SETOGiA
SEcukinumab vs TOcilizumab for the treatment of Giant Cell Arteritis

Phase 3 therapeutic trial
Objective: PHRC-N 2024

Conseil scientique GFEV – 5 septembre 2024

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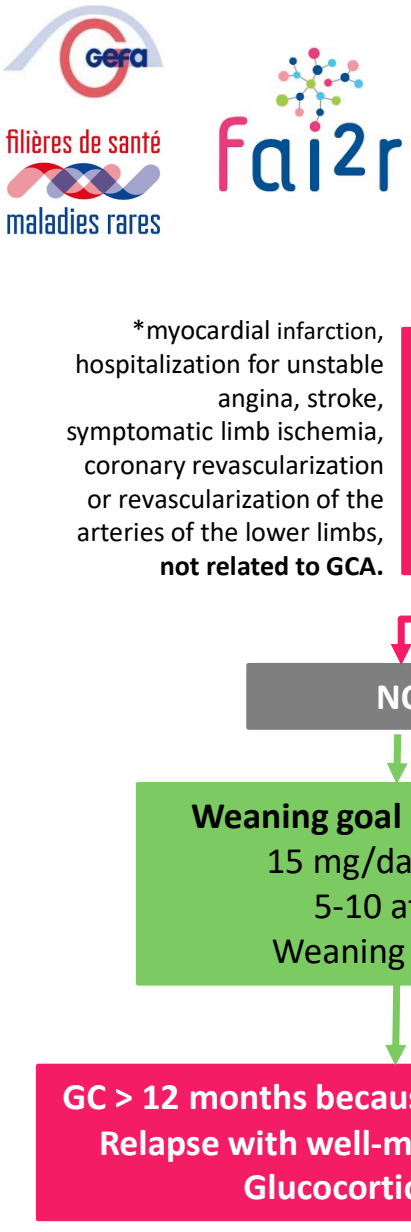
French recommendations 2024

Protocole National de Diagnostic et de Soins

Artérite à Cellules Géantes (Horton)

Valérie Devauchelle-Pensec
Hubert De Boysson
Maxime Samson



*myocardial infarction, hospitalization for unstable angina, stroke, symptomatic limb ischemia, coronary revascularization or revascularization of the arteries of the lower limbs, **not related to GCA.**

** delay <6 months possible after expert opinion

Tocilizumab is increasingly prescribed in GCA

Prescriptions will continue to rise

However, tocilizumab does not solve all problems…

- **Safety:**
  - Diverticulosis contraindicated
  - Liver toxicity, neutropenia
  - Altered lipid balance

- **Efficacy and physiopathology:**
  - TCZ non-responders
    - *IL6R* polymorphism through IL-17 production (*Grayson, ACR 2024*)

- **Patient follow up by the physician:**
  - Inability to use CRP, ESR for monitoring disease activity

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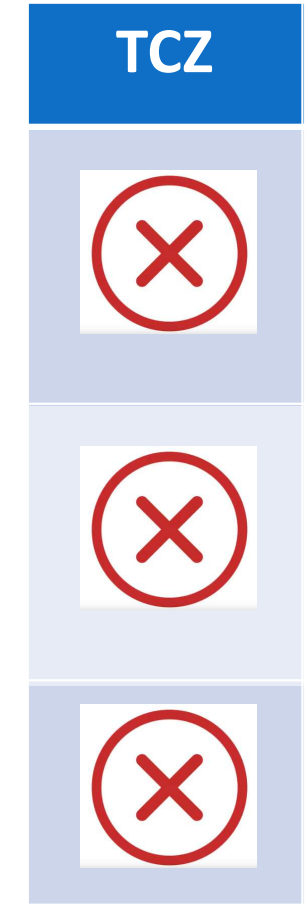


