GIANT CELL ARTERITIS:
ASSESSMENT OF NEW & EMERGING TREATMENT OPTIONS
This learning program is intended for Canadian healthcare professionals only and has been made possible with funding from Hoffmann-La Roche Limited.

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# Scientific Planning Committee

<table>
<thead>
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Learning Objectives

Upon completion of this program, participants will be able to:

1. **Appropriately screen, investigate & diagnose** patients suspected with possible giant cell arteritis (GCA)

2. **Discuss** the **standard of care** and clinical management of GCA in Canada, including steroid sparing agents

3. **Critically appraise** the evidence for new and emerging therapeutic options and assess the clinical impact for patients with GCA
 Appropriately screen, investigate & diagnose patients suspected with possible giant cell arteritis (GCA)
GCA: The most common primary systemic vasculitis in adults

- Involves the large and medium sized arteries\(^2,3\) of the body to include
  - **Temporal**
  - **Aorta and branches**
    - Subclavian
    - Carotids
    - Vertebrals

GCA, Giant Cell Arteritis

Epidemiological factors related to GCA

**AGE\(^{1,2}\):**
Occurs almost exclusively in patients aged \(\geq 50\) YEARS

**ETHNICITY\(^{1,2}\):**
More common among people of NORTHERN EUROPEAN DESCENT

**GENDER\(^{1,2}\):**
WOMEN ARE 2–3 TIMES more commonly affected than men

Clinical Case Vignette*

72-YEAR-OLD CAUCASIAN WOMAN PRESENTS WITH VISION LOSS IN THE RIGHT EYE

- Reports bi-temporal headache for two weeks, accompanied by pain and stiffness in the neck and shoulders
- Review of systems is positive for low-grade fever, fatigue, and weight loss
- On physical examination, there is tenderness of the scalp over the temporal areas and thickening of the temporal arteries
- No synovitis or tenderness of the peripheral joints. No carotid or subclavian bruits, and blood pressure is normal and equal in both arms
- Remainder of the examination is unremarkable

DIAGNOSTICS TEST:

- ESR: 80 mm/hour
- CRP: 67 mg/dL
- Eye examination reveals A-AION and visual acuity reduced to the perception of hand movements

DIAGNOSIS:

- High suspicion for diagnosis of giant cell arteritis

CRP, C-reactive protein; ESR, elevated sedimentation rate; A-AION, Arteritic anterior ischemic optic neuropathy
*Patient case is illustrative and is not reflective of an actual patient.
Clinical Case Vignette*

72-YEAR-OLD CAUCASIAN WOMAN PRESENTS WITH VISION LOSS IN THE RIGHT EYE

DISCUSSION:

• What symptoms prompt a suspected diagnosis of GCA?

• How do you confirm the diagnosis?

*Patient case is illustrative and is not reflective of an actual patient.
Clinical manifestations of GCA

**CRANIAL ARTERITIS**
- Headache: present in 2/3 of patients\(^1-3\)
- Scalp pain
- Jaw claudication: occurs in ~ 50% of patients\(^1-3\)
- Tender and thickened temporal arteries
- Transient or permanent visual loss

**EXTRACRANIAL ARTERITIS**
- Aortitis
- Aortic aneurysm and dissection
- Upper and lower extremity arterial ischemia
- Aortic valve insufficiency (rare)

**SYSTEMIC MANIFESTATIONS**
- Constitutional symptoms
- Polymyalgia rheumatica (PMR)
- ~40-60% of patients with GCA have PMR\(^1\)

**NEUROLOGIC MANIFESTATIONS**
- Diplopia
- Cranial neuropathy
- Strokes (rare)

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Visual disorders in GCA

• Up to 70% of patients with GCA have visual disorders\textsuperscript{1}
  – Arteritic anterior ischemic optic neuropathy [A-AION]
    • Leading cause of blindness: develops in 5%–15% of patients\textsuperscript{2}
  – Posterior ischemic optic neuropathy [PION] (rare)
  – Central retinal arterial occlusion
  – Amaurosis fugax
  – “Cotton-wool spots”
    (microinfarcts of the retinal nerve fiber layer)
  – Double vision

Untreated: \textbf{SECOND EYE} may go blind in up to 60% of patients, within a few days\textsuperscript{1}

Diagnosing GCA

• Laboratory investigations: Full blood count, creatinine and electrolytes, liver function tests, CRP and ESR\(^1\)

• Temporal artery (TA) biopsy is an option in diagnosing GCA as it is highly specific\(^1-5\)

• Skip lesions can render TA biopsy negative\(^1,2\)

• Limited sensitivity with TA biopsy – up to 44% of patients with a negative biopsy are diagnosed clinically with GCA\(^2,3\)

CRP, C-reactive protein; ESR, elevated sedimentation rate
Clinical Case Vignette*

73-YEAR-OLD FEMALE
• Presents with diffuse headache and jaw claudication of 3 weeks
• Examination of the temporal arteries was normal
• Physical examination reveals blood pressure in both arms is normal. There is an absence of vascular bruit and normal cardiac auscultation

LABORATORY FINDINGS:
• ESR: 78 mm/hour
• CRP: 6.8 mg/dL (normal)
• A 5-mm long biopsy of the right temporal artery showed no relevant disorders

WHAT IS THE BEST DIAGNOSTIC APPROACH FOR THIS PATIENT?

