WEGENER’S GRANULOMATOSIS IN FINLAND IN 1981-2000

Jouko Takala

ACADEMIC DISSERTATION

To be presented, with the permission of the Medical Faculty of the University of Helsinki, for public examination in the Lecture Hall 1, Meilahti Tower Hospital, Haartmaninkatu 4, Helsinki, on October 21th, 2011, at 12 o’clock noon.

Helsinki 2011
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# ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAV</td>
<td>ANCA-associated vasculitis</td>
</tr>
<tr>
<td>ACR</td>
<td>American College of Rheumatology</td>
</tr>
<tr>
<td>ANCA</td>
<td>anti-neutrophil cytoplasmic antibodies</td>
</tr>
<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
</tr>
<tr>
<td>AZA</td>
<td>azathioprine</td>
</tr>
<tr>
<td>c-ANCA</td>
<td>cytoplasmic ANCA</td>
</tr>
<tr>
<td>CD</td>
<td>cluster designation</td>
</tr>
<tr>
<td>CHCC</td>
<td>Chapel Hill Consensus Conference</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>cPR3</td>
<td>complementary PR3 (proteinase 3)</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CSS</td>
<td>Churg-Strauss syndrome</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>CYC</td>
<td>cyclophosphamide</td>
</tr>
<tr>
<td>DC</td>
<td>dendritic cell</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>EC</td>
<td>endothelial cell</td>
</tr>
<tr>
<td>ELK score (0-3)</td>
<td>number of simultaneously involved organ groups (ENT, Lung, Kidney)</td>
</tr>
<tr>
<td>ENT</td>
<td>ear, nose, throat</td>
</tr>
<tr>
<td>ESR</td>
<td>erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>ESRD</td>
<td>end-state renal disease</td>
</tr>
<tr>
<td>GC</td>
<td>glucocorticoid</td>
</tr>
<tr>
<td>GN</td>
<td>glomerulonephritis</td>
</tr>
<tr>
<td>GPA</td>
<td>granulomatosis with polyangitis (Wegener's)</td>
</tr>
<tr>
<td>HLA</td>
<td>human leukocyte antigen</td>
</tr>
<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>ICD</td>
<td>International Statistical Classification of Diseases and Related Health Problems</td>
</tr>
<tr>
<td>iDC</td>
<td>immature dendritic cell</td>
</tr>
<tr>
<td>IFNγ</td>
<td>interferon gamma</td>
</tr>
<tr>
<td>IQR</td>
<td>interquartile range</td>
</tr>
<tr>
<td>IRR</td>
<td>incidence rate ratio</td>
</tr>
<tr>
<td>LAMP-2</td>
<td>lysosomal membrane protein-2</td>
</tr>
<tr>
<td>mDC</td>
<td>mature dendritic cell</td>
</tr>
<tr>
<td>MHC</td>
<td>major histocompatibility complex</td>
</tr>
</tbody>
</table>
ABSTRACT

Objectives:
Wegener’s granulomatosis (WG) is a form of vasculitis of unknown origin with a predilection for the airways and kidneys. Several studies have demonstrated an increasing incidence of WG. With the development of treating regimens, the prognosis of WG has improved markedly. The aim of this study was to define the status of WG in Finland in 1981-2000 by evaluating its incidence, clinical presentation, diagnostic delay, risk of dialysis-dependent renal insufficiency and mortality. Variations of these parameters and factors contributing to their changes were also examined.

Patients and methods:
Retrospective data retrieval was performed using the Finnish hospital discharge register and reviewing all available hospital case reports. All patients diagnosed with and treated for WG in 1981-2000 were included, and their demographic and clinical data were recorded up till June 2005. The patients were crossed with the national kidney dialysis register and the national mortality statistics. Information about the beginning of dialysis and kidney transplantation was available until 8th October 2005 and about a patient’s death until 30th June 2005.

Results:
In 1981-2000, a total of 492 patients (243 men and 249 women) were diagnosed with WG at a mean age of 54 years (SD 18). The incidence increased from 1.9 to 9.3 per million per year during this period.

The median diagnostic delay simultaneously decreased from 17 to 4 months. Patients presented most often with symptoms of the ear, nose and throat (ENT) (45%), lung (36%), musculoskeletal system (22%) and kidney (11%). Constitutional symptoms were present in 36% of patients at presentation. Only minor changes occurred in clinical presentation in 1981-2000. Initial lung involvement, presence of constitutional symptoms, high erythrocyte sedimentation rate (ESR) and high ELK scores [(number of simultaneously involved organ groups (ENT, Lung, Kidney)] were associated with a shorter diagnostic delay.

Medical treatment of WG patients remained very similar in the 1980s and 1990s. Almost 90% of patients received cyclophosphamide (CYC) medication, either intravenously or orally, at some point during the course of the disease. More than 90% received glucocorticoids. Other drugs were rarely used.
At the time of the survey, 84 patients (17%) needed acute or chronic dialysis. Initial renal involvement and elevated serum creatinine values at diagnosis were related to an increased risk of dialysis-dependent kidney disease. In two-thirds of the patients, renal impairment was reversible; only one-third of patients with initially elevated serum creatinine values ended in dialysis, and more than one-third of the dialysed patients had recovered renal function. Thirty-two patients (6.5%) ended up with chronic (>3 months) dialysis. Nineteen patients (3.9%) received a kidney transplant.

Altogether 203 patients (99 men, 104 women) died before the end of June 2005. WG was the underlying cause of death in 37%. The crude one-year and five-year survival rates were 83.3% and 74.2%, respectively. The standardized mortality ratio for all patients was 3.43 (95% CI = 2.98 to 3.94); 4.38 (95% CI = 3.59 to 5.61) for women and 2.80 (95% CI = 2.28 to 3.41) for men. Older age and elevated creatinine level at diagnosis predicted shorter survival. ENT symptoms at presentation and treatment with CYC were associated with better outcome. There was no additional risk associated with male gender (HR= 1.11 [95% CI = 0.84 to 1.47]) or with either of the decades (1981-1990 and 1991-2000) of the study (HR=0.89 [95% CI = 0.64 to 1.24]).

Conclusions:

In 1981-2000, the incidence of WG increased ca. 4.5-fold and diagnostic delay decreased to about one-fourth, reflecting, at least partly, increased recognition of the disease and improved diagnostic means. WG patients are at great risk of developing dialysis-dependent renal insufficiency, which is often reversible. WG patients are also at an increased risk of dying compared with the rest of population. During the 20-year study period the proportion of patients treated with CYC and glucocorticoids did not change markedly, nor did the prognosis of WG improve.
Yleistä:


Potilaat ja menetelmät:


Tulokset:


Tavallisimmin (45 %:ssa) korva-nenä-kurkku (KNK) – elinryhmä antoi taudin ensimmäiset oireet, mutta myös varsin usein usein WG alko keuhkoista (36 %), tuki- ja liikuntaelimmistä (22 %) tai munuaisista (11 %). Taudin alussa 36 %:lla potilaista esiintyi yleisoireita kuten lämpöilyä, väsymystä, voimattomuutta, laihtumista tms. Tutkimuksen käsittämiin 20 vuoden aikana WG ilmaantui hyvin samanlaisin oirein.
Potilaat, joilla todettiin keuhkojen vaurio taudin alussa, joilla esiintyi yleisoireita, korkea lasko ja/tai useamman elinryhmän samanaikainen sairastuminen, diagnosoitiin lyhyemmällä viiveellä kuin muut.

Seurannan aikana 84 (17 %) potilasta joutui dialyysiin. Dialyysiin joutumista ennusti taudin alun munuaisvaurioon sopivat laboratoriolöydökset, etenkin diagnoosiajankohtana suurentunut seerumin kreatiniiniarvo (S-krea). Vaikka 150 potilaalla S-krea oli koholla diagnoosivuonna, vain 61 heistä joutui dialyysiin. 32 potilaalla dialyysi kesti yli 3 kk (=krooninen dialyysi). 19 potilasta (3,9 % kaikista WG-potilaista) tarvitsi munuaissiirtoa.


**Johtopäätökset:**

1. INTRODUCTION

Wegener’s granulomatosis (WG) belongs to a group of immune-mediated inflammatory diseases that affects 2-5% of the population. These are chronic diseases which, when untreated, often progress and lead to pronounced morbidity and mortality. In vasculitides, immune process damages blood vessels, leading to obstructions, dilatations or ruptures of the vessels. These damages in turn translate into symptoms and signs of ischaemia and/or haemorrhage. The clinical picture of vasculitis depends on the calibre and location of the vessels affected and the type of vascular damage. The classification of vasculitides is based primarily on the size of the vessels affected (Table 1).

Table 1. Classification of vasculitides.

<table>
<thead>
<tr>
<th>Large-vessel vasculitis</th>
<th>Medium-sized vessel vasculitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takayasu arteritis</td>
<td>Polyarteritis nodosa</td>
</tr>
<tr>
<td>Giant-cell arteritis</td>
<td>Kawasaki disease</td>
</tr>
<tr>
<td></td>
<td>Isolated central nervous system vasculitis</td>
</tr>
<tr>
<td>Small-vessel vasculitis</td>
<td></td>
</tr>
<tr>
<td>Churg-Strauss syndrome</td>
<td></td>
</tr>
<tr>
<td>Wegener’s granulomatosis</td>
<td></td>
</tr>
<tr>
<td>Microscopic polyangitis</td>
<td></td>
</tr>
<tr>
<td>Drug-induced ANCA-associated vasculitis</td>
<td></td>
</tr>
<tr>
<td>Henoch-Schönlein purpura</td>
<td></td>
</tr>
<tr>
<td>Essential cryoglobulinemic vasculitis</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity vasculitis</td>
<td></td>
</tr>
<tr>
<td>Vasculitis due to connective tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Vasculitis due to viral infections</td>
<td></td>
</tr>
<tr>
<td>Paraneoplastic small-vessel vasculitis</td>
<td></td>
</tr>
</tbody>
</table>

ANCA= anti-neutrophil cytoplasmic antibodies
Information adapted from Jennette et al.(1997).

Four of the small-vessel vasculitides—Churg-Strauss syndrome (CSS), WG, microscopic polyangitis (MPA) and drug-induced anti-neutrophil cytoplasmic
antibody (ANCA)-associated vasculitis—form the group of ANCA-related vasculitides. The presence of anti-neutrophil cytoplasmic antibodies is a common feature in these vasculitides (Jennette et al. 1997). WG is mainly associated with the presence of cytoplasmic ANCA (c-ANCA), which is similar to ANCA directed against proteinase 3 (PR3; PR3-ANCA). PR3-ANCA is seen in the sera of 66% of WG patients and MPO-ANCA in 24% (Kallenberg 2008). The other small-vessel ANCA-vasculitides (CSS, MPA and drug-induced ANCA-associated vasculitis) present mostly with perinuclear ANCA (p-ANCA), which is similar to ANCA directed against myeloperoxidase (MPO-ANCA) (Franssen et al. 2000, Gomez-Puerta et al. 2009).

Differences in clinical presentation exist between PR3-ANCA- and MPO-ANCA-associated vasculitides. PR3-associated WG develops granulomatous inflammation of the airways, while MPO-associated MPA shows a predilection for renal necrotizing vasculitis. PR3-ANCA is also associated with faster decline of renal function and more frequent relapses (Kallenberg 2011) (Table 2).

This year, a recommendation for a new name for WG was presented. The present trend is to abandon eponyms and apply a more disease-descriptive or aetiology-based nomenclature. Accordingly, the new name for WG would read granulomatosis with polyangiitis (Wegener’s), which can be abbreviated as GPA. Later on, the information in the parentheses can be omitted (Falk et al. 2011).

**Table 2.** Features of the three most important anti-neutrophil cytoplasmic antibody vasculitides.

<table>
<thead>
<tr>
<th>Vasculitis</th>
<th>Incidence/ million/yr</th>
<th>Granulomatous inflammation of airways</th>
<th>Lung haemorrhage</th>
<th>Necrotizing renal vasculitis</th>
<th>10-year survival, %</th>
<th>SMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSS</td>
<td>0.9-2.7</td>
<td>+</td>
<td>(+)</td>
<td>(+)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WG</td>
<td>7.9-9.8</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>65-75</td>
<td>1.77</td>
</tr>
<tr>
<td>MPA</td>
<td>2.4-10.1</td>
<td>(+)</td>
<td>+</td>
<td>+</td>
<td>43-55</td>
<td>3.95</td>
</tr>
</tbody>
</table>

CSS = Churg-Strauss syndrome
WG = Wegener’s granulomatosis
MPA = Microscopic polyangiitis

Information adapted from Gordon et al. (1993), Luqmani et al. (2001) and Mohammad et al. (2009).

Differentiation between MPA and WG can be achieved based on clinical picture, laboratory tests (e.g. ANCA subsets) and histology. Both are hazardous diseases and diagnosis calls for rapid interventions. CSS presents with asthma and pronounced eosinophilia, features which usually differentiate it from the other ANCA vasculitides. Goodpasture disease presenting with rapidly progressive renal failure and sometimes even with severe lung hemorrhage can be differentiated from ANCA vasculitides by detection of anti-glomerular basement membrane antibodies. WG is a vasculitis of
small and medium-sized vessels, and its clinical features include granulomatotic
vasculitis with a predilection for upper and lower airways along with necrotizing
vasculitis producing e.g. glomerulonephritis. Despite these organ predilections, WG
can affect virtually any organ or organ system.

Despite increasing knowledge, the aetiology of WG remains unclear. WG is known
to be an immune-mediated disease, but the precise mechanism of its aetiopathogenesis
is incompletely understood. Having had no proper diagnostic criteria, researchers
have used the American College of Rheumatology (ACR) classification criteria for
vasculitides 1990 (Leavitt et al. 1990, Table 3) and the Chapel Hill classification criteria
1994 (Jennette et al. 1994, Table 4) as substitutes. This has led to some incoherency
among the studies, and interpretation and comparison of results has been unreliable,
if not impossible. Propositions for diagnostic criteria of WG have been tendered only
recently (Sorensen et al. 2000, Watts et al. 2007, Tables 5 and 6).