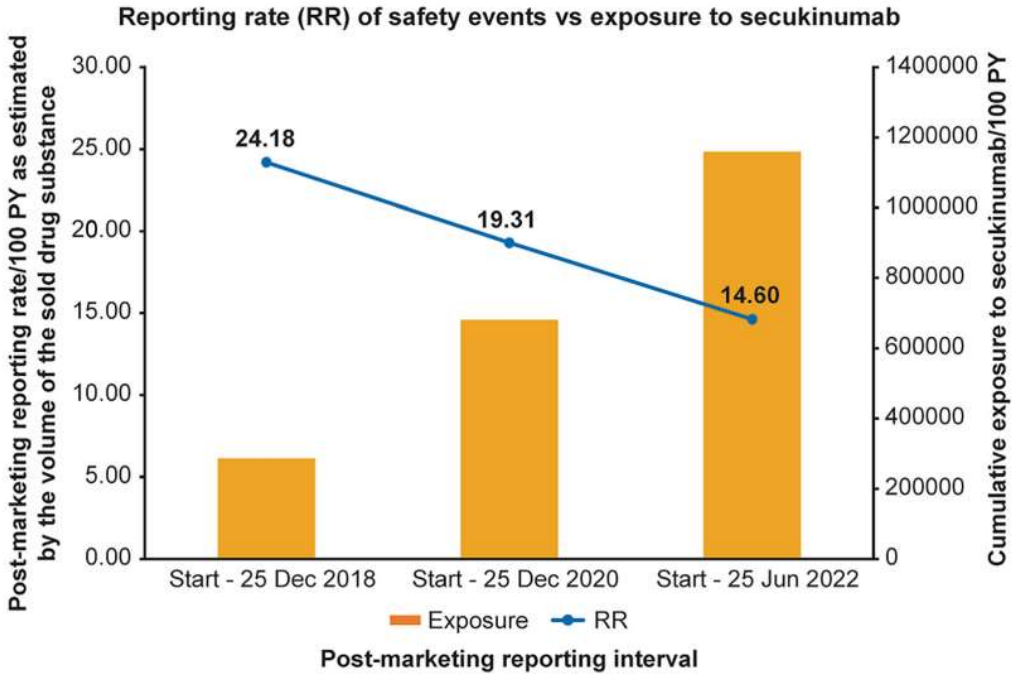
Advantages of secukinumab vs tocilizumab

Safety:

Safety of Secukinumab from 1 Million Patient-Years of Exposure: Experience from Post-Marketing Setting and Clinical Trials

Rui Sun · Mercedes Bustamante · Venkatesh Kumar Gurusamy · Mark Lebwohl · Alice B. Gottlieb · Philip J. Mease · Atul Deodhar · Weibin Bao · Meryl Mendelson · Brian Porter · Deepa Chand · Victor Dong

Dermatol Ther 2024



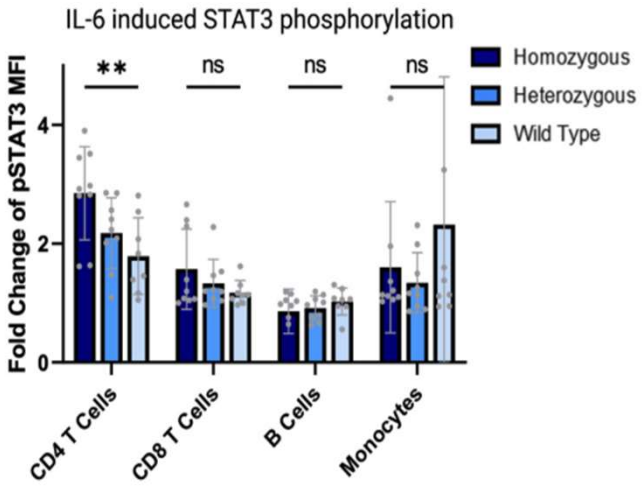
Advantages of secukinumab vs tocilizumab

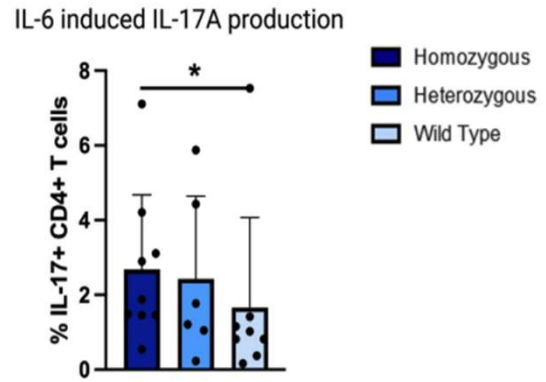
Efficacy and physiopathology:

TCZ non-responders: *IL6R* polymorphism through IL-17 production (*Grayson, ACR 2024*)

	Tocilizumab non-responder	Tocilizumab responder
IL-6R-no variant	0 (0%)	21 (100%)
IL-6R- variant	3 (30%)	7 (70%)

WT: 47%
Heterozygous: 35%
Homozygous: 18%





➔ **Rational for targetting IL-17 in these patients!**

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TCZ	SEC
	
	?
	

