Giant Cell Arteritis & Polymyalgia Rheumatica
- Novel Approaches -

HMS CME Course Internal Medicine: Comprehensive Review and Update 2022

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Disclosures

- Roche/Genentech, research support
- Kaniksa, consulting
- Janssen, consulting

I will be discussing “off-label” uses of the following medications:

- Methotrexate
- Ustekinumab
- Abatacept
- Mavrilimumab
- Secukinumab
- Upadacitinib
- Guselkumab

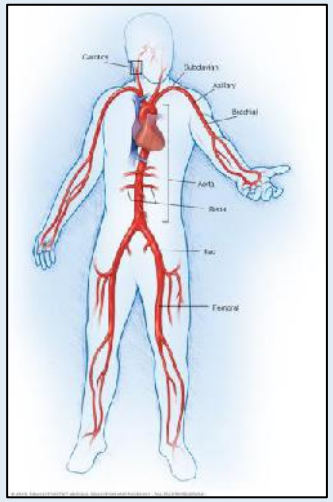
Objectives

- Review the epidemiology, clinical presentation, and diagnosis of giant cell arteritis (GCA) and polymyalgia rheumatica (PMR)
- Recognize the evidence supporting the standard of care for GCA and PMR
- Discuss recent treatment advances for GCA and PMR

GCA and PMR definition and epidemiology

GCA Definition

- Large / medium sized-vessel vasculitis
- Granulomatous inflammation
- Aorta and main aortic branches



PMR Definition

- Arthritis / periarthritis of the shoulder and hip girdles
  - Primary PMR
  - PMR associated with GCA

GCA Epidemiology

- Most common type of vasculitis in adults
- Elderly (peak age ~72 years)
- Caucasian population
- Lifetime risk 0.5% men - 1% women
- ~220,000 cases in the United States

PMR Epidemiology

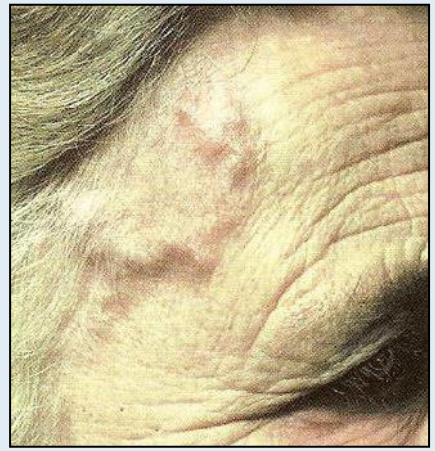
- Same as GCA
- 3 times more common than GCA
- Second most common rheumatic disease after rheumatoid arthritis

Salvarani at al. Nat Rev Rheumatol 2012

Clinical manifestations

- Cranial symptoms:
  - New onset headaches
  - Scalp tenderness
  - Jaw claudication
  - Temporal artery abnormalities
  - Visual symptoms (e.g., amaurosis fugax, episodic blurred vision, diplopia)
- Polymyalgia rheumatica (PMR)
  - 50-60% of GCA patients
  - 15% of primary PMR patients ”evolve” to GCA
- Constitutional symptoms
- Laboratory abnormalities (suggestive, but not specific)

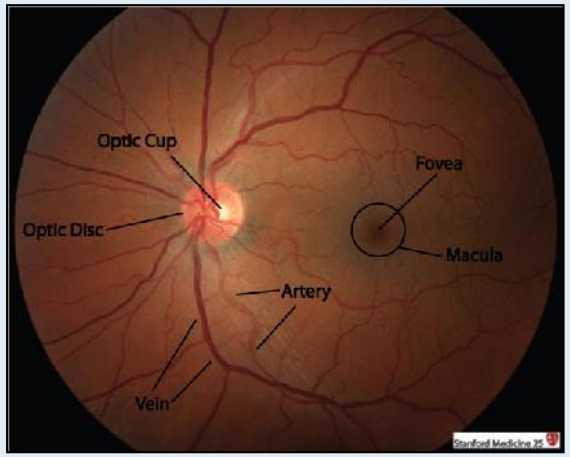
- Increased inflammatory markers (90-95%)
- Mild to moderate anemia, thrombocytosis, rarely leucocytosis

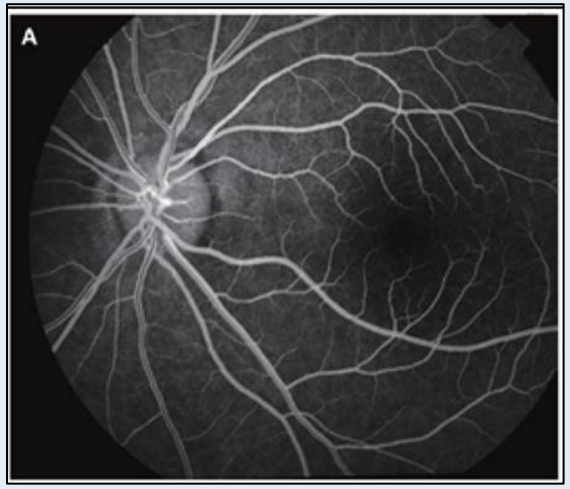


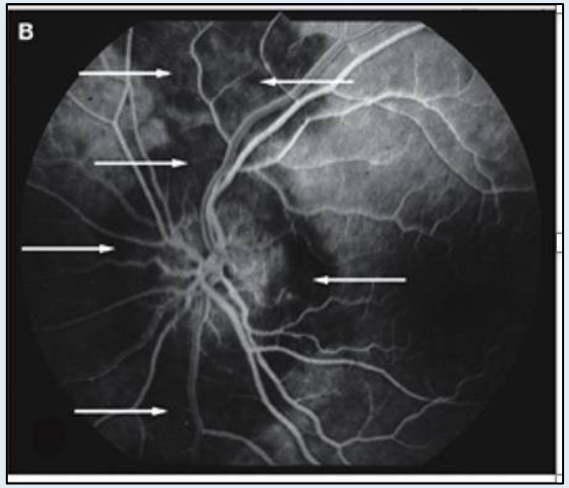
Salvarani at al. Nat Rev Rheumatol 2012

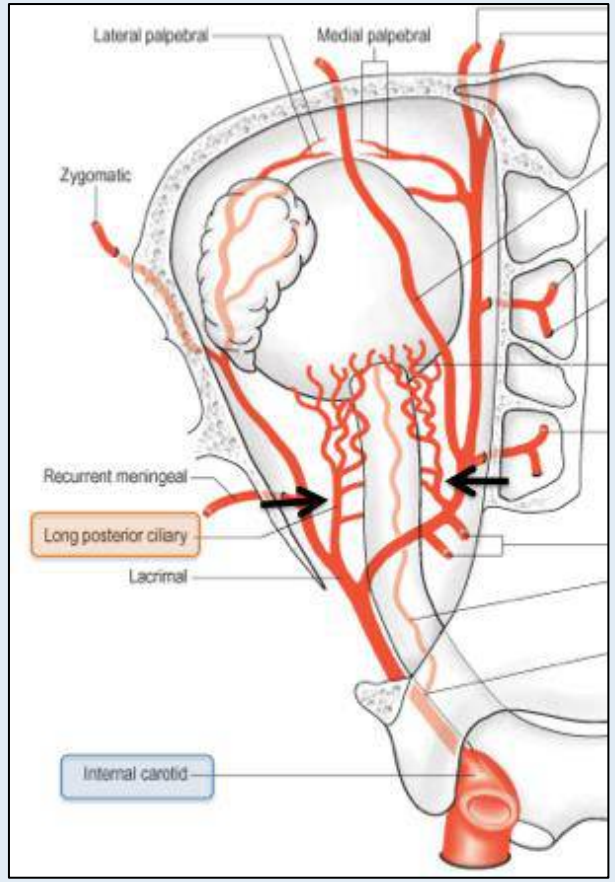
GCA diagnostic delay - Blindness 10-20%

Arteritic Anterior Ischemic Optic Neuropathy (A-AION)









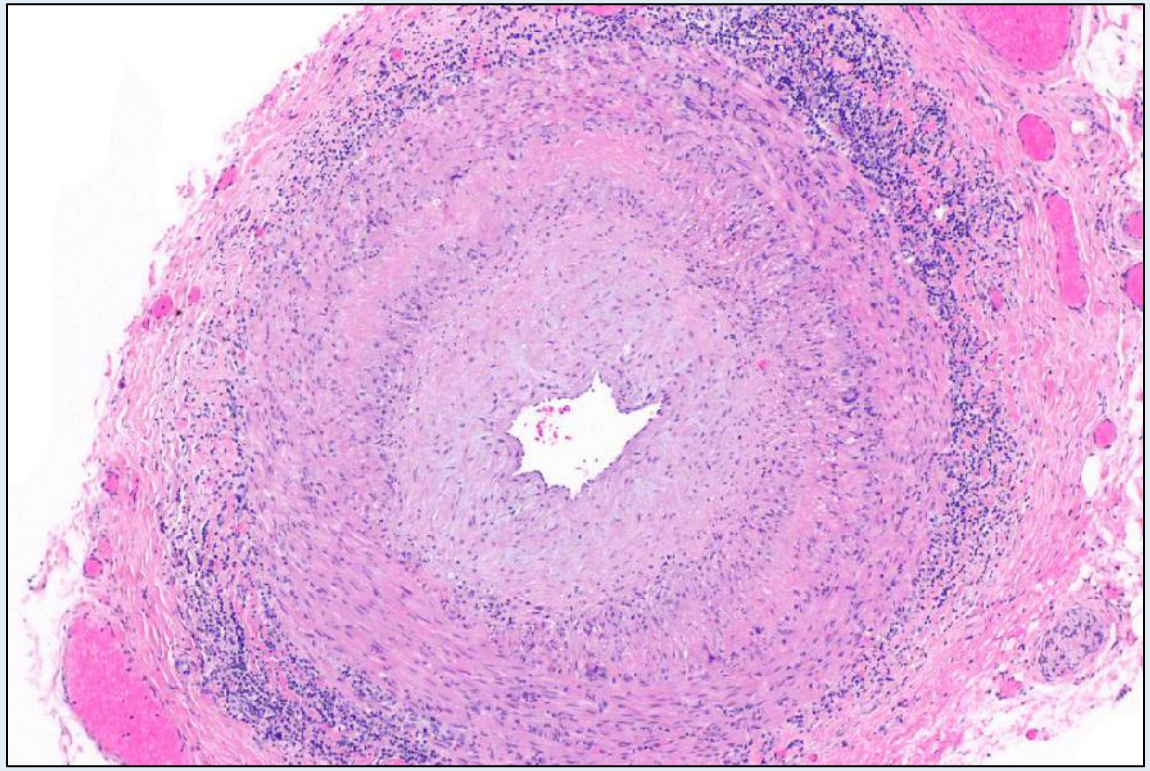
Occlusion of the long-posterior ciliary arteries (>90%)

GCA Diagnosis - Temporal artery biopsy

2021 American College of Rheumatology / Vasculitis Foundation Guideline for the Management of Giant Cell Arteritis and Takayasu Arteritis

Conditional recommendations

- Initial diagnostic test
- Unilateral over bilateral biopsies
- Length > 1 cm
- Within 2 weeks of starting glucocorticoids

