ΣΥΝΕΔΡΙΑ 14η
«Ρευματική Πολυμυαλγία και Κροταφική Αρτηριίτιδα»

Διάγνωση γιγαντοκυτταρικής αρτηριίτιδας: βιολογική θεραπεία εξαρχής ή μόνο σε πιθανή υποτροπή;

Χρήστος Κουτσιανάς MD, PhD

Ρευματολόγος – Ειδικός παθολόγος
Ακαδημαϊκός υπότροφος, Μονάδα Κλινικής Ανοσολογίας - Ρευματολογίας,
Β Πανεπιστημιακή Παθολογική Κλινική και Ομώνυμο Εργαστήριο, ΓΝΑ ««Ιπποκράτειο»

Honorary Consultant, Research & Development Department
The Dudley Group NHS Foundation Trust

ΓΕΝΙΚΟ ΝΟΣΟΚΟΜΕΙΟ ΑΘΗΝΩΝ
ΙΠΠΟΚΡΑΤΕΙΟ

NHS
The Dudley Group
NHS Foundation Trust

Conflict of interest

Καμία σύγκρουση συμφερόντων σχετική με αυτή την παρουσίαση

- Honoraria for lectures:
  Roche, Genesis Pharma, Abbvie, Novartis, Genesis Pharma, Eli-Lilly, Pfizer, Aenorasis, UCB, Glaxo-Smith-Kline
- Honoraria for advisory boards:
  Genesis Pharma, Pfizer, Abbvie, Viatris, Aenorasis
- Hospitality:
  Eli-Lilly, Novartis, Viatris, UCB, Genesis Pharma, Abbvie
- Research:
  Sub-investigator: Roche, UCB, Eli-Lilly, Novartis, BMS, Pfizer, Genesis Pharma, AMGEN, MSD, Abbvie, Aenorasis

Case: presentation

Γυναίκα 83 ετών
Ιούλιος 2022

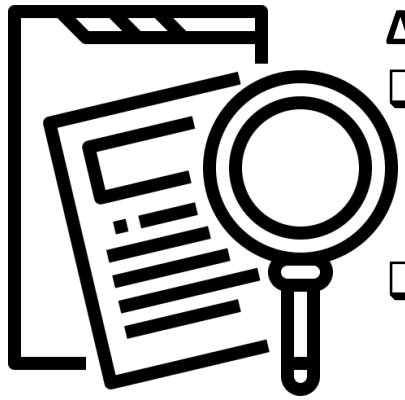
Παραπομπή από αιματολόγους

- Ορθόχρωμη ορθοκυτταρική αναιμία
  Hb: 10.1g/dL, Ht:32.3%, MCV: 88 fl
- Από έτους
- ? αιτιολογίας

Case: history

Ατομικό αναμνηστικό:

- ❑ Αρτηριακή υπέρταση
- ❑ Σακχαρώδης διαβήτης τύπου 2
- ❑ Οστεοπόρωση



Διερεύνηση από αιματολόγο:

- ❑ Καρυότυπος μη διαγνωστικός για μυελοδυσπλασία
- ❑ Οστεομυελική βιοψία: αντιδραστικού τύπου αλλοιώσεις

Φαρμακευτική αγωγή:

- ❑ Perindropril 10mg OD
- ❑ Amlodipine 10mg OD
- ❑ Furosemide 40mg OD
- ❑ Linagliptin 5mg OD
- ❑ Glimepiride 4mg OD
- ❑ Insulin glargine 12 iu OD
- ❑ Denosumab 60mcg q6mo

Case: initial work-up

Hb: 10.1g/dl Ht: 33%, MCV/MCH: 88/29

WBC: 7240 (N 70%) PLTs: 236000

CRP: 15.7 (<5 mg/dl), ΤΚΕ 38 mm/h

BUN: 79 mg/dL, Cr:0.9 mg/dl

Glu: 226 mg/dl

AST/ALT: 51/78 U/L (<34/<55)

γ-GT 13 IU/l LDH 213 IU/l CPK 47 IU/l

Γενική ούρων: WBC 0-1, RBC: 0-2

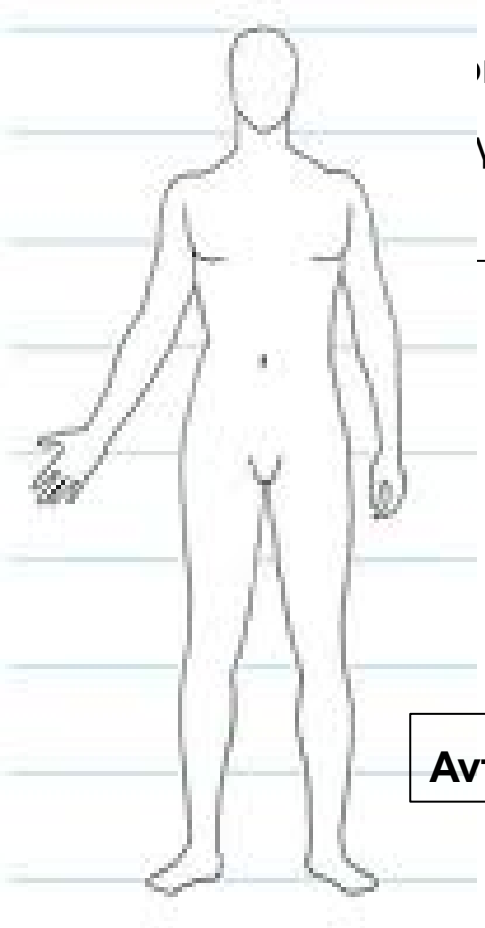
Hb (-), Pro: (+)

Ferritin: 316 ng/mL

Ακτινογραφία θώρακος: χωρίς κλινικά σημαντικά παθολογικά ευρήματα

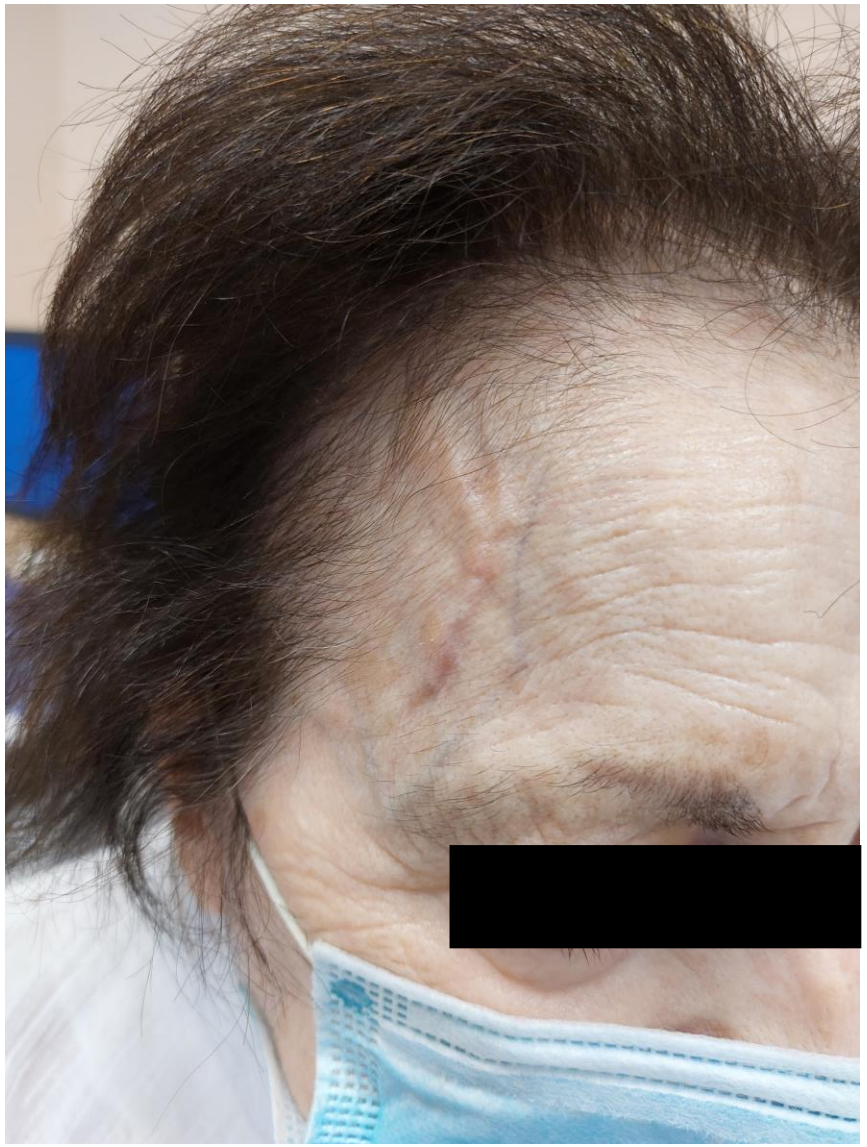
Αξονική τομο ιλίας:

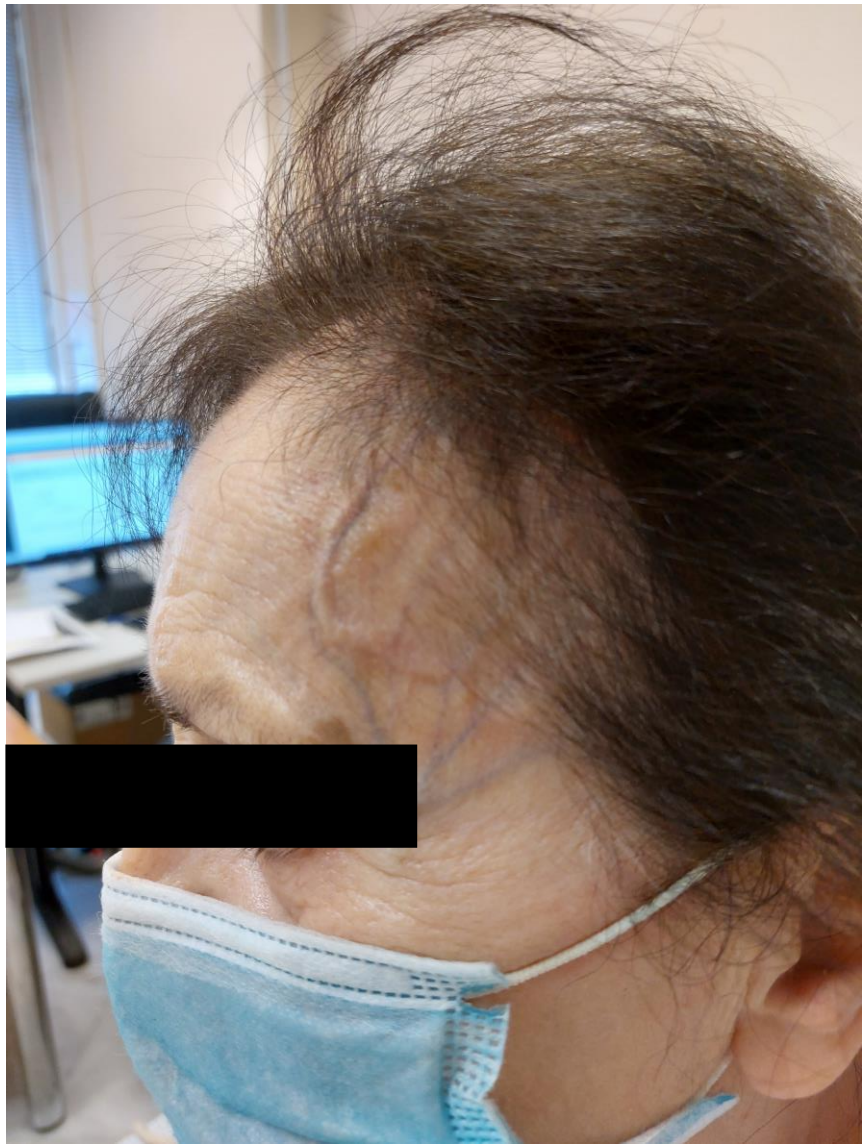
αρνητική για κ γικά ευρήματα



Αντικειμενική εξέταση

Case: clinical examination



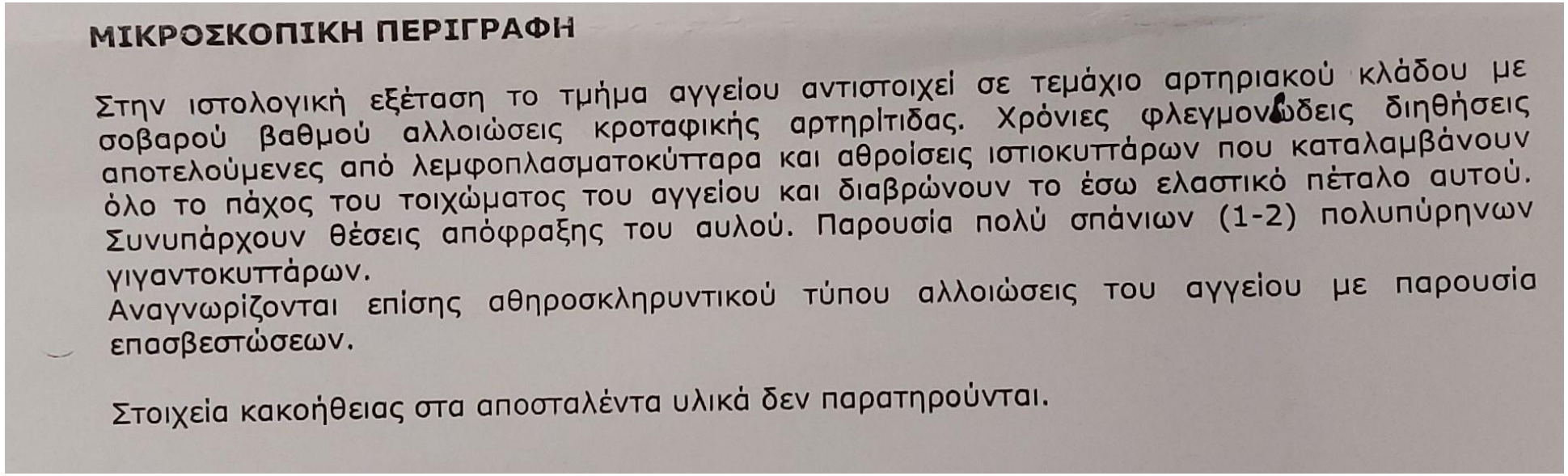


Case: investigations

TAUS:

(ΔΕ) κροταφική: **νηματοειδής ροή** σε όλα τα απεικονιζόμενα τμήματα

(ΑΡ) κροταφική: **νηματοειδής ροή** στο εγγύς τμήμα που απεικονιζεται. Απουσία ροής στο άπω τμήμα. δίδεται η **εντύπωση τοιχωματικής βλάβης περίπου 0.8 x 1.8 χιλ** στη μεσότητα του απεικονιζόμενου τμήματος της ΑΡ κροταφικής α

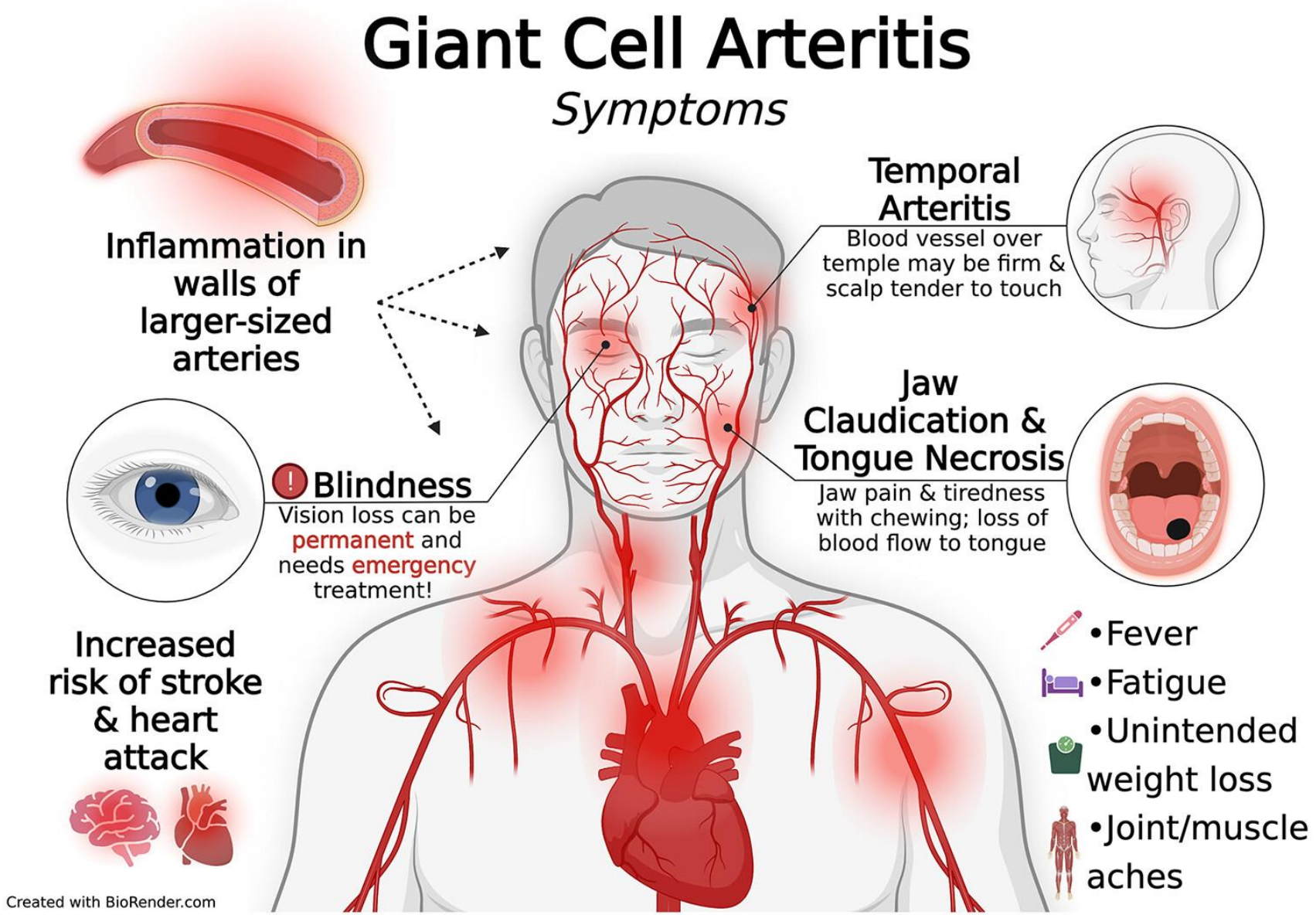


ΜΙΚΡΟΣΚΟΠΙΚΗ ΠΕΡΙΓΡΑΦΗ

Στην ιστολογική εξέταση το τμήμα αγγείου αντιστοιχεί σε τεμάχιο αρτηριακού κλάδου με σοβαρού βαθμού αλλοιώσεις κροταφικής αρτηρίτιδας. Χρόνιες φλεγμονώδεις διηθήσεις αποτελούμενες από λεμφοπλασματοκύτταρα και αθροίσεις ιστιοκυττάρων που καταλαμβάνουν όλο το πάχος του τοιχώματος του αγγείου και διαβρώνουν το έσω ελαστικό πέταλο αυτού. Συνυπάρχουν θέσεις απόφραξης του αυλού. Παρουσία πολύ σπάνιων (1-2) πολυπύρηνων γιγαντοκυττάρων.
Αναγνωρίζονται επίσης αθηροσκληρυντικού τύπου αλλοιώσεις του αγγείου με παρουσία επασβεστώσεων.

Στοιχεία κακοήθειας στα αποσταλέντα υλικά δεν παρατηρούνται.

Diagnosis



Sheth et al, Vascular Medicine 2022, Vol. 27(5) 521–524

Management considerations in GCA

Management: corticosteroids

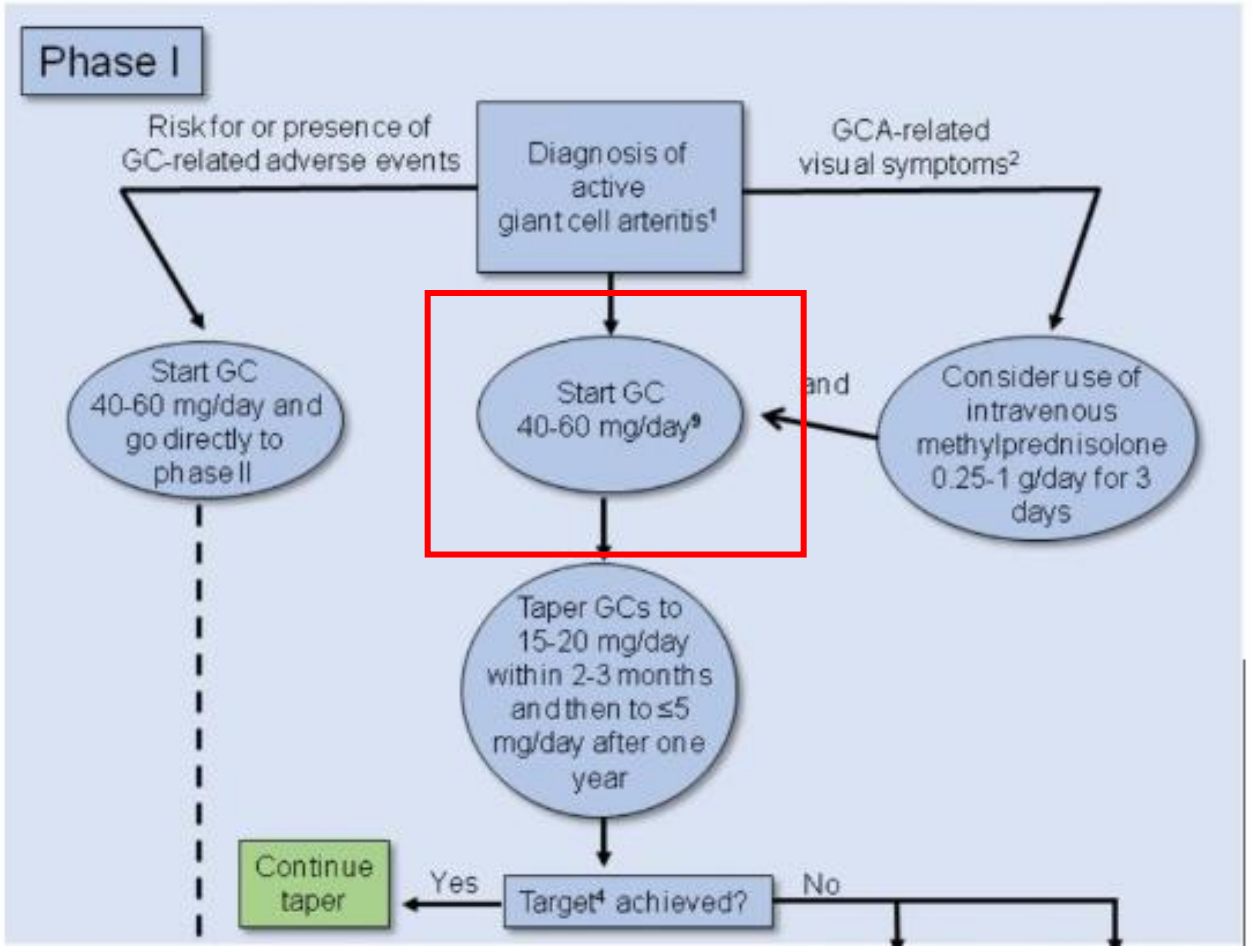
Horton 11-18-49

The history and clinical course that of temporal arteritis and I agree with Dr. Eaton. It is interesting to note that there seems to be some apparent relationship between the drop in temperature and the use of Cortisone, although subjectively the patient does not seem to be any better. I have not seen any previous case of temporal arteritis treated with Cortisone so I do not know what to expect following such therapy. We have been under the impression that the giving of histamine intravenously has given patients of this type symptomatic relief, and we wondered at the time whether it was due to increasing the intra- and extracranial circulation or not. It may well have been due to the fact that the giving of histamine liberates Compound E just as it liberates adrenalin.

The most serious complication I have encountered in this disease is sudden loss of vision and thus far I have seen no procedure which will prevent this from occurring. The use of dicumarol and heparin will not prevent it. Will Cortisone prevent such complications???

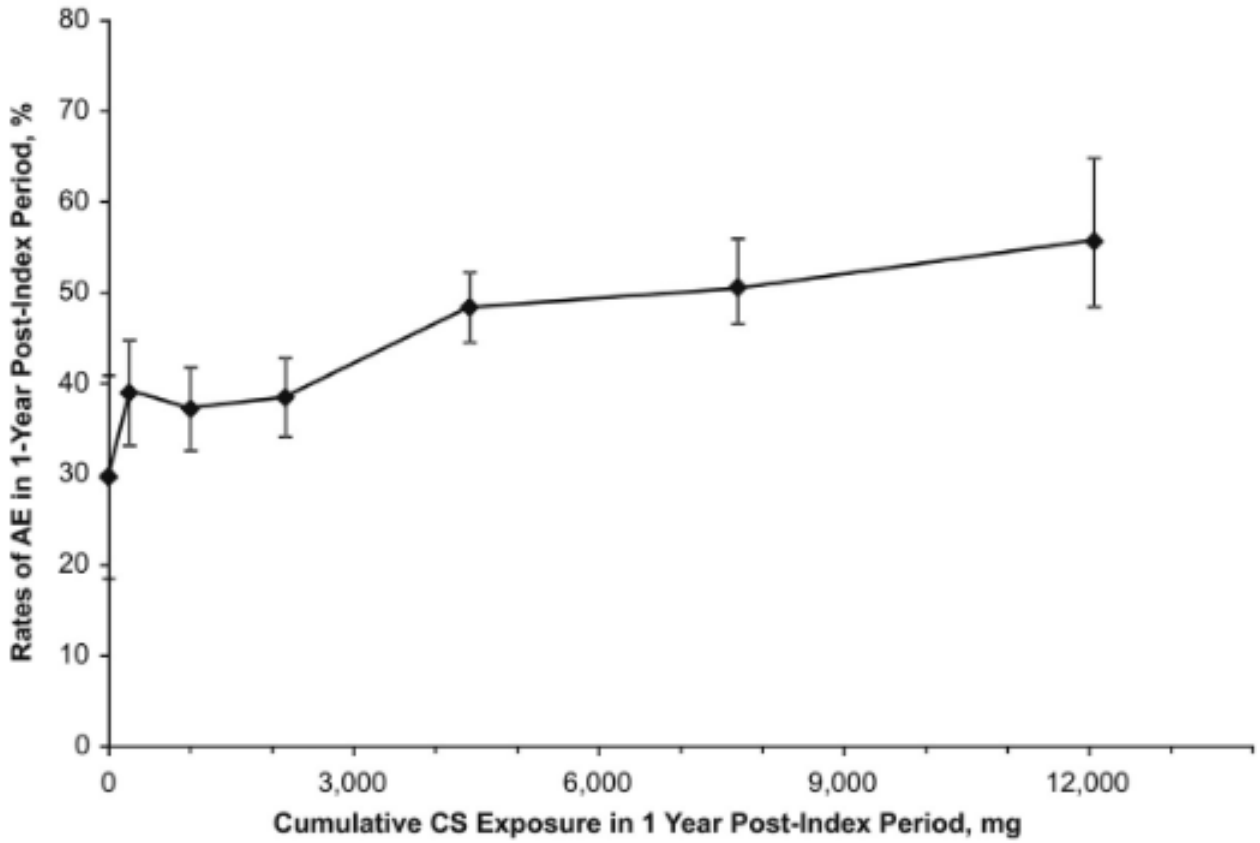
Management: corticosteroids 75 years later

