Hot Tips in Rheumatology GP CME Meeting,Christchurch 08.08.2010

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Disclosures

- Advisory Boards and speaker at meetings: Abbott, Roche, Pfizer/Wyeth, MSD, Novartis and Quintiles CRO.

- Investigator in clinical trials for: Boehringer Ingelheim, MSD, UCB, Medi-Immune, Centocor, Roche, Abbott and Pfizer.

Hot Tips:

1. Early referral for patients with inflammatory arthritis
2. Prescription of low-dose weekly Methotrexate
3. False positive ANA
4. Injection of carpal tunnel syndrome
5. Gout
6. Refer all patients with PMR/GCA

Take Home Message:

Rapid referral to a Rheumatologist of all inflammatory arthritis or when RA is suspected is crucial to the prognosis of the patient.

This may be supported by the presence of any of the following:

- $\geq$ 3 swollen joints
- MTP/MCP involvement
- morning stiffness of $\geq$ 30 minutes.

P Emery et al. ARD 2002;61:290-7

Typed by medical secretaries in NHS Greater Glasgow

The patient has no previous history of suicides.

The patient has left her white blood cells at another hospital.

Methotrexate in low doses (weekly) is not a cytotoxic. It is a safe immunosuppressant.

Problems:

- No data sheet in NZ specifically for low-dose, weekly Methotrexate.
- Inappropriate advice often given out by pharmacists for dispensing low-dose, weekly Methotrexate:
  - Avoid too much sunlight
  - Avoid Methotrexate with NSAIDs or Coxibs
  - Avoid Methotrexate with Sulphasalazine

Consider getting into the habit of writing NCL (no cautionary label) when prescribing low-dose, weekly Methotrexate.

Note: Community pharmacists do not dispense high-dose Methotrexate for cytotoxic purposes.

Monitoring Blood Tests for DMARDs

Consider developing the habit of checking patients have had recent monitoring blood tests (usually FBC, LFTs, CRP) especially in patients who are established on treatment and are having bloods done every 2-3 months.

Typed by medical secretaries in NHS Greater Glasgow

Patient's medical history has been remarkably insignificant with only a 40 pound weight gain in the past three days.

She has no rigors or shaking chills, but her husband states she was very hot in bed last night.

Antinuclear Antibody Testing

Approximately 27% (34% in women and 17% in men) of the general population have positive ANA. The vast majority are false positive. Don't recommend testing for patients with straightforward arthritis or muscle pain. Test if there is a strong suspicion of connective tissue disease, otherwise often raise unnecessary anxiety amongst patients.

Typed by medical secretaries in NHS Greater Glasgow

Patient has chest pain if she lies on her left side for over a year.

On the second day the knee was better and on the third day it disappeared.

The patient is tearful and crying constantly. She also appears to be depressed.

Injection of Carpal Tunnel Syndrome

Injection with methylprednisolone proximal to the carpal tunnel: randomised double-blind trial. JWHH Dammers et al. BMJ 1999, 319:884-6

- Use posterior route as in the diagram as less risk of damaging the median nerve. Also easier to do than injections into the carpal tunnel.
- A single injection with steroids close to the carpal tunnel may result in long-term improvement and should be considered before surgical decompression. This single injection is still effective at one year in half of the patients.

Typed by medical secretaries in NHS Greater Glasgow

The patient has been depressed since she began seeing me in 1993.

Discharge status: - Alive, but without my permission.

Healthy appearing, decrepit 69-year old male, mentally alert but forgetful.

Prescription and comorbidity screening following consultation for acute gout in primary care.

E. Roddy et al. Rheumatology 2010; 49:105-111

GP study looking at 673 new gout consultations (583 were for acute gout)

- Monitoring of lipids (5%)
- BP (26%)
- Glucose (6%)
- Renal function (21%)

measured within one month of index consultation

- 66% of patients treated with Colchicine were prescribed high-dose regimens (500mcg at least four times daily).
- Urate-lowering therapies (ULTs) were prescribed within 12 months in 23% of patients. 19% of ULTs were prescribed during acute attacks.

Opportunities for improving medication use and monitoring in gout

J.A. Singh et. al. Annals of Rheumatic Diseases 2009; 68:1265-70

Results:

- 643 patients received a new Allopurinol prescription
- 46% received continuous Allopurinol
- 10% received Colchicine prophylaxis
- 20% reached target uric acid of $\leq$6mg/dl ($\leq$0.35mmol/l)
- During episodes of renal insufficiency appropriate dose reduction/discontinuation of Probenacid was done in 77% of episodes and of Colchicine in 69% of episodes

Conclusions:

Important variations were found in patterns of medication used in monitoring in patients with gout with suboptimal care. A concerted effort is needed to improve the overall care of gout.

Concise Report: Gout: an independent risk factor for all-cause and cardiovascular mortality

C-F Kuo et. Al. Rheumatology 2010; 49: 141-6

Conclusion: This study demonstrates a link of gout, not hyperuricaemia, with a higher risk of death from all causes and cardiovascular diseases.

Review: The modern management of gout

T.G. Rider and K.M. Jordan

Rheumatology 2010; 49: 5-14

Gout

- A common debilitating arthritis affecting approximately 1% of the population
- Incidence and prevalence increasing steadily (approximately 200-300% increase from mid-1960s to mid-1990s)

Possible Explanations

1. Alarming rise of obesity
2. Aging of the population
3. Increasing prevalence of renal failure and hypertension
4. Widepsread use of thiazide diuretics and low-dose Aspirin
5. Rising consumption of beer

Epidemiology of Gout in Women

V. Bhole et. al. Arthritis and Rheumatism 2010; 62: 1069-76

- Prospective data from Framingham Heart Study over a 52-year period (1950-2002).
- Risk factors and incidence of gout in 2,476 women and 1,951 men were evaluated.

Conclusions:

1. Magnitude and rate of increase lower in women than that among men
2. Risk factors associated with incident gout in women:
    1. Increasing age (per 5 years)
    2. Obesity (body mass index $\geq$30Kg/M^2)
    3. Alcohol intake ($\geq$7 ounces of pure alcohol/week)
    4. Hypertension
    5. Diuretic use

Don’t forget women with gout too!