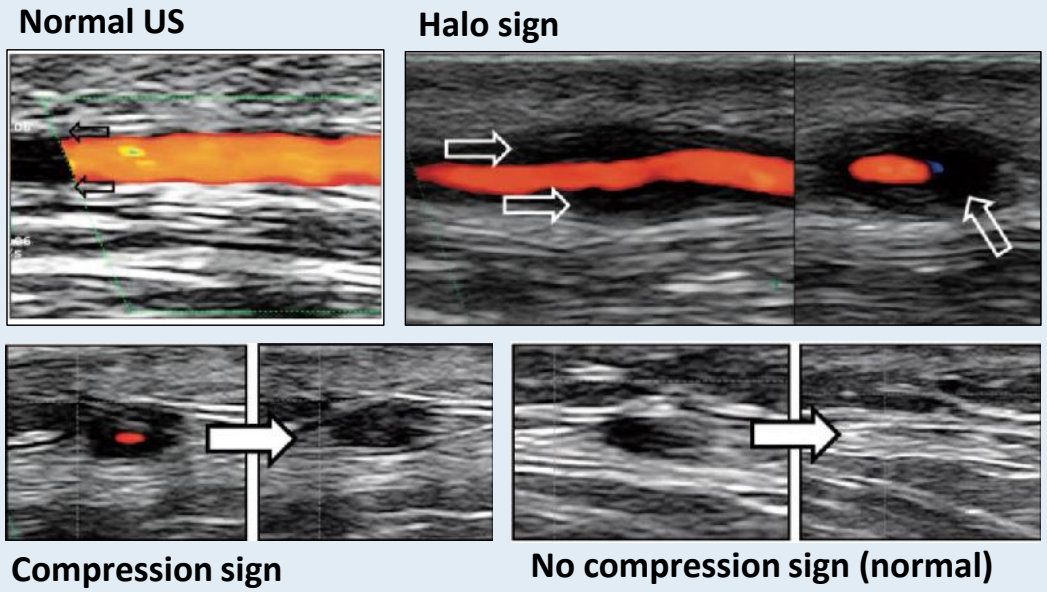


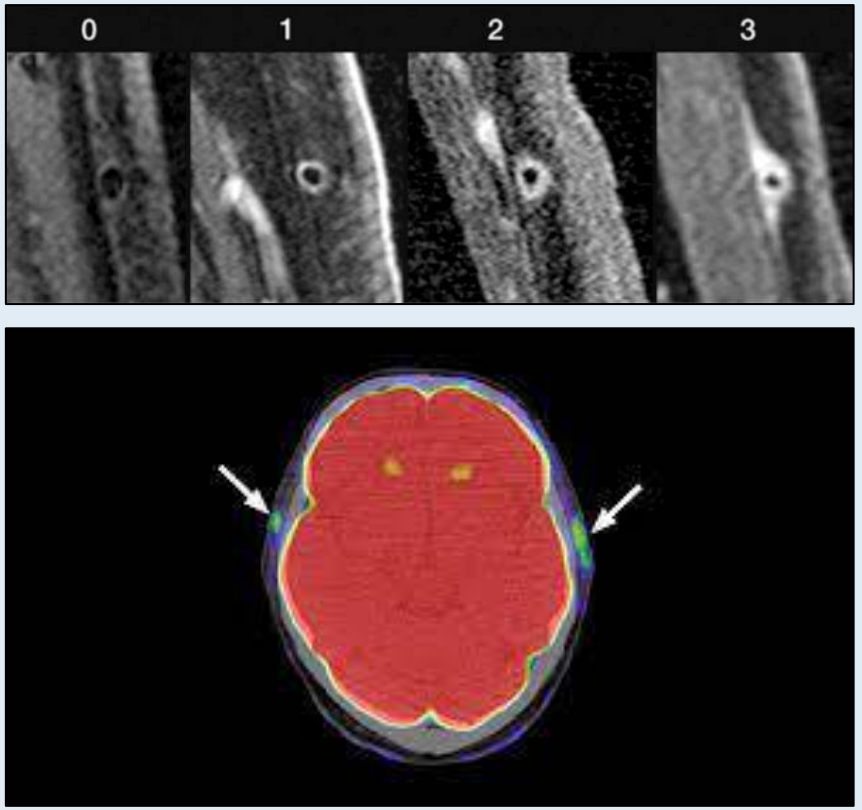
Maz et al. Arthritis Rheum 2021

GCA Diagnosis - Vascular imaging (extra-cranial arteries)

Superficial cranial arteries

- **Vascular ultrasound (US)** - Initial test recommended by the 2018 EULAR LVV imaging guidelines
- Magnetic resonance imaging (MRI)
- PET/CT



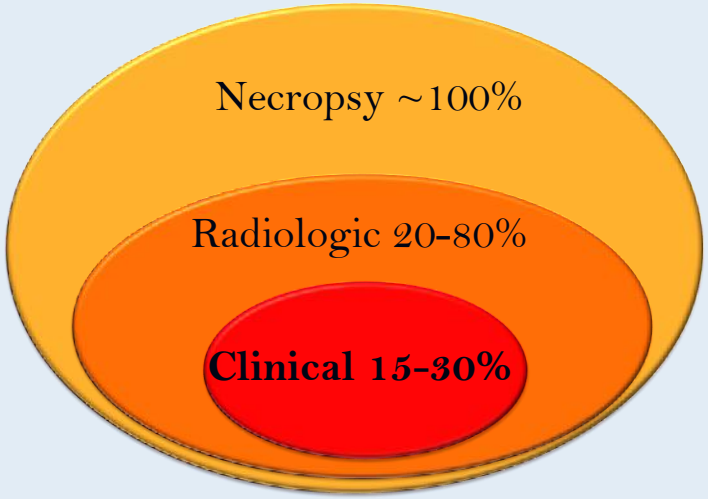


Dejaco et al. Ann Rheum Dis 2018

GCA Diagnosis - Vascular imaging (large arteries)

Large arteries

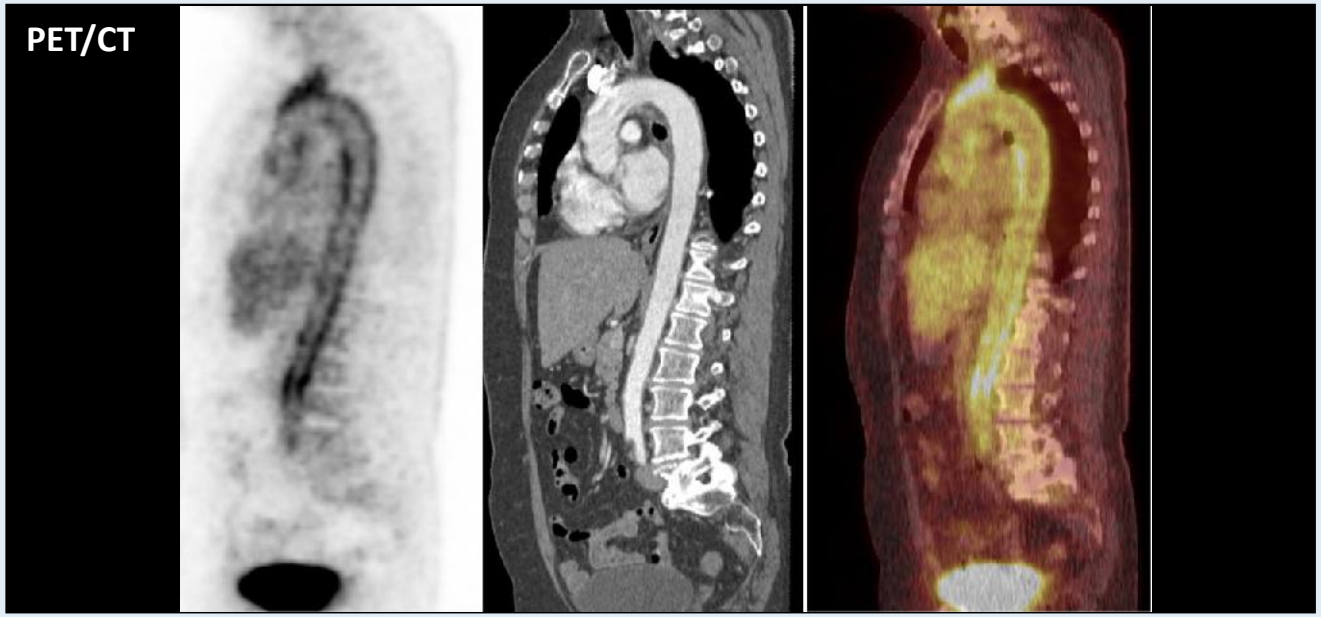
- Computed tomography angiography (CTA)
- MRI / MR angiography (MRA)
- Positron emission tomography (PET)
- PET/CTA and PET/MR
- Vascular ultrasound



Large vessel involvement

Radiologic lesions - "lumens and walls"

- Wall thickening, edema, contrast uptake and/or ^{18}F-FDG uptake
- Diffuse luminal stenosis, occlusion, and/or aneurysmal dilatation



Oseberg G. Acta Med Scan Suppl 1972; Kerman et al. Sem Arthritis Rheum 2018; Gonzalez-Gay et al. Medicine 2004; Nuenninghoff et al. Arthritis Rheum 2003; Garcia-Martinez et al. Arthritis Rheum 2008, Blockmans et al. Arthritis Rheum 2006; Garcia-Martinez et al. Ann Rheum Dis 2013

The diagnosis of primary PMR is clinical

2012 ACR/EULAR provisional classification criteria for PMR

Table 4 Scoring algorithm with and without optional ultrasound criterion—required criteria: age 50 years or greater, bilateral shoulder aching and abnormal CRP and/or ESR

	Clinical criteria (without ultrasound)*		Criteria including ultrasound†	
Criteria	Odds ratio (95% CI)	Points	Odds ratio (95% CI)	Points
Morning stiffness duration >45 min	6.2 (3.2 to 11.8)	2	5.0 (2.8 to 9.1)	2
Hip pain or limited range of motion	2.1 (1.1 to 4.0)	1	1.4 (0.8 to 2.6)	1
Absence of RF or ACPA	3.0 (1.3 to 6.8)	2	5.2 (2.1 to 12.6)	2
Absence of other joint pain	2.7 (1.4 to 5.0)	1	2.2 (1.3 to 4.0)	1
Ultrasound criteria				
At least one shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) and at least one hip with synovitis and/or trochanteric bursitis			2.6 (1.3 to 5.3)	1§
Both shoulders with subdeltoid bursitis, biceps tenosynovitis or glenohumeral synovitis			2.1 (1.2 to 3.7)	1¶

ACPA, anticitrullinated protein antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; CI, confidence interval.
*The optimal cut point is 4. A patient with a score of 4 or more is categorised as having polymyalgia rheumatica (PMR).
†The optimal cut point is 5. A patient with a score of 5 or more is categorised as having PMR.
§ $P = 0.008$.
¶ $P = 0.009$.

Cataratas del Iguazu
Misiones, Argentina

GCA TREATMENT

- Standard of care -

Treatment Quiz #1 - GCA

A 75 y/o patient with biopsy-confirmed GCA achieves clinical remission with prednisone 60 mg followed by taper. After 6 months of treatment, he now takes 7 mg/day of prednisone and reports renewed focal headache and PMR symptoms. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are elevated.

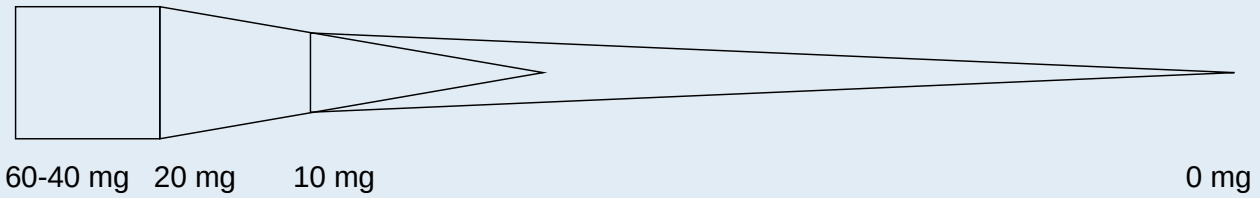
Your diagnosis is GCA relapse

What is your treatment recommendation?

A. Continue a slow prednisone taper by 1 mg every 4 weeks
B. Maintain the prednisone dose at 7 mg/day
C. Increase the prednisone dose to 40-60 mg/day
D. Increase the prednisone dose to 40-60 mg/day and add methotrexate
E. Increase the prednisone dose to 40-60 mg/day and add tocilizumab

Glucocorticoids for GCA

- Tapers over > 12 months
- Dose modification based on clinical disease activity
- Biomarkers to assess disease activity have limitations
- No standardized tapering regimen



~12-18 months, frequently more

Relapse rate in patients treated only with glucocorticoids

N/Follow-Up (years)	Relapse Rate	Relapse Definition	Author (design)
106/7.8	64%	Clinical ± APR	Alba (prospective)[1]
286/5.1	79%	Clinical or APR	Labarca (retrospective)[2]
157/6.7	36.5%	Clinical + APR	Restuccia (retrospective)[3]
75/~3.0	65.3%	Clinical ± APR	Hernandez-Rodriguez (retrospective)[4]

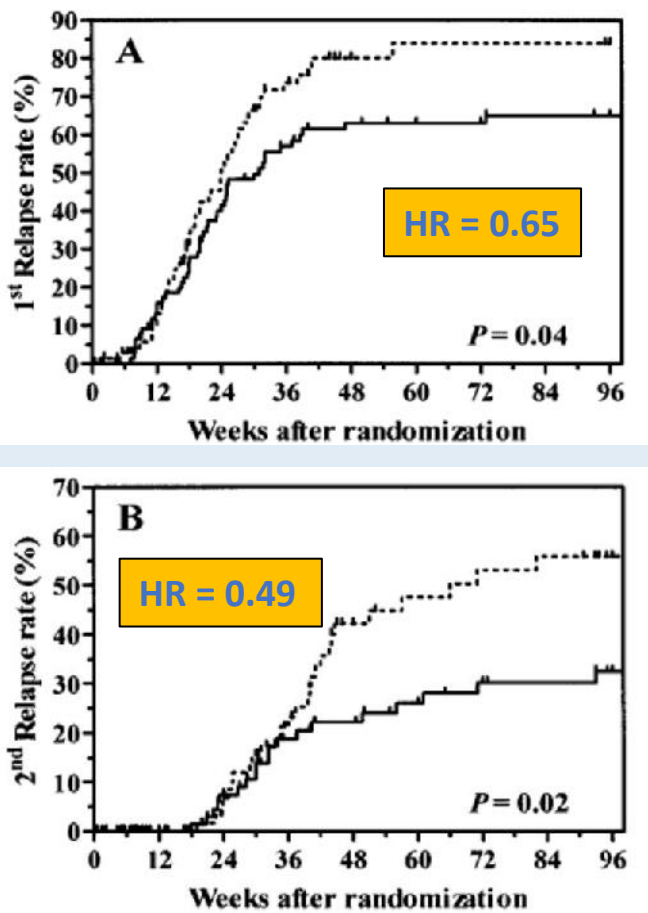
APR, acute phase reactants (C-reactive protein and erythrocyte sedimentation rate)