Secukinumab vs Tocilizumab?

	GiACTA	TiTAIN
number of patients	**n = 251**	**n = 52**
exposed to experimental treatment	n = 100 (TCZ 162/sem)	n = 27
Newly GCA	**47%**	**85%**
Relapsing GCA	53%	15%
Prednisone dose at inclusion	> 30 mg/j : 48%	≥ 40 mg/j : **70%**
Prednisone taper schedule (experimental arm)	20-60 mg/j à S0 et sevrage S26	25-60 mg/j à S0, sevrage S26
Sustained remission at W52	**TCZ : 56%** PLA GC 26 sem : 14% PLA GC 52 sem : 18%	**SCK : 59%** PLA GC 26 sem : 8%
Cumulative dose of GC	**TCZ : 1862 mg** PLA GC 26 sem : 3296 mg PLA GC 52 sem : 3818 mg	**SCK : 2506 mg** PLA GC 26 sem : 3466 mg
Treatment interruption for SAE	TCZ : 6% PLA GC 26 sem : 4% PLA GC 52 sem : 0%	SCK : 7% PLA GC 26 sem : 8%
SAE	TCZ : 15% PLA GC 26 sem : 22% PLA GC 52 sem : 25%	SCK : 22% PLA GC 26 sem : 44%

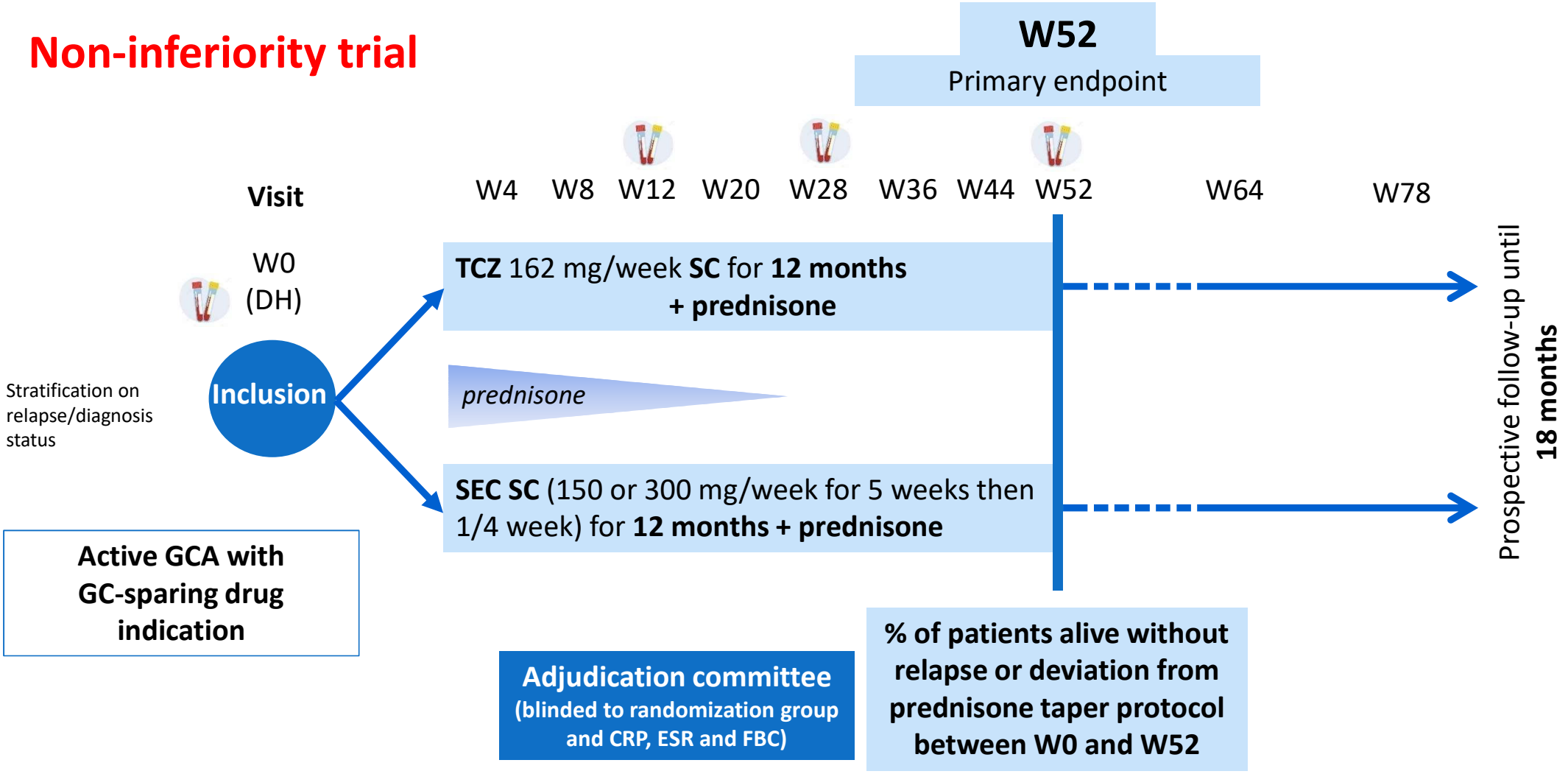
Sustained remission was defined as remission from week 12 through week 52 and adherence to the prednisone taper.
Patients who had a flare or could not adhere to the prednisone taper switched to open-label escape therapy with prednisone but continued to receive the assigned trial regimen (tocilizumab or placebo)

