PMR and Giant Cell Arteritis: Minimizing Risk of Steroid Use and Length of Therapy

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AGENDA

- **Introduction**
- Disease Overview
- Treatment Paradigms
- Reducing Steroid Burden
- Questions

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Polymyalgia Rheumatica (PMR) is a common inflammatory disorder in the elderly and is the second most common autoimmune disease after Rheumatoid Arthritis.

Clinical Features

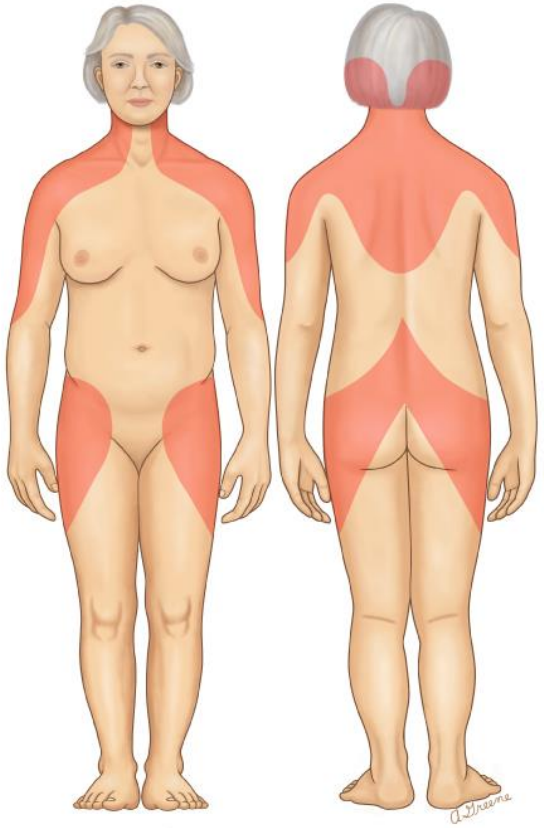
- First Described in the 1950s in an Italian Journal and finally coined Polymyalgia Rheumatica in 1957 by Stuart barber
- Subacute onset of:
  - Severe pain and stiffness in the proximal limbs (shoulder and hip/girdle) WITHOUT weakness
  - Abrupt Onset (<4 weeks)
  - Difficulty rising and dressing
  - Prolonged AM stiffness >45 minutes (gelling)
- May precede OR coincide w/ a new diagnosis of Giant Cell Arteritis (GCA)
- Labs: elevation of erythrocyte sedimentation rate (ESR) and C reactive protein (CRP)
- NOTE: The CRP is nearly always raised and is more clinically sensitive
- BRISK response to low dose steroids from 15-20 mg can solidify the diagnosis

The cause of PMR is unknown though recent data suggests an increase in IL-6 as the cause of the inflammation.

Symptoms distribution is fairly classic in PMR.

Physical Exam Findings

- Shoulders are involved 70-95% of the time
- Hips involved 50-70% of the time
- Can include small joints
- Periarticular structure involvement prominently in subdelotid/subacromial bursas
- Proximal muscle tenderness (not weakness like myositis)
- Shoulder bursitis restricts range of motion
- Small joint synovitis in hands, feet



Shuffling painful gait to the exam table and an inability to raise arms overhead are classic.

The American College of Rheumatology and the European League Against Rheumatism (EULAR) have a provisional set of criteria for PMR from 2012.

Diagnostic Criteria

- Patient must be 50 years or older
- Pain in both shoulders
- Morning stiffness >45 minutes
- Labs w/ abnormal CRP and/or ESR
- Other: Negative RF or CCP and no other joint involvement
- IF U/S available: patient must have at least one shoulder w/ subdeltoid bursitis, bicep tenosynovitis, glenohumeral synovitis, or hip synovitis

Currently no pathognomonic biological or imaging tests exist for a PMR diagnosis.

Classically patients are female, >50 y/o, and of Northern European descent.

Epidemiology

- Average age at dx is >70 y/o, w/ a peak at 70-80 y/o
- Can occur in those > 50 y/o, however if <50 y/o → *think something else*
- More common in women
- Women affected twice as often
- Annual incidence of 20-53/100,000 persons >age 50 amongst the high risk populations = Scandinavians and Northern Europeans
- 10/1000,000 > age 50 amongst low risk populations
- Epidemiologic data suggests that ~50% of patients w/ GCA also have PMR

Disease prevalence increases with advancing age.