1. Alba MA et al. Medicine. 2014; 2. Labarca C et al. Rheumatology. 2016; 3. Restuccia G et al. Medicine. 2016; 4. Hernandez-Rodriguez J et al. Arthritis Rheum. 2002

Non-biologic immunosuppressants for GCA

1st relapse

2nd relapse



Mahr et al Arthritis Rheum 2007

Ineffective

- Azathioprine - DaSilva et al. Ann Rheum Dis 1986
- Cyclophosphamide - De Vita at al. Intern Med 1992
- Cyclosporine - Schaufelberger et al. Scand J Rheumatol 2006
- Leflunomide - Adizie et al. Int J Clin Pract 2021

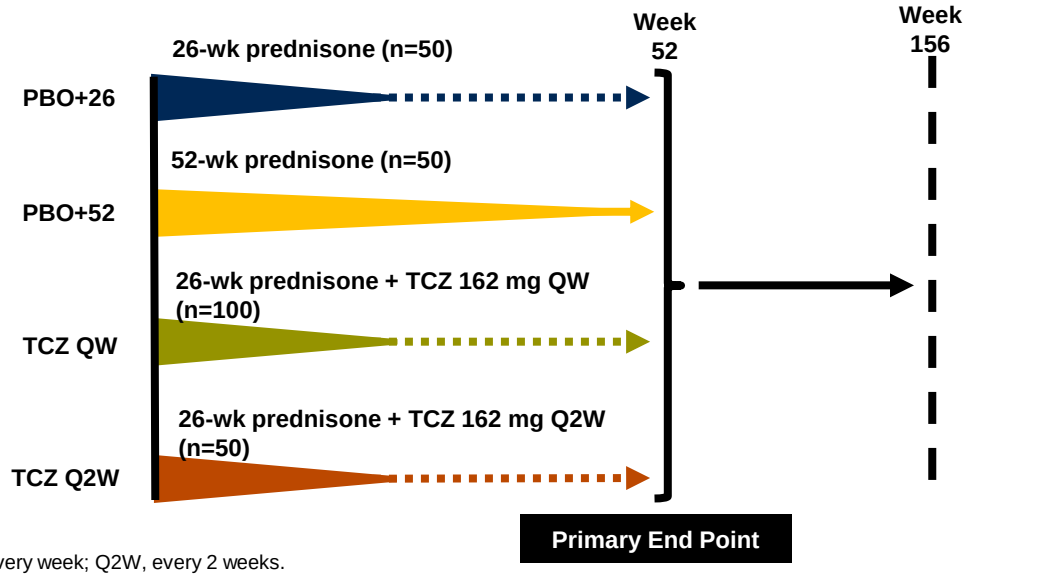
Partially effective

- Methotrexate

Spiera et al. Clini Exp Rheumatol 2001
Hoffman et al. Arthritis Rheum 2002
Jover et al. Medicine 2001

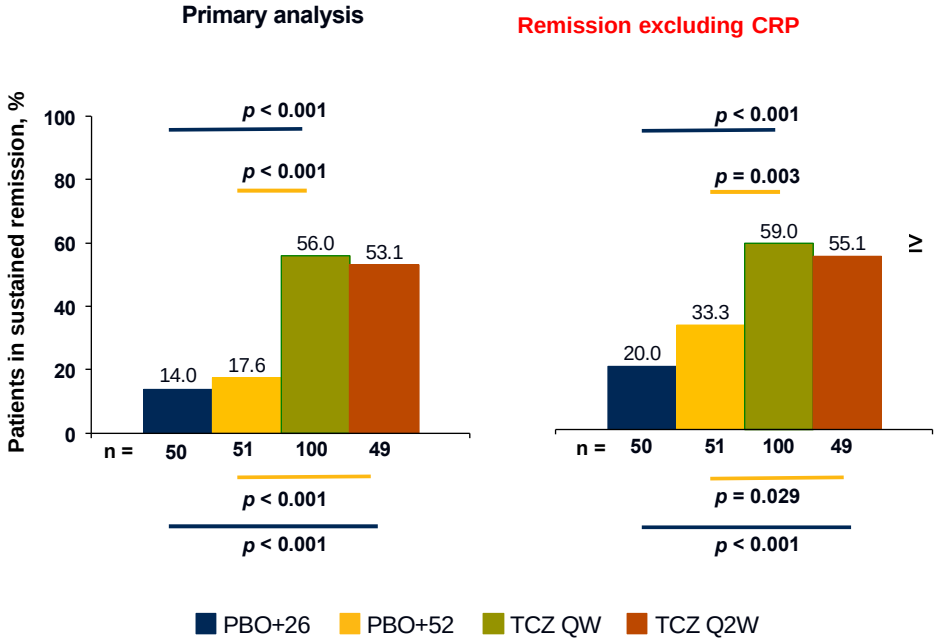
Tocilizumab (TCZ) - GiACTA study

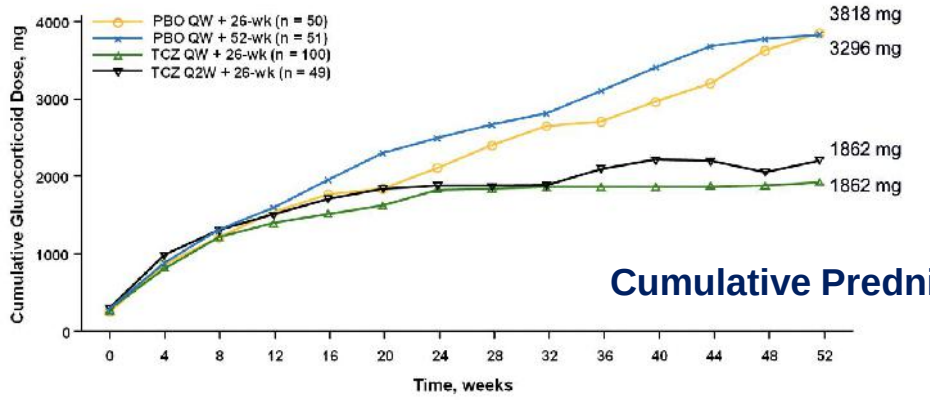
STUDY DESIGN



QW, every week; Q2W, every 2 weeks.

RESULTS - Sustained Remission



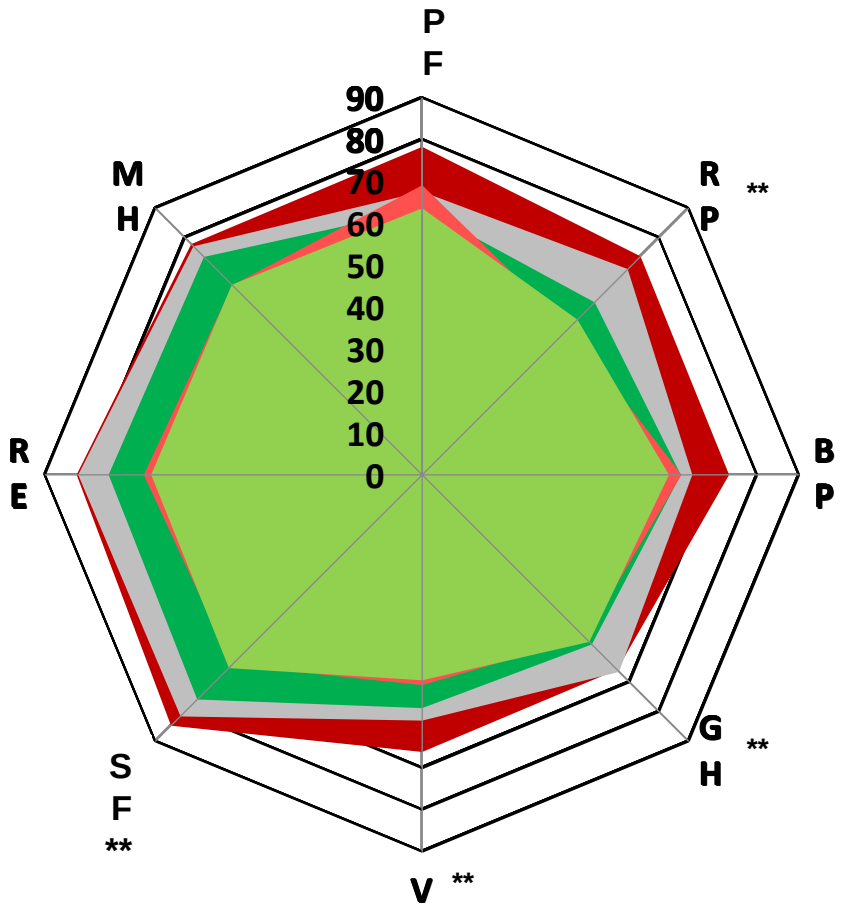


Cumulative Prednisone Dose

Stone et al. N Engl J Med. 2017

Health-related quality of life in GCA patients treated with TCZ

Short form (SF)-36 domain scores: TCZ QW vs PBO+26-week prednisone vs age-/gender-matched controls



BL, PBO+26 (n = 43)
BL, TCZ QW (n = 85)
Age-/gender-matched norms
Week 52, PBO+26 (n = 49-50)
Week 52, TCZ QW (n = 97-100)

BL, baseline

PF, physical function
RP, role physical
BP, bodily pain
GH, general health
V, vitality
SF, social function
RE, role emotional
MH, mental health

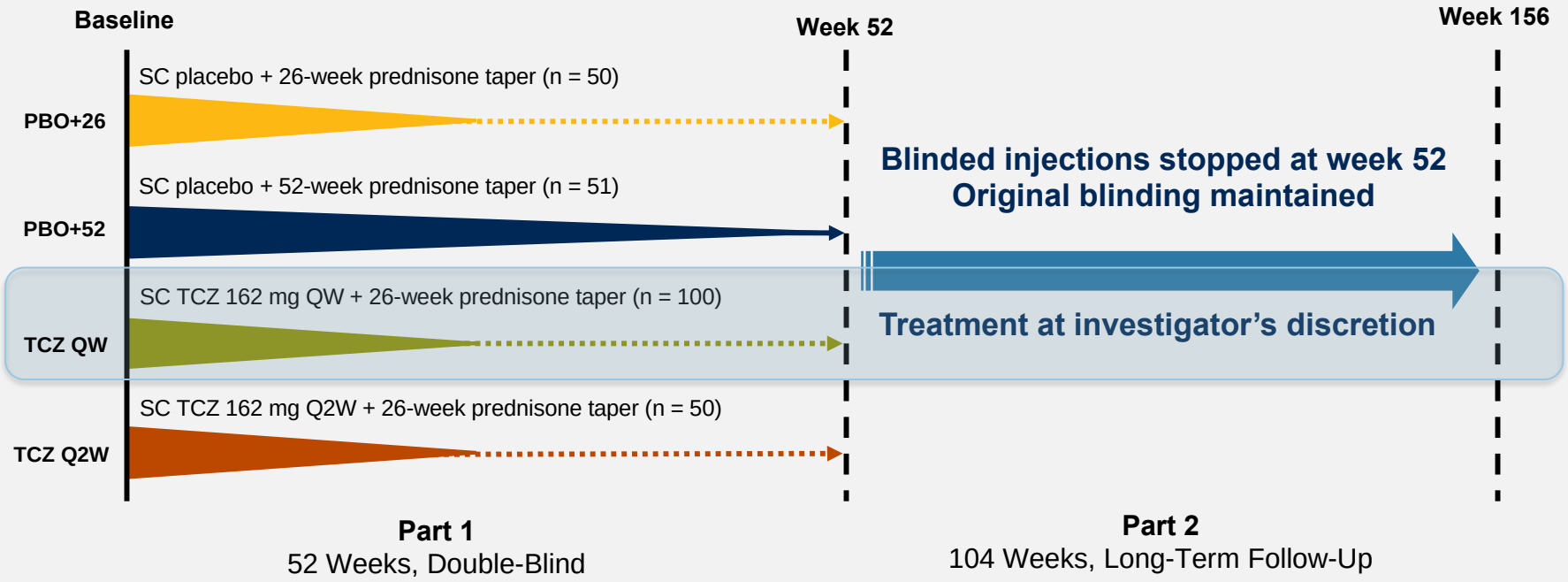
**$p < 0.01$

Strand et al. Arthritis Res Ther 2019

Durability of response to TCZ

Stone et al. Lancet Rheum 2021

Post hoc analysis of part 2 of the GiACTA trial



QW, every week; Q2W, every 2 weeks; SC, subcutaneous; TCZ, tocilizumab.