higher dose of GC at inclusion in TiTAIN

Stone J et al. NEJM 2017
Venhoff N et al. Lancet Rheumatol 2023

SETOGiA

Non-inferiority trial



Inclusion criteria

1/ Diagnosis of GCA:

- Age ≥50 years at disease onset

- **AND** history of ESR ≥50 mm/h OR CRP≥20 mg/L (not mandatory if TAB positive)

- **AND** at least one of the following:
  - unequivocal cranial symptoms of GCA
  - unequivocal symptoms of polymyalgia rheumatica (PMR)

- **AND** at least one of the following:
  - **TAB** compatible with GCA
  - Evidence of vasculitis of the temporal artery by **Doppler US-scan** (unilateral or bilateral halo sign)
  - Evidence of large vessel vasculitis (aorta and/or epiaortic arteries) by ***angio-CT, angio-MRI***, or ***PET scan***

Inclusion criteria

2 / Active GCA:

- ESR ≥30 mm/h or CRP ≥10 mg/L
- **AND** at least one of the following:
  - ≥1 unequivocal cranial symptoms of GCA
  - ≥1 unequivocal symptoms of PMR
  - any other feature(s) judged by the clinical investigator to be consistent with GCA or PMR flares

Inclusion criteria

3/ indication to start GC-sparing drug according to French recommendations :

- **At diagnosis of GCA :**
  - history of a MACE
  - Osteoporosis related fracture
  - history of psychiatric decompensation on GC
  - Complicated diabetes
  - History of prolonged corticosteroid therapy (>6 months), whatever the cause.
  - If an indication for GC sparing is deemed essential by the investigator:
    - BMI>30 Kg/m²
    - Severe atheromatous disease without previous MACE
    - Symptomatic involvement of large arteries
- **During GCA follow-up:**
  - When GC reduction targets are not met (≤ 15 mg/d at M3, ≤ 5 to 10 mg/d at M6, weaning at M12) due to persistent disease activity.
  - In case of relapse despite well-managed treatment.
  - When GC therapy is poorly tolerated.

≈60-70% of patients

Non-inclusion criteria

- **The same as in G-CAPTAIN trial**

- **AND contraindication to tocilizumab:**
  - **History of sigmoiditis**, inflammatory bowel disease, or any other gastrointestinal pathology predisposing to the risk of digestive perforation
  - **Biological abnormalities:**
    - Transaminases > 1.5N
    - Leukopenia (< 3G/L), neutropenia (<1.5 G/L), lymphopenia (<0.5 G/L), thrombopenia (<100 G/L)

Primary endpoint: definitions

Remission
No clinical signs of GCA **and** CRP ≤10 mg/L

Primary endpoint
% of patients alive without relapse or deviation from prednisone taper protocol between W0 and W52

