# Monitoring

- To minimize morbidity and mortality of the vasculitides and their therapy
- Differential diagnosis in pts with clinical deterioration
  - infection
  - Drug toxicity
  - Disease relapse
  - A new unrelated problem

## *Goals of treatments for Wegener's granulomatosis*

1. Patients survival
2. Induce remission of active disease
3. Reduce disease relapse
4. Minimize therapeutic toxicity
    - Use the least toxic yet effective treatment option
    - Actively pursue strategies to prevent and monitor for toxicity
    - Use treatment regimens at doses and schedules on which there data

Current therapies though effective in inducing remission are wanting in reducing relapses and high in toxicity

## *Challenges in conducting therapeutic trials in Wegener's granulomatosis*

1. Rarity of Wegener's granulomatosis
2. Potential for active disease to be life threatening
3. Available treatment of established efficacy
4. Definition of outcome measures
5. Imprecise means of assessing active disease
6. Extended follow-up is necessary to fully assess relapse and to reach study endpoint

# Management of Wegener's according to stage and evidence:

## Clinical subgrouping according to disease severity at presentation for ANCA-associated vasculitis

| Clinical subgroup | Constitutional symptoms | Typical ANCA status | Threatened vital organ function | Serum creatinine (μmol/L) |
|---|---|---|---|---|
| Localized | No | Negative | No | <120 |
| Early systemic | Yes | Positive or negative | No | <120 |
| Generalized | Yes | Positive | Yes | <500 |
| Severe | Yes | Positive | Organ failure | >500 if renal; hypoxia if pulmonary |
| Refractory | Yes | Positive or negative | Yes | any |

# Localized disease:

WG affecting the upper or lower respiratory tract alone without constitutional disturbance

Has been treated with prednisolone alone or with the antibiotic combination with TMP-SMX

Possible modes of activity:

1. anti-inflammatory and inh. formation of O2 radicals by activated neutrophils
2. WG are related to antimicrobial effects and inhibition of S. aureus driven proliferation of T lymphocytes and B lymphocytes, immunoglobulin and cytokine production

# Role of TMP-SMX in Wegener's granulomatosis

T/S has been found in several reports to be beneficial in limited WG

Interpretation of these results is confounded by:

1. their retrospective nature 2. by the use of concurrent immunosuppressive agents 3. by the difficulty in defining active upper airways disease, and 4. by the lack of controlling for infection

Two prospective studies found no role in limited WG


1. Hoffman GS: *Sarcoidosis Vasc Diffuse Lung Dis* 1996, 13: 249-252
2. Reinhold-Keller E, De Groot K. *Q J Med* 1996, 89: 15-23


Maintenance regime by TMP-SMX: NEJM 96- only URT flares

Never to be used alone in systemic vasculitis

Always in patients on CYS as PCP prophylaxis

# Early systemic disease

Comprises: A. localized WG with constitutional disturbance
or
B. WG which is multi-focal but without threatened organ function

- Cyclophosphamide and steroids has been standard therapy
- Several uncontrolled studies have reported disease remission in 60-70% with methotrexate and steroids used for induction therapy

**Methotrexate may be used in Wegener's as:**
**1. induction therapy 2. maintenance therapy**

**Remission maintenance in WG:**

NIH (n=32) with a F/U of 31 months.
CR 100% with no deaths and relapse rate of 16%

# Induction

## Comparison of three studies of methotrexate and prednisone in Wegener's granulomatosis

| | Sneller et al (1995) | De Groot et al (1998) | Tone et al (1999) |
|---|---|---|---|
| Total number | 42 | 17 | 19 |
| MTX/PRED as initial regimen (%) | 36 | 65 | 100 |
| > 3 organs at start of treatment | 60 | NA | 74 |
| GN at start of treatment (%) | 50 | 12 | 47 |
| ANCA (%) | 83 | 76 | 84 |
| Max MTX dose/week | 25 mg | 0.3 mg/kg | 22.5 mg |
| Route of MTX | Oral | Intravenous | Oral starting |
| PRED dose | 1 mg/kg/die | 10 mg/d (median) | 40 |
| PRED tapered to QOD | Yes | No | No |
| Improved (%) | 83 | 59 | 89 |
| Remission (%) | 71 | 35 | 74 |
| Developed GN on treatment (%) | 2 | 29 | 5 |
| Relapse (%) | 27 | 33 | 50 |
| Death (%) | 7 | 0 | 0 |
| Hepatotoxicity (%) | 24 | 0 | 32 |
| Opportunistic infections (%) | 10 | 0 | 0 |
| MTX pneumonitis (%) | 7 | 0 | 0 |
| Leukopenia (%) | 7 | 0 | 0 |

