Sarcoidosis Case

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Sarcoidosis Case

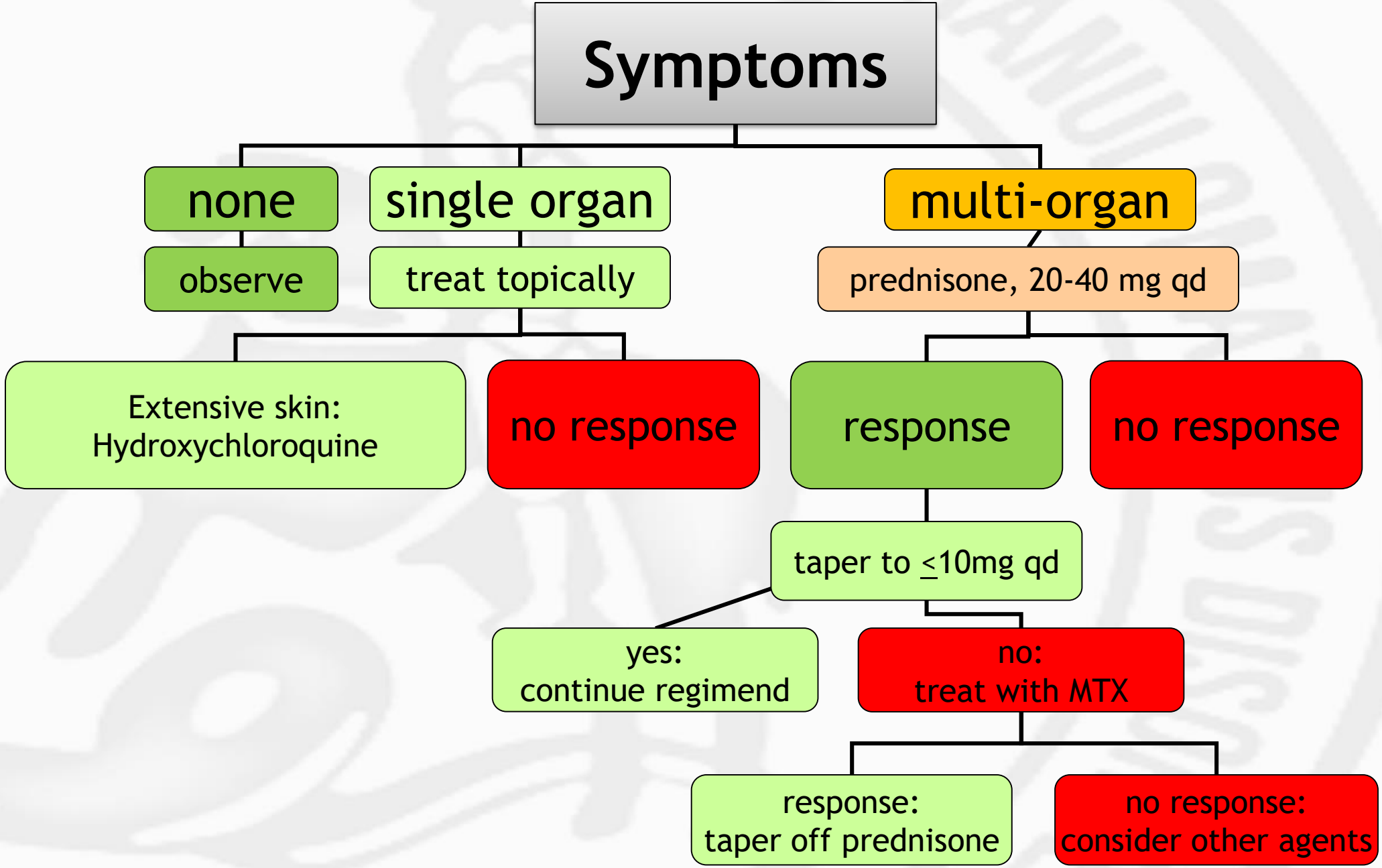
- patient is a Caucasian male
- age 46 was diagnosed with sarcoidosis
  - positive mediastinoscopy
- skin lesions on arms and back
- no pulmonary symptoms

Question 1: Would you treat this patient?

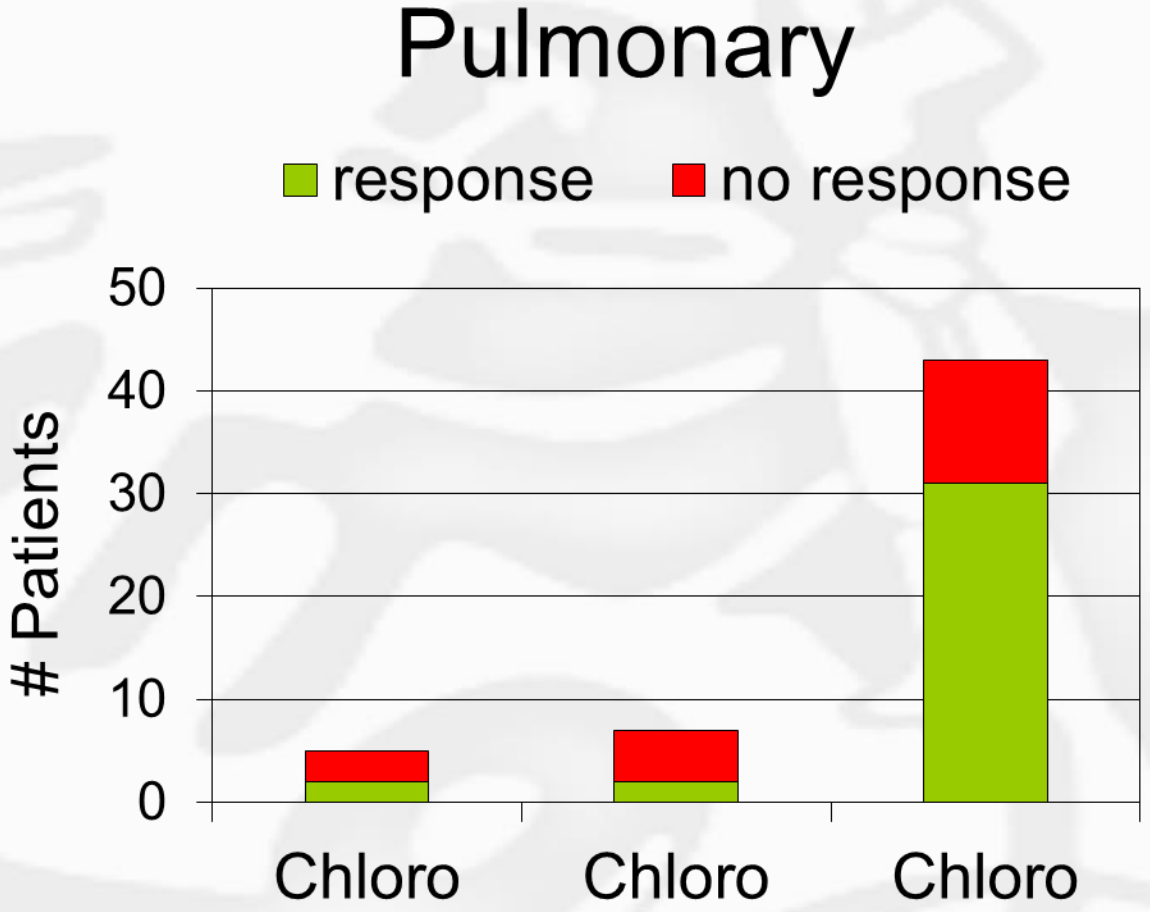
1. yes because he has lung involvement
2. yes because he has skin disease
3. no because he is not short of breath
4. no because his skin lesions are not on his face
5. I would let the patient decide

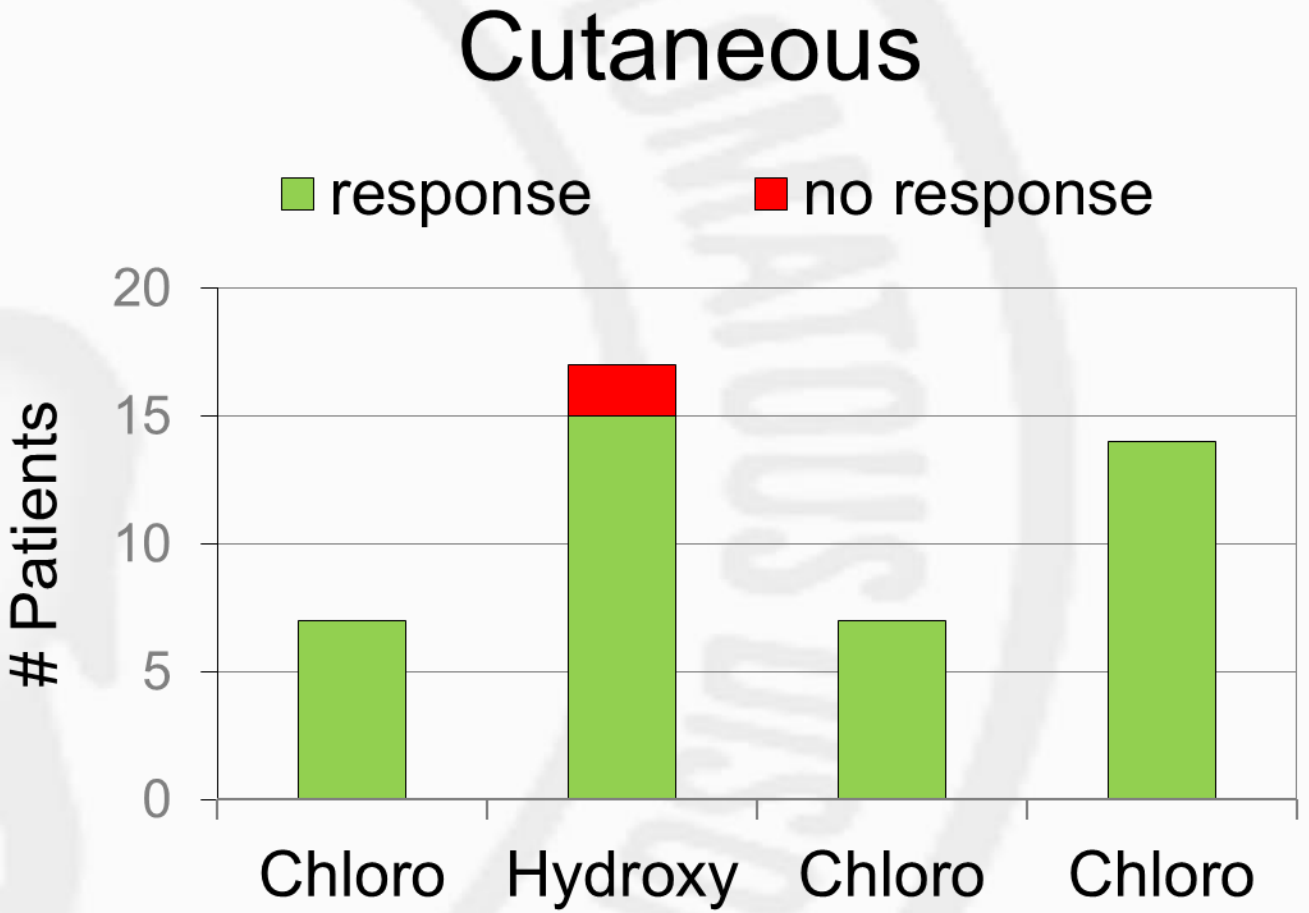
Question 2: Which systemic therapy would you initiate?

