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Rheumatology Therapeutic Clinical
Trials Centre
Timaru

Hot Tips in Rheumatology - Concurrent Workshop Repeated

Saturday, 17 August 2013

Start 2:00pm

Start 3:05pm

Duration: 55mins

Duration: 55mins

Plenary

Plenary



South GP CME 2013

General Practice Conference & Medical Exhibition

15-18 August | Edgar Centre | Dunedin

Hot Tips in Rheumatology GP CME Meeting, Dunedin 17.08.2013

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Disclosures

- Advisory Boards and speaker at meetings: Abbott/Abbvie, Roche, Pfizer/Wyeth, MSD, Novartis, Quintiles CRO and Janssen.
- Investigator in clinical trials for: Boehringer Ingelheim, MSD, UCB, Medi-Immune, Centocor, Roche, Abbott, Pfizer, Celgene, Lilly, Sanofi and Galapagos.



Hot Tips:

1. Early referral for patients with inflammatory arthritis/inflammatory back disease
2. Gout
3. False positive ANA
4. Choosing wisely
5. Injection of carpal tunnel syndrome
6. Prescription of low-dose weekly Methotrexate
7. Vaccinations in rheumatology patients on immunosuppressives
8. New treatment for Raynaud's phenomenon
9. Refer all patients with PMR/GCA



Take Home Message 1:

Ankylosing Spondylitis Action Pathway

Patients with persistent low back over three months and onset under 45 years plus:

1. Morning stiffness >30 minutes
2. Improvement with exercise but not rest
3. Awakening in the 2nd half of the night with pain
4. Alternating buttock pain



- 0-1 symptoms – consider mechanical LBP
- 3-4 symptoms – refer to rheumatology
- 2 symptoms – check other factors:
 - i. Family history of spondyloarthropathy
 - ii. Extra-articular features such as uveitis, psoriasis, enthesitis, inflammatory bowel disease and peripheral joint involvement
 - iii. Respond to NSAIDs within 48 hours



If only two symptoms and ...

- 0 factors – mechanical low back pain
- 1 factor – test for HLA-B27. If positive, refer to rheumatology. If negative, consider mechanical LBP
- 2-3 factors – refer to rheumatology



Take Home Message 2:

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:

- ≥ 3 swollen joints
- MTP/MCP involvement
- morning stiffness of ≥ 30 minutes.

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



NB: No blood tests in the alarm signals for early referral for potential RA

- Don't delay referral because of test results:

	% of negative tests
X-rays of hands and feet	80
CRP	50
RF and anti-CCP antibodies	40



Why early referral?

- Window of opportunity of up to six months to reset immunology of RA so Rheumatologists need to see patients within 12 weeks of onset of arthritis
- If achieved clinical remission within six months of onset of disease, can stop treatment in up to 80% of undifferentiated inflammatory arthritis



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 $\leq 6\text{mg/dl}$ ($\leq 0.35\text{mmol/l}$)
- 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.



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 $<0.36\text{mmol/l}$ 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 $<0.36\text{mmol/l}$, 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 ($<0.6\text{mg/dl}$ or $<0.36\text{mmol/l}$).
2. Dose escalation of Allopurinol to $>300\text{mg}$ 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 $<0.36\text{mmol/l}$.
- 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 1.0mg 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, ketoconazole, HIV protease inhibitors, etc.

Toxicity can also be increased by daily consumption of a litre of grapefruit juice, hepatic and renal impairment, statins, fibrates and digoxin.



Benzbromarone

- A uricosuric agent and non-competitive inhibitor of xanthine oxidase, available under Section 29 and special authority:
 - SUA >0.36 despite treatment with Allopurinol at doses of at least 600mg/day and appropriate doses of Probenecid
 - Or intolerable side effects from Allopurinol such that discontinuation is required and SUA $>0.36\text{mmol/l}$ despite Probenecid



- Or renal impairment and SUA >0.36 despite optimal treatment with Allopurinol and patient has creatinine clearance $\geq 20\text{ml/min}$
- Or patient is taking Azathioprine and requires urate lowering therapy and Allopurinol contraindicated and Probenecid ineffective or cannot be used due to reduced renal function
- And patient receiving monthly LFTs



Renewal

- Treatment remains appropriate and patient is benefiting from treatment and there is no evidence of liver toxicity and patient is receiving regular (at least every 3 months) LFTs.



Allopurinol

Starting Dose is a Risk Factor for Allopurinol Hypersensitivity Syndrome

L Stamp et al, A&R 2012; 64: 2529-2536

Starting Allopurinol at the dose of 1.5mg per unit of estimated GFR may be associated with a reduced risk of AHS. In patients who tolerate Allopurinol, the dose can be gradually increased to achieve to the targeted serum urate level.

Practically, it means starting Allopurinol at 50-100mg daily and increasing by 100mg monthly until SUA <0.36mmol/l.



