Vasculiti dell'anziano

Francesco Muratore

Reumatologia AUSL-IRCCS
Reggio Emilia

Torino 12 ottobre 2018

Agenda

Giant cell arteritis

1. Large vessel involvement in GCA
2. New frontiers in the treatment of GCA

Backgroud

- GCA is the most common systemic vasculitis in Western countries in individuals older than 50 years
- Reggio Emilia, Italy incidence rate 5.8 /10^5 (1986–2012)
- It mainly involves large and medium-sized arteries, especially the aorta and its major branches
- The increased availability of imaging techniques is making a profound impact in the evaluation and management of patients with GCA

Salvarani et al. N Engl J Med. 2002;347:261-71
Muratore et al. Best Pract Res Clin Rheumatol 2016;30:688–706
Catanoso M et al. Arthritis Care Res. 2017

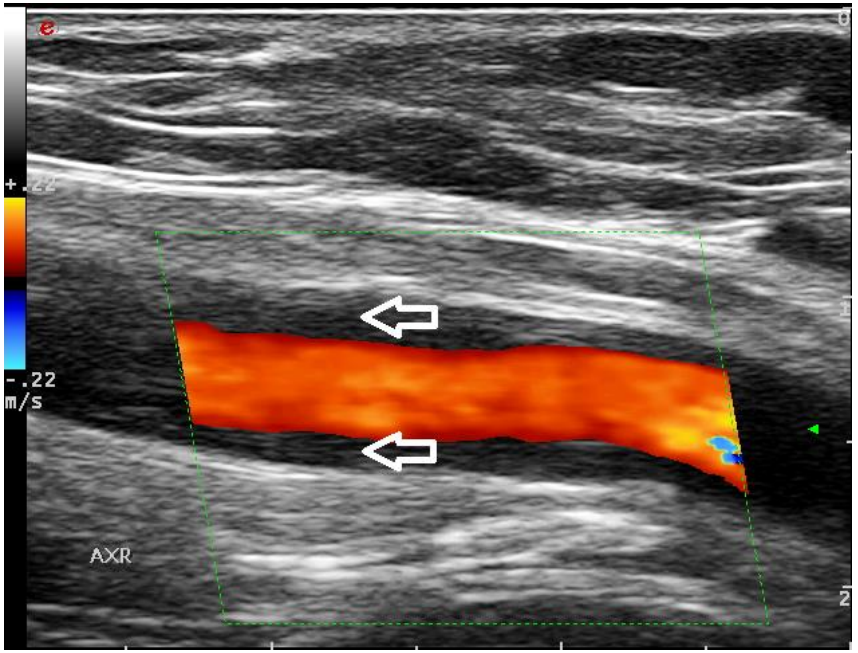
Large vessel involvement in GCA

- Clinical Symptoms
  - UE claudication 10-15% of patients

Salvarani et al. Lancet. 2008;372:234-451

Large vessel involvement in GCA

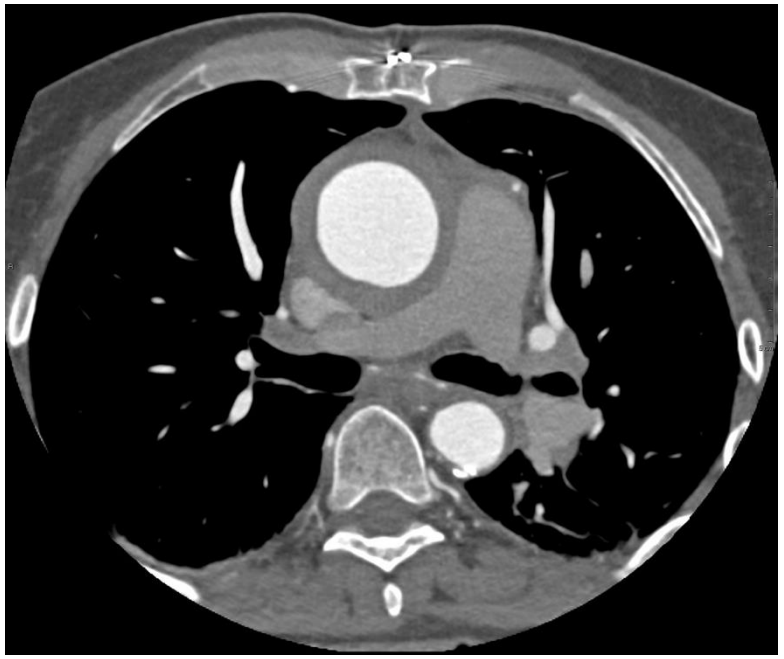
- Ultrasound in GCA
  - Wall swelling of the axillary, subclavian and/or proximal brachial arteries (30%)
  - Bilateral disease common



Schmidt et al. Rheumatology. 2008;47:96-101
Ghinoi et al. Rheumatology. 2012;51:730-4

Large vessel involvement in GCA

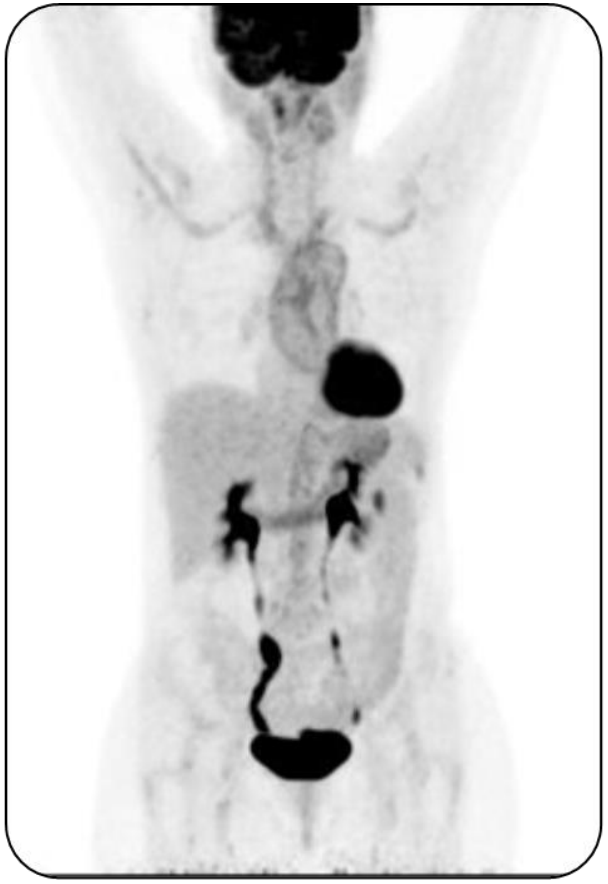
- CT angio in GCA:
  - LVV (67.5%)
  - Aorta (65%)
  - Subclavian arteries (42.5%)