WG has been considered a very rare disease and is still uncommon, although
increasing incidences have been presented in the literature, most prominently in
Norway and Sweden (Koldingsnes et al. 2000, Knight et al. 2006). The lack of
diagnostic criteria and the wide variety in clinical presentation of WG have often
rendered diagnosis challenging, leading to long diagnostic delays.

Since the introduction of cyclophosphamide (CYC) and glucocorticoid to treat
WG and other vasculitides (Fauci et al. 1973), the prognosis of patients has improved
markedly. This study was designed to depict the features of WG patients diagnosed
in Finland in 1981-2000. The period of 20 years was chosen as sufficiently long to
show any changes in epidemiology, diagnostics, treatment and prognosis of WG.
The register follow-up extended to 30 June 2005 in order to calculate 5-year survival
rates for all patients.

Table 3. The American College of Rheumatology criteria for the classification of Wegener’s granulomatosis
(Leavitt et al. 1990).

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Nasal or oral inflammation</td>
<td>Development of painful or painless oral ulcers or purulent or bloody nasal discharge</td>
</tr>
<tr>
<td>(2) Abnormal chest radiograph</td>
<td>Chest radiograph showing the presence of nodules, fixed infiltrates, or cavities</td>
</tr>
<tr>
<td>(3) Urinary sediment</td>
<td>Microhaematuria (&gt; 5 red blood cells per high-power field ) or red cell casts in urine sediment</td>
</tr>
<tr>
<td>(4) Granulomatous infiltration on biopsy</td>
<td>Histological changes showing granulomatous inflammation within the wall of an artery or in the perivascular area (artery or arteriole)</td>
</tr>
</tbody>
</table>

Two criteria required for classification of WG with a sensitivity of 88.2% and a specificity of 92.0%.
Table 4. Chapel Hill Consensus Conference criteria for the classification of Wegener’s granulomatosis (Jennette et al. 1994).

(1) Small-vessel vasculitis
and
(2) Granulomatous inflammation involving the upper and lower respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels
and
(3) Necrotizing glomerulonephritis is common

Table 5. Sorensen diagnostic criteria for Wegener’s granulomatosis (Sorensen et al. 2000).

(1) Biopsy or surrogate parameter† for granulomatous inflammation in the respiratory system
and
(2) Biopsy verified necrotising vasculitis in small to medium sized vessels or biopsy/surrogate parameter† for glomerulonephritis or positive PR3-ANCA test
and
(3) Lack of eosinophilia in blood and biopsy samples.

† Surrogate parameters

<table>
<thead>
<tr>
<th>Organ involvement</th>
<th>Surrogate parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerulonephritis</td>
<td>Proteinuria and haematuria with red blood casts</td>
</tr>
<tr>
<td>Arteritis</td>
<td>Angiographic or ultrasonic demonstration of aneurysms or stenoses in arteries provided the patient demonstrated other signs of vasculitis</td>
</tr>
<tr>
<td>Granulomatous inflammation in lower airways</td>
<td>Radiologically demonstrated pulmonary infiltrates or cavitations of more than one month’s duration provided that all other causes, such as infections and malignancies, were ruled out</td>
</tr>
<tr>
<td>Granulomatous inflammation in upper airways</td>
<td>Bloody nasal discharge and/or crusting of more than one month’s duration; chronic sinusitis, otitis and/or mastoiditis (proved by radiograph, CT or MRI); cranial bone and/or cartilage destruction; acute hearing loss, without signs of traumatic disease</td>
</tr>
</tbody>
</table>
Table 6. Watts diagnostic criteria for Wegener’s granulomatosis (Watts et al.2007).

A clinical diagnosis must first be made and where possible the patient followed for a minimum of 3 months.

The patient must be aged ≥16 years at the time of diagnosis.

The following three criteria must be fulfilled before classification:

(A) Symptoms and signs characteristic or compatible with diagnosis

(B) At least one of the following:
- Histological proof of vasculitis
- Positive serology for ANCA
- Specific investigations strongly suggestive of vasculitis and/or granuloma
- Eosinophilia (>10% or >1.5 x10^9/l)

(C) No other diagnosis to account for symptoms/signs.

Surrogate markers for Wegener’s granulomatosis (granulomatous disease) refer to symptoms suggestive of granulomatous disease affecting the upper and lower respiratory tract (in all cases other causes must be excluded):

Lower airways
- x-ray evidence of fixed pulmonary infiltrates, nodules or cavitations present for >1 month
- bronchial stenosis

Upper airways
- bloody nasal discharge and crusting for >1 month, or nasal ulceration
- chronic sinusitis, otitis media or mastoiditis for >3 months
- retro-orbital mass or inflammation (pseudotumour)
- subglottic stenosis
- saddle nose deformity/destructive sinonasal disease

Only one surrogate marker is necessary to support a diagnosis of Wegener’s granulomatosis

Surrogate markers for renal vasculitis (glomerulonephritis) are either
- haematuria associated with red cell casts or
- 10% dysmorphic erythrocytes or
- 2+ haematuria and 2+ proteinuria on urinalysis
2. REVIEW OF THE LITERATURE

The granulomatous vasculitis that used to be called Wegener’s granulomatosis [recent recommendation: granulomatosis with polyangiitis (Wegener)] was initially described by Klinger in 1931. He considered it to be a special form of polyarteritis nodosa (Klinger 1931). Friedrich Wegener, a German pathologist and a friend of Klinger’s, presented in 1936 the classical triad of this disease consisting of granulomatous inflammation in the upper and lower airways, systemic vasculitis and local necrotizing glomerulonephritis (Wegener 1936).

2.1 EPIDEMIOLOGY

Since its introduction in the 1930s, WG has become better known, and increasing incidences have been reported in the last few decades. Carruthers et al. (1996) found the annual incidence of WG to be 8.5 per million in Norfolk (UK) in 1988-1993, a higher rate than those previously published. Knight et al. (2006) reported a 3.6-fold rise in the annual incidence (from 3.3/ million to 11.9/ million) in 25 years. Koldingsnes et al. (2000) also presented a 2.3-fold rise (from 5.2/ million to 12.0/ million) in 15 years. Watts et al. (2000) reported a slowly increasing annual incidence of primary systemic vasculitides and, accordingly, of WG, similar to Gonzalez-Gay et al. (2003). Some studies have not, however, demonstrated rising incidences of WG (Watts et al. 2001, Reinhold-Keller et al. 2005, Watts et al. 2009) (Table 7). The incidence of WG in Finland in 1990 was 2.8/million/year of the adult population (Kaipiainen-Seppänen et al. 1996).

Besides increasing incidences, several studies have described increasing age at diagnosis of WG. Studies from the 1950s to the 1980s reported the mean age at onset to be 40-50 years (Kelley et al. 1993, Littlejohn et al. 1985, Hunder et al. 1990). Reinhold-Keller et al. (2005) and Knight et al. (2006) found a median age of about 60 years at diagnosis. The incidence has been reported to peak around the age of 70 years (Koldingsnes et al. 2000, Watts et al. 2000, Lane et al. 2005). Contrarily, several studies have described the age at diagnosis to be more or less stable throughout the survey period (Koldingsnes et al. 2000, Reinhold-Keller et al. 2005, Knight et al. 2006).

In some studies, WG has been found to be more common in Northern countries (Watts et al. 2004, Lane et al. 2005) and among people of Caucasian descent (Jagiello et al. 2005, Mahr et al. 2006). Seasonal variations in the incidence have occasionally been reported (Raynauld et al. 1993, Carruthers et al. 1996), whereas others have failed to find these variations (Duna et al. 1998, Koldingsnes et al. 2000) (Table 7).
Table 7. Studies on the incidence and prevalence of Wegener’s granulomatosis.

<table>
<thead>
<tr>
<th>Country</th>
<th>Survey period</th>
<th>N</th>
<th>M/F</th>
<th>Incidence / million *</th>
<th>Prevalence /million *</th>
<th>Age (years)</th>
<th>Seasonal variation</th>
<th>Criteria applied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carruthers et al. (1996)</td>
<td>UK, USA</td>
<td>1988-1993</td>
<td>27</td>
<td>1.6</td>
<td>8.5</td>
<td>62 (median)</td>
<td>yes</td>
<td>ACR</td>
</tr>
<tr>
<td>Gonzales-Gay et al. (2000) (PSV patients)</td>
<td>Spain</td>
<td>1980-2001</td>
<td>54</td>
<td>0.8</td>
<td>2.95 (N)</td>
<td>60.7 (mean)</td>
<td>..</td>
<td>CHCC (ACR)</td>
</tr>
<tr>
<td>Koldingsnes et al. (2000)</td>
<td>Norway</td>
<td>1984-1998</td>
<td>55</td>
<td>1.62</td>
<td>5.2-12.0 (+)</td>
<td>50 (median)</td>
<td>no</td>
<td>ACR</td>
</tr>
<tr>
<td>Watts et al. (2000)</td>
<td>UK</td>
<td>1988-1997</td>
<td>82</td>
<td>1.43</td>
<td>8.7-10.3 (+)</td>
<td>62.9/65.0 (mean/median)</td>
<td>No</td>
<td>ACR,CHCC</td>
</tr>
<tr>
<td>Watts et al. (2001)</td>
<td>Spain</td>
<td>1988-1998</td>
<td>11</td>
<td>0.57</td>
<td>4.9 (N)</td>
<td>..</td>
<td>..</td>
<td>ACR;CHCC</td>
</tr>
<tr>
<td></td>
<td>UK</td>
<td>1988-1998</td>
<td>48</td>
<td>1.09</td>
<td>10.6 (N)</td>
<td>..</td>
<td>..</td>
<td>ACR;CHCC</td>
</tr>
<tr>
<td>Reinhold-Keller et al. (2005)</td>
<td>Northern Germany</td>
<td>1998-2002</td>
<td>120</td>
<td>1.16</td>
<td>6-12 (+**)</td>
<td>58.4 (mean)</td>
<td>..</td>
<td>CHCC</td>
</tr>
<tr>
<td>Gibson et al. 2006</td>
<td>New Zealand</td>
<td>1999-2003</td>
<td>73</td>
<td>0.62</td>
<td>..</td>
<td>152 (5-year )</td>
<td>66 (mean)</td>
<td>..</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>131 (point)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knight et al. (2006)</td>
<td>Sweden</td>
<td>1975-2001</td>
<td>1638</td>
<td>1.18</td>
<td>3.3-7.7-11.9 (mean 7.8) (+)</td>
<td>62 (mean)</td>
<td>..</td>
<td>ACR</td>
</tr>
<tr>
<td>Watts et al. (2009)</td>
<td>UK</td>
<td>1990-2005</td>
<td>295</td>
<td>1.05</td>
<td>8.4 (N)</td>
<td>59 (median)</td>
<td>..</td>
<td>CHCC, ACR</td>
</tr>
</tbody>
</table>

* "+" depicts an increase, "N" indicates stable incidence/prevalence throughout the survey period.
** The incidence of primary systemic vasculitis (PSV) in general was stable, although the incidence of WG increased.
.. = not available
2.2. CLINICAL PICTURE

In WG, at least two kinds of disease processes are involved:
1. granulomatous inflammation, mostly confined to airways; and
2. necrotizing vasculitis, e.g., of the kidney.

The clinical picture of WG is highly variable. The following features are the most common (Fan et al. 1980, Savage et al. 1997, Burmester et al. 2003, Shoenfeld et al. 2008):

- **ENT symptoms and signs**: nasal stuffiness, crusty, bloody or purulent nasal discharge, sinusitis, otitis, pain and inflammatory signs in the pharynx or larynx.
- **pulmonary symptoms and signs**: cough, haemoptysis, abnormal chest x-ray findings or lung infections such as pneumonia or bronchitis
- **renal symptoms and signs**: haematuria, proteinuria, elevated serum creatinine values
- **musculoskeletal**: arthralgia, myalgia, arthritis
- **ophthalmic**: conjunctivitis, scleritis, episcleritis, uveitis, proptosis
- **indications of generalized inflammatory disease**: malaise, fatigue, fever, weight loss.

2.2.1. CLINICAL PICTURE AT PRESENTATION

WG often starts as a limited disease. The organ group most often involved at presentation is ENT (60-80%). Very frequently, in ca. 60% of cases, patients present with musculoskeletal symptoms and signs, such as arthralgias, arthritides and muscle aches and pains. Kidney (54%), lung (55%), eye (40%) and skin (21%) are fairly often involved at presentation (Table 8).

2.2.2. CLINICAL PICTURE DURING COURSE OF THE DISEASE

Occasionally, the disease remains limited to one organ group, e.g. ENT, but most patients develop a more extended disease. When the disease becomes more generalized, constitutional symptoms and signs grow more prominent. Fever, malaise and weight loss are frequent complaints. In the course of the disease, ENT is involved in over 90% of cases, and the kidney and lung in ca. 70%. Often the disease proceeds to simultaneously involve all organs of the ELK concept (ENT, Lung, Kidney) (DeRemee et al. 1976). Virtually any organ in the body can be afflicted by the disease (Shoenfeld et al 2008; Table 8).
Table 8. Organ involvement in Wegener's granulomatosis (%)

<table>
<thead>
<tr>
<th></th>
<th>ENT At presentation</th>
<th>Lung At diagnosis</th>
<th>Lung At any time</th>
<th>Kidney At presentation</th>
<th>Kidney At any time</th>
<th>Constitutional At presentation</th>
<th>Constitutional At any time</th>
</tr>
</thead>
<tbody>
<tr>
<td>D'Cruz et al. (1989)</td>
<td>100</td>
<td>..</td>
<td>..</td>
<td>77</td>
<td>..</td>
<td>100</td>
<td>..</td>
</tr>
<tr>
<td>Tidman et al. (1998)</td>
<td>..</td>
<td>..</td>
<td>74</td>
<td>..</td>
<td>58</td>
<td>47</td>
<td>..</td>
</tr>
<tr>
<td>Aasarød et al. (2000)</td>
<td>62</td>
<td>..</td>
<td>52</td>
<td>..</td>
<td>100*</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>Koldingsnes et al. (2000)</td>
<td>62</td>
<td>80</td>
<td>..</td>
<td>20</td>
<td>60</td>
<td>9</td>
<td>76</td>
</tr>
<tr>
<td>Reinhold-Keller et al. (2000)</td>
<td>93</td>
<td>99</td>
<td>55</td>
<td>66</td>
<td>54</td>
<td>70</td>
<td>..</td>
</tr>
<tr>
<td>Stone (2003)</td>
<td>77</td>
<td>..</td>
<td>..</td>
<td>60</td>
<td>..</td>
<td>54</td>
<td>..</td>
</tr>
<tr>
<td>Langford et al. (2005)</td>
<td>..</td>
<td>..</td>
<td>95</td>
<td>..</td>
<td>85</td>
<td>20</td>
<td>..</td>
</tr>
<tr>
<td>Gibson et al. (2006)</td>
<td>..</td>
<td>86</td>
<td>..</td>
<td>..</td>
<td>52</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>Cisternas et al. (2005)</td>
<td>..</td>
<td>..</td>
<td>95</td>
<td>..</td>
<td>62</td>
<td>78</td>
<td>..</td>
</tr>
<tr>
<td>Akikusa et al. (2007) (paediatric)</td>
<td>84</td>
<td>96</td>
<td>80</td>
<td>..</td>
<td>84</td>
<td>88</td>
<td>96</td>
</tr>
</tbody>
</table>

*Renal involvement was an inclusion criterion.
..=Not available
Fibromyalgia-like symptoms, including sleep disorders and depression, have been found to be more frequent in patients with WG than in the general population, irrespective of disease activity, damage or duration. These symptoms, whether they be a consequence of the disease itself or its treatment, limit the patient’s daily activities and reduce quality of life (Hajj-Ali Raet et al. 2011).