2018 Update of the EULAR recommendations for the management of large vessel vasculitis



Hellmich B, et al. Ann Rheum Dis 2020;79:19–30

Glucocorticoid toxicity and GCA: cumulative dose



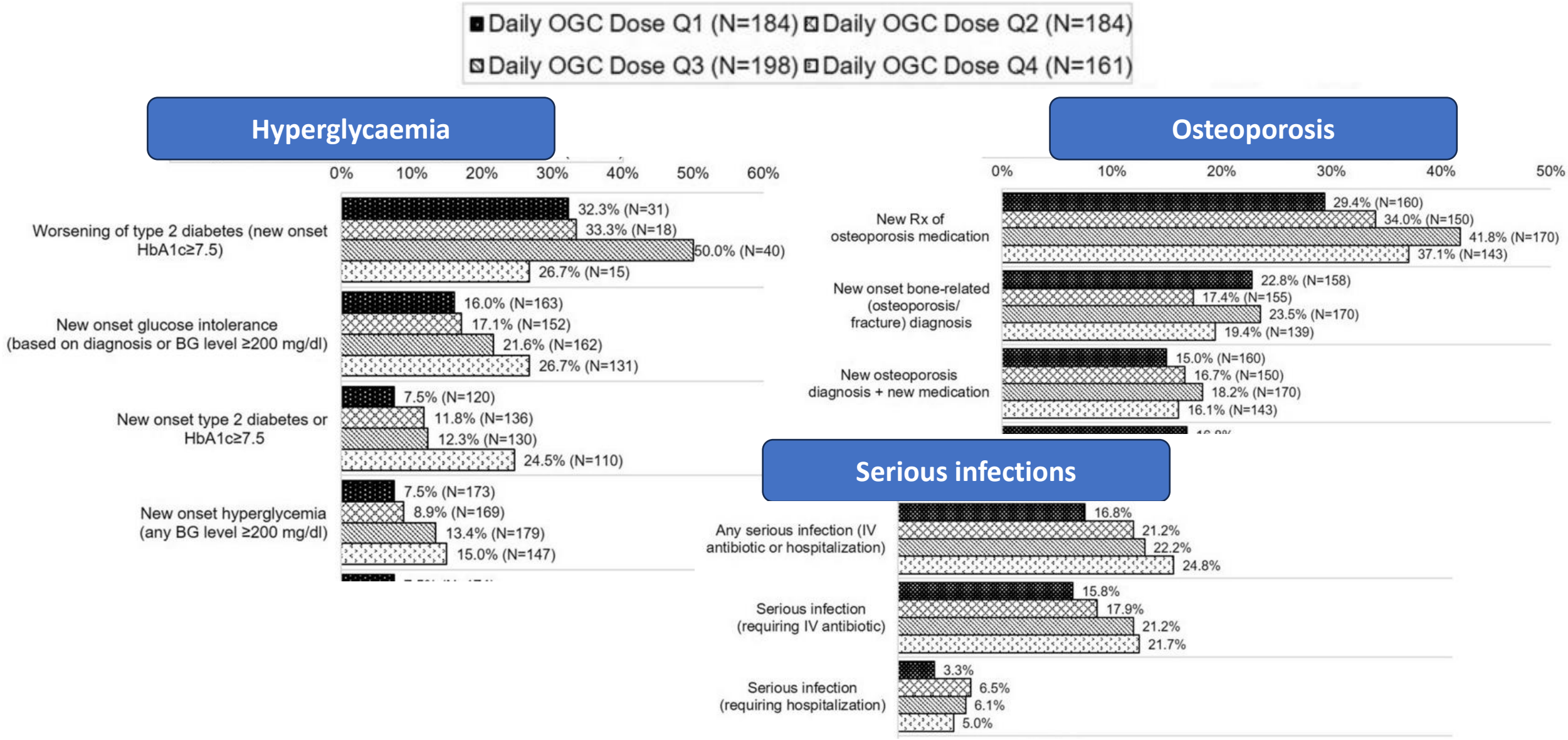
		Group 1 n = 64	Group 2 n = 267	Group 3 n = 425	Group 4 n = 489	Group 5 n = 635	Group 6 n = 475	Group 7 n = 142
AE rate, %		29.7	39.0	37.2	38.4	48.3	50.5	55.6
95% CI, %		18.5-40.9	33.1-44.8	32.6-41.8	34.1-42.8	44.5-52.2	46.0-55.0	47.5-63.8
Cumulative CS exposure, mg	Mean	0*	251.7	1,000.8	2,161.9	4,420.6	7,699.6	12,060.2
	Range	0-0	>0-500	>500-1,500	>1,500-3,000	>3,000-6,000	>6,000-10,000	>10,000-23,260

90% ασθενών είχαν τουλάχιστον 1 AE σχετιζόμενη με τα κορτικοστεροειδή (συχνότερες: καταρράκτης, οστεοπόρωση)

Για κάθε 1000mg αύξηση στην αθροιστική δόση κορτικοστεροειδών, η αύξηση του HR για GCAE ήταν 3%

Broder et al. Seminars Arthritis Rheum 2016;46(2):246-52

Glucocorticoid toxicity and GCA: dose related



Best et al. Rheumatology and Therapy 2019;6:599–610

Glucocorticoid and GCA: frequent relapses

Υποτροπές με τη μείωση της δόσης των κορτικοστεροειδών 34-75%

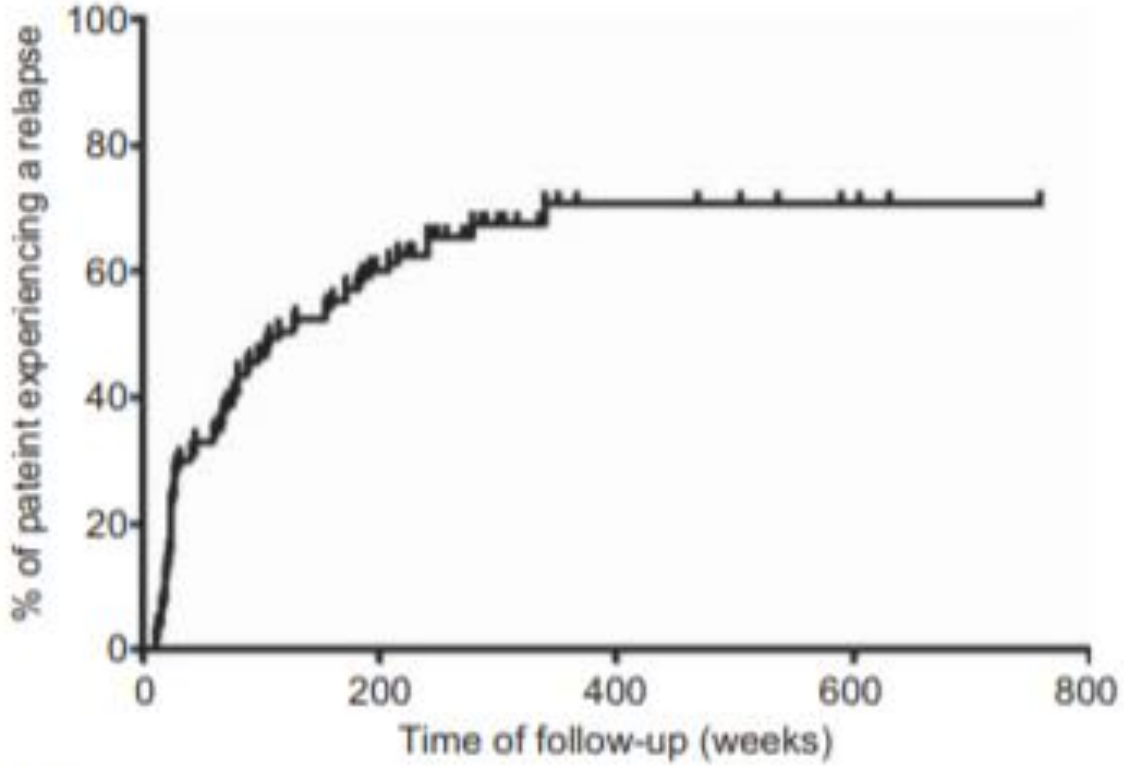
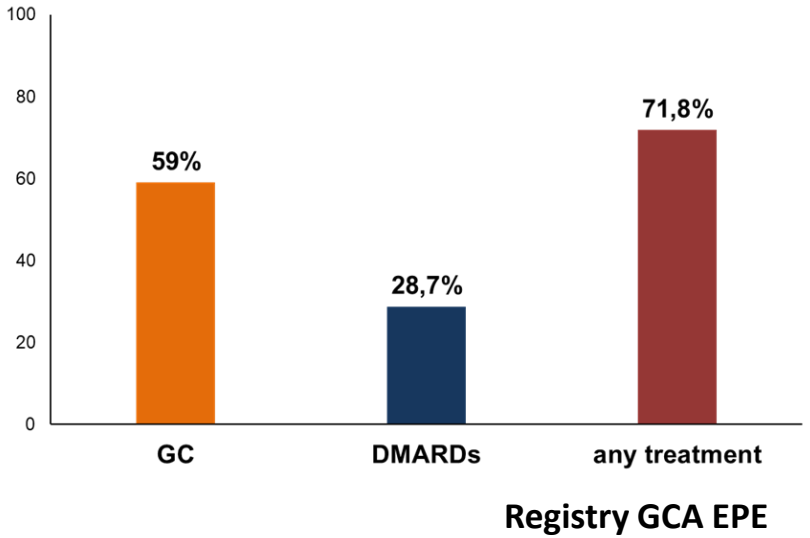


FIGURE 1. Kaplan-Meier plot of the entire series showing the probability of relapse over time.

Alba et al. Medicine 2014;93(5):194-201

Relapses in GCA: Greek registry data

Συνέχιση αγωγής στην επανεκτίμηση



Registry GCA EPE

Variables associated with relapse

Variable	Odds Ratio (95% confidence intervals)	*p*-value
Age	1.04 (0.98, 1.10)	0.20
Female sex	1.73 (0.68, 4.40)	0.25
Duration of the disease	0.85 (0.70, 1.03)	0.09
Treatment (any treatment for GCA)	2.79 (0.29, 26.66)	0.37
Corticosteroids initial dosage at diagnosis (mg)	**1.04 (1.00, 1.08)**	**0.04**
Treatment with DMARDS	1.05 (0.33, 3.30)	0.94
Treatment with bDMARDS	2.30 (0.38, 13.83)	0.37
Large vessel vasculitis at diagnosis	**4.22 (1.14, 15.58)**	**0.03**
ESR at diagnosis	1.00 (0.98, 1.01)	0.64
CVD during follow-up	**4.60 (1.11, 19.13)**	**0.04**

Μόνο **ένας στους τέσσερις** ασθενείς θα διακόψει τη θεραπεία μετά από 2 έτη

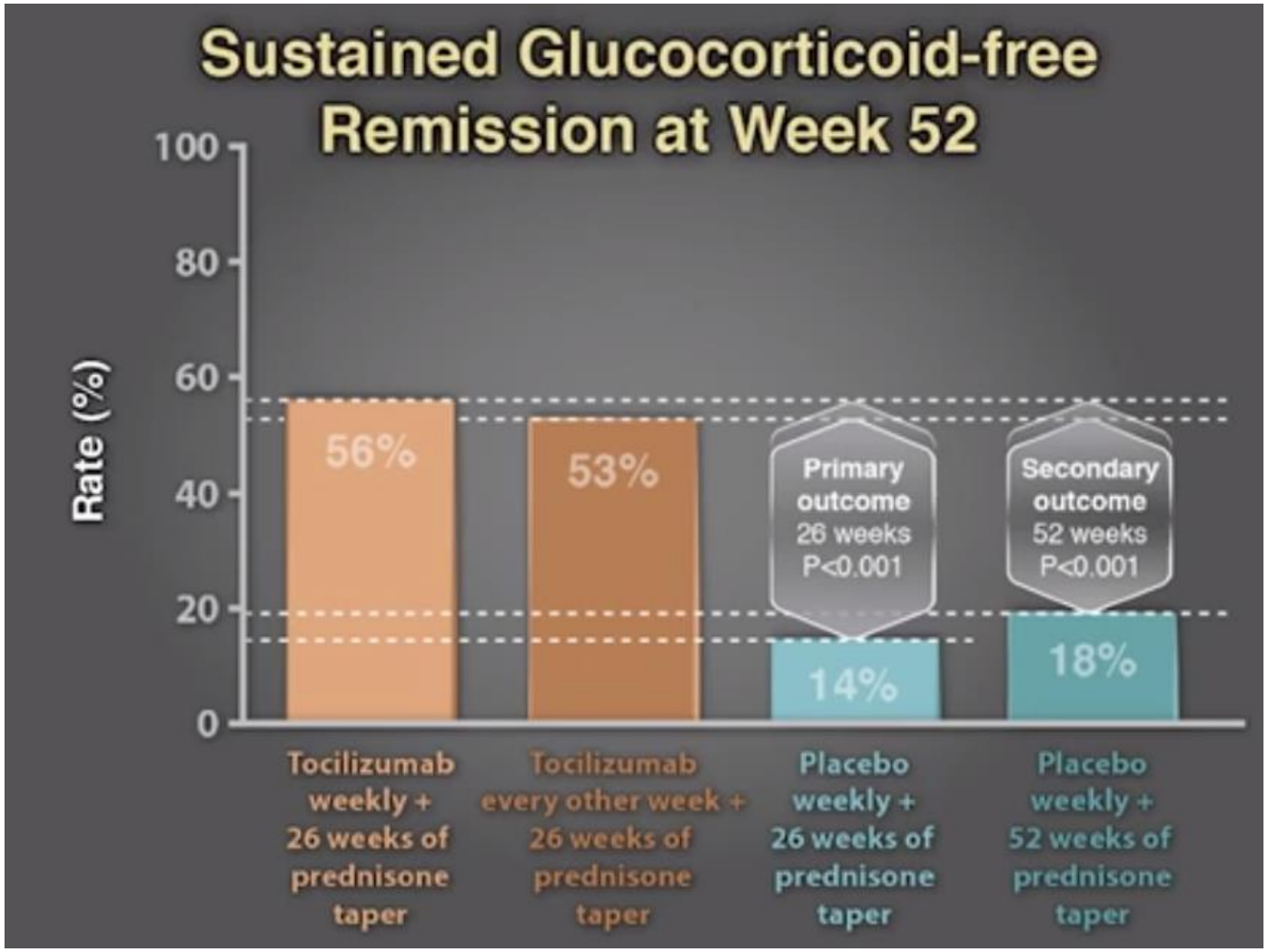
Παράγοντες που σχετίζονται με υποτροπή

- Διάρκεια νόσου
- Δόση κορτικοστεροειδών στη διάγνωση > 40mg
- Παρουσία αγγειίτιδας μεγάλων αγγείων
- Καρδιαγγειακή νόσος κατά το follow-up

Tsalapaki et al. EULAR 2023 POS0735

Targeted therapies in GCA

IL6-inhibition in GCA



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

TCZ QW vs PBO
+
6mo GC

RR for sustained remission 4.0
(95% CI 1.97, 8.12)

Stone et al. NEJM 2017; 377:317-328

IL6-inhibition in GCA

The NEW ENGLAND JOURNAL of MEDICINE
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Trial of Tocilizumab in Giant-Cell Arteritis