Weekly TCZ arm

85 patients entered Part 2, 81 were in clinical remission, and 59 were off treatment

- 25/59 (42%) maintained the treatment-free clinical remission for 2 years during Part 2

Aconcagua
Mendoza, Argentina

GCA TREATMENT

- Recent advances -

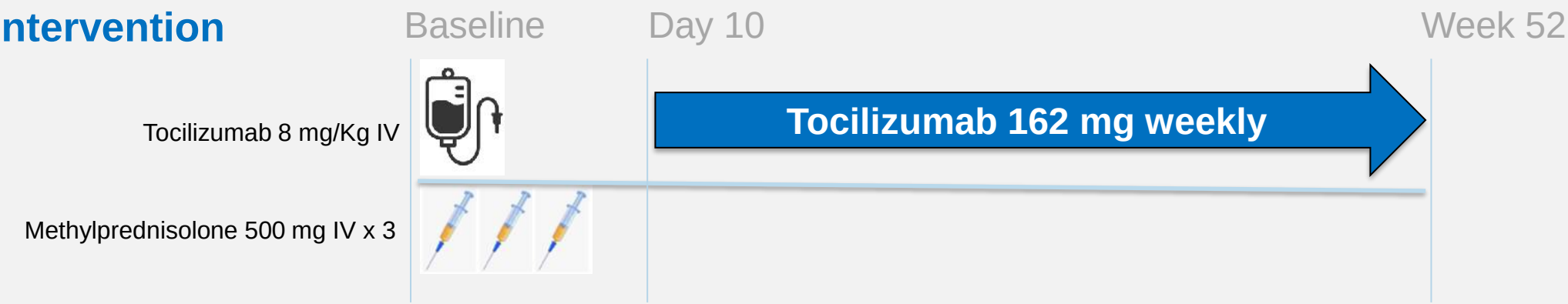
Is less than 6 months of prednisone possible in GCA?

TCZ plus ultra-short steroid course (GUSTO study)

DESIGN

- Prospective, single center, open-label trial of TCZ plus MP pulses for new-onset GCA pts with active disease

Intervention



Endpoints

- Primary endpoint: Remission by day 31 maintained through week 24
- Secondary endpoint: Relapse-free remission at week 52

Results

- 3/12 (25%)
- 13/18 (72%)

ClinicalTrials.gov Identifier: NCT03745586; EULAR 2021 (abstract)

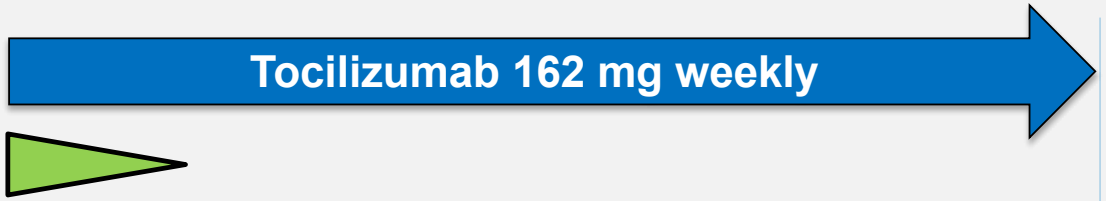
Is less than 6 months of prednisone possible in GCA?

TCZ plus 8 weeks of prednisone for GCA

DESIGN

- Prospective, single center, open-label trial of TCZ plus 8 weeks of prednisone for new onset / relapsing GCA patients with active disease

Intervention



8-week prednisone taper starting b/w 20 mg and 60 mg

Primary endpoint

- Prednisone-free remission at week 52

RESULTS

	GCA patients (n = 30)
Efficacy	
Sustained, prednisone-free remission by week 52	23.0 (76.7)
Cumulative prednisone dose (mg) at week 52, mean (SD)	1051.5 (390.3)
Relapse	7.0 (23.3)
Time to relapse, weeks: mean (SD)	15.8 (14.7)
Prednisone dose (mg/day) at relapse, mean (SD)	2.1 (5.2)
Cumulative prednisone dose (mg), mean (SD)	1883.1 (699.2)

ClinicalTrials.gov Identifier: NCT03726749 – PI Unizony

Pathophysiology and potential treatment targets

Agents under investigation

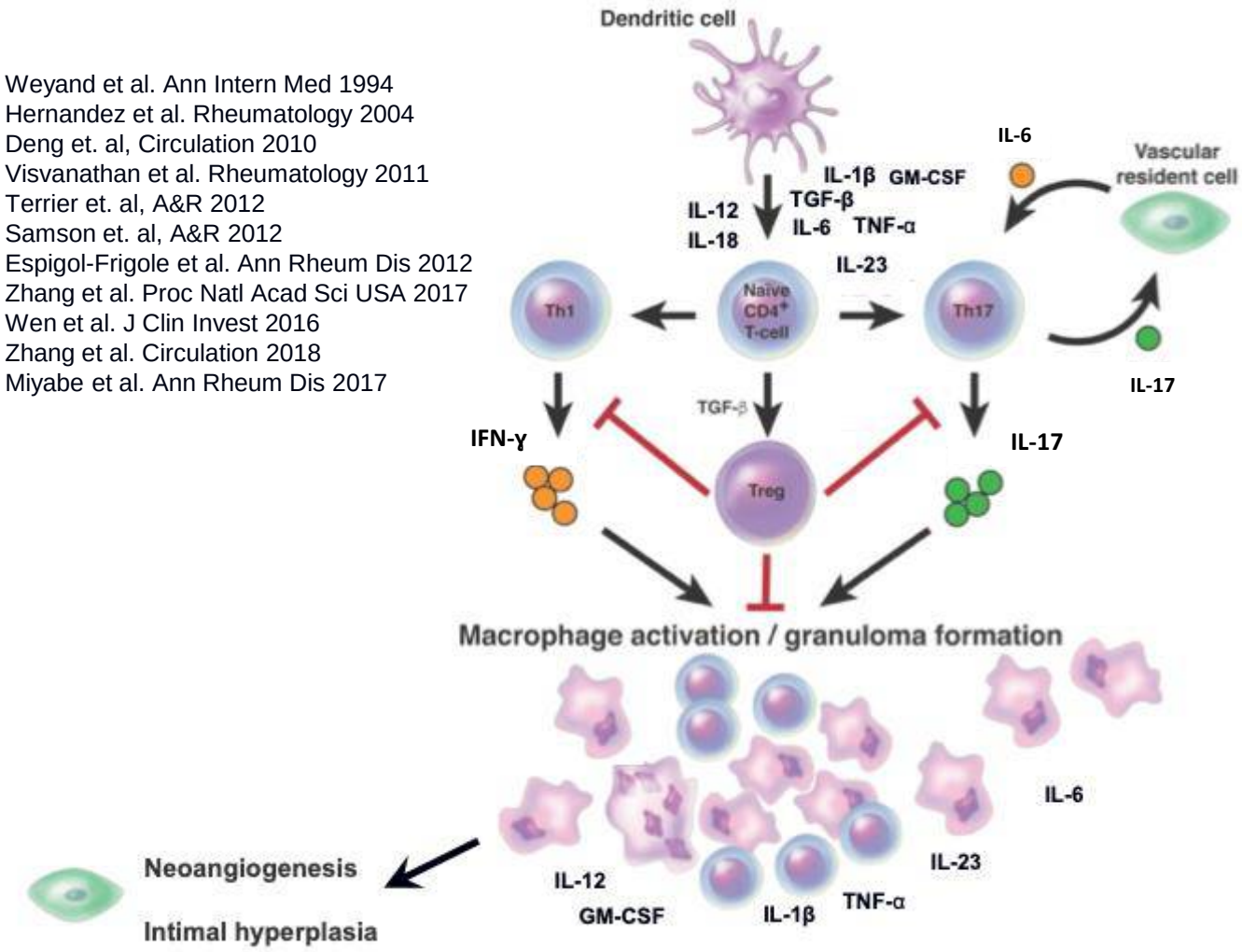
- Results available

- **Ustekinumab** (IL-12/23 p40) – Uncontrolled
- **Abatacept** (CD4⁺ T-cell co-stimulation) - Phase 2 RCT
- **Mavrilimumab** (GM-CSF) - Phase 2 RCT
- **Secukinumab** (IL-17) - Phase 2 RCT
- **Baricitinib** (JAK/STAT) – Uncontrolled
- **Sirukumab** (IL-6) - Phase 3 RCT terminated

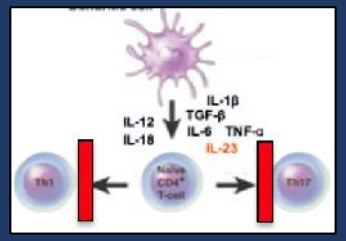
- No results available yet

- **Upadacitinib** (JAK/STAT) - Phase 3 RCT
- **Secukinumab** (IL-17) - Phase 3 RCT
- **Guselkumab** (IL-23 p19) - Phase 2 RCT

Weyand et al. Ann Intern Med 1994
Hernandez et al. Rheumatology 2004
Deng et. al, Circulation 2010
Visvanathan et al. Rheumatology 2011
Terrier et. al, A&R 2012
Samson et. al, A&R 2012
Espigol-Frigole et al. Ann Rheum Dis 2012
Zhang et al. Proc Natl Acad Sci USA 2017
Wen et al. J Clin Invest 2016
Zhang et al. Circulation 2018
Miyabe et al. Ann Rheum Dis 2017



Ustekinumab for GCA

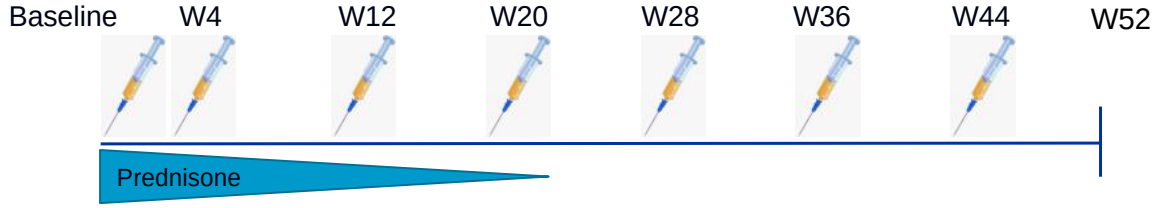


Irish study, Conway et al.

- UST 90 mg SQ at week 0, week 4, and Q3 months
- **No relapses seen over 52 weeks**
- **Prednisolone discontinuation not required**
- **75% of patients were still on prednisone (median dose 5 mg/day) by week 52**

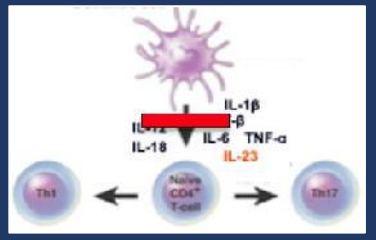
MGH study, Matza et al.