The most significant quality gaps in gout pharmacotherapy are:

1. Delayed initiation of urate-lowering therapy (ULT)
2. Inadequate dosing of ULT
3. Failure to document response to ULT
4. Failure to use gout flare prophylaxis during initiation of ULT
5. Initiation of ULT during acute gout flares

Delayed initiation of urate-lowering therapy (ULT)

- Once patient starts to get recurrent and incapacitating attacks, initiate Allopurinol but NOT at 300mg once daily. Recommend starting at 100mg once daily even if normal renal function, less in patients with impaired renal function.
- Educate patient to improve compliance, i.e. Allopurinol is a preventer and might precipitate gout during initiation (I always tell patients that one of the best ways to exacerbate gout would be to stop and start Allopurinol intermittently but once a patient is established on it and is taking the correct dose and is compliant, he/she should not get gout again).

Inadequate dosing of ULT

- Allopurinol 300mg once daily achieves therapeutic treatment target of uric acid of <0.36mmol/l in only 26% of patients
- Interrupting Allopurinol use (especially during gouty attacks unless severe polyarticular tophaceous gout) leads to more frequent exacerbations and flares.

Failure to document response to ULT

- Need to titrate dose of Allopurinol or other ULT so SUA persistently <0.36mmol/l, especially in-between attacks.
- Remember non-compliance. 56% of patients are non-adherent. L.R. Harrold et. al. Arthritis Research Therapeutics 2009; 11: R46.

Editorial: Treatment-failure gout: A moving target.

N Lawrence Edwards. Arthritis and Rheumatism 2008; 58: 2587-90.

Prof Larry Edwards emphasised the following:

1. There is now an accepted target for urate-lowering (<0.6mg/dl or <0.36mmol/l).
2. Dose escalation of Allopurinol to >300mg per day is required to achieve this goal in most gout patients. (Allopurinol 300mg per day or less rarely (22%) achieved therapeutic SUA levels).
3. The widely published guidelines to restrict the maximum dose of Allopurinol in patients with chronic kidney disease have not led to improved safety or outcomes.

Failure to use gout flare prophylaxis during initiation of ULT

- Optimal duration of NSAID and/or Colchicine prophylaxis unknown - suggestions have included 2 or 3 or 6 months once SUA <0.36mmol/l.
- Studies have shown that there is an increased risk of a flare of gout up to 6 months after initiating a ULT.

Initiation of ULT during acute gout flares

- Recommend waiting 2-4 weeks after resolution of last attack of gout before starting ULT.
- NZRA consensus statement on the use of Colchicine in the treatment of gout. www.rheumatology.org.nz/position_statement.cfm

- In most patients, NSAIDs and corticosteroids are the treatment of choice for acute gout. When NSAIDs are contraindicated and corticosteroids are not providing an adequate response, Colchicine is an option, particularly if taken within the first 24 hours of onset of pain

- 2-hourly dosing of Colchicine to treat acute gout no longer appropriate especially in older patients, because of serious adverse effects arising from large doses.

- Recommended dose of Colchicine in the treatment of acute gout is 1.0mg stat, followed by 0.5mg stat 6-hourly up to a maximum dose of 2.0mg/24 hours on the first day.

- Alternative regimen is to consider an acute gout of <12 hours duration of 0.1mg stat followed by 0.5mg one hour later. On subsequent days, the total dose should not exceed 1.5mg daily. Total dose should not exceed 6mg over four days.

- A prophylactic dose of Colchicine may then be started after three days. Corticosteroids can be used in combination with NSAIDS or Colchicine to prevent further acute gout.

- Colchicine can also be used prophylactically in the treatment of gout with a dose ranging from 0.5mg every other day to 0.5mg twice a day, just short of that which will induce diarrhoea or soft stools in the patient.

High vs low dosing of oral Colchicine for early acute gout flare

R.A. Terkeltaub et. al. Arthritis and Rheumatism 2010; 62: 1060-8

- High-dose is 4.8mg over 6 hours
- Low-dose is 1.8mg over 1 hour

- Responders in low-dose is 37.8% and 32.7% in high-dose, and 15.5% in placebo.
- High-dose: 76.9% diarrhoea, 19.2% severe diarrhoea and 17.3% vomiting.
- Low-dose: 23.0% diarrhoea and no severe diarrhoea nor vomiting.

Conclusion:

- Low-dose Colchicine (1.8mg total over one hour) yielded both maximum plasma concentration in early gout flare efficacy compared with that of high-dose Colchicine (4.8mg total over 6 hours), with a safety profile indistinguishable from that of placebo.

NZRA Consensus Statement on Colchicine

Fatal and non-fatal cases of Colchicine toxicity have been reported with concomitant use of P-gp and CYP3A4 inhibitors such as cyclosporine, clarithromycin, erythromycin, verapamil, diltiazem, ketaconazole, HIV protease inhibitors, etc. Toxicity can also be increased by daily consumption of a litre of grapefruit juice, hepatic and renal impairement, statins, fibrates and digoxin.

New treatments for gout (not currently available in NZ):

- Febuxostat, a new selective inhibitor of xanthine oxidase. Efficacious in renal impairment with no significant relationship between renal function and urate-lowering efficacy. 40-120mg once daily orally.
- Poly(ethylene) glycol-uricase (PEG-uricase) or Pegloticase. IV 8mg every two weeks. Effective in resolving tophi, so use in 'debulking' tophi in advanced gout before switching to another agent for maintenance treatment.

Future Treatments:

1. Anakrina, an interleukin-1 receptor antagonist. MSU crystals stimulate inflammasome leading to interleukin-1β secretion.
2. Rilonacept and Canakinumab which are both interleukin-1 inhibitors.
3. Apremilast, an oral, small molecule inhibitor of phosphodiesterase-4 and tumour necrosis factor-alpha.

Typed by medical secretaries in NHS Greater Glasgow

Patient had waffles for breakfast and anorexia for lunch.