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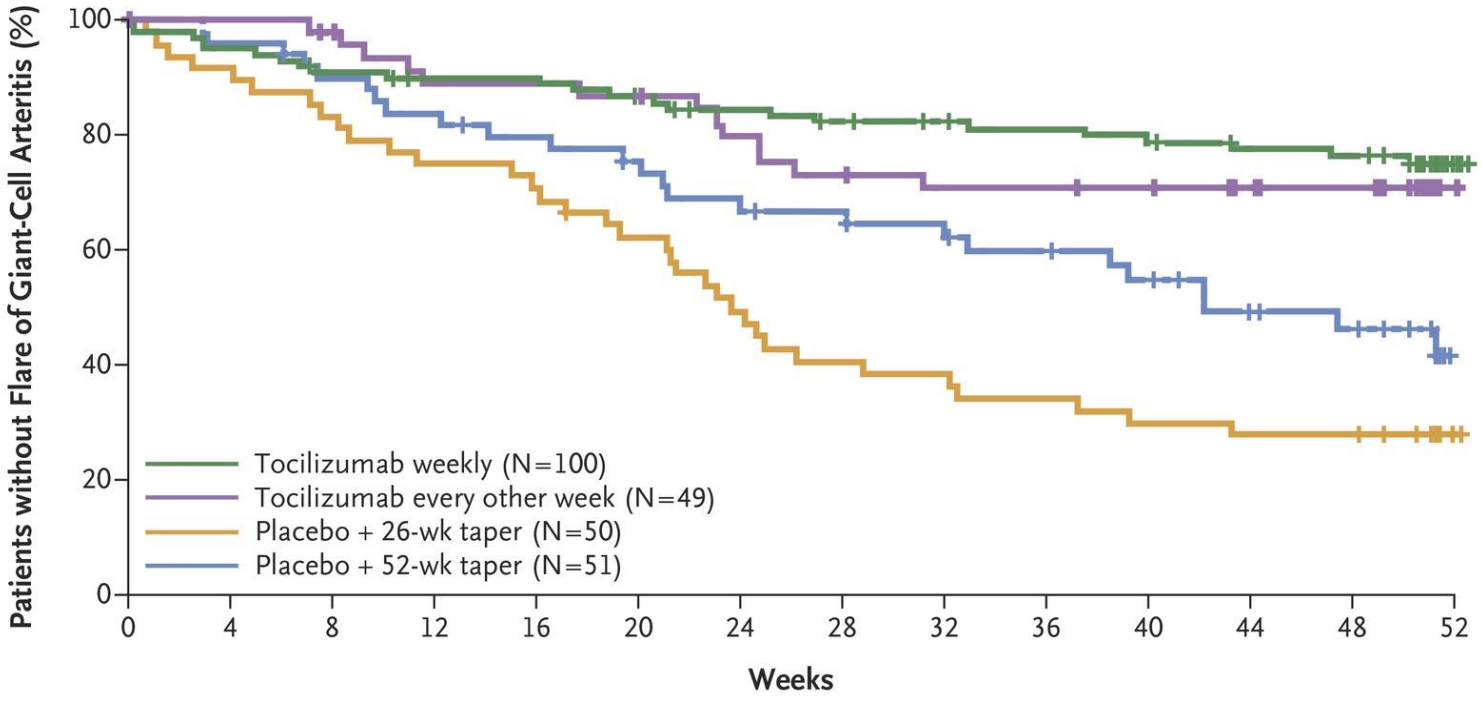


No. at Risk

Tocilizumab weekly	100	93	88	85	85	81	77	74	71	69	67	64	63	5
Tocilizumab every other week	49	47	45	40	40	39	35	32	30	30	29	26	24	2
Placebo + 26-wk taper	50	44	40	36	34	29	23	19	18	16	14	13	13	3
Placebo + 52-wk taper	51	48	44	41	38	35	32	30	28	25	22	17	15	0

Increase in relapse-free survival at 1 year

RR 3.57 (95% CI 2.29-5.55)

Stone et al. NEJM 2017; 377:317-328

Approval of tocilizumab in GCA

FDA NEWS RELEASE

FDA approves first drug to specifically treat giant cell arteritis

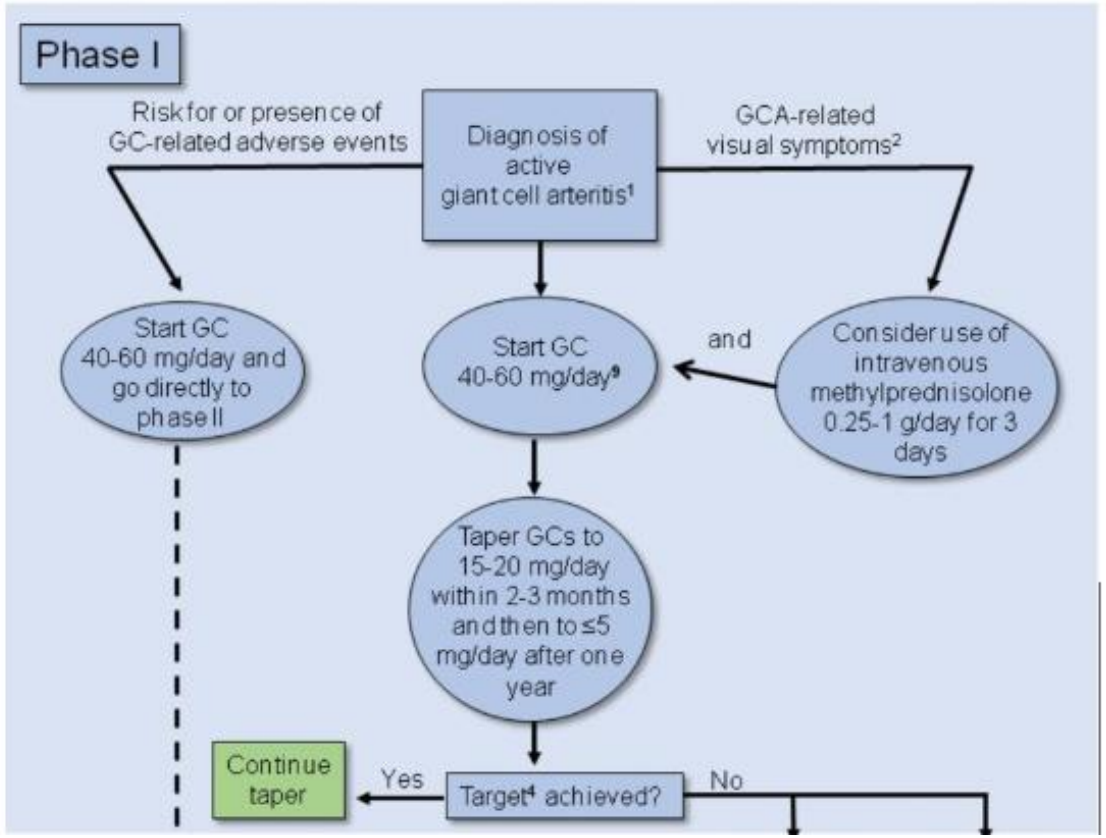
Share Tweet Linkedin Email Print

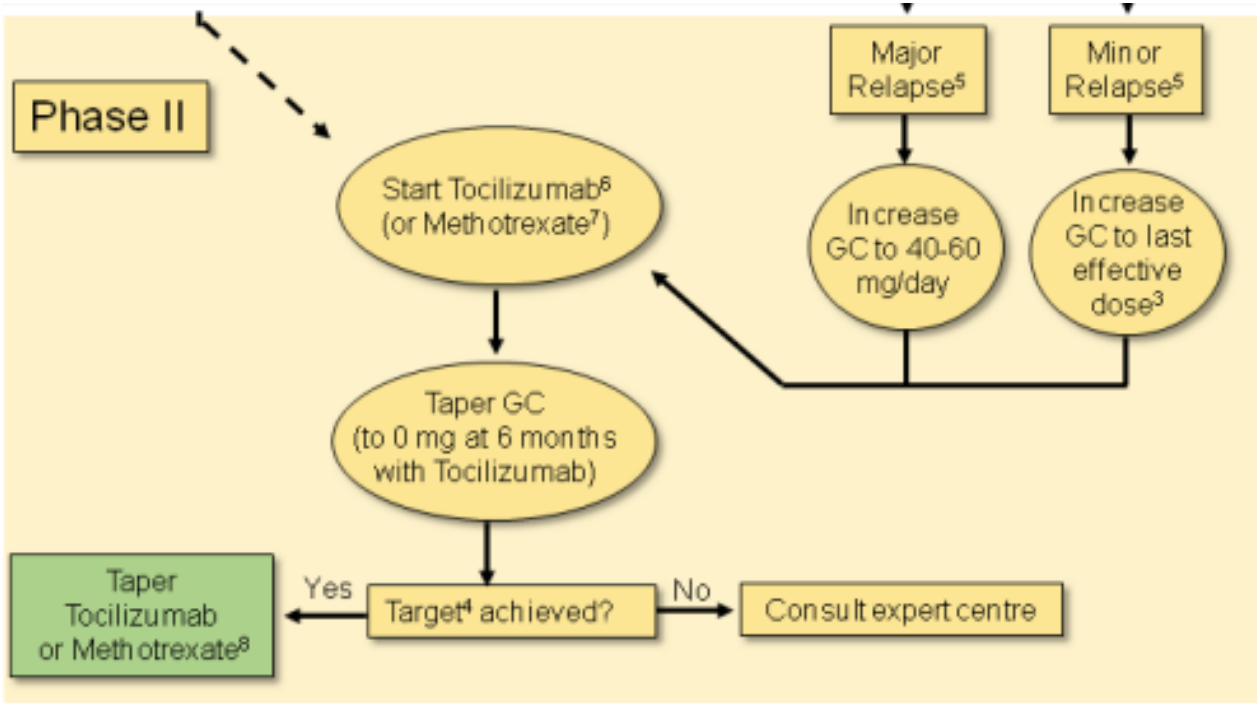
For Immediate Release: May 22, 2017

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 July 2017
EMA/562609/2017
Committee for Medicinal Products for Human Use (CHMP)

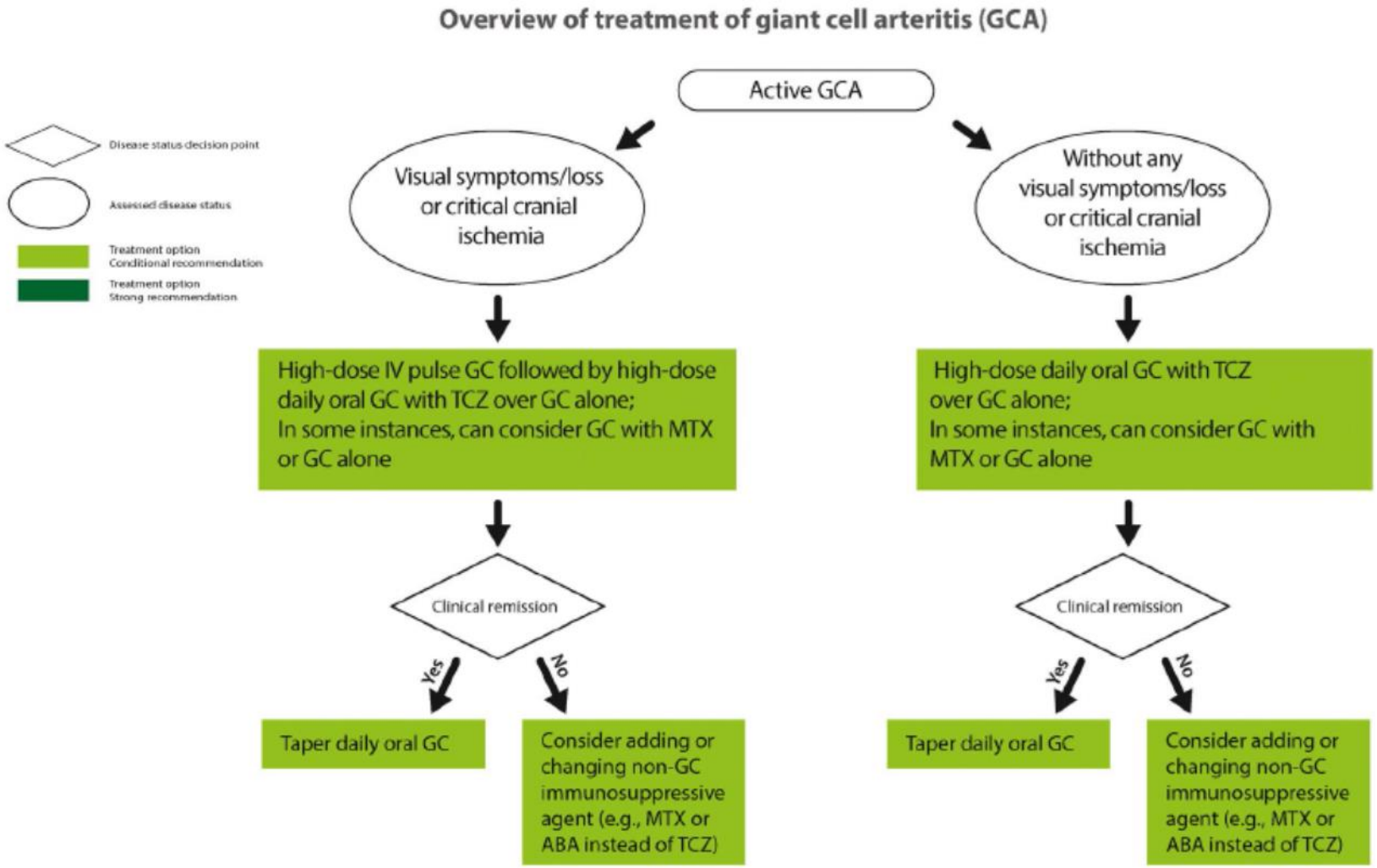
2018 Update of the EULAR recommendations for the management of large vessel vasculitis