CRP, C-reactive protein; ESR, elevated sedimentation rate
*Patient case is illustrative and is not reflective of an actual patient.
A negative temporal artery biopsy does not rule out a diagnosis of GCA

- Samples of <5 mm in length seldom yield positive results

- TA biopsy of ≥ 10 mm in length recommended (EULAR/BSR)

- Contralateral biopsy not routinely indicated

  - Treatment must not be delayed if GCA suspected

- Negative biopsies, if indicated by clinical, laboratory or imaging signs should be managed as having GCA

- Medical imaging techniques can further support the diagnosis GCA

EULAR, European League Against Rheumatism; BSR; British Society for Rheumatology

Vascular imaging can add diagnostic value in GCA\(^1-3\)

**Color Doppler Ultrasonography:**

- Noninvasive, sensitive, and highly specific\(^1,4\)
  - Meta-analyses demonstrated ultrasound is an accurate diagnostic test for GCA with sensitivity ranging from 69% - 75% and specificity from 82% - 98%\(^1\)
- Used to examine: temporal, axillary, and carotid arteries for inflammation\(^3\)
- Inflammatory edema of the vascular wall shown as hypoechoic wall thickening ("halo")\(^1,4-6\)
- Consider use in first-line investigation, if available\(^4,7\)
- Operator-dependent variability may affect results\(^1,3-5\)

Vascular imaging can add diagnostic value in GCA contd.¹⁻³

CT or MR Angiography:
- Used to examine aortic arch and branches
- Demonstrate large-vessel involvement
- Determine extent of arterial involvement such as the presence of stenosis or aneurysms in patients with biopsy-confirmed GCA
- Monitor vascular lesions for signs of progression

PET-CT (where available):
- Demonstrate large-vessel involvement in the chest, neck, and abdomen
- High specificity for GCA diagnosis (91%-98%), lower sensitivity (85% -90%)⁴,⁵

High-resolution MRI:
- Detailed imaging of the walls and lumina of the superficial cranial arteries plus occipital and facial arteries
- Inflamed wall segments can be distinguished from unaffected segments
- High sensitivity comparable to color duplex ultrasonography⁶,⁷
- May be used as initial diagnostic procedure, with TA biopsy reserved for patients with abnormal MRI findings⁹

MRA, magnetic resonance angiography; CTA, computed tomography angiography; PET-CT, positron emission tomography-computed tomography
Clinical Case Vignette*

68-YEAR-OLD CAUCASIAN FEMALE

- Presents with a three month history of malaise, myalgias of the shoulder and hip girdle and occasional headache. Patient has no comorbidities
- Physical examination reveals blood pressure on the right 130/80 and on the left 110/70 with no abnormal appearance or palpation of the temporal arteries and a left sided subclavian bruit

LABORATORY FINDINGS:

- ESR: 128 mm/hour
- CRP: 73 mg/dL

IMAGING RESULTS:

- MRA: showing stenosis at the left subclavian with wall thickening at the right subclavian and both carotid arteries

DIAGNOSIS:

- GCA

*Patient case is illustrative and is not reflective of an actual patient.
CRP, C-reactive protein; ESR, elevated sedimentation rate
†PET-CT or CTA may be used where available
MRA, magnetic resonance angiography; PET-CT, positron emission tomography-computed tomography, CTA, computed tomography angiography
Clinical Case Vignette*

68-YEAR-OLD CAUCASIAN FEMALE
• Presents with a three month history of malaise, myalgia of the shoulder and hip girdle and occasional headache

DISCUSSION:
• What percentage of your patients present with large-vessel involvement?

• How do these patients compare to those with cranial vessel involvement in terms of:
  • Prognosis?
  • Treatment?
  • Long-term outcomes?

*Patient case is illustrative and is not reflective of an actual patient.
Involvement of the large vessels in GCA

• FDG-PET detected **vascular arterial uptake** in 87% of patients with GCA\(^1\)

• **Aortic aneurysms** and **stenoses** of the vessels can occur\(^2\)

• Aortic involvement is associated with 2.6-fold increased mortality
  – Thoracic aortic aneurysms are 17 times more common
  – Abdominal aneurysms are 2.4 times more common
  – Aortic dissections can occur

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Clinical Case Vignette*

72-YEAR-OLD CAUCASIAN WOMAN PRESENTS WITH VISION LOSS IN THE RIGHT EYE

DISCUSSION:

• What is the current clinical protocol to treat this patient?

• What are the limitations with current regimens?

*Patient case is illustrative and is not reflective of an actual patient.
Discuss current standard of care and clinical management of GCA in Canada, including steroid sparing agents.
Glucocorticoids: The current standard of care for GCA

- Glucocorticoids (GC) are the mainstay of treatment for GCA\textsuperscript{1-4}
- Start GC treatment immediately on strong clinical suspicion of GCA to prevent irreversible ischemic complications, prior to TA biopsy\textsuperscript{1-4}

\textit{EULAR and BSR recommendation}

- GC treatment lead to rapid and effective suppression of inflammation\textsuperscript{1-4}
- Duration of GC treatment varies by patient because of disease relapse both on or off treatment\textsuperscript{5}
  - Mean treatment duration: 5-6 years\textsuperscript{5}

Relapse occurs in \textbf{APPROXIMATELY 50\%} of patients within the \textbf{1st} year and \textbf{80\%} by year 5\textsuperscript{4}