3.3. AETIOPATHOGENESIS

Although the aetiology of WG is unknown, some theories have been presented. WG is one of many immune-mediated inflammatory diseases caused by failure of self-tolerance or of regulation of the inflammatory process (Huang et al. 2001). These phenomena may, in turn, result from immune responses against self-antigens or microbial antigens. Some evidence has emerged that genetic factors, infections, environmental exposures and drugs can contribute to the breakdown of self-tolerance, and thus, be connected to the risk of developing WG (Dolman et al. 1993, Somer et al. 1995, George et al. 1997, Duna et al. 1998, Huang et al. 2001, Jagiello et al. 2005a, Hogan et al. 2007, Knight et al. 2010).

3.3.1. IMMUNOPATHOLOGICAL MECHANISMS

The immunopathological mechanisms in the development of the inflammatory process in WG are not altogether clear. As in other immune-mediated diseases, the pathogenesis of WG is considered to be connected to a failure of self-tolerance. Proteinase 3 (PR3), as an autoantigen, obviously has a pivotal role. This enzyme is normally inaccessible to antibodies in azurophilic granules of resting polymorphonuclear leukocytes (PMNs). Some noxious agent, e.g., an inhaled precipitant, causes an inflammatory reaction in mucosal cells with secretion of pro-inflammatory cytokines. This, in turn, leads to the development of adhesion molecules on PMNs and endothelial cells (ECs), and PR3 is translocated to the cell surface. PR3 activates protease-activated receptor-2 (PAR-2), leading to maturation of immature dendritic cells. Mature dendritic cells, in turn, activate T-cells, which induce development of B-cells into ANCA-producing plasma cells. PMNs adhere to ECs and, due to the PR3-ANCA binding reaction, begin to activate and degranulate. This leads to endothelial damage and to necrotizing vasculitis (Burmester et al. 2003, Csernok et al. 2008a,b) (Figure 1). PR3-ANCA is mostly associated with granulomatous vasculitis and relapsing disease, whereas MPO-ANCA is associated with necrotizing vasculitis without granuloma formation (Kallenberg et al. 2008).
Figure 1. *The gate-way receptor model*: In WG expression of PR3 in the extracellular space is increased. PR3 stimulates the expression of PAR-2 on DC and activates PAR-2 resulting in maturation of DC, as indicated by expression of CD80, CD83, CD86 and HLA-DR and these PR3-maturated DCs stimulate CD4+ T cells to generate increased expression of IFN-γ. Hypothetically, T-cell activation by PR3-maturated DCs may finally promote the development of B-cells towards ANCA-producing plasma cells. [Csernok E, Holle JU, Gross WL. Proteinase 3, protease-activated receptor-2 and interleukin-32: linking innate and autoimmunity in Wegener’s granulomatosis. Clin Exp Rheumatol 2008 May-Jun;26(3 Suppl 49):S112-7, with permission].

PR3= proteinase 3, PAR-2= protease-activated receptor-2, DC= dendritic cell, IFN-γ= interferon-gamma, MHC= major histocompatibility complex, iDC= immature dendritic cell, mDC= mature dendritic cell, TCR= T-cell receptor.

Pendergraft et al. (2004) recently found that patients with autoimmune disorders had, besides antibodies to autoantigens, antibodies to proteins coded by the antisense strands of the very DNA coding the autoantigen. The authors proposed a theory that these antisense or complementary proteins could elicit antibody formation. These antibodies, in turn, could elicit anti-idiotypic antibody formation. These anti-idiotypic antibodies could react with autoantigens, thus provoking an autoimmune disease. The immune response against PR3 in WG may be initiated by responses against anti-sense PR3. Complementary PR3 (cPR3) also resembles some microbial antigens, which may explain the alleged aetiological role of microbes (e.g. *Staphylococcus aureus*) in the pathogenesis of WG (Pendergraft et al. 2004, Bruner et al. 2010, Wilde et al. 2011).

A recent discovery of autoantibodies against lysosomal membrane protein-2 (LAMP-2) in patients with ANCA-associated glomerulonephritis, even in the absence of PR3- or MPO-ANCA, has contributed a piece to the puzzle of the aetiology of ANCA-associated vasculitis (AAV). Patients with localized AAV generally do not have anti-LAMP-2 antibodies, whereas patients with glomerulonephritis do. Moreover, anti-LAMP-2 cross-react with FimH, an adhesin molecule of some Gram-negative
pathogenic bacteria; this could be another potential explanation for microbe-related aetiology (Kain et al. 2008).

Although AAV has been considered pauci-immune, i.e. lacking immune complexes or complement factors, evidence for the role of complement in the inflammatory process of AAV has mounted (Wilde et al. 2011).

In AAV, T-cell subsets have their roles in pathogenesis. Elevated quantities of effector memory T-cells (Tem) have been demonstrated in WG. These T-cells also seem to be major effectors in granuloma formation and in the autoimmune process in WG (Lamprecht et al. 2006, Wilde et al. 2009). Recent studies have shown functional impairment of regulatory T-cells (Tregs) in WG (Abdulahad et al. 2007, Morgan et al. 2010). It can be speculated that lack of regulation leads to Tems expansion and persistent T-cell activation (Wilde et al. 2011).

Recent findings suggest that granulomas are in fact tertiary lymphoid organs (TLOs). They develop in several chronic inflammatory conditions such as rejection of organ transplants or autoimmune diseases. These TLOs resemble secondary lymphoid organs (SLOs, e.g. lymph nodes) in many ways; they have similar layer organization of T-cells, B-cells and dendritic cells. Autoantigen presentation and production of ANCA are proposed to take place in these TLOs. In TLOs, lymph flow and antigen-presenting cell trafficking are less organized than in SLOs. This may result in chronic non-physiological T-cell activation and persistent autoimmune inflammation (Aloisi et al. 2006, Wilde et al. 2011).

Though granulomas seldom exist in AAV related glomerulonephritis, some lymphoid neogenesis with DC-T-cell aggregates has been observed in renal biopsies. Hypothetically, activation of effector T-cells and stimulation of the immune response take place, possibly locally attenuated by Tregs (Wilde et al. 2011). In glomerulonephritic kidneys of AAV, formation and deposition of neutrophil extracellular traps (NETs), containing such cytoplasmic proteins as PR3, MPO and elastase, have been found. NET formation is associated with defence against microbial invaders (Brinkmann et al. 2004), but probably also has a role in autoimmunity leading to AAV (Wilde et al. 2011).

One example of an agent initiating the primary inflammatory process is the mechanism of silica exposure in the development of small-vessel vasculitis (SVV). Crushing silica yields radicals that react with water to produce hydroxyl radicals. Once absorbed into tissue, silica is not metabolized or destroyed by macrophages, which leads to the production of chemokines, inflammatory cytokines and growth factors, and these ongoing effects likely contribute to an immune-modulating defect. Silica particles might, through the release of reactive oxygen radicals and inflammatory cytokines, trigger immunopathological mechanisms. Other factors, such as genetic predisposal, probably also contribute (Moulin et al. 2004, Csernok et al. 2006, Novick et al. 2006, Hogan et al. 2007, de Lind van Wijngaarden et al. 2008).
2.3.2. GENETIC FACTORS

Some evidence of genetic susceptibility to systemic vasculitides exists. Family clusters have been described (Muniain et al. 1986, Knudsen et al. 1988, Hay et al. 1991, Stoney et al. 1991). WG patients with thyreoiditis and relapsing polychondritis have been reported, suggesting a role of genes in susceptibility to autoimmune diseases (Small et al. 1980, Masor et al. 1994). T-cell function–associated genetic factors predisposing to granulomatous inflammation (HLA DPB1*0401) and PR3-ANCA seropositivity (PTPN22*620W) have been determined. Haplotype DPB1*0401/RXRBo3 showed a very strong association with WG (OR=6.41) (Jagiello et al. 2004 & 2005a,b).

Several gene loci have been connected to the risk and pathogenesis of WG. These include HLA-genes associated with MHC class II function (Szyld et al. 2006) and intracellular tyrosine phosphatase as well as alpha-1-antitrypsine and PR3 expression on the cell surface (Jagiello et al. 2005).

2.3.3. INFECTIONS

Davies et al. (1982) suspected group A arbovirus to be an aetiological factor in segmental necrotizing glomerulonephritis. Finkel et al. (1994) reported serological evidence of persistent infection by Parvovirus B 19 in vasculitis patients, and discussed the aetiological connection. Several bacteria (e.g. Klebsiella aerogenes, Staphylococcus aureus, Haemophilus influenzae, and Bacillus subtilis) have been speculated to promote relapses of WG or even start the disease process (Pinching et al. 1980). The evidence concerning Staphylococcus aureus has been most convincing. Preceding Staphylococcus infection could trigger the onset of WG, and/or chronic nasal carriage could maintain disease activity (Pinching et al. 1980, Stegeman et al. 1994, Somer et al. 1995, George et al. 1997) (Table 9).

2.3.4. ENVIRONMENTAL EXPOSURES

WG is more common in northern countries than in southern countries (Watts et al. 2001, Lane et al. 2005). This has led to assumptions that environmental strain on airways, such as cold air and more abundant viral airway infections during Nordic winters, could be an aetiopathological mechanism of WG. If this were true, seasonal differences in the onset of WG should also exist. Results on this topic have, however been contradictory (Raynauld et al. 1993, Carruthers et al. 1996, Duna et al. 1998, Koldingsnes et al. 2000).

Exposure to silicon compounds has been known to be hazardous to the lungs. Nuyts et al. (1995) observed that inhalation of silicon-containing compounds produced a nearly sevenfold risk of WG, and Hogan et al. (2007) reported especially
long-standing silica exposure to be a risk of evolving ANCA-associated small-vessel vasculitis (SVV). Observations also indicate that occupational exposure to silicon compounds poses a risk of developing renal disease (Kallenberg et al. 1995, de Broe et al. 1996). Duna et al. (2008) investigated the relationship of WG with exposure to fumes and particulate materials as well as pesticides. Their study suggested risk relationships, although the results were not conclusive. Knight et al. (2010) found no clear occupational risk factors for WG in their recent case-control study in Sweden.

Table 9. Infectious agents with possible aetiological impact on Wegener’s granulomatosis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Infectious agent</th>
<th>Clinical association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pinching et al. (1980)</td>
<td>Bacterial infections</td>
<td>Role in relapses of Wegener’s granulomatosis</td>
</tr>
<tr>
<td>Davies et al. (1982)</td>
<td>Arbovirus group A</td>
<td>Segmental necrotising glomerulonephritis</td>
</tr>
<tr>
<td>el-Roiey et al. (1987)</td>
<td>Klebsiella pneumoniae</td>
<td>Klebsiella infection in connection with autoantibody production</td>
</tr>
<tr>
<td>Finkel et al. (1994)</td>
<td>Parvovirus B 19</td>
<td>Chronic virus infection in patients with polyarteritis nodosa and of Wegener’s granulomatosis</td>
</tr>
<tr>
<td>Pinching et al. (1980)</td>
<td></td>
<td>Preceding infection or chronic nasal carriage/ triggering the disease process and/or maintenance of disease activity</td>
</tr>
<tr>
<td>Stegeman et al. (1994)</td>
<td>Staphylococcus aureus</td>
<td>Anti-neutrophil cytoplasmic antibody formation in patients with Entamoeba histolytica infection</td>
</tr>
<tr>
<td>George et al. (1997)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pudifin et al. (1994)</td>
<td>Entamoeba histolytica</td>
<td></td>
</tr>
</tbody>
</table>

2.3.5. DRUGS

Many drugs have been suspected and even proven to cause autoimmune diseases, among these vasculitides such as WG. In a review of the published cases of drug-induced vasculitis with cutaneous and/or systemic manifestations, ten Holder et al. (2002) found propylthiouracil, hydralazine, colony-stimulating factors, allopurinol, cefaclor, minocycline, D-penicillamine, phenytoin, isotretinoin and methotrexate to be the drugs most frequently associated with vasculitis. In most cases, vasculitis resolved after discontinuing the drug. Severe cases requiring aggressive treatment also occurred. There was an overall 10% death rate.

Bonaci-Nikolic et al. (2005) compared 56 idiopathic ANCA vasculitides and 16 antithyroid drug-induced ANCA vasculitides. Patients with antithyroid drug-induced autoimmune diseases were more often female and considerably younger than patients with idiopathic vasculitides. Moreover, they presented with less constitutional, pulmonary, central nervous system (CNS) and renal symptoms,
but with more skin manifestations. Their diseases also had a more benign course. Dolman et al. (1993) and Kitahara et al. (1997) reported similar results.