PMR has a broad differential diagnosis, which is part of the challenge in making the diagnosis.

Differential Diagnosis

- Seronegative Rheumatoid Arthritis
- RS3PE
- Drug Induced Myalgia
- Fibromyalgia
- Hypothyroidism
- Paraneoplastic Syndrome
- Crowned Dens Syndrome
- Bone Disease (Multiple Myeloma, Hyperparathyroidism, Skeletal mets)

There are many cases which can overlap with Rheumatoid Arthritis or Senile Onset of RA.

Steroids remain the backbone of therapy for PMR.

Treatment

- ACR/EULAR guidelines for therapy:
    - No less than 7.5 mg and no greater than 30 mg
    - Average length of treatment 6-9 months, but there can be a range → rapid tapers lead to recurrence
    - If relapse, increase prednisone to pre-relapse dose, not back to the starting dose
    - Early introduction of steroid sparing agents w/ difficulty tapering to minimize steroid burden
- Brisk and rapid response to steroids is a hallmark of therapy
- Sx usually 50-70% improved w/in 3 days w/ near complete resolution by 3 weeks on the appropriate dose
- Must monitor for prednisone side effects: BP, glucose, bone density, weight, mood, skin thinning, cataracts, reflux

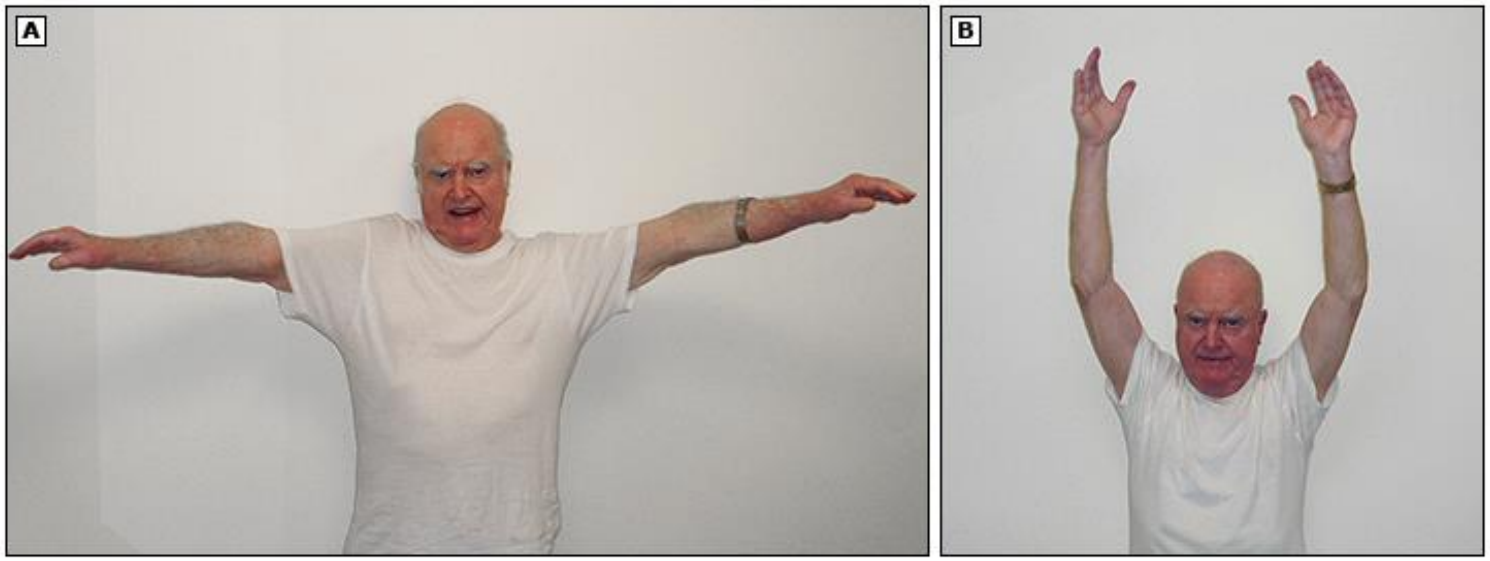
Response to therapy can be monitored subjectively and objectively with repeat ESR/CRP lab studies.