New treatments for gout:

- Febuxostat (Adenuric), a new selective inhibitor of xanthine oxidase. Efficacious in renal impairment with no significant relationship between renal function and urate-lowering efficacy. 80-120mg once daily orally.
- Poly(ethylene) glycol-uricase (PEG-uricase) or Pegloticase. IV 8mg (4-12mg) every two weeks. Effective in resolving tophi, so use in 'debulking' tophi in advanced gout before switching to another agent for maintenance treatment. (Not available in NZ).





Antinuclear Antibody Testing

Approximately 27% (34% in women and 17% in men) of the general population have positive ANA.

The vast majority are false positives. 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.



Choosing Wisely

- 1. Don't test ANA sub-serologies without positive ANA**
2. Don't test for Lyme disease as a cause for musculoskeletal symptoms without an exposure history and appropriate examination findings
3. Don't perform MRI of peripheral joints to routinely monitor inflammatory arthritis
4. Don't prescribe biologics for RA before a trial of MTX or other conventional non-biologic DMARDs
- 5. Don't routinely repeat DXA scans more often than once every 2-3 years**



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.



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.



Recommendation for vaccinations in rheumatology patients on immunosuppressives

- Pneumococcal vaccination every five years
- Annual influenza vaccination
- No live vaccines

(Ref: ACR 2012 guidelines on treatment of RA)



New treatment for Raynaud's Phenomenon

SILDENAFIL,
A Phosphodiesterase Type 5 inhibitor



Pharmac criteria

1. Patient has Raynaud's phenomenon and
2. Patient has severe digital ischaemia (defined as severe pain requiring hospital admission or high likelihood of digital ulcers or gangrene and
3. Patient following lifestyle management (avoiding of cold exposure, sufficient protection, smoking cessation support, avoidance of sympathomimetic drugs) and
4. Patient is being treated with calcium channel blockers and nitrates (or these are contraindicated/not tolerated).