Prieto-Gonzalez et al. Ann Rheum Dis. 2012;71:1170–6

Large vessel involvement in GCA

- PET scan in GCA:
  - FDG uptake in large vessel (83%)
  - Subclavian arteries (74%)
  - Aorta (50%)



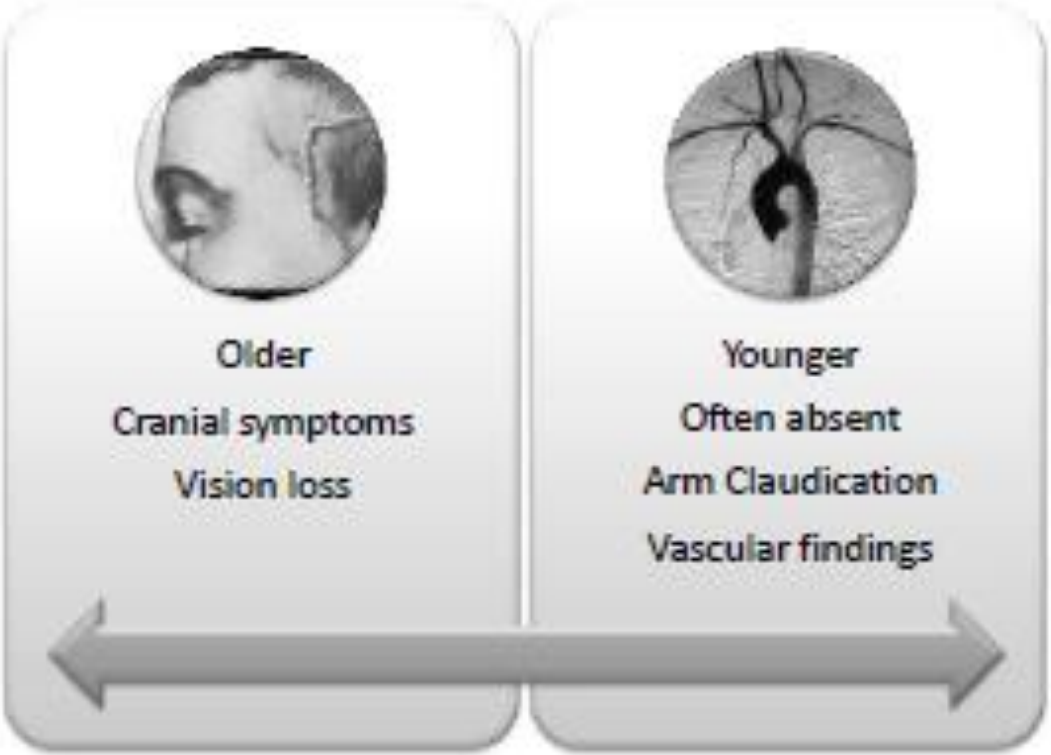
Blockmans et al. Arthritis Rheum. 2006;55:131-7
Blockmans et al. Rheumatology. 2007;46:672–77
Cimmino et al. Rheumatology. 2008;47:926-7

Large vessel involvement in GCA

- Onset
  - Concurrent with GCA diagnosis (75%)
  - 1-2 years from diagnosis

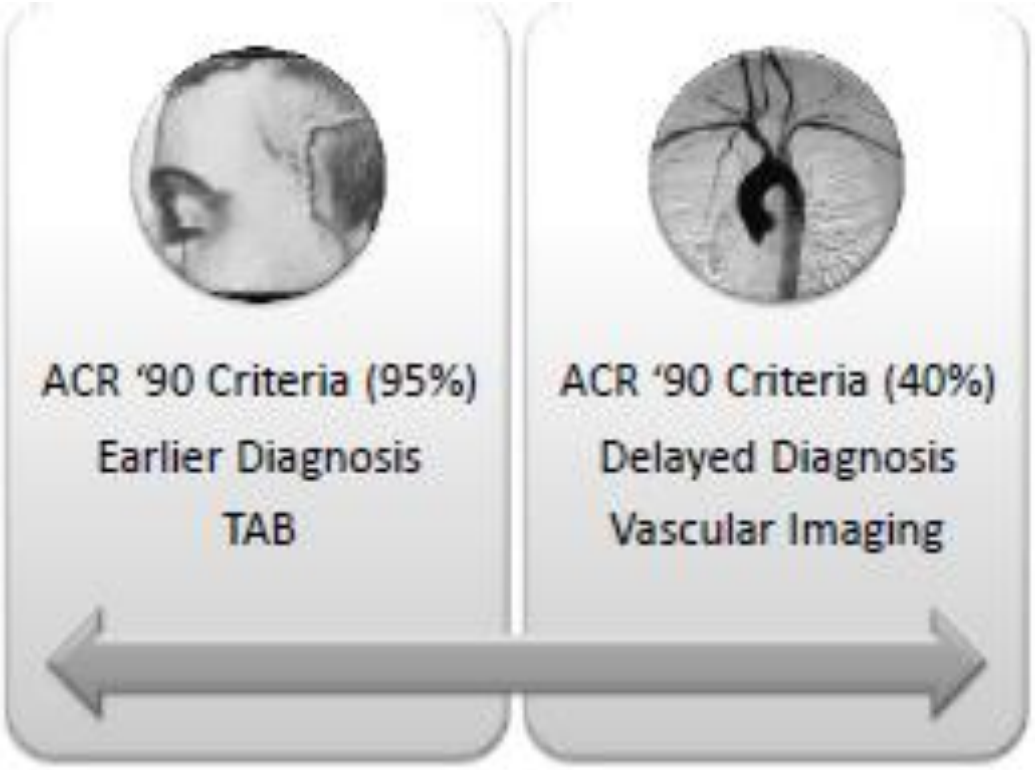
Muratore et al. Rheumatology. 2015;54:463-70
Kermani et al. Ann Rheum Dis. 2013;72:1989–1994

