CLINICAL PRACTICE

Polymyalgia Rheumatica

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

SUMMARY

Polymyalgia rheumatica is an inflammatory condition that affects persons older than 50 years of age and is characterized by pain in both shoulders with or without hip or neck pain (or both) and with pronounced morning stiffness. The condition is typically diagnosed on the basis of these hallmark symptoms along with elevated inflammation markers (erythrocyte sedimentation rate and C-reactive protein level) and the ruling out of other conditions including giant-cell arteritis. Glucocorticoids are the primary treatment, which provide rapid symptom relief. The initial dose, usually 12.5 to 25 mg of prednisone equivalent daily, is gradually reduced, ideally over 12 months or less, although the disease course varies and polymyalgia rheumatica may persist for a longer duration. Relapses are common and sometimes warrant the use of interleukin-6 receptor inhibitors or methotrexate to minimize glucocorticoid exposure.

A 74-year-old woman with diet-controlled diabetes mellitus presents with 6 weeks of progressive pain in the shoulders and neck, fatigue, and pronounced stiffness that is worse in the morning and limits her daily activities. Physical examination is notable for tenderness in the muscles of both upper arms and absence of joint swelling or tenderness. Her erythrocyte sedimentation rate (ESR) is 67 mm in the first hour (normal value, <20 mm per hour), C-reactive protein (CRP) level 2.35 mg per deciliter (normal value, <0.5 mg per deciliter), and glycated hemoglobin level 6.8%, and she has a mild normochromic, normocytic anemia. How should the patient be evaluated and treated?

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CME

THE CLINICAL PROBLEM

Polymyalgia rheumatica is a chronic inflammatory disease in persons older than 50 years of age that characteristically affects the shoulders and pelvic girdle as well as the neck, causing pain and stiffness that are typically worse in the morning and after physical inactivity.[1] It is the second most common inflammatory rheumatic disease in older persons after rheumatoid arthritis. Approximately 75% of patients with polymyalgia rheumatica are women. Persons of northern European descent have the highest incidence, with 34 to 113 new cases per 100,000 persons each year among those 50 years of age or older, as compared with 3 to 27 new cases among persons of southern European descent.[2]

The lifetime risk of polymyalgia rheumatica is 2.4% among women and 1.7% among men.[3]

There is no specific test for polymyalgia rheumatica. The diagnosis is clinical, so substantial uncertainty remains in daily practice. An observational study showed that approximately one third of the patients with a provisional diagnosis of polymyalgia rheumatica were eventually reclassified as having another disease such as inflammatory arthritis (35%), a noninflammatory musculoskeletal disorder (13%), vasculitis (12%), infection (9%), or cancer (9%).[4] Ultrasonography, magnetic resonance imaging (MRI), and positron-emission tomography with computed tomography (PET-CT) have been used to assist in the diagnosis but are still the subject of research (Fig. 1).