Relapse
Reappearance of clinical signs of GCA **with or without** CRP elevation

Isolated elevation of CRP?
Not considered a relapse in the absence of clinical or radiological signs of active GCA

Secondary criteria

- **sustained remission without AE + suspension of TCZ/SEC** at W52 ➔ **superiority**

- **relapse-free survival** in the 2 arms at W28, W52, W78
- % relapse at W28, W52, W78
- % of patients alive without relapse or deviation from the GC taper protocol at W28, W78
- % of patients in remission with ≤5 mg/d of prednisone at W28, W52, W78
- % of patients in remission without prednisone at W28, W52, W78
- Number of patients to be treated to avoid one relapse at W28, W52, W78

- **Cumulative prednisone** dose at W28, W52, W78

- **Medico-economic study**

Secondary criteria

- **GTI at S12, S24**
- **Safety (SA, SAE...)**

- **Quality of life and fatigue at W0, W28, W52**

- **Biological collection** (W0, W12, W28, W52)
  - DNA (inclusion)
  - serum: all centers
  - PBMCs: limited number of centers

- **Imaging: PET CT at W0 and W52** *(limited number of centers)*
  - % of patients alive without relapse or deviation from the GC taper protocol and **a negative TEP*** at W52

**no arterial territory with a ≥2 grade hypermetabolism*

TCZ and SEC

TCZ group: RoACTEMRA, TYENNE or other biosimilar

- TCZ 162 mg/week SC from W0 to W51 (52 injections)
- **Indication**: AMM
- **Drug supply:** general pharmacy

SEC group :

- **Refus de NOVARTIS**
- Dose: 150 or 300 mg/4 weeks depending on G-CAPTAIN results
- **Drug supply**: general pharmacy

Glucocorticoids

Choice of the starting dose
26 weeks prednisone taper

At diagnosis, prefer 40 or 60 mg/day

For relapses, prefer 20 or 30 mg/day

Week	GC prednisone taper according to the starting dose (prednisone, mg/day)				
1	80	60	40	30	20
2	60	50	35	25	20
3	50	40	30	20	17,5
4	40	35	25	17,5	17,5
5	30	30	20	17,5	15
6	25	25	17,5	15	15
7	20	20	15	15	12,5
8	15	15	15	12,5	12,5
9	12,5	12,5	12,5	12,5	10
10	12,5	12,5	12,5	10	10
11	10	10	10	10	10
12	9	9	9	9	9
13	8	8	8	8	8
14	7	7	7	7	7
15	6	6	6	6	6
16	6	6	6	6	6
17	5	5	5	5	5
18	5	5	5	5	5
19	4	4	4	4	4
20	4	4	4	4	4
21	3	3	3	3	3
22	3	3	3	3	3
23	2	2	2	2	2
24	2	2	2	2	2
25	1	1	1	1	1
26	1	1	1	1	1
27	0	0	0	0	0
28	0	0	0	0	0

Number of subjects required

- Non-inferiority trial
- Non inferiority margin = 20%
- Power = 0.81

Power	N TCZ	N SCK	%success expected with TCZ	%success expected with SCK	Non inferiority margin
0.81	98	98	0.56	0.56	0.20
0.80	172	172	0.56	0.56	0.15
0.80	387	387	0.56	0.56	0.10

➔ **98 patients per group**

➔ **+ 15% margin for patients who should not be analyzed in PP analysis**

➔ **115 patients per group for a TOTAL of 230 patients**

Feasibility and timeline

- Our team has a **great experience** in conducting GCA trials. Most recent ones are:
  - ***METOGiA*** : 230 patients (inclusions closed in 3 years)
  - ***ULTRA*** : 40 patients (inclusions closed in 3 years)
  - ***MAGICA :*** 23/120 patients, ongoing

- **Highly efficient network**
  - **>50 french centers**
  - **Support of scientific groups**

Feasibility and timeline

- **Increasingly broad indications for GC sparing in GCA**

- Highly efficient network of hospitals caring for large numbers of GCA patients: same centers as METOGiA and MAGICA ➔ **> 45 centers**

- Recruitment period = 3 years
- Follow-up = 2 years
- Study duration = 5 years

- **Objective**: submission to PHRC-N 2024 ➔ trial starting in **Q3 2027**

SETOGIA STUDY: timelines

Merci de votre attention

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