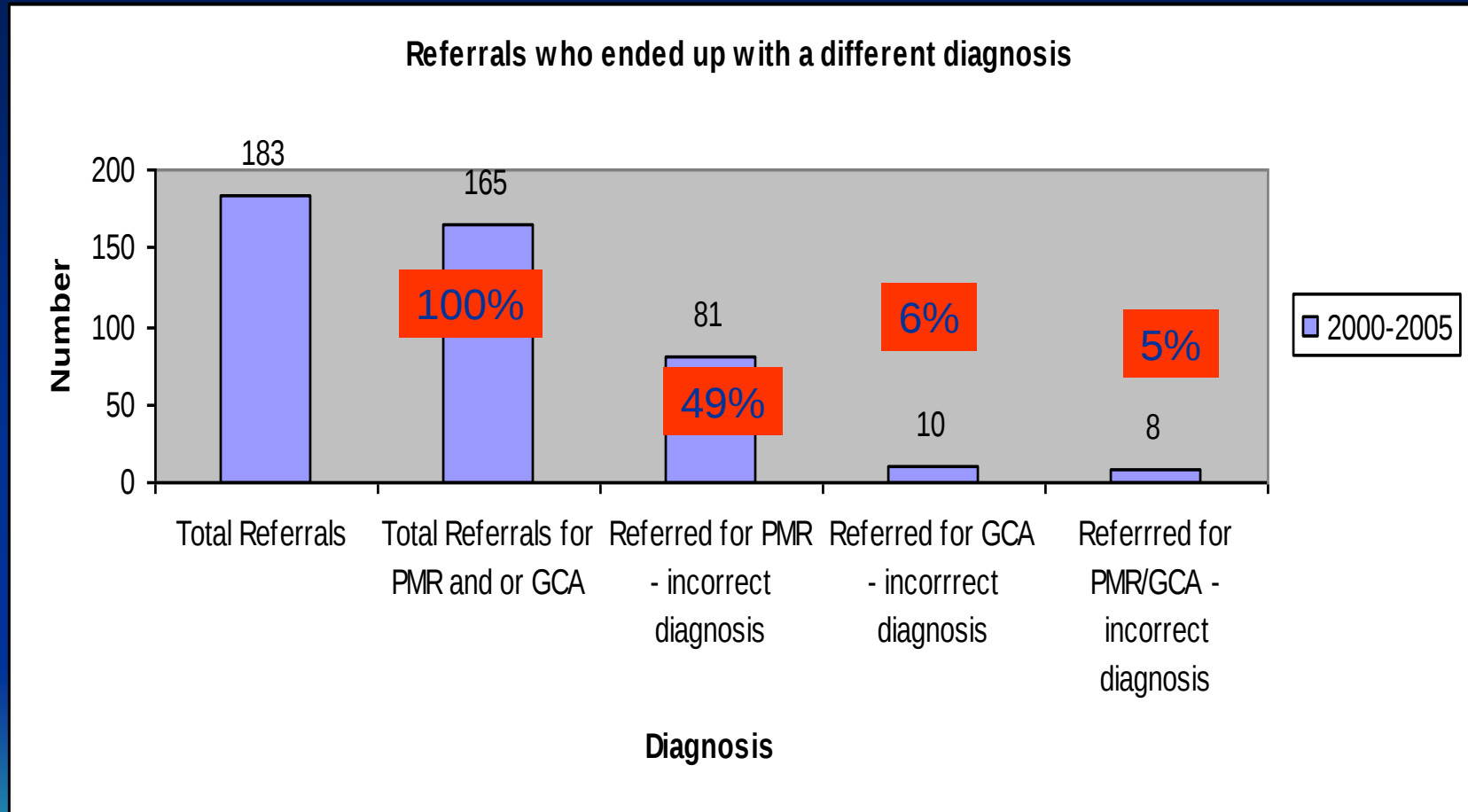


Audit of Polymyalgia Rheumatica and Giant Cell Arteritis 2000 to 2005

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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.

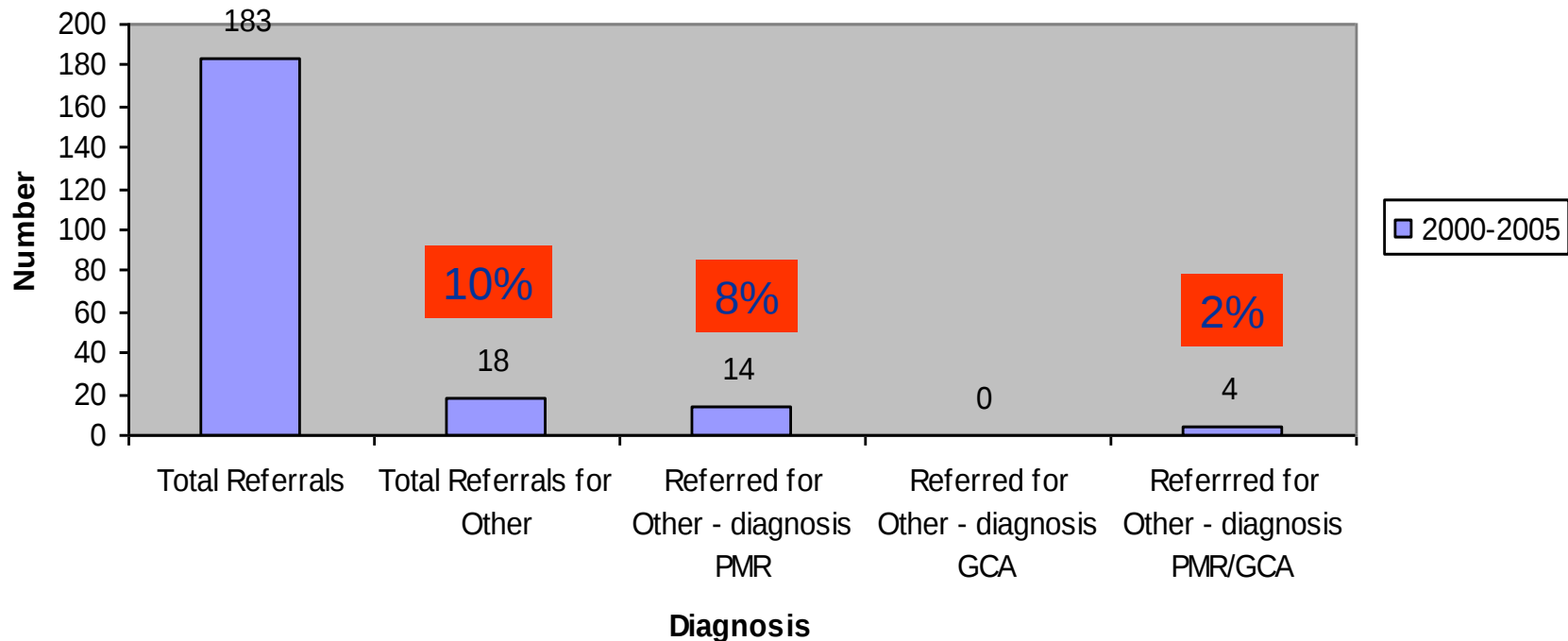
The accuracy of diagnosis in PMR:
Results from a PMR referral clinic.
Rheumatol 2000; 39 (A1): 157.