Monitoring Therapy

- Monitor acute phase reactants w/ de-escalating steroid doses
- Change therapy only if symptoms worsen with a corresponding rise in acute phase reactants, do not treat asymptomatic increases
- Be mindful that steroids address other prevalent non inflammatory MSK problems like rotator cuff tendonitis and OA, which can worsen with tapering
- Important to distinguish inflammatory vs. non-inflammatory pain → steroids make a lot of things better
- Indications for steroid sparing agents:
    - Pre-existing comorbidities such as Diabetes, Osteoporosis
    - Serious Glucocorticoid side effects
    - Recurrent relapses
    - Prolonged steroid use w/ difficult tapering (~9 months)

Pre and post therapy patients should be now able to painlessly active abduct their shoulders.

Monitoring Therapy



There are several steroid sparing agent options.

Steroid Sparing Agents

Hydroxychloroquine

- Most benign option, consider in elderly patients on low doses of steroids close to fully wean

Methotrexate

- RCT data of MTX are generally favourable and improve:
    a) Cumulative glucocorticoid dose
    b) Relapse rate
    c) Time to discontinuation of glucocorticoid treatment
- START w/ low dose MTX from 10-15 mg/week and use it to help taper steroids

TNF

- Studies do not show an increase in TNFa levels in PMR patients and thus several studies have failed to demonstrate a significant benefit w/ TNF
- In patients w/ a RF/CCP or small joint synovitis that appear to have more seronegative RA overlap, TNF can be helpful

IL-6

- Sarilumab (FDA approved) for PMR and Tociluzimab both been shown to increase the rate of glucocorticoid free remission compared to placebo

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A diagnosis of Giant Cell Arteritis should be considered in patients over the age of 50 with appropriate clinical features.

Clinical Features

- Classic Triad:
  1. Jaw Claudication → seen in 50% of patients, severe pain at after start of chewing, the most likely predictor of a positive biopsy
  2. Visual Changes: monocular, abrupt, partial field, curtain effect, diplopia, vision loss occurs in 10-20% and is rarely reversible
  3. Headache → seen in 2/3 of patients, usually temporal BUT can be frontal or occipital +/- scalp tenderness

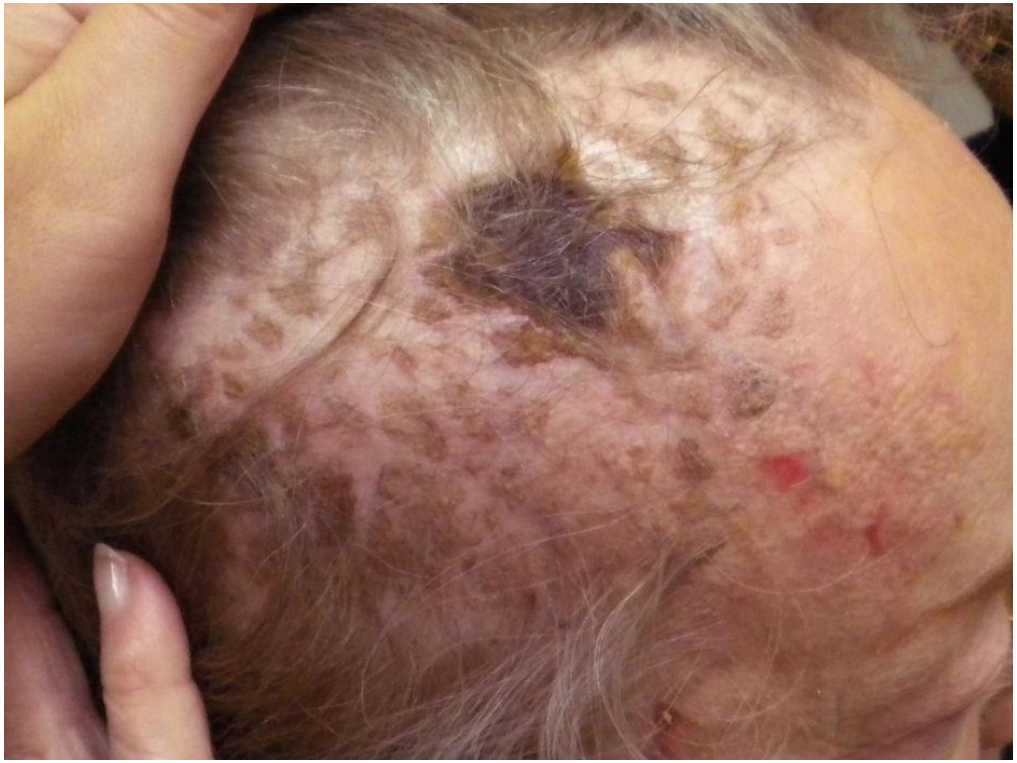
- Additional features may be:
  - Fever → in up to 50% of patients, usually low grade
  - Anorexia +/- weight loss
  - Fatigue → can be predominant symptom
  - Abnormal Temporal Artery → in up to 50% of patients, the artery may be enlarged, difficult to compress, pulseless or nodular