She is numb from her toes down.

While in ER, she was examined, x-rated and sent home.

Audit of Polymyalgia Rheumatica and Giant Cell Arteritis 2000 to 2005

Dr D.W.T. Ching, Consultant Rheumatologist
Ms K. Cameron, Rheumatology Nurse
Timaru Hospital & Community Services
Timaru
New Zealand

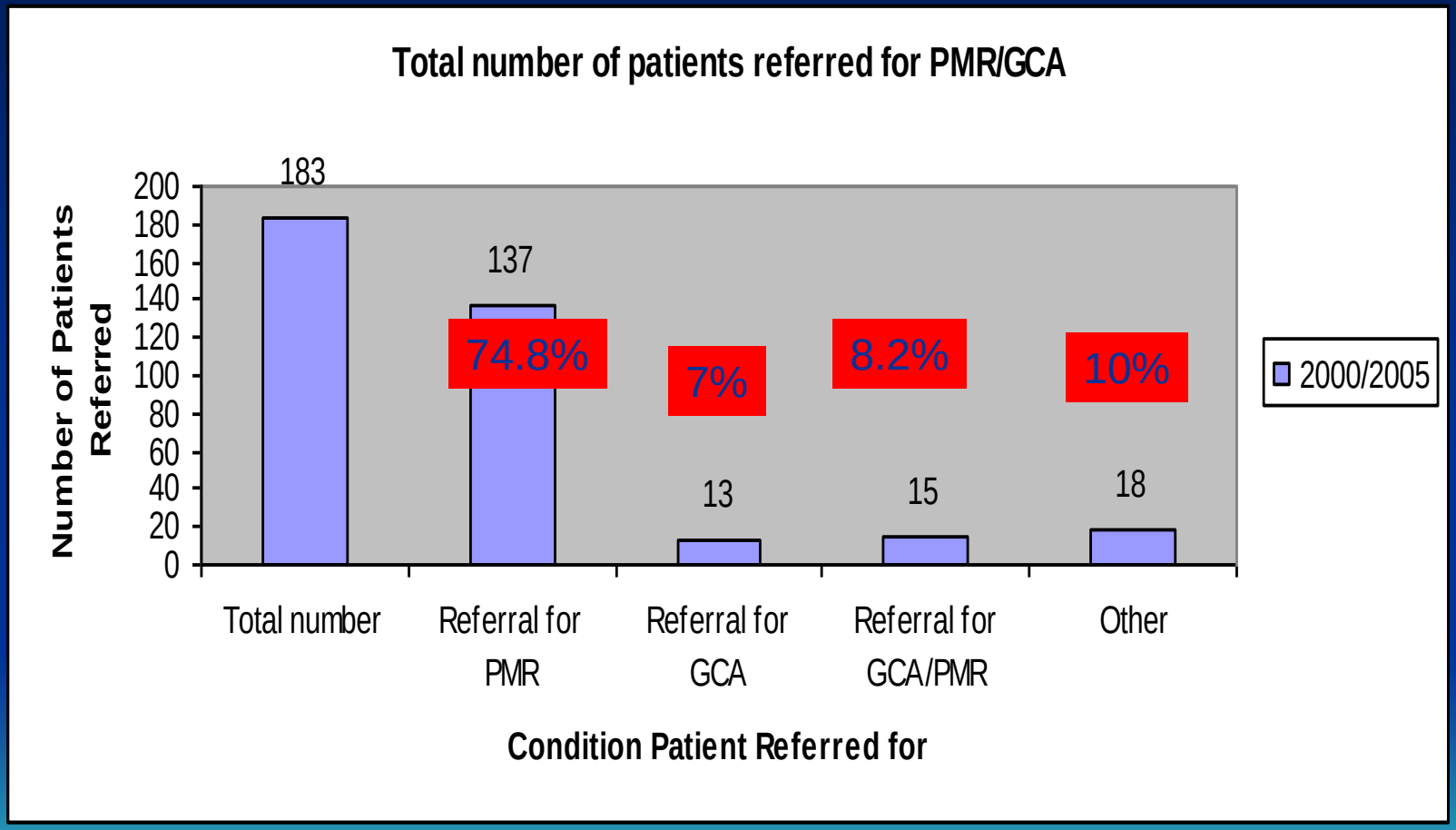
Method

- Solo practice in Timaru Hospital and in private practice since December 1991
- Area of Practice (Ashburton to Stewart Island)
- Copies of all new patient letters kept in 'Rheumatology File' (RhF)
- Laborious search of referrals by looking through RhF for patients seen with a possible diagnosis of PMR/GCA
- Reviewed referral letters of all patients with PMR/GCA