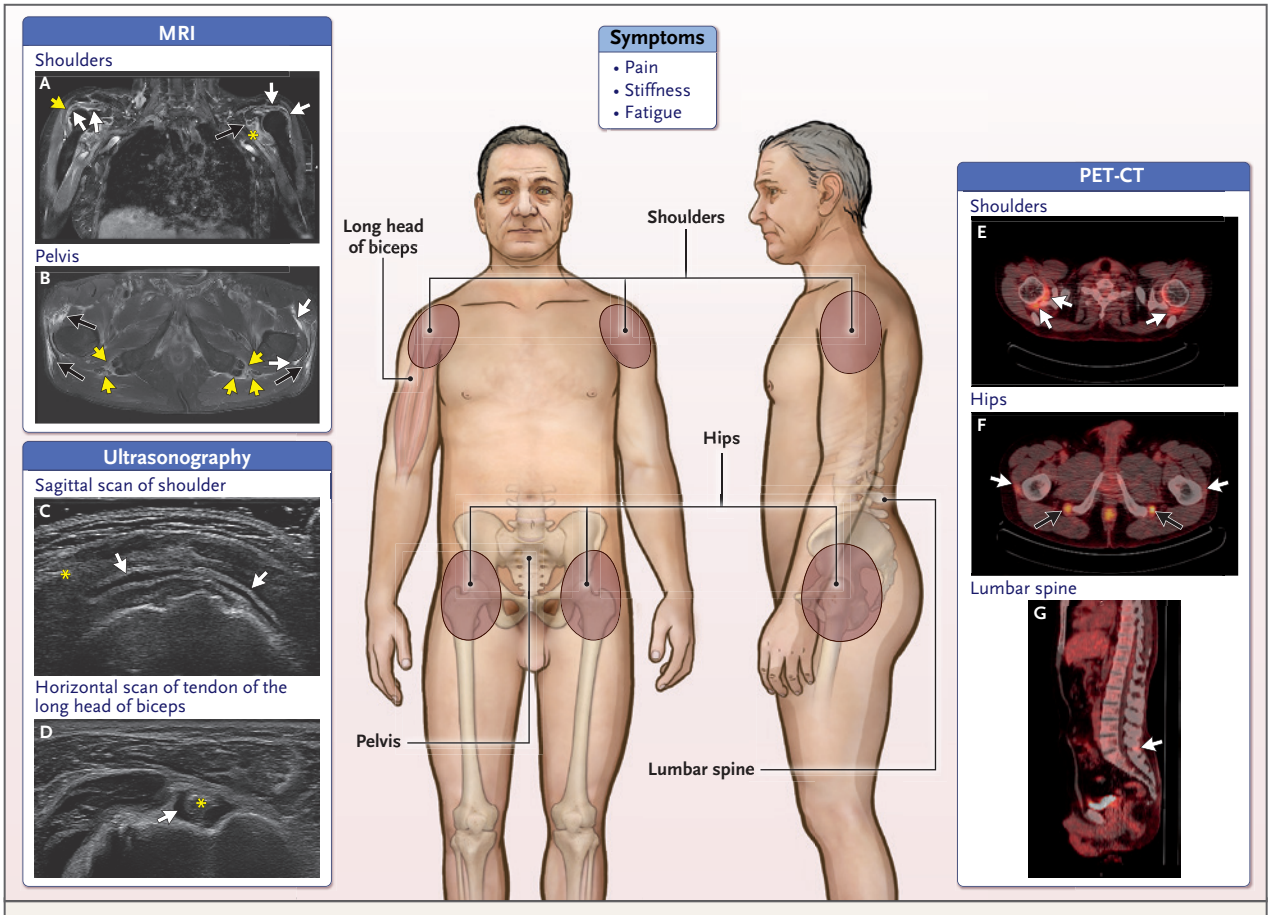

Figure 1. Symptoms and Imaging Findings in Polymyalgia Rheumatica.

The center image shows characteristic symptoms and their locations in patients with polymyalgia rheumatica. Pain and stiffness are typically located at the shoulders, neck, and pelvis. Shoulder pain may radiate distally toward the elbows, and pelvic-girdle pain often extends to the groin and lateral aspects of the hips and frequently radiates to the posterior thighs and knees. Panel A shows bilateral periarticular inflammation on Dixon MRI of the shoulders in the coronal T1-weighted view with contrast agent (gadolinium). Subdeltoid bursitis (yellow arrow), peritendinitis of the supraspinatus tendon and moderate myofascial contrast enhancement (white arrows), subcoracoid bursitis with intrabursal fluid and parietal contrast enhancement (black arrow), and peritendon inflammation of the subscapular tendon and enhancement of the capsule of the glenohumeral joint (asterisk) are seen. Panel B shows bilateral trochanteric bursitis (white arrows) and peritendinous contrast enhancement (peritendinitis, black arrows) on spectral presaturation with inversion recovery MRI of the pelvis in the axial T1-weighted view with contrast agent (gadolinium). Peritendinous contrast enhancement of hamstring muscle tendons (yellow arrows) is also seen. Panel C shows subdeltoid bursitis (arrows) on sagittal ultrasonography of the shoulder; the acromion (asterisk) is also shown. Panel D shows fluid collection within the bicipital recess (arrow) on horizontal ultrasonography of the tendon of the long head of the biceps in the distal part of the bicipital sulcus (asterisk). Panel E shows increased tracer uptake in the anatomical area of the rotator cuff (arrows) on positron-emission tomography–computed tomography (PET-CT) of the shoulders, indicating bilateral periarticular inflammation. Panel F shows increased tracer uptake in the anatomical area of the trochanteric bursa (white arrows) and the insertion of the hamstring muscles (black arrows) on PET-CT of the hips. Panel G shows increased tracer uptake in the anatomical area of the interspinous bursa between the fifth lumbar vertebrae and the sacrum (S1, arrow) on PET-CT of the lumbar spine.

Polymyalgia rheumatica and giant-cell arteritis are closely related. Features of polymyalgia rheumatica occur in approximately 42% of patients with giant-cell arteritis, and 3 to 46% of patients with polymyalgia rheumatica have evidence of large-vessel inflammation on imaging, which has led some investigators to regard polymyalgia rheumatica and giant-cell arteritis as a disease spectrum.[5-7] The relevance of large-vessel vasculitis in clinically isolated polymyalgia rheumatica is as yet uncertain, and patients are usually treated as having polymyalgia rheumatica.

Glucocorticoids are the cornerstone of treatment for polymyalgia rheumatica.[8] Response is usually rapid and initially gratifying for both patients and clinicians. Polymyalgia rheumatica does not appear to affect life expectancy but may profoundly affect quality of life.[1,9] Although glucocorticoids can markedly decrease the often severe and disabling pain and stiffness, glucocorticoid-related side effects are a major long-term burden. Up to 43% of patients have at least one relapse.[10] Rapid dose reduction is associated with a higher risk of relapse than gradual tapering. Relapses are usually treated with an incremental increase in the prednisone dose; consequently, each relapse prolongs the duration of glucocorticoid treatment. A meta-analysis showed that 51% of patients are still taking glucocorticoids (commonly prednisone at a dose of 2.5 to 5 mg per day) 2 years after initiating treatment, and 25% receive glucocorticoids for 5 years or longer.[10] Weight gain and change in appearance are among the numerous side effects that concern patients,[11] and long-term treatment with glucocorticoids, even at a daily prednisone dose of 5 mg or less, increases the risk of infections and cardiovascular events.[12,13]

STRATEGIES AND EVIDENCE

EVALUATION

The diagnosis of polymyalgia rheumatica is made on the basis of clinical grounds by combining characteristic signs and symptoms with laboratory findings and ruling out common mimickers such as late-onset rheumatoid arthritis and pseudogout, among others (Fig. 2). Pain in both shoulders occurs in 70 to 90% of patients.[1] Although pain might start on one side of the body, it usually extends to both sides within a few days or weeks. The onset of polymyalgia rheumatica symptoms is usually abrupt but can be insidious over several weeks. In some patients, symptoms can be so severe that they have difficulty standing up from a chair or bed or even raising their arms above their head.[14] Approximately half the patients have

