Review

Polymyalgia Rheumatica and Giant Cell Arteritis
A Systematic Review

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IMPORTANCE Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are related inflammatory disorders occurring in persons aged 50 years and older. Diagnostic and therapeutic approaches are heterogeneous in clinical practice.

OBJECTIVE To summarize current evidence regarding optimal methods for diagnosing and treating PMR and GCA.

EVIDENCE REVIEW MEDLINE, EMBASE, and Cochrane databases were searched from their inception dates to March 30, 2016. Screening by 2 authors resulted in 6626 abstracts, of which 50 articles met the inclusion criteria. Study quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool or American College of Cardiology Foundation/American Heart Association methodology.

FINDINGS Twenty randomized clinical trials for therapy (n = 1016 participants) and 30 imaging studies for diagnosis and/or assessing response to therapy (n = 2080 participants) were included. The diagnosis of PMR is based on clinical features such as new-onset bilateral shoulder pain, including subdeltoid bursitis, muscle or joint stiffness, and functional impairment. Headache and visual disturbances including loss of vision are characteristic of GCA. Constitutional symptoms and elevated inflammatory markers (>90%) are common in both diseases. Ultrasound imaging enables detection of bilateral subdeltoid bursitis in 69% of PMR patients. In GCA, temporal artery biopsy remains the standard for definitive diagnosis. Ultrasound and magnetic resonance imaging (MRI) of large vessels revealing inflammation-induced wall thickening support the diagnosis of GCA (specificity 78%-100% for ultrasound and 73%-97% for MRI). Glucocorticoids remain the primary treatment, but the optimal initial dose and tapering treatment regimens are unknown. According to consensus-based recommendations, initial therapy for PMR is prednisone, 12.5 to 25 mg/day or equivalent, and 40 to 60 mg/day for GCA, followed by individualized tapering regimens in both diseases. Adjunctive methotrexate may reduce cumulative glucocorticoid dosage by 20% to 44% and relapses by 36% to 54% in both PMR and GCA. Use of tocilizumab as additional treatment with prednisone showed a 2- to 4-fold increase in remission rates of GCA in a randomized clinical trial (N = 30).

CONCLUSIONS AND RELEVANCE Diagnosis of PMR/GCA is made by clinical features and elevated inflammatory markers. In PMR, ultrasound imaging may improve diagnostic accuracy. In GCA, temporal artery biopsy may not be required in patients with typical disease features accompanied by characteristic ultrasound or MRI findings. Consensus-based recommendations suggest glucocorticoids as the most effective therapy for PMR/GCA. Methotrexate may be added to glucocorticoids in patients at risk for relapse and in those with glucocorticoid-related adverse effects or need for prolonged glucocorticoid therapy.

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Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are related inflammatory disorders of unknown etiology that may occur in persons aged 50 years and older. PMR typically presents acutely with bilateral upper extremity pain. GCA typically presents with unilateral or bilateral headache, myalgias, fatigue, fever, weight loss, and sometimes acute vision loss. PMR and GCA represent either different manifestations of the same disease or overlapping conditions. GCA may present as classic cranial (temporal) arteritis, large-vessel vasculitis, or single-organ arteritis. From 40% to 60% of patients diagnosed with GCA also have PMR, and 16% to 21% of PMR patients have GCA.[1-5] PMR occurs 3 to 10 times more frequently than GCA.[6,7]

In 2008, it was estimated that 711 000 US residents had PMR and that 228 000 had GCA.[7] The highest incidence of PMR occurs in persons of northern European descent, ranging from 41 to 113 cases per 100 000 among persons aged 50 years and older.[1,3,8-15] In the United States, GCA is the most frequent primary vasculitis with an incidence of 18 per 100 000.[7] Women have a higher lifetime risk for PMR (2.4%) and GCA (1.0%) than men (1.7% for PMR and 0.5% for GCA).[6-8]

This review summarizes the highest-quality evidence regarding optimal diagnosis and treatment of these common diseases.

Methods

Details on key questions, search and adjudication process, data synthesis, quality assessment, and approaches to reach conclusions are provided in eMethods in the Supplement.

In brief, 2 authors (C.D. and F.B.) searched Ovid-MEDLINE (1946), EMBASE (1988), Cochrane Central Register of Controlled Trials (1996), and Cochrane Systematic Reviews (1993) databases from their inception dates to March 30, 2016 (eFigure 1 in the Supplement).

For diagnostic accuracy studies, the following inclusion criteria were applied: full reports of prospective diagnostic ultrasound, magnetic resonance imaging (MRI), and/or fluorodeoxyglucose F 18 positron emission tomography (^{18}F-FDG-PET) studies investigating at least 20 patients with suspected PMR, GCA, or both; use of appropriate reference standards for diagnosis (ie, clinical diagnosis or published criteria[16-22]); and/or positive temporal artery biopsy. The QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool was used to assess quality, including risk of bias and applicability of studies to the review question (eTable 1 in the Supplement).[23]

Only randomized clinical trials (RCTs) of therapeutic interventions were included. Quality was assessed using the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) clinical practice guideline methodology.[24] Each study was appraised by 2 authors (C.D. and F.B.) with regard to risk of bias, relevance, and fidelity of implementation and rated as being fatally flawed (+) or of low (++), intermediate (+++), or high-quality (++++). Discrepancies between authors were resolved by discussion.

Results

PMR and GCA share genetic risk factors (such as susceptibility to HLA-DRB1*01 and HLA-DRB1*04 genotypes) and pathogenetic pathways involving both the innate and adaptive immune system.[25] GCA is a granulomatous large-vessel vasculitis in which T cells that produce interferon-γ and interleukin (IL)-17 are recruited in the arterial wall.[2,26] These cytokines activate macrophages and other cell types, induce vascular remodeling, and may lead to the ischemic manifestations in patients with GCA. Increased cytokine expression (IL-6, IL1-β) is associated with systemic manifestations (eFigure 2 in the Supplement). PMR may represent an early subclinical vasculitis with a prominent systemic inflammatory response and articular or periarticular inflammation.

The value of imaging for diagnosis, assessing response to therapy, or both was reported in 30 studies retrieved by the systematic literature review (eFigure 1 in the Supplement). Of these diagnostic studies, 4 were excluded because of a high risk of bias or poor applicability (see eMethods in the Supplement).[23,27-30]

Main findings of diagnostic imaging studies are summarized in **Table 1**; quality assessment is detailed in eTable 1 (in the Supplement).

Diagnosis of PMR

Diagnosis of PMR is primarily based on clinical features that include new-onset bilateral shoulder pain and stiffness (**Figure 1**). Symptoms often begin acutely and with functional impairment, including difficulties in rising, dressing, lifting, and reaching. Constitutional symptoms such as fatigue, depression, night sweats, weight loss, and low-grade fever are frequent.[1] Elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), or both are present in more than 90% of PMR patients; however, these tests are nonspecific. A Westergren ESR of greater than 30 or 40 mm/h has often been defined as abnormal in clinical studies and classification criteria[16-20,22,31]; however, the optimal cutoff for diagnostic purposes is undefined. Further tests to consider in the evaluation of possible PMR are detailed in Figure 1.[1,2,50,51]

Ultrasound and ^{18}F-FDG-PET for Diagnosis and Assessing Response to Therapy

Subdeltoid bursitis, biceps tenosynovitis, and/or glenohumeral/hip synovitis are characteristic findings in PMR (eFigure 3 in the Supplement). Ultrasound detection of these abnormalities may improve diagnostic accuracy.

There is 1 prospective study (N = 61) of ultrasonography of shoulders and peripheral joints for diagnosis of PMR in a cohort of patients with symptoms of polymyalgia. The combination of clinical judgement after 1 year and ultrasonography/radiographic data was used to diagnose PMR in 29 cases; 32 patients had other diseases. Subdeltoid bursitis identified on ultrasound had the highest combination of sensitivity and specificity for PMR diagnosis. Unilateral lesions were observed in 79% of PMR patients and bilateral lesions were observed in 69%, compared with 41% for unilateral lesions and 22% for bilateral lesions among controls.[31]

The 2012 European League Against Rheumatism/American College of Rheumatology (EULAR-ACR) classification criteria study included a prospective, longitudinal substudy of ultrasonography (not matching the review criteria), which reported a sensitivity of 59% and a specificity of 57% for bilateral shoulder involvement and for involvement of 1 shoulder plus 1 hip, a sensitivity of 33% and a specificity of 84%.[16] Ultrasonography parameters are included in these criteria.[16]

Table 1. Summary of Diagnostic Studies of Ultrasound, MRI, and ^{18}F-FDG-PET in PMR and GCA[a]