Monitoring disease activity in GCA

- Inflammatory markers aid in decision to alter therapy\textsuperscript{1,2}:
  - Relapse associated with rise ESR and CRP

- Suspect relapse in patients with\textsuperscript{1}:
  - return of symptoms of GCA
  - ischemic complications
  - unexplained fever
  - polymyalgic symptoms

- Consider large vessel imaging in patients with blood pressure difference of >10mm Hg systolic, new bruit, or unexplained symptoms of fever or weight loss\textsuperscript{2}

- Repeat imaging should be considered at regular intervals (concern over aneurysm progression)\textsuperscript{2}

- Normal inflammatory markers in symptomatic patients, should raise suspicion of alternative diagnosis\textsuperscript{2}

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein
**Guideline Recommendations: Glucocorticoids Administration for patients with GCA**

**INDUCTION THERAPY**

- **BSR/BHPR Guidelines**
  - GCA with no visual symptoms or jaw claudication: 40 mg–60 mg prednisolone/day
  - GCA with established visual symptoms or jaw claudication: 60 mg/day
  - GCA with evolving visual symptoms: 500 mg to 1 g of IV methylprednisolone for 3 days before oral glucocorticoids

- **EULAR Guidelines**
  - Initial prednisolone dose of 1 mg/kg/day (max 60 mg/day)

**MAINTENANCE THERAPY**

- **BSR/BHPR Guidelines**
  - Continue 40 mg/day–60 mg/day until symptoms and laboratory abnormalities resolve (at least 3–4 weeks), then taper:
    - Reduce dose by 10 mg every 2 weeks down to 20 mg
    - Then reduce by 2.5 mg every 2–4 weeks down to 10 mg
    - Then reduce by 1 mg every 1–2 months until relapse

- **EULAR Guidelines**
  - Maintain initial high dose for one month, then taper gradually
    - By 3 months, dose should be between 10 mg/day–15 mg/day

**MANAGEMENT OF RELAPSE**

- **BSR/BHPR Guidelines**
  - Headache: use previous higher dose of prednisolone
    - Jaw claudication: 60 mg/day prednisolone
    - Eye symptoms: 60 mg/day prednisolone or IV methylprednisolone

- **EULAR Guidelines**
  - For patients in clinical remission who discontinued therapy:
    - Treat as per new patients
  - For patients still on glucocorticoids:
    - Increase 5 mg/day–10 mg/day
    - Increase to full induction dose (1 mg/kg/day) if visual or neurological symptoms occur

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BSR, British Society for Rheumatology; BHPR, British Health Professionals in Rheumatology; EULAR, European League Against Rheumatism
Glucocorticoid-related adverse events in GCA

86% of patients suffer glucocorticoid-related adverse events at 10-year follow-up\textsuperscript{1,5}

ADVERSE EVENTS INCLUDE\textsuperscript{1-5}:

- Cataracts (41\%)\textsuperscript{4}
- Fractures (38\%)\textsuperscript{4}
- Bone Loss/Osteoporosis
- Avascular necrosis of the hip
- Infection (31\%)\textsuperscript{4}
- Hypertension (22\%)\textsuperscript{4}
- Diabetes Mellitus (9\%)\textsuperscript{4}
- Hyperglycemia
- Gastrointestinal bleeding (4\%)\textsuperscript{4}
- Glaucoma
- Pneumonia
- Depression
- Psychosis

Therapy with GC is associated with significant morbidity

Each cumulative 1000-mg of GC 
**INCREASED RISK** of AEs by **3%**

- Significant association between increased GC exposure and AE risk
  - Bone-related AEs \( p < 0.001 \)
  - Cataract \( p < 0.001 \)
  - Glaucoma \( p = 0.005 \)
  - Pneumonia \( p < 0.003 \)
  - Diabetes mellitus \( p < 0.001 \)

**Graph:**
- **X-axis:** Cumulative GC exposure in 1 year post-index period, mg
- **Y-axis:** Rates of AE in 1-year post-index period, %

Retrospective cohort study 2,497 GCA patients
AE, adverse event; GC, glucocorticoid; PY, patient years

Broder MS et al. Seminars in Arthritis and Rheumatism 2016;46:246–252
Acetylsalicylic acid (ASA) in the treatment of GCA

- EULAR recommends the use of low-dose aspirin (75–150 mg/day) in all patients with GCA*¹

- Retrospective analyses reported a protective effect against cardiovascular and cerebrovascular events associated with GCA¹-³

- **COCHRANE REPORT:** There is currently no evidence from RCTs to determine the safety and efficacy of low-dose aspirin as an adjunctive treatment in GCA⁴

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EULAR, European League Against Rheumatism
*In the absence of contraindication
Adjunctive use of MTX: Treatment failure & disease relapse

No benefit to adjunctive use of MTX to control disease activity or to decrease the cumulative dose and of glucocorticoid

MTX=methotrexate


MTX= methotrexate
Adjunctive treatment with MTX lowers the risk of relapse and reduces exposure to glucocorticoids