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

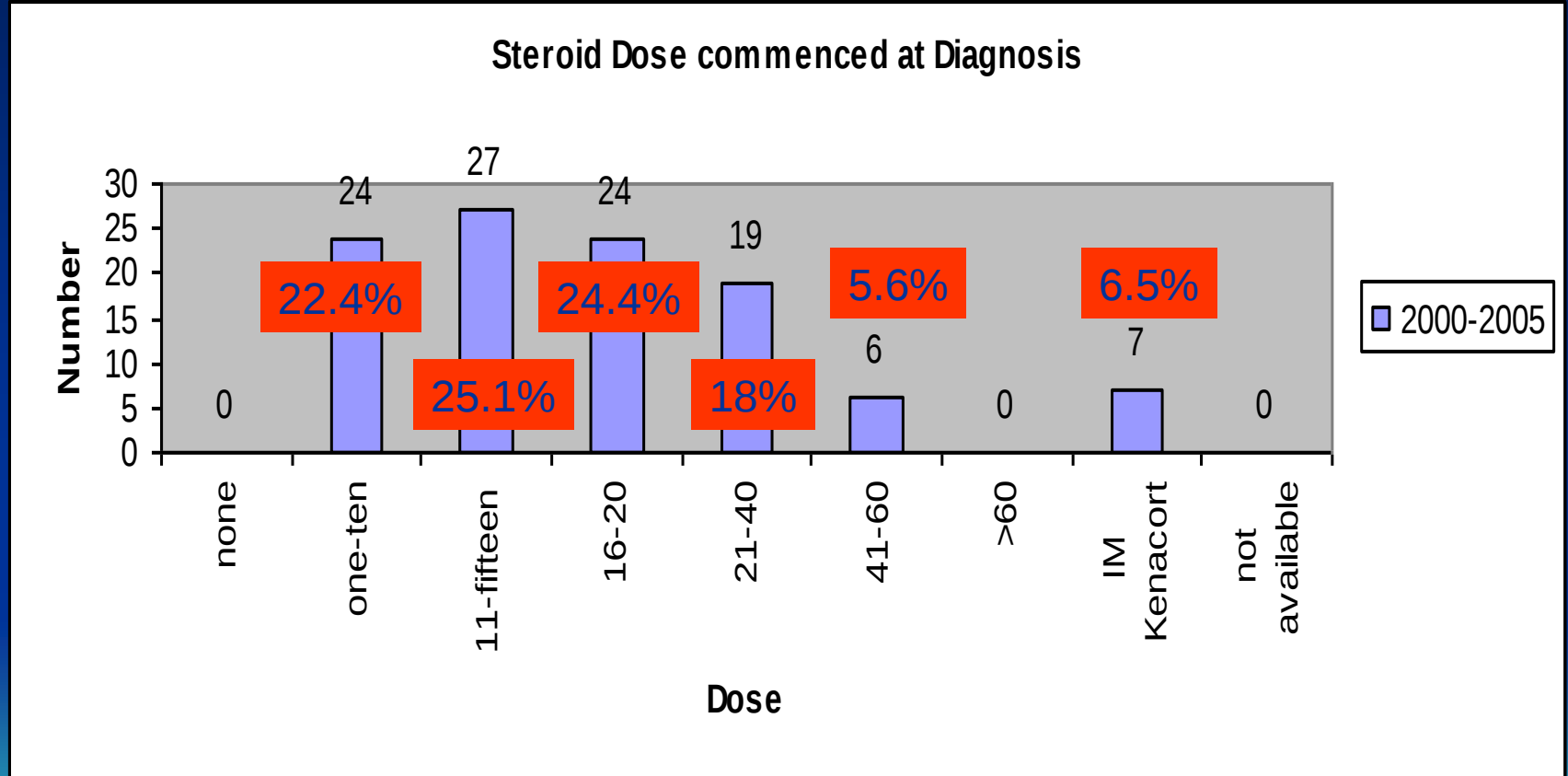


Diagnosis of Patients referred to service for something other than PMR/GCA whose final diagnosis was PMR/GCA

Total Referrals for Other who ended up with a Final Diagnosis of PMR or 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