- UST 90 mg SQ at week 0, week 4, and Q2 months
- **>50% of the patients relapsed over 52 weeks**
- **Prednisone taper over 6 months per protocol**



Conway et al. Semin Arthritis Rheum 2018, Matza et al. Arthritis Care Res (Hoboken). 2020

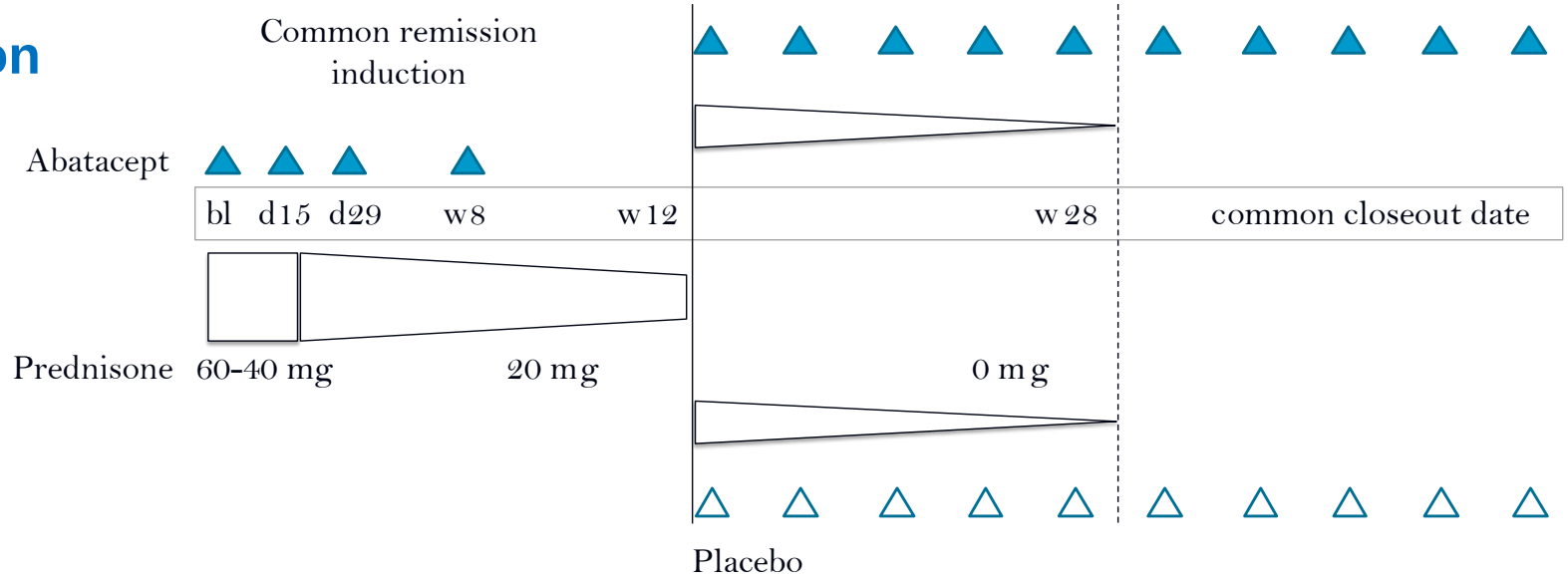
Abatacept for GCA



DESIGN

- Phase II, randomized, double-blind, placebo-controlled trial – withdrawal randomization

Intervention



Primary endpoint

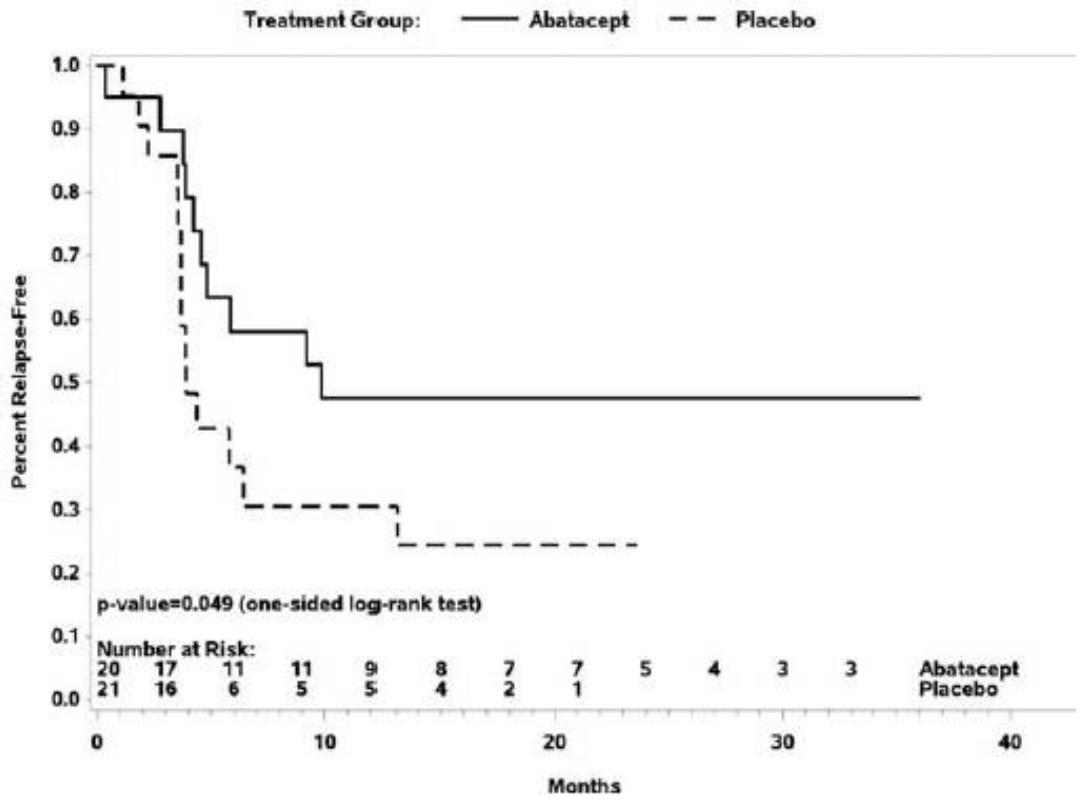
- Relapse-free survival (duration of remission)

Langford et al. Arthritis Rheum 2017

Abatacept for GCA

RESULTS

- Efficacy



Relapse-free survival at 12 months

Abatacept 48%, Placebo 31% (P = 0.049)

Median duration of remission

Abatacept 9.9 months, Placebo 3.9 months (P = 0.023)

Langford et al. Arthritis Rheum 2017

GM-CSF biology

GM-CSF

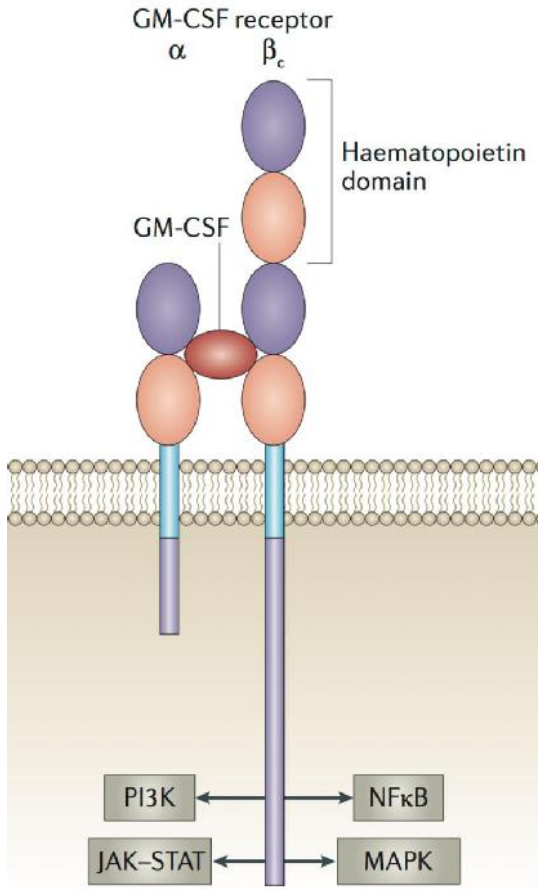
- Colony-stimulating factor (CSF) family of hematopoietic growth factors

Sources

- B and T cells
- Dendritic cells (DC)
- NK cells
- Myeloid cells (monocytes/macrophages, neutrophils)
- Tissue resident cells (endothelium, fibroblasts, VSMCs)

Functions

- Bone marrow stimulation of the myeloid linage
- DC maturation and differentiation
- Macrophage activation and function
- Myeloid-cell trafficking
- Angiogenesis
- Neutrophil priming, activation and function
- B cell IgM production
- Nociception



Wicks and Roberts. Nat Rev Rheumatol 2016

GM-CSF in GCA

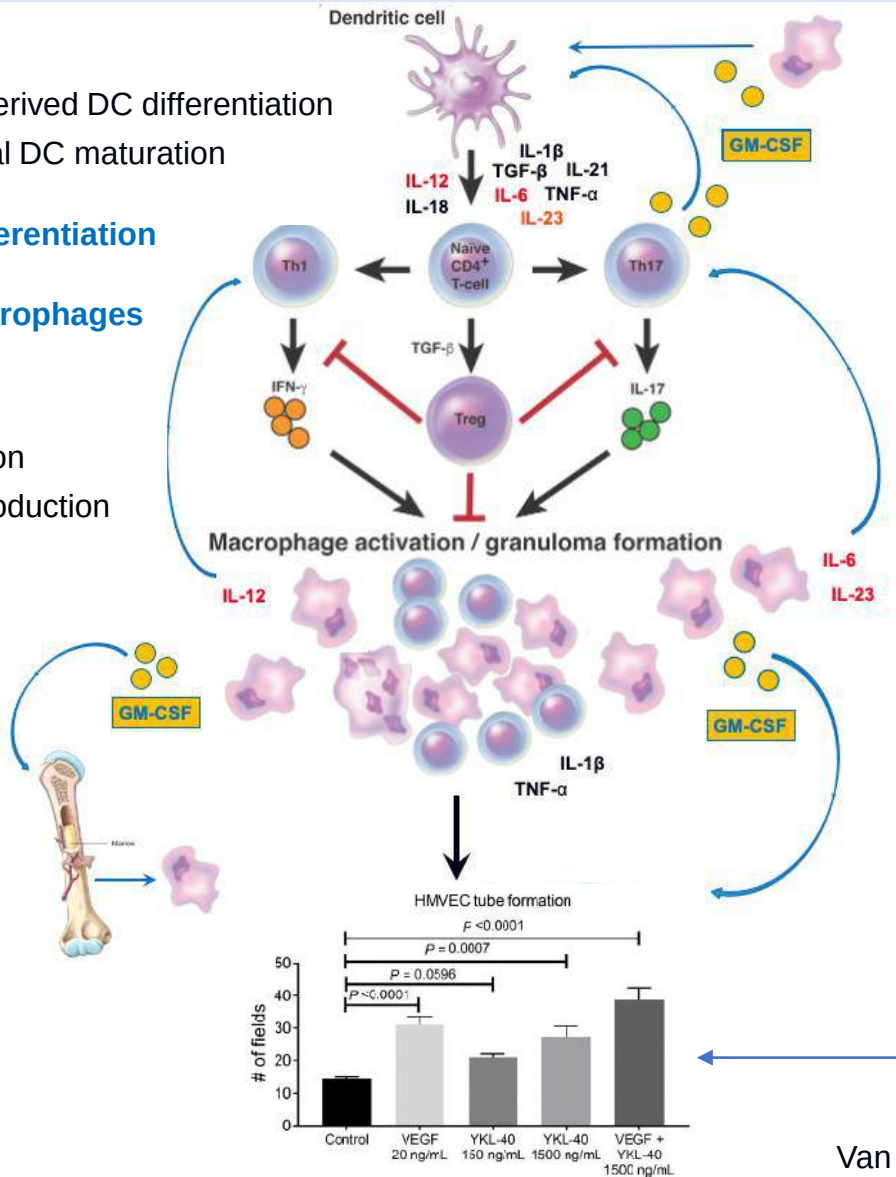
Dendritic cells

- Monocyte-derived DC differentiation
- Conventional DC maturation

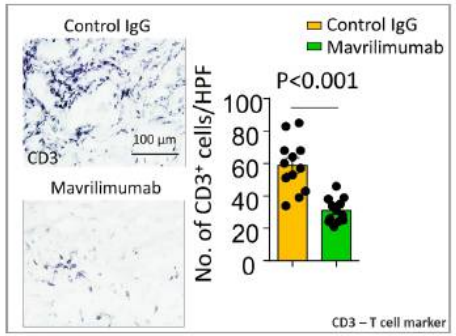
CD4 T-cell differentiation

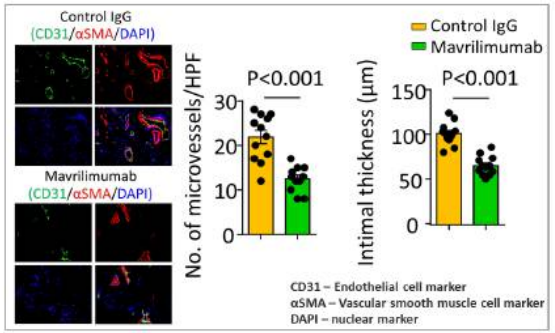
Monocyte/Macrophages

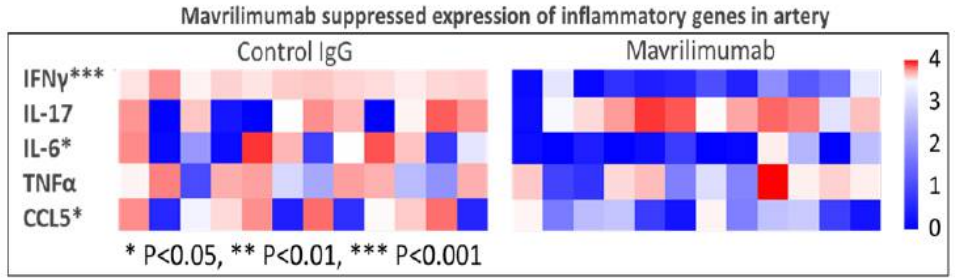
- Proliferation
- Survival
- Differentiation
- Cytokine production
- Trafficking