1. none
2. prednisone
3. hydroxychloroquine
4. methotrexate
5. infliximab


Symptoms
none
single organ
multi-organ
observe
treat topically
prednisone, 20-40 mg qd
Extensive skin:
Hydroxychloroquine
no response
response
no response
taper to ≤10mg qd
yes:
continue regimend
no:
treat with MTX
response:
taper off prednisone
no response:
consider other agents

Antimalarials in sarcoidosis



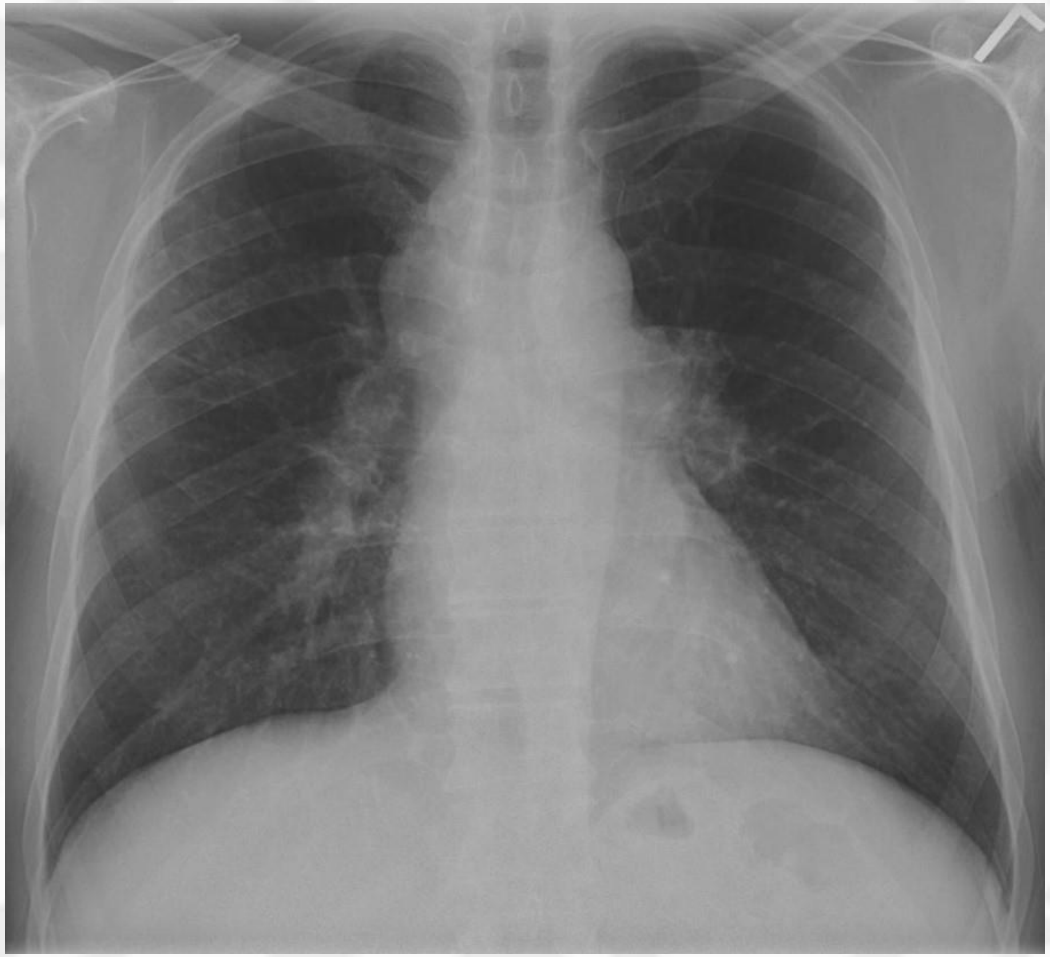


Davies D. Br J Dis Chest 1963; 57:30-6.; Hirsch JG. Am Rev Respir Dis 1961; 84:52; Jones E, et al. J Am Acad Dermatol 1990; 23:487; Morse SI, et al. Am J Med 1961; 779. Siltzbach LE, Teirstein AS. Acta Med Scand 1964; 425:302S.

Treatment course

- for two years skin did well with hydroxychloroquine and topical steroids
- presents in 2004 with worsening skin lesions despite hydroxychloroquine
- has no pulmonary symptoms, although still has thoracic sarcoidosis

Sarcoidosis Case: 2004



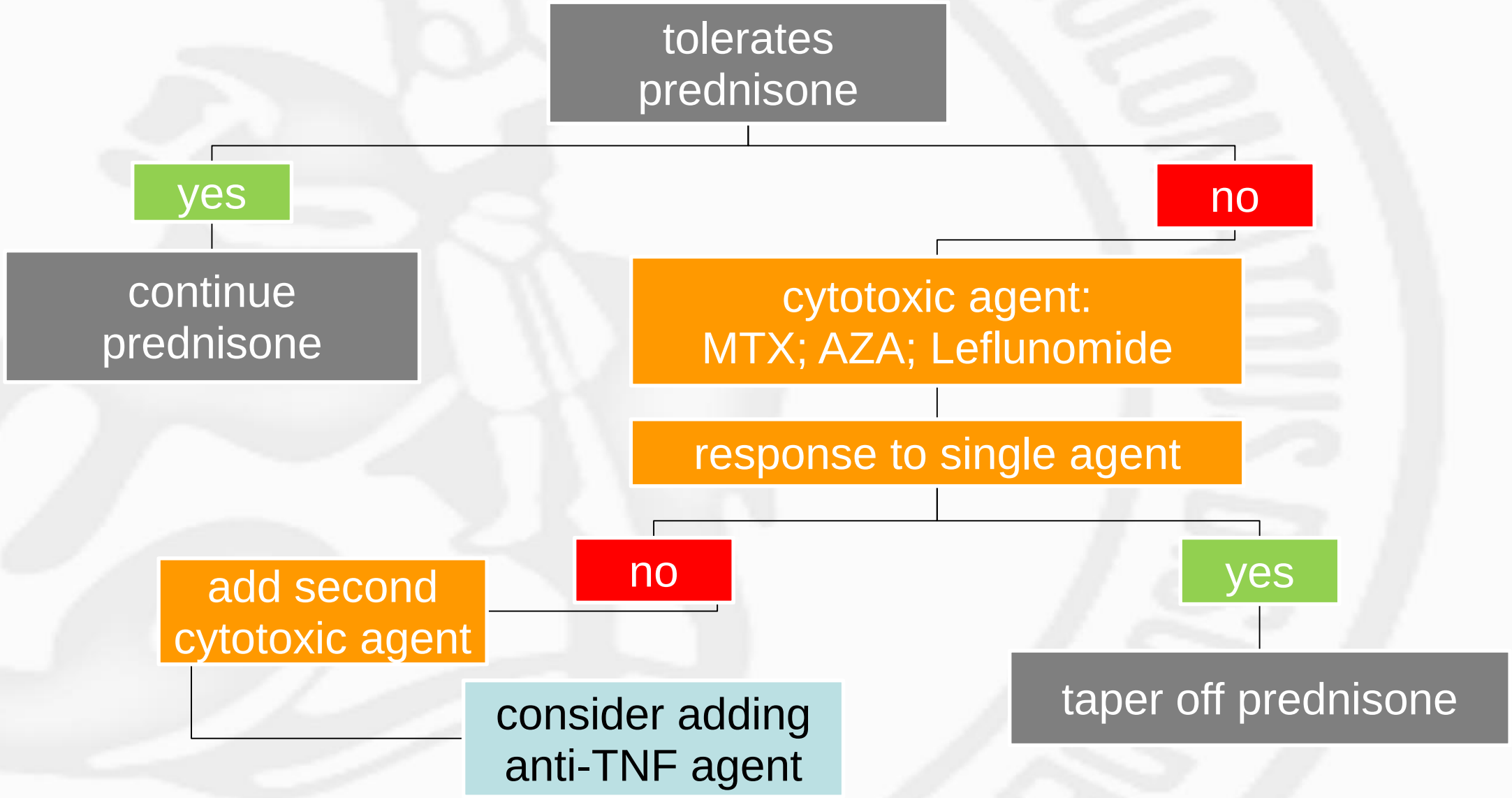
Question 3: Which systemic therapy would you initiate?

1. stop all therapy
2. prednisone
3. stay with hydroxychloroquine
4. methotrexate
5. infliximab

Refractory skin lesions

- no response to hydroxychloroquine
- patient would like to avoid prednisone at this point
- started on methotrexate
  - 10 mg once a week
- skin lesions improve