Hellmich B, et al. Ann Rheum Dis 2020;79:19–30

2021 ACR/VF Guideline for the management of GCA

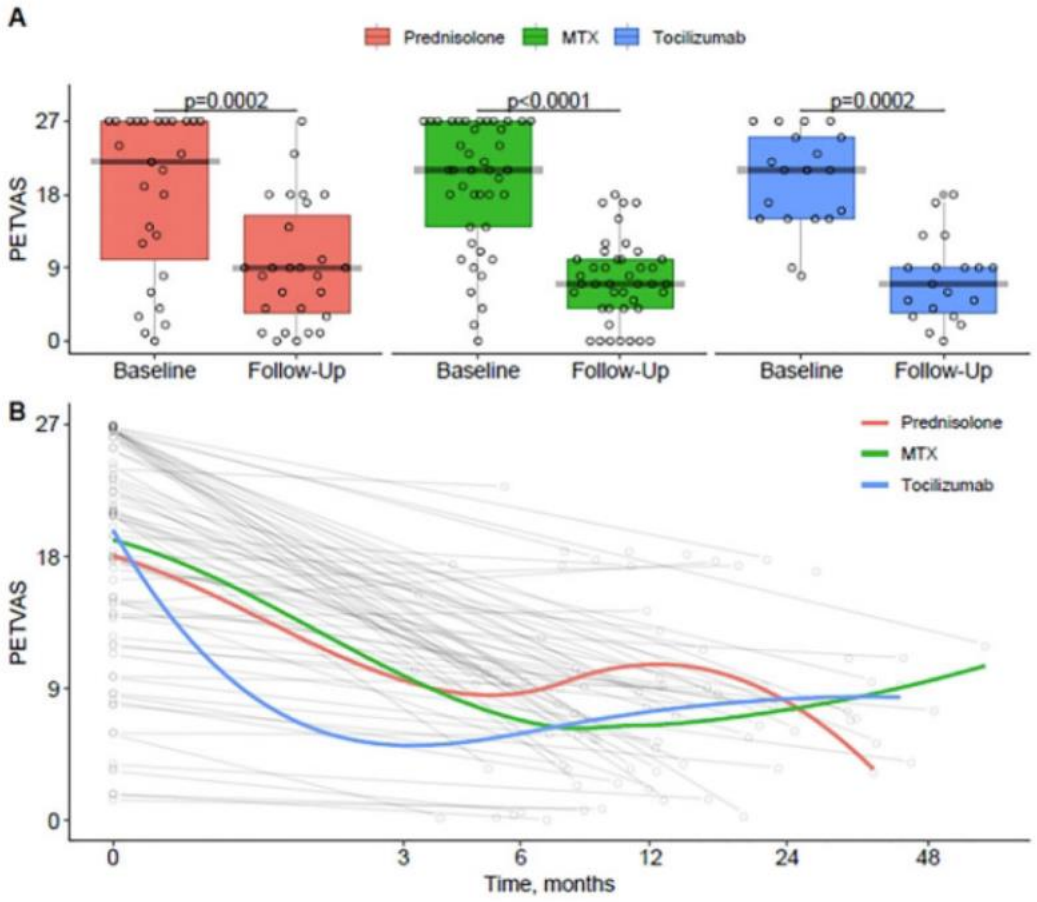


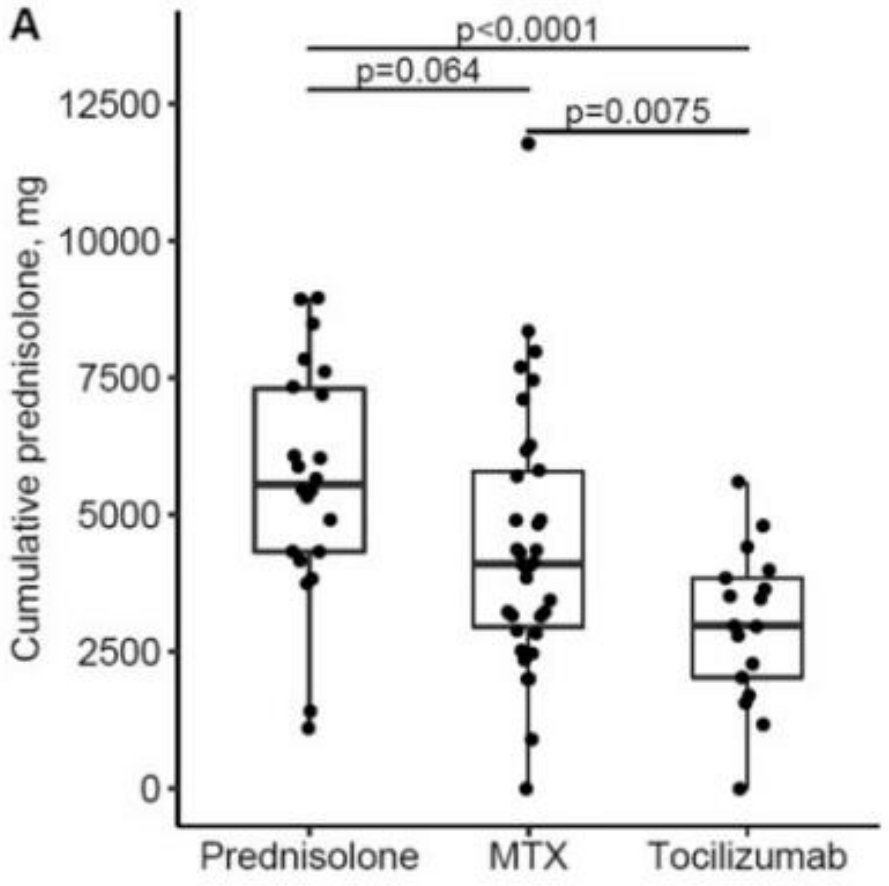
ABA = abatacept, AZA = azathioprine, GC = glucocorticoids, IV = intravenous, MTX = methotrexate, TCZ = tocilizumab

Maz M. et al, Arthritis & Rheumatology 2021

No doubt on the steroid-sparing effect of TOC

RIGA study
n=88 LV-GCA pts





Schonau et al Rheumatology 2021;60(8):3851-61

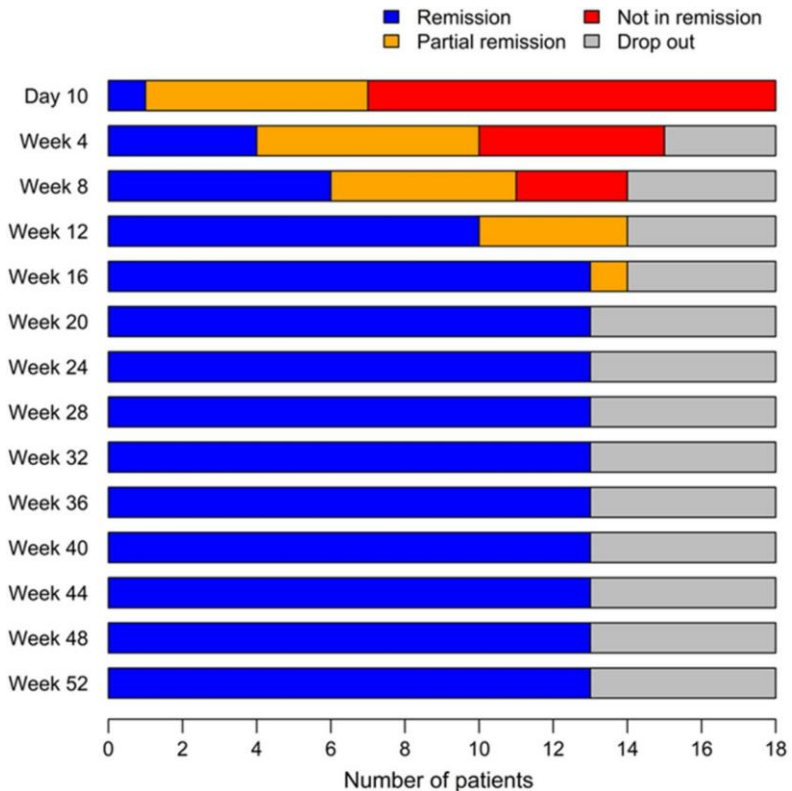
“Ultra-short” GC regimens for GCA

GUSTO study
n=18 GCA pts

Phase 2 open label trial – proof of concept

Intervention

- ✓ IV methylprednisiolone 500mg pulses x 3 (Day 0-2)
- ✓ IV tocilizumab 8mg/kg at Day 3
- ✓ SC tocilizumab 162mg every week until week 52



14/18 (78%) remission within 24 weeks
13/18 (72%) no relapse within 52 weeks

3/18 (17%) no response
1 patient AION at 2 weeks

Christ et al. Lancet Rheumatol 2021;3:e619-26

“Ultra-short” GC regimens for GCA

TOPAZIO study
n=18 LV-GCA pts

Phase 2 open label trial

Intervention

- ✓ IV methylprednisiolone 500mg pulses x 3 (Day 0-2)
- ✓ SC tocilizumab 162mg every week until week 52

PET/CT scans at baseline, wk24 and wk52

Outcome	Week 24	Week 52
Primary end points		
Change in PETVAS compared with baseline, mean differences (95% CI)	−8.6 (−11.5 to −5.7)	−10.4 (−13.6 to −7.2)
P-value	0.001	0.002
Proportion of patients with relapse-free remission, *n* (%, 95% CI)	10/18 (56, 31–78)	8/17 (47, 23–72)
Secondary end points		
Proportion of patients with relapse-free clinical remission, *n* (%, 95% CI)	15/18 (83, 59–96)	13/17 (76, 50–93)
Proportion of patients with relapse-free EULAR remission, *n* (%, 95% CI)	13/18 (72, 47–90)	10/17 (59, 33–82)
Proportion of patients with new aortic dilation, *n* (%, 95% CI)	0	0
End point of interest		
Proportion of patients with progressive aortic damage compared with baseline, *n* (%, 95% CI)	3/16 (19, 4–46)	4/14 (29, 8–58)

PETVAS: PET vascular activity score.

Muratore et al. Rheumatology 2023;00:1-8

Tocilizumab: unanswered questions

Tocilizumab: unanswered questions

1. **Η αναστολή της IL-6 είναι η «πανάκεια» για την GCA;**

2. **Ο έλεγχος της φλεγμονής προλαμβάνει τις αγγειακές επιπλοκές;**

3. **Ποια είναι η κατάλληλη διάρκεια θεραπείας;**

4. **Σε ποιους ασθενείς τελικά να το χρησιμοποιήσουμε; Ισορροπία μεταξύ οφέλους και βλάβης;**

Tocilizumab: unanswered questions

1. **Η αναστολή της IL-6 είναι η «πανάκεια» για την GCA;**
2. **Ο έλεγχος της φλεγμονής προλαμβάνει τις αγγειακές επιπλοκές;**
3. **Ποια είναι η κατάλληλη διάρκεια θεραπείας;**
4. **Σε ποιους ασθενείς τελικά να το χρησιμοποιήσουμε; Ισορροπία μεταξύ οφέλους και βλάβης;**

Relapses still happen on TOC

Arthritis & Rheumatology
AN OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF RHEUMATOLOGY
Original Article | Open Access

Glucocorticoid Dosages and Acute-Phase Reactant Levels at Giant Cell Arteritis Flare in a Randomized Trial of Tocilizumab

John H. Stone MD, MPH, Katie Tuckwell PhD, Sophie Dimonaco MSc, Micki Klearman MD, PhD, Martin Aringer MD, Daniel Blockmans MD, Elisabeth Brouwer MD, PhD, Maria C. Cid MD ... See all authors

Assessment at time of GCA flare	PBO + Pred-26 (n = 50)	PBO + Pred-52 (n = 51)	TCZ-QW + Pred-26 (n = 100)	TCZ-Q2W + Pred-26 (n = 49)
Flare experienced after remission	34 (68.0)	25 (49.0)	23 (23.0)	13 (26.5)
Receiving steroids at time of first flare†¶	21 (61.8)	24 (96)	17 (73.9)	6 (46.2)
Prednisone dosage at flare, median (range) mg/day	2.5 (0.0–30.0)	8.0 (0.0–20.0)	7.0 (0.0–25.0)	0.0 (0.0–12.5)

58%

24%

5mg/d

2mg/d

Stone et al. Arthritis Rheumatol 2019; 71:1329–38

Relapses still happen on TOC

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Assessment at time of GCA flare	PBO + Pred-26 (n = 50)	PBO + Pred-52 (n = 51)	TCZ-QW + Pred-26 (n = 100)	TCZ-Q2W + Pred-26 (n = 49)
CRP level preceding flare, median (range) mg/liter#	23.1 (1.4–119.0)	17.3 (0.2–122.0)	0.4 (0.2–93.2)	1.0 (0.2–18.1)
Presence of elev at time of flare		17 (68)	1 (4)	2 (15)
Presence of elev without flare#		31 (60.8)	5 (5.0)	3 (6.1)
ESR preceding fl (range) mm/h		0 (4.0–138.0)	5.0 (0.0–80.0)	5.0 (1.0–43.0)

- **Το 1/3 όλων των εξάρσεων συνέβη με φυσιολογικούς δείκτες φλεγμονής**
- **Στα TCZ σκέλη της μελέτης το ποσοστό ανέρχεται στο 92%**

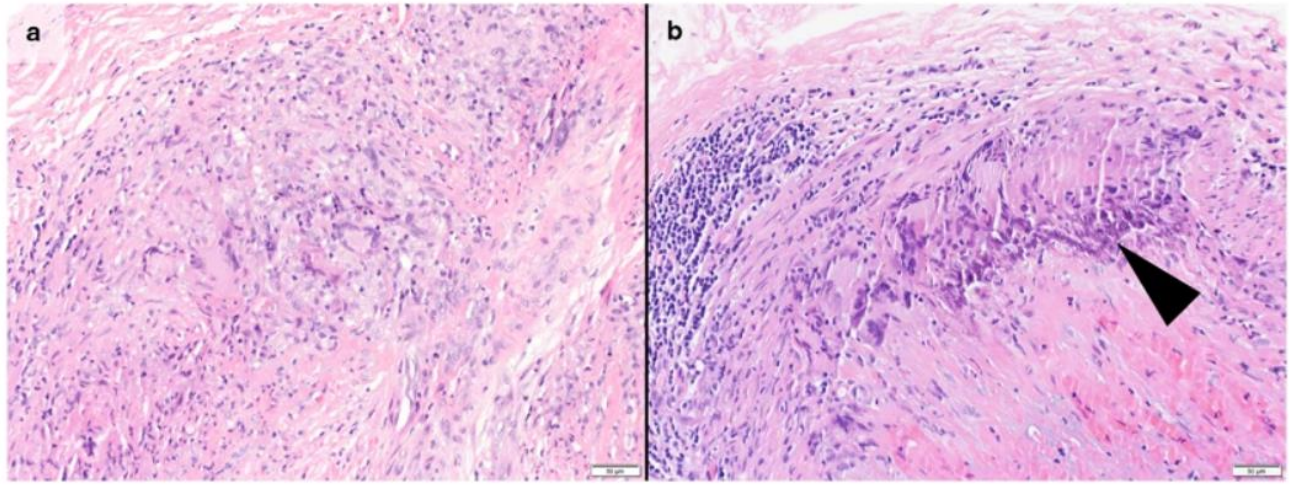
Αξιολόγηση της κλινικής εξέτασης και των συμπτωμάτων του ασθενούς

Stone et al. Arthritis Rheumatol 2019; 71:1329–38

Tocilizumab: unanswered questions

1. Η αναστολή της IL-6 είναι η «πανάκεια» για την GCA;
2. **Ο έλεγχος της φλεγμονής προλαμβάνει τις αγγειακές επιπλοκές;**
3. Ποια είναι η κατάλληλη διάρκεια θεραπείας;
4. Σε ποιους ασθενείς τελικά να το χρησιμοποιήσουμε; Ισορροπία μεταξύ οφέλους και βλάβης;

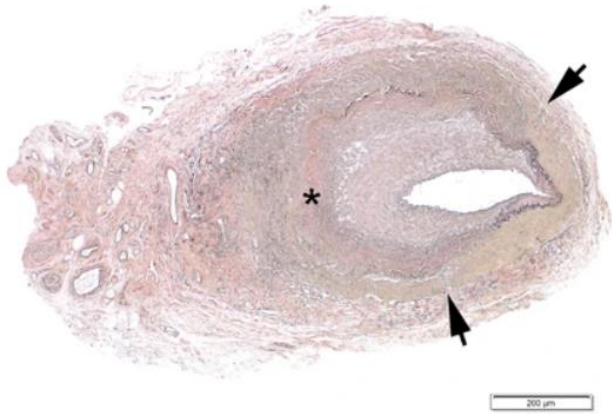
Evidence of microscopic vascular inflammation despite GC therapy



Example Photomicrographs exhibiting (**a**) a temporal artery with active granulomatous arteritis at the time of initial biopsy and (**b**) ongoing active granulomatous arteritis at 6 months, post biopsy (hematoxylin and eosin staining; original magnifications, × 200). Early calcification is also apparent in the follow-up sample (arrowhead).