2.4. DIAGNOSTIC AND CLASSIFICATION CRITERIA

When Heinz Klinger (1931) originally presented WG, he thought it was a special form of polyarteritis nodosa (PAN). Friedrich Wegener considered WG to be a disease of its own, and he described a classical symptom triad, from a series of three obductions (Wegener 1936).

For long, this symptom triad formed the diagnostic criteria of WG. Along with the ACR classification criteria for vasculitides in 1990 (Leavitt et al. 1990; Table 3) and the criteria of the Chapel Hill Consensus Conference (CHCC) in 1994 (Jennette et al. 1994; Table 4), a consensus concerning the classification criteria of WG was reached. Although these criteria were meant to be classification criteria for vasculitides, they have also widely been used for diagnostic purposes. The need for diagnostic criteria for WG has long been recognized. In 2000, Sorensen et al. proposed their diagnostic criteria (Table 5) largely based on CHCC criteria and complemented with surrogate criteria for the frequently missing biopsy results. The Sorensen criteria have been criticized for ruling out patients with eosinophilia (Lane et al. 2002). Watts et al. (2007) developed a new algorithm for classification of ANCA vasculitides in 2006 (Table 6). This was validated by Liu et al. (2008) in a large cohort of Chinese vasculitis patients and found to be a useful method.

2.5. TREATMENT

2.5.1. GLUCOCORTICOIDS

Glucocorticoids (GCs) were the first agents used to treat WG. In many instances, their effect was positive and their use prolonged survival time moderately, from a median of 5 months to 12.5 months (Hollander et al. 1967). Their effect was poor in WG with major organ (particularly the kidney) involvement (Hollander et al. 1967, Hoffman 1993, Langford et al. 2001). GC monotherapy can alleviate the disease process, but it cannot keep the disease from progressing, nor can it produce a sustained remission (Hoffman 1993). The use of GCs brings along well-known side-effects; they reduce glucose tolerance and increase the risk of diabetes, as well as the risk of hypertension, gastrointestinal haemorrhage, obesity and increased ocular tension. Prolonged use also causes adrenal suppression and risk of osteoporosis.
2.5.2. CYCLOPHOSPHAMIDE AND GLUCOCORTICOIDs

A major improvement in the treatment of WG took place when Fauci and Wolff (1973) developed a treatment combining daily cyclophosphamide (CYC) and GC. The standard regimen comprised oral CYC 2 mg/kg/day and prednisolone 1 mg/kg/day. Prednisolone dose was tapered slowly after one month to a maintenance dose by 3-4 months, and the drug was discontinued by 6-12 months. CYC was used one year past remission, thereafter being tapered and discontinued (Fauci et al. 1973). Increased doses of CYC (3-4 mg/kg/day for a few days) (Fauci et al. 1983) and prednisone (higher dose than 1 mg/kg/day) could also be used with critically and fulminantly ill patients.

Combination treatment with CYC and GCs induces remission in about 90% of patients (de Groot et al. 2009), and this regimen has prolonged the survival of WG patients considerably, from a median of 5 months to as long as 21 years (Reinhold-Keller et al. 2000). Several problems occur, especially drug toxicity and frequent relapses.

The toxicity of CYC has been a great concern in treating WG. The bone marrow toxicity of CYC often compels a reduced dosage, and CYC-induced leukopenia renders the patient susceptible to life-threatening bacterial infections and induction of immunosuppression to opportunistic infections, e.g. *Pneumocystis jiroveci* pneumonia (Khellaf et al. 2009). CYC’s toxicity to germinal cells bears a risk of infertility. There is also a increased risk of malignancies, especially bladder cancer. In a study by Talar-Williams et al. (1996), 50% of the 145 WG patients receiving CYC had non-glomerular haematuria. Seven patients (5%) developed bladder cancer. All but one had received a cumulative CYC dose of more than 100 g and the duration of CYC therapy had exceeded 2.7 years. Reinhold-Keller et al. (2000) noted that the amount of adverse effects (CYC-induced cystitis and myelodysplastic syndrome) increased with cumulative CYC doses exceeding 100 g. Knight et al. (2004) observed an increasing risk of bladder cancer with increasing total doses of CYC. Faurschou et al. (2008) reported significantly increased incidences of acute myeloid leukaemia with cumulative CYC dose exceeding 36 g. Because the risk of adverse effects mount with increasing cumulative total doses of CYC, regimens with the aim of decreasing the total doses have been developed. A few studies have proved that treatment with high-dose intravenous CYC pulses reduces the total dose of CYC and is fairly efficacious in inducing remission; however, with higher rates of relapses occur (Hoffman et al. 1990, Guillevin et al. 1997). de Groot et al. (2009) found in their recent study that the pulse CYC regimen induced remission of ANCA-associated vasculitis as well as the daily oral regimen at a reduced cumulative CYC dose and caused fewer cases of leukopenia.

Whether treated with oral or intravenous CYC, the relapse rate is high. According to several studies, about 50% of the WG patients treated with a combination of CYC plus GC who had reached remission experienced one or more disease relapses.
(Tervaert et al. 1990, Hoffman et al. 1992) after a medium of 27 months (Westman et al. 1998). Reinhold-Keller et al. (2000) found that the relapse rate increased with time: 38% for ≤5 years vs. 71% for >5 years.

2.5.3. METHOTREXATE AND GLUCOCORTICOIDS

Methotrexate (MTX) is also capable of inducing remission in active WG. It was found to be as effective as CYC in remission induction. About 90% of patients reached remission with both CYC and MTX by 6 months. Delayed remission was common in patients with more extensive disease or pulmonary involvement (de Groot et al. 2005). MTX has been used in patients with active but not life-threatening disease (Sneller et al. 1995, Langford et al. 1997). When inducing remission, MTX is given at 20-25 mg/week and continued 1-2 years past remission, then tapered and discontinued. Prednisolone is used in combination with MTX similarly as with CYC.

MTX treatment, like CYC treatment, is complicated by a susceptibility to *Pneumocystis jiroveci* pneumonia. Liver toxicity, leukopenia, stomatitis and pneumonitis also occur. To lessen these toxicities, antibiotic prophylaxis against *Pneumocystis* and administration of folic acid have been recommended (Morgan et al. 1994).

2.5.4. CYCLOPHOSPHAMIDE FOR INDUCTION AND METHOTREXATE FOR REMISSION MAINTENANCE

Due to considerably high toxicity during CYC treatment, a shorter course with CYC has been proposed. In this regimen, the patient is treated with CYC 2 mg/kg/day along with prednisone until remission, which is achieved in a medium of 3 months. CYC is then changed to MTX 20-25 mg/week. This kind of therapy was found to be a good alternative regimen with less toxicity than the standard CYC regimen (de Groot et al. 1996, Langford et al. 1999). Up to 30-50% of the patients on remission maintenance medication with low-dose MTX experience a relapse after a median of 15-19 months. The relapse rate of the patients on remission maintenance with MTX does not differ significantly from those on CYC (Reinhold-Keller et al. 2002, Langford et al. 2003).

2.5.5 OTHER CYTOTOXIC AND IMMUNOSUPPRESSIVE AGENTS

CYC and MTX seem to be the two most powerful drugs to induce remission in WG. In some instances, their use is not feasible. In cases of previous CYC-induced bladder injury, lymphoproliferative disease or bladder cancer, CYC is not recommended.
Liver disease, severe renal insufficiency and severe pulmonary impairment preclude the use of MTX. In case of contraindications, alternative drugs must be considered.

Azathioprine (AZA) does not induce remission successfully, but it can be used instead of MTX to sustain CYC-induced remission (Fauci et al. 1983). Relapse rates during maintenance therapy on AZA (58% during 18 months) are similar to those on CYC, but AZA is considered a safer medication (Jayne et al. 2003, Slot et al. 2004). In more recent studies, relapse rates with AZA maintenance therapy, have been 15.5-17.8% at 18 months and 50-52% at 32 months (Pagnoux et al. 2008).

Leflunomide at a dose of 30 mg/day is at least as effective as MTX in maintaining remission, but it has more adverse effects such as hypertension, neuropathies and leukopenia (Metzler et al. 2007).

Mycophenolate mofetil (MMF) can be used for maintenance of remission in WG (Nowack et al. 1999). While it was well tolerated, it was associated with a relapse rate of 43% at a median of 10 months after remission (Langford et al. 2004). Silva et al. (2010) found MMF to be a good alternative for induction and maintenance of remission in microscopic polyangiitis.

2.5.6. BIOLOGICAL AGENTS

Interferon gamma (IFNγ), interleukins and tumour necrosis factor alpha (TNFα) have been demonstrated to be important factors in the disease process of WG, in particular in granuloma formation (Komocsi et al. 2002, Lamprecht et al. 2002a). Therefore, therapies targeted against cytokines are under extensive investigation and development.

Biological agents have been developed and adapted into clinical use since the 1990s. They have not had a role in the first-line treatment for WG, but rather as a rescue therapy in refractory cases. A few reports of successful treatment of adult patients with infliximab exist (Lamprecht et al. 2002b&c, Rozin et al. 2003, Hermann et al. 2006, Svozilova et al. 2006, Fujikawa et al. 2008). In paediatric cases, the therapy has not been promising. Etanercept has not proven efficacious in WG (Wilkinson et al. 2006, Ramos-Casals et al. 2008). Interleukin-1-antagonist (anakinra) and anti-CD-20-antibody (rituximab) have shown promise, especially in the treatment of WG with renal involvement (Borgmann et al. 2003, Jayne et al. 2009). Rituximab has proven effective in preponderantly vasculitic WG, with few adverse effects (Hinze et al. 2008, Moosig et al. 2008, Sanchez-Cano et al. 2008, Wong 2008). In two recent studies, rituximab and CYC were compared in the treatment of AAV; the drugs were equally efficacious and had equal amounts of adverse effects (Jones et al. 2010, Stone et al. 2010).

Biological therapy is shadowed by frequent side-effects. Serious infections (e.g. re-activation of tuberculosis) on anti-TNF therapies are of the greatest concern (Bruns et al. 2009).
Although occasional promising results have been presented, much consideration is still required in the use of biological agents to treat WG (Langford 2008). With no risk of infertility (in contrast to CYC), they can be a good alternative for patients in their fertile years (Ntatsaki et al. 2011).

2.5.7. OTHER THERAPIES

Because of the alleged role of *Staphylococcus aureus* in the aetiopathogenesis of WG, long-term antibiotic treatment has been used in a limited form of the disease. Trimethoprim-sulphamethoxazole treatment has been found to be useful in preventing relapses (DeRemee et al. 1985, Stegeman et al. 1994 and 1996, Zycinska et al. 2008). Mupirocin ointment has been used to reduce nasal carriage of *S. aureus* (Crossley et al. 2009).

Intravenous immunoglobulin infusions have been used occasionally to treat WG. Some good results have been reported, but others have been controversial. Generally, the therapy is well tolerated (Richter et al 1995, Jayne et al. 1996, Lockwood 1996).

Plasma exchange is indicated for severe renal vasculitis, leading to a renal recovery rate of up to 80%. Plasma exchange has been used as an adjuvant rescue therapy with simultaneously continuing CYC and prednisolone medication (Jayne 2009).

2.6. COURSE OF THE DISEASE

Evidence indicates that WG with granulomatous predominance runs a more prolonged but benign course than WG with vasculitic predominance (Mahr et al. 2001, Mukhtyar et al. 2008).

2.6.1 PROGNOSIS

Long after the introduction of WG in the 1930s, its prognosis remained quite sinister, although occasional spontaneous recoveries occurred (Thomas et al. 2007). With no efficient treatment available, the mean life expectancy after diagnosis was about 5 months in the 1950s, with a one-year mortality of 80% (Walton 1958). The use of GCs improved the prognosis slightly, approximately doubling the survival time (Hollander et al. 1967, Hoffman 1993, Langford 2001). The development of combination treatments with cytotoxic drugs (in particular CYC) and GCs revolutionized the treatment of WG, improving the prognosis markedly (Fauci et al. 1983).
Nowadays, WG patients live even decades after diagnosis. However, ANCA-associated vasculitis still means excess mortality compared with the general population. In a recent study, patients with ANCA-vasculitides in 1995-2002 had a standardized mortality ratio (SMR) of 2.6 (Flossmann et al. 2011). Treatment can be associated with adverse events, such as leukopenia, which leads to susceptibility to severe infections. Treating young patients with cytotoxic agents is associated with a risk of infertility. In addition a risk of long-term adverse effects, such as malignancies, presents with prolonged use of CYC at high cumulative doses. Long-term treatment with GCs increases the risk for diabetes, elevated blood pressure, osteoporosis and cataract (Knight et al. 2004, Faurschou et al. 2008).

Kidneys are involved in ca. 70% of WG patients at the time of diagnosis (Cisternas et al. 2005, Gottenberg et al. 2007), and the proportion rises to 85% in the course of the disease. Approximately 20% of WG patients develop renal failure (Aasarod et al. 2000, Cisternas et al. 2005, Geetha et al. 2007). Left untreated, renal failure is inevitably fatal. The development of methods of dialysis and renal transplantation has dramatically improved the outcome of patients with end-state renal disease (ESRD). These patients can survive for long periods on dialysis, but their lives are very restricted. Only after successful kidney transplantation can they lead fairly normal lives (Geetha et al. 2007).

If untreated, patients with WG would probably succumb to organ failure due to vasculitis (renal insufficiency, pulmonary haemorrhage, respiratory failure, etc.) With effective treatment regimens, the inflammatory process of WG as the immediate cause of death has become more uncommon. In three recent studies with mean follow-up times of 1.9-8.8 years, vasculitis itself was responsible for 24-50% and infections for 33-48% of the deaths of WG patients (Mahr et al. 2001, Bligny et al. 2004, Flores-Suaréz et al. 2007).