Chronic disease

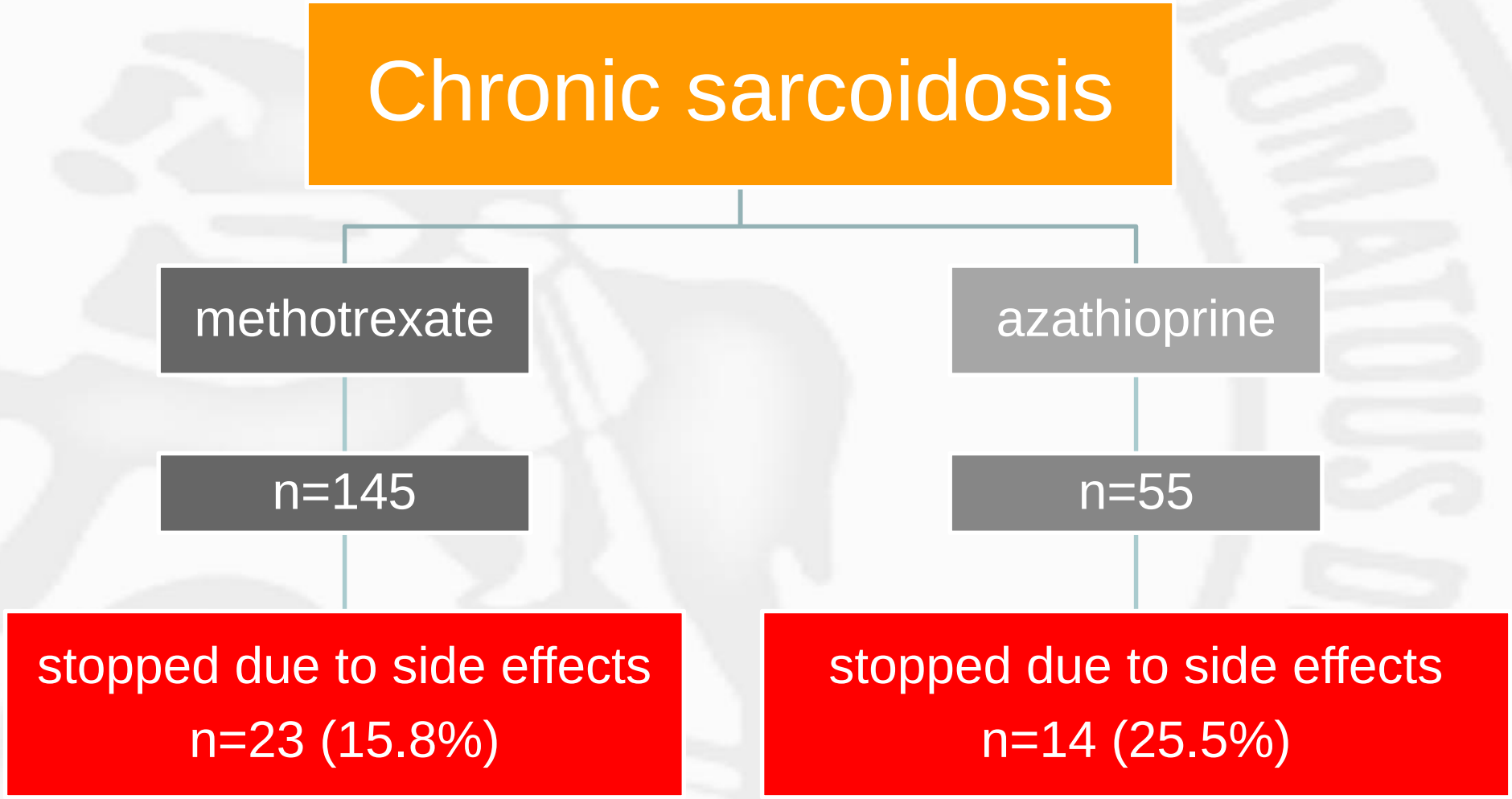


Methotrexate (MTX) vs azathioprine (AZA)

- retrospective study of treatment of these agents as steroid sparing agents
- two sites employing different therapy
  - one site: methotrexate
  - other site: azathioprine

Vorselaars AD, et al. Chest 2013.

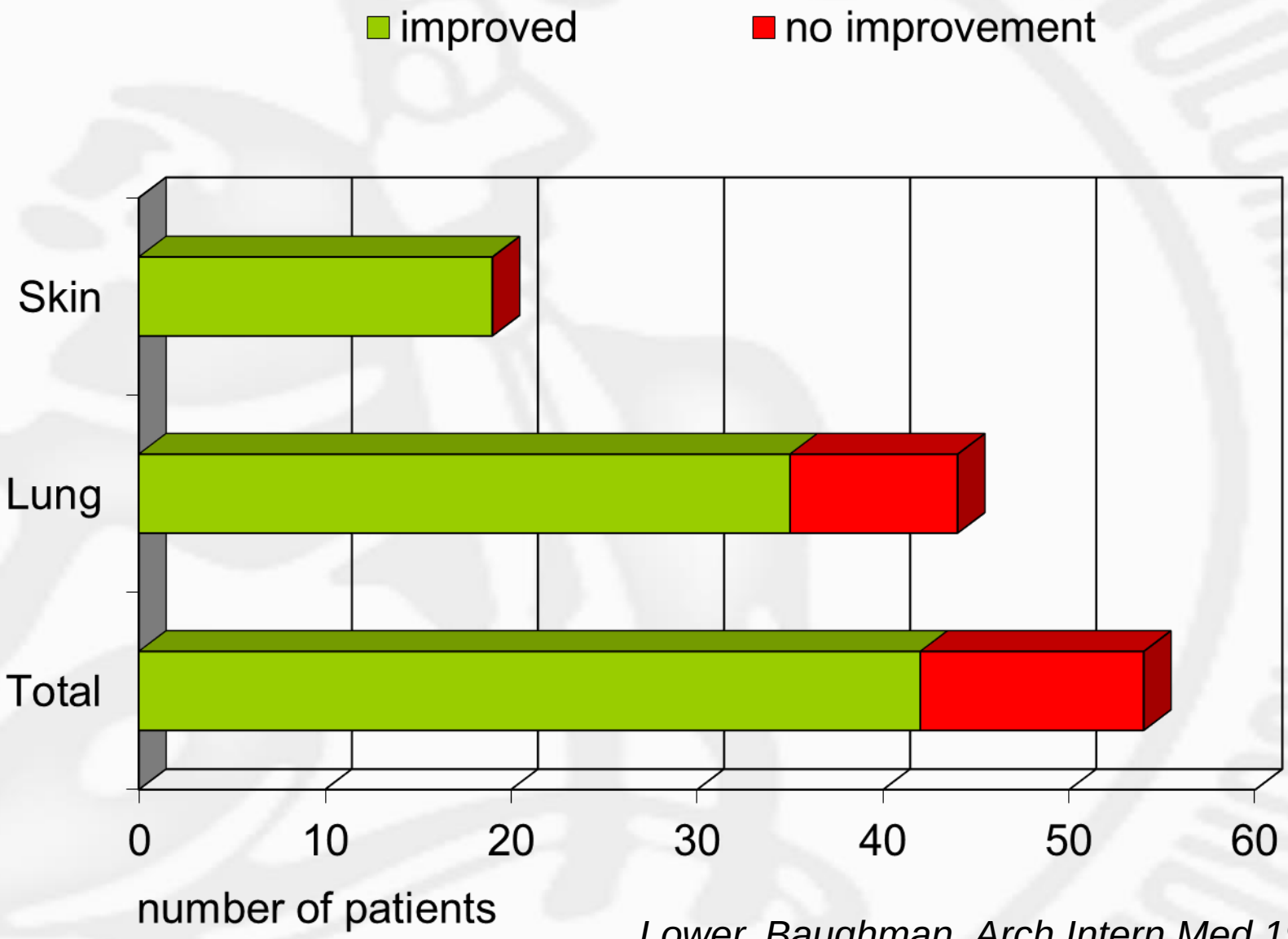
Comparison of methotrexate to azathioprine



Outcome of treatment

- reduction of dose of prednisone
  - for those on >1 year treatment: 10 mg
  - no difference between groups
- improvement in FVC
  - 95 ml/year
  - no difference between groups
- infections more likely for those on azathioprine
  - methotrexte 18.1%
  - azathioprine 34.6%
    - p=0.01

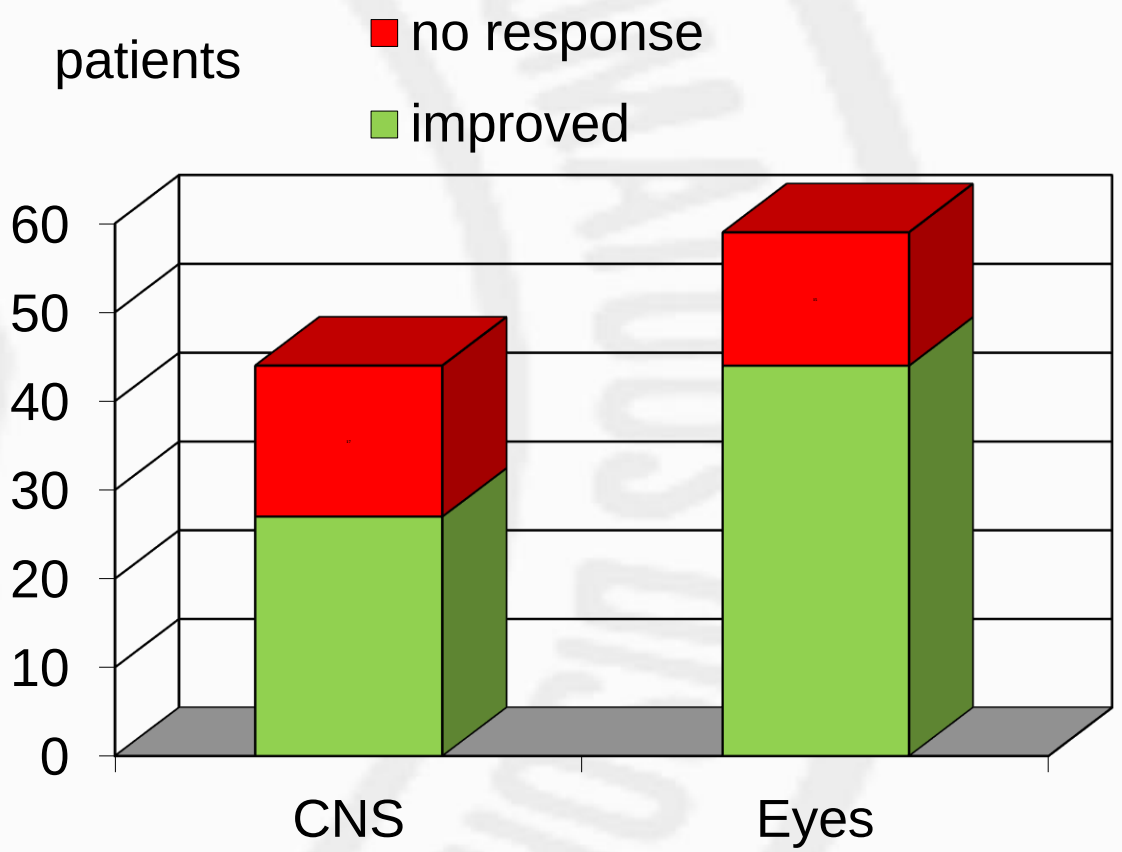
Treatment with MTX for > 2 years: response to MTX



Lower, Baughman. Arch Intern Med 1995; 155: 846-851.