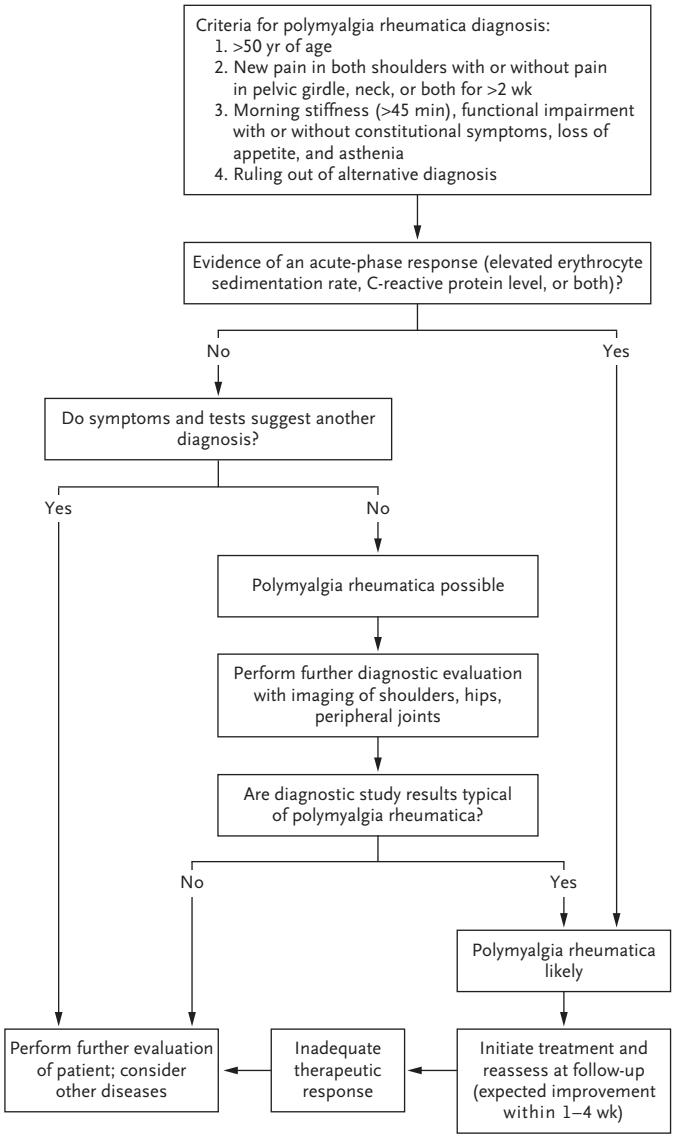

Figure 2. Diagnostic Evaluation for Polymyalgia Rheumatica.

Imaging methods may include ultrasonography, MRI, or, less often, PET-CT. If a diagnosis of polymyalgia rheumatica is likely, initial laboratory tests such as serum glucose level, creatinine level, liver-function tests, or urinalysis should be considered. Additional tests for the assessment of risk factors related to glucocorticoids and other immunosuppressive therapies include tuberculosis testing, chest radiography, bone densitometry, vitamin D levels, glycated hemoglobin level, blood pressure, cholesterol level, and carotid and abdominal ultrasonography. Patients are considered to have an inadequate therapeutic response if a high glucocorticoid dose is warranted to control symptoms or if frequent relapses occur.

pain in the pelvic girdle and thighs or report neck pain.[1]

Peripheral-joint involvement is present in approximately 25% of patients owing to nonerosive arthritis or tenosynovitis, which typically affects the knees or wrists. Diffuse swelling of the distal extremities, mainly the hands but occasionally also the feet, occurs in approximately 12% of patients.[15] Systemic symptoms such as low-grade fever, profound fatigue, and weight loss may be present in approximately 40% of patients.[1] The ESR, CRP level, or both are elevated in almost all patients; normal values for these acute-phase reactants render the diagnosis unlikely.[16]

A rapid response to glucocorticoids with amelioration of symptoms of more than 70% within a few days and up to 4 weeks is observed in 40 to 96% of patients and is often considered to be diagnostic of polymyalgia rheumatica.[17-19] However, this response is not specific to polymyalgia rheumatica given that some mimickers of the disease may also respond to this treatment.

DIFFERENTIAL DIAGNOSIS

The clinical features of polymyalgia rheumatica are common to several conditions (Table 1). Late-onset rheumatoid arthritis and pseudogout are among the conditions most frequently misdiagnosed as polymyalgia rheumatica. In contrast to rheumatoid arthritis with onset at a younger age, late-onset rheumatoid arthritis may manifest with pain and stiffness of proximal muscle girdles together with a marked acute-phase response.[20] Clues that favor a diagnosis of late-onset rheumatoid arthritis over polymyalgia rheumatica include symmetric involvement of small joints of the hands or feet, the presence of joint erosions on imaging, and positivity for rheumatoid factor or anti–cyclic citrullinated peptide antibodies.[21] Remitting seronegative symmetric synovitis with pitting edema, a rare condition causing puffy hands or feet owing to tenosynovitis and subcutaneous edema, can also occur with polymyalgia rheumatica, and both diseases usually respond rapidly to prednisone therapy (Table 1). In patients with pseudogout, articular chondrocalcinosis may be seen on radiographs of affected joints, and joint aspiration may reveal typical calcium pyrophosphate dihydrate crystals in synovial fluid.

Among other diagnoses to consider are osteoarthritis, fibromyalgia, late-onset spondylarthritis, myositis or other connective-tissue diseases, small- and medium-vessel vasculitis, infections, endocrine diseases, cancer, neurodegenerative disorders, and drug-related myopathy. In patients with symptoms similar to those of polymyalgia rheumatica owing to treatment with an immune-checkpoint inhibitor, peripheral involvement is