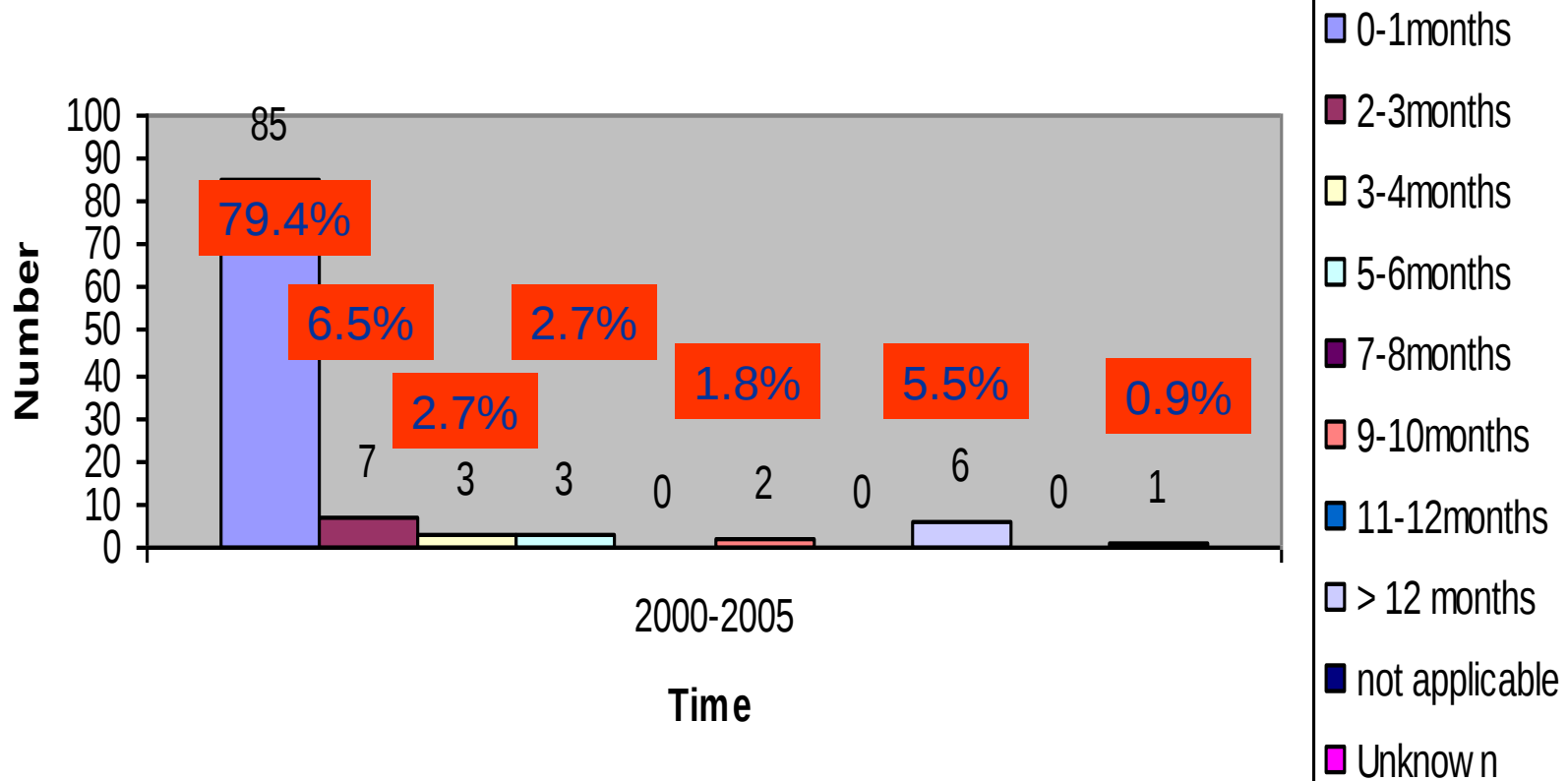
V Kyle, B Hazleman. Ann Rheum Dis 1993; 52: 847-50.

- 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

Duration of prednisone treatment before bone protection treatment started?