Source	Sample Size/No. of Women (%)	Study Population	Biopsy, No. (%)	No. of Patients/ Controls	Technical Settings[b]	Structures Investigated	Pathologies	% (95% CI)		Reference Standard	LoB/ LoA
								Sensitivity	Specificity		
Ultrasound (PMR)											
Falsetti et al,[31] 2011	61/35 (57)	Polymyalgic syndrome	NA	29/32	10 MHz	Shoulders, hips, elbows, wrists, metacarpophalangeal joints, metatarsophalangeal joints	Subdeltoid bursitis Biceps tenosynovitis Shoulder power Doppler >0 Coxofemoral synovitis	79 (60-92) 79 (60-92) 7 (1-23) 24 (10-44)	59 (42-76) 38 (21-56) 78 (60-91) 88 (71-97)	Clinical diagnosis after 1 y	7/3
Ultrasound (GCA)											
Aschwanden et al,[32] 2015	60/40 (67)	Suspected GCA	18 (30)	24/36	17 MHz	Temporal arteries	Compression sign	75 (51-88)	100 (88-100)	ACR criteria[c]	8/3
Aschwanden et al,[33] 2013	80/55 (69)	Suspected GCA	53 (66)	43/37	17 MHz	Temporal arteries	Halo Stenosis Occlusion Compression sign	79 (62-89) 12 (4-25) 8 (1-19) 79 (62-89)	100 (88-100) 100 (88-100) 100 (88-100) 100 (88-100)	ACR criteria[c]	8/3
Aschwanden et al,[34] 2010	72/45 (63)	Suspected GCA	56 (78)	38/34	9 MHz; 17 MHz	Temporal, carotid, vertebral, subclavian, axillary, femoral, and popliteal arteries	Halo (≥1 vascular segment)	55 (37-70)	100 (88-100)	ACR criteria[c]	6/2
Diamantopoulos et al,[35] 2014	88/54 (61)	Suspected GCA (with ≥1 of the following: CRP >5 mg/dL, headache, jaw claudication, fever, PMR, tenderness of temporal arteries, visual impairment)	58 (66)	46/42	13 MHz	Temporal, carotid, and axillary arteries	Halo	100 (90-100)	91 (75-96)	Clinical diagnosis at 6 mo, biopsy result	9/3
Habib et al,[36] 2012	32/19 (59)	Suspected GCA (with ≥1 of the following: ESR >50 mm/h, headache, jaw claudication, fever, PMR, tenderness of temporal arteries, visual impairment	32 (100)	16/16	10 MHz	Temporal arteries	Halo Stenosis/occlusion	81 (54-96) 25 (7-52)	88 (62-99) 81 (54-96)	ACR criteria,[c] biopsy result, clinical diagnosis at 3 mo	8/2
Karahaliou et al,[37] 2006	60/30 (55)[d]	Suspected GCA (with ≥1 of the following: ESR >50 mm/h, headache, jaw claudication, fever, PMR, tenderness of temporal arteries, visual impairment	49 (89)	22/33	11 MHz	Temporal arteries	Halo Stenosis	82 (60-95) 41 (21-64)	91 (76-98) 73 (55-87)	Biopsy result Clinical diagnosis at 3 mo	7/3
LeSar et al,[38] 2002	32/21 (60)	Suspected GCA	32 (100)	7/25	10 MHz	Temporal arteries	Halo Stenosis	86 (42-100) 43 (10-82)	92 (74-99) 84 (64-95)	Biopsy result	5/2
Nesher et al,[39]2002	69/NA	Suspected GCA	32 (46)	14/55	15 MHz	Temporal arteries	Halo	86 (57-98)	78 (65-88)	ACR criteria[c]	5/3
Reinhard et al,[40] 2004	83/49 (59)	Suspected GCA	48 (58)	43/40	10 MHz	Temporal arteries	Halo	60 (43-74)	100 (89-100)	ACR criteria[c]	5/3
Romera-Villegas et al,[41] 2004	68/48 (71)	3 of 5 ACR criteria[c]	68 (100)	22/46	10 MHz	Temporal arteries	Halo	95 (77-100)	91 (79-98)	Biopsy result	9/3
Schmidt et al,[42] 1997	112/NA	Suspected GCA or PMR plus temporal artery biopsy available	47 (42)	30/82	10 MHz	Temporal arteries	Halo Stenosis/occlusion	73 (52-86) 80 (61-92)	100 (94-100) 93 (85-97)	Biopsy result Clinical diagnosis	7/2

(continued)

Table 1. Summary of Diagnostic Studies of Ultrasound, MRI, and ^{18}F-FDG-PET in PMR and GCA[a] (continued)

Source	Sample Size/No. of Women (%)	Study Population	Biopsy, No. (%)	No. of Patients/ Controls	Technical Settings[b]	Structures Investigated	Pathologies	% (95% CI) Sensitivity	% (95% CI) Specificity	Reference Standard	LoB/ LoA
MRI (GCA)											
Bley et al,[43] 2007	64/31 (48)	Suspected GCA plus ≥1 of the following: headache, tenderness of temporal arteries, visual impairment, elevated acute phase reactants	32 (50)	31/33	1.5 T (45%); 3 T (55%)	Temporal and occipital arteries	Wall thickening plus enhancement (score 0-3)	81 (63-93)	97 (84-100)	ACR criteria[c]	9/2
Bley et al,[44] 2005	21/11 (52)	Suspected GCA	10 (48)	9/12	3 T	Temporal and occipital arteries	Wall thickening plus enhancement (score 0-3)	89 (52-100)	92 (62-100)	ACR criteria[c]	8/3
Geiger et al,[45] 2010	43/30 (70)	Suspected GCA (ACR criteria[c])	15 (35)	28/15	3 T	Temporal and occipital arteries	Wall thickening plus enhancement (score 0-3)	68 (48-84)	73 (45-92)	ACR criteria[c]	7/3
Veldhoen et al,[46] 2014	245/68 (69)[e]	Suspected GCA plus temporal biopsy plus MRI of deep temporal arteries and temporal muscle available	99 (100)[f]	61/38	1.5 T; 3 T	Deep temporal arteries, temporal muscle	Wall thickening plus enhancement (artery wall/temporal muscle)	20 (11-32)	95 (82-99)	Biopsy result	5/3
Klink et al,[47] 2014	185/125 (68)	Suspected GCA (≥1 of the following: headache, tenderness or pulse reduction of temporal arteries, elevated acute phase reactants) plus MRI available	98 (53)	102/83	1.5 T; 3 T	Temporal and occipital arteries	Wall thickening plus enhancement (score 0-3)	81 (73-88)	88 (79-94)	ACR criteria[c]	8/3
Siemonsen et al,[48] 2015	28/21 (84)[g]	Suspected GCA	11 (39)	20/5	3 T	Temporal, occipital, and intracranial arteries	Temporal and occipital arteries (wall thickening plus enhancement) Intracranial arteries (enhancement)	80 (56-94) 50 (26-70)	80 (28-100) 100 (40-100)	ACR criteria[c]	9/3
^{18}F-FDG-PET (GCA)											
Blockmans et al,[49] 2000	69/38 (55)	ESR ≥40 mm/h, headache, fever, PMR, weight loss	69 (100)	13/56	CTI-Siemens	Aorta, carotid, subclavian, femoral, popliteal, and tibial arteries	Enhancement (score 0-3 per vascular bed)	77 (46-95)	66 (52-78)	Biopsy result	8/2

Abbreviations: ^{18}F-FDG-PET, fluorodeoxyglucose F 18 positron emission tomography; ACR, American College of Rheumatology; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; LoA, number of questions of evaluation revealing low concerns regarding applicability to the review question; LoB, number of questions of evaluation with low risk of bias; MRI, magnetic resonance imaging; NA, not available; QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies; PMR, polymyalgia rheumatica.

[a] In relation to the QUADAS-2 tool, we included only studies yielding a low risk of bias (in ≥5 of 10 questions) and low concerns of applicability (in ≥2 of 3 questions). All were cohort studies, and the samples were consecutive (except Habib,[36] Reinhard,[40] and Veldhoen,[46] [in which the sample selections were not described]).

[b] Column header indicates units of measure for ultrasound, MRI, and ^{18}-F-FDG-PET settings.

[c] ACR criteria for GCA: (1) age at disease onset ≥50 years; (2) new headache; (3) temporal artery abnormality; (4) elevated ESR; and (5) abnormal artery biopsy.