Table 1. Differential Diagnoses for Polymyalgia Rheumatica.*

Condition	Suggestive Features and Findings
Rheumatic musculoskeletal diseases	
Osteoarthritis or tendinopathy	Often unilateral, insidious onset Usually noninflammatory pain Levels of acute-phase reactants in normal range
Giant-cell arteritis	New-onset headache, jaw claudication, and visual symptoms (e.g., amaurosis fugax) Prominent constitutional symptoms Positive temporal-artery biopsy Imaging evidence of vasculitis of temporal artery or other large arteries on ultrasonography, MRI, computed tomographic angiography, or positron-emission tomography with computed tomography
Late-onset rheumatoid arthritis	Symmetric polyarthritis of small joints of the hands and feet Presence of rheumatoid factor and anti–cyclic citrullinated peptide antibodies Erosions on joint imaging
Remitting seronegative symmetric synovitis with pitting edema	Rare syndrome characterized by symmetric swelling and pitting edema of both hands, and occasionally the feet, due to tenosynovitis May occur alone, as a paraneoplastic symptom, or as an unusual manifestation of polymyalgia rheumatica Affects men more often than women (2:1 ratio), in contrast to polymyalgia rheumatica Absence of rheumatoid factor and anti–cyclic citrullinated peptide antibodies Usually rapid response to glucocorticoid therapy Search for underlying cancer recommended

Table 1. (Continued.)

Condition	Suggestive Features and Findings
Calcium pyrophosphate disease	Sudden joint swelling, predominantly in large joints Symptoms associated with hyperparathyroidism, hypothyroidism, hemochromatosis, and hypomagnesemia Articular chondrocalcinosis on imaging Calcium pyrophosphate crystals in synovial-fluid analysis
Fibromyalgia	Insidious onset of widespread pain including diffuse muscle pain Unusual for symptoms to start after 50 yr of age Acute-phase reactant levels in normal range Somatic symptoms such as fatigue, waking unrefreshed, cognitive symptoms, irritable bowel syndrome, depression, and others
Other forms of systemic vasculitis such as granulomatosis with polyangiitis, microscopic polyangiitis, polyarteritis nodosa, and others	Pleomorphic clinical manifestations affecting ears, nose, throat, joints, kidneys, nervous system, lungs, skin, gastrointestinal tract, testis, and others Marked constitutional symptoms, generalized myalgia without muscle stiffness Antineutrophil cytoplasmic antibodies present in granulomatosis with polyangiitis or microscopic polyangiitis Evidence of inflammation on biopsy or vascular imaging
Late-onset polymyositis and dermatomyositis	Proximal muscle weakness, often painless, without stiffness Increased muscle enzymes (e.g., creatine kinase and aldolase) Abnormal electromyography and characteristic findings on muscle imaging or biopsy
Late-onset spondylarthritis	Inflammatory low back pain Inflammatory arthritis of large joints and enthesitis Often presence of HLA-B27 Sacroiliitis or spondylitis on imaging
Late-onset systemic lupus erythematosus	Pleomorphic clinical manifestations affecting kidneys, nervous system, lungs, skin, hematologic system (cytopenia), and others Polyarthritis in small joints of the hands and feet Antinuclear antibodies; anti-Smith, anti-Ro,† anti-La,‡ and anti–double-stranded DNA antibodies; and reduced serum levels of complement components 3 and 4
Other diseases and conditions	
Chronic infections such as endocarditis and tuberculosis	Diffuse myalgia and fever Positive blood, synovial, or tissue cultures Organ-directed imaging (e.g., echocardiography)
Myopathy related to a drug (e.g., statin)	Muscle weakness with or without muscle pain Increased muscle enzymes (e.g., creatine kinase, aldolase) Abnormal electromyography Anti-HMGCR antibodies
Endocrinopathies such as hypothyroidism, hypercortisolism, and hyperparathyroidism	Diffuse myalgias, weakness, tremor, and muscle cramping Abnormal findings for at least one of the following: thyroid-stimulating hormone, triiodothyronine, thyroxine, thyroid antibodies, cortisol, calcium, phosphorus, or parathyroid hormone
Hematologic disorders such as leukemia, myelodysplastic disorders, plasmacytoma, and amyloidosis	Myalgias, usually without stiffness Abnormal findings for peripheral blood count, peripheral-blood smear or serum protein electrophoresis, and organ-directed biopsy
Solid tumor	Diffuse myalgia and no clear stiffness Symptoms related to the affected organ
Neurodegenerative disorders such as Parkinson's disease and amyotrophic lateral sclerosis	Generalized stiffness and movement disorder with or without diffuse myalgia Acute-phase reactants in normal range
Osteomalacia	Diffuse musculoskeletal pain Low vitamin D levels Characteristic findings on bone imaging

* HMGCR denotes 3-hydroxy-3-methylglutaryl–coenzyme A reductase.
† Anti-Ro antibodies are also known as SSA antibodies.
‡ Anti-La antibodies are also known as SSB antibodies.

more common and weight loss and ESR elevation are less frequent. Polymyalgia rheumatica and giant-cell arteritis are closely related, and approximately 3 to 10% of patients with an initial diagnosis of polymyalgia rheumatica are subsequently found to have giant-cell arteritis, particularly those with refractory or relapsing disease.[7,22]

TREATMENT

Initial Management

The treatment goal for patients with polymyalgia rheumatica is having and maintaining remission, which is the absence of clinical symptoms and systemic inflammation.[23] Educating patients about the disease and its treatment and involving them in the decision making regarding the risks and benefits of the treatment approach are crucial in order to manage expectations, minimize adverse outcomes that matter most to patients, maximize adherence to treatment and follow-up, and decrease the risk of relapse.[23]

Glucocorticoids are the first-line therapy. Abatement of symptoms and inflammatory signs is usually rapid (Fig. 3). The 2015 joint recommendations from the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR; formerly the European League Against Rheumatism) suggest prednisone equivalent at a starting dose between 12.5 mg and 25 mg, administered once in the morning and individualized according to risk factors for glucocorticoid-related adverse events or prolonged glucocorticoid therapy.[8] A lower initial glucocorticoid dose might be preferred in patients who, for example, are at higher risk for or have diabetes, heart disease, or osteoporosis. Splitting the prednisone dose into morning and evening doses may help patients with prominent night pain who have tapered the dose to less than 5 mg daily.[8] Polymyalgia rheumatica symptoms may sometimes respond better to methylprednisolone than to prednisone.[24]