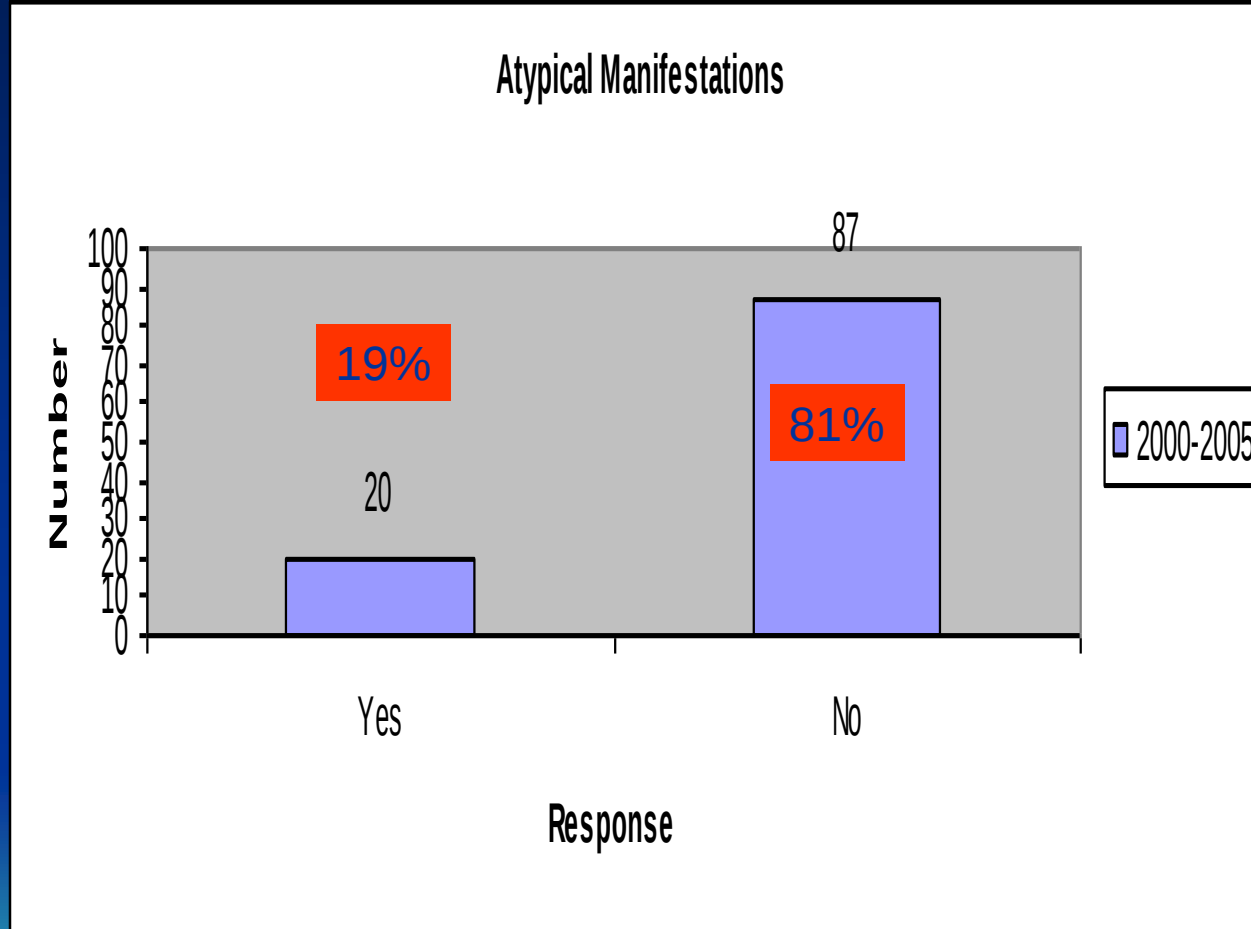


JT Gran & G Myklebust. Rheum 2000; 39: 283-7.

- 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

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: Leflunomide efficacious in case series studies and Interleukin-6 inhibitor (Tocilizumab) trial about to start.



Mean Duration of Steroid Treatment

- Mean duration: 31.8 months. Range: 9-134 months (over 11 years for one patient).
- Median duration: 24 months.
 - 50 patients (53.76%) required Prednisone for >2 years.
 - 28 patients (30.11%) required Prednisone for >3 years.
 - 19 patients (20.43%) required Prednisone for >4 years.
 - 5 patients (5.37%) required Prednisone for >5 years.



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Back up Slides for Gout



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. Widespread 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 $\geq 30 \text{ Kg/M}^2$)
 3. Alcohol intake (≥ 7 ounces of pure alcohol/week)
 4. Hypertension
 5. Diuretic use

Don't forget women with gout too!