Frequency of Manifestations

Symptom	Percentage of Time Present
Headache	70%
Jaw claudication	50%
Constitutional symptoms	50%
Polymyalgia rheumatica	40%
Visual loss	20%
Abnormal temporal artery	50%
Anemia	80%
ESR >50 mm/hr	90%

Clinical Features

- Scalp necrosis and alopecia can occur in late presentations of GCA

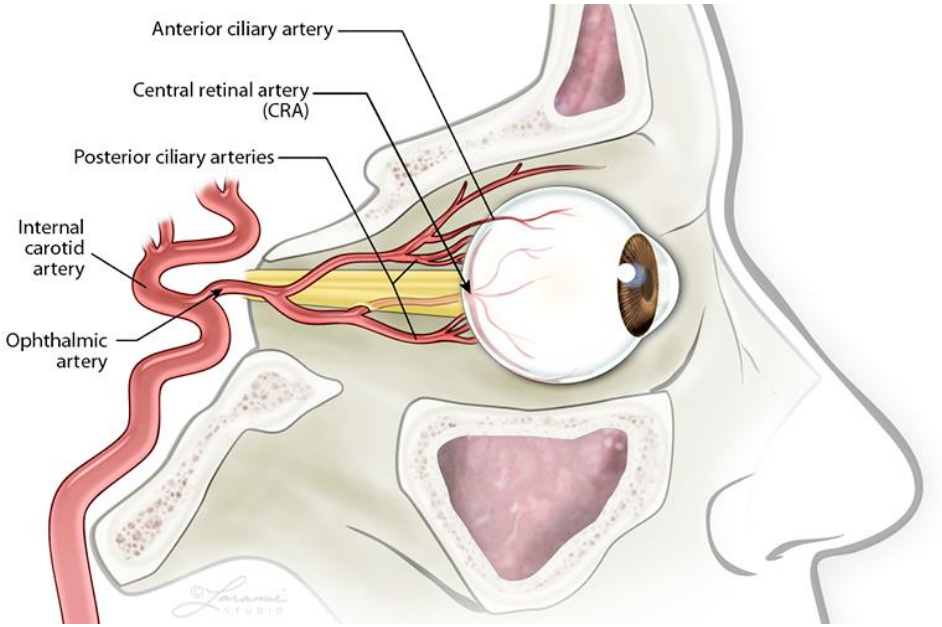


Uffelmann, Nicholas C; Kozel, Jessica; Chaudhry, Sofia B; & Vidal, Claudia I. (2012). Reticulated lesion as an early diagnostic sign for giant cell arteritis. Dermatology Online Journal, 18(6).

The feared complication of GCA will always be vision loss.

Vision Loss

- 80% of cases of vision loss in GCA 2/2 to Arteritic anterior ischemic optic neuropathy (AION)
- Classically posterior ciliary artery (main supply to optic nerve) is occluded
- REMEMBER the MAJORITY of AION are 2/2 to non arteritic involvement from atherosclerotic disease
- ~10-20% of cases 2/2 to Central retinal artery occlusion



Giant Cell Arteritis (GCA) is the most common vasculitis in adults aged >50 y/o.