Large vessel involvement in GCA
Clinical Features



Muratore et al. Rheumatology. 2015;54:463-70
Schmidt et al. Rheumatology. 2008;47:96-101
Brack et al. Arthritis Rheum. 1999;42:311-7
Prieto-Gonzalez et al. Ann Rheum Dis. 2012;71:1170–6

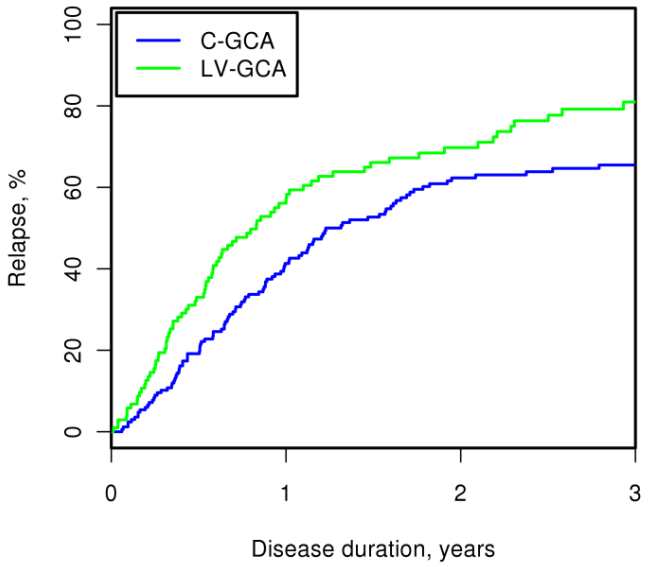
Large vessel involvement in GCA
Diagnosis



Muratore et al. Rheumatology. 2015;54:463-70
Schmidt et al. Rheumatology. 2008;47:96-101
Brack et al. Arthritis Rheum. 1999;42:311-7
Prieto-Gonzalez et al. Ann Rheum Dis. 2012;71:1170–6

Large vessel involvement in GCA
Treatment Course (only retrospective studies)

- Compared to C-GCA
  - Same disease course[1]
  - More relapses[2]
  - Higher cumulative steroid dose[2]
  - Longer to reach 0 mg[2,3]
  - Higher risk of aortic dilatation[2,3]

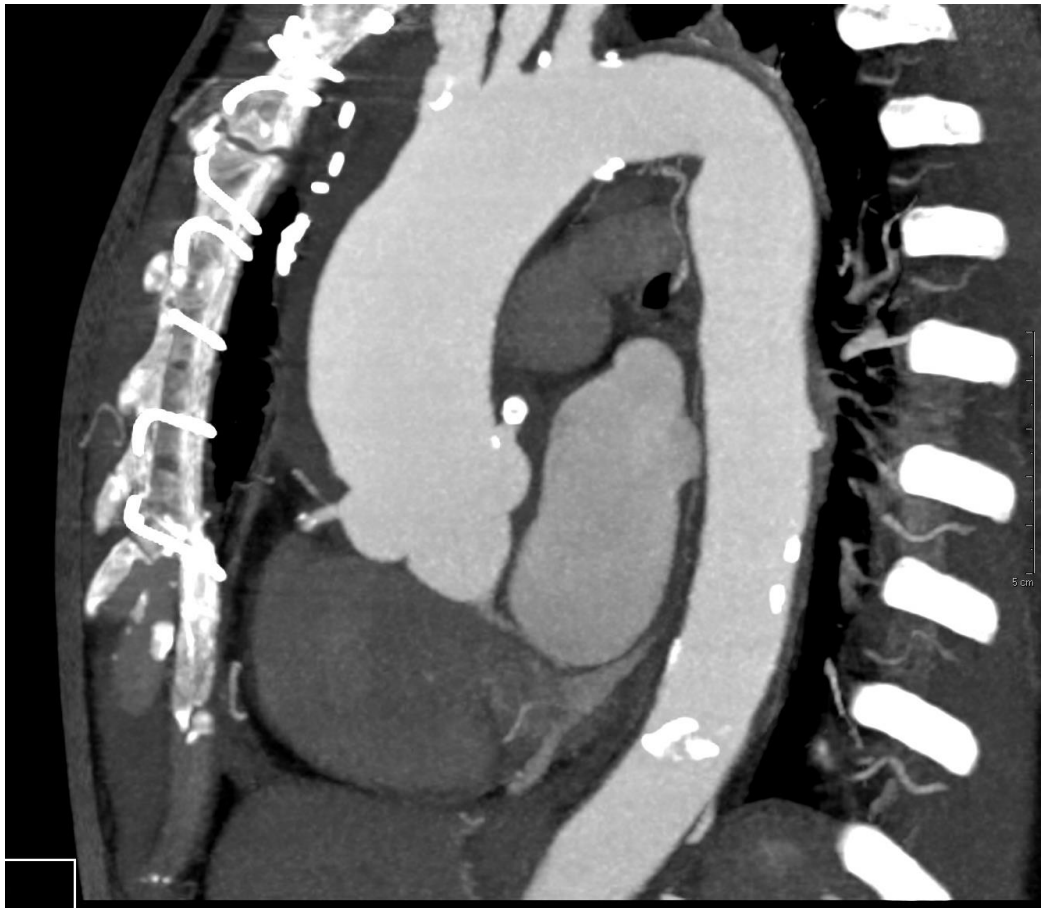


1. Schmidt et al. Rheumatology. 2008;47:96-101
2. Muratore et al. Rheumatology. 2015;54:463-70
3. de Boysson et al. Autoimmun Rev. 2018;17:391-398

Large vessel involvement in GCA
Key points

- Large-vessel GCA may be under-recognized
- Careful history and examination
  - Vascular system: pulses, bruit
  - BP measurement
- Vascular Imaging
- LV-GCA may have more features of refractory disease and might require more tailored therapy

LV-GCA
Aortic aneurysm



LV-GCA
Aortic aneurysm

- Thoracic Aortic Aneurysms
  - 17.3 – fold increased risk[1]
  - 6.6 – fold increased risk[2]