Back up Slides for PMR/GCA



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

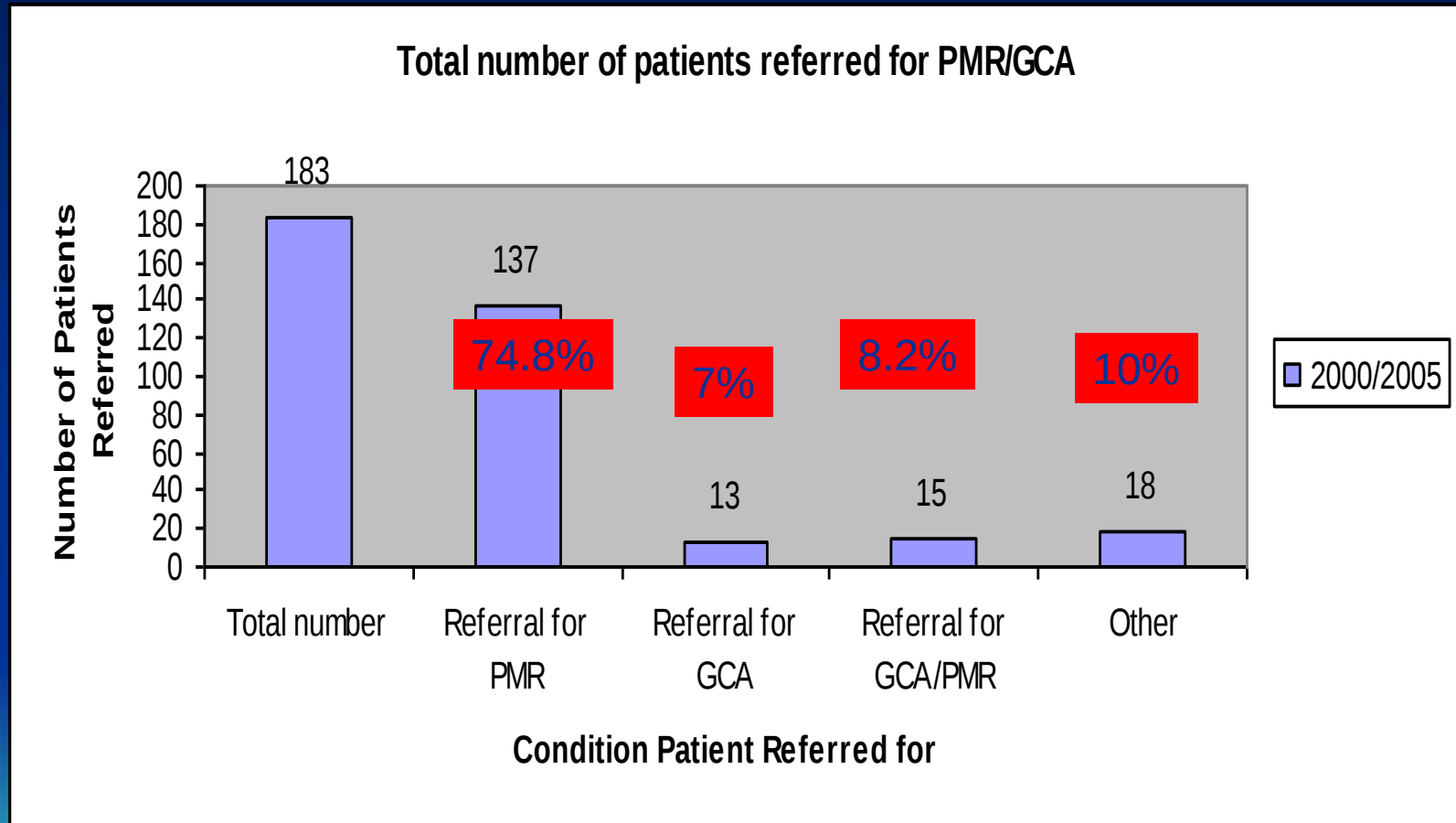


Results

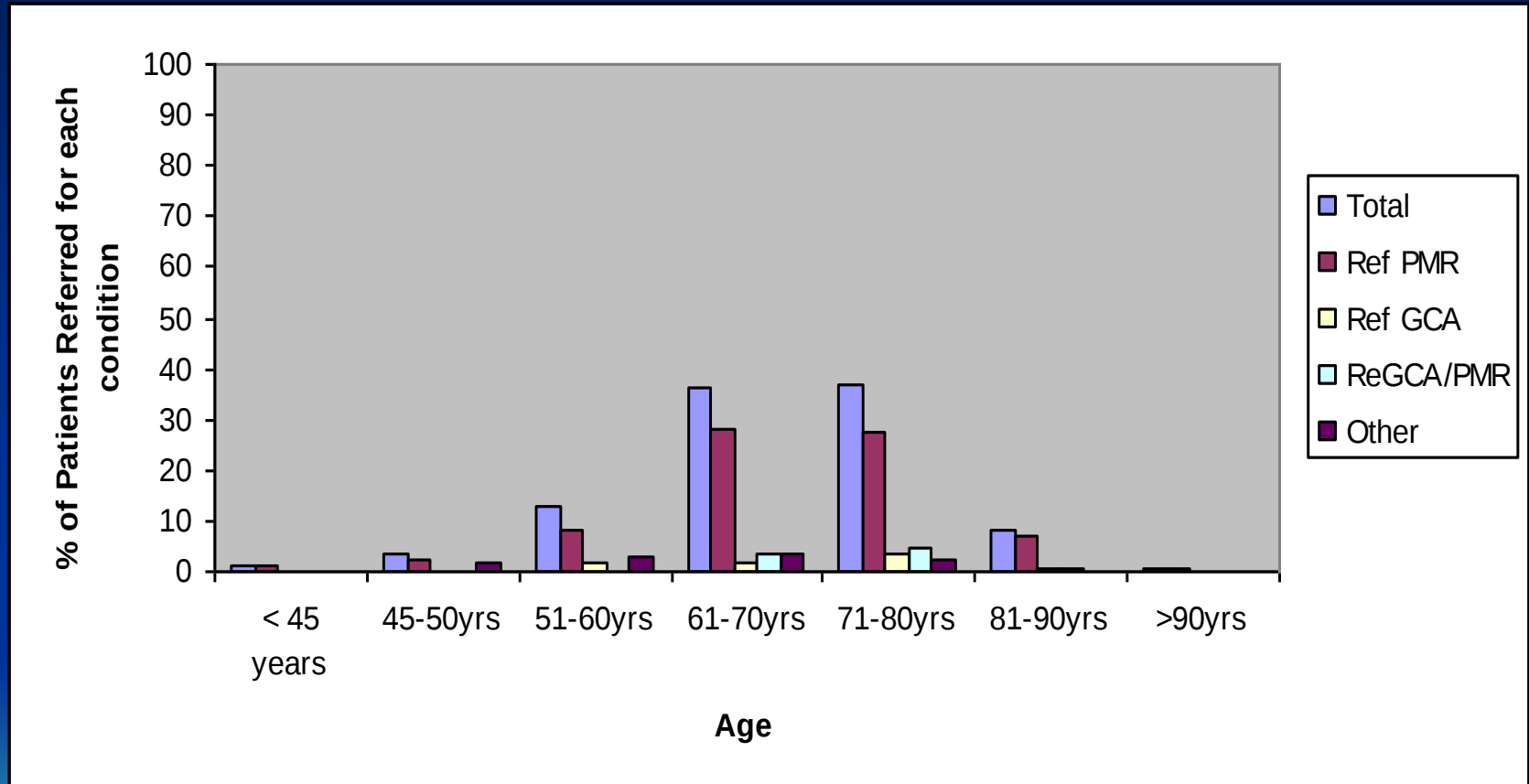
- 183 referrals were identified as suitable for the audit. There were 107 cases of PMR, 15 cases of GCA including 12 cases who had both PMR and GCA.
- 10.3% of referrals sent as cases of PMR or PMR and GCA were diagnosed as having RA, and another 50% of these referrals did not have PMR or RA.