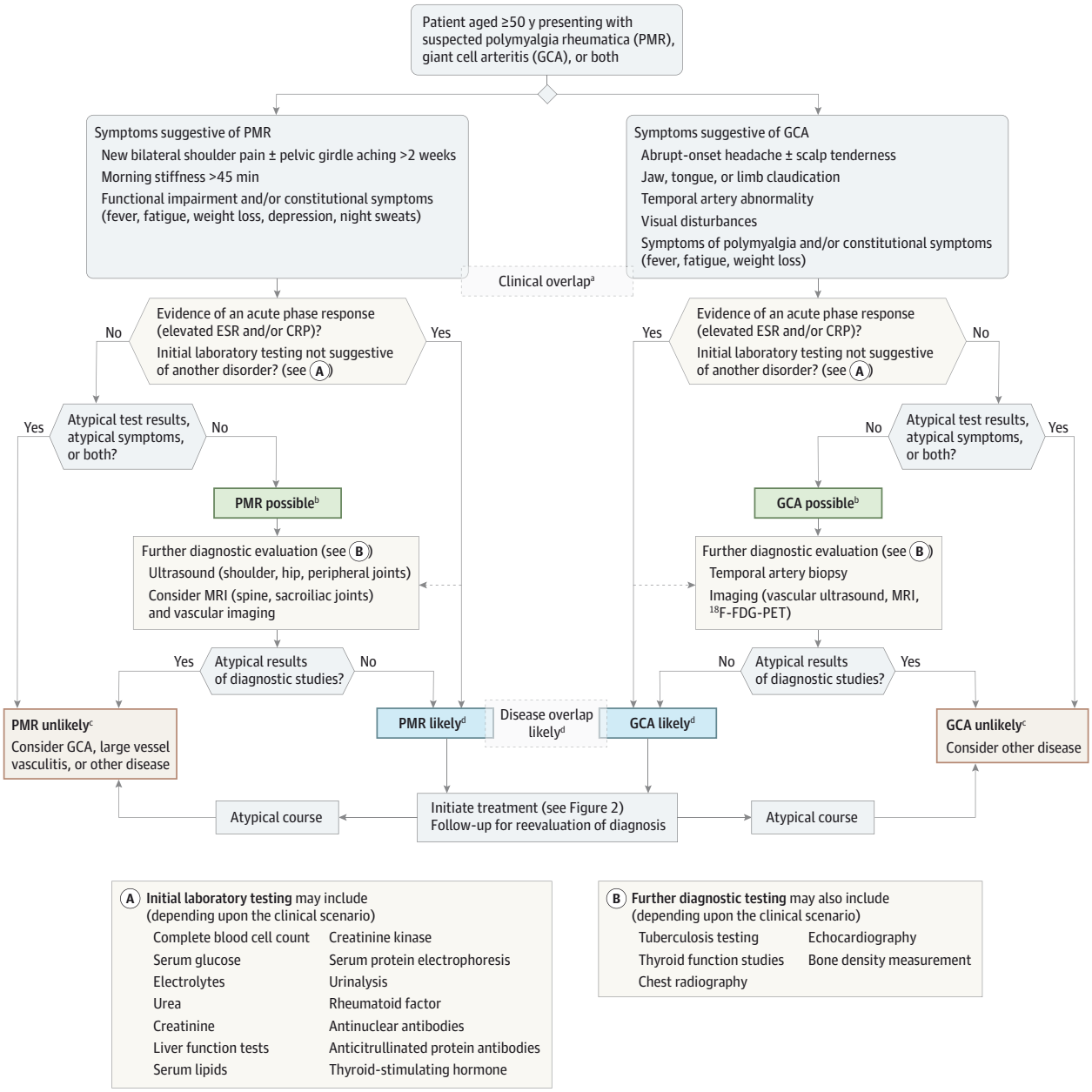
[d] Fifty-five of 60 patients recruited for the study were included in the final analysis. Percentage of women is based on the number included in the final analysis not the sample size.

[e] Ninety-nine of 245 patients recruited for the study were included in the final analysis. Percentage of women is based on the number included in the final analysis not the sample size.

[f] Percentage is based on the number included in the final analysis (99) not the sample size (245).

[g] Twenty-five of 28 patients recruited for the study were included in the final analysis. Percentage of women is based on the number included in the final analysis not the sample size.

Figure 1. Clinical Disease Characteristics and Suggested Algorithm for Diagnostic Evaluation of Patients With Symptoms of Polymyalgia Rheumatica or Suspected Giant Cell Arteritis



The approach incorporates the currently most useful investigations for ascertaining the diagnosis of polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) and exclusion of relevant mimicking conditions. This algorithm is based upon assessment of the available literature. It has not been formally tested in a randomized clinical trial. ^{18}F-FDG-PET indicates fluorodeoxyglucose F 18 positron emission tomography and MRI indicates magnetic resonance imaging.

[a] From 40% to 60% of patients diagnosed with GCA also have PMR, and 16% to 21% of PMR patients have GCA.

[b] PMR and GCA (including disease overlap) is possible if there are both typical and atypical symptoms and signs, including normal erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP), and/or abnormal findings at initial laboratory investigations that prompt further evaluation.

[c] PMR and GCA (including disease overlap) is unlikely (but not ruled out) since inflammatory markers are elevated in more than 90% of patients in both diseases.

[d] PMR and GCA (including disease overlap) is likely if there are typical symptoms and signs including raised ESR, CRP, or both and no abnormal findings that prompt further evaluation.

Two prospective studies demonstrated that abnormal ultrasonography findings resolved in 17 of 34 (50%) PMR patients after 4 weeks of treatment,[52] and in 19 of 56 (33%) PMR patients at 24 weeks.[53] In an ^{18}F-FDG-PET study of 21 PMR patients, a reduction of tracer uptake in the shoulders, pelvis, and spine was observed after 12 weeks of tocilizumab treatment.[54]

Diagnosis of GCA

Patients with GCA frequently have cranial and/or systemic manifestations. Cranial features include new headache (≈ 2/3 of patients[55,56]), temporal artery abnormality (a prominent, beaded and/or tender artery with decreased pulse [≤30% of patients][57]), and abnormal temporal artery biopsy (Figure 1). These features are included in the 1990 ACR Classification Criteria.[21] Systemic features include polymyalgic symptoms, weight loss, fatigue, and fever.

Vision loss occurs in as many as 20% of patients with GCA, stressing the urgency of diagnosis and treatment.[58] Rapid evaluation of patients may reduce risk of vision loss, particularly because ischemic complications usually occur before glucocorticoid treatment.[59] Rarer ischemic complications of GCA include stroke, cranial nerve palsy, and scalp necrosis.[2] Large-vessel aneurysms and/or stenoses (eFigure 4 in the Supplement) are potential short- and/or long-term complications of GCA, and can be associated with chest pain, upper or lower extremity claudication, or stroke.[2] ESR, CRP, or both are elevated in more than 95% of GCA cases. Temporal artery biopsy with specimen length of at least 1 cm, performed by an experienced surgeon and revealing histopathologic features of temporal arteritis, is the standard test for diagnosis of cranial GCA. Other tests to consider are outlined in Figure 1 and in the subsections entitled ultrasonography, MRI, and ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET).[1,2,50,51]

Ultrasonography

Color-duplex ultrasonography can be used to assess vascular inflammation of the superficial temporal and accessible large arteries. A typical ultrasonography finding in GCA is the "halo sign", a hypoechoic ring around the arterial lumen representing inflammation-induced edematous thickening of the arterial wall (eFigure 3 in the Supplement).

The systematic literature review revealed ultrasonography studies in GCA to be heterogeneous because of different inclusion criteria,[41,42] differences in technical equipment,[33,35,36,38,40-42] different vessels scanned,[33,36-42] and various diagnostic standards.[33-37,40,42]

Sensitivity ranged from 55% to 100% and specifity ranged from 78% to 100% in 10 studies (n = 696 patients).[33-42] Stenosis or occlusion (often considered as a single pathology) in 5 studies (n = 316) had similar specificity (73%-100%) but was less sensitive (8%-80%) with highly dispersed data. Two studies from 1 center (total n = 140) investigated the compression-sign in suspected GCA. A positive compression-sign is when the vessel wall remains visible (because of inflammation-induced wall thickening) on compression of the vessel lumen with the ultrasound probe. It had a sensitivity of 75% to 79% (present in 52 of 67 GCA patients) and a specificity of 100% (absent in all 73 controls) for GCA diagnosis (according to ACR criteria).[32,33]

Ultrasonography follow-up data for patients undergoing treatment were available from 4 studies.[36,37,42,60] One study reported the halo disappeared in 95% of 30 cases after a median of 8 (range 2-30) weeks.[60] The other 3 studies, totaling 51 patients, reported disappearance of the halo in all patients after a mean of 14 to 22 days.[36,37,42]

MRI

In GCA, contrast-enhanced high-resolution MRI can demonstrate arterial wall thickening with mural and periadventitial contrast enhancement.

Five prospective MRI studies (n = 341; 1 study [Bley et al][44] contributing data from 21 patients to 2 publications) assessed temporal and occipital arteries for GCA diagnosis (ACR criteria) and reported sensitivities of 68% to 89% and specificities of 73% to 97%.[43-45,47,48] In one of these studies (n = 25), the sensitivity of MRI detected enhancement of intracranial arteries for diagnosis was 50% (10 of 20 GCA patients with positive result) and specificity was 100% (absent in all 5 controls).[48] Inflammation of the deep temporal artery and the temporal muscle was assessed in a subset of patients in a multicenter cohort (n = 245) reporting low sensitivity (20%; 12 of 61 with positive temporal artery biopsy) but high specificity (95%; 2 of 38 with negative temporal artery biopsy) for GCA diagnosis.[46]

^{18}F-FDG-PET

^{18}F-FDG-PET, usually combined with low-dose computed tomography, can be used to detect inflamed vascular territories in GCA based on the intensity of the glucose analogue uptake.