- No consistent clinical predictors
  - Aortic regurgitation

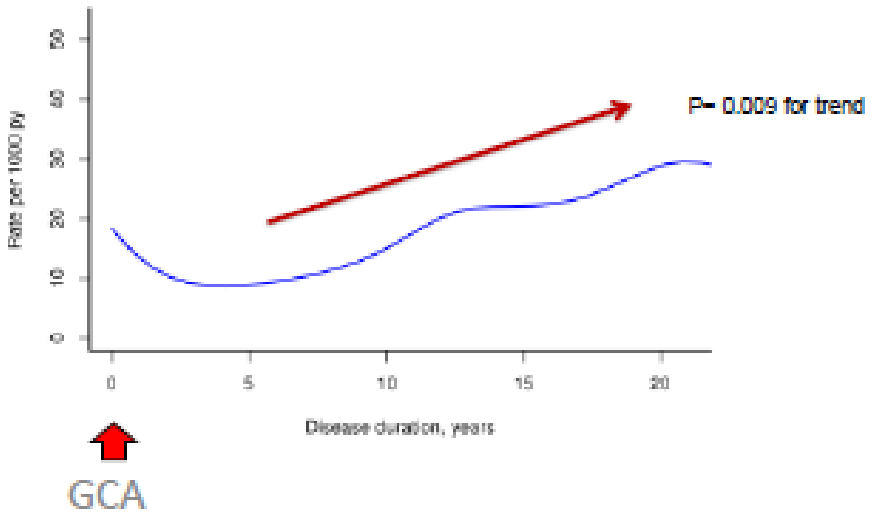
1. Evans et al. Ann Intern Med 1995;122:502-7
2. Robson et al. Ann Rheum Dis. 2015;74:129-135

LV-GCA
Aortic Aneurysm - Timing

- At diagnosis
  - 15-23% of patients had aortic dilatation
- As a late complication
  - 9.5–18% after a median time of 3–6 years (retrospective studies)

Prieto-González et al. Ann Rheum Dis. 2012;71:1170–6
Agard et al. Arthritis Rheum. 2008;59:670–6
Muratore et al. *Clin Exp Rheumatol 2014; 32 (Suppl. 82): S106-S111*

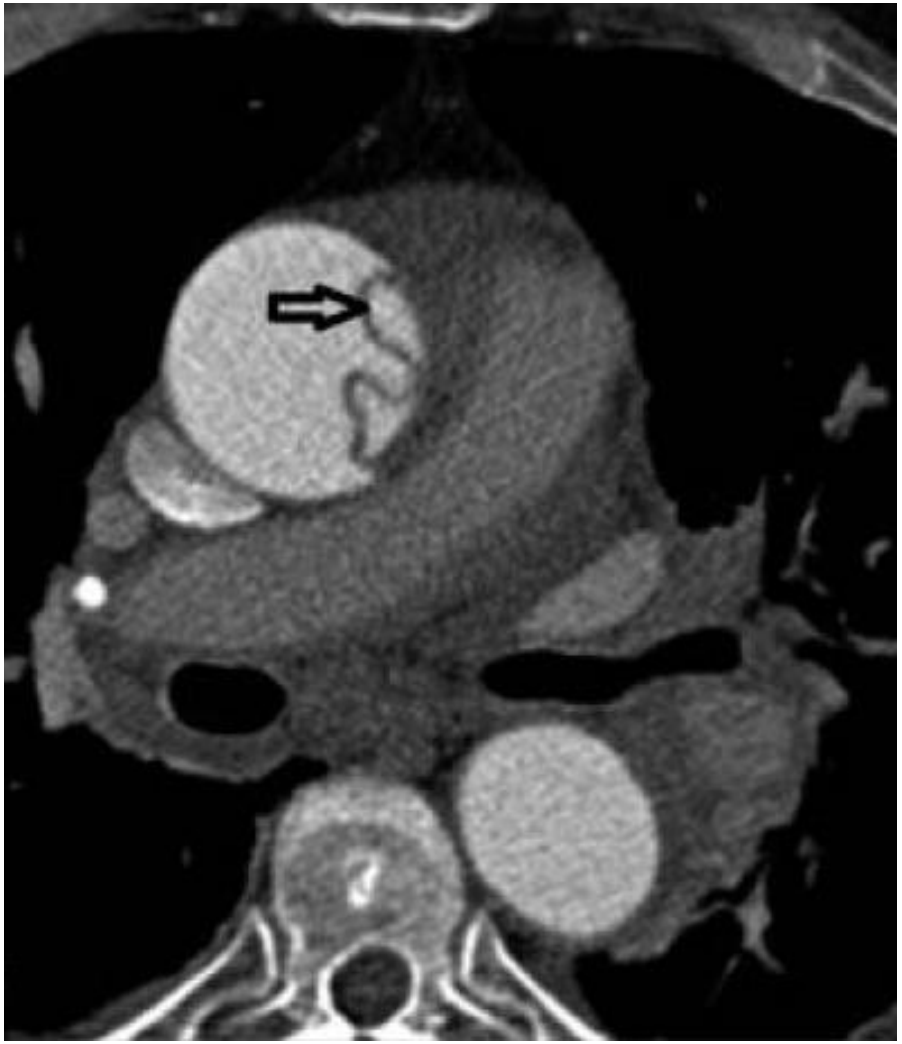
LV-GCA
Aortic Aneurysm - Timing



- The incidence of aortic aneurysm increases 5 years after GCA diagnosis and continues to increase over the period of observation (median follow-up 8.8 years)