GM-CSF is pathogenic in a translational model of vasculitis

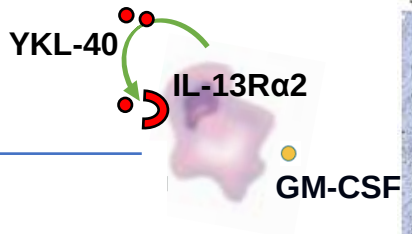


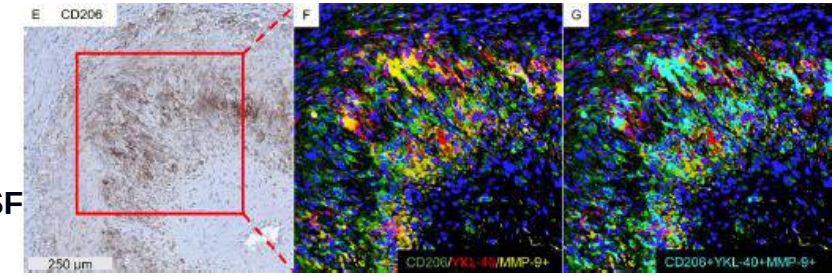




Watanabe et al. ACR 2019

GM-CSF induces expression of YKL-40 and MMP-9 in macrophages



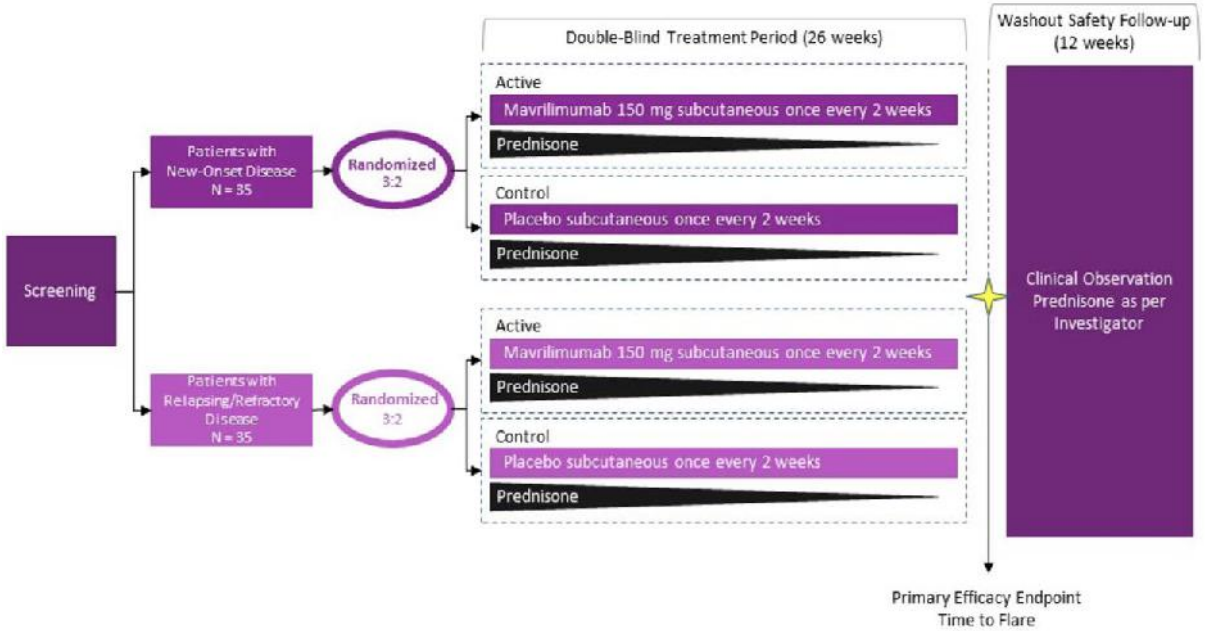


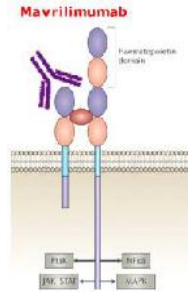
Van Sleen et al. Arthritis Rheum 2021

Phase 2 trial of Mavrilimumab for GCA

DESIGN

- Phase II, randomized, double-blind, placebo-controlled trial





Study Population
- Positive temporal artery biopsy or vascular imaging
- Active disease within 6 weeks of randomization
- Glucocorticoid-induced remission by day 0

- **Primary endpoint:** Time to adjudicated flare within 26 weeks

  Definition: ESR or CRP elevation plus clinical cranial or extra-cranial manifestations or new/worsening vasculitis captured by imaging

- **Key secondary endpoint:** Sustained Remission at week 26

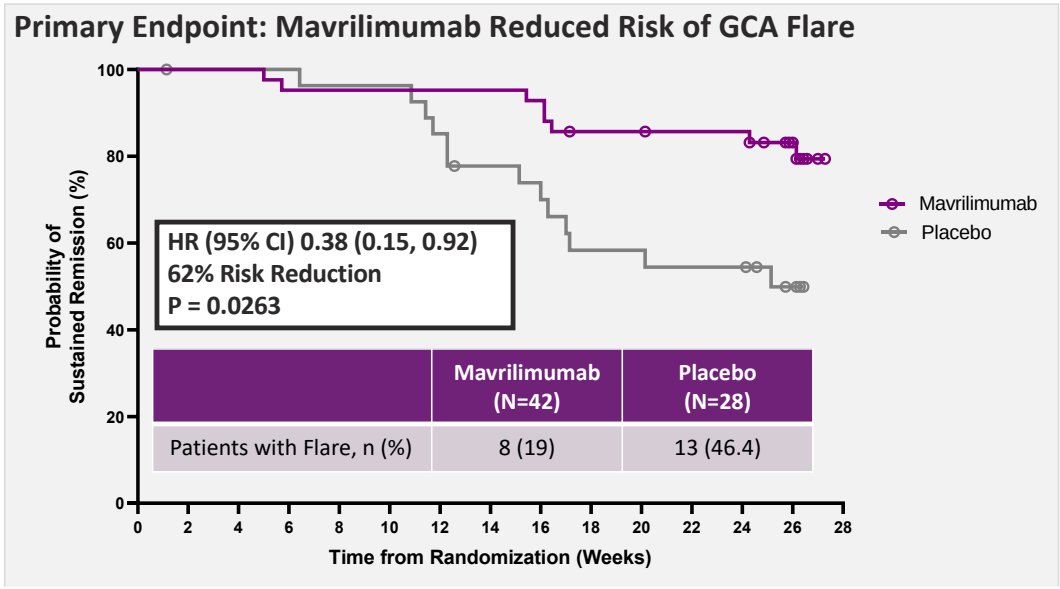
  Definition: absence of flare from baseline through week 26

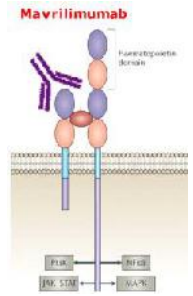
Cid M*, Unizony S* et al. Ann Rheum Dis 2022. * co-principal investigators

Phase 2 trial of Mavrilimumab for GCA

RESULTS

- **Efficacy**





Cid M*, Unizony S* et al. Ann Rheum Dis 2022. * co-principal investigators

Phase 2 trial of Mavrilimumab for GCA

RESULTS

- **Safety**

Table 4 Treatment-emergent adverse events

Adverse events	Mavrilimumab* (N=42)	Placebo (N=28)
Patients with ≥1 adverse event	33 (78.6%)	25 (89.3%)
Serious adverse event	2 (4.8%)	3 (10.7%)
Serious adverse event related to study drug	0	0
Adverse event resulting in death	0	0
Adverse event leading to study drug discontinuation	1 (2.4%)	1 (3.6%)
Adverse events by maximum severity†		
Mild	18 (42.9%)	13 (46.4%)
Moderate	14 (33.3%)	11 (39.3%)
Severe	1 (2.4%)	1 (3.6%)
Most common adverse events‡		
Headache	6 (14.3%)	7 (25.0%)
Nasopharyngitis	5 (11.9%)	3 (10.7%)
Neck pain	4 (9.5%)	2 (7.1%)
Arthralgia	2 (4.8%)	4 (14.3%)
Hypertension	1 (2.4%)	4 (14.3%)
Back pain	3 (7.1%)	3 (10.7%)
Muscle spasms	3 (7.1%)	3 (10.7%)
Upper respiratory tract infection	3 (7.1%)	2 (7.1%)
Constipation	3 (7.1%)	0
Diarrhoea	0	3 (10.7%)
Fall	2 (4.8%)	5 (17.9%)

- Rates of AEs were similar across treatment groups
- No drug-related SAEs
- No deaths, alveolar proteinosis or vision loss occurred during the trial

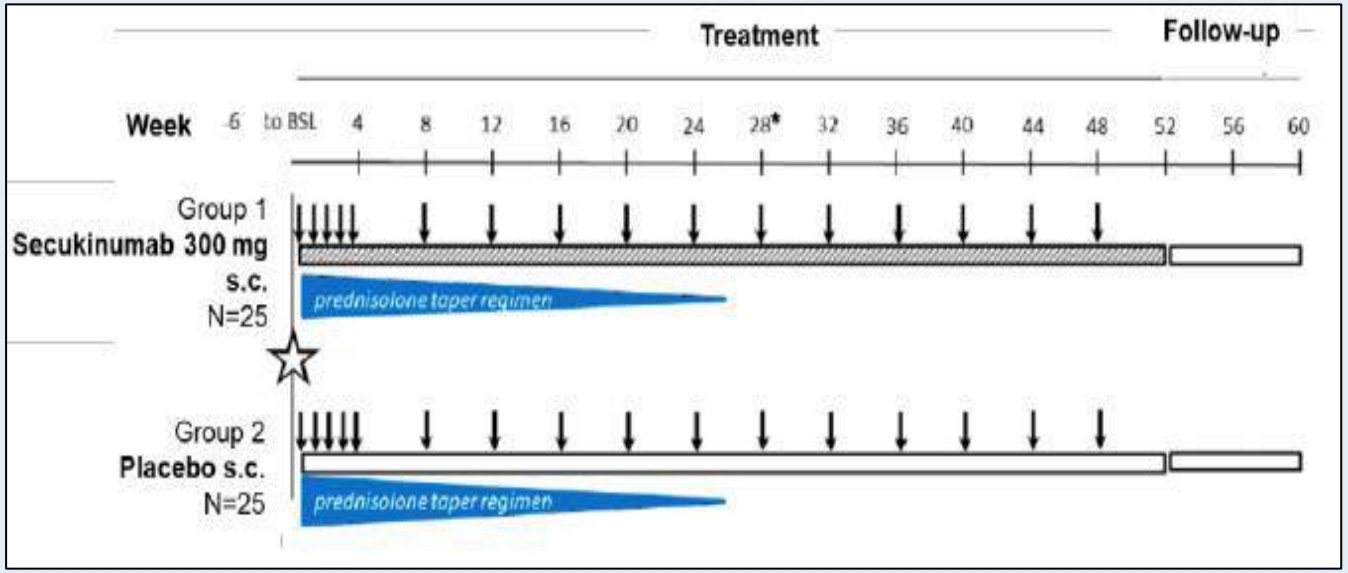
Cid M*, Unizony S* et al. Ann Rheum Dis 2022. * co-principal investigators

Phase 2 trial of Secukinumab for GCA

DESIGN

- Phase II, randomized, double-blind, placebo-controlled trial for patients with new-onset / relapsed GCA (N = 36)

Intervention



Experimental arm
Secukinumab (SEC) + 28 weeks of prednisone

Control arm
Placebo (PBO) + 28 weeks of prednisone

Primary endpoint

- Remission at 28 weeks

Secondary endpoints

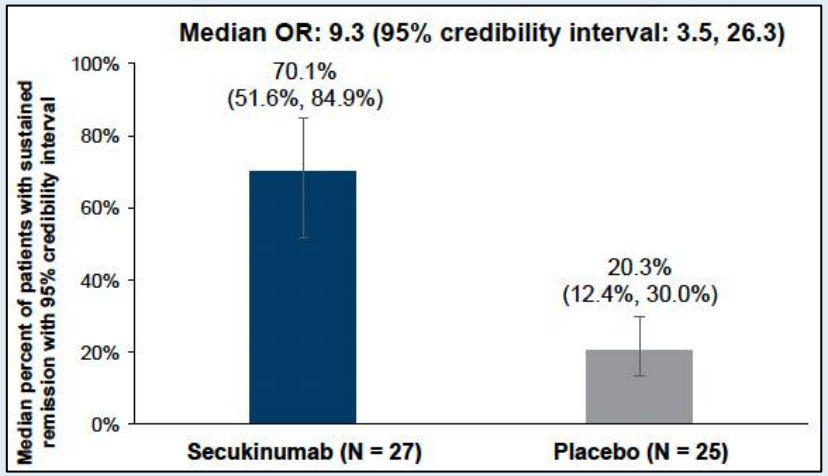
- Remission at 52 weeks
- Time to flare
- Cumulative prednisone dose at 52 weeks
- Safety