<table>
<thead>
<tr>
<th>Study</th>
<th>MTX (n/N)</th>
<th>PBO (n/N)</th>
<th>HR (95% CI)</th>
<th>HR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Risk of 1&lt;sup&gt;st&lt;/sup&gt; relapse</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Spiera et al. 2001</td>
<td>6/12</td>
<td>3/9</td>
<td>1.28</td>
<td>(0.14–5.15)</td>
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<td>Jover et al. 2001</td>
<td>9/21</td>
<td>16/21</td>
<td>0.33</td>
<td>(0.15–0.76)</td>
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<tr>
<td>Hoffman et al. 2002</td>
<td>32/51</td>
<td>32/47</td>
<td>0.77</td>
<td>(0.47–1.27)</td>
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<tr>
<td>Total</td>
<td>47/84</td>
<td>51/77</td>
<td>0.65</td>
<td>(0.44–0.98)</td>
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<tr>
<td>Risk of 2&lt;sup&gt;nd&lt;/sup&gt; relapse</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3/12</td>
<td>1/9</td>
<td>1.36</td>
<td>(0.14–13.78)</td>
</tr>
<tr>
<td></td>
<td>2/21</td>
<td>9/21</td>
<td>0.17</td>
<td>(0.04–0.77)</td>
</tr>
<tr>
<td></td>
<td>14/51</td>
<td>17/47</td>
<td>0.60</td>
<td>(0.30–1.23)</td>
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<tr>
<td>Total</td>
<td>19/84</td>
<td>27/77</td>
<td>0.49</td>
<td>(0.27–0.89)</td>
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</tbody>
</table>

Meta-analysis: HRs for occurrence of first or second relapse of GCA in patients receiving adjunctive MTX versus those receiving placebo (PBO)<sup>1</sup>

CI=confidence interval; HR=hazard ratios; MTX=methotrexate; PBO=placebo

Anti-tumor necrosis factor α therapy in GCA

No convincing evidence that anti-TNFα therapy provides additional benefit beyond prednisone monotherapy in GCA

*Infliximab, etanercept, adalimumab biw, twice weekly


*Infliximab, etanercept, adalimumab

P = 0.561

Patient at risk, n

Infliximab 28 28 27 27 26 16 9
Placebo 16 16 16 16 13 4

Patients (%) able to control disease activity without steroids

P = ns
Anti-tumor necrosis factor α therapy in GCA

No convincing evidence that anti-TNFα therapy provides additional benefit beyond prednisone monotherapy in GCA\(^{1-3}\)*

\*Infliximab, etanercept, adalimumab

Q2W, once every 2 weeks


*Infliximab, etanercept, adalimumab

Q2W, once every 2 weeks

Clinical Case Vignette*

PATIENT AND CLINICAL FACTORS

WHAT IF:

• The patient has a history of diabetes mellitus?
• The patient has glaucoma?
• The patient has osteoporosis?

• How would this impact your approach to the management of this patient?

*Patient case is illustrative and is not reflective of an actual patient.
Critically appraise the evidence for new and emerging therapeutic options and assess the clinical impact for patients with GCA.
**Advanced knowledge of pathophysiology of GCA**

The IL-6–IL-17 cytokine cluster in giant cell arteritis

- **IL-1β**, Interleukin 1 beta; **IL-6**, Interleukin 6; **IL-17**, Interleukin 17; **IL-21**, Interleukin 21; **IL-22**, Interleukin 22; **IL-23**, Interleukin 23; **TH17**, T helper 17 cells; **TReg**, regulatory T cells; **CCL20**, Chemokine (C-C motif) ligand 20, NK cell, Natural killer cells; **CD8+ T cell**, cluster of differentiation 8 positive T cell

Advanced knowledge of pathophysiology of GCA

• Role of IL-6
  – Stimulates hepatocytes to release the ESR and CRP
  – Believed to play a critical role in promoting the switch from acute to chronic inflammation
  – Elevated levels found in inflamed arteries and peripheral circulation of patients with GCA

• Role of Th1 and Th17
  – Increased Th1 and Th17 cell activity in the blood and vascular tissues of GCA patients
  – GCs effective at dampening Th17 signal but do not suppress Th1 cells
  – Anti-IL-12 and -23 potentially inhibit Th1 and Th17 pathways simultaneously

• Role of T cells
  – T cells play a key role in development of systemic and vascular manifestations of GCA
  – Expressed on T cells, CTLA-4 serve as an immune checkpoint by binding to CD80/86 on antigen-presenting cells effectively preventing T-cell activation

IL-6, Interleukin-6; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; IL-12, Interleukin-12; IL-23, Interleukin-23
GiACTA: Efficacy and safety of tocilizumab in patients with giant cell arteritis

**Study Population (N=251)**
- Aged ≥50 years
- Active GCA confirmed by temporal artery biopsy or cross-sectional imaging and documented acute-phase reactant elevation attributable to GCA
- Randomization stratified by baseline prednisone dose (≤30 or >30 mg/day)

**Primary Endpoint:** TCZ + 26-week prednisone versus 26-week prednisone only: sustained remission from week 12 to week 52 AND adherence to the protocol-defined prednisone taper

**Key Secondary Endpoint:** TCZ + 26-week prednisone versus 52-week prednisone: sustained remission from week 12 to week 52 AND adherence to the protocol-defined prednisone taper

**Other Secondary Endpoints:** Time to flare, Cumulative glucocorticoid use, Quality of life, Safety

TCZ, tocilizumab; PBO, placebo
Tocilizumab: Sustained remission

Patients in Sustained Remission, %

- **PBO + Prednisone 26 wks (n=50)**: 14%
- **PBO + Prednisone 52 wks (n=51)**: 17.6%
- **Weekly SC Tocilizumab (n=100)**: 56%
- **Biweekly SC Tocilizumab (n=49)**: 53.1%