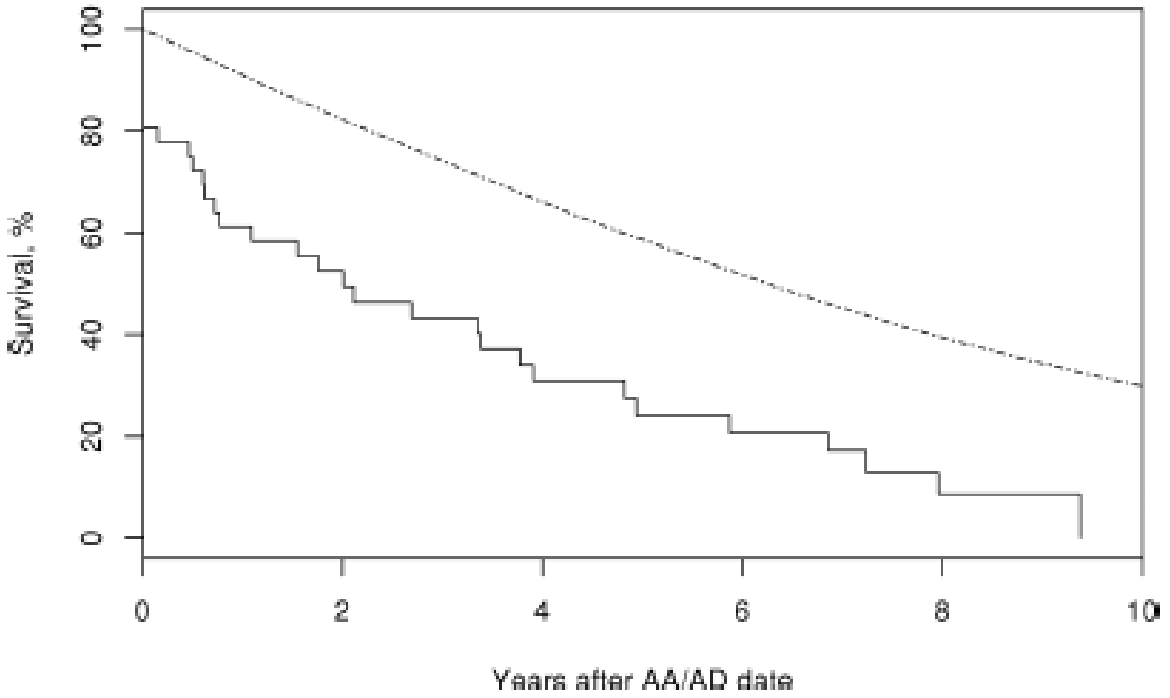
Kermani et al. Ann Rheum Dis. 2013;72:1989–1994

LV-GCA
Aortic Dissection



LV-GCA
Aortic Dissection

- Aneurysm/Dissection is associated with increased mortality



Survival in patients with GCA who develop AA/AD (solid line) compared with the general population (dotted line), logrank $p<0.001$

Kermani et al. Ann Rheum Dis. 2013;72:1989–1994

LV-GCA

Risk factors for aortic dissection/rupture

- No association between aneurysm size and rate of growth and risk of dissection/rupture
- GCA pts with smaller aneurysms may still be at increased risk of dissection
- Decision regarding timing of surgery may differ between inflammatory and noninflammatory aortic aneurysm

Kermani et al. J Clin Rheumatol. 2016 Jun;22:184-7

Agenda

1. Large vessel involvement in GCA
2. New frontiers in the treatment of GCA

Glucocorticoids are the treatment of choice for GCA

- Adequate GC doses quickly suppress clinical manifestations of GCA and prevent ischemic complications
- If visual loss has occurred before starting therapy, it is not usually reversed
- An empiric initial dose of 40-60 mg daily of prednisone (or equivalent) as a single or divided dose is recommended

Salvarani et al, N Engl J Med 2002, Lancet 2008, Nat Rev Rheumatol 2012

Box 2 | Treating patients with GCA presenting with cranial ischaemic events

Recommended treatment

Patients with anterior ischaemic optic neuropathy with a low index of suspicion but awaiting the temporal artery biopsy result

- Start oral prednisone 1 mg/kg/day

Patients at high risk of cranial ischaemic events (history of amaurosis fugax or unilateral visual loss)

- Immediately start 500–1,000 mg/day of intravenous methylprednisolone for 3 days followed by oral prednisone 1 mg/kg/day
- Start oral prednisone 1 mg/kg/day if intravenous pulse cannot be rapidly initiated

Patients with established bilateral visual loss

- Start oral prednisone 1 mg/kg/day

Soriano et al. Nat Rev Rheumatol. 2017

Glucocorticoids are the treatment of choice for GCA

- The necessary duration of GC therapy is variable, but in about 50-60% of patients it can be discontinued within 1-2 years

- Some patients have a chronic relapsing course and may require low doses of GCs for several years or even indefinitely

Salvarani et al, Lancet 2008, N Engl J Med 2002, Nat Rev Rheumatol 2012

Points to consider in the therapy of GCA

- The morbidity of GCA is related to the impact of long-term therapy with glucocorticoids in elderly patients, who often have many comorbidities

- In a population based study
  - ✓ Adverse events in 86% of 120 patients
  - ✓ 2 or more adverse events occurred in 58%

Proven et al, Arthritis Rheum 2003

Major adverse events that occurred in 103 of 120 patients with giant cell arteritis

Type of adverse event	Patients with the event, number (%)
Diabetes mellitus	11 (9)
Total fractures	46 (38)
Hip fracture	19 (16)
Vertebral fracture	27 (23)
Colles' fracture	3 (2.5)
Other fractures	11 (9)
Gastrointestinal bleeding	5 (4)
Hypertension	26 (22)
Infection	37 (31)
Posterior subcapsular cataract	49 (41)

Key points

- We need effective treatments in GCA to reduce the exposure to glucocorticoids

Steroid-sparing agents in GCA: evidence from RCTs

- Pulse GC therapy: 2 RCTs

Mazlumzadeh et al, Arthritis Rheum 2006 ; Chevalet et al, J Rheumatol 2000

- Methotrexate: 3 RCTs and 1 meta-analysis

Spiera et al,Clin Exp Rheumatol 2001; Hoffman et al,Arthritis Rheum 2002;
Jover et al,Ann Intern Med 2001; Mahr et al, Arthritis Rheum 2006

- Azathioprine: 1 RCT

Silva and Hazleman, Ann Rheum Dis 1986

- Infliximab: 1 RCT

Hoffman et al, Ann Intern Med 2007

- Etanercept: 1 RCT

Martinez-Taboada et al, Ann Rheum Dis 2008

- Adalimumab: 1 RCT

Seror et al, Ann Rheum Dis 2014

- Abatacept: 1 RCT

Langford et al, Arthritis & Rheumatol 2017

- Tocilizumab: 2 RCT

Villiger et al, Lancet 2016; Stone et al, N Engl J Med 2017

What is the evidence from RCTs?