Epidemiology

- Lifetime risk of 1% in women and 0.5% in men
- > 80% of patients are over 70 y/o
- Heavy smoking is an increased risk factor in women
- Higher incidence rates in people of Northern European (Scandinavian) descent
- There are shared sequence polymorphisms with PMR: HLA-DRB1 and HLA-DR4
- ~15-40% of PMR patients will have GCA

Pathogenesis

- Dendritic cells in vessel wall initiate the pathogenic cascade → recruitment of T cells and macrophages to form granulomatous infiltrates or "giant cells"
- Effector cytokines are released into the arterial wall
- Activation of inflammatory cells and target endothelial cells, vascular smooth muscle cells, and fibroblasts leading to remodeling of the arterial wall with luminal occlusion

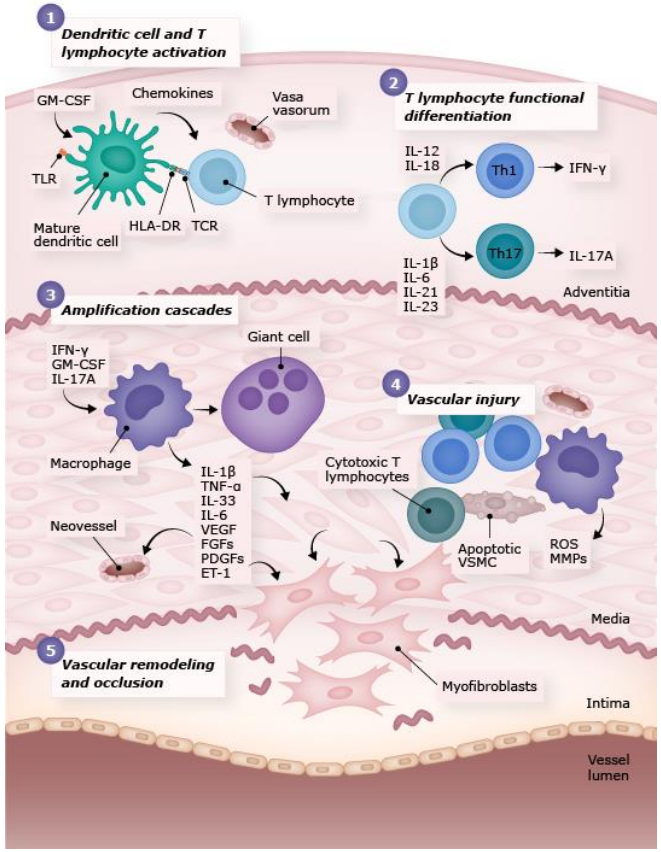


Figure created by Dr. Nekane Terrades Garcia (Catalyzing Science).

Diagnosis

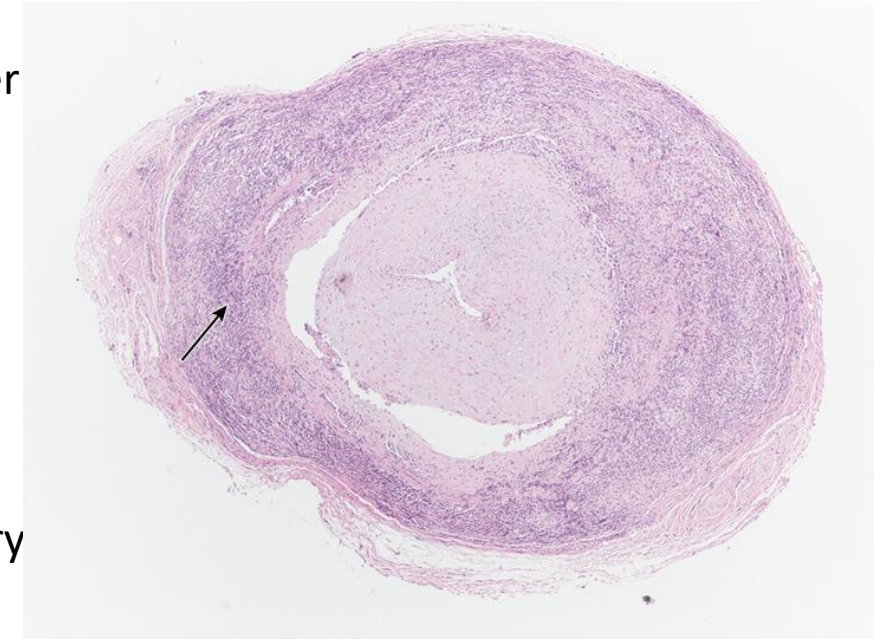
- Lab findings are notable for:
  - ESR and CRP significantly elevated (<5% of patients will have normal labs)
  - Normochromic normocytic anemia
  - Thrombocytosis