P <.0001

P = .0002

P < .0001

P < .0001

PBO, placebo
Sensitivity analysis: Impact of CRP

Including CRP did **NOT** alter the primary outcome

TCZ, tocilizumab; PBO, placebo; QW, weekly; Q2W, bi-weekly
Tocilizumab: Time to first flare following clinical remission

TCZ, tocilizumab; PBO, placebo; QW, weekly; Q2W, bi-weekly
Tocilizumab: Time to first flare – patients with new-onset disease

TCZ, tocilizumab; PBO, placebo; QW, weekly; Q2W, bi-weekly
Tocilizumab: Time to first flare – patients with relapsing disease

TCZ, tocilizumab; PBO, placebo; QW, weekly; Q2W, bi-weekly
Tocilizumab: Reduction in the cumulative prednisone doses

TCZ, tocilizumab; PBO, placebo; QW, weekly; Q2W, bi-weekly
Tocilizumab: Safety Overview

No gastrointestinal perforations were reported, and no patients died.† Values are reported for the entire trial population; that is, values were included for 50 patients in the group that received tocilizumab every other week (i.e., including the patient who did not receive tocilizumab).‡ Values are for flares of giant-cell arteritis that met the protocol-defined criteria for being reported as a serious adverse event.§ This patient had anterior ischemic optic neuropathy after randomization.¶ Values were those reported in at least 1% of the patients overall. Patients may have had more than one class of serious adverse event.‖ One patient in the group that received tocilizumab every other week had a benign ovarian adenoma.


<table>
<thead>
<tr>
<th></th>
<th>TCZ QW (N=100)</th>
<th>TCZ Q2W (N=49)</th>
<th>Placebo + 26-Wk Taper (N = 50)</th>
<th>Placebo + 52-Wk Taper (N = 51)</th>
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<tbody>
<tr>
<td>Duration in trial — patient-yr</td>
<td>92.9</td>
<td>45.6</td>
<td>47.4</td>
<td>48.1</td>
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<td>Patients with ≥1 adverse event — no. (%)</td>
<td>98 (98)</td>
<td>47 (96)</td>
<td>48 (96)</td>
<td>47 (92)</td>
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<td><strong>Adverse events</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>No. of events</td>
<td>810</td>
<td>432</td>
<td>470</td>
<td>486</td>
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<td>Patients with ≥1 infection — no. (%)</td>
<td>75 (75)</td>
<td>36 (73)</td>
<td>38 (76)</td>
<td>33 (65)</td>
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<tr>
<td>Any</td>
<td>7 (7)</td>
<td>2 (4)</td>
<td>2 (4)</td>
<td>6 (12)</td>
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<tr>
<td>Serious</td>
<td>7 (7)</td>
<td>2 (4)</td>
<td>6 (12)</td>
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<td>Patients who withdrew from the trial because of adverse events — no. (%)†</td>
<td>6 (6)</td>
<td>3 (6)</td>
<td>2 (4)</td>
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<td>Patients with injection-site reaction — no. (%)</td>
<td>7 (7)</td>
<td>7 (14)</td>
<td>5 (10)</td>
<td>1 (2)</td>
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<td>Flare of giant-cell arteritis reported as serious adverse event — no. (%)‡</td>
<td>1 (1)</td>
<td>1 (2)§</td>
<td>1 (2)</td>
<td>1 (2)</td>
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<tr>
<td>Patients with ≥1 serious adverse event — no. (%)</td>
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<tr>
<td>According to system organ class†</td>
<td>15 (15)</td>
<td>7 (14)</td>
<td>11 (22)</td>
<td>13 (25)</td>
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<td>Infection or infestation</td>
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<td>Vascular disorder</td>
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<td>Respiratory, thoracic, or mediastinal disorder</td>
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<td>2 (4)</td>
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<td>Injury, poisoning, or procedural complication</td>
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<td>1 (2)</td>
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<td>Nervous system disorder</td>
<td>1 (1)</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>1 (2)</td>
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<td>Cardiac disorder</td>
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<td>0</td>
<td>0</td>
<td>2 (4)</td>
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<td>Musculoskeletal or connective-tissue disorder</td>
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<td>0</td>
<td>1 (2)</td>
<td>2 (4)</td>
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<td>Gastrointestinal disorder</td>
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<td>2 (4)</td>
<td>0</td>
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<tr>
<td>Cancer</td>
<td>0</td>
<td>0‖</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

* No gastrointestinal perforations were reported, and no patients died.† Values are reported for the entire trial population; that is, values were included for 50 patients in the group that received tocilizumab every other week (i.e., including the patient who did not receive tocilizumab).‡ Values are for flares of giant-cell arteritis that met the protocol-defined criteria for being reported as a serious adverse event.§ This patient had anterior ischemic optic neuropathy after randomization.¶ Values were those reported in at least 1% of the patients overall. Patients may have had more than one class of serious adverse event.‖ One patient in the group that received tocilizumab every other week had a benign ovarian adenoma.
Tocilizumab: Indication & Dosage Information

• ACTEMRA (tocilizumab): is indicated for the treatment of giant cell arteritis (GCA) in adult patients