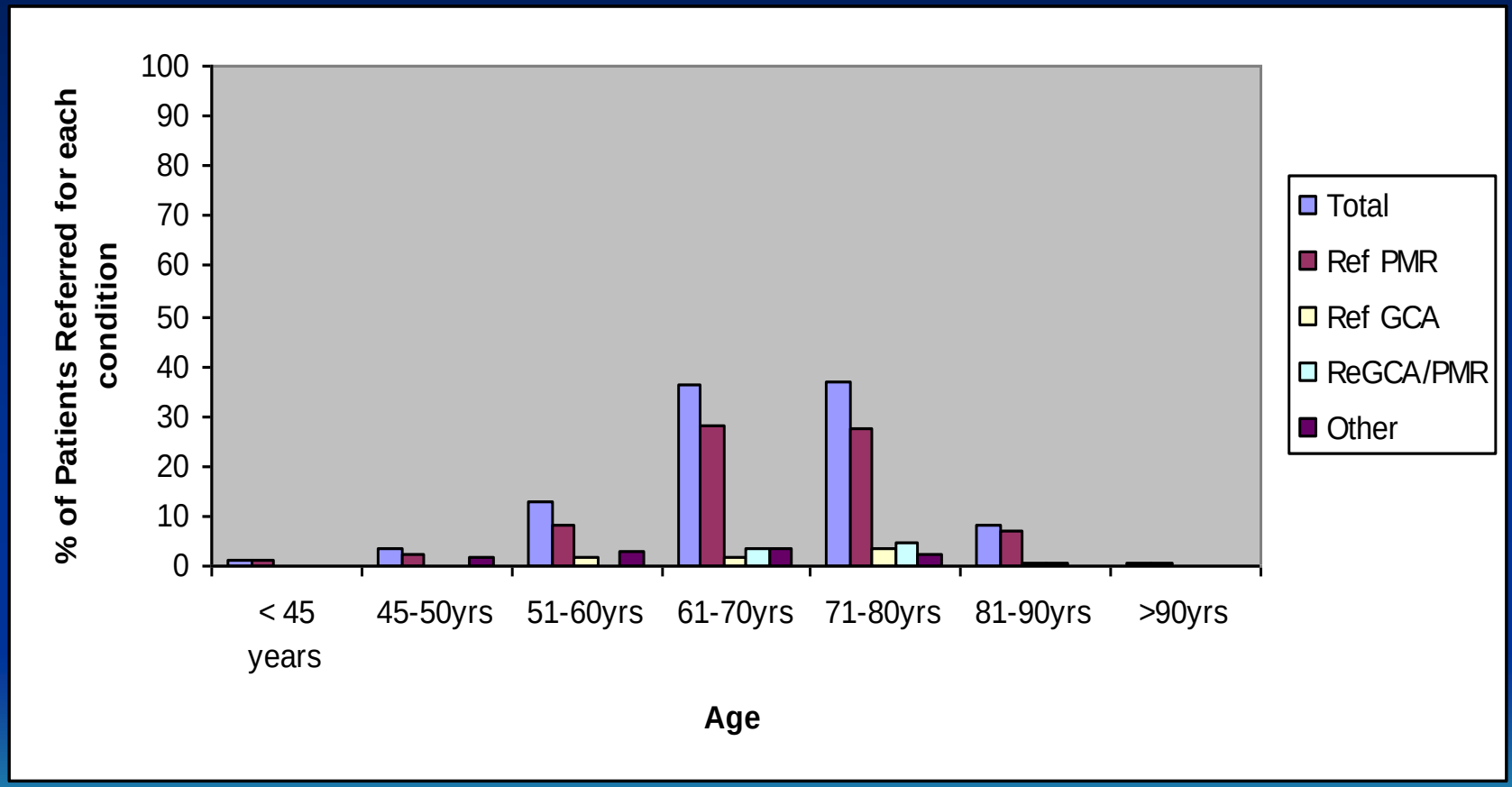
Results

- 183 referrals were identified as suitable for the audit. There were 107 cases of PMR, 15 cases of GCA including 12 cases who had both PMR and GCA.
- 10.3% of referrals sent as cases of PMR or PMR and GCA were diagnosed as having RA, and another 50% of these referrals did not have PMR or RA.

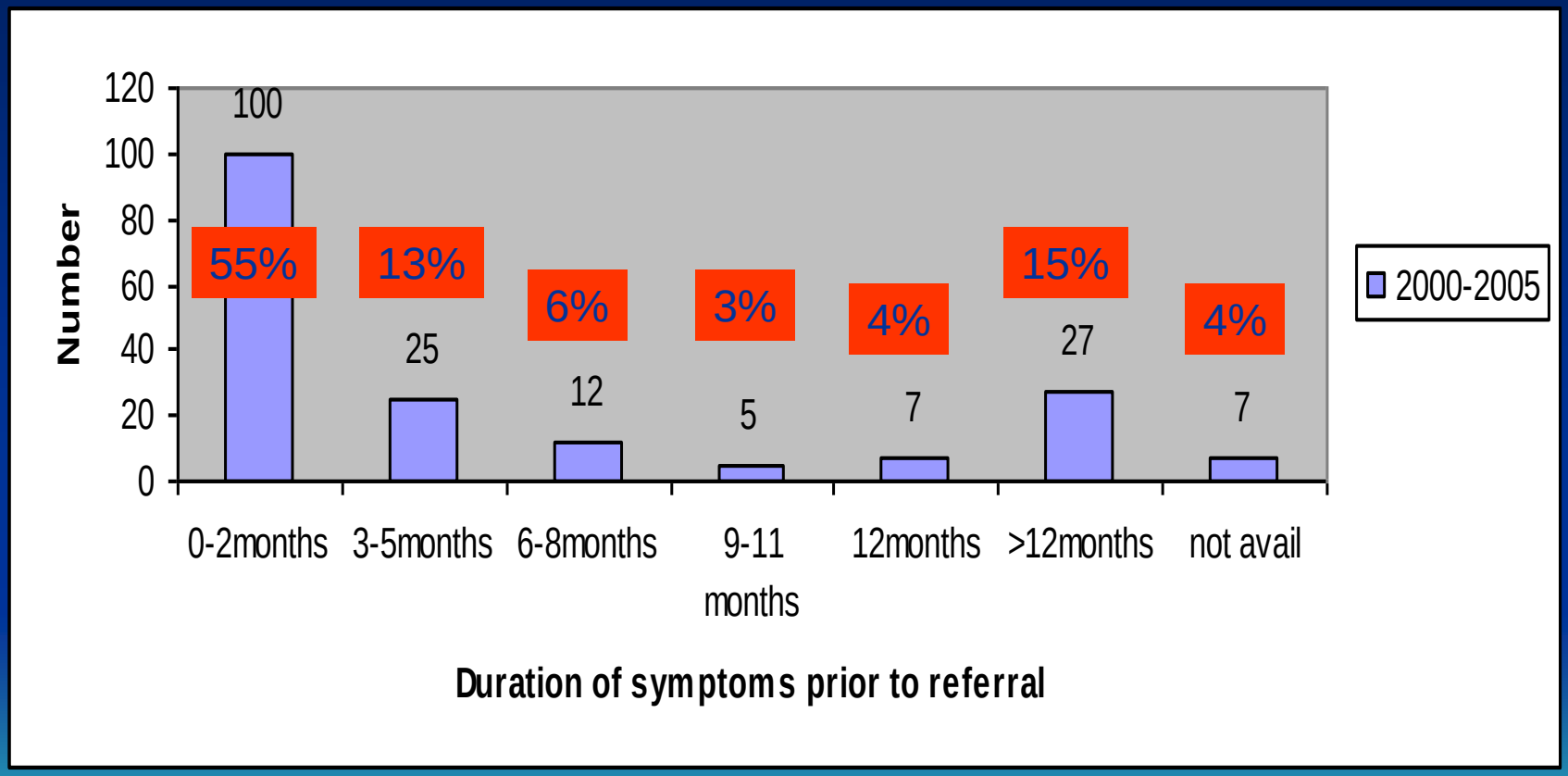
Results:


Total number of patients referred for PMR/GCA
Number of Patients Referred
200
180
160
140
120
100
80
60
40
20
0
183
137
13
15
18
74.8%
7%
8.2%
10%
Total number
Referral for PMR
Referral for GCA
Referral for GCA/PMR
Other
Condition Patient Referred for
2000/2005

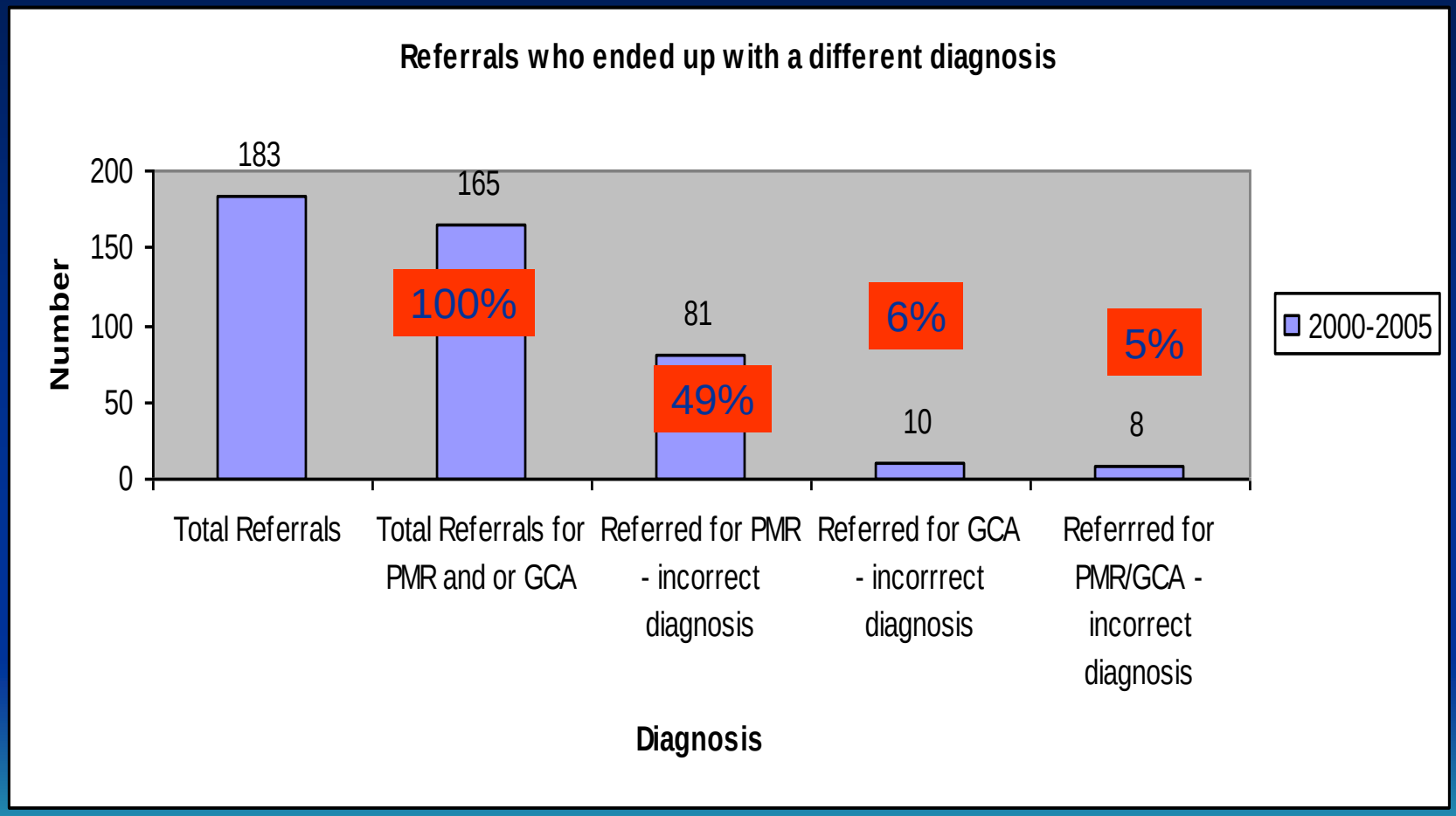
Age of Patients referred to Rheumatology Service with PMR and or GCA



Duration of Symptoms prior to referral letter being sent to Rheumatologist



Rheumatological Diagnosis of Patients referred as PMR/GCA who ended up with a different diagnosis