Effectiveness of MTX for specific organ involvement

- Neurologic disease (CNS)
  - non responders to methotrexate usually treated with cyclophosphamide
- Eye disease
  - non responders to methotrexate usually responded to combination cytotoxic drugs

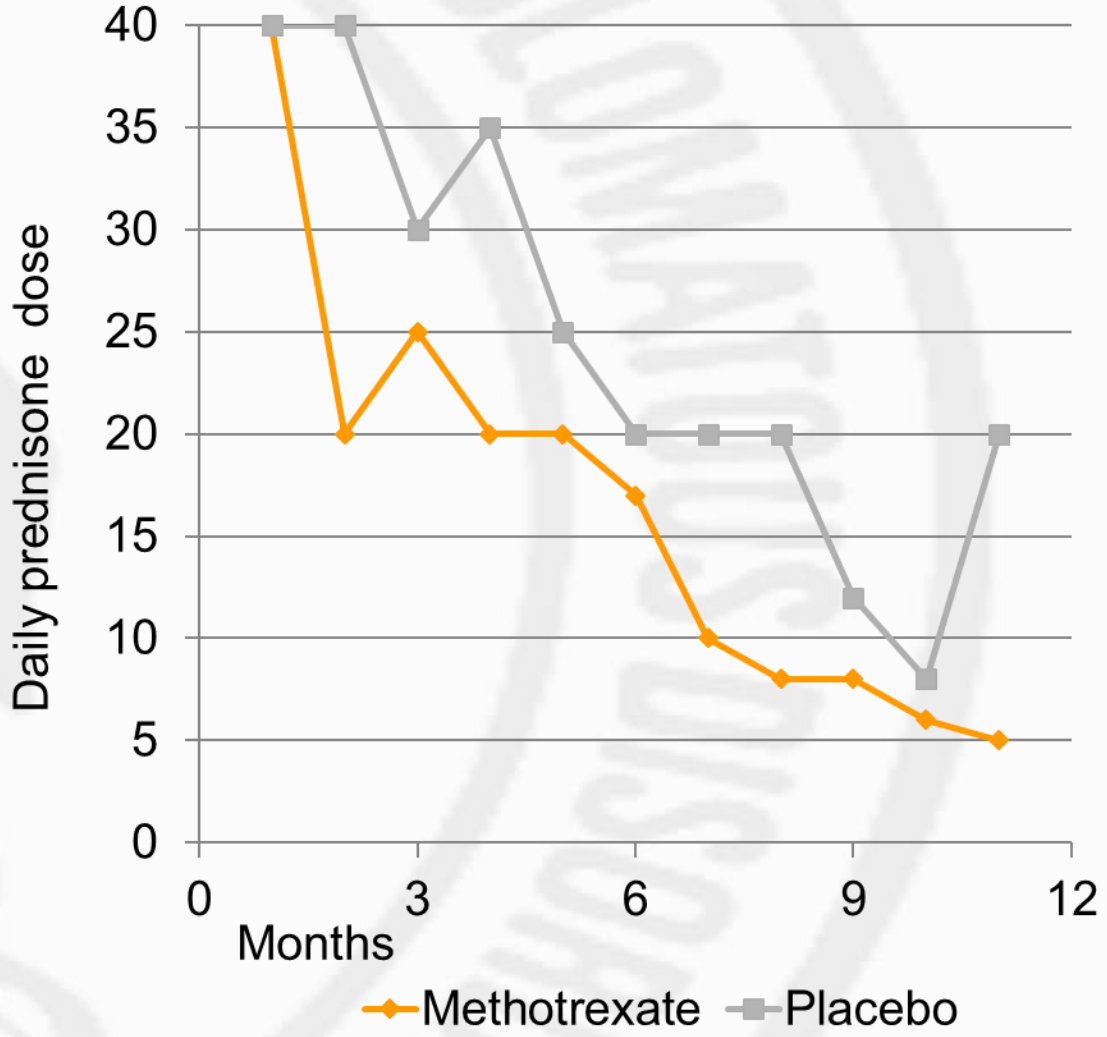


Lower, et al. Arch Intern Med 1997; Baughman, et al. Sarcoidosis

Steroid sparing effect of MTX for acute sarcoidosis

- methotrexate (MTX) patients had a significant lower prednisone dose in the last six months of study

- this was associated with significantly less weight gain for patients on MTX

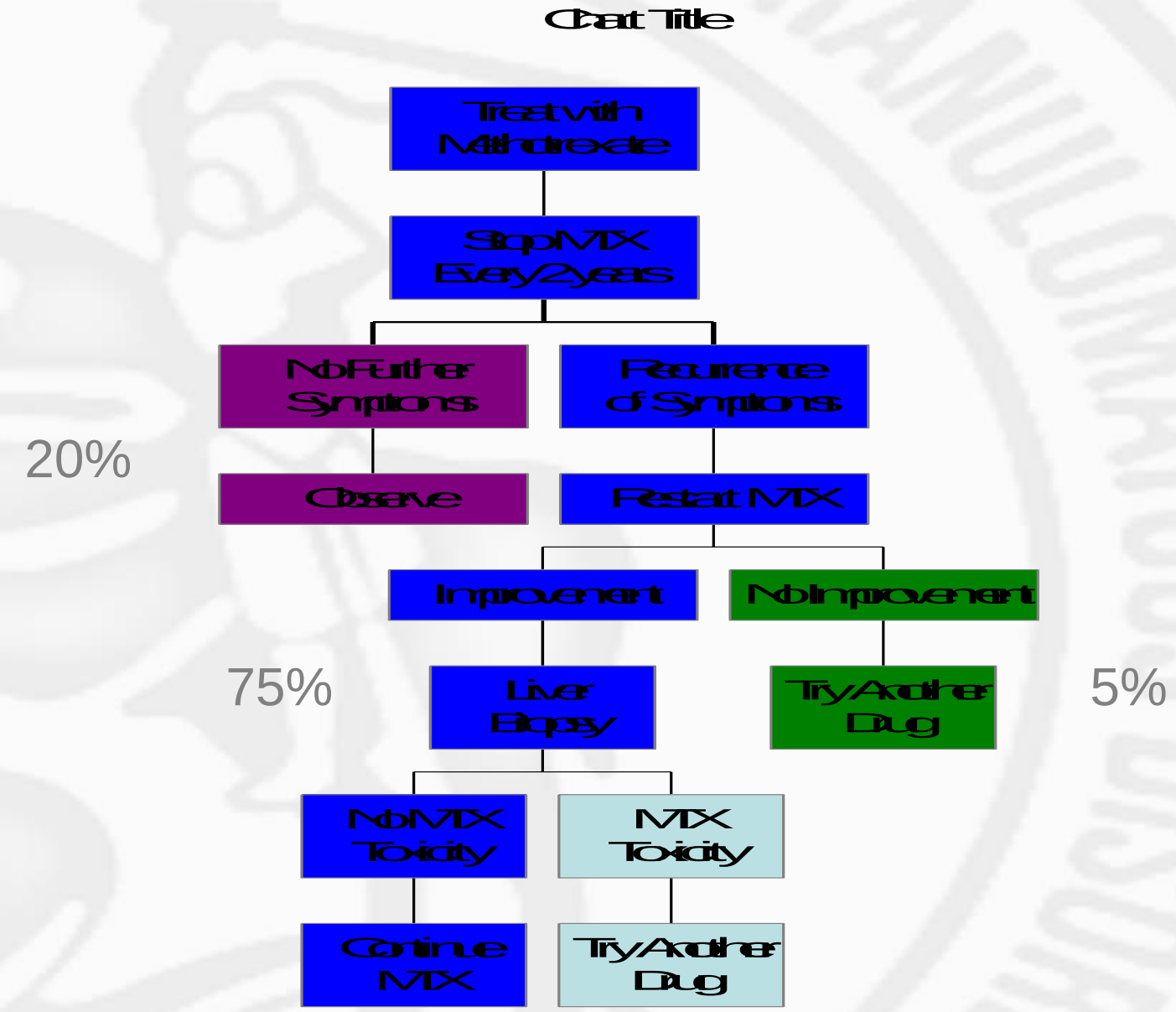


Baughman, et al. Sarcoidosis 2000; 17: 60-66.

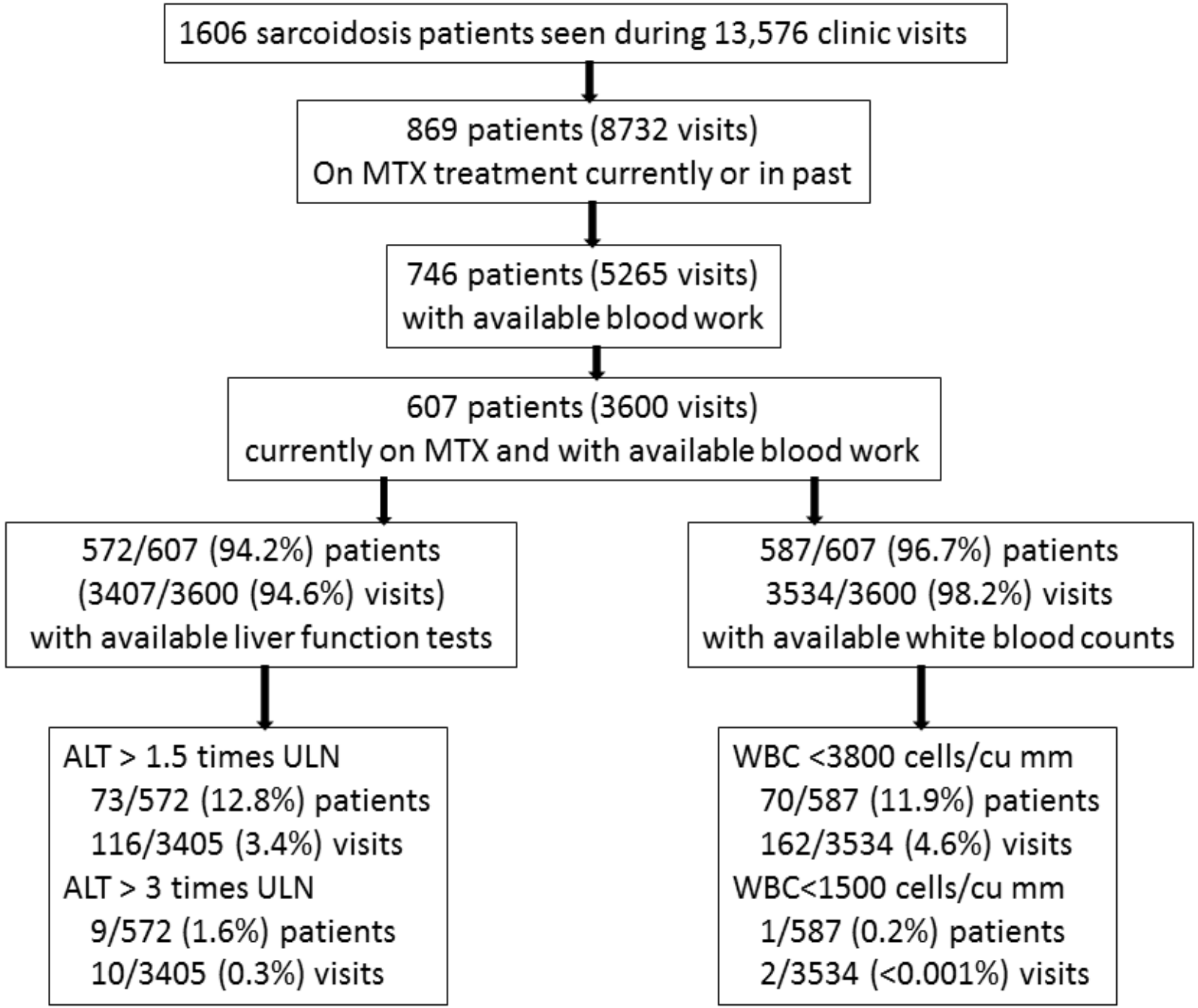
Methotrexate therapy for sarcoidosis

- initial and follow-up laboratory data
  - CBC
  - hepatic function
  - renal function
- initial dose
  - 10 mg per week
- maximal dose 15-20 mg per week
- to reduce toxicity
  - half dose one day, rest next day
  - folate 1 mg per day

    Morgan SL, et al. Ann Intern Med; 21:833-841.
- reduction of dose for neutropenia



Baughman and Lower. Thorax 1999; 54: 742-746.