75% of patients at 6 months

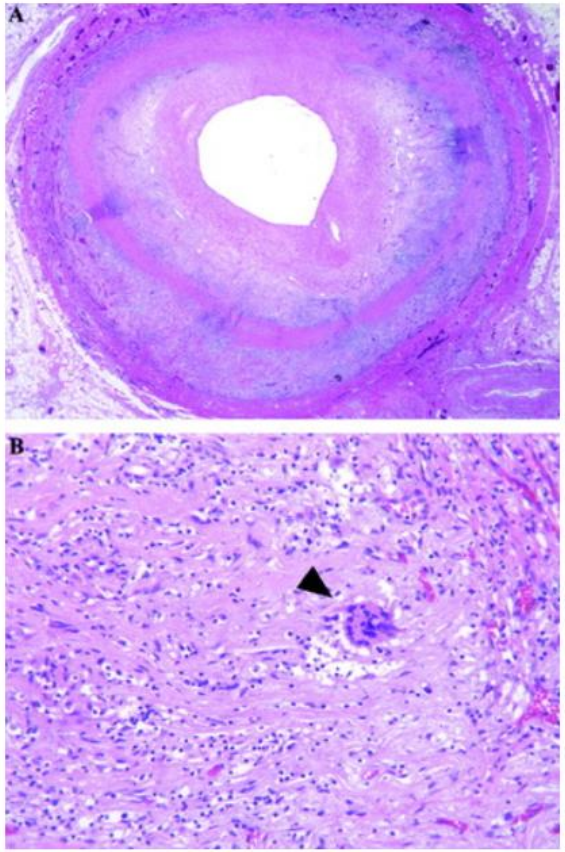
44% of patients at 12 months



Example photomicrograph showing extensive chronic remodeling, characterized by medial disruption (arrows), extensive medial fibrosis (asterisk) and loss of the internal elastic membrane (Verhoeff-van Giesson staining; original magnification, ×

Maleszewski et al. *Mod. Pathol.* **30**, 788–796 (2017)

Ongoing vascular inflammation after TOC treatment



Επιμένουσα φλεγμονή παρά την επίτευξη κλινικής ύφεσης για 6 μ

Unizony et al. Arthritis Care Res 2012; 64:1720-9

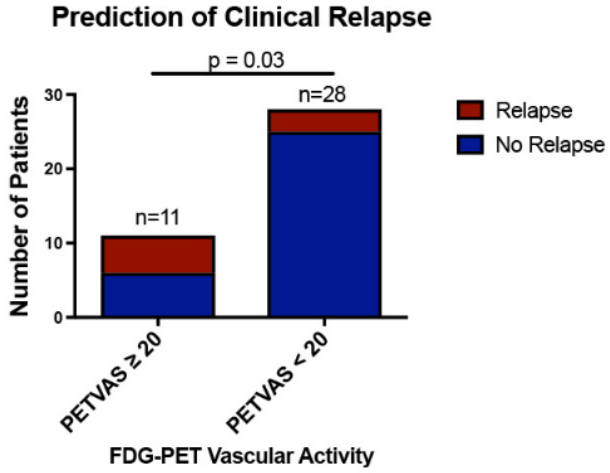
RHEUMATOLOGY
Concise report
Rheumatology 2019;58:1639–1643
doi:10.1093/rheumatology/kez091
Advance Access publication 26 March 2019

Risk of relapse after discontinuation of tocilizumab therapy in giant cell arteritis

Sabine Adler[1,2], Stephan Reichenbach[2], Andrea Gloor[2], Daniel Yerly[3], Jennifer L. Cullmann[4] and Peter M. Villiger[2]

57% των ασθενών που ήταν σε κλινική ύφεση είχαν πρόσληψη σκιαγραφικού στην MRA κατά τη διάρκεια του follow up

Adler et al. Rheumatology 2019; 58:1639–43



Αυξημένη πρόσληψη FDG στο τοίχωμα των μεγάλων αγγείων: αυξημένος κίνδυνος υποτροπής και αγγειακών επιπλοκών (ανευρύσματα)

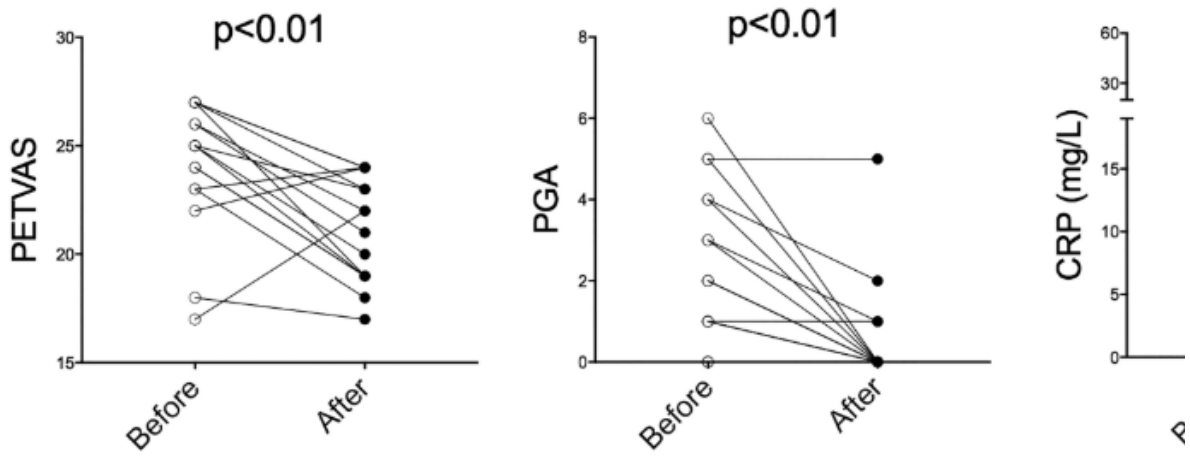
Grayson et al Arthritis Rheumatol 2018;70:439-49
Martínez-Rodríguez et al Semin. Arthritis Rheum2018;47:530-7

Positive PET/CT scans despite TOC treatment

Effect of Treatment on Imaging, Clinical, and Serologic Assessments of Disease Activity in Large-vessel Vasculitis

Shubhasree Banerjee, Kaitlin A. Q
Ali Cahid Civelek, Elaine Novako

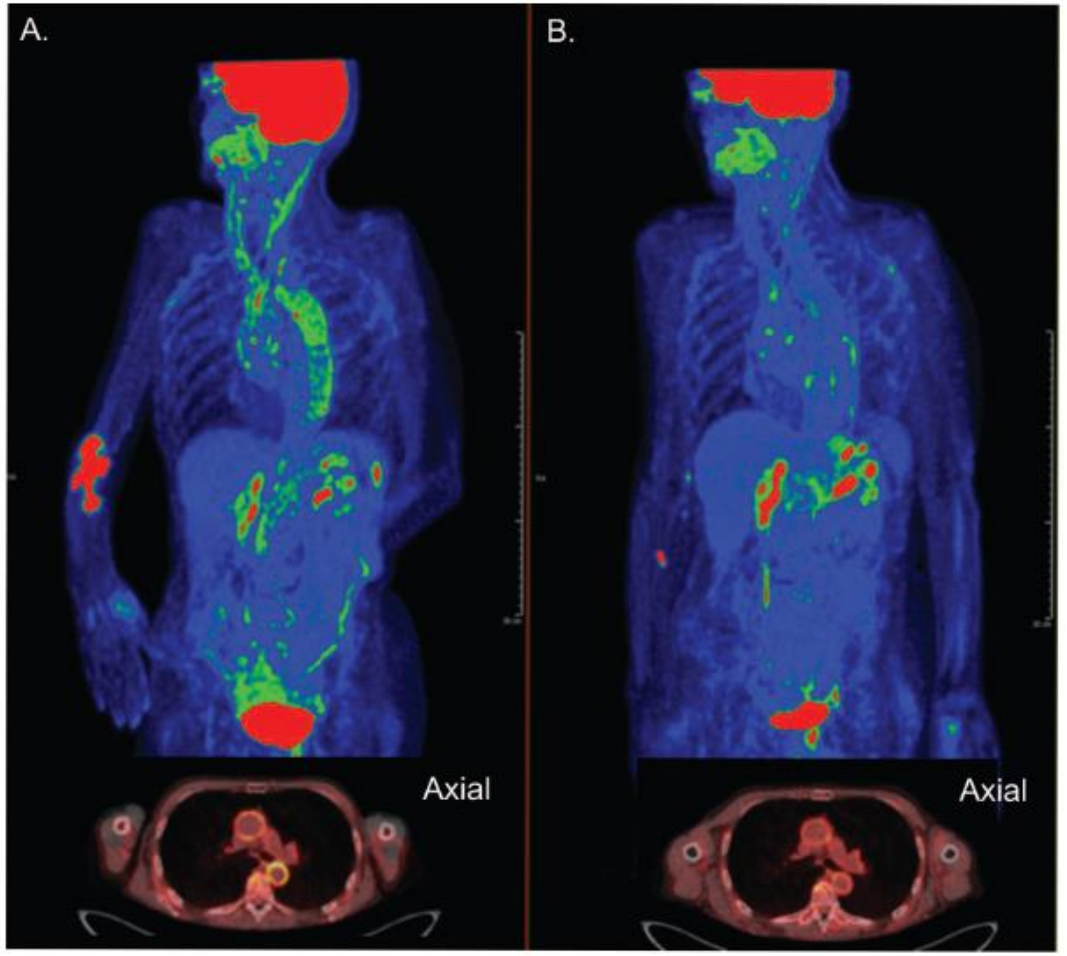
Tocilizumab in Giant Cell Arteritis



Σημαντική βελτίωση στο PETVAS score σε ασθενείς που έλαβαν TCZ

Κλινική ύφεση: 14/17 (82%)

Μόνο 3/17 (18%) είχαν αρνητικοποίηση του PET/CT



Banerjee et al. J Rheumatol 2020 Jan;47(1):99-107

Tocilizumab: unanswered questions

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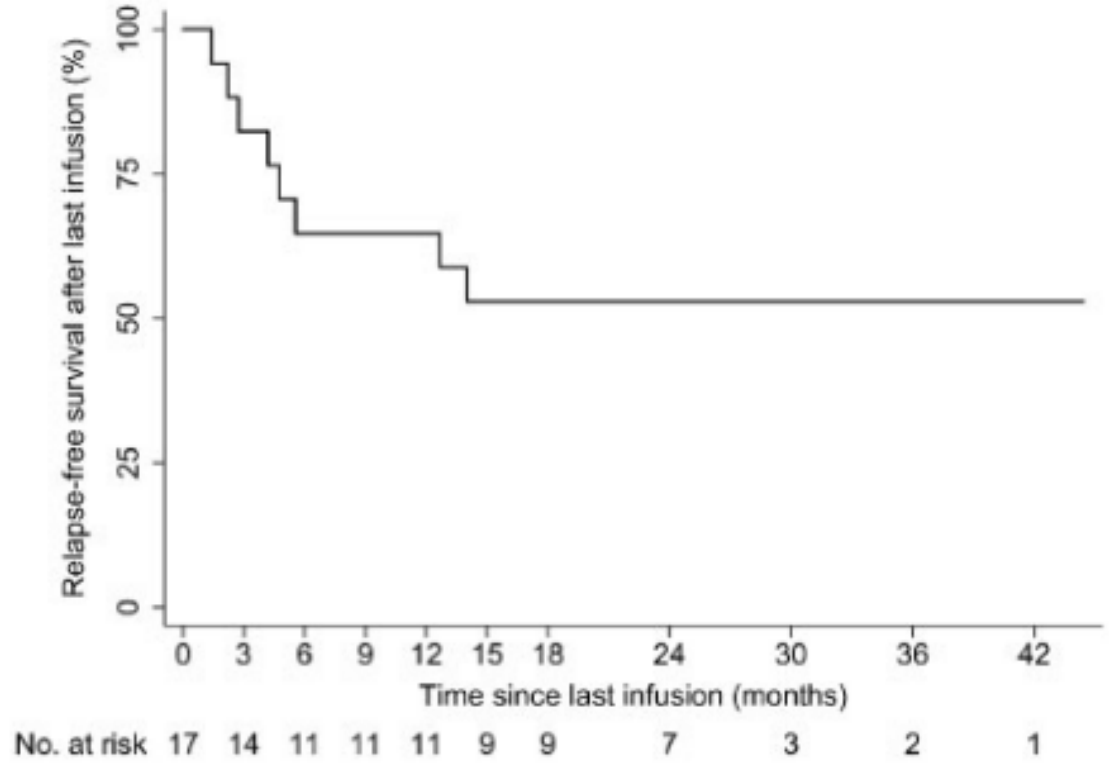
What happens after 1 year of TOC?