The control of early renal vasculitis, with normal or modest creatinine elevation with methotrexate is more controversial

- Two studies have reported stabilization of excretory function;
- Others have found renal vasculitis to predict refractory, progressive disease after methotrexate
- Inability to reduce the steroid dose and relapsing disease have been predictive of more widespread vasculitis after methotrexate therapy


1. Langford CA. Arthritis Rheum 2000; 43:1836-1840
2. De froot K, Reinhold-Keller. Arthritis Rheum 1996; 39:2052-2061
3. Stone JH, Tun W, Hellman DB. J Rheumatol 1999; 26: 1134-1139


In the **NORAM trial,100 newly diagnosed patients with s. Cr <150mol/l and no life or** organ-threatening involvement randomized to Mtx and Cyc.

At the primary endpoint (remission at 6 m), equal remission (MTX 89.8% vs CYC 93.5%).

The relapse rate at 1 yr was unacceptably high (69.5% MTX and 45% CYC)

Mean time to relapse was 13.5 months

# Generalized/renal disease

## A six-month corticosteroid taper

- Initiated treatment with 1 mg/kg/d of prednisone for the first month up to a max of 80 mg/d
- After 1 month, prednisone is tapered by 10 mg/wk. The goal is to achieve a dose of 20 mg/d by the end of 8 to 10 weeks of therapy
- Then, maintain dose of 20 mg/d for 2 weeks
- Then, reduce dose by 2.5 mg/wk until a dose of 10 mg/d is reached
- Then, reduce dose by 1 mg/wk until off

*Patients with fulminant disease may receive intravenous methyl prednisone (1 g/d for 3 days) at the start of corticosteroid therapy. For patients with limited disease, the initial dose of corticosteroids may be lower (e.g., 0.5-0.8 mg/kg/d)

# Cyclophosphamide for generalized Wegener's

Data from historic controls show the marked improvement in disease remission induction with CYC.
Current remission rates are 75-90% but relapse rates are still 50%.
This is at expense of marked toxicity.

| | Bad Bramstedt (n= 155) | NIH (n= 158) |
|---|---|---|
| Mediam follow-up (years) | 7 | 8 |
| Patients taking CYC/CS | 92% | 84% |
| MESNA use | Yes | No |
| Alternate-day prednisone tapering | No | Yes |
| Complete remission achieved | 54% | 75% |
| Relapses (after complete remission) | 60% | 50% |
| Overall mortality | 14% | 20% |
| Mortality (due to WG or treatment) | 12% | 13% |
| Serious infections | 26% | 46% |
| Deaths as a result of infection | 3% | 3% |
| Myelodysplasia | 8% | 2% |
| Cyclophosphamide induced- cystitis | 12% | 43% |
| Bladder cancer | <1% | 3% |

Cyc is a powerful agent with good remission rates but has unacceptable toxicity in the long run
Some of these (gonadal, bladder Ca, MDS/leukemia) are dose dependent

## Using cyclophosphamide safely

- Limit duration of CYC use (ideally 3-6 months for remission induction)
- Take medication in morning; drink eight 8-oz glasses of water daily
- Adjust dose to maintain white blood cell count greater than 4000 mm3
- Check complete blood count every 2 weeks and a urinalysis monthly
- Adjust dose for renal dysfunction (see algorithm below)*
- Always use *Pneumocystis carinii prophylaxis*
- Long-term surveillance for CYC-induced bladder injury (annual urinalyses, with cystoscopy as indicated by hematuria or abnormal cytologic findings)

| Creatinine clearance (mL/min) | CYC dose (mg/kg/d) |
|---|---|
| > 100 | 2.0 |
| 50-99 | 1.5 |
| 25-49 | 1.2 |
| 15-24 | 1.0 |
| <15 or on dialysis | 0.8 |

# Critical analysis of trials comparing "pulse" to daily oral cyclophosphamide

| | Daily oral | Pulse | Comparison |
|---|---|---|---|
| Remission rate | 77% | 93% | Odds ratio 0.3 |
| Relapse rate | 29% | 42% | Odds ratio 2.2 |
| Infection | 58% | 39% | Odds ratio 0.24 |
| Death | 22% | 20% | No difference |
| End-stage renal failure | 15% | 17% | No difference |
| Cyclophosphamide dose | 34 g | 17 g | P< 0.001 |

- All of the studies concluded that adverse effects were more frequent with daily oral cyclophosphamide
- A higher relapse rate after intravenous pulse use