- Additional investigations are needed on the use of pulse GC at the onset of treatment for GCA to confirm whether this regimen reduces GC toxicity
- MTX and AZA have a small steroid-sparing effect and does not decrease the incidence of steroid-related side effects
- Infliximab and adalimumab do not have a steroid-sparing effect in newly diagnosed patients
- Etanercept could have a steroid-sparing effect in patients with GC side-effects
- Abatacept slightly reduces relapses and increases duration of remission

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 27, 2017 VOL. 377 NO. 4

Trial of Tocilizumab in Giant-Cell Arteritis

J.H. Stone, K. Tuckwell, S. Dimonaco, M. Klearman, M. Aringer, D. Blockmans, E. Brouwer, M.C. Cid, B. Dasgupta, J. Rech, C. Salvarani, G. Schett, H. Schulze-Koops, R. Spiera, S.H. Unizony, and N. Collinson

Aim: to study the efficacy and safey of Tocilizumab in patients with newly diagnosed or recurrent GCA

Eligibility Criteria

- Age at onset > 50 years
- ESR > 50 mm/h (or CRP ≥ 2.45 mg/dL)

AND

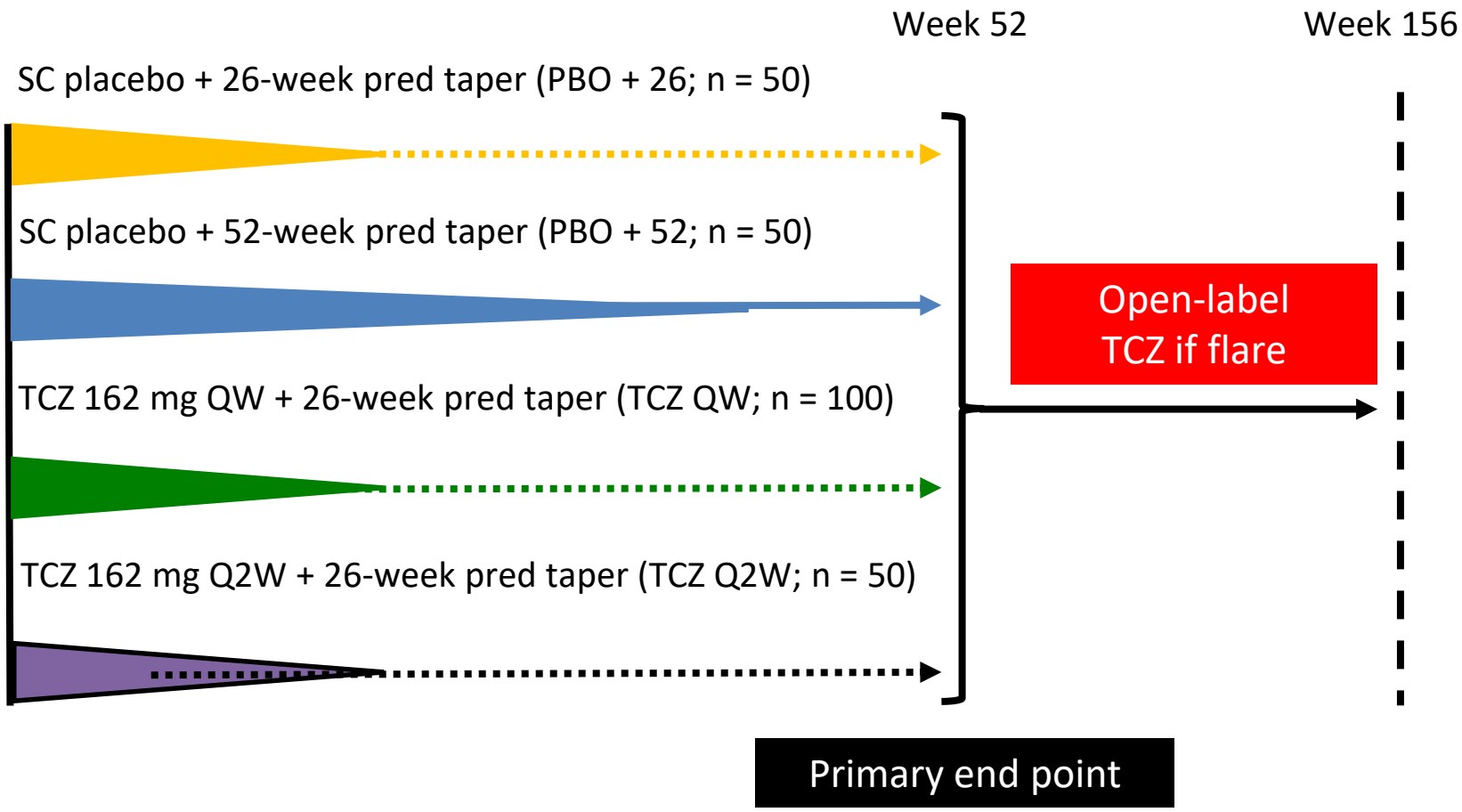
- Unequivocal cranial symptoms of GCA and/or Unequivocal symptoms of PMR

AND

- Temporal artery biopsy and/or Imaging evidence of large-vessel vasculitis

Stone et al, NEJM 2017

Four Groups



PBO, placebo; pred, prednisone; Q2W, once every 2 weeks; QW, once a week; SC, subcutaneous.