3.6.2 PROGNOSTIC FACTORS

Mukhtyar et al. (2008) found in their review of 61 articles different survival rates between genders. Men had a somewhat greater mortality risk. Mortality risk ratio (MRR) was 4.0 for men and 3.4 for women. In various studies, a relationship between increasing age at diagnosis and decreasing survival has been reported. Kidney involvement, particularly elevated serum creatinine value at an early stage of the disease, has been associated with worse prognosis, as has lung involvement, elevated ESR values (Mahr et al. 2001) and reduced blood haemoglobin (Bligny et al. 2004). By contrast, ENT involvement has predicted a better prognosis (Mahr et al. 2001, Koldingsnes et al. 2002, Bligny et al. 2004, Pavone et al. 2006, Mukhtyar et al. 2008, Mohammad et al. 2009).
3. AIMS OF THE STUDY

1. To investigate the incidence of WG and its changes in Finland in 1981-2000.
2. To evaluate clinical presentation, diagnostic delay and factors affecting the delay in patients diagnosed with WG in Finland in 1981-2000.
3. To determine the occurrence of dialysis dependent renal disease and factors affecting the risk of dialysis in patients diagnosed with WG in Finland in 1981-2000.
4. PATIENTS AND METHODS

4.1. PATIENTS

Hospital discharge registers (National Research and Development Centre for Welfare and Health, STAKES) were screened for all patients with a discharge diagnosis of WG during 1981-2000 (1981-1986 based on ICD8, 1987-1995 on ICD9, 1996-2000 on ICD10). These patients were allegedly WG patients, but the reason for their hospital admission was not necessarily connected to WG. The register data showed in which hospital the patient was treated and for how long. All available patient files were then reviewed. To estimate the risk of dialysis-dependent renal insufficiency and kidney transplant, this information was complemented with files provided by the Finnish Registry for Kidney Diseases. Statistics Finland provided the dates and causes of death of the patients. From the registry files, data were collected up to year 2005 in order to have a sufficiently long follow-up for 5-year survival statistics.

Patients treated only in health centres were not included in this study (n=45) because their data would not have been comparable with the data for the rest of the patients.

In all, 661 patients treated in Finnish hospitals in 1981-2000 had WG as one of the discharge diagnoses in the hospital discharge registers. At least some data were available on 585 patients in patient files. After the review of patient files, the diagnosis of WG was confirmed for 513 patients. In 492 cases, the diagnosis was set in 1981-2000 (Figure 2).
Figure 2. Flowchart of data retrieval.

661 patients treated in 1981-2000 with a discharge diagnosis of WG

45 patients treated only in health centres

616 patients treated in hospitals of specialized health care

Data not available for 31 patients

Data available for 585 patients

72 patients with erroneous code or inadequate data

513 WG patients with verified diagnosis treated in hospitals of specialized care care

21 patients diagnosed before 1981

492 patients diagnosed in 1981-2000
4.2. ETHICAL ASPECTS

The Ethics Committees of Helsinki University Central Hospital and Kajaani Central Hospital and the National Advisory Board on Health Care Ethics approved the study protocol.

4.3. METHODS

From patient files, data were collected on:

1. clinical features (consistent with WG, see page 19) at presentation, at diagnosis and cumulative features thereafter
2. laboratory results (annually):
   - blood test for haemoglobin, leukocyte count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum creatinine and anti-neutrophil cytoplasmic antibodies (ANCA†),
   - urine tests for haematuria and proteinuria
3. histology for diagnosis of WG
4. medical treatment for WG
5. all significant comorbidities
6. malignancies

In the process of data collection, the following definitions were applied:

Symptom onset: The time the first WG-related symptom appeared. Persistence of WG-related symptoms subsequently led to the suspicion of WG.

Date of diagnosis: The point at which the treating physician suggested WG in the patient’s files was interpreted as the time of diagnosis. If not otherwise defined, the day CYC therapy was started was regarded as the day of diagnosis.

The diagnosis of WG was ascertained, based on cumulative clinical features consistent with the presentation of WG (see page 19):

- appropriate ENT (ear, nose, throat), pulmonary and renal symptoms and signs
- indications of generalized inflammatory disease
  * malaise, fatigue, fever
- relevant laboratory findings
  * anaemia, high ESR, high level of CRP, positive ANCA† test
  * proteinuria, haematuria, urine sediment consistent with glomerulonephritis, elevated serum creatinine values
- histology consistent with WG

'ANCA depicted as positive or negative (see section 5.5)

Based on the cumulative information available, the extent to which a patient’s characteristics agreed with ACR classification criteria, Sorensen diagnostic criteria and Watts diagnostic criteria was determined (Leavitt et al. 1990, Sorensen et al. 2000, Watts et al. 2007; Tables 3, 5, 6).


4.4. STATISTICAL ANALYSES

The results were expressed as mean or median, standard deviation (SD) or interquartile range (IQR), and 95% confidence intervals (95% CIs). The statistical significance between groups was evaluated with analysis of variance (ANOVA), Kruskall-Wallis test, Mann-Whitney U-test or χ² test with a Monte Carlo p-value when appropriate. Statistical significance for hypotheses of linearity was evaluated by using ANOVA, Jonckheere–Terpstra test, Cochran–Armitage test, χ² test and median regression analysis (least–absolute-value models).

Time-to-event analysis was based on the product limit estimate (Kaplan-Meier) of the cumulative “survival” function. The prognostic factors to predict the duration of progression-free “survival” and to estimate the age- and sex-adjusted risk for mortality were analysed using multivariate proportional hazard regression models (Cox’s regression models). The proportional hazard assumption was tested for all variables in the selected models graphically and formally. The ratio between observed and expected numbers, the standardized mortality ratio (SMR), was calculated using subject-year methods with 95% CIs, assuming a Poisson distribution. Probabilities of survival in an age- and sex-matched sample of the general population were calculated from data from the Official Statistics of Finland.

Patients and the population at risk were stratified by gender and age (5-14, 15-24, 25-34, 35-44, 45-54, 55-64, 65-74 and 75+), and crude and adjusted incidence rates with 95% CIs were calculated. Standardized estimates of WG incidence rate ratios (IRRs) were calculated by using Poisson or negative binomial regression models when appropriate.
5. RESULTS AND DISCUSSION

5.1 PATIENTS

Altogether 492 patients, 243 men and 249 women, were diagnosed with WG at a mean age of 53.7 (SD 18.1) years (median 56 years). At diagnosis, patients of the last 5-year period were some 9 years older than those of the first period. During the first three 5-year periods, female patients slightly outnumbered male patients, but in 1996-2000, the situation was reversed (Table 10).

The results are in line with other studies from the Nordic countries. In a Norwegian epidemiological study in 1992-1996, a clear majority (65%) of PSV patients were female; WG patients were not singled out (Haugeberg et al. 1998). In another Norwegian study of WG patients in 1984-1998, men predominated (62%) (Koldingsnes et al. 2000). In Sweden, 64% of WG patients in 1975-2001 were male (Knight et al. 2006).

5.2 INCIDENCE (I)

The crude incidence in this study was 1.9 per million per year in 1981-1985, and this rose to 9.3 per million per year in 1996-2000. The corresponding annual age-adjusted incidence rate ratio (IRR) was 5.2 per million for men and 4.0 per million for women. The incidence was somewhat higher in women in the first three 5-year periods, but in 1996-2000 there was a slight male predominance. Also age at diagnosis increased from 46 years in the first 5-year period (1981-1985) to 55 years in the last 5-year period (1996-2000) (p between periods=0.014). Incidence peaked in the age group 65-74 years among both sexes (Table 11).

A 4.5-fold increase occurred in the incidence of WG during the study period. This finding is fairly consistent with other results in recent years, especially from Nordic countries. In Sweden and Norway, the incidence of WG increased 2.3-fold in 15 years (Koldingsnes et al. 2000, Knight et al. 2006). In the UK, a small rise in incidence was observed in 10 years (Watts et al. 2000). Some other studies have, however, failed to show any increase in incidence (Watts et al. 2001, Reinhold-Keller et al. 2005).

Discussions and speculations have centred around whether the increased incidence of WG is due to improved recognition of the disease or better diagnostic
methods and whether the incidence in fact is truly rising (Carruthers DM et al. 1996). All of these factors may contribute to the results.

Tests for ANCA antibodies became available in the mid-1980s. ANCA tests were first performed in Finland in 1985. The tests rapidly became popular in the clinics, facilitating recognition and diagnosis of WG. In this study, a clear increase occurred in the incidence of WG from 1985 onwards. The increase coincides well with increasing use of ANCA tests (Figures 3 and 4). Results show, however, that although virtually all new WG patients were tested for ANCA in 1991-1995 as well as in 1996-2000, the incidence increased between these periods (Tables 10 and 11). This implies that testing for ANCA is not the sole reason for the increasing incidence, although it is an important one. It can also be assumed that ANCA tests had improved in accuracy and sensitivity in 1985-2000, making comparison of test results somewhat unreliable. There could also have been a genuine increase in the incidence of WG.

The introduction of the ACR criteria in 1990 may also have facilitated diagnosis of WG and made it more accurate. On the other hand, our results reveal that patients diagnosed in the 1980s were more often ACR-positive than those diagnosed in the 1990s (Table 10).
Table 10. Demographic features of 492 Wegener’s granulomatosis patients.

<table>
<thead>
<tr>
<th>Period years</th>
<th>Number</th>
<th>Male patients (%)</th>
<th>Age at diagnosis (years), mean (SD)</th>
<th>Time from symptom onset to diagnosis (months), median (IQR)</th>
<th>ESR at diagnosis, mm/h, median (IQR)</th>
<th>ACR classification criteria present ≥2 (%)</th>
<th>ANCA-examined (%)</th>
<th>ANCA-positive (% of all patients )*</th>
<th>ANCA-positive (% of all tested)*</th>
<th>ANCA-positive (% of all patients )**</th>
<th>ANCA-positive (% of all tested)**</th>
<th>All periods</th>
<th>P-value between periods †</th>
</tr>
</thead>
<tbody>
<tr>
<td>1981-1985</td>
<td>43</td>
<td>19 (44)</td>
<td>45.8 (16.5)</td>
<td>17 (3 , 44)</td>
<td>80 (55 , 102)</td>
<td>40 (93)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>1 (100)</td>
<td>19 (44)</td>
<td>19 (70)</td>
<td>492</td>
<td>0.42</td>
</tr>
<tr>
<td>1986-1990</td>
<td>83</td>
<td>40 (48)</td>
<td>51.1 (17.4)</td>
<td>8 (3 , 41)</td>
<td>78 (48 , 105)</td>
<td>71 (86)</td>
<td>61 (74)</td>
<td>58 (70)</td>
<td>58 (95)</td>
<td>60 (72)</td>
<td>60 (85)</td>
<td>83</td>
<td>0.014</td>
</tr>
<tr>
<td>1991-1995</td>
<td>141</td>
<td>64 (45)</td>
<td>53.7 (17.6)</td>
<td>5 (1 , 17)</td>
<td>61 (34 , 95)</td>
<td>115 (82)</td>
<td>133 (94)</td>
<td>119 (84)</td>
<td>119 (90)</td>
<td>120 (85)</td>
<td>120 (90)</td>
<td>82</td>
<td>0.11</td>
</tr>
<tr>
<td>1996-2000</td>
<td>225</td>
<td>120 (53)</td>
<td>55.0 (18.6)</td>
<td>4 (1 , 12)</td>
<td>80 (50 , 100)</td>
<td>184 (82)</td>
<td>219 (97)</td>
<td>212 (94)</td>
<td>212 (97)</td>
<td>211 (94)</td>
<td>211 (97)</td>
<td>83</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>243 (49)</td>
<td>53.2 (18.1)</td>
<td>5 (2 , 20)</td>
<td>75 (45 , 100)</td>
<td>410 (83)</td>
<td>414 (84)</td>
<td>390 (79)</td>
<td>390 (94)</td>
<td>410 (83)</td>
<td>410 (91)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*ANCA examined in the year of diagnosis, **ANCA examined at any time during the disease, † Test for linearity
SD = standard deviation, IQR = interquartile range, ESR= erythrocyte sedimentation rate, ACR = American College of Rheumatology, ANCA= anti-neutrophil cytoplasmic antibodies.
Table 11. Incidence per million of Wegener’s granulomatosis in Finland in 1981-2000.

<table>
<thead>
<tr>
<th>Period</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>19</td>
<td>40</td>
<td>64</td>
</tr>
<tr>
<td>Crude incidence (95% CI)</td>
<td>2.0 (1.3 to 3.0)</td>
<td>3.6 (2.6 to 4.3)</td>
<td>6.3 (5.0 to 7.9)</td>
</tr>
<tr>
<td>Age-adjusted incidence rate ratio (95% CI)</td>
<td>Indicator (1)</td>
<td>2.0 (1.2 to 3.5)</td>
<td>3.0 (1.8 to 5.0)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>24</td>
<td>43</td>
<td>77</td>
</tr>
<tr>
<td>Crude incidence (95% CI)</td>
<td>1.7 (1.0 to 2.7)</td>
<td>3.6 (2.6 to 4.9)</td>
<td>5.6 (4.3 to 7.1)</td>
</tr>
<tr>
<td>Age-adjusted incidence rate ratio (95% CI)</td>
<td>Indicator (1)</td>
<td>1.8 (1.1 to 2.9)</td>
<td>3.0 (1.9 to 4.8)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>43</td>
<td>83</td>
<td>141</td>
</tr>
<tr>
<td>Crude incidence (95% CI)</td>
<td>1.9 (1.4 to 2.6)</td>
<td>3.6 (2.9 to 4.4)</td>
<td>6.0 (5.0 to 7.0)</td>
</tr>
<tr>
<td>Age- and sex-adjusted incidence rate ratio (95% CI)</td>
<td>Indicator (1)</td>
<td>1.9 (1.4 to 2.4)</td>
<td>3.0 (2.4 to 3.8)</td>
</tr>
</tbody>
</table>
Figure 3. Annual incidence of Wegener's granulomatosis in Finland in 1981-2000.

Figure 4. ANCA tests performed on Wegener's granulomatosis patients in the year of diagnosis in Finland in 1981-2000.

The development of other diagnostic methods likely had an impact on diagnosis of WG. Novel imaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), may reveal otherwise inaccessible disease
manifestations, e.g. in the central nervous system. Improved surgical and minimvasive methods and endoscopic equipment have provided better tissue samples.