Only 1 diagnostic ^{18}F-FDG-PET study (n = 69) met the inclusion criteria, reporting a sensitivity of 77% (positive result in 10 of 13 patients with positive temporal artery biopsy) and specificity of 66% (negative in 37 of 56 cases with negative temporal artery biopsy).[49]

^{18}F-FDG-PET scan uptake persists on treatment. A study of 35 GCA patients showed tracer uptake in the aorta and large arteries in 80% of patients prior to therapy and, despite the absence of clinical activity in all patients, in 75% of cases after 6 months.[61] An abnormal ^{18}F-FDG-PET finding in the thoracic aorta at baseline was associated with aortic dilatation after approximately 4 years in another GCA study.[62] Repeat ^{18}F-FDG-PET scans in 36 PMR patients, in whom temporal arteritis was excluded by negative temporal artery biopsy, showed that one-third of patients had vascular uptake before glucocorticoid treatment that persisted in more than 60% of cases at 3 and 6 months.[63]

Color-duplex ultrasonography may be considered in every patient with clinically suspected GCA; MRI might be used as an alternative to sonography. ^{18}F-FDG-PET is valuable for patients with suspected large-vessel vasculitis in addition to or instead of ultrasonography or MRI. Temporal artery biopsy is unnecessary when the diagnosis is very unlikely or certain, but it remains the standard for definitive diagnosis of cranial GCA and should be considered when GCA can neither be confirmed nor ruled out based on clinical symptoms and other diagnostic tests including imaging.

Medications for PMR and GCA

Twenty RCTs for therapy were selected (eFigure 1 in the Supplement). Main findings are summarized in **Table 2**; quality assessment is detailed in eTable 2 in the Supplement. None of these RCTs addressed the value of aspirin in GCA.

Glucocorticoid Treatment

Consensus-based recommendations uniformly consider glucocorticoids as the therapy of choice for PMR and GCA[50,51,85,86]; however, there is uncertainty regarding best dosing practices. Only 4 RCTs investigating alternative glucocorticoid dosing or administration regimens were found.

One single-center, open-label 2-month RCT (N = 74 patients [39 PMR and 35 GCA]) compared initial glucocorticoid doses (high doses, 19 PMR vs 20 GCA; low doses, 20 PMR vs 15 GCA; Jones and

Table 2. Summary of Randomized Clinical Trials Related to Efficacy and Safety of Glucocorticoids and Immunosuppressive Agents in Polymyalgia Rheumatica and Giant Cell Arteritis

Source	Design	Follow-up, wk	Population	Intervention	Control	Sample Size, No.	No. (%)		Main Findings[a]	Quality[b]
							Women	Completed Follow-up		
Glucocorticoid Starting Doses in PMR Treatment										
Dasgupta et al,[64] 1998 Dolan et al,[65] 1997	Multicenter, double blinded	96	PMR, new untreated	Intramuscular methylprednisolone, 120 mg every 3 wk	Oral prednisone, 15 mg	60	43 (72)	49 (82)	Cumulative glucocorticoid dose (96 wk): 2.0 g vs 3.5 g; $P < .001$ Glucocorticoid adverse events (96 wk): weight gain 0.8 kg vs 3.4 kg; $P < .001$ No difference between groups: Remission (12 wk): 18 (60%) vs 20 (67%) Remission (96 wk): 10 (33%) vs 9 (30%) Discontinuation of glucocorticoids (96 wk): 10 (33%) vs 14 (47%) Mortality (96 wk): 1 (3%) vs 3 (10%)	+ + +
Glucocorticoid Starting Doses in GCA Treatment										
Mazlumzadeh et al,[66] 2006	Single center, double blinded	78	GCA, new (cranial), receiving glucocorticoids ≤10 d, no ocular or vascular manifestation	Methylprednisolone, 15 mg/kg (3 d), plus oral prednisone, 40 mg	Oral prednisone, 40 mg	27	19 (70)	25 (93)	Remission on ≤5 mg oral prednisone: 36 wk: 10 (71%) vs 2 (15%); $P = .003$ 52 wk: 11 (79%) vs 2 (15%); $P = .001$ 78 wk: 12 (86%) vs 4 (33%); $P = .006$ Cumulative glucocorticoid dose (78 wk): 5.6 g vs 7.9 g; $P = .001$ (pulses not counted) Relapse rate (78 wk): 21 (in 14 patients) vs 37 relapses (in 13 patients); $P = .028$ Discontinuation of glucocorticoids (78 wk): 6 (43%) vs 0; $P < .05$ No difference between groups for treatment-related adverse events (78 wk): 38 vs 37 events	+ + +
Chevalet et al,[67] 2000	Multicenter, open	52	GCA, new (cranial), no ocular or vascular manifestation	Group 1: methylprednisolone, 240 mg (single shot), plus oral prednisone, 0.7 mg/kg Group 2: methylprednisolone, 240 mg (single shot), plus oral prednisone, 0.5 mg/kg	Group 3: oral prednisone, 0.7 mg/kg	164	116 (71)	133 (81)	No difference between groups (1 y): Cumulative glucocorticoid dose (pulses not counted): 5.8 g vs 5.2 g vs 5.6 g Discontinuation of glucocorticoids: 9 (15%) vs 6 (11%) vs 12 (23%) Patients with treatment-related adverse events: 28 (46%) vs 18 (36%) vs 18 (34%) Patients with GCA complications: 1 (2%) vs 2 (4%) vs 1 (2%)	+
Glucocorticoid Starting Doses in PMR and GCA Treatment										
Kyle and Hazleman,[68] 1989	Single center, open	8	PMR and GCA, new, untreated	PMR: oral prednisone, 20 mg GCA: oral prednisone, 40 mg	PMR: oral prednisone, 10 mg GCA: oral prednisone, 20 mg	39 35	NA	74 (100)	PMR patients with ≥1 relapse (2 mo): 2 (11%) vs 13 (65%); $P < .001$ No difference between groups for GCA patients with ≥1 relapse (2 mo): 4 (20%) vs 6 (40%)	+ +

(continued)

Table 2. Summary of Randomized Clinical Trials Related to Efficacy and Safety of Glucocorticoids and Immunosuppressive Agents in Polymyalgia Rheumatica and Giant Cell Arteritis (continued)

Source	Design	Follow-up, wk	Population	Intervention	Control	Sample Size, No.	No. (%)		Main Findings[a]	Quality[b]
							Women	Completed Follow-up		
Conventional Disease-Modifying Antirheumatic Drugs in PMR Treatment										
Caporali et al,[69] 2004	Multicenter, double blinded	76	PMR, new, untreated	Methotrexate, 10 mg per wk plus oral prednisone, 25 mg	Oral prednisone, 25 mg	72	48 (67)	62 (86)	Patients with ≥1 relapse: 24-48 wk: 10 (31%) vs 19 (63%); *P* = .02 76 wk: 15 (47%) vs 22 (73%); *P* = .04 Cumulative glucocorticoid dose (76 wk): 2.1 g vs 3.0 g; *P* = .003. Discontinuation of glucocorticoids: 48 wk: 26 (81%) vs 14 (47%); *P* = .008 76 wk: 28 (88%) vs 16 (53%); *P* = .003 No difference between groups for glucocorticoid adverse events (76 wk): 26 vs 29 events Methotrexate-related adverse event (76 wk) (gastrointestinal events were numerically higher in the methotrexate group): 12 vs 4 events	+ + + +
Ferraccioli et al,[70] 1996	Multicenter, open	52	PMR, new	Methotrexate, 10 mg/wk plus oral prednisone, 25 mg	Oral prednisone, 15 mg	24	22 (92)	24 (100)	Patients with ≥1 relapse (12 mo): 6 (50%) vs 12 (100%); *P* = .013 Discontinuation of glucocorticoids (12 mo): 6 (50%) vs 0; *P* = .013 Cumulative glucocorticoid dose (12 mo): 1.8 g vs 3.2 g; *P* = .0001 No difference between groups for glucocorticoid adverse events (12 mo): 0 vs 7 events Methotrexate-related adverse events (12 mo) (numerically higher in the methotrexate group): Nausea: 2 vs 0 events Elevation of liver enzymes: 4 vs 0 events	+ +
Conventional Disease-Modifying Antirheumatic Drugs in GCA Treatment										
Spiera et al,[71] 2001	Single center, double blinded	NA	GCA; new (extra cranial); receiving glucocorticoids ≤1 mo; oral prednisone, 30mg/d at randomization; initial treatment between 40 mg and 1 g	Methotrexate, 7.5 mg/wk plus oral prednisone	Oral prednisone	21	13 (62)	NA	No difference between groups (unknown length of follow-up): Patients with ≥1 relapse: 6 (50%) vs 3 (33%) Duration of glucocorticoid therapy: 68 vs 60 wk Cumulative glucocorticoid dose: 6.5 g vs 5.9 g Glucocorticoid adverse events: 51 vs 39 events Quality of life (no data reported) Methotrexate-related adverse events (numerically higher in the intervention group): 17 vs 11 events	+ +
Jover et al,[72] 2001	Single center, double blinded	104	GCA, new (cranial), receiving glucocorticoids <14 d	Methotrexate 10 mg/wk plus oral prednisone, 60 mg	Oral prednisone, 60 mg	42	29 (69)	39 (93)	Patients without a relapse (24 mo): 11 (55%) vs 3 (16%); *P* = .004 Cumulative glucocorticoid dose (24 mo): 4.3 g vs 5.4 g; *P* = .01 Duration of glucocorticoid therapy: 29 wk vs 94 wk; *P* = .002 Glucocorticoid adverse events (24 mo): Numerically lower rates of diabetes: 3 (15%) vs 7 (37%) Hypertension: 12 (60%) vs 16 (84%) Cushingoid habitus: 3 (15%) vs 6 (32%) (in methotrexate group) Methotrexate-related adverse events (required to stop the drug): 3 vs 0	+ + + +