Venhoff et al. ACR 2021. ClinicalTrials.gov Identifier: NCT03765788

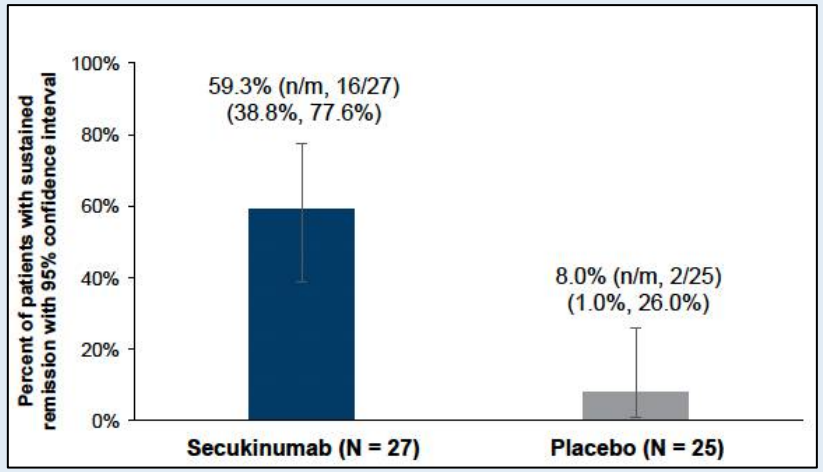
Results

- 27 patients received SEC and 25 patients received PBO

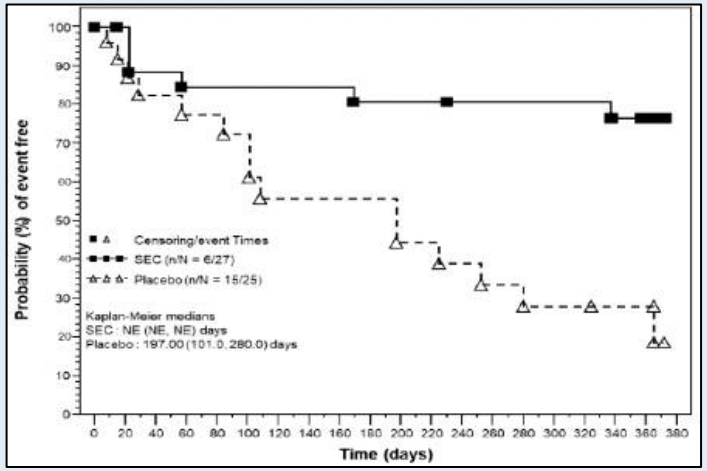
Primary endpoint (SR at 28 weeks)



SR at 52 weeks



Time to flare



Prednisone use

Time period	Secukinumab (N = 27)	Placebo (N = 25)
Baseline to Week 28 (mg), mean (SD)	2689.70 (935.860)	2693.74 (1241.907)
Baseline to Week 52 (mg), mean (SD)	2841.26 (1116.192)	3375.58 (1720.978)

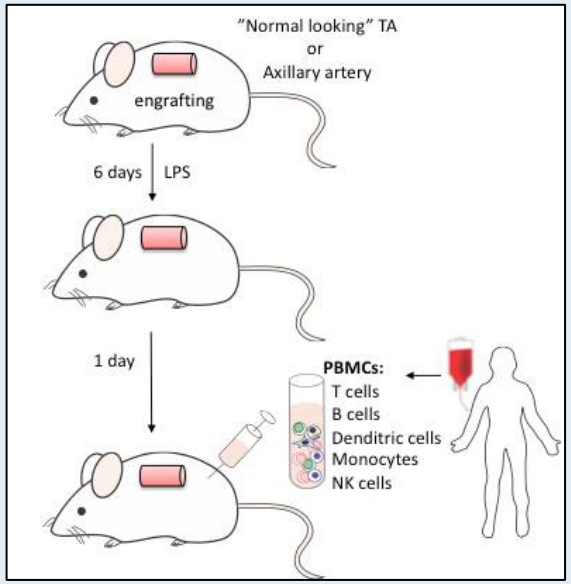
Venhoff et al. ACR 2021. ClinicalTrials.gov Identifier: NCT03765788

JAK/STAT inhibition in GCA

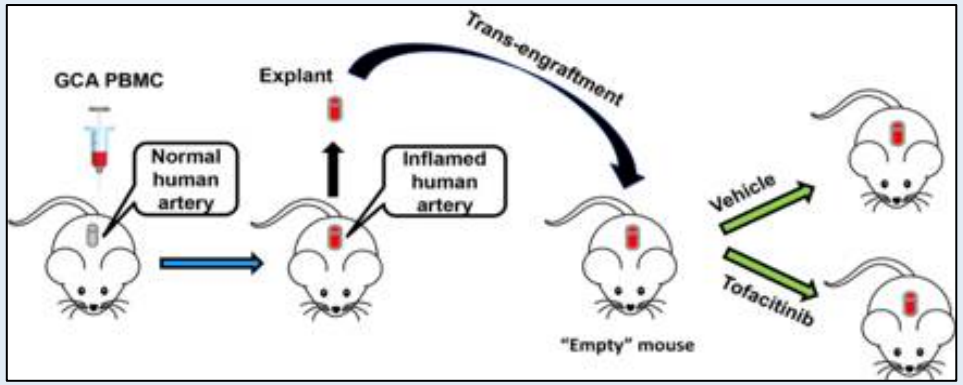
Circulation

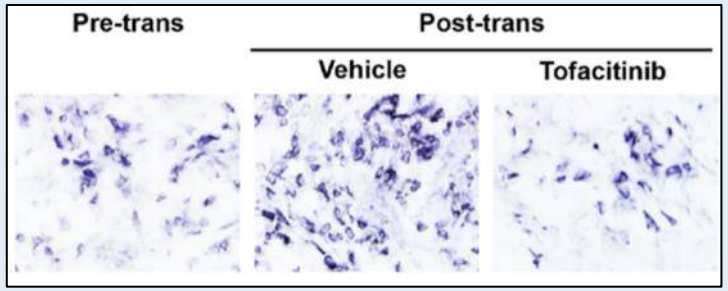
ORIGINAL RESEARCH ARTICLE

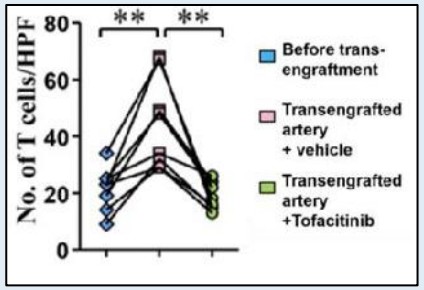
Inhibition of JAK-STAT Signaling Suppresses Pathogenic Immune Responses in Medium and Large Vessel Vasculitis



Human Artery–Severe Combined Immunodeficiency Mouse Chimeras







Zhang et al. Circulation 2018

POSTER SESSION C

1396. Baricitinib in Relapsing Giant Cell Arteritis: A Prospective Open-Label Single-Institution Study

Matthew Koster, MD
Mayo Clinic
Dr.

ClinicalTrials.gov Identifier: NCT03026504

N = 15
- 1 patient withdrawn
- 1 patients relapsed
- 13 patients maintained remission through week 52
- 1 patient had a SAE (thrombocytopenia)
- No MACE, malignancy or VTE

Pathophysiology and potential treatment targets

Agents under investigation

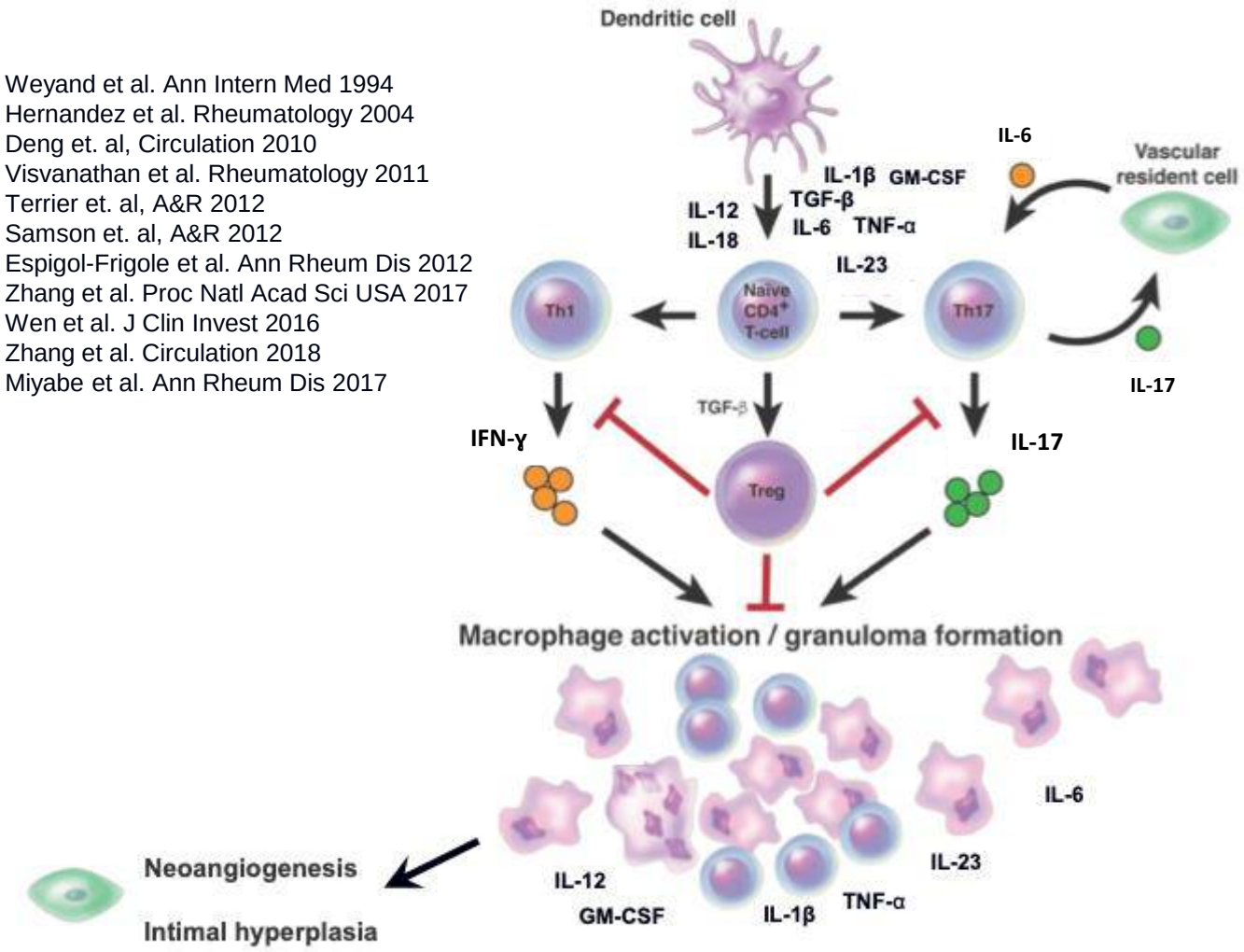
- Results available

- **Ustekinumab** (IL-12/23 p40) – Uncontrolled
- **Abatacept** (CD4⁺ T-cell co-stimulation) - Phase 2 RCT
- **Mavrilimumab** (GM-CSF) - Phase 2 RCT
- **Secukinumab** (IL-17) - Phase 2 RCT
- **Baricitinib** (JAK/STAT) – Uncontrolled
- **Sirukumab** (IL-6) - Phase 3 RCT terminated

- No results available yet

- **Upadacitinib** (JAK/STAT) - Phase 3 RCT
- **Secukinumab** (IL-17) - Phase 3 RCT
- **Guselkumab** (IL-23 p19) - Phase 2 RCT

Weyand et al. Ann Intern Med 1994
Hernandez et al. Rheumatology 2004
Deng et. al, Circulation 2010
Visvanathan et al. Rheumatology 2011
Terrier et. al, A&R 2012
Samson et. al, A&R 2012
Espigol-Frigole et al. Ann Rheum Dis 2012
Zhang et al. Proc Natl Acad Sci USA 2017
Wen et al. J Clin Invest 2016
Zhang et al. Circulation 2018
Miyabe et al. Ann Rheum Dis 2017



GCA Guidelines - ACR/VF

2021 ACR / Vasculitis Foundation

- New-onset disease: Glucocorticoids plus tocilizumab
- Relapse on moderate to high dose glucocorticoids: Add tocilizumab
- Relapse with cranial or ischemic symptoms: Add tocilizumab
- Relapse with PMR symptoms: No formal recommendations
- Active large-vessel involvement: Glucocorticoids plus tocilizumab

Note:

MTX or abatacept are options in case of tocilizumab inefficacy, side-effects or accessibility barriers (e.g., cost)

Maz et al. Arthritis Rheum 2021

Glaciar Perito Moreno
Chubut (Patagonia), Argentina

PMR treatment

Treatment Quiz #2 - PMR

A 73 y/o patient with PMR achieves clinical remission with prednisone 15 mg followed by taper. After 6 months of treatment, he now takes 5 mg/day of prednisone and reports renewed PMR symptoms. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are elevated.

Your diagnosis is GCA relapse

What is your treatment recommendation?