The incidence of WG might actually be on the rise, too. This is suggested by the parallel results of independent studies (Koldingsnes et al. 2000, Knight et al. 2006), including the present study. The question then becomes: If the incidence is truly increasing, what is the cause? Hypotheses include elevated amounts of inhaled unhealthy substances, heretofore unknown infectious agents and changed microbiological environment that alters immunological reactions (de Lind van Wijngaarden et al. 2008).

Studies reported mean ages of 40-50 years at onset of WG in the 1950s to 1980s (Littlejohn et al. 1985, Hunder et al. 1990, Kelley et al. 1993). By contrast, studies in the 2000s have demonstrated median ages of about 60 years at diagnosis (Reinhold-Keller et al. 2005, Knight et al. 2006). However, several studies have failed to report increasing ages at diagnosis (Koldingsnes et al. 2000, Reinhold-Keller et al. 2005, Knight et al. 2006). The results of the present study show uniform increasing ages at diagnosis throughout the two decades of the survey (Table 10). Previous studies have shown a peak in incidence around the age of 70, consistent with our findings (Koldingsnes et al. 2000, Watts et al. 2000, Lane et al. 2005).

Some unknown factor seems to postpone WG to a more advanced age nowadays. Better hygiene and more rigorous control of infections, diminishing the strain on immunologic defence, are potential contributing factors. However, the increasing incidence of WG contradicts this possibility.

5.3. CLINICAL PRESENTATION (I, II)

Data on involvement of different organ groups in various stages of disease were available for 489 patients. An average of 1.8 organ groups were simultaneously involved at the beginning of WG-related symptoms. The ENT (ear, nose and throat) system was affected most frequently, in 45% of patients. Lungs were involved in 36% of cases, and 36% of patients presented with constitutional symptoms and signs (fever, malaise, fatigue, other aberrations of general well-being and inflammation-related laboratory findings) (Table 12).

Within the first six months of onset of WG symptoms, ENT was the still the most frequently involved organ group (63% of cases). Pulmonary involvement was present in 59% of cases. Constitutional symptoms were present in 60% of patients. Kidneys were involved in 40%, musculoskeletal system in 39%, eyes in 17% and skin in 17% of cases. In 1981-1985, 49% of patients had constitutional symptoms during the first six months of their symptomatic period, but in 1996-2000 as many as 66%. This change was statistically significant, but not after multiplicity adjustment. No significant change occurred in initial ELK score (Figure 5, Table 13).
Proportions of involvement of all major organ groups grew over the course of the disease. Involvement of kidneys and eyes increased 6-fold, other organ groups less, albeit markedly (Table 12).

The agreement of patient data with the criteria of ACR (Leavitt et al. 1990), Sorensen (Sorensen et al. 2000) and Watts (Watts et al. 2007) was tested with respect to the four 5-year periods. The best agreement was with the criteria of Watts (90%) and ACR (83%) (Table 14). Only the agreement with the Watts et al. criteria differed significantly between the 5-year periods (p<0.001).

Presenting features at disease onset remained quite similar during the study. Only constitutional symptoms became somewhat more common with time (Table 13).

WG has a clear tendency to develop from its restricted form to a more generalized disease. This is shown by numerous preceding studies (Table 8), and also by the present study (Table 12).

Consistent with a Norwegian study (Koldigsnes et al. 2000), our study demonstrates a stable clinical picture in the initial stages of WG over years (Table 13). Although the disease is recognized increasingly rapidly, the disease has remained uniformly aggressive. It can be hypothesized that perhaps the same factors that contribute to the increased incidence (e.g. infections, inhaled substances, pollution, silica) alter the very character of WG.

Table 12. Organ involvement (%) in different phases of the disease in 489 patients.

<table>
<thead>
<tr>
<th>Phase of disease</th>
<th>At presentation</th>
<th>First 6 months</th>
<th>At diagnosis</th>
<th>At any time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>11</td>
<td>40</td>
<td>60</td>
<td>64</td>
</tr>
<tr>
<td>ENT</td>
<td>45</td>
<td>63</td>
<td>75</td>
<td>82</td>
</tr>
<tr>
<td>Lung</td>
<td>36</td>
<td>59</td>
<td>77</td>
<td>85</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>22</td>
<td>39</td>
<td>48</td>
<td>57</td>
</tr>
<tr>
<td>Eye</td>
<td>5</td>
<td>17</td>
<td>28</td>
<td>37</td>
</tr>
<tr>
<td>Constitutional</td>
<td>36</td>
<td>60</td>
<td>83</td>
<td>87</td>
</tr>
</tbody>
</table>
Figure 5: Proportions (%) of organ group involvement during the first six months after onset of Wegener’s granulomatosis-related symptoms.

ENT=Ear, nose and throat
Musc=Musculoskeletal
Constit=Constitutional symptoms=symptoms and signs of generalized inflammatory disease, including fever, malaise, fatigue and other aberrations of general well-being, or abnormal laboratory findings related to general inflammation such as anaemia and elevated values of erythrocyte sedimentation rate and C-reactive protein.
† Cochran-Armitage linear trend test. No adjustment made for multiple testing.
Table 13. Proportions of organ group involvement during the first six months after onset of Wegener’s granulomatosis-related symptoms. Extent of organ system involvement also expressed with an ELK score of 0-3.

<table>
<thead>
<tr>
<th>Organ involvement</th>
<th>Time period</th>
<th>All</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>39</td>
<td>46</td>
<td>38</td>
</tr>
<tr>
<td>Ear, nose and throat</td>
<td>59</td>
<td>70</td>
<td>68</td>
</tr>
<tr>
<td>Lung</td>
<td>54</td>
<td>54</td>
<td>61</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>39</td>
<td>35</td>
<td>40</td>
</tr>
<tr>
<td>Eye</td>
<td>24</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>49</td>
<td>55</td>
<td>62</td>
</tr>
</tbody>
</table>

ELK score

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>10</td>
<td>2</td>
<td>9</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>1</td>
<td>49</td>
<td>42</td>
<td>38</td>
<td>35</td>
<td>37</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>39</td>
<td>32</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>17</td>
<td>22</td>
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</tbody>
</table>

ELK: Ear, nose, throat, Lung, Kidney

Constitutional symptoms = symptoms and signs of generalized inflammatory disease, including fever, malaise, fatigue and other aberrations of general well-being, or abnormal laboratory findings related to general inflammation such as anaemia and elevated values of erythrocyte sedimentation rate and C-reactive protein.

† Cochrán-Armitage linear trend test. No adjustment made for multiple testing.

‡ Chi-square test.
Table 14. Agreement of the patient data with classification criteria of Wegener’s granulomatosis.

<table>
<thead>
<tr>
<th></th>
<th>5-year period</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=43</td>
<td>N=83</td>
<td>N=141</td>
<td>N=225</td>
<td>N=492</td>
</tr>
<tr>
<td>ACR classification*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 criteria present</td>
<td>2 (5)</td>
<td>1 (1)</td>
<td>3 (2)</td>
<td>6 (3)</td>
<td>12 (2)</td>
</tr>
<tr>
<td>1 criteria present</td>
<td>1 (2)</td>
<td>11 (13)</td>
<td>23 (16)</td>
<td>35 (16)</td>
<td>70 (14)</td>
</tr>
<tr>
<td>2 criteria present</td>
<td>6 (14)</td>
<td>21 (25)</td>
<td>38 (27)</td>
<td>80 (36)</td>
<td>145 (29)</td>
</tr>
<tr>
<td>3 criteria present</td>
<td>20 (47)</td>
<td>29 (35)</td>
<td>57 (40)</td>
<td>84 (37)</td>
<td>190 (39)</td>
</tr>
<tr>
<td>4 criteria present</td>
<td>14 (33)</td>
<td>21 (25)</td>
<td>20 (14)</td>
<td>20 (9)</td>
<td>75 (15)</td>
</tr>
<tr>
<td>≥2 criteria present (=ACR+)</td>
<td>40 (93)</td>
<td>71 (86)</td>
<td>115 (82)</td>
<td>184 (82)</td>
<td>410 (83)</td>
</tr>
<tr>
<td></td>
<td>Sorensen criteria**</td>
<td>17 (40)</td>
<td>32 (39)</td>
<td>48 (34)</td>
<td>84 (37)</td>
</tr>
<tr>
<td></td>
<td>Watts criteria***</td>
<td>26 (61)</td>
<td>78 (94)</td>
<td>128 (91)</td>
<td>210 (93)</td>
</tr>
</tbody>
</table>

* Leavitt et al. 1990
** Sorensen et al. 2000
*** Watts et al. 2007

5.4. DIAGNOSTIC DELAY (II)

Diagnostic delay was calculated for every patient for whom the data on the initial stages of the disease were available (N=489). Diagnostic delay was defined as a median period of time starting the day the first symptoms and signs consistent with WG appeared and ending on the day of diagnosis. Moreover, that at least one WG-related symptom had to be present constantly until the diagnosis was set. We also analysed factors with an impact on diagnostic delay.

The diagnostic delay shortened from a median of 17 months in 1981-1985 to 4 months in 1996-2000. The change in diagnostic delay was most prominent between the first and second 5-year periods (Table 10).

Gender and age had no significant effect on diagnostic delay, but patients with initial lung involvement and constitutional symptoms had a significantly shorter delay (Table 15), as did patients with an initially high ESR. High ELK score also associated with a shorter diagnostic delay. Patients with ELK scores of 2 and 3 had a median diagnostic delay of 3 (IQR 1 , 5.5) and 2 (IQR 1 , 6) months, respectively. The corresponding median delay values were 17 (IQR 12 , 35) and 11.5 (IQR 4 , 46) months for patients with ELK scores of 0 and 1. This trend was significant (p<0.001).
Table 15. Median regression analysis for the effect of gender, age and organ involvement on diagnostic delay.

<table>
<thead>
<tr>
<th>Variable</th>
<th>β (95%CI†)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>-1 (-3 to 1)</td>
<td>0.21</td>
</tr>
<tr>
<td>Age</td>
<td>0 (0 to 0)</td>
<td>0.99</td>
</tr>
<tr>
<td>Kidney involvement</td>
<td>-1 (-2 to 0)</td>
<td>0.16</td>
</tr>
<tr>
<td>ENT involvement</td>
<td>-1 (-2 to 0)</td>
<td>0.29</td>
</tr>
<tr>
<td>Lung involvement</td>
<td>-4 (-7 to -1)</td>
<td>0.005</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>-9 (-13 to -5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Constant</td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ENT=ear, nose and throat; constitutional symptoms=symptoms and signs of generalized inflammatory disease including fever, malaise, fatigue and other aberrations of general well-being, or abnormal laboratory findings related to general inflammation such as anaemia, elevated values of erythrocyte sedimentation rate and C-reactive protein.

† Bootstrap standard errors.

Reasons for the decrease in diagnostic delay were probably mostly the same as for the increase in incidence: increased awareness of the disease, availability of ANCA tests and other improved diagnostic facilities. Despite these, however, the disease did not become milder over time, but instead presented with more constitutional symptoms, which supposedly led to prompt investigations and diagnosis (Table 13). In addition, a high ELK score is an indicator of a widespread disease, and a patient with a widespread disease is evidently investigated promptly. Thus, patients with higher ELK scores had considerably shorter median diagnostic delay than patients with less advanced disease.

The results of diagnostic delay are in line with the median value of 4.5 months in a previous study (Lane et al. 2005). In a recent Swedish study of 95 WG and MPA patients, no significant difference in diagnostic delay was found between the periods 1978-1996 and 1997-2005. A minor tendency did, however, emerge; delays were 186 days (about 6 months) and 121 days (about 4 months), respectively (Eriksson et al. 2009). These results are quite similar to ours.

5.5. ROLE ON ANCA ANTIBODY TESTS IN THE DIAGNOSIS

ANCA tests were introduced to the diagnostic repertoire in 1985 and PR3-ANCA in 1986 in Finland (Figure 4). Only 30 of the patients of this study were diagnosed with WG before 1985 (“pre-ANCA era”). Of them, 18 were tested for ANCA later in the course of their diseases; 11 were ANCA-positive (Table 10). Of the 423 patients examined for ANCA antibodies in the year of diagnosis, 399 (94%) were ANCA-positive. Of the 24 patients negative for ANCA during the first year, five became
ANCA-positive later. The diagnostic delay decreased the most after the introduction of ANCA tests in 1985 and PR3-ANCA in 1986.

The methods for detecting ANCA antibodies were heterogeneous, particularly in the 1980s.

Often no information of ANCA subclasses could be found in hospital records. Therefore, patients of this study were depicted merely as ANCA-positive or -negative. Of the 411 ANCA-positive patients, 219 were tested and found to be positive for PR3-ANCA and 28 for MPO-ANCA. ANCA tests in the 1980s and 1990s likely differed in sensitivity and specificity, making interpretation of test results unreliable.

In an epidemiologic study by Koldigsnes et al. (2000) in Norway in 1984-1998, only patients fulfilling ACR criteria were included. The annual incidence increased more than 2-fold (from 5.2 to 12.0/ million/year), although ANCA testing was not used as an inclusion criterion. In a Swedish study by Knight et al. (2006), the incidence of WG more than tripled in 1971-2001 (from 3.3 to 11.9/ million/year). The increase partly coincided with the introduction of ANCA into routine use, but some increase took place even in the pre-ANCA period.

Performing ANCA tests probably also decreases the number of biopsies taken. A biopsy consistent with WG was performed on 76.7% of patients in 1981-1985, in contrast to 59.1% in 1996-2000 (p=0.002). A similar trend was evident in a recent large study in USA (Abdou et al. 2002).

5.6. TREATMENT

The treatment of WG followed similar lines throughout the 20 years. Of all WG patients, 75.4% were treated initially with CYC for a known period of time in 1981-1990 and 78.1% in 1991-2000. In some stage of their illnesses, 86.6% of patients were treated with CYC (91.3% vs. 85.0% for the two decades, respectively). Both genders were treated equally often with CYC, but in females the medication was frequently started later. In 55% of women and 35% of men, CYC was started six or more months after the appearance of the first symptoms of WG. The cumulative dose of CYC could be calculated for 367 patients. The median cumulative dose was smaller in women (32.6 g [IQR 12.4, 59.7]) than in men (41.6 g [IQR 13.2, 77.8]). The total doses of CYC decreased somewhat during the survey; the median cumulative total dose was 50.5, 50.1, 41.3 and 23.3 grams per patient during the four consecutive 5-year periods (1981-1985, 1986-1990, 1991-1995, 1996-2000).

