
<td>Yes</td>
<td>Chlorambucil, azathioprine</td>
<td>Dead at 23 months</td>
</tr>
</tbody>
</table>

* Current information by personal communication December 1969–February 1970.
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Table II.

WEGENER'S GRANULOMATOSIS WITHOUT RENAL INVOLVEMENT TREATED BY CYTOTOXIC DRUGS.

<table>
<thead>
<tr>
<th>Case</th>
<th>Reference</th>
<th>Steroids</th>
<th>Cytotoxics</th>
<th>Known survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>19.</td>
<td>Von Leden and</td>
<td>Yes</td>
<td>Methotrexate (intra-arterial and oral)</td>
<td>Alive at 36 months</td>
</tr>
<tr>
<td></td>
<td>Schiff, 1964</td>
<td></td>
<td>5-Fluorouracil</td>
<td>Dead at 100 months</td>
</tr>
<tr>
<td>20.</td>
<td>Greenspan, 1965</td>
<td>Yes</td>
<td>Methotrexate</td>
<td>Alive at 68 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chlorambucil</td>
<td>Dead at 47 months</td>
</tr>
<tr>
<td>21.</td>
<td>McIlvanie, 1960</td>
<td>No</td>
<td>Chlorambucil</td>
<td>Alive and symptom-free at 24 months</td>
</tr>
<tr>
<td></td>
<td>(Case 1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22.</td>
<td>McIlvanie, 1960</td>
<td>No</td>
<td>Chlorambucil</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Case 2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23.</td>
<td>McIlvanie.*</td>
<td>Yes</td>
<td>Chlorambucil</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Previously un-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>published)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Current information by personal communication, December 1969–February 1970.

In Table I are included all patients who fulfil the diagnostic criteria of Godman and Churg (1954). The survival of patients in this series (series C) is compared in Fig. 1 with that found in two previous series where cytotoxic drugs were not used (series A: Walton, 1958; series B: Hollander and Manning, 1967). The one patient common to both these previous series who received cytotoxic drugs (Case I in Table I) was transferred to series C. The same diagnostic criteria were used in all three series, and survival was similarly calculated from the onset of symptoms referable to the disease until the last known date alive. Survival was only insignificantly better in patients treated with high doses of steroids (series B) than in those where steroids were generally not given (series A). However, in patients who received cytotoxic drugs (series C) survival was significantly better \( p < 0.01 \) than in series B at 12, 24 and 36 months. Mean survival in series A, B and C was 5, 6 and 36 months respectively (C cf. B, \( p < 0.01 \)), and two-year mortality was 95, 92 and 28 per cent respectively (C cf. B, \( p < 0.001 \)).

The original diagnostic criteria for WG included renal involvement (Fahey, Leonard, Churg and Godman, 1954), which is usually a manifestation of advanced disease. Patients who fulfilled the diagnostic criteria for WG except that they showed no evidence of renal lesions, may thus have been effectively treated early in the course of the disease or may have had a less severe form of the disease. Such patients (including one previously unreported case) who were treated with cytotoxic drugs are considered separately in Table II and Fig. I (series D). Their mean survival was 55 months and the two-year mortality was zero \( p < 0.05 \), cf. series C).

Case reports

Case 15.

A previously fit 29-year-old nurse developed eustachian tube obstruction in October, 1964, and otitis media complicated by facial palsy in August, 1965.
Mastoidectomy, performed in September, was followed by persistent fever, unproductive cough and weight loss. Six weeks later she had become emaciated and confused, with hoarseness, haemorrhagic nasal discharge and ulceration of the tongue and epiglottis; skin papules were present over the elbows and there was a small ischaemic lesion on one finger; basal pulmonary crepitations and a transient pericardial rub were heard. Haemoglobin was 7.9 g./100 ml., a polymorph leukocytosis was present, E.S.R. was 67 mm./hour, and serum levels of immunoglobulins A and G were increased. Chest radiograph showed scattered nodular opacities in both lungs, and fluid levels were demonstrated in both antra. Urine contained no protein or abnormal microscopic deposit and blood urea was normal. Necrotizing arteriolitis was found in a biopsied skin papule (Dr. O. C. Lloyd). Treatment with prednisone 100 mg./day was followed by marked clinical improvement and clearing of the chest radiographs. Subsequent reduction of prednisone resulted in a recurrence of fever, anaemia.
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and pulmonary opacities. However, increasing the dose to 40 mg./day was associated with the development of paranoid psychosis. When the prednisone was reduced to 20 mg./day and azathioprine 100 mg./day was started, her general and psychiatric state improved. In June 1966, her clinical condition remained satisfactory, although there was perforation of her nasal septum, urine contained albumin and red blood cells, and urea clearance was 50 per cent of normal. The azathioprine was increased to 200 mg./day and the prednisone reduced to 10 mg./day. On this regime she was able to resume part-time work. Full details of her subsequent course and treatment during 1967 are unavailable, but she is reported to have deteriorated rapidly with generalized arthropathy in September, and died in October, 1967.

Case 16.