• Recommended adult dose – subcutaneous (SC) formulation only:
  – The recommended dose of ACTEMRA is 162 mg given once every week as a subcutaneous injection, in combination with a tapering course of glucocorticoids
  – A dose of 162 mg given once every other week as a subcutaneous injection, in combination with a tapering course of glucocorticoids, may be prescribed based on clinical considerations

• ACTEMRA can be used alone following discontinuation of glucocorticoids

• Dose adjustment may be needed for management of dose-related laboratory abnormalities including elevated liver enzymes, neutropenia, and thrombocytopenia

Abatacept: Efficacy and safety in patients with Giant Cell Arteritis

Primary Endpoint: Duration of remission (relapse free survival, RFS)

Multicentre, Randomized, Double-Blind, Placebo-Controlled, Withdrawal Trial

Study Population (N=49)
- Newly diagnosed or relapsing GCA

Abatacept 10 mg/kg IV on days 1, 15, 29 and wk 8 + 40-60 mg/day prednisone with standardized prednisone taper

Wk 12
Remission

1:1

Abatacept 10 mg/kg IV every 28 days + Prednisone taper N=20

Placebo every 28 days + Prednisone taper N=21

Wk 28
Prednisone discontinuation

Abatacept: Relapse free survival

RELAPSE-FREE SURVIVAL COMPARING TREATMENT WITH ABATACEPT TO PLACEBO IN PATIENTS WITH GCA

- Abatacept
- Placebo

p-value=0.049 (one-sided log-rank test)

Number at Risk:

<table>
<thead>
<tr>
<th>Months</th>
<th>Abatacept</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>2-3</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>4-5</td>
<td>11</td>
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<td>6-7</td>
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<td>8-9</td>
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<td>10-11</td>
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<td>12-13</td>
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<td>16-17</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>18-19</td>
<td>3</td>
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</tr>
<tr>
<td>20-21</td>
<td>3</td>
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<tr>
<td>22-23</td>
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<td>24-25</td>
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<td>38-39</td>
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<tr>
<td>40-41</td>
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</tr>
</tbody>
</table>

Abatacept: Safety overview

- No difference in the frequency or severity of adverse events between the treatment arms, including the rate of infection or the rate of serious adverse events

- Three patients developed malignancies (2 in the abatacept arm and 1 in the placebo arm)

- No deaths occurred during the study

Ustekinumab: Efficacy and safety in patients with giant cell arteritis

Prospective open label study

Study Population (N=25)
- Patients with refractory GCA
- Unable to taper significant GCs and median of 1 other immunosuppressant
- Median IQR of 2 prior relapses of GCA
- 84% had experienced significant GC AEs

Efficacy
- Median (IQR) steroid dose decreased significantly from 15mg to 5mg (p=0.002)
- Follow-up imaging for large vessel vasculitis: Demonstrated improvement of wall thickening in all 7 patients with no new stenoses or aneurysms

Safety
- No relapse of GCA during treatment
- 11 adverse events reported
- 3 patients discontinued ustekinumab due to adverse events or personal preference
- 2 patients subsequently had flares of polymyalgia rheumatica

GC, Glucocorticoids; IQR, interquartile range; AEs, adverse events
## Emerging agents: Phase II/III trials

<table>
<thead>
<tr>
<th></th>
<th>Trial Type</th>
<th>Population</th>
<th>Dosing/Administration</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baricitinib</strong></td>
<td>Phase II, Single-institution, Open-label Pilot Study</td>
<td>Relapsing GCA: Relapse with active GCA within 6 weeks of study entry</td>
<td>Baricitinib 4 milligrams oral daily for 52 weeks + standardized glucocorticoid taper</td>
<td>Primary Endpoint: Percentage of subjects experiencing adverse events at Week 52</td>
</tr>
<tr>
<td>JAK1/ JAK2 inhibitor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=15</td>
<td>NCT03026504</td>
<td></td>
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</tr>
<tr>
<td><strong>Sirukumab</strong></td>
<td>Phase III randomized, double-blind, placebo-controlled, parallel group study</td>
<td>Diagnosis of GCA and active disease within 6 weeks of baseline</td>
<td>Part A: Experimental Sirukumab 100mg SC q2w for 52 weeks + pre-specified oral prednisone taper (3-month or 6-month) Sirukumab 50mg SC q4w for 52 weeks + pre-specified oral prednisone taper (6-month) Part B: Open-label Sirukumab 100 mg SC q2w for a maximum of 52 weeks</td>
<td>Primary Endpoint: Proportion of patients in sustained remission at Week 52</td>
</tr>
<tr>
<td>Fully human anti-interleukin-6 monoclonal antibody</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=204</td>
<td>NCT02531633</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Ustekinumab</strong></td>
<td>Phase I/II Open Label Study Intervention Model: Single Group Assignment</td>
<td>Active new-onset or relapsing active disease</td>
<td>Ustekinumab 90 mg SC administered at baseline, week 4, week 12, week 20, week 28, week 36 and week 44 + Prednisone tapered according to predefined schedules starting at either 60 mg, 40 mg or 20 mg for 6 months</td>
<td>Primary Endpoint: Percentage of patients in glucocorticoid-free remission at Week 52</td>
</tr>
<tr>
<td>Humanized monoclonal antibody interleukin-12 and -23 antagonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=20</td>
<td>NCT02955147</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
MANAGING RELAPSE DURING TREATMENT

• The patient is back in your office for a routine check-up
• Current medications include:
  • 5 mg/day of prednisone
  • Low dose aspirin 81mg per day
  • Bisphosphonate, calcium and vitamin D
  • Patient has reported that the bi-temporal headache and pain and stiffness in the neck and shoulders have returned
  • ESR and CRP previously normal, have increased

• How would you manage this patient?