Immunosuppressive agents other than CYC (azathioprine, methotrexate, cyclosporine, leflunomide, mycophenolate mofetil, podophyllotoxin, vincristine, cytarabine) were seldom used. Only 4.3% of all patients were treated with them and never received CYC.
GC treatment was used in a vast majority of the patients; 87.3% of patients in 1981-1990 and 93.7% in 1991-2000 were treated with GCs at least temporarily. Five patients were treated with a TNFα blocking agent (infliximab) after unsuccessful treatment with CYC. The use of a long-term antibiotic medication (mostly sulphatrimethoprim) increased from 1981-1990 to 1996-2000 (16.7% vs. 28.2%, respectively).

No real progress in the treatment of WG took place in the 1980s and the 1990s. Treatment was mostly based on Fauci’s scheme (Fauci et al. 1973). Some modifications of the scheme were developed to reduce the total dose, and hence, the adverse effects of CYC (Hoffman et al. 1990, Guillevin et al. 1997). Reducing total CYC doses was also an aim in Finland in 1981-2000 (see above).

5.7. OUTCOME

5.7.1. KIDNEY SURVIVAL (III)

5.7.1.1. Renal insufficiency

At the year of diagnosis, 150 patients (30.1% of all patients) had impending renal insufficiency, i.e. serum creatinine values of 160 mmol/l or more. Of them, 47 (9.6% of all patients) had serum creatinine values ≥500 µmol/l.

5.7.1.2. Dialysis

Eighty-four patients (34 women and 50 men; 17% of all 492 WG patients) needed dialysis before 8 October 2005. In this patient group, the median time from the the first WG-related symptoms to dialysis was 9 months (IQR 1, 63). The product-limit estimate of the rate of developing kidney involvement leading to transient or permanent dialysis for renal insufficiency was 14.6% (95% CI: 11.6 to 18.2) at 5 years and 29.6% (95% CI: 21.5 to 40.0) at 20 years after onset of WG symptoms. The 5-year and 20-year rates were 11.7% (95% CI: 8.0 to 16.8) and 31.3% (95% CI: 18.5 to 49.9), respectively, in women and 17.5% (95% CI: 13.1 to 23.2) and 27.8% (95% CI: 19.9 to 38.1) in men; the age-adjusted hazard ratio was 1.53 (95% CI 0.98 to 2.37) (p=0.059).
Sixty-three percent of patients needing dialysis were male. The age of dialysed patients at diagnosis did not differ significantly from that of non-dialysed. Dialysed patients significantly more often had kidney involvement during the first six months after onset of WG symptoms ($p=0.009$) and elevated serum creatinine values at diagnosis ($p<0.001$) than non-dialysed patients.

Although 150 patients (30%) had elevated serum creatinine values ($\geq 160\, \mu\text{mol/l}$) in the year of their WG diagnosis, only 61 of them received dialysis. Of the remaining 89 (non-dialysed) patients, 47 died during the survey. Thus, 42 of those 150 patients (28%) with impending renal insufficiency survived and were never dialysed.

Even 12 of the 47 patients with serum creatinine values $\geq 500\, \mu\text{mol/l}$ were never dialysed. Nine of these patients died before the end of the survey, but three of them survived and their renal function recovered (Figure 8).

In previous studies, the frequency of renal involvement at presentation of WG has been reported to be 11-18%, risk of chronic renal insufficiency ~ 40% (Samarkos et al. 2005) and risk for end-stage renal disease ~ 20% in patients with ANCA-associated vasculitis (Geetha et al. 2007).

5.7.1.3. Chronic dialysis

In 32 of the 84 dialysed patients (38%), the first dialysis became chronic, i.e. it was prolonged for three months or more. Of these patients, 18 (56%) were male. Patients with chronic dialysis and the rest of the WG patients differed significantly in age at diagnosis (mean 46.1 vs. 54.2 years; $p=0.014$), but not in the delay from the first WG-related symptoms until diagnosis (mean 42.1 vs. 27.7 months). They were equally often positive for ANCA tests and ACR criteria; their organ system involvement during the first six months differed only for renal involvement ($p<0.015$). The delay from the first WG-related symptoms until CYC medication (median 11 vs. 7 months) and until GC medication (median 4 vs. 4 months) did not differ significantly.

5.7.1.4. Risk factors for acute and chronic dialysis

The most significant risk factor for acute and chronic dialysis was elevated serum creatinine level at diagnosis of WG. Renal involvement at 6 months was a risk factor for acute dialysis, but not for chronic dialysis (Table 16).

Elevated serum creatinine value and advanced age at disease initiation have been shown to be risk factors for acute and chronic dialysis in several studies (Aasarod et al. 2000, Koldigsnes et al. 2002, Gottenberg et al. 2007).
Figure 6. Patients needing dialysis and outcome of dialysed patients according to baseline serum creatinine values.
Table 16. Cox regression model for the risk of acute and chronic dialysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Acute dialysis (&lt;3 months)</th>
<th>Chronic dialysis (≥3 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)*</td>
<td>p-value</td>
</tr>
<tr>
<td>Gender, male</td>
<td>1.59 (0.57 to 4.39)</td>
<td>0.38</td>
</tr>
<tr>
<td>Age, years</td>
<td>0.99 (0.96 to 1.03)</td>
<td>0.62</td>
</tr>
<tr>
<td>Symptoms within 6 months from onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>2.40 (1.03 to 5.59)</td>
<td><strong>0.042</strong></td>
</tr>
<tr>
<td>ENT</td>
<td>1.05 (0.39 to 2.86)</td>
<td>0.93</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>1.15 (0.41 to 3.26)</td>
<td>0.78</td>
</tr>
<tr>
<td>Constitutional</td>
<td>0.65 (0.27 to 1.57)</td>
<td>0.34</td>
</tr>
<tr>
<td>ESR at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I tertile (≤55 mm/h)</td>
<td>1.00 (reference)</td>
<td></td>
</tr>
<tr>
<td>II tertile (56-89 mm/h)</td>
<td>1.25 (0.42 to 3.66)</td>
<td>0.70 (0.18 to 2.72)</td>
</tr>
<tr>
<td>III tertile (≥90 mm/h)</td>
<td>0.99 (0.27 to 5.60)</td>
<td>1.23 (0.36 to 4.22)</td>
</tr>
<tr>
<td>Serum creatinine at diagnosis</td>
<td>&lt;<strong>0.001</strong>†</td>
<td></td>
</tr>
<tr>
<td>I tertile (≤100 µmol/l)</td>
<td>1.00 (reference)</td>
<td></td>
</tr>
<tr>
<td>II tertile (101-200 µmol/l)</td>
<td>3.41 (0.77 to 15.14)</td>
<td>3.54 (0.63 to 19.89)</td>
</tr>
<tr>
<td>III tertile (&gt;200 µmol/l)</td>
<td>14.12 (3.66 to 54.47)</td>
<td>20.67 (4.11 to 104)</td>
</tr>
</tbody>
</table>

ENT: Ear, nose and throat
ESR: Erythrocyte sedimentation rate
*HR: Hazard ratio (95% confidence interval)
† Test for linearity
5.7.1.5. Transplantation

Nineteen patients (8 women, 11 men; 22.6% of dialysed patients, 3.9% of all patients) received a renal transplant. Median time from the first dialysis to transplantation was 3.1 years (IQR 1.5, 6.5). The long-term survival of transplanted kidneys was good. One patient was transplanted twice because of acute rejection of the first transplant and another patient needed dialysis again 5.5 years after his transplantation.

Similar good results have been published elsewhere (Wrenger et al. 1997, Ounissi et al. 2009). Patients transplanted for WG-related renal disease have been found to do better than those transplanted for other renal diseases (Shen et al. 2010).

The good results imply that kidney transplantations were prepared and conducted with great care. Preparations include treating the disease process of WG to remission and finding a suitable donor. This procedure takes a lot of time, and patients must spend months and even years on dialysis waiting for the transplantation. After transplantation, proper anti-rejection medication is needed; this medication probably precludes recurrence of the underlying vasculitis. The relapse rate of AAV after kidney transplantation has been reported to be 0.006-0.1 per patient per year (Geetha et al. 2007) or 12-17.3% (Rostaing et al. 1997, Nachman et al. 1999). Unfortunately possible AAV recurrences in the patients of the present study are unknown.

5.7.1.6 Renal outcome

Information on the cause of discontinuation of the first dialysis was available for 75 of the 84 dialysed patients. In 32 (38%) of the dialysed patients, renal function recovered. Fifteen patients (18%) received a renal transplant, and 27 patients (32%) died during the first dialysis. Active treatment was withdrawn from one patient who succumbed shortly thereafter. Eleven patients needed re-dialysis later after having temporarily recovered. Altogether 19 patients (3.9% of all 492 WG patients) received a kidney transplant.

One hundred and fifty patients (30% of WG patients) had an elevated serum creatinine value (≥160 µmol/l) in the year of diagnosis. Sixty of them plus another 24 patients were dialysed. Forty-seven patients had a creatinine value as high as ≥500 µmol/l in the year of diagnosis. Yet only 35 of them were ever dialysed. Of the 12 non-dialysed patients, 3 were alive at the end of the follow-up (Figure 6).

Of those 84 patients needing dialysis at some point in their disease, dialysis was discontinued for 32, often temporarily, due to recovery of renal function. One hundred and seventy-four patients (35%) had at least impending renal insufficiency in some phase of their diseases. Of these, 122 patients (70% of patients with renal insufficiency) regained their renal function, often temporarily, with WG treatment.
These findings are in line with previously published studies (Aasarod et al. 2000, Koldingsnes et al. 2002, Jayne 2009). Rarely, patients with serum creatinine as high as ≥500 µmol/l may regain renal function.

All 174 patients in the present study with impending or manifest renal insufficiency probably would have had lost kidney function totally and permanently without treatment. Even for five of the 32 patients dialysed ≥3 months, kidney function recovered with treatment and dialysis could be ceased. Thus, chronic dialysis (≥3 months) does not always represent an irreversible and final end-state renal disease (ESRD) (Figure 6).

Forty-one (48.8%) of all 84 dialyzed WG patients were alive on 8 October 2005; 16 were alive with a functioning kidney transplant, 14 were on dialysis and 11 had their own functioning kidneys and were not on dialysis.

5.7.2. MALIGNANCIES

Eighty-three (18.9%) of the 492 WG patients were diagnosed with 113 malignancies, a majority of which were malignancies of the skin (n=42), followed by malignancies of the gastrointestinal tract (n=20) and urinary bladder (n=11). Of the 53 patients treated with AZA, 10 were diagnosed with cancer; 4 of them were cancers of the skin.

Because of the small number of cancer patients and the lack of population control data on the incidence of malignancies, there was no opportunity to estimate whether WG patients had a medication-related enhanced risk of malignant neoplasms. However, our results imply that CYC has a role in the aetiology of bladder cancer. The vast majority (9/11) of the patients with bladder cancer belong to the group of patients receiving the largest total doses of CYC (Figure 7).
CYC-treated patients have been reported to have an increased risk of malignancies, especially leukaemia and urinary bladder cancer (Faurschou et al. 2008). AZA treatment has been found to increase lymphoma risk four-fold (Kandiel et al. 2005).

In a recent Norwegian study, some increase, albeit not significant, was observed in the incidence of various malignancies among 75 patients with systemic autoimmune diseases previously treated with intravenous CYC. In that study, even when no mesna prophylaxis was given, neither haemorrhagic cystitis nor urinary bladder cancer occurred (Goransson et al. 2008).

### 5.7.3. MORTALITY (IV)

Of the 492 patients, 203 (99 men and 104 women) died before the end of June 2005. WG or another connective tissue disease was the most frequent underlying cause of death (39%)*, followed by cardiovascular events and neoplasms. Twenty-seven patients died of cancer, most often of malignancies of the gastrointestinal tract (n=7), haematological malignancies (n=5) and malignancies of the respiratory tract (n=4). Urinary bladder cancer caused only one death. The relative proportions of causes of death did not differ much between the two decades (Figure 8).

*All patients had been diagnosed with WG during their lifetime, but in 4 patients the underlying cause of death was recorded as rheumatoid arthritis (n=2), systemic lupus erythematosus (n=1) or vasculitis (n=1).
Figure 8. Causes of death of Wegener’s granulomatosis patients by 10-year periods.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>WG and closely related diseases</td>
<td>34</td>
<td>42</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>31</td>
<td>26</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Respiratory</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Infections</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Kidney</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Others</td>
<td>7</td>
<td>9</td>
</tr>
</tbody>
</table>

No significant difference in mortality existed between patients in the earlier and those in the later 10-year period (gender- and age-adjusted hazard ratio 0.89 [95% CI: 0.64 to 1.24]) (Figure 9).

Figure 9: Age- and sex-adjusted survival of Wegener’s granulomatosis patients in the two 10-year periods.

No significant difference in mortality existed between women and men (age-adjusted hazard ratio 1.11 [95% CI = 0.84 to 1.47]). The standardized mortality ratio (SMR) for all WG patients diagnosed in 1981-2000 was 3.43 (95% CI = 2.98 to 3.94), 4.38 (95% CI = 3.59 to 5.61) for women and 2.80 (95% CI = 2.28 to 3.41) for men (Table 17, Figure 10).
Table 17. Proportions of patients surviving one, three and five years after diagnosis of Wegener’s granulomatosis, grouped by gender and 10-year period of diagnosis.

<table>
<thead>
<tr>
<th>Gender</th>
<th>1-year survival, % (95% CI)</th>
<th>3-year survival, % (95% CI)</th>
<th>5-year survival, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>84.8 (72.7-91.8)</td>
<td>80.4 (73.9-85.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>81.4 (68.9-89.2)</td>
<td>73.9 (67.0-79.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>78.0 (65.1-86.6)</td>
<td>70.6 (63.5-76.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>85.1 (74.0-91.7)</td>
<td>84.1 (77.9-88.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>80.6 (68.9-88.2)</td>
<td>80.2 (73.7-85.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>73.1 (60.8-82.1)</td>
<td>76.4 (69.5-81.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>84.9 (77.4-90.1)</td>
<td>82.2 (77.9-85.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>81.0 (72.9-86.8)</td>
<td>77.1 (72.4-81.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>75.4 (66.9-82.0)</td>
<td>73.5 (68.7-77.7)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 10. Age-adjusted survival of male and female Wegener’s granulomatosis patients with 95% confidence intervals.