A. Continue a slow prednisone taper by 1 mg every 4 weeks
B. Maintain the prednisone dose at 5 mg/day
C. Increase the prednisone dose to 10-15 mg/day
D. Increase the prednisone dose to 10-15 mg/day and add methotrexate
E. Increase the prednisone dose to 10-15 mg/day and add tocilizumab

PMR treatment - Glucocorticoids

- Initial dose is typically 15 mg/day
- No standardized tapering regimen
- Tapers over > 12 months

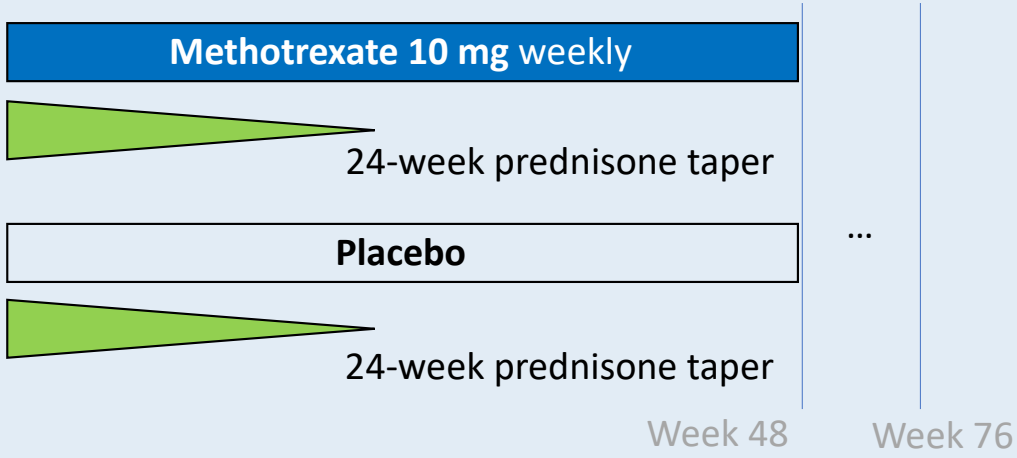
- >60% of patients relapse upon tapering the glucocorticoids
- Biomarkers to assess disease activity have limitations
- Dose modification based on clinical disease activity
- Glucocorticoid-related toxicity in 65%

Methotrexate for PMR

DESIGN

- Phase II, randomized, double-blind, placebo-controlled trial for patients with new-onset PMR (N = 72)

Intervention

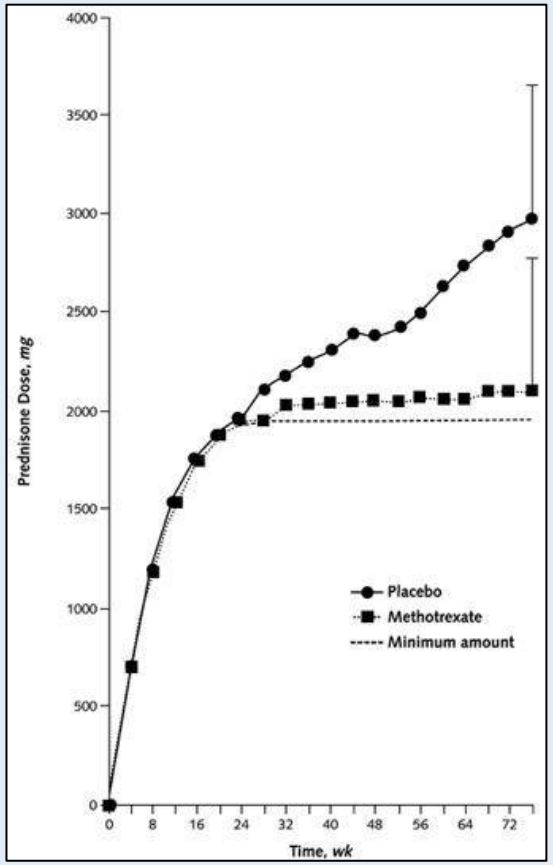


Endpoint

- Proportion of patients off prednisone at week 76
- Relapse
- Cumulative prednisone dose at week 76

Results

- 87.5% versus 53.3%
- 47% versus 73%
- ~2.1 gr versus ~3 gr



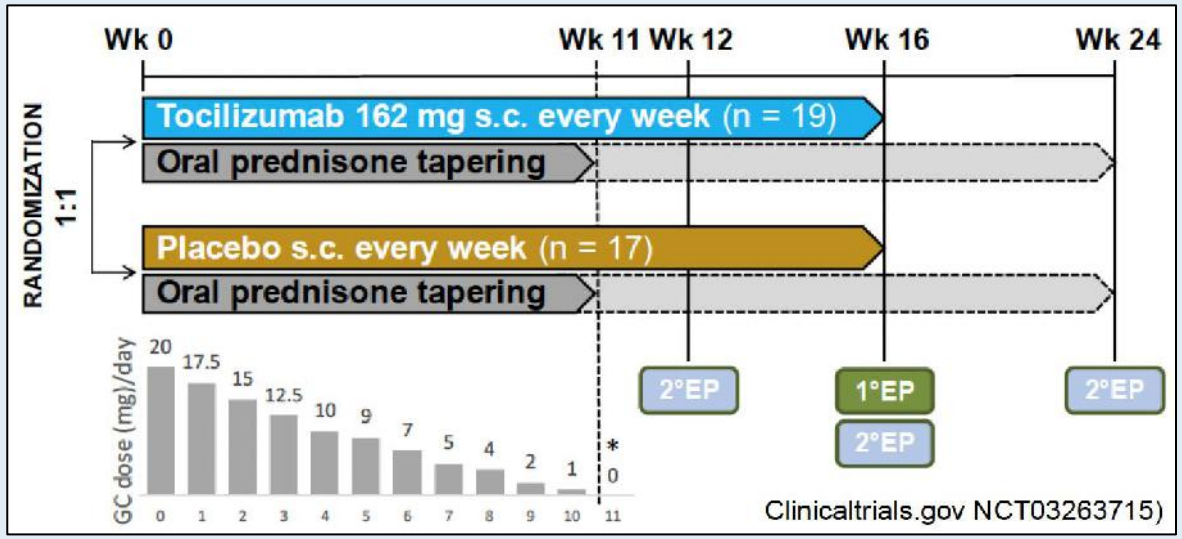
Caporali et al. Ann Intern Med 2004

Tocilizumab for PMR

DESIGN

- Phase II/III, randomized, double-blind, placebo-controlled trial for patients with new-onset PMR (N = 36)

Intervention



Experimental arm

Tocilizumab (TCZ) + 11 weeks of prednisone

Control arm

Placebo (PBO) + 11 weeks of prednisone

Primary endpoint

- Glucocorticoid (GC)-free remission at 16 weeks

Secondary endpoints

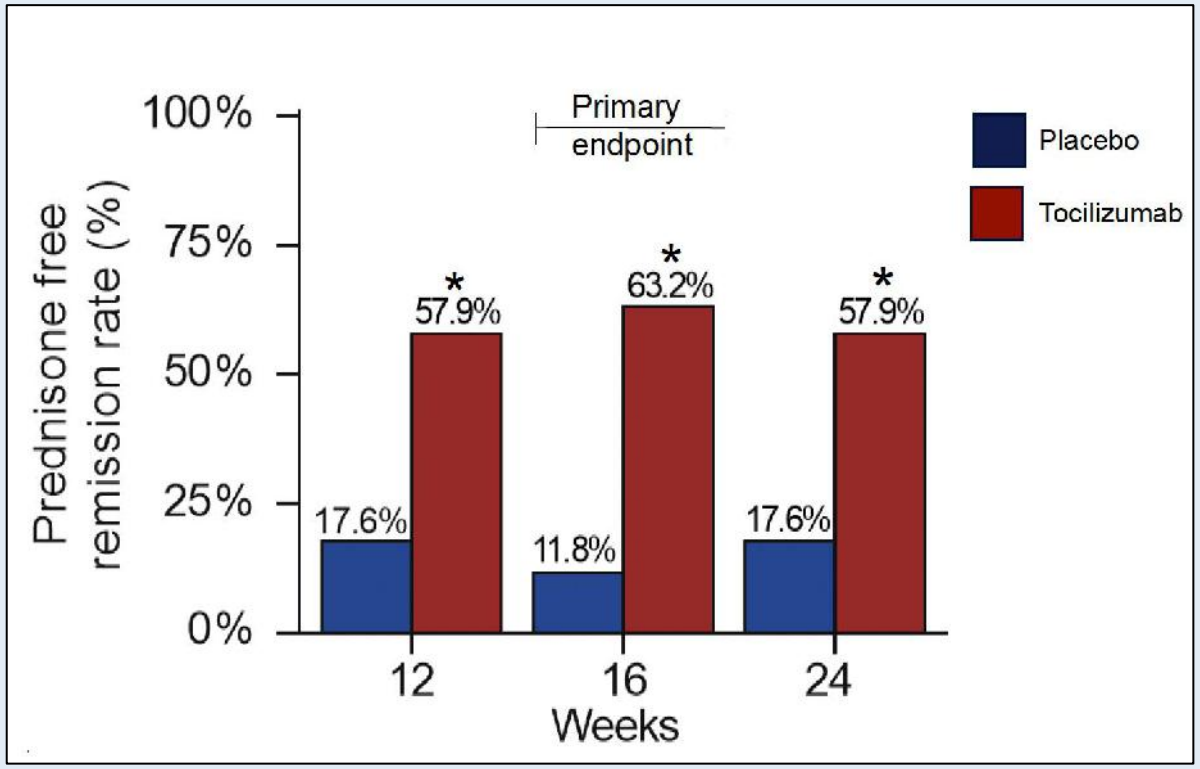
- GC-free remission at 12 and 24 weeks
- Time to flare
- Cumulative prednisone dose at 16 and 24 weeks

Bonelli et al. Ann Rheum Dis 2022

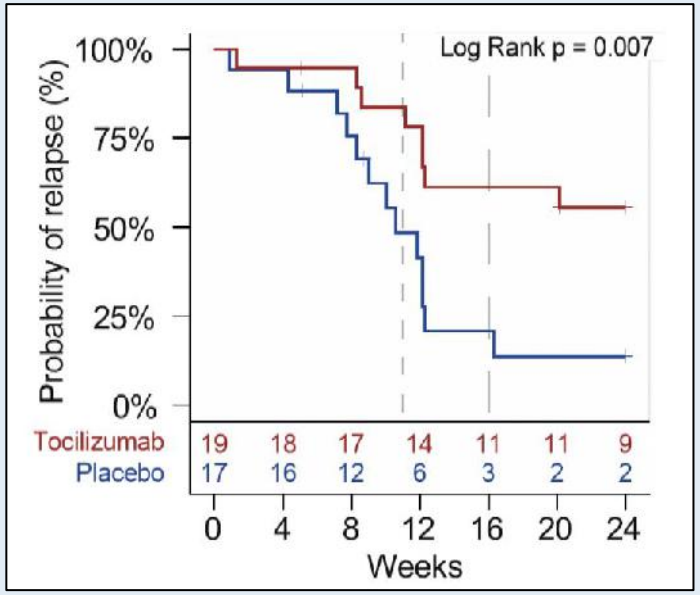
Results

- 19 patients received TCZ and 17 patients received PBO
- Balanced baseline characteristics

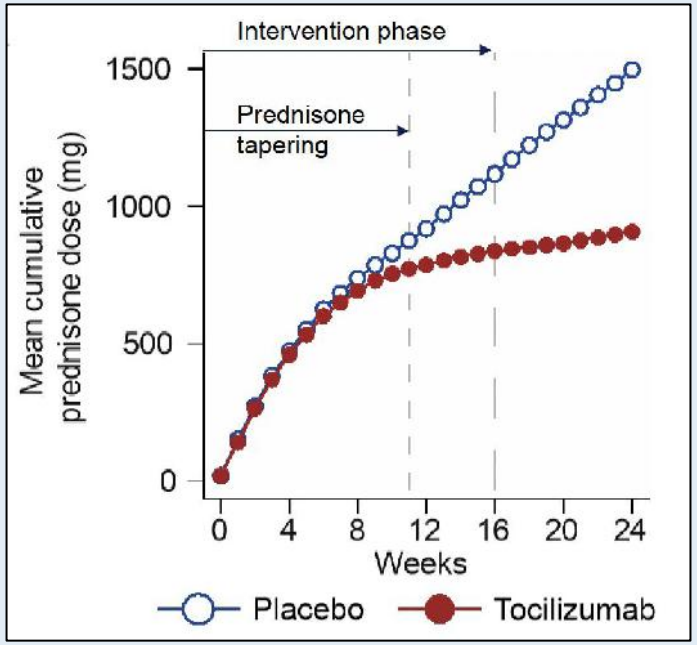
Glucocorticoid-free remission at 12, 16 and 24 weeks



Time to flare



Prednisone use



Thank you

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