(continued)

Table 2. Summary of Randomized Clinical Trials Related to Efficacy and Safety of Glucocorticoids and Immunosuppressive Agents in Polymyalgia Rheumatica and Giant Cell Arteritis (continued)

Source	Design	Follow-up, wk	Population	Intervention	Control	Sample Size, No.	No. (%)		Main Findings[a]	Quality[b]
							Women	Completed Follow-up		
Hoffman et al,[73] 2002	Multicenter, double blinded	52	GCA, new (extracranial, response to glucocorticoid therapy ≤5 d, receiving glucocorticoids ≤21 d	Methotrexate 15 mg/wk plus oral prednisone, 1 mg/kg	Oral prednisone, 1 mg/kg	98	70 (71)	NA	No difference between groups (12 mo): Relapse: 31 (61%) vs 31 (66%) Treatment failure (= 2 relapses or persistence of disease activity despite increment of glucocorticoid dose): 22 (43%) vs 24 (51%) Cumulative glucocorticoid dose: 5.4 g vs 5.3 g Duration of glucocorticoid therapy: 5.4 mo vs 5.6 mo GCA complications: 4 (8%) vs 4 (9%) Mortality: 2 (4%) vs 1 (2%) No difference between groups for glucocorticoid adverse events (12 mo): Fractures: 2 (4%) vs 1 (2%) Serious infections: 1 (2%) vs 2 (4%) Patients with methotrexate-related adverse events requiring a dose reduction or drug discontinuation were numerically higher in intervention group: 4 (8%) vs 0 Power calculation reconducted during study—reduction of sample size	+ + +
Liozon et al,[74] 1993	Multicenter, open	NA	GCA, new (cranial), untreated	Dapsone, 50-100 mg/d plus oral prednisone, 0.7 mg/kg	Oral prednisone, 0.7mg/kg	47	30 (64)	21 (45)	One or more relapses (unknown length of follow-up): 5 (24%) vs 13 (65%); $P < .05$ No difference between groups (unknown length of follow-up): Glucocorticoid-free remission: 8 (38%) vs 2 (10%) Duration of glucocorticoid therapy: 14 vs 13 mo Dapsone-related adverse events resulted in early termination of the study: Hemolytic anemia: 10 (56%) vs 1 (6%); $P < .05$ Agranulocytosis: 2 (11%) vs 0 Severe rash: 3 (17%) vs 0	+
Schaufelberger et al,[75] 2006	Multicenter, open	52	GCA, new (cranial), receiving glucocorticoids ≤1 mo	Cyclosporine A, 2.0-3.5 mg/kg plus oral prednisone	Oral prednisone	60	38 (63)	59 (98)	No data reported concerning efficacy outcomes (remission, relapse, cumulative glucocorticoid dose) Adverse events led to early drug discontinuation: 9 (30%) patients in cyclosporine A group (3 [10%] with hypertension, 6 [20%] with creatinine increment) vs 0 in the control group (highest tolerable cyclosporine A dose was 2.2 mg/kg)	+
Conventional Disease-Modifying Antirheumatic Drugs in PMR and GCA Treatment										
van der Veen et al,[76] 1996	Multicenter, double blinded	104	PMR and GCA, new	Methotrexate, 7.5 mg/wk plus oral prednisone, 20 mg	Oral prednisone, 20 mg	40	30 (75)	21 (53)	No difference between groups (24 mo): Glucocorticoid-free remission at any time: 11 (55%) vs 9 (45%) One or more relapses: 10 (50%) vs 9 (45%) Cumulative glucocorticoid dose: 2.4 g vs 3.0 g Duration of glucocorticoid treatment: 41 vs 29 wk GCA complications: 0 in both groups Glucocorticoid adverse events: 36 vs 28 events Methotrexate-related adverse events (24 mo): Elevation of liver enzymes: 15 (75%) vs 8 (40%) patients, $P < .05$ (higher in intervention group) No difference between groups Gastrointestinal concerns: 5 (25%) in both groups) Hair loss: 1 (5%) vs 0 Oral ulceration: 3 (15%) in both groups Withdrew for various reasons: 19 (48% [9 {45%}] in the methotrexate group vs [10 {50%}] in the placebo group)	+

(continued)

Table 2. Summary of Randomized Clinical Trials Related to Efficacy and Safety of Glucocorticoids and Immunosuppressive Agents in Polymyalgia Rheumatica and Giant Cell Arteritis (continued)

Source	Design	Follow-up, wk	Population	Intervention	Control	Sample Size, No.	No. (%)		Main Findings[a]	Quality[b]
							Women	Completed Follow-up		
De Silva and Hazleman[77] 1986	Single center, double blinded	52	PMR or GCA in remission; ≥3 mo stable oral prednisone, >5mg/d	Azathioprine, 150 mg/d plud oral prednisone (not specified)	Oral prednisone (not specified)	31	24 (77)	20 (65)	Daily glucocorticoid dose (52 wk): 1.9 mg vs 4.2 mg; $P < .05$ Azathioprine-related adverse events requiring drug discontinuation (numerically higher in the intervention group): 7 (44%) vs 3 (20%)	+ +
Schaufelberger et al,[78] 1998	Single center, open	26	PMR or GCA ≥1 y; stable oral prednisone, >5mg/d	Cyclosporine A, 2.0 mg/kg plus oral prednisone	Oral prednisone	22	20 (91)	21 (95)	No difference between groups (6 mo): Patients' global assessment score[c]: 1.3 vs 1.7 Physicians' global assessment score[c]: 1.3 vs 1.9 Duration of morning stiffness: 6 min vs 37 min Erythrocyte sedimentation rate >30 mm/h: 7 (64%) vs 2 (18%) C-reactive protein >15 mg/L: 3 (27%) vs 1 (9%) Patients with cyclosporin A–related adverse events requiring drug discontinuation (numerically higher in the intervention group): 2 (18%) vs 0	+
Biological Disease-Modifying Antirheumatic Drugs in PMR Treatment										
Salvarani et al,[79] 2007	Multicenter, double blinded	52	PMR, new, untreated	Infliximab, 3 mg/kg for 8 weeks plus oral prednisone, 15 mg	Oral prednisone, 15 mg	51	31 (61)	47 (92)	No difference between groups (52 wk): Patients without a relapse: 6 (30%) vs 10 (37%) Discontinuation of glucocorticoids: 10 (50%) vs 14 (54%) Duration of glucocorticoid therapy: 26 wk vs 22 wk Cumulative glucocorticoid dose: 1.7 g vs 1.2 g Glucocorticoid adverse events: 1 vs 6 events Infliximab-related adverse events (52 wk): Numerically higher rate of infusion reactions: 4 vs 0 events Systemic infections: 1 vs 0 (in infliximab group)	+ + + +
Kreiner and Galbo,[80] 2010	Single center, double blinded	2	PMR, new, untreated	Etanercept, 25 mg, twice per week	Placebo, twice per week	22	NA	20 (91)	No difference between groups (2 wk): PMR activity score (32 vs 31 points)[d] Etanercept-related adverse events (2 wk): local injection reactions occurred in 2 (20%) vs 1 (8%)	+ + +
Biological Disease-Modifying Antirheumatic Drugs in GCA Treatment										
Hoffmann et al,[81] 2007	Multicenter, double blinded	54	GCA, new (cranial) response to glucocorticoid therapy ≤5 d, receiving glucocorticoids ≤4 wk; stable oral prednisone, 40-60 mg, ≥1 wk	Infliximab, 5 mg/kg for 8 weeks plus oral prednisone, 40-60 mg	Oral prednisone, 40-60 mg	44	35 (80)	17 (39)	No difference between groups (22 wk): Patients without a relapse: 12 (43%) vs 8 (50%) Patients in glucocorticoid-free remission: 11 (39%) vs 7 (44%) Cumulative glucocorticoid dose: 3.2 g vs 3.1 g Infliximab-related adverse events (numerically higher in infliximab group): Patients with ≥1 infection: 20 (71%) vs 9 (56%) Patients with ≥1 serious infection: 3 (11%) vs 1 (6%) (Significantly higher proportion of patients with infusion reactions in intervention group: 6 [21%] vs 0; $P < .05$) Study prematurely terminated after failure of primary end point (patients without a relapse at 22 wk)	+ + + +

(continued)