1606 sarcoidosis patients seen during 13,576 clinic visits
869 patients (8732 visits)
On MTX treatment currently or in past
746 patients (5265 visits)
with available blood work
607 patients (3600 visits)
currently on MTX and with available blood work
572/607 (94.2%) patients
(3407/3600 (94.6%) visits)
with available liver function tests
587/607 (96.7%) patients
3534/3600 (98.2%) visits
with available white blood counts
ALT > 1.5 times ULN
73/572 (12.8%) patients
116/3405 (3.4%) visits
ALT > 3 times ULN
9/572 (1.6%) patients
10/3405 (0.3%) visits
WBC <3800 cells/cu mm
70/587 (11.9%) patients
162/3534 (4.6%) visits
WBC<1500 cells/cu mm
1/587 (0.2%) patients
2/3534 (<0.001%) visits

Leukopenia in MTX treated patients

	leukopenia (WBC<3800 cells/cu mm)	no leukopenia (WBC>3800 Cells/cu mm)	p value
total	70 (11.9%)	517 (88.1%)	
age, years	50 ± 9.5 *	50 ± 10.7	>0.05
female	47 (67%)	387 (75%)	>0.05
African American §	39 (56%)	215 (42%)	0.027
serum creatinine >1.2 mg/dL	4 (5%)	28 (6%)	>0.05
hepatic sarcoidosis	5 (7%)	47 (9%)	>0.05
MTX dosage mg/week	9.0 ± 2.5	9.9 ± 2.9	<0.0001
concurrent prednisone	36 (51%)	307 (60%)	>0.05

Liver test abnormalities on methotrexate (MTX)

	LTA (ALT >1.5 time ULN)	no LTA (ALT<1.5 times ULN)	p value
total	73 (12.8%)	499 (87%)	
age, years	48 ± 9.8 *	50 ± 10.8	>0.05
female §	63 (86%)	324 (72%)	0.01
African American	33 (46%)	219 (44%)	>0.05
serum creatinine >1.2 mg/dL	3 (4%)	22 (95%)	>0.05
liver sarcoidosis §	13 (8%)	36 (8%)	0.008
MTX dosage mg/week	9.9 ± 2.6	9.8 ± 3.1	>0.05
concurrent prednisone	50 (68%)	260 (58%)	>0.05

Most LFT abnormalities grade 1-2

	Alanine aminotransferase (ALT)	Asparate aminotransferase (AST)	Alkaline phosphatase (ALP)
>1.5 times ULN	73 (12.8%) *	18 (3.2%)	22 (3.9%)
>3 times ULN	9 (1.6%)	4 (0.7%)	6 (1.1%)
>5 times ULN	1 (0.2%)	1 (0.2%)	2 (.04%)

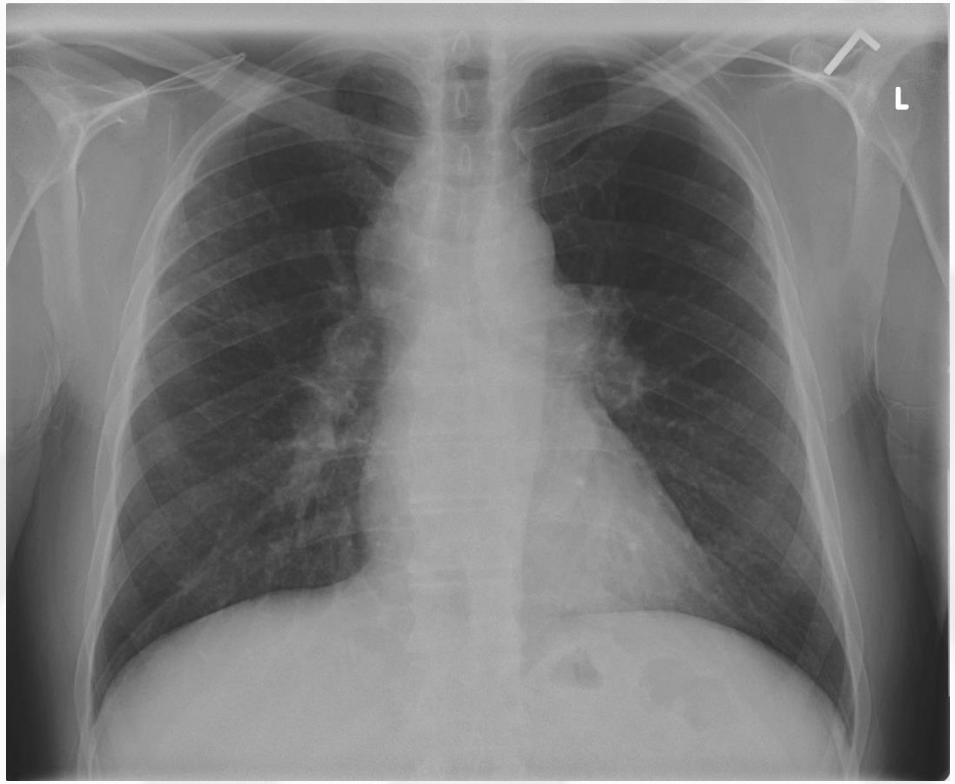
Methotrexate course

- patient takes methotrexate
  - total resolution of skin lesions after six months
- after two years of methotrexate stop drug
- recurrence of skin lesions
- restart methotrexate
- lesions improve
- liver biopsy performed
  - no methotrexate toxicity

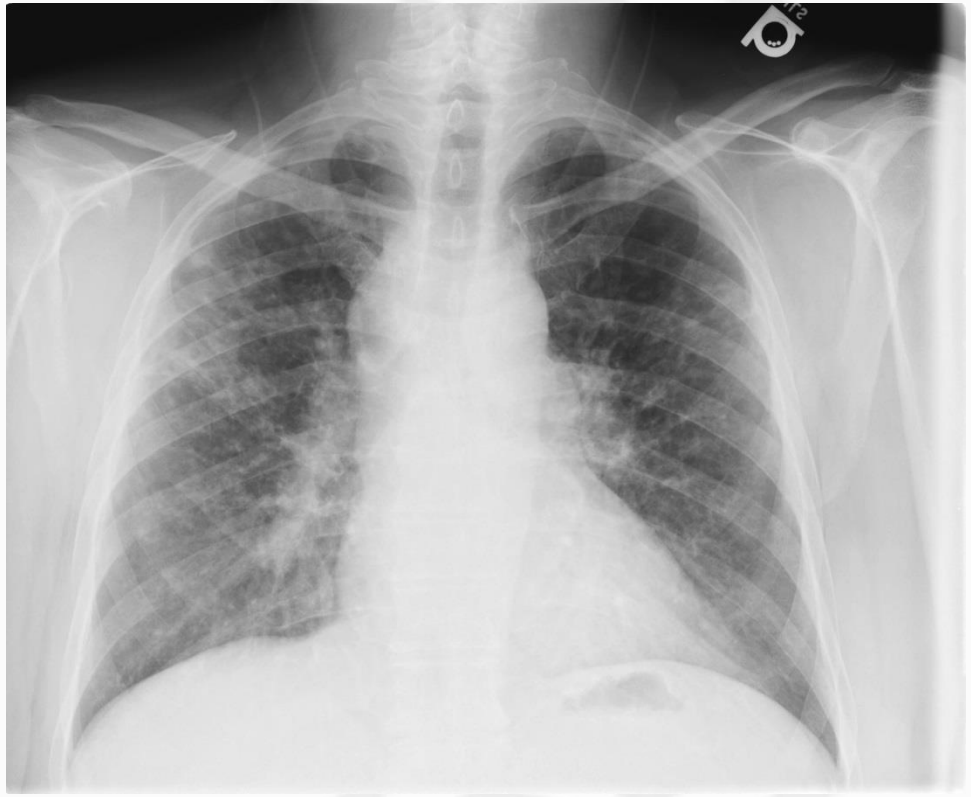
Methotrexate second time

- after six months of methotrexate
  - skin lesions improved
- patient develops cough
- now dyspneic
- worsening of chest roentgenogram

Sarcoidosis case



2004



2007

Question 4: What would you do now?