Once a patient is in remission, the dose of glucocorticoids is tapered gradually, with the goal being 10 mg of prednisone equivalent 4 to 8 weeks after the start of treatment and discontinuation within 1 year, provided relapse does not occur.[8] Up to 37% of patients may be able to discontinue glucocorticoids more rapidly.[25] Faster tapering of the dose of glucocorticoids, with discontinuation within 11 to 14 weeks after the start of treatment, may be possible in patients treated with glucocorticoid-sparing agents, particularly interleukin-6 receptor inhibitors (sarilumab and tocilizumab).[26-28]

Nonsteroidal antiinflammatory drugs and other analgesic agents are not primary therapies for polymyalgia rheumatica but may be helpful to attenuate symptoms of degenerative disorders such as osteoarthritis or rotator-cuff diseases.[8] Injections of glucocorticoids into the subdeltoid bursae as well as intramuscular glucocorticoid injections have occasionally been studied in polymyalgia rheumatica but are not common clinical practice.[29]

Relapse Management

Relapses occur in up to 43% of patients, particularly when prednisone is tapered below 10 mg per day.[10] Although a universally accepted definition of relapse has not been established pragmatically or in formal studies, the term denotes the reappearance of clinical symptoms and an increase in acute-phase reactants that warrant intensification or reinstitution of therapy.[23] Relapses are the only confirmed risk factor for prolonged glucocorticoid therapy, because every relapse leads to an extension of glucocorticoid treatment duration.[10] Symptoms are often the same as at disease onset but may also be characterized by nonspecific features such as asthenia, fatigue, or constitutional symptoms. In most cases, acute-phase reactants are elevated, sometimes only slightly above the cutoff of the normal range. Relapses without increased levels of inflammatory markers may occasionally occur.[30] An isolated elevation of ESR or CRP level is insufficient to diagnose a relapse and should not prompt the escalation of glucocorticoid therapy.[1]

Relapses are common in patients with polymyalgia rheumatica; however, an unsatisfactory response to treatment or persistently elevated acute-phase reactants should prompt reevaluation of the diagnosis.[8] Although true adrenal insufficiency as a result of long-term glucocorticoid treatment develops in only approximately 2 to 11% of patients, symptoms compatible with adrenal insufficiency such as arthralgia, myalgia, malaise, and fatigue occur in up to one third of patients when tapering prednisone, particularly at doses below 7.5 mg per day.[31] Inflammatory markers are typically normal, and symptoms usually resolve with gradual reduction of the glucocorticoid dose.

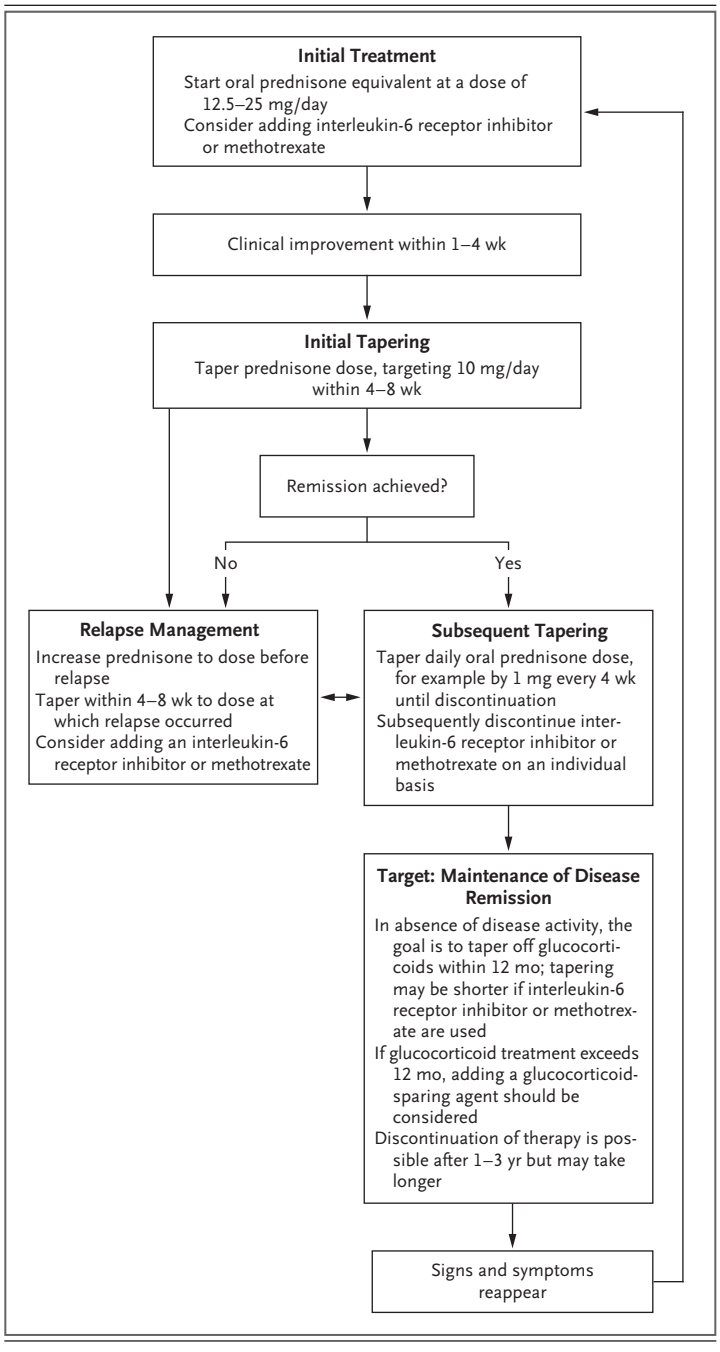

Figure 3. Treatment Algorithm for Polymyalgia Rheumatica.