Table 2. Summary of Randomized Clinical Trials Related to Efficacy and Safety of Glucocorticoids and Immunosuppressive Agents in Polymyalgia Rheumatica and Giant Cell Arteritis (continued)

Source	Design	Follow-up, wk	Population	Intervention	Control	Sample Size, No.	No. (%)		Main Findings[a]	Quality[b]
							Women	Completed Follow-up		
Martinez-Taboada et al,[82] 2008	Multicenter, double blinded	60	GCA in remission; stable oral prednisone, ≥10 mg/d for ≥4 wk plus ≥1 glucocorticoid adverse event	Etanercept, 25 mg, twice per wk plus current dose oral prednisone	Current dose oral prednisone	17	14 (82)	5 (29)	Cumulative glucocorticoid dose (12 mo): 1.5 g vs 3.0 g; $P = .03$ No difference between groups (12 mo): Discontinuation of glucocorticoids: 4 (50%) vs 2 (22%) Patients with ≥1 relapse: 4 (50%) vs 7 (78%) Glucocorticoid adverse events (no data reported) No difference between groups for etanercept-related adverse events (15 mo): Infections: 4 vs 4 events Injection site reactions: 1 vs 2 events	+
Seror et al,[83] 2014	Multicenter, double blinded	52	GCA, new (cranial), receiving glucocorticoids <14 d, no ocular or vascular manifestation	Adalimumab, 40 mg for 2 wk plus oral prednisone, 0.7 mg/kg plus aspirin	Oral prednisone, 0.7 mg/kg plus aspirin	70	52 (74)	54 (77)	No difference between groups (52 wk): Patients in remission receiving <0.1 mg/kg oral prednisone: 14 (64%) vs 22 (71%) Patients with ≥1 relapse: 20 (74%) vs 26 (74%) Adalimumab-related adverse events (52 wk): Patients with ≥1 infection: 20 (59%) vs 11 (31%) Patients with ≥1 serious infection: 3 (9%) vs 8 (22%)	+ + +
Villiger et al,[84] 2016	Single center, double blinded	52	GCA, new or relapsing, (extracranial), with elevated erythrocyte sedimentation rate and C-reactive protein	Tocilizumab, 8mg/kg for 4 wk plus oral prednisone, 1 mg/kg plus aspirin	Oral prednisone, 1 mg/kg plus aspirin	30	21 (70)	23 (76.7)	Complete remission: 12 wk: 17 (85%) vs 4 (40%); $P = .03$ 52 wk: 17 (85%) vs 2 (20%); $P = .001$ Time to relapse: 50 wk vs 25 wk; $P < .001$ Discontinuation of glucocorticoids (52 wk): 16 (80%) vs 2 (20%); $P = .004$ Time to discontinuation of glucocorticoids: 38 wk vs 50 wk; $P < .001$ Cumulative glucocorticoid dose: 12 wk: 34 mg/kg vs 36 mg/kg; $P = .048$ 26 wk: 41 mg/kg vs 66 mg/kg; $P = .002$ 52 wk: 43 mg/kg vs 110 mg/kg; $P < .001$ Tocilizumab-related adverse events (52 wk): Infections: 10 vs 1 event Cardiovascular disease: 1 vs 5 events Neutropenia: 9 vs 0 events Leukopenia: 15 vs 1 events No infusion-related adverse events	+ + +

Abbreviations: CFU, number (percentage) patients with complete follow-up; GCA, giant cell arteritis; GCA/PMR, giant cell arteritis and polymyalgia rheumatica patients analyzed as a single group; NA, not available.

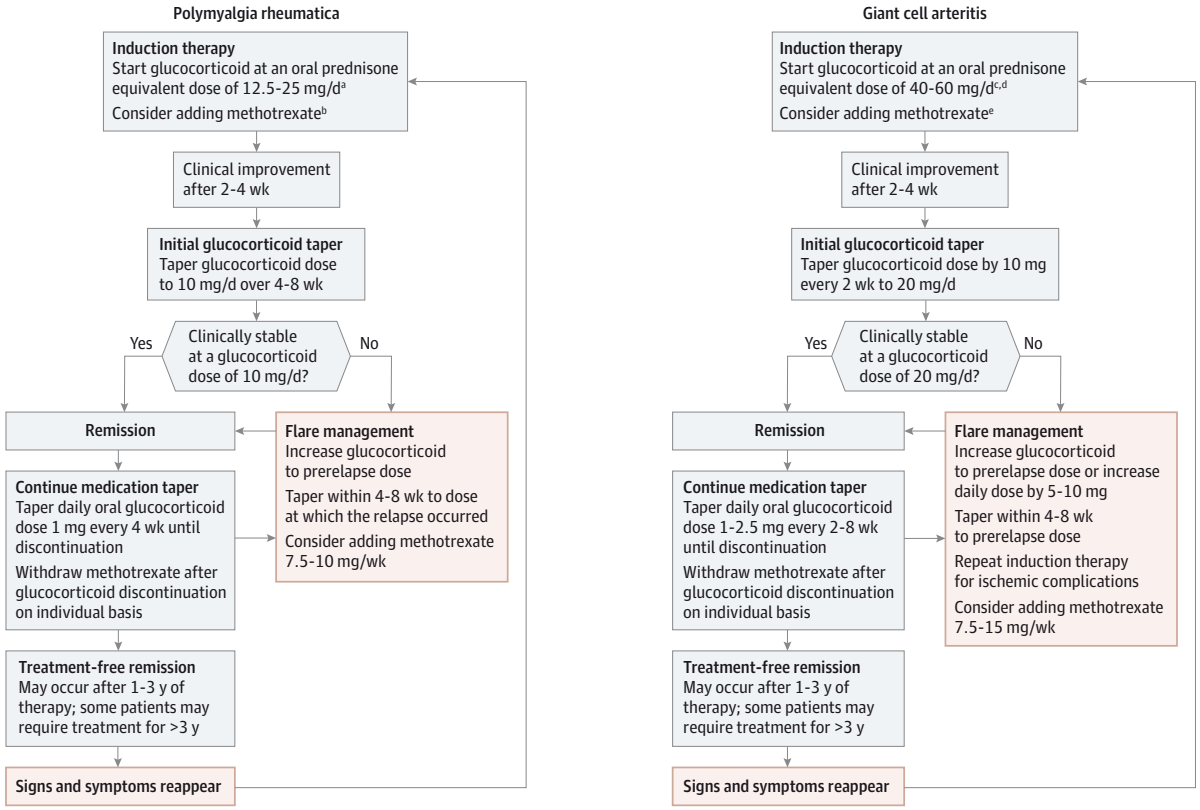
[a] All results are reported in the following order: intervention vs control group or groups 1 vs 2 vs 3 (as appropriate).

[b] Overall quality assessment according to the American College of Cardiology Foundation/American Heart Association Clinical Practice Guideline Methodology[24] appraising risk of bias, relevance and fidelity of implementation: fatally flawed study (+), low-quality study (+ +), intermediate-quality study (+ + +), and high-quality study (+ + + +).

[c] Global assessment score was measured on a scale ranging from 1 to 5 (1 indicates best; 5 indicates worst).

[d] PMR activity score range: 0 (best) to >50.

Figure 2. Suggested Treatment Algorithms for the Management of Polymyalgia Rheumatica and Giant Cell Arteritis



This algorithm is based upon assessment of the available literature. It has not been formally tested in a randomized clinical trial.

[a] Alternatively, administer intramuscular methylprednisolone, 120 mg, every 3 weeks.

[b] Consider methotrexate, 7.5 to 10 mg/week, for polymyalgia rheumatica.

[c] Administer intravenous methylprednisolone, 0.5 to 1g/day, for 3 days (in complicated giant cell arteritis [GCA] and in individual GCA patients without ischemic complications).

[d] If there is established visual loss, start glucocorticoid at an oral prednisone equivalent dose of 60 mg/day to protect the contralateral eye.

[e] For GCA, consider methotrexate, 7.5 to 15 mg/week, in addition to glucocorticoids in patients at high risk for glucocorticoid adverse effects, relapse, and/or prolonged therapy; consider osteoporosis prevention or therapy according to current recommendations.

Hazleman criteria[20]; eTable 3 in the Supplement). A lower relapse rate at 2 months was found among PMR patients initially treated with 20 mg/day of oral prednisone (11% of patients) compared with 10 mg/day (65% of patients; $P < .001$), but there was no measurable difference among GCA patients treated with 40 mg/day of oral prednisone (20% of patients) or 20 mg/day (40% of patients; P value was nonsignificant) (Table 2).[68]

The efficacy of intramuscular methylprednisolone in PMR was addressed by a 96-week double-blinded RCT (n = 60).[64,65] New PMR patients (Jones and Hazleman criteria[20]) received 120 mg of methylprednisolone every 3 weeks (n = 30) or 15 mg/day of oral prednisone (n = 30). Remission rates were comparable, but cumulative glucocorticoid dose (2.0 g vs 3.5 g; $P < .001$) and weight gain (0.8 kg vs 3.4 kg; $P < .001$) were lower in the methylprednisolone group.[64,65] Based on these results, intramuscular methylprednisolone may be considered as a treatment alternative in PMR patients (**Figure 2**).