1. add prednisone to methotrexate
2. switch from methotrexate to leflunomide
3. stop methotrexate and initiate infliximab

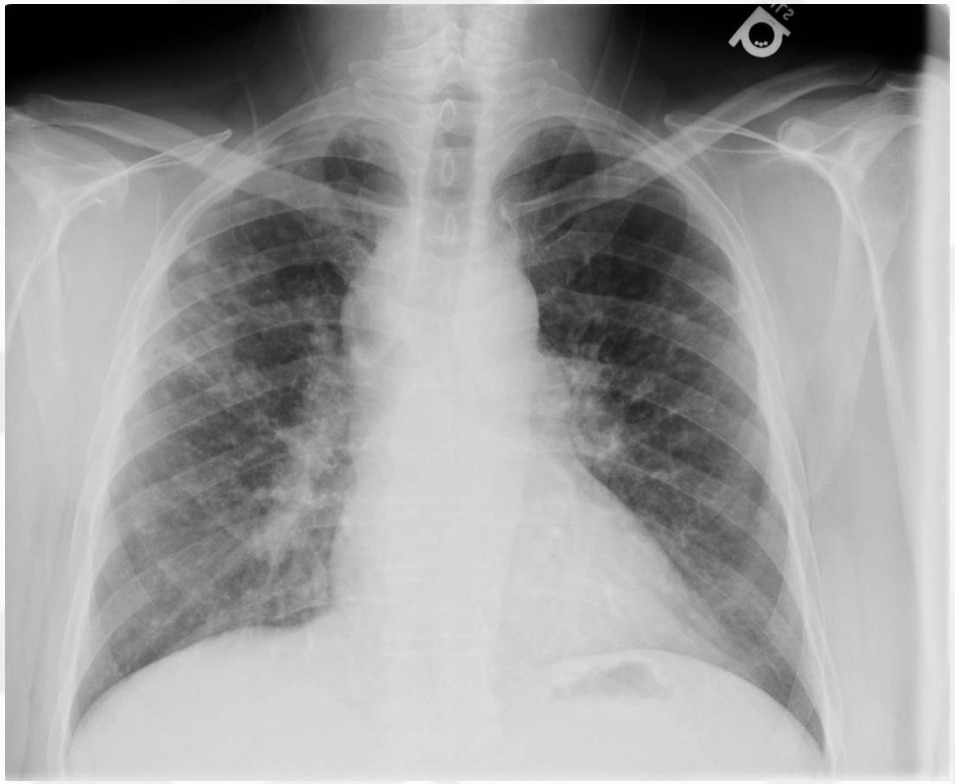
Cough and dyspnea

- stop methotrexate
  - cough associated with methotrexate was reported in 6 of 54 patients treated for two or more years of methotrexate
  - *Lower, Baughman. Arch Intern Med 1995; 155: 846-851.*
- added prednisone
- cough resolved