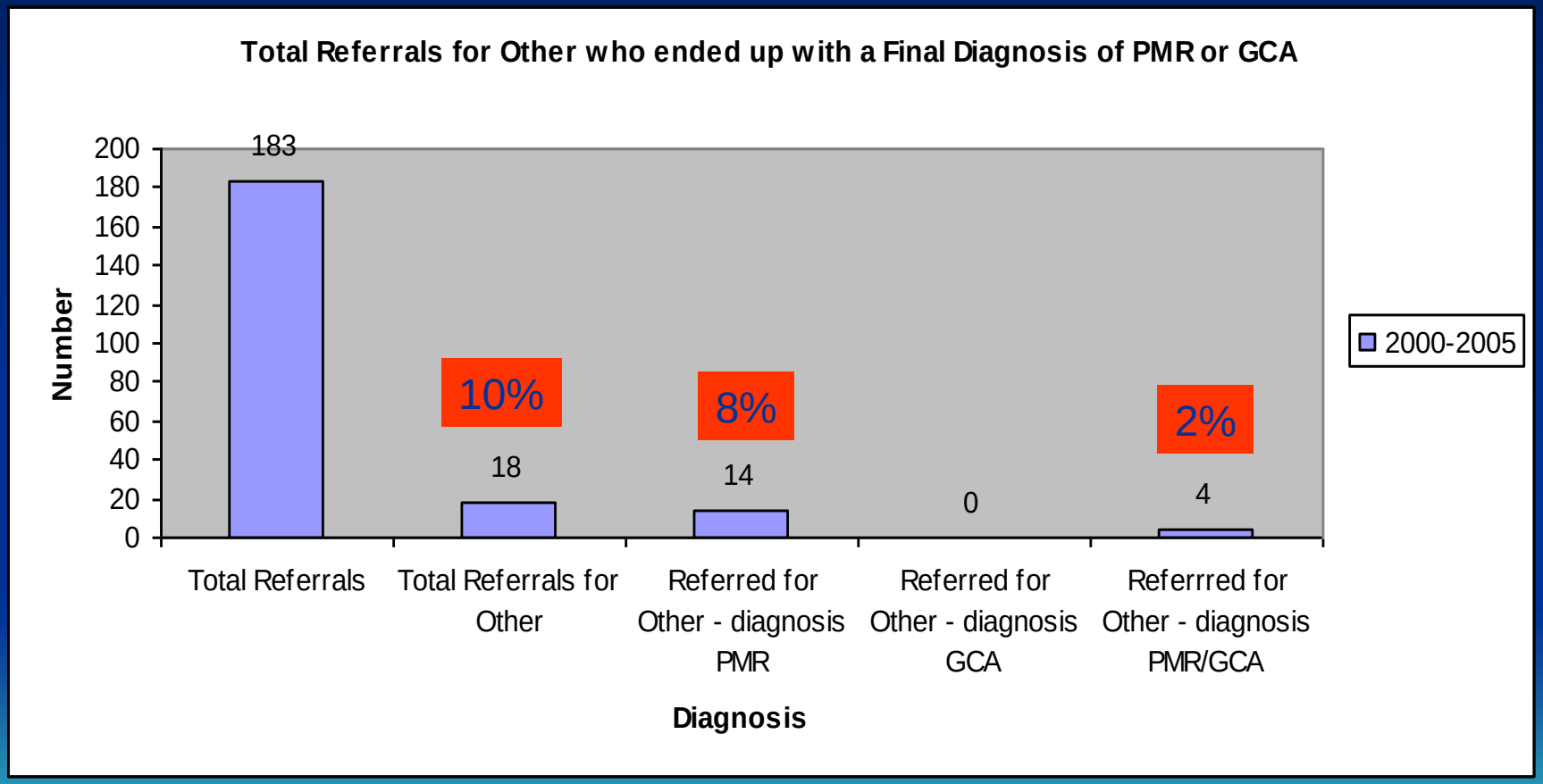
S Bahlas et al. Clin Rheumatol 2000; 19: 278-280.

- 123 referrals to a tertiary rheumatology clinic
- Accuracy of diagnosis of PMR was 24%
- Costs of investigations significantly higher than necessary to diagnose PMR compared to those advocated by nine rheumatologists
- Specifically targeted CME programme on PMR

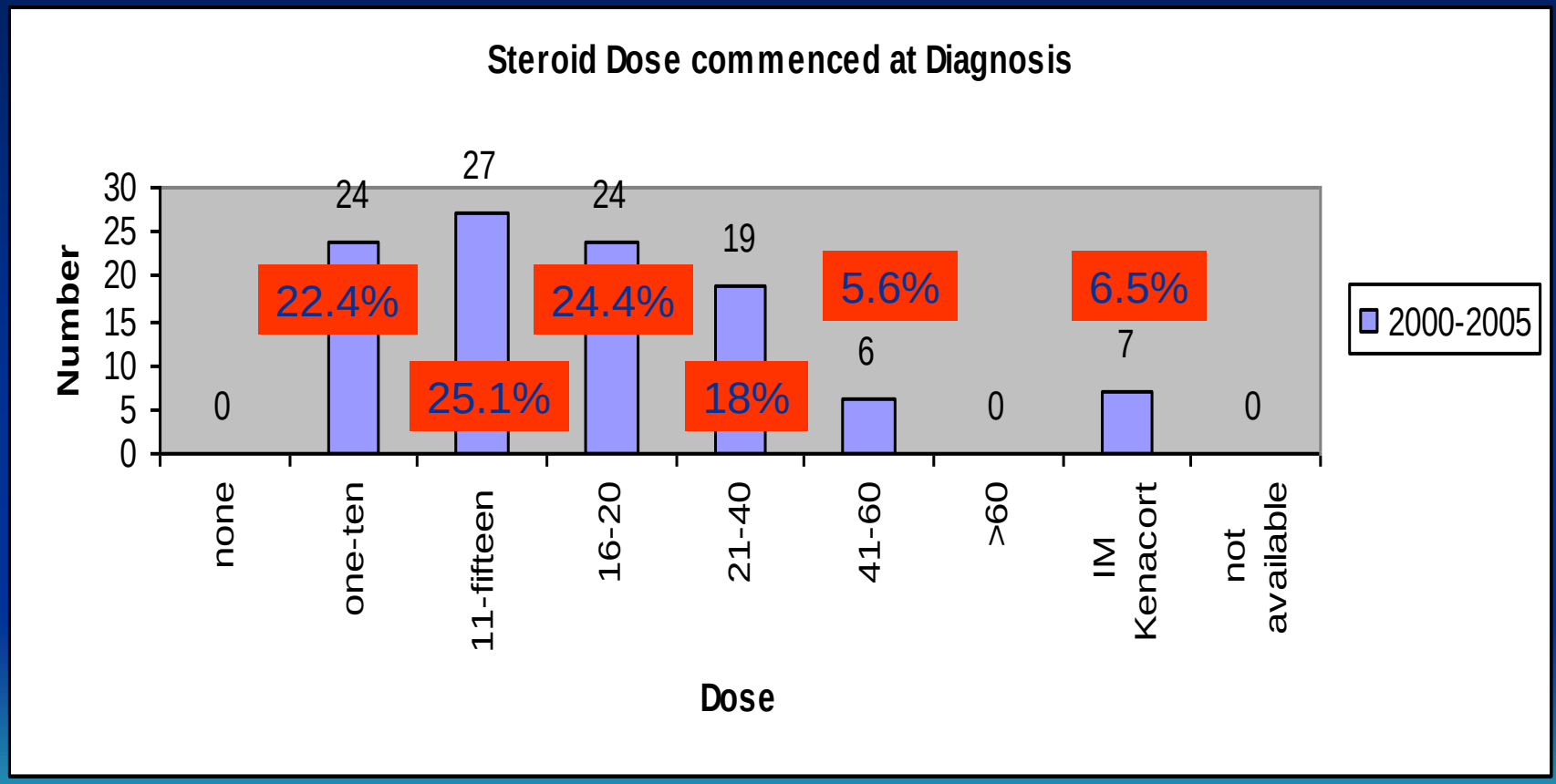
S Kalke, B Dasgupta. The accuracy of diagnosis in PMR: Results from a PMR referral clinic. Rheumatol 2000; 39 (A1): 157.