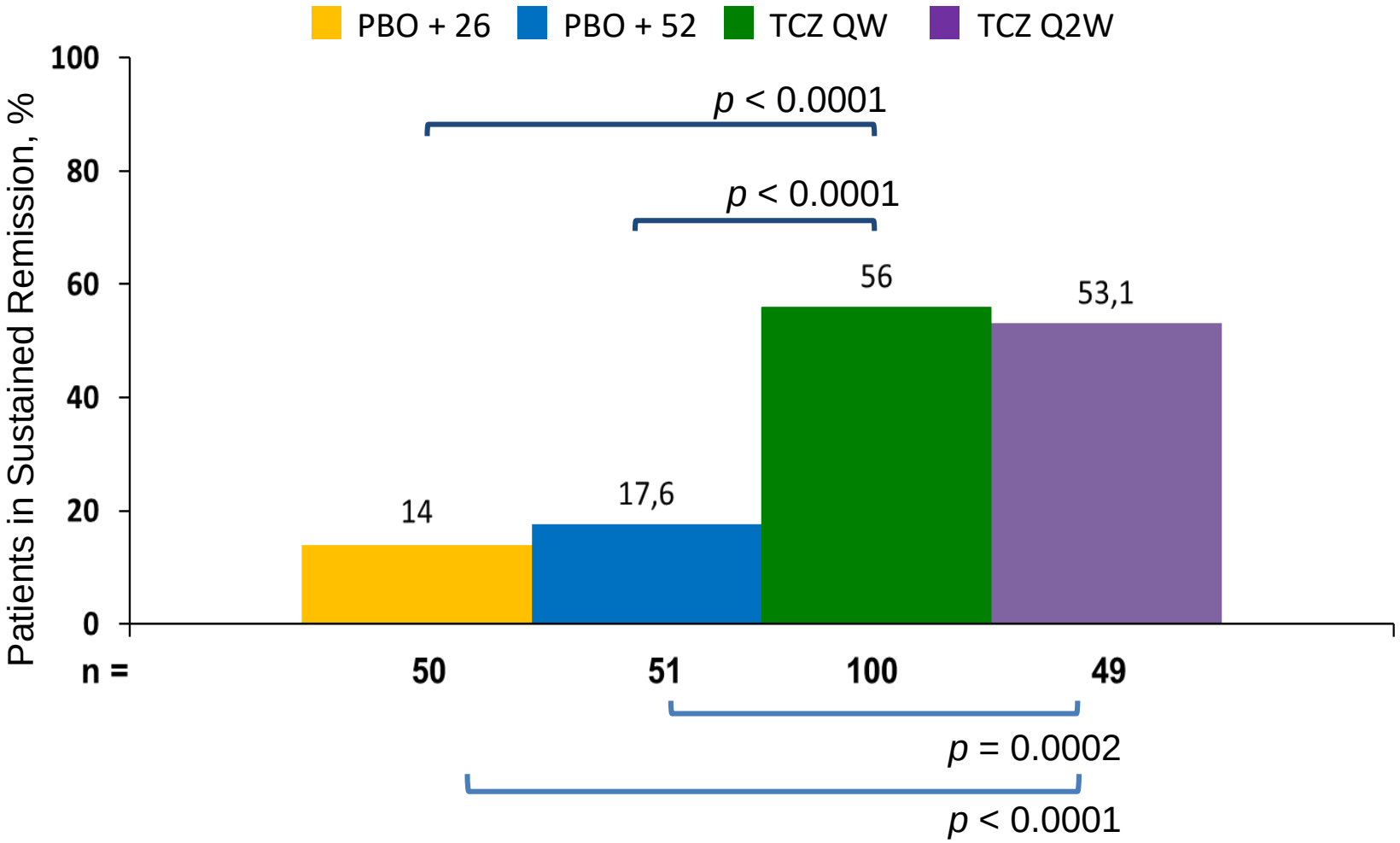
Results

Baseline Characteristics	All Patients N = 251
Age, mean (SD)	69.0 (8.2)
Female, %	74.9
Caucasian, %	96.8
Newly diagnosed, %	47.4
Relapsing, %	52.6

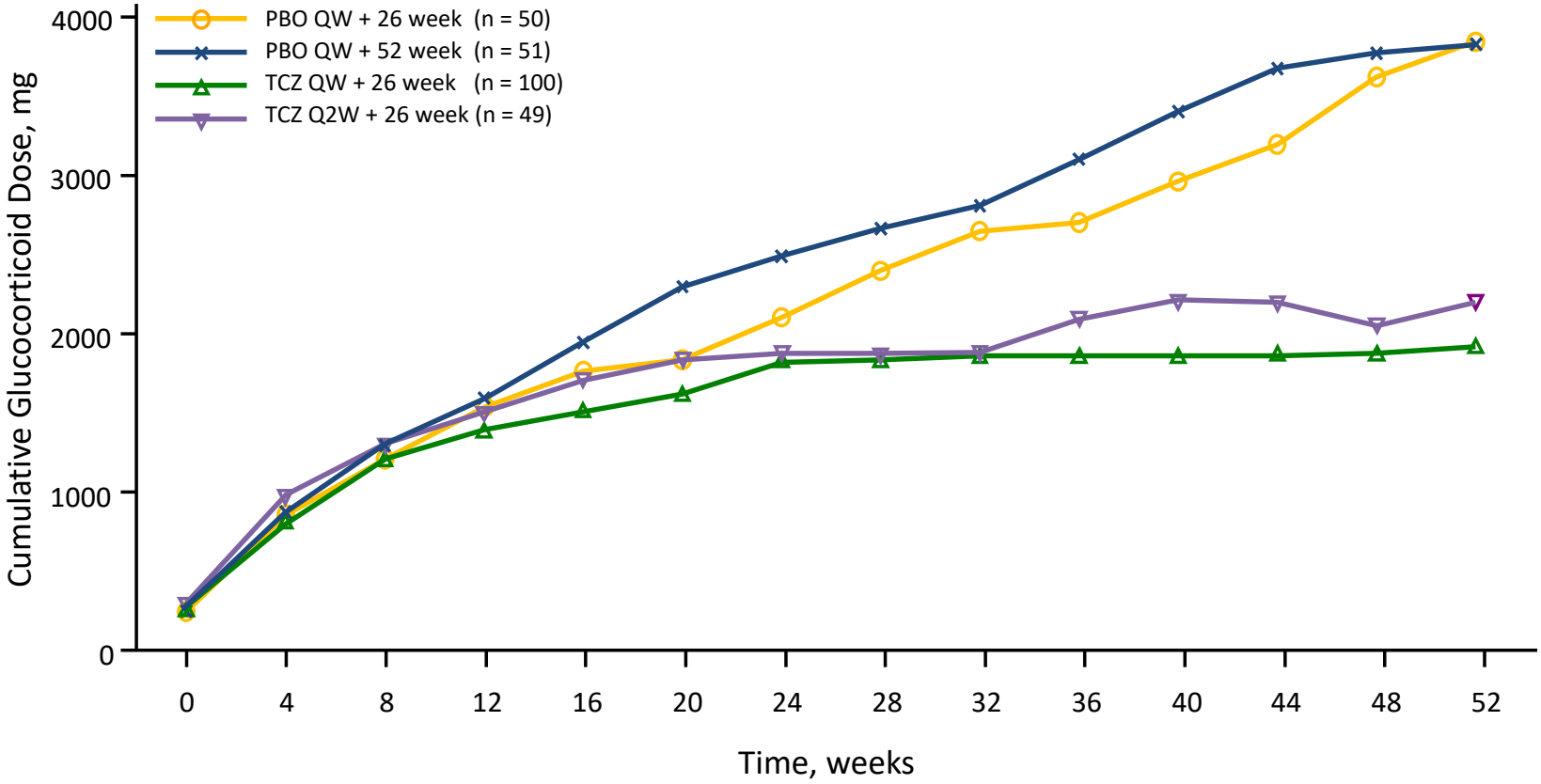
SD, standard deviation.