- CTA/MRA can identify large vessel involvement (stenosis, dissection, aneurysm)
- TA duplex US may show homogenous wall thickening "Halo sign" → sensitivity is 55-100% and specificity is 78-100% and is highly operator and technique dependent
- Gold standard remains biopsy, though GCA can cause skip lesions and can have false negatives
- Patients w/ aortitis and large vessel involvement alone typically do not have cranial symptoms and negative biopsies, PETCT can help to confirm the diagnosis

Histology

- "Classic" Pattern in 50% of cases → granulomatous inflammation of the inner half of the media centered on the internal elastic lamina w/ mononuclear infiltrate, multinucleate giant cells and fragmentation of the internal elastic lamina

- "Other" Pattern in the other 50% → non specific pan-arteritis, mixed inflammatory infiltrates composed largely of CD4+ T Cells and macrophages w/ a few eosinophils, rare neutrophils



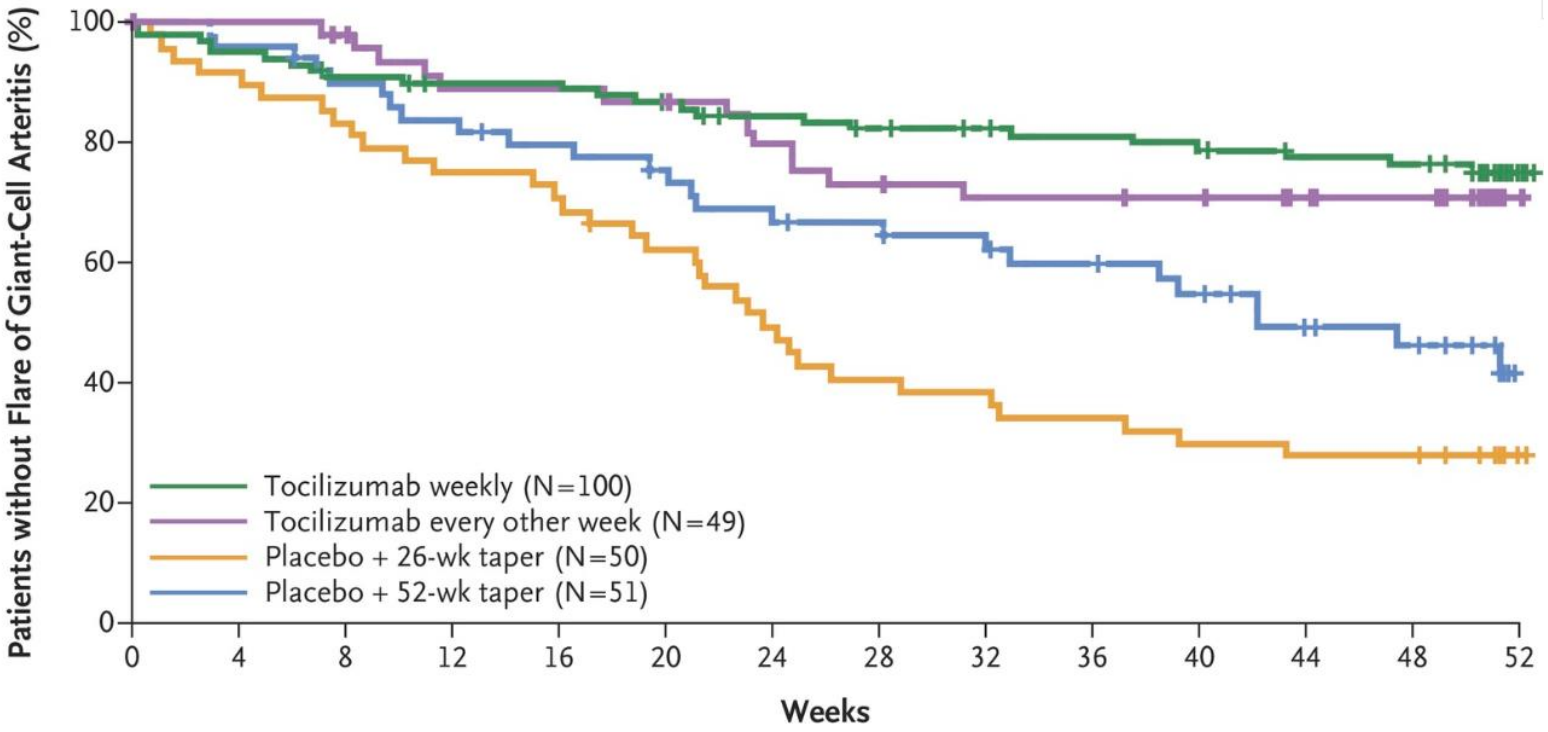
Temporal artery biopsy showing the classic histologic picture of transmural inflammatory infiltrate (arrow) in GCA.