No marked improvements in the treatment of WG took place in the 1980s and 1990s. Rather similar treatment schemes prevailed, CYC and GCs being the favourite drugs. Prognosis remained constant; in fact, the prognosis seemed to be poorer in the later decade (Table 17). After adjustment for age and gender, the difference disappeared. Men and women lived equally long after the diagnosis of WG. However, if not for WG, women would outlive men by many years. This explains women’s considerably higher SMR.

In the 1970s and 1980s, rapid strides occurred in the development of therapies for WG and other vasculitides, and prognosis improved markedly (Fauci et al. 1983). The survival results of the present study concur fairly well with other published data (Mahr et al. 2001, Koldingsnes et al. 2002, Bligny et al. 2004).
Along with mortality, factors with an impact on mortality of WG patients were analysed. Risk of dying increased with increasing age, and also elevated serum creatinine levels at diagnosis predicted poorer prognosis. Patients with initial ENT involvement had a considerably better prognosis than those without. Treatment with CYC had an independently positive effect on survival. Male or female gender was not a marked risk. In the initial phase, i.e. during the first six months of WG-related symptoms, men had significantly more renal symptoms (p=0.014) and more pulmonary and constitutional symptoms. Diagnostic delay, fulfilling ACR criteria, high ELK score or high ESR at diagnosis had no impact on mortality from WG, although any one of these factors could be considered to be indicative of a more severe and/or widespread disease. It can be hypothesized that the prompt use of CYC, which has an independently favourable impact on prognosis, explains this phenomenon, at least partly (Table 18).

The overall survival of dialysed WG patients seemed to be as good as that of non-dialyzed patients. Although no significant difference emerged between the groups, in looking at survival curves, the dialysed patients had an initial 1- to 2-year period of excessive mortality. Patients dying during the first two years after dialysis perished most often (57%) due to the disease process of WG itself and in; 24% died due to cardiovascular events. After the first couple of years, the mortality curves are more or less parallel (Figure 11).

ANCA-positivity in the year of WG diagnosis was associated with a better prognosis than ANCA-negativity. However, continuously ANCA-negative patients had a better prognosis than those even once ANCA-positive (Figure 12 a & b). ANCA-positive and ANCA-negative patients had malignancies equally often (p=0.52).

We can only speculate about the connection of ANCA with survival. If a patient was tested initially and found to be ANCA-positive, he/she was probably treated promptly and properly and had a better prognosis than an ANCA-negative patient (Figure 12 a). However, if a patient was constantly negative for ANCA, the prognosis would be even better. (Figure 12 b)

In several other studies (Mahr et al. 2001, Koldingsnes et al. 2002, Bligny et al. 2004, Pavone et al. 2006), poorer survival with advancing age and developing renal insufficiency has been shown. The disease course of permanently ANCA-negative patients appears to be more restricted and milder (Fienkielman et al. 2007; Gomez-Puerta et al. 2009)
Table 18. Age- and gender-adjusted hazard ratios (HRs) for individual factors affecting survival of patients with Wegener’s granulomatosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male</td>
<td>1.11 (0.84 to 1.47)</td>
<td>0.46</td>
</tr>
<tr>
<td>Age, years</td>
<td>1.07 (1.06 to 1.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diagnostic delay, months</td>
<td></td>
<td>0.16†</td>
</tr>
<tr>
<td>&lt;6</td>
<td>1.00 (reference)</td>
<td></td>
</tr>
<tr>
<td>6-11</td>
<td>1.06 (0.70 to 1.62)</td>
<td></td>
</tr>
<tr>
<td>12-23</td>
<td>0.90 (0.57 to 1.43)</td>
<td></td>
</tr>
<tr>
<td>≥24</td>
<td>1.37 (0.97 to 1.93)</td>
<td></td>
</tr>
<tr>
<td>ACR criteria ≥2</td>
<td>1.02 (0.71 to 1.46)</td>
<td>0.92</td>
</tr>
<tr>
<td>Symptoms within 6 months of onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>1.05 (0.79 to 1.40)</td>
<td>0.72</td>
</tr>
<tr>
<td>ENT</td>
<td>0.70 (0.53 to 0.93)</td>
<td><strong>0.014</strong></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>0.98 (0.73 to 1.30)</td>
<td>0.87</td>
</tr>
<tr>
<td>Constitutional</td>
<td>0.77 (0.58 to 1.03)</td>
<td>0.074</td>
</tr>
<tr>
<td>Serum creatinine level at diagnosis</td>
<td></td>
<td><strong>0.011†</strong></td>
</tr>
<tr>
<td>I tertile (≤89 (\mu)mol/l)</td>
<td>1.00 (reference)</td>
<td></td>
</tr>
<tr>
<td>II tertile (90-180 (\mu)mol/l)</td>
<td>1.32 (0.87 to 2.00)</td>
<td></td>
</tr>
<tr>
<td>III tertile (≥181 (\mu)mol/l)</td>
<td>1.68 (1.13 to 2.50)</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide used</td>
<td>0.64 (0.47 to 0.87)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

ACR: American College of Rheumatology
ELK score (0-3): number of organ systems (ear, nose and throat; lung; kidney) simultaneously involved
ENT: ear, nose and throat
ESR: erythrocyte sedimentation rate
† Test for linearity (between tertiles)

Figure 11. Survival of dialysed and non-dialyzed WG patients.
a) ANCA examined in the year of WG diagnosis

Thus, our data do not support the possibility that ANCA-negative patients have underlying malignancies and that their vasculitis is in fact paraneoplastic.

b) ANCA examined at any time during the course of the disease

Thus, our data do not support the possibility that ANCA-negative patients have underlying malignancies and that their vasculitis is in fact paraneoplastic.
The survival of dialysed patients was as good as that of non-dialyzed patients, at least after the initial 1-2 years (Figure 9). Patients with kidney transplants seemed to survive even better than the rest of WG patients and better than the rest of dialysed WG patients. If the patient coped with the first fulminant phase of the disease and the vasculitis process had mostly receded, the chances for survival were fairly good. Moreover, patients must have been in remission for long, i.e. the disease process virtually extinguished, before they were considered for a kidney transplantation. Thus, transplanted patients were in clinical remission from the disease, and therefore, their prognosis was good. After transplantation, patients are on continuous immunosuppressive medication to preclude the rejection of the transplant. Immunosuppression may also preclude recurrence of vasculitis.
6. GENERAL DISCUSSION

WG remains an uncommon disease, although its incidence has increased markedly. WG has serious consequences; diagnosis probably means years on medication with potential numerous side-effects, frequent visits to hospital wards and outpatient departments, repeated laboratory tests, risk of renal insufficiency (often dialysis-dependent) and risk of increased mortality rate. Because of the complexity and variety of its presentation and the often insidious progress, the recognition of WG calls for the vigilance and cooperation of several specialties in medicine. Vague persisting constitutional symptoms and musculoskeletal aches and pains may finally lead to referral to a rheumatologist; cutaneous vasculitides are seen by dermatologists; refractory adult otitis or sinusitis calls for an ENT specialist; pulmonary examinations start after prolonged cough or alarming haemoptysis. All of these situations may arouse suspicions, and WG may be revealed. ENT physicians often have a key role in diagnostics because WG most frequently begins in their field. Fairly often, patient’s first contact may be with an ophthalmologist or a dermatologist for their symptoms.

Recognition of WG has improved constantly in recent decades along with developments in diagnostic means, as discussed previously. In particular, the introduction of ANCA tests into diagnostic use has improved recognition of WG and related vasculitides. C-ANCA and especially PR3-ANCA are very specific to WG, whereas p-ANCA and MPO-ANCA are typical of MPA. These subclasses are useful in differential diagnosis of ANCA vasculitides, although some overlapping in specificity occurs. The initial phases and localized forms of WG in patients with vague and unspecific symptoms are the most difficult to diagnose. These patients also tend to remain ANCA-negative, and therefore tests do not support the diagnosis.

The incidence of WG has increased, at least partly because of improved recognition, but the growth seems to have ceased since 1996. The awareness of WG among physicians may have reached a stand-still and perhaps diagnostic means have not improved further. Recent figures may therefore represent the true incidence of WG.

This study, like several previous ones, shows that WG is a disease warranting early recognition and treatment. The prognosis of WG has greatly improved since the 1930s and 1950s along with developments in the treatment regimens. Nowadays, the diagnosis of WG is not the death sentence that it used to be in the 1950s and 1960s.

During the two-decade survey period, the treatment regimen remained constant, as were the results and survival rates. Thus, the results are reliable and they can be generalized. Biological agents have, at least theoretically, advantages over traditional medications. The great challenge in the treatment of WG, as well as of
other autoimmune diseases, is to suppress selectively the autoimmune reaction responsible for the disease process. Treatment with cytotoxic agents and GCs leads to an overly extended immunosuppression, rendering the patient susceptible to infections and perhaps malignancies. Although the prognosis of WG patients has improved, morbidity and mortality are still a concern. The NIH treatment scheme (Fauci’s scheme) was revolutionary, but it can be associated with troublesome adverse effects, including increased risk of malignancies with elevated cumulative doses of CYC. The results in Finland in 1981-200 are in line with these findings. After realizing the risks, treatment strategies have been developed towards shorter courses and smaller total doses of CYC and other immunosuppressive therapies with wider safety profiles. After achieving remission, CYC medication is switched to MTX, AZA, leflunomide or MFF. These alternatives are similarly effective as CYC in remission maintenance. While, in general, they have fewer adverse effects than CYC, they are not without problems (see sections 3.5.4-5).

The discovery of biological targeted drugs and their great success in the treatment of inflammatory arthritides have raised interest and hope in their efficacy on vasculitides. Until now, treatment with biological agents has been far from targeted. They block or reduce the effect of inflammatory cytokines (TNFα, INFγ or IL-1) or reduce the number of cells producing mediators of inflammation (Lee 2008, Manna 2008, Ramos-Casals 2008, Lamprect 2009). Although some good results have been presented, these drugs seem to increase infectious complications without being effective in WG. Improved knowledge of aetiology and disease mechanisms will allow better therapies to be developed. Ideally, these would be therapies that treat the disease alone, without causing untoward harm. In this respect, rituximab has shown promising results, especially in vasculitis-type WG with few adverse effects. It may provide a good treatment alternative, particularly for young patients.

Although new treatment regimens have been developed during the past decades, CYC is still considered to be the cornerstone of medical therapy for WG. In a generalized disease, the medication is usually started with a combination of CYC and GC. MTX can be used in combination with GCs in non-organ-threatening or non-life-threatening generalized disease. After achieving remission, CYC medication may be switched to MTX, AZA, leflunomide or MFF. The remission-maintenance therapy is continued for at least 18 months. If the disease is localized to the airways, trimethoprim-sulfamethoxazole treatment can be used as a monotherapy or in combination with GC (and perhaps MTX), as both a remission-inducing and remission-maintenance therapy. In life- or organ-threatening disease, the remission-inducing treatment can be complemented with methylprednisone pulses and/or plasmapheresis and/or intravenous immunoglobulin infusions (Bosch et al.2007, Ozaki et al. 2007, Mukhtyar et al. 2009, Pettersson et al. 2010).

As might be expected, early recognition and intervention of WG are favourable for the prognosis of patients. This was not, however, shown in the present study.
In 1981-2000, while diagnostic delay decreased markedly, survival rate did not improve. Nonetheless, the results imply that CYC medication is favourable per se. The most critically ill are likely diagnosed much more rapidly, although their disease cannot be completely suppressed. The similar results in patients with full-blown disease and those with mild, restricted disease speaks in favour of the efficacy of individually tailored treatment strategies.
The incidence of WG increased considerably in Finland in 1981-2000 probably for several reasons. The clinical picture of WG remained essentially the same during these two decades. Most often, the disease started with ENT (45%), pulmonary (36%) or constitutional symptoms (36%). The clinical picture tended to evolve into a more generalized form of a disease; in a minority of cases, WG remained in a localized form.

The majority of WG patients were treated according to the “Fauci scheme” with CYC and GCs. The survival of WG patients has improved dramatically from the 1950s and 1960s, but excess mortality still occurs compared with the rest of the population. The prognosis has not improved further in the 1980s and 1990s, and the serious adverse effects of the toxic medications are of great concern, calling for new treatment protocols.

At diagnosis of WG, 30% of patients had impending renal insufficiency. About in one-third of these patients, renal function recovered and dialysis was not needed. With WG treatment, 30% of the 84 patients needing dialysis regained their renal function, at least temporarily. Nineteen (3.9% of all WG patients) patients received a kidney transplant; sixteen of them were alive and not on dialysis at the end of the survey.

This study, like several other recent studies, shows that WG is a disease warranting early recognition and treatment. The treatment results during the twenty years of the study are by far superior to those of the preceding decades.

Strengths of this study are that the hospital discharge register covers the whole of Finland and that the hospital records of all patients with a discharge diagnosis of WG and treated at hospitals of specialized heath care were reviewed and their diagnoses confirmed.

A weakness of our study is that we included only patients treated at a hospital ward at least once. Information was gathered retrospectively from patient files and some information was probably missing. Also diagnostic criteria varied with district and time. We have probably missed some patients treated only at health centres who had a limited form of the disease.
8. ACKNOWLEDGEMENTS

For long, it was not my intention to write any scientific article, let alone a thesis. However, during my health centre years in Äänekoski, I got to know Hannu Kautiainen, who eventually talked me into scientific research. Without him, this thesis would not have been started. Hannu also persuaded Professor Marjatta Leirisalo-Repo to guide me in the project. Had it not been for her, the thesis would never have proceeded. These two key persons offered me their priceless support and supervision in methodological and clinical problems. I owe them my warmest thanks for their time and effort.

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9. REFERENCES


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