In a single-center, 78-week double-blinded RCT of new GCA patients (ACR criteria) without ischemic manifestations (n = 27), 14 patients were randomized to receive "pulse" glucocorticoid therapy (15 mg/kg/d intravenous methylprednisolone for 3 days) plus 40 mg/day of oral prednisone in comparison with 13 participants randomized to placebo plus 40 mg/day of oral prednisone. The cumulative oral glucocorticoid dose was lower (5.6 g vs 7.9 g; $P = .001$) at 78 weeks, and in the pulse group, remission rates were higher on reaching 5 mg/day or less of oral prednisone at 36 to 78 weeks (71%-86% vs 15%-33%; $P < .01$).[66] A 12-month open RCT (n = 164) of new GCA patients (ACR criteria) reported no advantage of pulse treatment over oral prednisone alone.[67]

Current evidence does not support the routine use of pulse glucocorticoid therapy in every case of newly diagnosed GCA.

Methotrexate and Other Disease-Modifying Antirheumatic Drugs

In PMR, a multicenter, 76-week double-blind RCT (n = 72) and a multicenter, 12-month open RCT (n = 24) reported that methotrexate, 10 mg/week, was associated with a lower relapse rate and a lower cumulative glucocorticoid dose compared with placebo.[69,70] In the latter study, the initial prednisone dose was 25 mg/day in the methotrexate group compared with 15 mg/day in the control group. Another multicenter, 24-month double-blind RCT (n = 40) that included PMR patients with and without GCA did not find an effect of methotrexate, 7.5 mg/week on any of the

outcomes studied.[76] The high drop-out rate (48%) in this study limits its validity.[76]

In GCA, a single-center, 24-month double-blind RCT (n = 42) reported a lower number of relapses, lower cumulative glucocorticoid doses, and a shorter duration of glucocorticoid therapy in patients receiving methotrexate, 10 mg/week.[72] Two other studies observed no benefit of methotrexate (a single-center double-blind RCT [n = 21 patients who received 7.5 mg/week] and a multicenter, 12-month double-blind RCT [n = 98 instead of 300 originally planned, who received 15 mg/week]) in addition to oral glucocorticoid (Table 2).[71,73]

A meta-analysis pooling the individual data of the 3 methotrexate trials in GCA (described previously)[71-73] revealed a lower rate of first relapse (hazard ratio, 0.65; $P = .04$), a higher rate of glucocorticoid-free remission (hazard ratio, 2.8; $P = .001$), and lower cumulative glucocorticoid doses (mean difference, −1.1 g at week 96; $P = .007$) in the methotrexate vs the control group.[87]

Azathioprine, 150 mg/d, was investigated in 1 single-center, 52-week double-blind RCT (n = 31) in patients with PMR, GCA, or both who required at least 5 mg/d of oral prednisone to control disease activity. The daily glucocorticoid dose at the end of follow-up was lower in the azathioprine vs the placebo group.[77] Cyclosporine A (2 studies[75,78]; total n = 82) and dapsone (1 study[74]; n = 47) were associated with high toxicity (cyclosporine: hypertension, creatinine increment; dapsone: anemia, agranulocytosis, rash), but cyclosporine showed no clinical efficacy and dapsone showed only a moderate level (Table 2).[74,75,78]

Overall, highest-quality studies suggest that methotrexate is beneficial for treatment of PMR and GCA. Negative trials were of lower quality. The addition of methotrexate to glucocorticoids should, therefore, be considered on an individual basis in patients at high risk for glucocorticoid-related adverse events, relapsing disease, and/or prolonged glucocorticoid therapy (Figure 2, Box). The use of other disease modifying antirheumatic drugs (DMARDs) is not supported by evidence.

Biological Agents

In PMR, a multicenter, 52-week double-blind RCT (n = 51) of infliximab (3 mg/kg every 8 weeks) and a single-center, 2-week double-blind RCT (n = 22) of etanercept (25 mg twice per week) failed to meet their primary end points.[79,80]

In GCA, infliximab and adalimumab were ineffective in a multicenter, 52-week double-blind RCT (n = 44) and a multicenter, 52-week double-blind RCT (n = 70).[81,83] A single-center, 15-month double-blind RCT (n = 17) of GCA patients in remission found a lower cumulative glucocorticoid dose in the etanercept group compared with placebo. Only 6 of 17 patients completed the first 12 months of this trial.[82] The interleukin-6 receptor blocker tocilizumab (8 mg/kg every 4 weeks) was tested in a small phase 2, 52-week double-blind RCT (n = 30) in GCA. Higher remission rates, lower cumulative glucocorticoid doses, and a shorter duration of glucocorticoid therapy were observed in the tocilizumab vs the placebo group.[84]

There appears to be no evidence supporting the role for TNF-α–blocking agents for treatment of PMR or GCA. Tocilizumab may have benefit, but more data are needed to support its use in GCA.

Box. Suggestions for the Use of Methotrexate as Adjunctive Therapy in the Treatment of Polymyalgia Rheumatica and Giant Cell Arteritis

Early Use

Patients at high risk of glucocorticoid-related adverse effects

Patients with comorbidities that may be exacerbated by glucocorticoid therapy
- Diabetes
- Glaucoma
- Osteoporosis

Patients at high risk of relapse or prolonged glucocorticoid therapy
- Women
- High initial erythrocyte sedimentation rate
- High initial C-reactive protein
- Peripheral arthritis

During Follow-up in Difficult-to-Treat Cases

Patients with the following:
- Insufficient response to glucocorticoids
- Recurrent relapses
- Failure to wean glucocorticoids
- Pronounced glucocorticoid-related adverse effects

Key Messages

Polymyalgia rheumatica (PMR) and giant cell arteritis (GCA) are related inflammatory diseases of older people

Rapid and accurate diagnosis of GCA with prompt initiation of treatment is essential to prevent visual loss and other ischemic complications

Diagnosis of PMR and GCA is primarily based on typical clinical and laboratory features

Ultrasonography of shoulders and hips may improve diagnostic accuracy and monitoring of PMR

In GCA, temporal artery biopsy remains the standard for definitive diagnosis, but this can be supported by imaging techniques

Glucocorticoids are the mainstay of therapy, but adverse events are common and require careful monitoring

Adjunctive therapies may be required in both diseases with methotrexate currently demonstrating best evidence

Evaluation of alternative therapies is a priority area for future research

Discussion

Ultrasound imaging improves diagnostic accuracy for PMR by detecting subdeltoid bursitis in about two-thirds of patients. For diagnosing GCA, ultrasound is highly sensitive (55%-100%) and specific (78%-100%), and MRI is also highly sensitive (68%-89%) and specific (73%-97%). ^{18}F-FDG-PET (specificity, 66%) may be less specific than ultrasound and MRI. Ultrasound is a less-expensive modality than MRI and can be considered for evaluation of patients with suspected GCA; ^{18}F-FDG-PET is valuable for suspected large-vessel vasculitis. These tests require expertise, which may not always be available in clinical practice. If a diagnosis of GCA cannot be confirmed nor ruled out by clinical, laboratory, and imaging findings, a temporal artery biopsy should be performed.

Table 3. Medications for Treatment of Polymyalgia Rheumatica and Giant Cell Arteritis