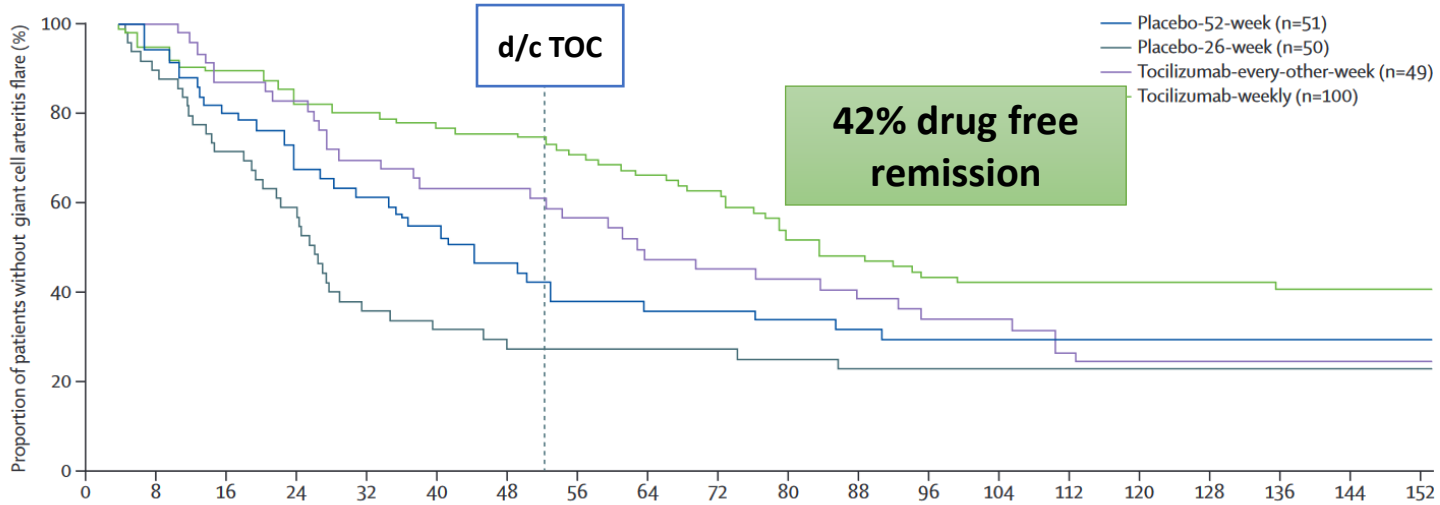
FIG. 1 Kaplan–Meier curve of relapse-free survival after discontinuation of tocilizumab



8/17 pts in remission relapsed after a mean of 6.3 months

Adler et al. Rheumatology 2019;58:1639-43

What happens after 1 year of TOC? GiACTA 2



Number at risk

Placebo-26-week	50	45	41	35	33	28	22	18	17	16	15	14	13	12	12	12	12	12	12	11	11	11	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Placebo-52-week	51	48	44	41	38	35	32	30	29	26	24	22	21	18	18	18	17	17	17	16	16	16	15	14	14	14	14	14	14	14	14	14	14	14	14	13	12	10
Tocilizumab-weekly	100	93	88	85	85	79	75	72	70	68	66	65	64	62	60	57	55	52	49	48	43	40	40	38	36	35	35	35	35	35	35	35	35	35	35	34	34	34	34
Tocilizumab-every-other-week	49	47	46	41	41	39	35	32	31	29	29	29	29	27	25	23	21	21	20	19	19	18	17	17	15	14	14	13	11	10	10	10	10	10	10	10	10	10

	Placebo-26-week	Placebo-52-week	Tocilizumab-weekly	Tocilizumab-every-other-week
In clinical remission at week 52*	33/44 (75%)	34/46 (74%)	81/85 (95%)	36/40 (90%)
Maintained clinical remission throughout part two, regardless of tocilizumab and glucocorticoid treatment†	18/33 (55%)	20/34 (59%)	38/81 (47%)	13/36 (36%)
Maintained clinical remission throughout part two and tocilizumab-free and glucocorticoid-free throughout part two‡	7/18 (39%)	10/20 (50%)	25/38 (66%)	8/13 (62%)
In clinical remission at week 52 and receiving no tocilizumab and glucocorticoid treatment at week 52*	12/44 (27%)	16/46 (35%)	59/85 (69%)	28/40 (70%)
In clinical remission at week 52, receiving no tocilizumab and glucocorticoid treatment at week 52, and maintained tocilizumab- and glucocorticoid-free clinical remission throughout part two§	7/12 (58%)	10/16 (63%)	25/59 (42%)	8/28 (29%)

TOC every week arm

85 pts in clinical remission at wk52

59 pts in clinical remission at wk52 off treatment

25 pts in clinical remission drug free and for the whole of part 2

29% drug free remission at year 3

Stone et al. Lancet Rheumatol 2021;3(5):e328-36

One year is not enough – maybe taper TOC instead?

TCZOPT study
n=231 GCA pts
in prolonged remission

After a median of 12 months : **TCZ dose optimisation**
IV TCZ from 8 to 4mg/kg/4weeks in (44%)
SC TCZ from 162mg/w to 162mg/every-other-week (65%)

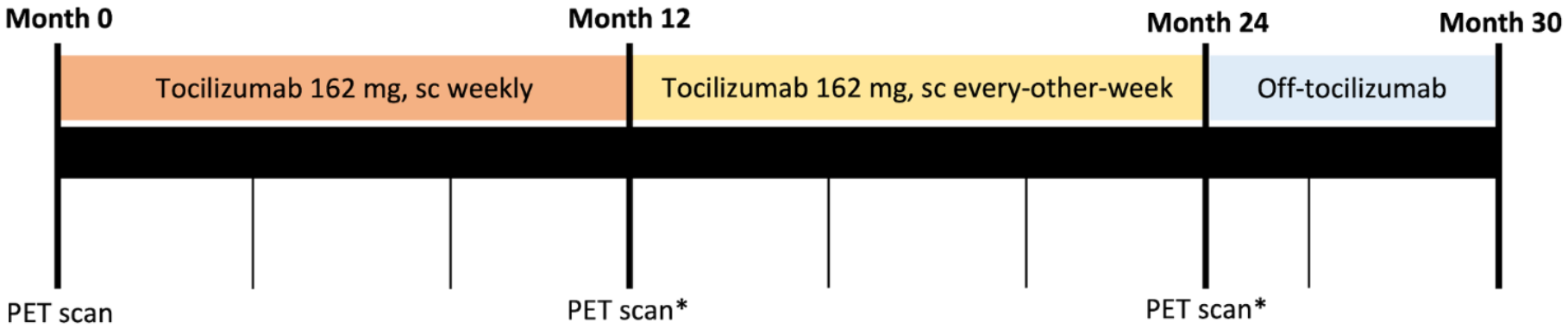
	Optimised TCZ Group (n=125)	Non-optimised TCZ Group (n=106)	*p*
Follow-up on TCZ therapy (months), median [IQR]	24 [19-24]	20 [14-24]	0.001
Prolonged remission at the end of follow-up, n (%)	68/87 (78.2)	80/95 (84.2)	0.296
Patients with relapses, n (%)	7 (5.6)	11 (10.4)	0.177
Side effects, n (100 patients-year)			
Serious side-effects	29 (12.9)	26 (15.3)	0.813
Severe infections	15 (6.6)	22 (12.9)	0.009

IQR: interquartile range; TCZ: tocilizumab.

Calderon-Goercke et al. Clin Exp Rheumatol 2023;41(4):829-36

One year is not enough – maybe taper TOC instead?

Italian prosective study
n=23 GCA pts



Only two patients (**9%**) experienced a **minor clinical relapse** while on every-other-week tocilizumab monotherapy

Tomelleri et al. Seminar Arthritis Rheum 2023;59:152-74

Tocilizumab: unanswered questions

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TOC safety data in GCA

Variable	Tocilizumab Weekly (N=100)	Tocilizumab Every Other Week (N=49)	Placebo +26-Wk Taper (N=50)	Placebo +52-Wk Taper (N=51)
Duration in trial — patient-yr	92.9	45.6	47.4	48.1
Patients with ≥1 adverse event — no. (%)	98 (98)	47 (96)	48 (96)	47 (92)
Adverse events				
No. of events	810			
Rate per 100 patient-yr (95% CI)	872.0 (813.0–934.2)	(		
Patients with ≥1 infection — no. (%)				
Any	75 (75)			
Serious	7 (7)			
Patients who withdrew from the trial because of adverse events — no. (%)†	6 (6)			
Patients with injection-site reaction — no. (%)	7 (7)			
Flare of giant-cell arteritis reported as serious adverse event — no. (%)‡	1 (1)			
Patients with ≥1 serious adverse event — no. (%)				
Any	15 (15)			
According to system organ class¶				
Infection or infestation	7 (7)			
Vascular disorder	4 (4)			
Respiratory, thoracic, or mediastinal disorder	2 (2)			
Injury, poisoning, or procedural complication	3 (3)			
Nervous system disorder	1 (1)	1 (2)	2 (4)	1 (2)
Cardiac disorder	2 (2)	0	0	2 (4)
Musculoskeletal or connective-tissue disorder	1 (1)	0	1 (2)	2 (4)
Gastrointestinal disorder	1 (1)	0	2 (4)	0
Cancer	0	0	1 (2)	1 (2)

	Never-received-tocilizumab n=101	Ever-received-tocilizumab n=199
Total patient-years at risk*	193·8	492·7
Total adverse events	1233; 636·3 (601·3–672·9)	2652; 538·3 (518·0–559·2)
Serious adverse events	45; 23·2 (17·0–31·1)	125; 25·4 (21·1–30·2)
Death	0	4†
Infections	236; 121·8 (106·8–138·4)	592; 120·2 (110·7–130·2)
Serious infections	9; 4·6 (2·1–8·8)	17; 3·5 (2·0–5·5)
Malignancy	4; 2·1 (0·6–5·3)	9; 1·8 (0·8–3·5)
Stroke	3; 1·6 (0·3–4·5)	8; 1·6 (0·7–3·2)
Myocardial infarction	0	3; 0·6 (0·1–1·8)
Gastrointestinal perforation	0	1; 0·2 (0·0–1·1)

Stone et al. NEJM 2017; 377:317-328; Stone et al. Lancet Rheumatol 2021;3(5):e328-36

TOC safety data in GCA: real life?

UK descriptive study
n=22 GCA pts

RMD Open
Rheumatic & Musculoskeletal Diseases

Clinical case

Efficacy and safety of tocilizumab in giant cell arteritis: a single centre NHS experience using imaging (ultrasound and PET-CT) as a diagnostic and monitoring tool

Table 3 Adverse events on TCZ

Patient	Adverse event	TCZ outcome	Duration of TCZ suspension
Patient 1	Varicella Zoster infection	Restarted	6 weeks
Patient 3	Chicken pox	Restarted	4 weeks
Patient 4	Dental abscess	Restarted	8 weeks
Patient 5	Myocardial infarction	Restarted	2 weeks
Patient 6	Severe allergic reaction	Discontinued	–
Patient 8	Leg ulcer	On Hold	3 weeks
Patient 10	Injection site reaction	Restarted	7 weeks
Patient 13	Bladder cancer	Discontinued	–
Patient 16	Urinary tract infection	Restarted	2 weeks

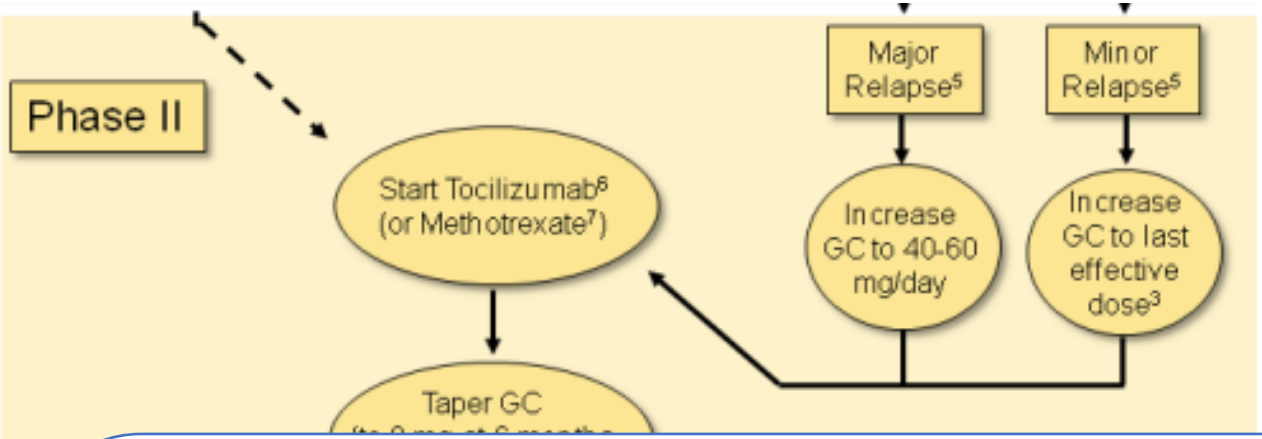
US retrospective study
n=65 GCA pts

Table 4 Safety in patients with GCA

	(N=65)
Patients with ≥1 AE	48 (73.8)
Total no of non-serious AEs	121
Related or possibly related to prednisone exclusively*	23 (19.0)
Related or possibly related to TCZ exclusively*	48 (39.7)
Related or possibly related to prednisone or TCZ*	9 (7.4)
Patients with ≥1 SAE	11 (16.9)
Total no of SAEs	13
Related or possibly related to prednisone exclusively†	3 (23.1)
Diabetic ketoacidosis	1
Stroke	1
Vertebral fracture	1
Related or possibly related to TCZ exclusively†	4 (30.8)
Bacteraemia of unclear source	1
COVID-19	1
Diverticulitis	1
Postsurgical skin and soft-tissue infection	1
Related or possibly related to prednisone or TCZ†	2 (15.4)
Pneumonia	1
Sepsis from urinary tract infection	1

Sebastian et al. RMD Open 2020 Nov;6(3):e001417. Matza et al. RMD Open 2023;9:e002923

In the end: when to use TOC?