Treatment

- AION is a true medical emergency, therapy SHOULD NOT be delayed → Prednisone 1 mg/kg oral vs. Pulse dose steroids 1g Solumedrol usually for 3 days w/ a plan to reduce by 10-20% every two weeks
- Empiric initiation of steroids at 50-60 mg/day with suspicion of disease and biopsy WITHIN 14 days for highest yield

Early introduction of steroid sparing agents is now the standard approach to GCA therapy after GiACTA (2017 trial) with sustained time without flare off of steroids.

IL-6 Use in GCA



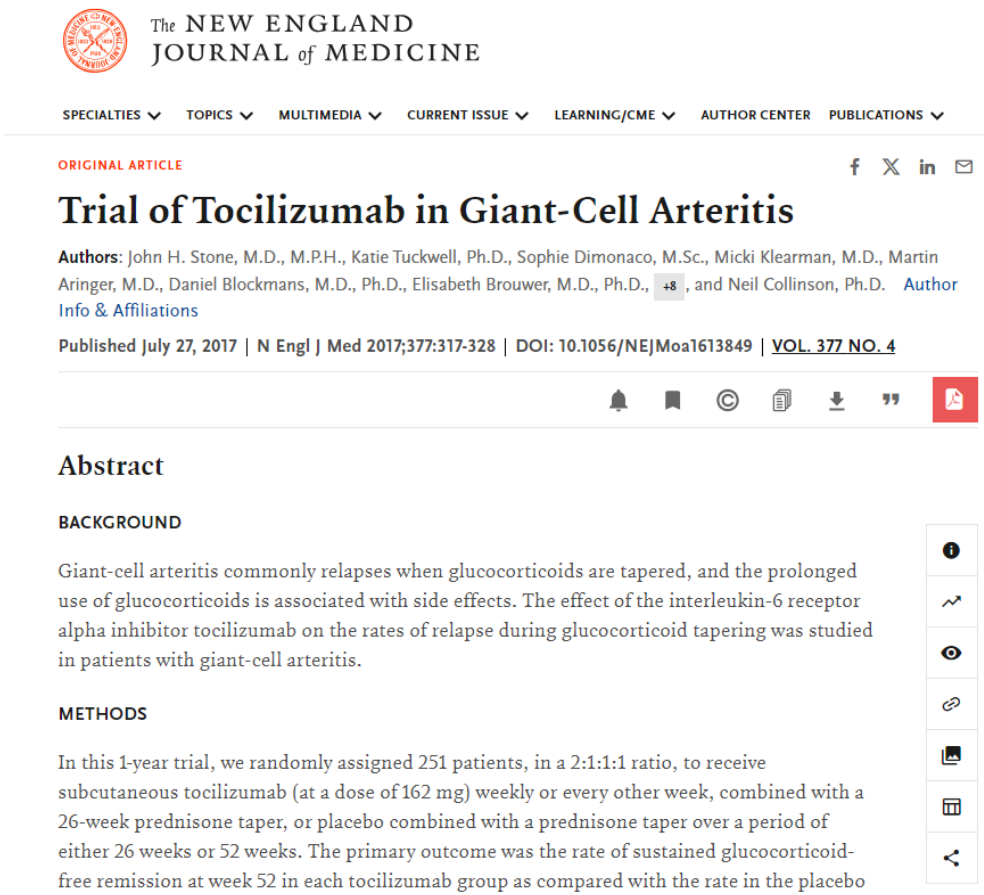
Stone JH et al. 2017. Trial of Tocilizumab in Giant-Cell Arteritis. N Engl J Med. Jul 27;377(4):317-328.