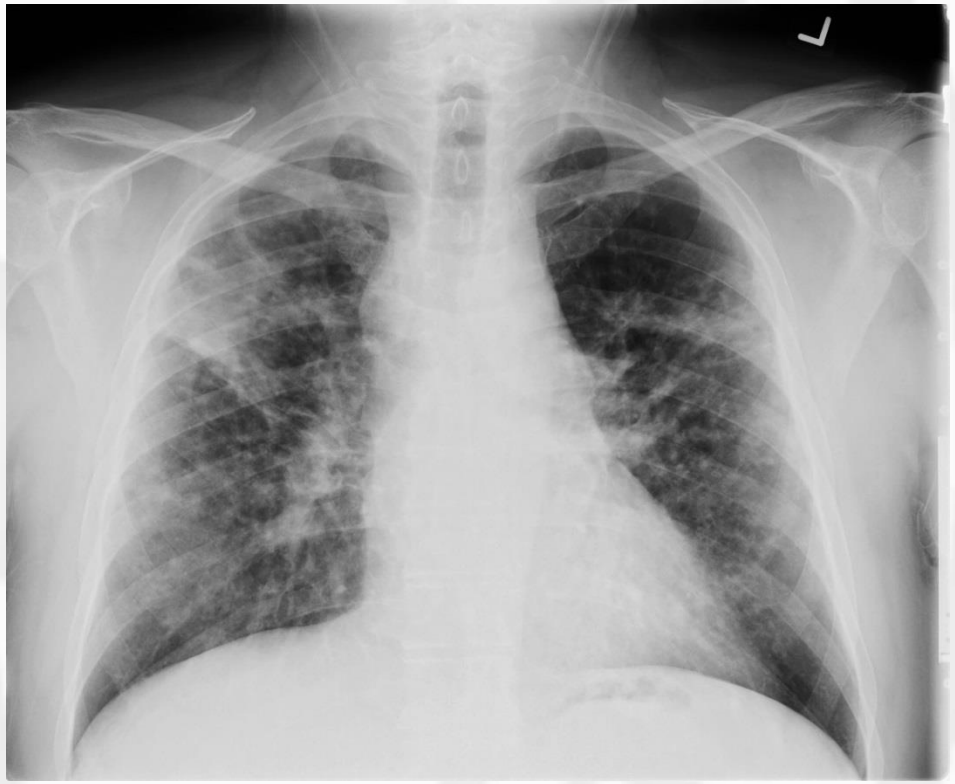
Stopping methotrexate

- cough improved
- dyspnea persisted
- worsening of chest roentgenogram

Sarcoidosis case

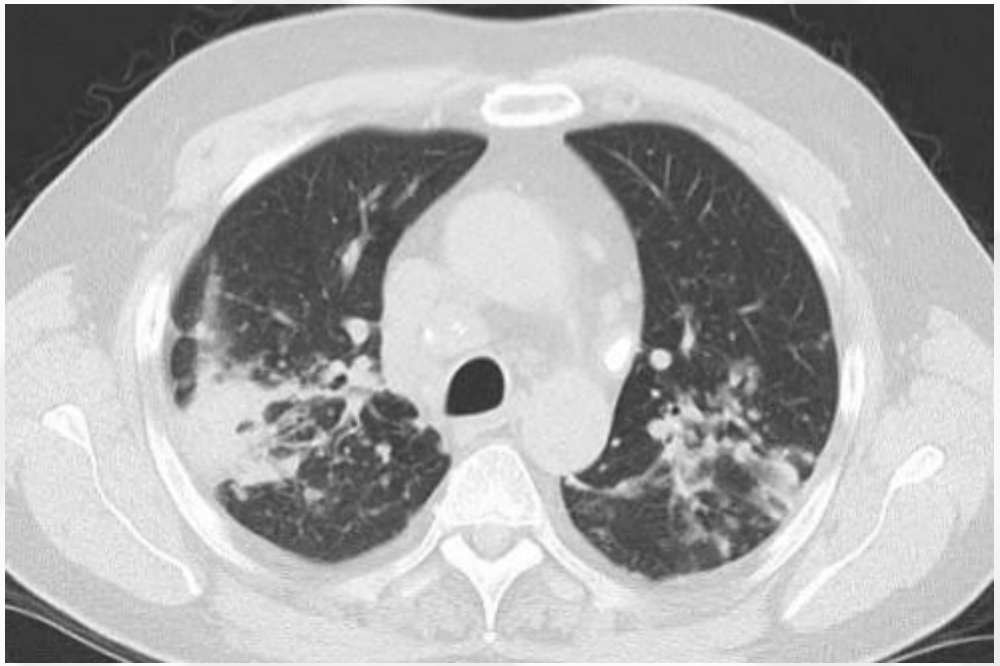


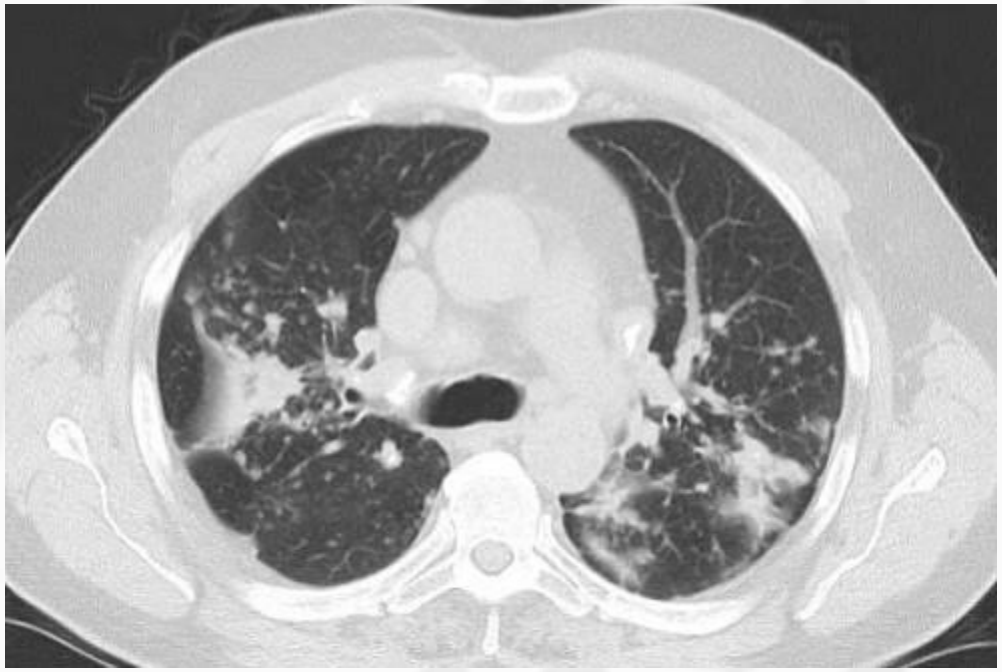
2007



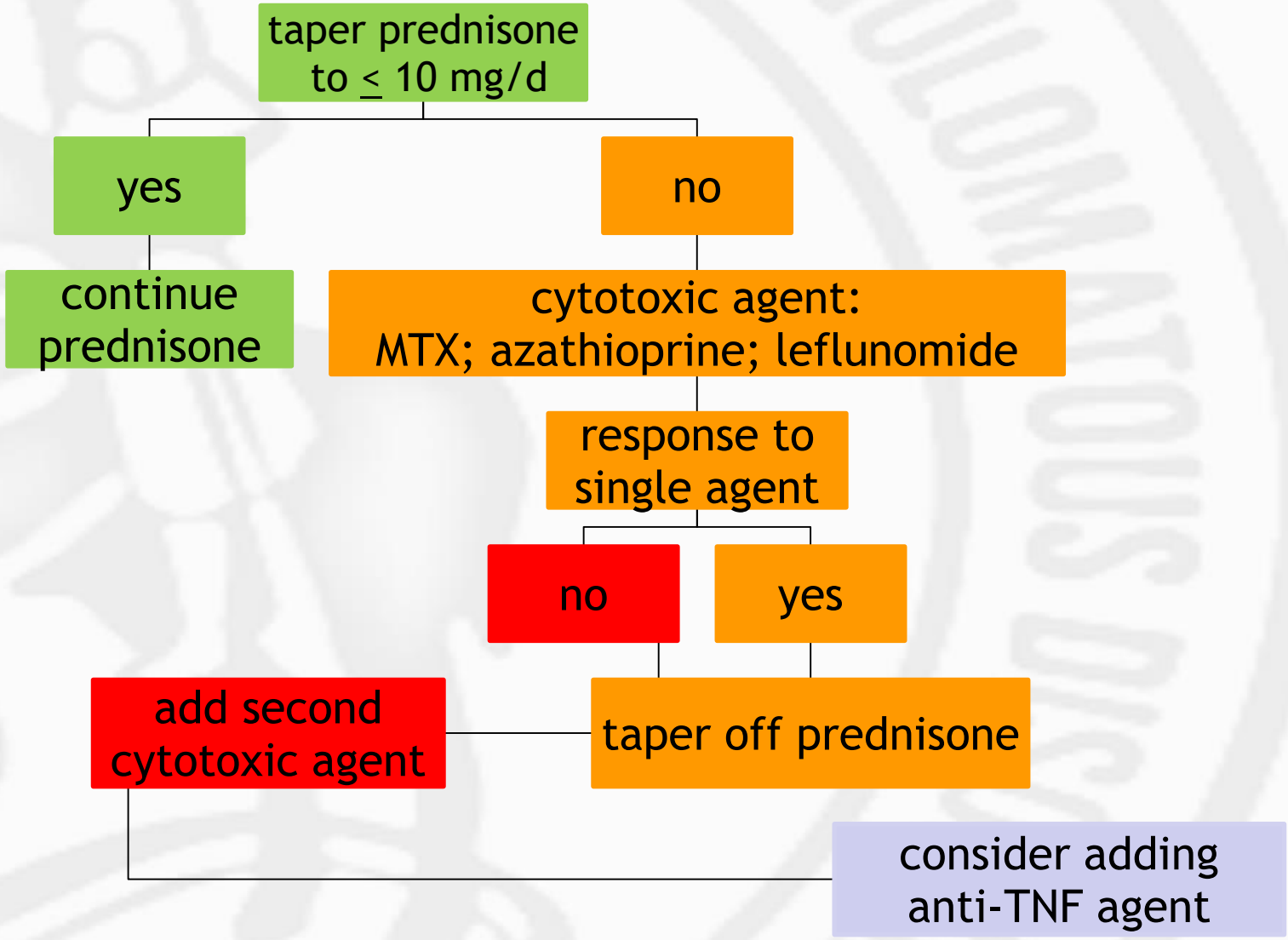
2009

Sarcoidosis case: CT 2009





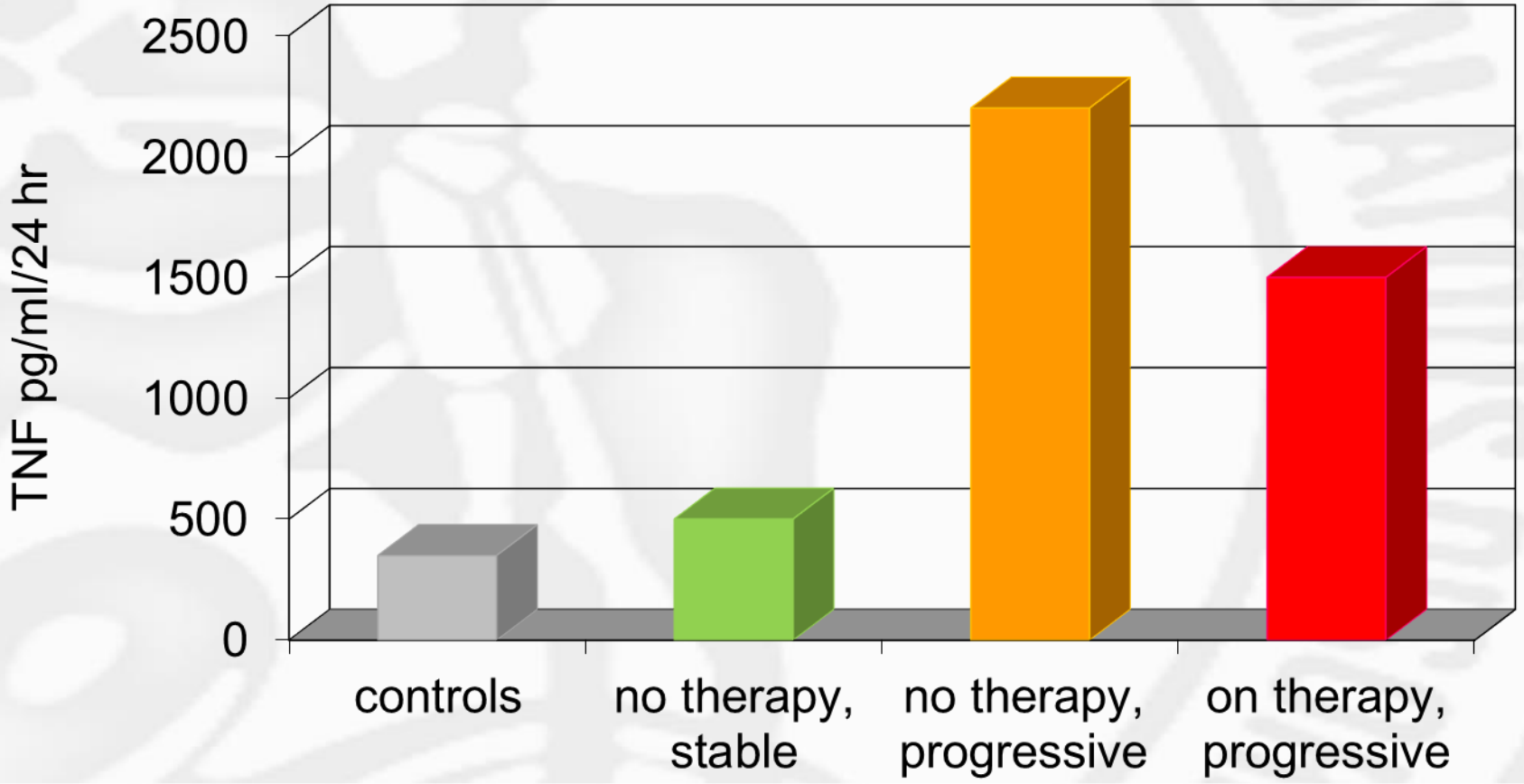
Chronic disease



Tumor Necrosis Factor

- TNF is a central cytokine in chronic inflammatory conditions
- it is secreted by several effector cells
  - especially macrophages
- it has multiple effects in the cytokine cascade
  - initiation of the granulomatous reaction
  - neutrophil chemotaxtic

TNF release of BAL retrieved alveolar macrophages

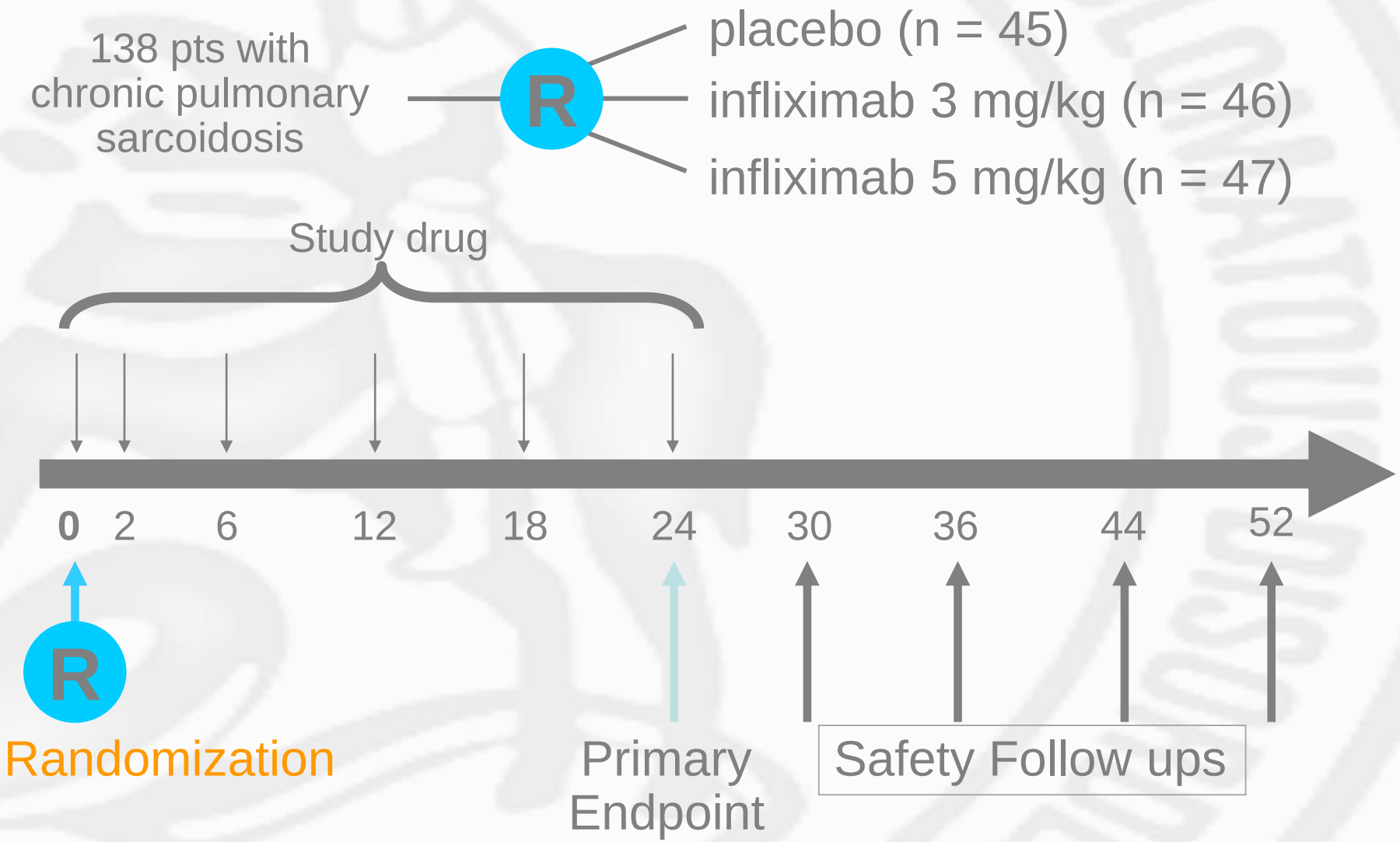


Anti-TNF therapy for sarcoidosis

- a large randomized trial demonstrated benefit for treating chronic pulmonary sarcoidosis
  - 135 patients in a double blind randomized trial 2:1 infliximab to placebo
  - primary endpoint improvement in FVC
- this study to confirm observations made by case series and a smaller clinical trial