An initial risk assessment for glucocorticoid-related adverse events is performed at the start of treatment. For patients with refractory or incomplete response to therapy, intolerance of glucocorticoids, or high risk of glucocorticoid-related side effects (e.g., osteoporosis, diabetes, infection, or cardiovascular disease), an interleukin-6 receptor inhibitor (e.g., sarilumab at a dose of 200 mg every 2 weeks or tocilizumab at a dose of 162 mg every week) or methotrexate at a dose of 7.5 to 25 mg per week orally or subcutaneously should be considered during initial treatment. The suggestions for reducing the glucocorticoid dose (and consequently the total duration of glucocorticoid therapy) are not evidence based; a faster taper of glucocorticoids may be possible in some patients. If relapse occurs, patients should be reevaluated for an alternative diagnosis; referral to a specialist should be considered.

Consensus recommendations for relapse management suggest increasing prednisone to the last dose that had been effective before relapse had occurred.[8] Although this approach may work well for most patients, those with more severe flares warrant higher glucocorticoid doses to control symptoms. A practical approach is to add 5 mg of prednisone to the dose at which the flare had occurred and reassess disease activity, including laboratory markers of active inflammation (e.g., CRP level and ESR), over the following week or two. Subsequent tapering is gradual, with a goal of reaching the dose at which a relapse had occurred within 4 to 8 weeks after the dose increase, followed by the original tapering protocol.[8]

Glucocorticoid-Sparing Agents

Interest is emerging regarding the use of glucocorticoid-sparing agents for the treatment of polymyalgia rheumatica in view of the high cumulative doses of prednisone often reached during the disease course and the associated adverse events.[10] According to the 2015 ACR and EULAR recommendations, methotrexate should be considered for all patients with an incident relapse as well as for those with a new diagnosis of polymyalgia rheumatica and risk factors for relapse or those at higher risk for glucocorticoid-related adverse events.[8] However, evidence of a benefit with methotrexate is not compelling, as detailed in Table 2.[29]

Among several new options for the management of polymyalgia rheumatica, interleukin-6 receptor inhibitors have been studied the most extensively.[26-28] These agents block the interaction between interleukin-6 and its receptor, which is expressed on several immune cells, including T cells and macrophages. Both interleukin-6 and these cells are enriched in the synovial and periarticular tissues in persons with polymyalgia rheumatica. Tocilizumab was tested in two randomized, controlled trials, one of which involved 36 patients with new-onset polymyalgia

Table 2. Glucocorticoid-Sparing Agents for Polymyalgia Rheumatica.*

Agent and Trial†	Comparison in Trial	Trial Results and Primary End Points
First line		
Methotrexate‡§ Dose: 7.5–25 mg every week (7.5–10 mg in trials), orally or subcutaneously Adverse events: nausea, headache, tiredness, hair loss, hepatotoxic effects, cytopenia Glucocorticoid tapering protocol: starting doses of prednisone at 15–25 mg per day, tapered off within 24–41 wk		
Caporali et al.[32]	Oral methotrexate at 10 mg/wk vs. placebo for 48 wk in 72 patients with new-onset disease¶	At 76 wk, discontinuation of glucocorticoids in 88% with methotrexate vs. 53% with placebo (P=0.003); ≥1 relapse in 47% vs. 73% (P=0.04); cumulative glucocorticoid dose, 2.1 g vs. 3.0 g (P=0.03)‖
Ferraccioli et al.[33]	Intramuscular methotrexate at 10 mg/wk vs. no methotrexate for 12 mo in 24 patients with new-onset disease	At 12 mo, discontinuation of glucocorticoids in 50% with methotrexate vs. 0% with control (P=0.01); cumulative glucocorticoid dose, 1.8 g vs. 3.2 g (P<0.001)‖
van der Veen et al.[34]	Oral methotrexate at 7.5 mg/wk for a median of 47 wk vs. placebo for a median of 35 wk in 40 patients with new-onset disease**	At 24 mo, no difference between the methotrexate and placebo groups in time to remission, duration of remission, number of relapses, or cumulative prednisone dose‖
Nazarinia et al.[35]	Oral methotrexate at 10 mg/wk vs. no methotrexate for 44 wk in 58 patients with new-onset disease	At 44 wk, remission in 44% with methotrexate vs. 8% with control (P=0.006); no difference in relapse rates (P=0.92); cumulative glucocorticoid dose, 3.2 g vs. 3.7 g (P=0.026)‖
Sarilumab††‡‡ Dose: 200 mg every other week, subcutaneously Adverse events: injection-site reactions, infections, diverticulitis, neutropenia Glucocorticoid tapering protocol: prednisone starting dose of 15 mg/day, tapered off within 14 wk		
Spiera et al.[28]	Subcutaneous sarilumab at 200 mg every other week vs. placebo for 52 wk in 118 patients with relapse	Sustained remission at 52 wk (remission by wk 12, no disease flare, persistent normalization of CRP level, and adherence to glucocorticoid taper from 12 to 52 wk) in 28% with sarilumab vs. 10% with placebo (P=0.02)
Tocilizumab‡‡‡ Dose: 162 mg every wk subcutaneously or 8 mg/kg of body weight every 4 wk intravenously Adverse events: injection-site reactions, infections, diverticulitis, neutropenia Glucocorticoid tapering protocol: varies according to trial§§		
Bonelli et al.[26]	Subcutaneous tocilizumab at 162 mg/wk vs. placebo for 16 wk in 36 patients with new-onset disease[26]	Glucocorticoid-free remission at 16 wk in 63% with tocilizumab vs. 12% with placebo (P=0.002)
Devauchelle-Pensec et al.[27]	Intravenous tocilizumab at 8 mg/kg every 4 wk for 24 wk in 101 patients with glucocorticoid dependency (PMR-AS >10 at prednisone dose of <10 mg/day)[27]	PMR-AS <10 and prednisone dose of ≤5 mg or decrease in prednisone dose of ≥10 mg from baseline to 24 wk in 67% with tocilizumab vs. 31% with placebo (P<0.001)