- 46.5% referrals had PMR and/or GCA
  - *Timaru cohort of 165 referrals for PMR and/or GCA, 40% accurate diagnosis*

Diagnosis of Patients referred to service for something other than PMR/GCA whose final diagnosis was PMR/GCA



Initial Steroid Dose for all PMR patients



V Kyle, B Hazleman. Ann Rheum Dis 1989; 48: 658-61.

- Patients with PMR needed 15-20 mg of Prednisone initially; 65% relapsed on an initial dose of 10 mg/day

SE Gabriel et al. A&R 1997; 40: 1873-8.

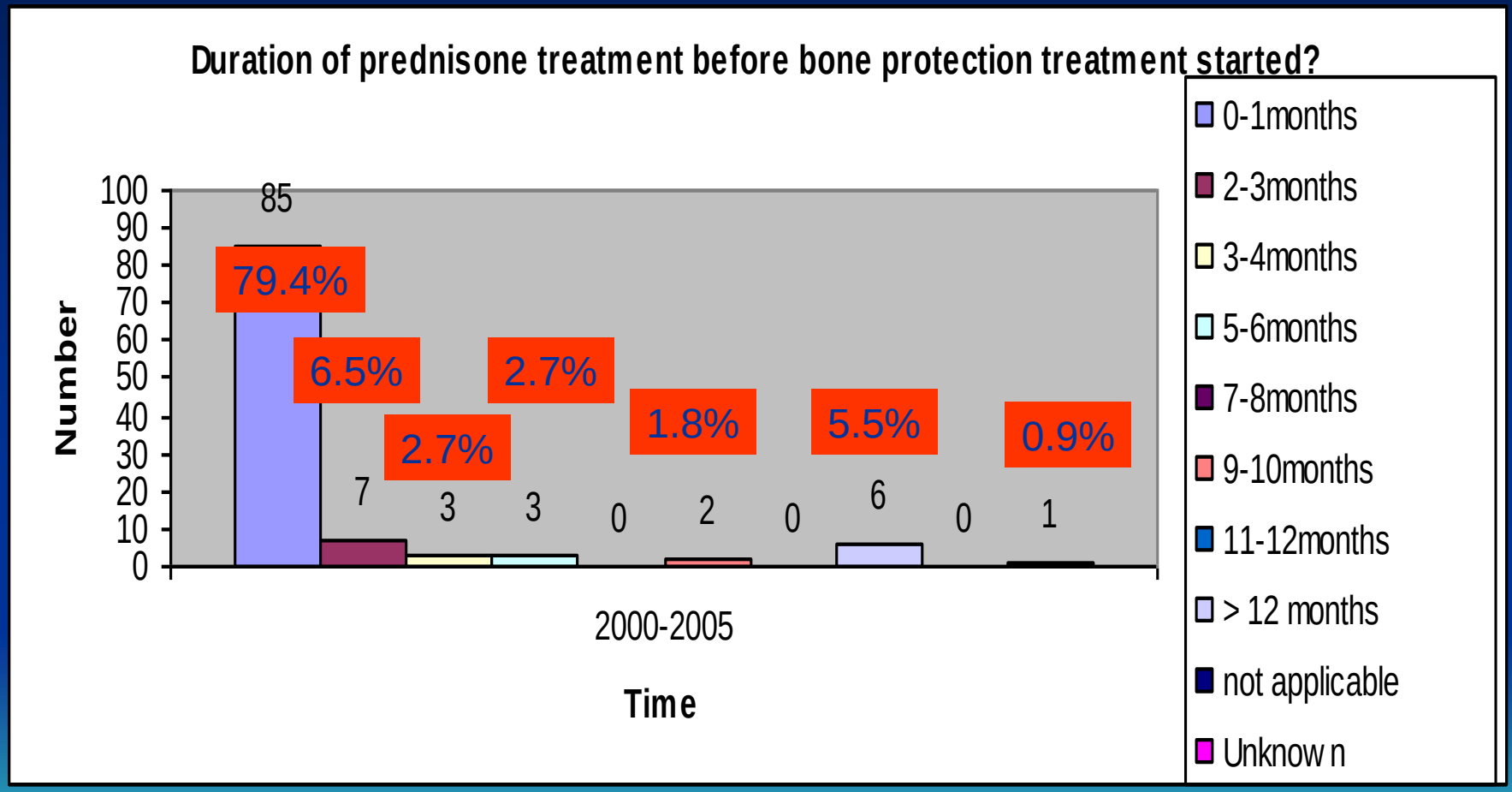
- Medical care or consultation by a rheumatologist was a significant predictor of a lower initial corticosteroid dose

V Kyle, B Hazleman. Ann Rheum Dis 1993; 52: 847-50.