Adjunctive therapy should be used in selected patients with GCA (refractory or relapsing disease, the presence or an increased risk of GC related adverse effects or complications) using TCZ. Methotrexate may be used as an alternative

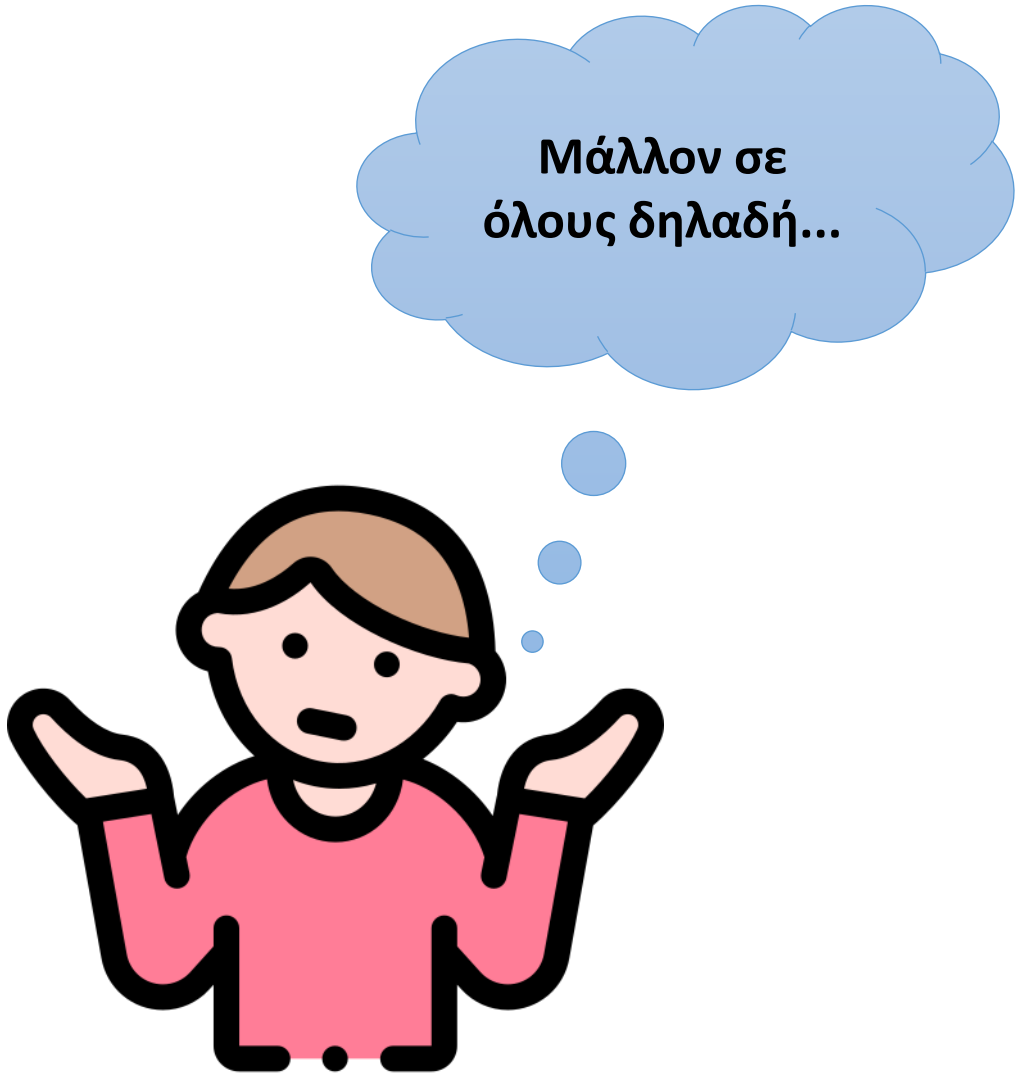
The original recommendations suggested adjunctive immunosuppressive therapy in all patients with LVV. However, although the risk of relapse in GCA is high, a substantial number of patients with GCA treated with GC monotherapy do not relapse and are able to taper the GC dose according to a target of ≤5 mg/day after 1 year,[49 50 52] a dose which the EULAR task force considered to be acceptably safe.[68] Therefore, we recommend limiting the use of adjunctive therapy to patients who have already developed, or have either an increased risk of developing GC-related side effects or complications, such as osteoporosis, diabetes, cardiovascular disease or glaucoma, or for relapsing patients irrespective of other risk factors. Given the high prevalence of comorbidities in the elderly population affected by GCA, the decision to use adjunctive immunosuppressive therapy in the individual patient should be balanced against potential risks for treatment-related complications, such as the increased risk of lower intestinal perforations reported in patients with rheumatoid arthritis receiving TCZ.[69]So far, no consistent factors have been identified at the time of diagnosis to predict an increased relapse risk and risk for sub
[55] Therefore, the identification of reliable predictive factors for relapse and prolonged
topic for future research.

Εξατομίκευση θεραπείας

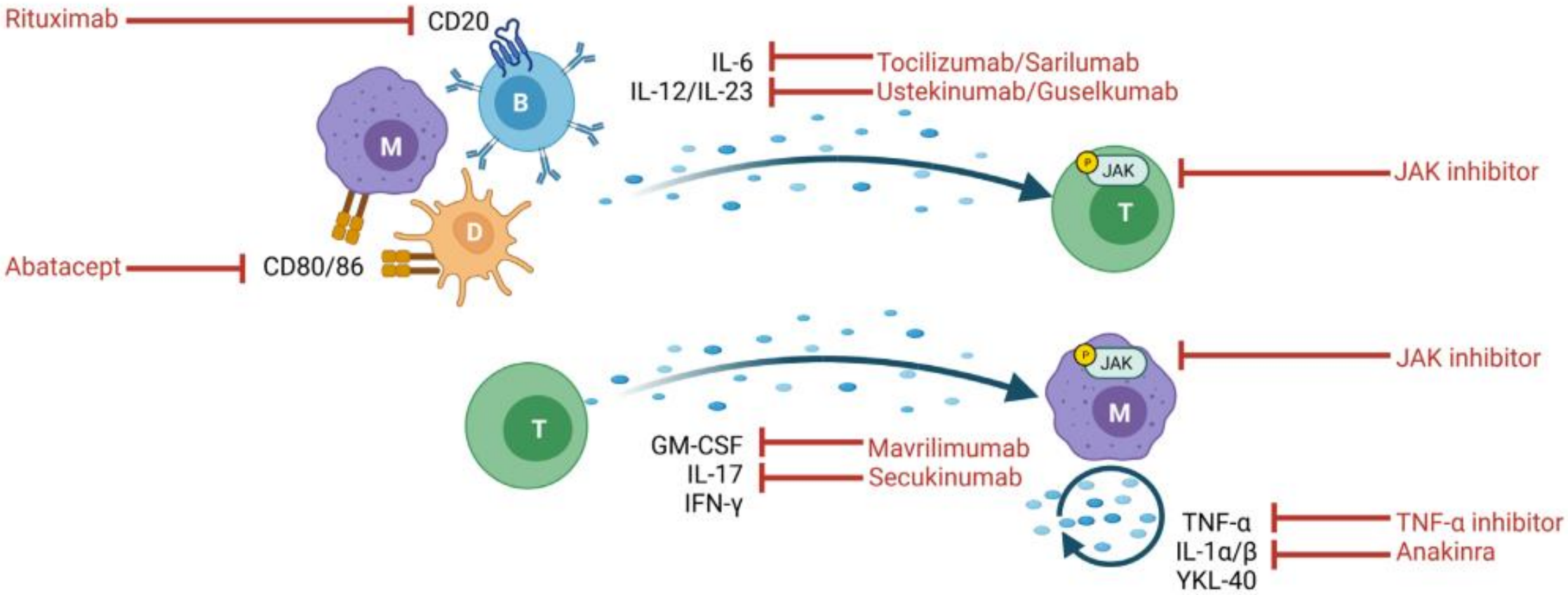
Hellmich B, et al. Ann Rheum Dis 2020;79:19–30

In the end: when to use TOC?

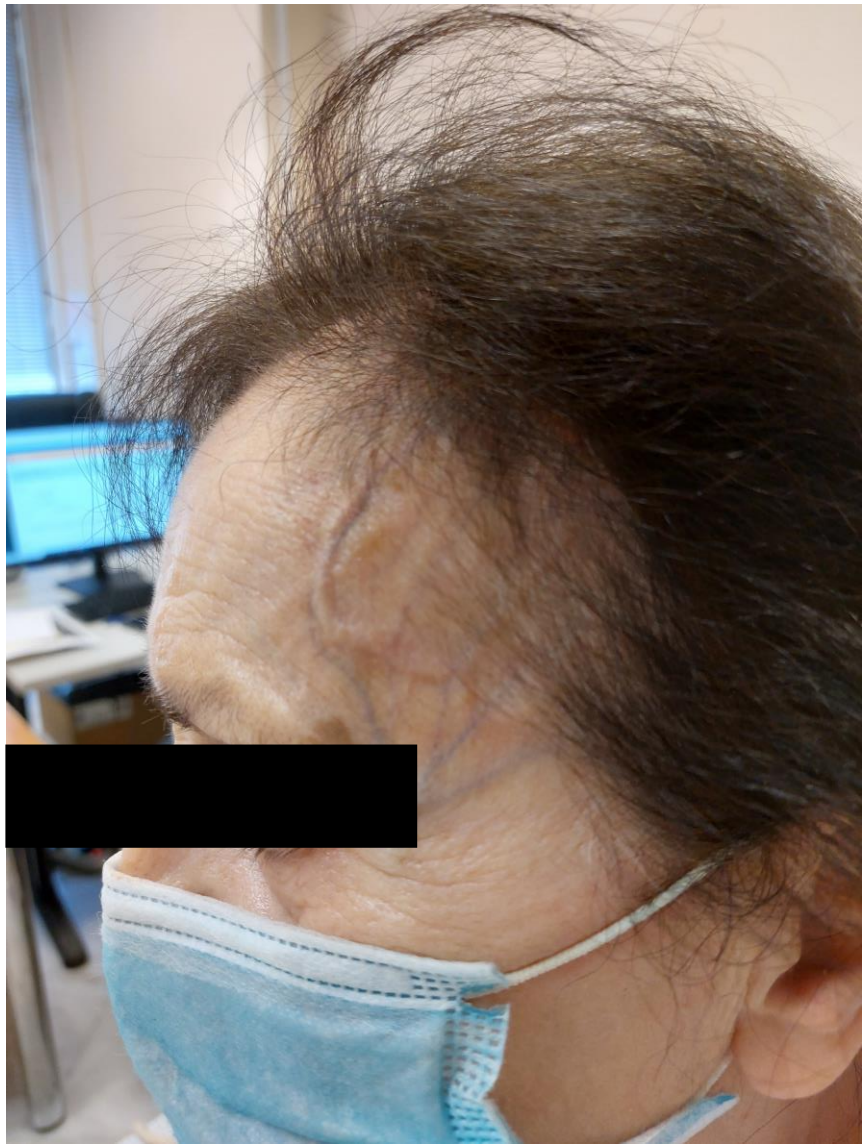
- ✓ **Ανθεκτική νόσος**
- ✓ **Υποτροπιάζουσα νόσος**
- ✓ **Παρουσία παραγόντων κινδύνου για GCAEs**
- ✓ **Παρουσία παραγόντων κινδύνου για επιπλοκές**



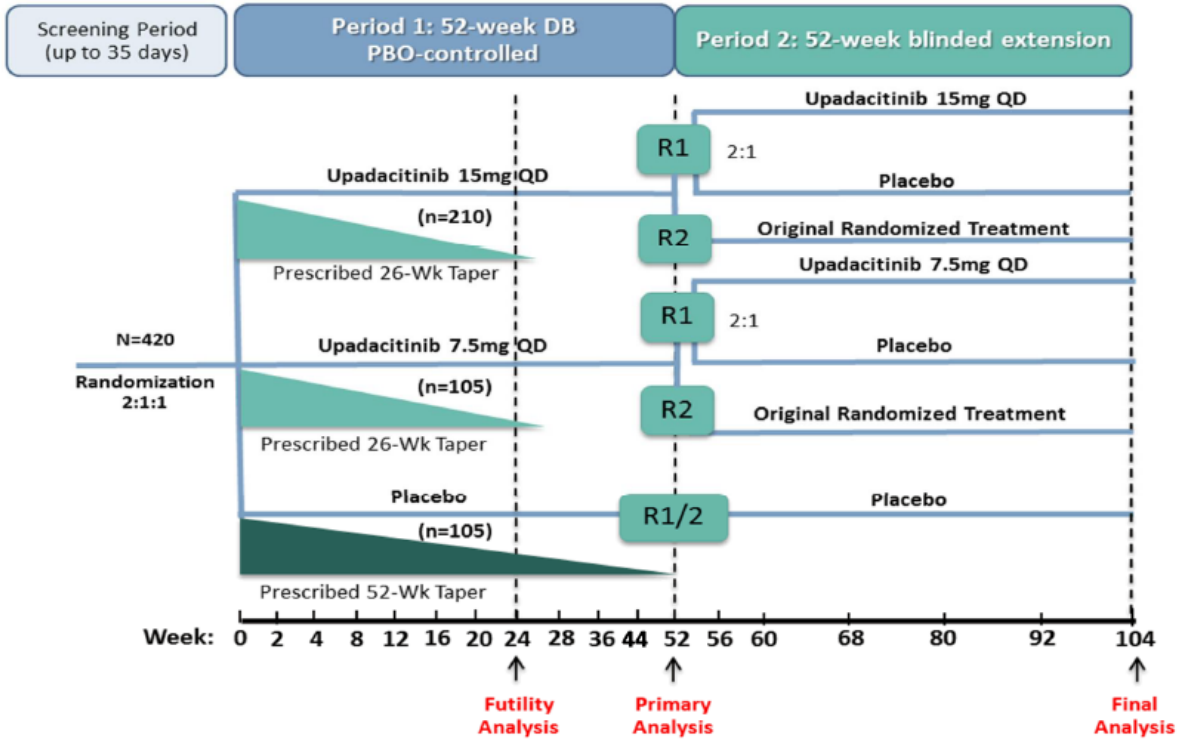
Other targeted treatments



Case: follow up



Κλινική μελέτη



R1 = sustained remission for 24 consecutive weeks prior to Week 52; R2 = remission at Week 52 only

Visit month 9: χωρίς κλινική υποτροή

Conclusions

- Τα κορτικοστεροειδή είναι απαραίτητα στην αρχική θεραπεία, αλλά πρέπει να χρησιμοποιούνται για το μικρότερο δυνατό διάστημα
- Η στοχευμένη θεραπεία είναι το παρόν και το μέλλον στην GCA
- Η αναστολή της IL-6 έχει υψηλή αποτελεσματικότητα και αποδεδειγμένα αποτελέσματα στο steroid sparing
- Χρήση σε ασθενείς με ανθεκτική ή υποτροπιάζουσα νόσο και σε ασθενείς με υψηλό κίνδυνο για επιπλοκές από τα κορτικοστεροειδή...
  ...δηλαδή σε όλους???
- Research!!!! – νέες υποσχόμενες θεραπείες