CRP, C-reactive protein; ESR, elevated sedimentation rate
*Patient case is illustrative and is not reflective of an actual patient.
### Guideline Recommendations for the management of relapse in patients with GCA

**BSR/BHPR GUIDELINES**
- Headache: use previous higher dose of prednisolone
- Jaw claudication: 60 mg/day prednisolone
- Visual symptoms: 60 mg/day prednisolone or IV methylprednisolone

**EULAR GUIDELINES**

Patients in clinical remission who discontinued therapy:
- Treat as per new patients

Patients still on glucocorticoids:
- Increase 5 mg/day – 10 mg/day
- Increase to full induction dose (1 mg/kg/day) if visual or neurological symptoms occur

---

BSR, British Society for Rheumatology; BHPR, British Health Professionals in Rheumatology; EULAR, European League Against Rheumatism
Practical recommendations: Diagnosis, treatment, and Monitoring of GCA

TIMELY DIAGNOSIS AND TREATMENT

• GCA is a heterogeneous disease with variable clinical presentation. Speed and accuracy essential in GCA diagnosis
• EULAR and BSR guidelines highlight the need for early recognition and treatment
• Glucocorticoids therapy should be initiated immediately once clinical suspicion of GCA is raised
  – The addition of low-dose aspirin protects against cardiovascular and cerebrovascular events
  – Preventative measures should be taken with administration of glucocorticoids and ASA treatments

OPTIMIZING GCA REFERRALS

• Urgent referral for specialist evaluation is suggested for all patients with GCA

STEROID SPARING AGENTS

• Prevent disease and treatment morbidity

NEW & EMERGING AGENTS

• Tocilizumab approved by Health Canada for GCA
• Agents under investigation provide the promise for additional treatment options for the right patients

BSR, British Society for Rheumatology; BHPR, British Health Professionals in Rheumatology; EULAR, European League Against Rheumatism
BACK-UP SLIDES
The American College of Rheumatology 1990 GCA Classification Criteria

- Age at onset ≥50 years
- A new headache
- Temporal artery abnormality: tenderness to palpation or decreased pulsation
- ESR ≥50 mm/h
- Abnormal artery biopsy: vasculitis with mononuclear cell or granulomatous inflammation, usually with giant cells

At least 3 of 5 parameters must be present, which yields a sensitivity of 93% and a specificity of 91%, in relation to controls with other vasculitides.

ESR, elevated sedimentation rate
GiACTA Diagnosis Criteria for GCA

• Age $\geq$50 years
• History of ESR $\geq$ 50mm/h
• And at least 1 of the following:
  – Unequivocal cranial symptoms of GCA (new onset localized headache, scalp or temporal artery tenderness, ischemia-related vision loss, or otherwise unexplained mouth or jaw pain upon mastication)
  – Unequivocal symptoms of PMR (shoulder and/or hip girdle pain associated with inflammatory stiffness)
• And at least 1 of the following:
  – Temporal artery biopsy revealing features of GCA
  – Evidence of large vessel vasculitis by angiography or cross-sectional imaging study such as MRA, CTA, or PET-CT

ESR, erythrocyte sedimentation rate; PMR, polymyalgia rheumatic; MRA, magnetic resonance angiography; CTA, computed tomography angiography; PET-CT, positron emission tomography-computed tomography

Proposed diagnostic algorithm in GCA

Clinical suspicion of GCA

Positive biopsy
- Confirmed diagnosis

Negative biopsy
- High clinical suspicion
- Treat and assess clinical and analytical response**
- Low clinical suspicion
- Diagnosis ruled out

CDUS, Color Doppler ultrasonography; MRA, Magnetic resonance angiography; CTA, computed tomographic angiography; PET-CT, positron emission tomography-computed tomography. *Especially in cases of negative biopsy of less than 5 mm in length. **Only in cases in which all available diagnostic tests have been exhausted and other diagnoses have been reasonably ruled out

Adapted from Calvo Romero JM. Rev Clin Esp. 2015;215:331-337
Proposed Diagnostic Algorithm for GCA

Clinical suspicion of GCA

Low or Moderate

Scalp Artery MRI

High

Ultrasound:
If halo present = GCA
If not present proceed with Algorithm

Normal MRI

Abnormal MRI

Temporal Artery Biopsy

Treat according to Physician Diagnosis

Not GCA Look for other Diagnosis

Negative TAB

Treat as Biopsy-Negative GCA

Positive TAB

Treat for GCA

McMaster GCA Working Group (unpublished) - Rheaume, Khalidi, Pagnoux, Rebello
Suggestion for BSR Guidelines

Clinical suspicion of GCA

PERFORM ULTRASOUND*

Low clinical probability
- US -
- US +/±

GCA ruled out
Perform biopsy

Intermediate clinical probability
- US -/±
- US +

Perform biopsy
GCA confirmed

High clinical probability
- US -/±
- US +

Perform biopsy
GCA confirmed

US, ultrasound
*Consider PET-CT or other in unclear situation / severe constitutional symptoms
Conditions that should be considered in the differential diagnosis of GCA