- A cohort of 74 patients
- 20% of patients with PMR developed GCA
- 24% of patients with GCA developed PMR from the onset

- *12/107 (11.2%) of Timaru cohort of patients with PMR were diagnosed with GCA at presentation or subsequently*

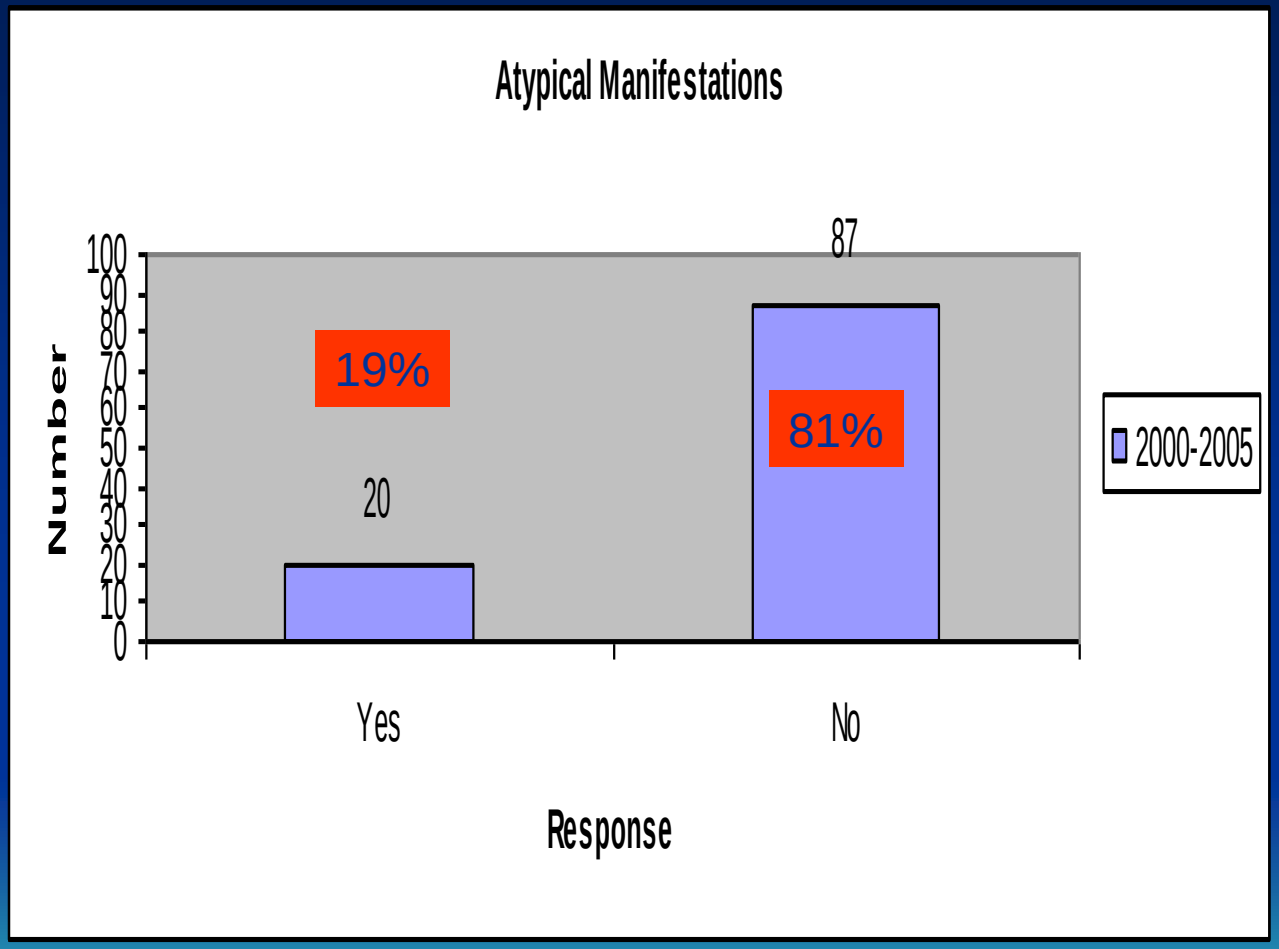
Duration of Prednisone Treatment before bone protection treatment started



JT Gran & G Myklebust. Rheum 2000; 39: 283-7.

- 231 cases of PMR and GCA
- 38.5% presented with peripheral arthritis at diagnosis or during disease course
- RA developed in 4.8%

Atypical Manifestations



- Low ESR x 4
- Low ESR/CRP x 3
- Normal ESR x 2
- Normal ESR/slightly raised CRP
- Normal CRP
- Slightly raised ESR
- Increase ESR, no drop in Hb or rise in platelet count
- ESR/CRP not raised initially
- No pain or stiffness in pelvic girdle x 2
- < 50 years of age
- Not stiff in shoulder girdle –R) & L) arm discomfort
- Calf & abdominal symptoms
- Pain & stiffness started after prednisone started
- Pain below calves

- V Kyle, B Hazleman. Ann Rheum Dis 1993; 52: 847-50.
  - 17/35 of their patients with GCA (48.6%) had PMR.

- G Hunder. UpToDate 2006; Version 14.2.
  - PMR occurs in 40-50% of patients with GCA.

- Timaru cohort. 2000-2005.
  - 12/15 (80%) of patients with GCA had PMR.

CONCLUSIONS

1. All patients diagnosed with PMR/GCA should be referred to a rheumatologist as a significant percentage of patients have peripheral arthritis or were diagnosed with RA (10.3%) or progress to RA (2.7%) or have a different rheumatological diagnosis such as fibromyalgia.

CONCLUSIONS

2. Methotrexate was efficacious as a steroid sparing agent in 65% of cases of PMR and GCA when used. Azathioprine was used in 4 cases of PMR and was either ineffective or caused adverse effects.

3. Need to develop more steroid sparing agents, ?Interleukin-6 inhibitor (Tocilizumab), ?Leflunomide.

Internet Joke

Airline ticket office, Copenhagen:

"We take your bags and send them in all directions."