- Flare defined as clinical recurrence of initial symptoms, w/ ESR >30 mm/hr
- Primary outcome: 56% on weekly tociluzimab had sustained remission at 52 weeks, 14-18% on prednisone monotherapy

IL-6 Use in GCA (cont'd)

- The cumulative median prednisone dose over the 52 week period was **1862** mg in each tociluzimab group compared to **3296 mg** in the placebo group (26 week taper) and **3818 mg** (52 week taper)

- Serious adverse events occurred in 14% of those in the weekly tociluzimab group versus 22-25% in the placebo groups depending on length of taper



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ORIGINAL ARTICLE

Trial of Tocilizumab in Giant-Cell Arteritis

Authors: John H. Stone, M.D., M.P.H., Katie Tuckwell, Ph.D., Sophie Dimonaco, M.Sc., Micki Klearman, M.D., Martin Aringer, M.D., Daniel Blockmans, M.D., Ph.D., Elisabeth Brouwer, M.D., Ph.D., +8, and Neil Collinson, Ph.D. Author Info & Affiliations

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Abstract

BACKGROUND

Giant-cell arteritis commonly relapses when glucocorticoids are tapered, and the prolonged use of glucocorticoids is associated with side effects. The effect of the interleukin-6 receptor alpha inhibitor tocilizumab on the rates of relapse during glucocorticoid tapering was studied in patients with giant-cell arteritis.

METHODS

In this 1-year trial, we randomly assigned 251 patients, in a 2:1:1:1 ratio, to receive subcutaneous tocilizumab (at a dose of 162 mg) weekly or every other week, combined with a 26-week prednisone taper, or placebo combined with a prednisone taper over a period of either 26 weeks or 52 weeks. The primary outcome was the rate of sustained glucocorticoid-free remission at week 52 in each tocilizumab group as compared with the rate in the placebo

GiACTA part 2

- 2 year extension of the original trial
- Nearly half the patients treated w/ Tociluzimab weekly maintained clinical remission for the entirety of part 2, though flares occurred with discontinuation of therapy
- Cumulative glucorticoid dose over 3 years were lower in patients originally assigned to Tociluzimab than those assigned to placebo
- No new safety signals were identified

- CONCULSION: Tociluzimab qweek delays the time to flare and reduces cumulative glucocorticoid dose in patients with relapsing GCA and new-onset GCA
- These data support initiating Tociluzimab as part of first-line therapy in all patients with active GCA.

Disease Overview

PMR	GCA
Inflammatory Arthritis	Large Vessel Vasculitis
Bilateral Shoulders and Pelvic Girdle	Classic Triad: Headache, Jaw claudication, Visual Change
Dx: Labs & Clinical Hx	Dx: Biopsy, Ultrasound, PET, Labs, Clinical Hx
Tx: Prednisone +/- steroid sparing agents	Tx: Prednisone + Tociluzimab

Quiz Question 1

A 72 y/o F w/ b/l shoulder aches / stiffness x 3 months. Now with bilatera hip stiffness x 3 weeks. There is no weakness, synovitis, visual changes, HA, jaw claudication.

Home meds include Tylenol (no help) and simvastatin.

VS: BP 140/70, wt 62 kg, deltoid / thigh tenderness on exam w/o weakness or temporal tenderness

Labs: ESR 72 mm/hr, hgb 10.1 (MCV 90), normal TSH/CPK

Which of the following should be done now?

1. Naproxen 500 mg BID
2. Methotrexate 15 mg weekly
3. Prednisone 15 mg daily
4. Prednisone 60 mg daily
5. Discontinue simvastatin

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Quiz Question 2

67 y/o F w PMHx including CAD and DM. 3 days of new pulsatile, right frontal headache. Scalp tenderness when washing her hair. Refractory to home ibuprofen

Exam w/ right temporal tenderness, decreased pulsation, subclavian bruit, blurred vision to the right eye, BRP 160/90, wt 62 kg, temp 99.9 F

ESR 88 mm/hr, CRP 50 mg/L

What should be done first?

(a) Emergent ophthalmology assessment
(b) Methotrexate 15 mg weekly
(c) CTA head / neck or ultrasound
(d) Prednisone 60 mg / pulse dose steroid
(e) Emergent right temporal artery biopsy

What should be done first?

(a) Emergent ophthalmology assessment
(b) Methotrexate 15 mg weekly
(c) CTA head / neck or ultrasound
(d) Prednisone 60 mg / pulse dose steroid
(e) Emergent right temporal artery biopsy

Thank you for having me!

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