Alternative treatments in individual cases		
Rituximab‡¶¶ Dose: 1000-mg single infusion of rituximab plus 50-mg single infusion of prednisone Adverse events: allergic reaction, infections, hypogammaglobulinemia, lymphopenia Glucocorticoid tapering protocol: starting dose of 15 mg per day, tapered off within 17 wk		
Marsman et al.[36]	One intravenous infusion of rituximab at 1 g vs. placebo in 47 patients (38 with new-onset disease and 9 with relapsing disease)	Glucocorticoid-free remission (PMR-AS <10) at 21 wk in 48% with rituximab vs. 21% with placebo (P=0.049) and at 52 wk (standard care after 21 wk) in 52% vs. 21% (P=0.04)[37]
Tofacitinib‡‖‖ Dose: 5 mg twice daily Adverse events: infections (herpes zoster in particular), potentially increased cardiovascular risk and risk of cancer Glucocorticoid tapering protocol: no concomitant glucocorticoid treatment used		
Yang et al.[38]	Oral tofacitinib at 5 mg twice daily (without glucocorticoids) for 24 wk vs. prednisone at 15 mg/day with consecutive taper in 76 patients with new-onset disease	PMR-AS <10 at 12 and 24 wk in 100% of patients in both groups
Baricitinib‡‖‖ Dose: 4 mg once daily Adverse events: infections (herpes zoster in particular), potentially increased cardiovascular risk, and potentially increased risk of cancer Glucocorticoid tapering protocol: no concomitant glucocorticoid treatment used		
Saraux et al.[39]	Oral baricitinib at 4 mg/day or placebo for 12 wk followed by baricitinib at 2 mg/day or placebo for 12 wk in 34 patients with new-onset disease	PMR-AS ≤10 without oral glucocorticoids at 12 wk in 78% with baricitinib vs. 13% with placebo (P<0.001)

* CRP denotes C-reactive protein, and PMR-AS polymyalgia rheumatica activity score.
† The glucocorticoid tapering protocol is shown for the groups that received active treatment in cited randomized, controlled trials that investigated methotrexate, sarilumab, tocilizumab, and rituximab.
‡ These drugs are not approved by the Food and Drug Administration or the European Medicines Agency for treatment of polymyalgia rheumatica.
§ Contraindications to methotrexate include renal insufficiency (estimated glomerular filtration rate <40 ml per minute per 1.73 m^2) and advanced liver insufficiency.
¶ The 5-year follow-up data (standard care after double-blind period) did not suggest any difference between the methotrexate and placebo groups with respect to the percentage of patients still taking glucocorticoids, the cumulative glucocorticoid dose, or the percentage of patients with relapse or side effects from treatment.[40]
‖ The trial authors did not report a single primary end point but rather multiple end points.
** After discontinuation of prednisone, methotrexate or placebo was taken once every 2 weeks for three administrations, then stopped.
†† Sarilumab is approved for treatment of patients with refractory or relapsing polymyalgia rheumatica.
‡‡ Contraindications to sarilumab and tocilizumab include recurrent diverticulitis and ongoing infection.
§§ In the trial by Bonelli et al.,[26] a starting dose of 20 mg per day was tapered off within 11 weeks. In the trial by Devauchelle-Pensec et al.,[27] the starting dose was not specified, and the target prednisone dose was 5 mg or lower at 24 weeks.
¶¶ Contraindications to rituximab include ongoing infection, severe hypogammaglobulinemia, and advanced heart failure.
‖‖ Contraindications tofacitinib and baricitinib include ongoing infections, previous cardiovascular events or untreated cardiovascular risk factors, and previous or ongoing cancer.

rheumatica who had received glucocorticoid treatment for less than 2 weeks before trial enrollment[26] and the other involved 101 patients with polymyalgia rheumatica who were dependent on glucocorticoid therapy,[27] with dependency defined as an increase in disease activity when the prednisone dose was reduced to less than 10 mg per day. In both trials, the patients receiving tocilizumab had better disease control, a higher probability of glucocorticoid discontinuation, and a greater reduction of cumulative glucocorticoid dose than the patients receiving placebo. Another interleukin-6 receptor inhibitor, sarilumab, was tested in a randomized trial involving 118 patients with polymyalgia rheumatica who had had at least one pretrial relapse. Sarilumab plus a 14-week taper of prednisone was superior to placebo plus a 52-week taper of prednisone with respect to the percentage of patients with a sustained remission at 52 weeks (28% vs. 10%; P=0.02).[28] The median cumulative prednisone dose was 777 mg in the sarilumab group as compared with 2044 mg in the placebo group. Currently, only sarilumab is approved for patients with refractory or relapsing polymyalgia rheumatica.

Small studies have shown promising results with other agents that led to decreases in glucocorticoid doses for the management of polymyalgia rheumatica, including the oral Janus kinase inhibitors tofacitinib and baricitinib, as well as intravenous rituximab and the antimetabolite leflunomide.[29,36-39] None of these agents are as yet approved for the treatment of polymyalgia rheumatica. Abatacept, infliximab, and etanercept have not shown any clinically meaningful effect in polymyalgia rheumatica.[29]

Monitoring

The recommended treat-to-target approach for polymyalgia rheumatica involves follow-up visits every 1 to 4 weeks until the patient is in remission and every 3 to 6 months once the patient is in stable remission while receiving treatment.[23] The frequency of follow-up visits for patients who have discontinued therapy should be discussed on an individual basis. All follow-up visits should include, at minimum, a clinical and laboratory assessment (ESR or CRP level and complete blood count, with other assessments such as renal- and liver-function tests or glucose test performed according to clinical need) to evaluate disease activity and drug toxicity, and clinicians should address pain, stiffness, and mobility restrictions as well as treatment-related adverse events.