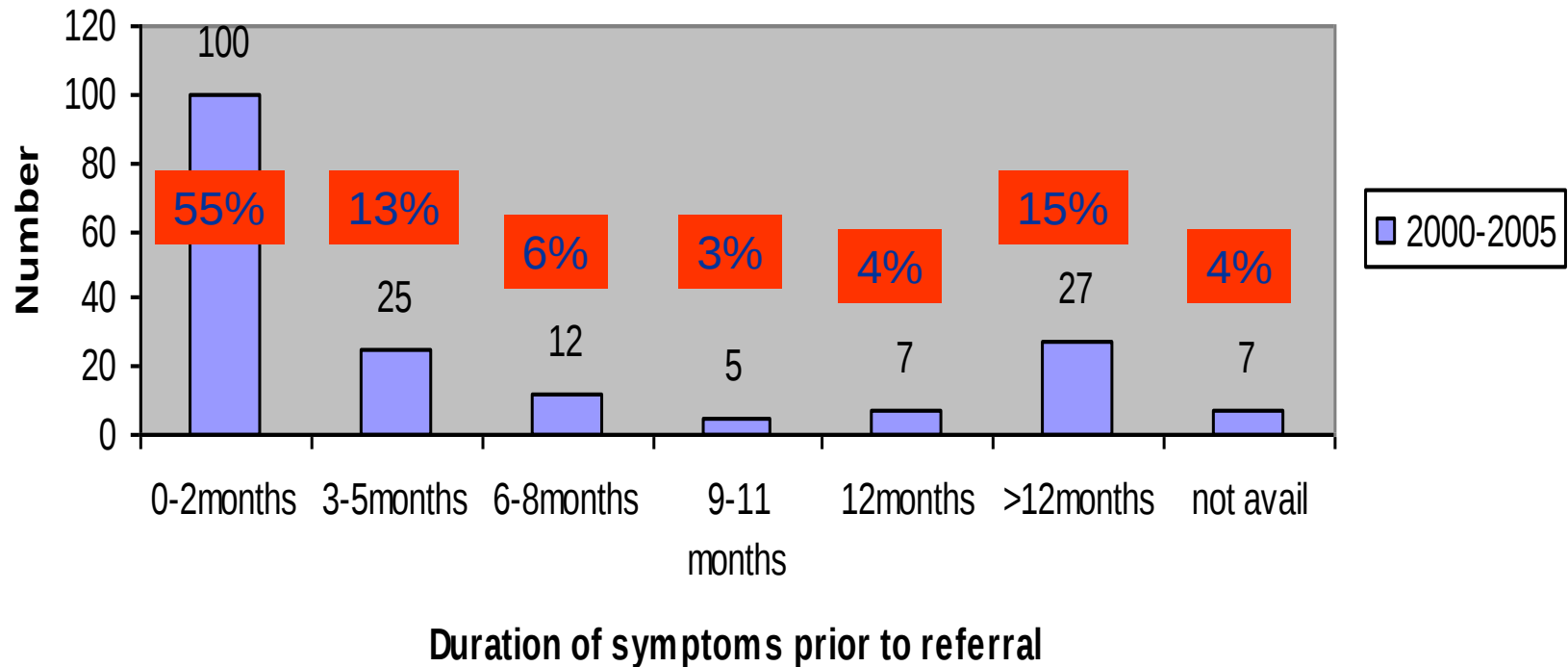
Results:



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



Duration of Symptoms prior to referral letter being sent to Rheumatologist



- 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.