A 25-year-old housewife presented in February, 1967 with epistaxes and severe nasal pain. Biopsy of the nasal septum showed giant-cell vasculitis (Dr. A. Levene). Treatment with betamethasone 4 mg./day and antibiotics was started in March, but she then developed bilateral otitis media, left facial palsy and bilateral conductive deafness, followed by exertional dyspnoea and haemoptysis. In July, she was critically ill and cyanosed but afebrile. The nasal septum was perforated, and purulent exudate covered both choanae and tympanic membranes. The antra were radiologically opaque; chest radiographs showed consolidation and cavitation of the right lower lobe and thin-walled cavities in both upper lobes. Staphylococcus aureus was cultured from the sputum and from the nose and ears. Haemoglobin was 9.6 g./100 ml., polymorph leukocytosis was present, E.S.R. was 135 mm./hour, and serum levels of immunoglobulins A and M were increased. Urine contained albumin but no red blood cells and blood urea was normal. She was treated with prednisone 80 mg./day and antibiotics, but developed a right pneumothorax and became acutely depressed. Prednisone was reduced to 15 mg./day and azathioprine 150 mg./day was given, together with a course of 400 rads of 250 kV irradiation to the nasopharyngeal lesions. Clinical improvement followed, with partial resolution of the facial pain and deafness; the upper lobe cavities disappeared, but the right lower lobe remained collapsed; haemoglobin rose to 12 g./100 ml. She has since then continued to take azathioprine 150 mg./day and prednisone 15–30 mg./day. Staphylococcal lung infections recurred during 1968, and in October bronchoscopy showed stenosis of the right middle and lower lobe bronchi; mucosal biopsies revealed chronic inflammation with eosinophilic infiltration. She has otherwise remained generally well, but still experiences occasional haemoptysis. In addition she carried through a normal pregnancy and delivered a normal infant in July, 1969 (Cooper, Stafford and Turner-Warwick, 1970).

Case 17.

A 28-year-old housewife developed WG in January, 1968, with typical nasal, pulmonary and renal lesions, confirmed by renal biopsy. On prednisone 80 mg./day her nasal symptoms improved, but haematuria and evidence of impaired glomerular filtration rate persisted. The haematuria ceased when
azathioprine 250 mg./day was added, but in October, taking azathioprine 200 mg./day and prednisone 5 mg./day, tiredness, pyrexia and epistaxes recurred. The prednisone was increased to 40 mg./day for ten days, and by December, 1968, all symptoms had disappeared. She has subsequently remained well, taking azathioprine 200 mg./day and prednisone 15 mg./day, with normal urine and creatinine clearance.

Case 18.
A 28-year-old man presented in February, 1969, with an 18 month history of intermittent paranasal pain, haemorrhagic nasal discharge and productive cough. He was cachectic and febrile, with marked tenderness over the antra. Urine contained albumin, red cells and casts. Blood urea was 66 mg./100 ml. The pyrexia settled with chlorambucil 10 mg./day, but he again deteriorated and in April methyl prednisolone was added, in an initial dose of 64 mg./day. In July bilateral infiltration of the lungs and diabetes mellitus had developed. Azathioprine 150 mg./day was substituted for the chlorambucil. The pulmonary infiltration rapidly cleared, but after leaving hospital he deteriorated and died in August, 1969, in renal failure. Necropsy showed active lesions of WG in the upper respiratory tract, lungs, kidneys and spleen.

Discussion
The prognosis in reported cases of WG treated with cytotoxic drugs has been compared with that found in previous series where such drugs were not used. Cytotoxic drugs appear to improve the prognosis substantially. This conclusion must be regarded with caution since a concurrent improvement in supportive measures may have contributed to the better survival found in this most recent series; however, the difference in prognosis is sufficiently striking to suggest that it is due to the use of cytotoxic drugs. Moreover, the relatively low morbidity associated with such treatment is illustrated by the four case histories described. Cases 15, 16 and 17 show that azathioprine with a small dose of steroids can dramatically improve patients who are critically ill with rapidly progressive disease, and enable them to lead reasonably normal lives to the extent of coming through a normal pregnancy while still on treatment. Of the available cytotoxic drugs, azathioprine appears to be most free from serious side-effects (New Eng. Med. J., 1968). Steroids need to be given in high doses to be effective when used alone, the average dose of prednisone being 44 mg./day in the series described by Hollander and Manning (1967). Such doses carry a high risk of long-term side-effects and may also cause intolerable acute side-effects, as illustrated in cases 15 and 16. Most patients who receive cytotoxic drugs were also treated with steroids, but these could then be given in tolerably small doses. Beneficial results have been reported in three patients treated with cytotoxic drugs alone (cases 4, 21 and 22). Moreover, in two reported patients (cases 10 and 19) there was an excellent local response to regional

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perfusion with cytotoxic drugs, while the disease remained active outside the perfused area, as confirmed at necropsy in one (case 10). Further evidence of the value of cytotoxic drugs is provided by the necropsy finding both of healed lesions and of a fresh crop of active lesions in a patient who received continuous steroid therapy together with a course of azathioprine which was discontinued some months before death (Brown, 1969). In the majority of patients, the disease remains potentially active, and continuous suppressive therapy is needed. Azathioprine is not always effective in preventing the fatal progress of the disease, as in cases 15 and 18: in case 18 renal function was impaired before treatment was started and the dose of azathioprine used was relatively small; in case 15 details of therapy in the last months of life were not available; in both, treatment with azathioprine was associated with some initial improvement. However, one patient treated with cytotoxic drugs remained symptom-free four years after the onset of the disease and one year after discontinuing all therapy (case 6), and two further patients, who died from other causes possibly attributable to side-effects of therapy, were found to have no evidence of active WG at necropsy (cases 20 and 22). It is concluded that treatment with adequate doses of azathioprine together with small doses of steroids offers the best hope of tolerable survival in patients with WG.

Addendum

Case 16 has now survived 50 months, being physically well when seen in April, 1971. She has occasional epistaxes and Staphylococcal nasal discharge, but the urine is normal and there have been no haemoptyses for several months. The chest radiograph is unchanged from 1968, and the E.S.R. ranges from 3-70 mm./hr, with a persistent elevation of immunoglobulin M. She is still controlled on azathioprine 150 mg./day and prednisone 15 mg./day, but reduction of the latter dosage exacerbates her nasal pain. Her last child is developing normally.

Acknowledgements

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REFERENCES

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