Sustained Remission at week 52: Primary and Key Secondary End Points

Superior efficacy of TCZ + 26-week prednisone versus 26-week and 52-week prednisone alone



TCZ Had a Significant Steroid-Sparing Effect



Actual Cumulative Dose to Week 52, mg	PBO + 26 n = 50	PBO + 52 n = 51	TCZ QW n = 100	TCZ Q2W n = 49
Median	**3296**	**3818**	**1862**	**1862**

Includes prednisone received as part of the taper, escape prednisone, and concomitant steroids.
$p \leq 0.0003$ for all comparisons of TCZ to PBO.

Safety Overview

- AEs balanced across groups
- No new safety signals/laboratory abnormalities observed
- AION developed in 1 pt treated with TCZ every other week
- No deaths
- No bowel perforations
- 2 malignancies (both in prednisone-only groups)

	PBO + 26 n = 50	PBO + 52 n = 51	TCZ QW n = 100	TCZ Q2W n = 49
Pts with ≥1 AE, %	96.0	92.2	98.0	95.9
Total AEs, n	470	486	810	432
Pts with ≥1 SAE, %	22.0	25.5	15.0	14.3
Pts with ≥1 SI, %	4.0	11.8	7.0	4.1

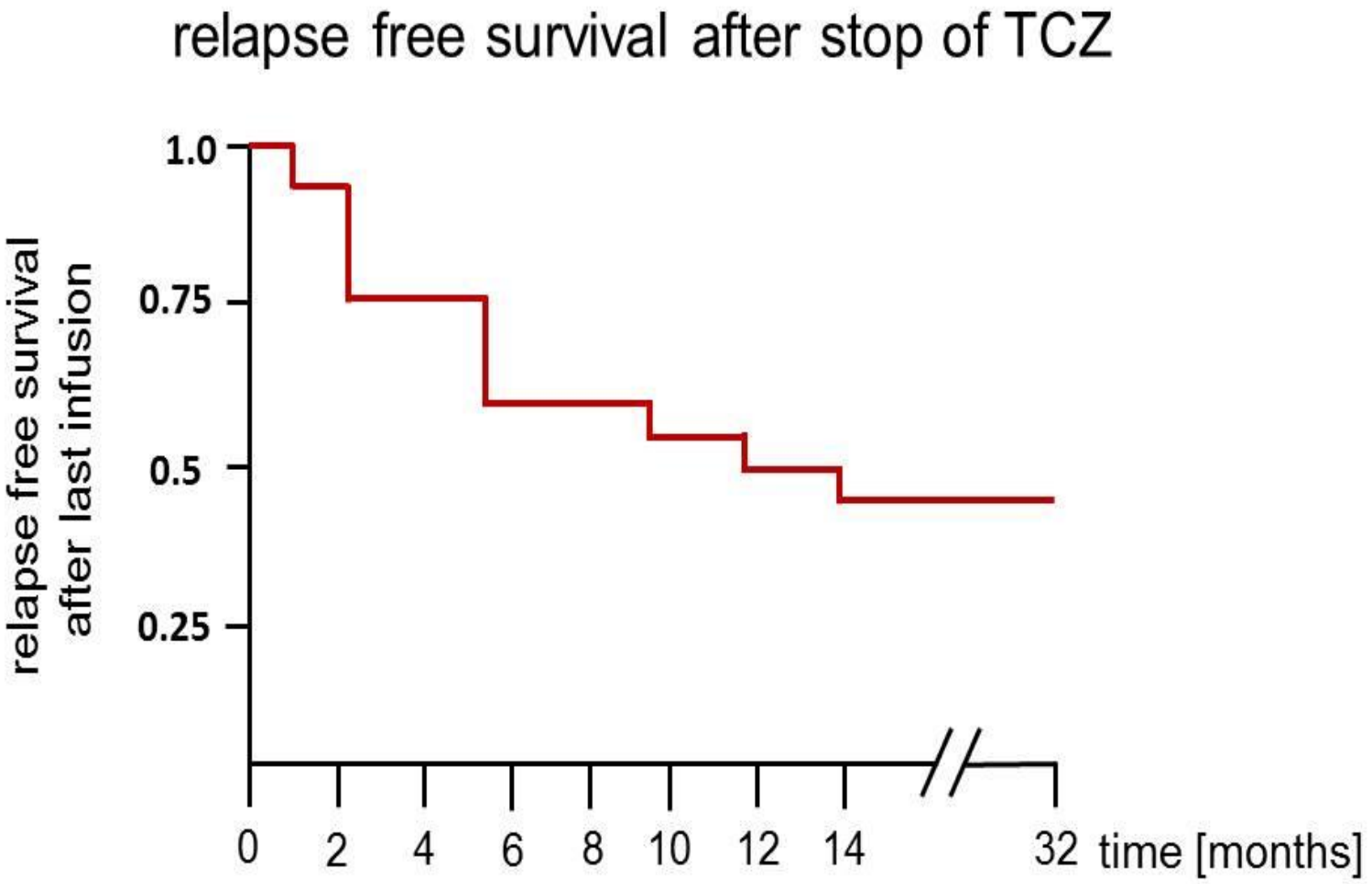
AE, adverse event; pts, patients; SAE, serious adverse event; SI, serious infection.

Three conclusions

1. There is something new in GCA

2. TCZ has a powerful steroid-sparing effect in GCA

3. TCZ is safe in GCA



Termination of Tocilizumab-Treatment in GCA: Follow-up of Patients after the RCT (median 12.5 months, range 3-32)

Adler et al, Abstract n 867, ACR 2016

Open questions

- Which patients should be treated?
  - Pts at high risk for serious side effects from PDN
  - Pts with repeated flares that are not manageable with low doses of PDN

- How long we have to treat the patients?

Grazie

francesco.muratore@ausl.re.it