Condition	Dosing	Key Efficacy Data	More Common Potential Adverse Effects[a]
Medication: Glucocorticoids (eg, Prednisone, Prednisolone, Methylprednisolone)			
Polymyalgia rheumatica	Initial dose: prednisone equivalent, 12.5-25 mg/d (consider 120 mg intramuscular methylpred-nisolone every 3 weeks as an alternative in individual patients)	One small RCT (n = 39) reported a lower relapse rate among patients treated with oral prednisone, 20 mg/d vs 10 mg/d (2 [11%] vs 13 [65%]; $P < .001$)[68] One RCT (n = 60) reported a lower cumulative glucocorticoid dose (2.0 g vs 3.5 g; $P < .001$) and lower weight gain (0.8 kg vs 3.4 kg; $P < .001$) with intramuscular methylprednisolone compared with oral prednisone (starting with 15 mg/d) at 96 weeks[64,65]	Cushingoid appearance, weight gain, osteoporosis, hypertension, cardiovascular disease, hyperglycemia and diabetes mellitus, infections, skin atrophy, cataracts
Giant cell arteritis	Initial dose: prednisone equivalent, 40-60 mg/d (consider 0.5-1 g/d of intravenous methylprednisolone for 3 days (in complicated GCA and in individual GCA patients without ischemic complications)	Insufficient evidence regarding initial oral prednisone dose: In 1 small RCT (n = 27) among patients with uncomplicated giant cell arteritis, intravenous methylprednisolone led to higher remission rates vs placebo at week 36 (10 [71%] vs 2 [15%] patients), week 52 (11 [79%] vs 2 [15%] patients), and week 78 (12 [86%] vs 4 [33%] patients; for all comparisons, $P < .01$]) A lower cumulative glucocorticoid dose (5.6 g vs 7.9 g; $P = .001$), lower relapse rate (21 vs 37 patients; $P = .028$), and higher rate of glucocorticoid discontinuation (6 [43%] vs 0 patients; $P < .05$) at week 78 were also observed[66] No data were available regarding patients with visual symptoms	
Medication: Immunosuppressive Agents (Methotrexate)			
Polymyalgia rheumatica	7.5-10mg1×/wk	Adjunctive methotrexate reduced the relapse rate in 2 RCTs: In one trial (n = 72), patients with ≥1 relapse were observed at week 76 (15 [47%] in the methotrexate group vs 22 [73%] in the placebo group; $P = .04$)[69] In the second trial (n = 24), 6 (50%) patients had ≥1 relapse at 12 mo vs 12 (100%) in the placebo group ($P = .013$)[70] Cumulative glucocorticoid dose was 2.1 g in the methotrexate group vs 3.0 g in the placebo group ($P = .003$) at 76 weeks in the first trial[69] Cumulative glucocorticoid dose was 1.8 g in the methotrexate group vs 3.2 g in the placebo group ($P < .001$) at 12 mo in the second trial[70] More patients discontinued glucocorticoids in the methotrexate group vs the placebo group At week 76 in the first trial: 28 (88%) vs 16 (53%) ($P = .003$)[69] At 12 mo in the second trial: (6 [50%] vs 0 ($P = .013$)[70]	Dizziness, nausea, vomiting, loss of appetite, temporary hair loss, elevated liver enzymes, low white blood cell count, predisposition to infection, teratogenicity, mouth sores
Giant cell arteritis	7.5-15mg1×/wk	In 1 RCT (n = 42), adjunctive methotrexate increased the number of patients without a relapse at 24 mo (11 [55%] in the methotrexate group vs 3 [16%] in the placebo group; $P = .004$), reduced the cumulative glucocorticoid dose (4.3 g in the methotrexate group vs 5.4 g in the placebo group; $P = .01$), and shortened the duration of glucocorticoid therapy (from 29 weeks in the methotrexate group vs from 94 wk in the placebo group; $P < .016$)[72]	

Abbreviation: RCT, randomized clinical trial.

[a] For both medication categories, potential adverse effects apply for patients with polymyalgia rheumatica and also for giant cell arteritis.

Glucocorticoids remain the standard for treating PMR and GCA. Reduction in the cumulative glucocorticoid dose was achieved by administering intramuscular methylprednisolone in PMR (43% less compared with oral glucocorticoids in 1 RCT[64,65]), glucocorticoid pulse therapy in GCA (29% less compared with the control group in 1 of 2 RCTs[66]), by adjunctive methotrexate in PMR (30%-44% less compared with control groups in 2 of 2 trials[69,70]) and also in GCA (20% less in 1 of 3 trials[72]), and by tocilizumab in GCA (61% less in 1 trial[84]). RCTs of other conventional DMARDs and TNF-α inhibitors did not demonstrate glucocorticoid-sparing effects.

The quality of imaging studies (Table 1) was limited by inconsistencies in the reference standard (usually because temporal artery biopsy was performed only in a subset of patients) and by the potential for lack of independence between the index test and reference standard. For example, in some studies,[31,33] imaging results were used to establish the final diagnosis, which was subsequently applied as the reference standard. In other studies,[36,37,39,40] ultrasound-guided temporal artery biopsies were performed. Many studies were not explicit about whether physicians conducting the reference standard were blinded to results of the index test.[34,38,44-49]

There are no high-quality trials on optimal initial glucocorticoid dose, administration routes, or tapering regimens in PMR or GCA. Available studies are limited by insufficient blinding and selective outcome reporting. Clinical practice recommendations are mostly consensus based and support an individualized glucocorticoid treatment plan.[50,51,85,86]

The quality of DMARD trials is variable. Moderate- to high-quality trials suggest a benefit of methotrexate for both PMR and GCA, while low-quality studies are mostly negative. Important limitations of low-quality trials are the absence of blinding and attrition bias. In one study on methotrexate in PMR and GCA patients, for example, 48% of patients were lost to follow-up and missing data were inadequately addressed.[76] In another negative study of methotrexate in GCA, the power calculation was reconducted during the trial, reducing the number of participants by two-thirds.[73] It is unclear how patients lost to follow-up were included in the analysis.[73] While available evidence is not strong enough to support a nonindividualized use of methotrexate in PMR or GCA, this drug should be considered in patients at risk for relapse, prolonged glucocorticoid therapy, and glucocorticoid-related AEs (Figure 2, Box; eTable 3 in the Supplement).[50,51,85,86]

TNF-α inhibitors appear to be ineffective for treatment of PMR and GCA; whereas, a small RCT reported a benefit of tocilizumab for GCA.[84] However, until results of larger trials become available, this drug should be used in cases refractory to other treatments.

The optimal follow-up strategy for patients undergoing treatment is not established, but the assessment of response to therapy in PMR and GCA should be primarily based on clinical and laboratory findings. The utility of serial ultrasonography, MRI, or ^{18}F-FDG-PET examinations is unclear.

Limitations

First, evidence regarding the best approach to the diagnosis and treatment of PMR and GCA is limited by the paucity of high-quality trials.

Second, different reference standards were used for diagnosis, but none have optimal sensitivity and specificity. Although a positive temporal artery biopsy is highly specific for GCA, a negative biopsy does not rule out the disease because histopathological lesions are not identified in as many as 29% of cases.[88] The ACR criteria lack specificity but are more sensitive because patients can be classified as having GCA in the absence of a positive temporal artery biopsy. In a patient fulfilling ACR criteria, a positive imaging test could be a true positive, but if the histology is negative, the test could be a false positive.

Third, because only highest-quality evidence was considered, some lower-quality information on clinical experience with imaging techniques and therapeutic interventions may not have been included.

Fourth, the conclusions presented in this article were agreed upon by the authors and were not the result of a project involving all stakeholders relevant to PMR and GCA management (eg, patients' representatives, other physicians and health care professionals).

The conclusions from this systematic literature research are consistent with recently elaborated EULAR-ACR recommendations for the management of PMR and with the EULAR and British Society of Rheumatology guidelines for treatment of GCA (Figure 2, **Table 3**; eTable 3).[51,85,86] These guidelines recommend glucocorticoid "pulse" therapy (usually 0.5-1 g/d of intravenous methylprednisolone for 3 consecutive days) for GCA patients at risk of or with severe ischemic complications.[51,86] Results of this systematic literature review support this approach in GCA patients without ischemic manifestations for reduction of the cumulative oral glucocorticoid dose.[66]

Glucocorticoid dose tapering should be individualized according to the clinical course (Figure 2). Treatment of PMR and GCA is usually required for 1 to 3 years but frequently longer (often with glucocorticoid doses of 1-5 mg/d).

In conclusion, diagnosis of PMR and GCA is made by clinical features and elevated inflammatory markers. In PMR, ultrasound imaging may improve diagnostic accuracy. In GCA, temporal artery biopsy may not be required in patients with typical disease features accompanied by characteristic ultrasound or MRI findings. Consensus-based recommendations suggest glucocorticoids as the most effective therapy for PMR and GCA. Methotrexate may be added to glucocorticoids in patients at risk for relapse and in those with glucocorticoid-related adverse effects or needing prolonged glucocorticoid therapy.

ARTICLE INFORMATION

Author Contributions: Drs Buttgereit and Dejaco had full access to all of the data in the study, take responsibility for the integrity of the data and the accuracy of the data analysis, and contributed equally to the this article.
Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Dejaco, Buttgereit.
Administrative, technical, or material support: Buttgereit, Dejaco.
Study supervision: Buttgereit, Matteson, Dasgupta.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Buttgereit reports receipt of consultancy fees, honoraria, and travel expenses from Horizon Pharma (formerly Nitec Pharma), Mundipharma International, and Roche; grant support from Horizon Pharma; and serving as coprincipal investigator and site investigator in a Mundipharma-sponsored trial in polymyalgia rheumatica investigating the effects of modified-release prednisone. Dr Dejaco reports receipt of consultancy fees and honoraria from MSD, Pfizer, UCB, AbbVie, Roche, Novartis, Lilly, Celgene, Merck, and Signatis Pharma; clinical trials design advisory board consultancies with GlaxoSmithKline; and unrestricted grant support from Pfizer and MSD. Dr Matteson reports serving as coordinating investigator with Novartis and consultant with GlaxoSmithKline in PMR trials; consultant with GlaxoSmithKline and Endocyte and site investigator in GCA trials with Bristol Meyer Squibb, Hoffman-LaRoche, Genentech, GlaxoSmithKline; and editor and contributor for polymyalgia rheumatica and giant cell arteritis with UpToDate and Paradigm. Dr Dasgupta reported clinical trials design advisory board consultancies with Roche, Servier, GlaxoSmithKline, Mundipharma, Pfizer, Merck, Sobi; unrestricted grant support from Napp and Roche; and speakers honoraria from UCB and Merck.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Edward Livingston, MD, at Edward.livingston@jamanetwork.org or Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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