AREAS OF UNCERTAINTY

Uncertainties remain with respect to the diagnosis of polymyalgia rheumatica. There is no specific test for the disease, and the role of imaging for this indication is unsettled.[41] Although polymyalgia rheumatica is often diagnosed and managed by general practitioners,[42] recent international recommendations suggest that all patients with suspected polymyalgia rheumatica should be seen by a specialist to confirm the diagnosis and for risk stratification.[43] The feasibility of this approach is still unclear given the current and expected shortage of the rheumatology workforce.

Imaging signs of large-vessel inflammation are found in 3 to 46% of patients with clinical polymyalgia rheumatica, mainly in the axillary arteries.[6,7] These patients cannot be distinguished from those without large-vessel involvement on the basis of symptoms.[44] Whether patients with large-vessel inflammation should be classified as having polymyalgia rheumatica or giant-cell arteritis is unclear. Recent studies using vascular ultrasonography have shown that these patients have a higher relapse rate and more frequent use of glucocorticoids than patients without large-vessel inflammation, a conclusion not confirmed with PET-CT.[45,46] Treatment should therefore be based on clinical grounds, not imaging results, as outlined in Figure 3. Routine screening of patients for large-vessel vasculitis is not current practice.

Although remission is the most relevant treatment target in polymyalgia rheumatica, there is no uniformly accepted definition for this disease status nor for low disease activity.[47] A validated polymyalgia rheumatica–specific instrument to evaluate patient-reported outcomes is still lacking. Assessment of relapse is challenging in patients treated with an interleukin-6 receptor inhibitor because these drugs directly suppress the CRP level and ESR. In these cases, relapse assessment is currently based primarily on best clinical judgment.[47]

KEY POINTS

POLYMYALGIA RHEUMATICA

- Polymyalgia rheumatica affects persons older than 50 years of age; clinical features include new pain in both shoulders and pronounced morning stiffness. Many patients also have hip and neck pain on both sides; peripheral arthritis may also occur.
- There is no specific test for polymyalgia rheumatica. The diagnosis is clinical and is based on characteristic symptoms, increased erythrocyte sedimentation rate or C-reactive protein level, and the ruling out of possible differential diagnoses including giant-cell arteritis, rheumatoid arthritis, pseudogout, and others.
- Glucocorticoids are the mainstay of treatment for polymyalgia rheumatica. The initial dose is 12.5 to 25 mg of prednisone equivalent daily, which is tapered off within 12 months or less. The initial response to treatment is typically rapid, occurring over a few days to a few weeks, but is not diagnostic and often not complete.
- The disease course is highly variable, lasting from approximately 9 to 12 months but possibly persisting for years. Relapses occur in approximately 40% of patients during the tapering of glucocorticoids. Each relapse prolongs disease duration and treatment.
- An interleukin-6 receptor inhibitor (i.e., sarilumab or tocilizumab) should be considered in selected patients to reduce the cumulative glucocorticoid dose. Methotrexate might be an alternative.

Recommendations for the initial glucocorticoid dose and tapering protocols are all based on expert consensus and lack data support from clinical trials. Interleukin-6 receptor inhibitors appear to be more effective than methotrexate in allowing accelerated glucocorticoid tapering,[48] although the minimum glucocorticoid dose and treatment duration to achieve and maintain remission with any glucocorticoid-sparing agent are unclear.[29]

GUIDELINES

Current international and national guidelines emphasize the importance of accurate diagnosis, the ruling out of mimicking conditions, patient education and involvement in medical decision making, supportive measures such as individualized exercise programs, and regular monitoring of disease activity and potential side effects from treatment.[8,23,49] The 2015 ACR and EULAR recommendations for managing polymyalgia rheumatica represent the current standard treatment guidelines, which suggest oral glucocorticoids as first-line treatment and consideration of methotrexate for selected patients.[8] Whereas a recent national guideline also specifies methotrexate as the first-line glucocorticoid-sparing agent,[50] other guidelines suggest the preferential use of interleukin-6 receptor inhibitors in addition to glucocorticoids.[49]

CONCLUSIONS AND RECOMMENDATIONS

To enhance diagnostic certainty for the patient in the vignette, the next tests would be rheumatoid factor, anti–cyclic citrullinated peptide antibodies (to test for rheumatoid arthritis), electrophoresis (to test for cancer), and thyrotropin. Because this patient has diabetes, we would evaluate cardiovascular risk (at minimum, blood pressure and lipid levels) and perform bone densitometry. Our initial treatment would be prednisone at a dose of 15 mg, tapered to 10 mg after 4 weeks.

Because of the presence of diabetes, and if additional risk factors for glucocorticoid-related adverse events emerge, we would discuss with the patient the early introduction of sarilumab or tocilizumab (both off label for new-onset polymyalgia rheumatica). To treat relapse, we would prescribe sarilumab at a dose of 200 mg administered subcutaneously every other week (approved for relapsing polymyalgia rheumatica), and if sarilumab is contraindicated, we would consider methotrexate at a dose of 15 mg weekly. We would plan to taper off prednisone within 12 months or less, or within 4 months if an interleukin-6 receptor inhibitor is used. Follow-up visits to assess disease activity and manage coexisting conditions would occur at 1 and 3 months and every 3 months thereafter. The patient would

be offered disease education and an individualized exercise program.

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