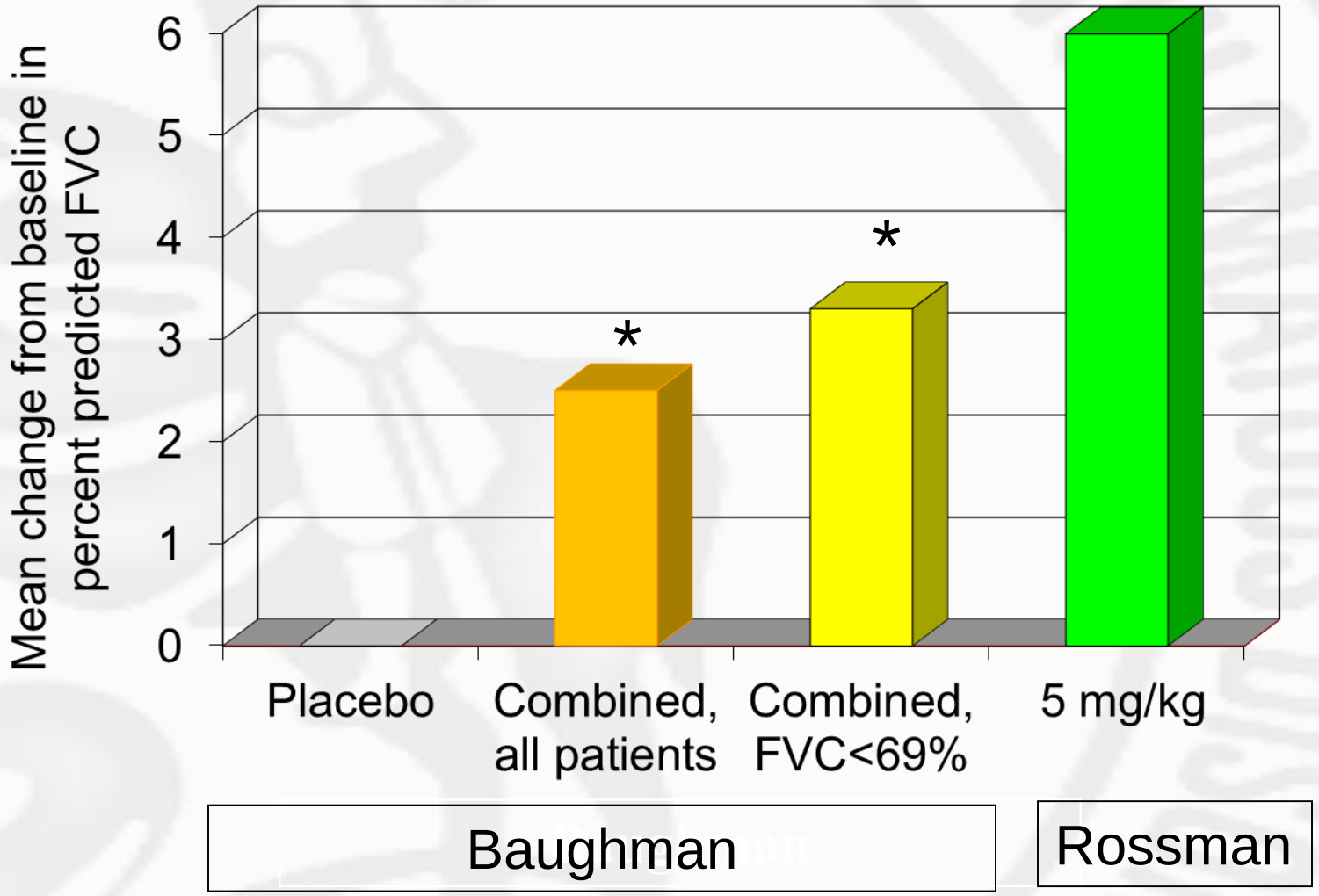
Baughman RP, et al. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. Am J Respir Crit Care Med 2006; 174: 795-782.

Study Design



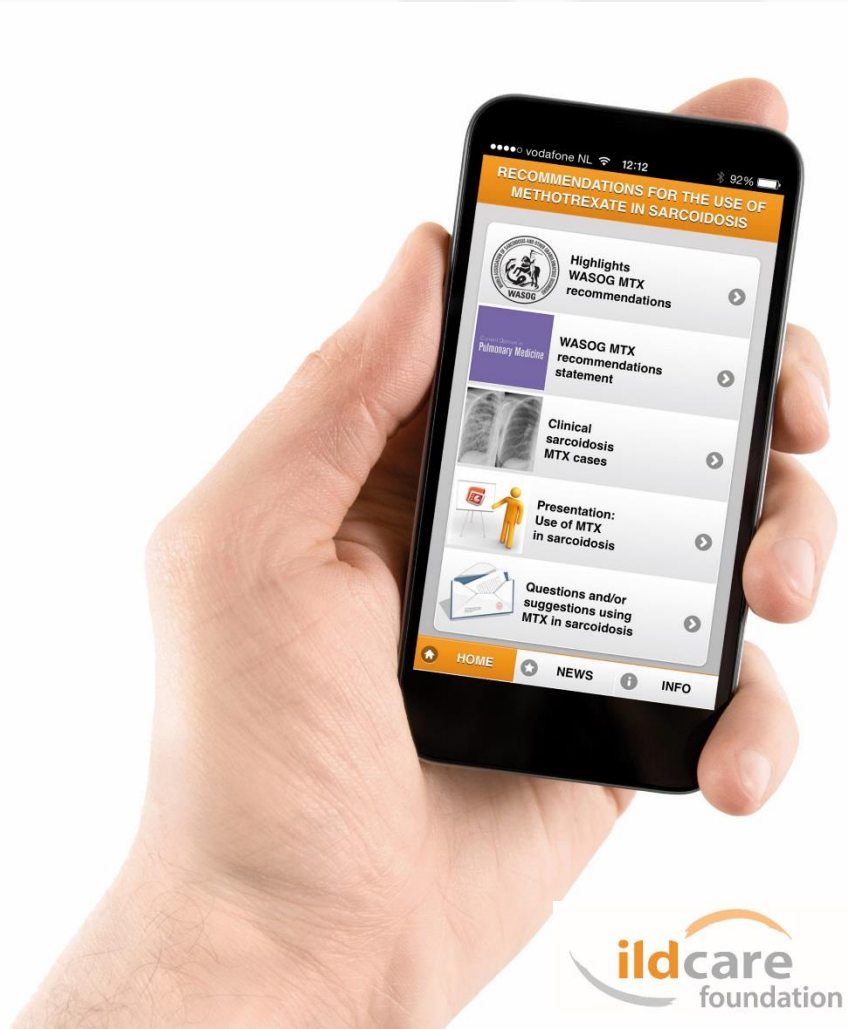
Total daily dose of corticosteroid at baseline: prednisone equivalent (mg)

	Placebo (n = 45)	3 mg/kg (n = 46)	5 mg/kg (n = 47)
number on corticosteroids	42	40	40
mean (SD)	13.9 (9.3)	12.1 (6.9)	12.2 (5.6)
range	(2.5, 50.0)	(2.5, 40.0)	(3.3, 25.0)



* *p<0.05 compared to placebo Baughman RP, et al. Am J Respir Crit Care Med 2006; 174:795-802. Rossman MD, et al., Sarcoidosis Vasc Diffuse Lung Dis 2006; 23:201-208.*

Everything you've always wanted to know about the use of MTX in sarcoidosis…



Help is at hand.

There's an app for that!

The app was developed on behalf of the ild care foundation (www.ildcare.eu) and the WASOG.

You can find it in the Apple Store or Google Play Store. Download it for free!

Multinational evidence-based WASOG recommendations for the use of MTX in sarcoidosis. Cremers JA, et al. Curr Opin Pulm Med 2013.

Multinational Recommendations

1	**Indications for MTX in sarcoidosis** •Second-line agent In steroid-refractory cases In steroid-associated adverse effects As steroid-sparing agent •First-line agent MTX/steroid combination therapy Monotherapy in exceptional situations
2	**Recommended initial MTX dosage 5-15mg weekly**
3	**Folic acid with MTX is recommended** •at least 5 mg weekly or 1 mg daily

Multinational Recommendations

4	**Pre-administration work-up before starting MTX** • AST, ALT, ALP, bilirubin • CBC, creatinine • When indicated: serology for HIV, hepatitis B/C and IGRA test
5	**Consider some contraindications before starting MTX** • Renal disease • Hepatic disease other than sarcoidosis • Bone marrow depression • Acute or chronic infection
6	**When starting MTX or increasing the dose** • Monitor ALT/AST, creatinine and CBC every 3-6 weeks • After a stable dose every 1-3 months • After stabilization every 6 months

Multinational Recommendations

7	**Gastrointestinal side-effects** • Splitting the oral dose with ingestion within a 12-h period • Parenteral administration • Alternative immunosuppressive drug
8	**Confirmed increase in ALT/AST** • Exclude other causes • MTX dose reduction or withdrawal • Liver biopsy • Additional folic acid supplementation • After normalization alternative immunosuppressive drug
9	**MTX is appropriate for long-term use**
10	**MTX should not be used** • By men or women for 3 months before planned pregnancy • During pregnancy or breast feeding

Possible misconceptions

- ‘MTX is not useful as anti-inflammatory agent due to major toxicity’
  - 11% of pulmonologists do not prescribe MTX
  - in sarcoidosis discontinuation of MTX only 0-10%
    - GI complaints most reported reason
  - in RA MTX less frequently discontinued than other DMARDs [1]
- ‘MTX p.o. is as effective as s.c.’
  - only 42% of experts prescribed MTX subcutaneous in GI toxicity
  - parenteral MTX higher effectiveness en less GI toxicity [2]
  - other option: splitting oral dose [2]
- ‘Males with child wish need to stop MTX because of the risk of malformations/teratogenicity’
  - we don’t know yet

[1] *Salliot C, et al. Long-term safety of MTX monotherapy in patients with rheumatoid arthritis: a systematic literature research. Ann Rheum Dis 2009.*
[2] *Hoekstra M, et al. Bioavailability of higher dose MTX comparing oral and subcutaneous administration in patients with rheumatoid arthritis. J Rheumatol 2004.*

Conclusion

- MTX is first-choice second-line agent in sarcoidosis
- optimization of its use is important
- multinational recommendations serve to promote this
- future research
  - establishment possible misconceptions
  - revealing mechanism of anti-inflammatory action

Recommendations use of TNF-α inhibitors specifically targeting sarcoidosis

Recommendation dosage:

- Infliximab: dosage of 5 mg/kg i.v. at week 0, 2, 6 and every 4 weeks thereafter
- Adalimumab: dosage of 80-160 mg s.c. at week 0, 40 mg at week 1, and 40 mg once every week thereafter

Discontinuation in case of:

- severe uncontrolled side-effects
- primary ineffectiveness during 3-6 months treatment
- secondary ineffectiveness due to antibody formation
- or stable disease during treatment with TNF-α inhibitors for at least 6-12 months *discontinuation should be considered.*

Drent M, et al. Practical eminence and experience-based recommendations for the use of TNF-a inhibitors in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2014;31:91-107.

Summary

- sarcoidosis is a granulomatous disease affecting multiple organs
- its therapeutic management is very challenging
- curative treatment is currently not available for sarcoidosis

Summary

- nonspecific immunosuppression with prednisone remains the first-choice therapy
- chronic use of corticosteroids is accompanied with severe adverse events
- timely implementation of appropriate steroid-sparing cytotoxic agents is important

Acknowledgements

- Dr. Elyse Lower, Co-director of ILD/Sarcoidosis Clinic
- Dr. Peter Engel, Co-Director of PH Clinic
- Research coordinator, Rebecca Ingledue

  University of Cincinnati, USA
- Our patients

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