- Sinusitis
- Dental and temporo-mandibular conditions
- Non-arteritic anterior ischemic optic neuropathy
- Subacute thyroiditis
- Chronic infections (infective endocarditis, etc.)
- Trigeminal neuralgia
- Malignancy
- Atherosclerotic cardiovascular disease

Abatacept: Serious adverse events during the study*

<table>
<thead>
<tr>
<th>Event</th>
<th>Nonrandomized (n=8)</th>
<th>Abatacept (n=20)</th>
<th>Placebo (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea (3 months after abatacept)</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Syncope, melena (3 months after abatacept)</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Urinary tract infection (4 months after abatacept)</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Deep venous thrombosis (6 months after abatacept)</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anticoagulation hematoma (6 months after abatacept)</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Squamous cell carcinoma skin</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea/dehydration</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Diverticulitis</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Spinal surgery</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Syncope</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Branch retinal artery occlusion</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Partial vision loss</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Narcotic withdrawal</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>Dyspnea</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>Transitional cell carcinoma</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Endometrial carcinoma</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Urine electrolyte disturbance</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Knee replacement</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Deep venous thrombosis after knee replacement</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

*Values are the number of serious adverse events (summary of 23 events in 15 patients). None of the P values were significant between the groups.

### Tocilizumab: Demographic and Disease Characteristics of the Patients at Baseline.*

<table>
<thead>
<tr>
<th></th>
<th>TCZ QW (N=100)</th>
<th>TCZ Q2W (N=49)</th>
<th>Placebo + 26-Wk Taper (N = 50)</th>
<th>Placebo + 52-Wk Taper (N = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age — yr</strong></td>
<td>69.5±8.5</td>
<td>69.4±8.2</td>
<td>69.3±8.1</td>
<td>67.8±7.7</td>
</tr>
<tr>
<td><strong>Female sex — no. (%)</strong></td>
<td>78 (78)</td>
<td>35 (70)</td>
<td>38 (76)</td>
<td>37 (73)</td>
</tr>
<tr>
<td><strong>Race — no. (%)†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Black</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1)</td>
<td>1 (2)</td>
<td>50 (100)</td>
<td>49 (96)</td>
</tr>
<tr>
<td>White</td>
<td>97 (97)</td>
<td>47 (94)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (1)</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Weight — kg</strong></td>
<td>69.8±13.8</td>
<td>70.8±16.1</td>
<td>70.1±15.8</td>
<td>73.1±15.3</td>
</tr>
<tr>
<td><strong>Body-mass index‡</strong></td>
<td>26.0±4.4</td>
<td>26.0±6.2</td>
<td>25.7±4.5</td>
<td>25.8±4.1</td>
</tr>
<tr>
<td><strong>Giant-cell arteritis — no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newly diagnosed</td>
<td>47 (47)</td>
<td>26 (52)</td>
<td>23 (46)</td>
<td>23 (45)</td>
</tr>
<tr>
<td>Relapsing</td>
<td>53 (53)</td>
<td>24 (48)</td>
<td>27 (54)</td>
<td>28 (55)</td>
</tr>
<tr>
<td><strong>Prednisone dose — no. (%)</strong></td>
<td></td>
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<tr>
<td>≤30 mg/day</td>
<td>52 (52)</td>
<td>25 (50)</td>
<td>27 (54)</td>
<td>26 (51)</td>
</tr>
<tr>
<td>&gt;30 mg/day</td>
<td>48 (48)</td>
<td>25 (50)</td>
<td>23 (46)</td>
<td>25 (49)</td>
</tr>
<tr>
<td><strong>Disease duration — days</strong></td>
<td>307±564</td>
<td>258±501</td>
<td>365±570</td>
<td>255±436</td>
</tr>
<tr>
<td><strong>Cranial signs or symptoms — no. (%)§</strong></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>78 (78)</td>
<td>41 (82)</td>
<td>40 (80)</td>
<td>40 (78)</td>
</tr>
<tr>
<td><strong>Symptoms of polymyalgia rheumatica — no. (%)¶</strong></td>
<td></td>
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<tr>
<td></td>
<td>59 (59)</td>
<td>32 (64)</td>
<td>30 (60)</td>
<td>35 (69)</td>
</tr>
<tr>
<td><strong>Erythrocyte sedimentation rate — mm/hr</strong></td>
<td></td>
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<tr>
<td></td>
<td>24.6±18.7</td>
<td>20.8±18.1</td>
<td>28.8±25.4</td>
<td>24.2±18.2</td>
</tr>
<tr>
<td><strong>Diagnosis — no. (%)‖</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>By means of positive temporal-artery biopsy</td>
<td>57 (57)</td>
<td>34 (68)</td>
<td>36 (72)</td>
<td>29 (57)</td>
</tr>
<tr>
<td>By means of positive imaging</td>
<td>50 (50)</td>
<td>23 (46)</td>
<td>19 (38)</td>
<td>23 (45)</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. There were no significant differences among the four trial groups. † Race was reported by the patients and confirmed by the investigators during screening.‡ The body-mass index is the weight in kilograms divided by the square of the height in meters. § Cranial signs and symptoms were new-onset localized headache, scalp tenderness, temporal-artery tenderness, decreased pulsation, or jaw or mouth claudication. ¶ Symptoms of polymyalgia rheumatica were morning stiffness or pain in the shoulder or hip girdles. ‖ The diagnosis could have been based on either or both types of assessment.