19.11.11 Polymyalgia rheumatica 4584 Bhaskar Dasgu

19.11.11 Polymyalgia rheumatica 4584 Bhaskar Dasgupta and Eric L. Matteson

section 19 Rheumatological disorders 4584 and canakinumab and tocilizumab have been used in limited case series with variable rates of success in refractory eye and CNS disease. Prognosis Young men have the highest morbidity and mortality. Women have less severe disease than men. Major vessel disease and neurological involve- ment are the main causes of death. Eye inflammation and its greatest damage occur during the first two years. The disease tends to abate after 40 years of age, but CNS involvement and major vessel disease may have a late onset (5–10 years after diagnosis). Loss of useful vision ensues in about 10–15% of male patients with eye disease despite therapy. Mortality attributable to Behçet's syndrome decreases with time after diagnosis, which is the opposite of the situation in rheumatoid arthritis and systemic lupus erythematosus. This may be due both to self-abating disease activity, and to the fact that atherosclerosis is not accelerated in Behçet's syndrome in the same way that it is in rheuma- toid arthritis and systemic lupus erythematosus. A recent study of pul- monary arterial aneurysms has shown that the related mortality rate has decreased from 50% to around 20% in the last decade, due to ei- ther earlier recognition or more rational use of immunosuppressives. Overall, the outlook for patients with eye disease and the mucocutaneous manifestations of Behçet's syndrome is consider- ably better than it was in the past, but management of CNS disease and thrombophilia/major vascular complications, including throm- botic events, remains problematic.

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the shoulder and pelvic

19.11.11 Polymyalgia rheumatica 4585 A recent large primary care database study from the United Kingdom reported an incidence of 84/100 000 with a female:male ratio of 2.0. This is the only study that also reported a marked in- crease in the incidence of polymyalgia rheumatica throughout the 1990s, from 69/100 000 person-years in 1990 to 93/100 000 person-years in 2001. A similar temporal increase in incidence has not been observed in other studies. It is unclear whether there is a true increase in incidence of polymyalgia rheumatica, overdiagnosis, or increased recognition of polymyalgia rheumatica in more recent years. The prevalence of polymyalgia rheumatica among individuals over 50 years of age in the year 2000 is estimated at 739/100 000, with a higher prevalence in females than in males. The prevalence in- creases dramatically with age: from 21/100 000 for ages 50–54 years to 4213/100 000 for ages 90–95 years. With these prevalence es- timates, 711 000 Americans are estimated to have polymyalgia rheumatica. Survival was also examined in various studies and they all indicate that survival in patients with this condition is similar to that in the general population. This has been in part attributed to in- creased medical surveillance during the disease course. Pathogenesis The current concept is that giant cell arteritis and polymyalgia rheumatica are the opposite ends of the same pathophysiologic spec- trum, with the absence of vascular involvement in pure polymyalgia rheumatica. Synovitis, bursitis, and tenosynovitis around the joints are all seen in this condition. Inflammation is initiated inside the tissue (synovium or bursa) with recognition of putative antigen by dendritic cells (DCs) or macrophages. Activated DCs or macrophages secrete inflammatory mediators, including IL-1, IL-6, and tumour necrosis factor alpha (TNFα), which are responsible for the systemic features of the dis- ease. These cells migrate to central lymphoid organs where they present antigen to T cells, which then migrate to the synovium, en- hance the adaptive immune response, and secrete further cytokines promoting local inflammation. Two different T-cell subsets, Th17 (glucocorticoid-sensitive acute lesions) and Th1 (glucocorticoid- insensitive chronic lesions) may relate to the persistence of disease in giant cell arteritis, and a similar mechanism for disease persist- ence may be relevant to polymyalgia rheumatica. A recent study has shown that vasoactive intestinal polypeptide, a neuropeptide locally produced inside the synovium, can induce a change in T-cell phenotype from Th1 to Th2. Th2-type cells do not secrete interferon (IFN)-γ, a key cytokine in giant cell arteritis, which is a possible explanation why most patients with polymyalgia rheumatica do not develop giant cell arteritis. Most studies regarding circulating cytokines focus on IL-6. These show high levels of IL-6 in both polymyalgia rheumatica and giant cell arteritis. The data on other cytokines (IL-1, IL-2, TNFα, IFN-γ, IL-10, and so on) are too scant to draw any definitive conclusions about their role in disease pathogenesis. Most studies in polymyalgia rheumatica have shown that levels of circulating IL-6 decrease sig- nificantly with the remission of clinical symptoms, hence IL-6 blockade could be a potential target for therapy, especially in pa- tients with polymyalgia rheumatica. girdle muscles, with an acute phase response (elevated erythrocyte sedimentation rate and/or C-reactive protein). Evaluation can be challenging, as many clinical and laboratory features may also be present in other conditions, including other rheumatological dis- eases, infection, and neoplasia. Management—the mainstay of therapy is glucocorticoids. Adjunctive therapy can be initiated early in the disease course in patients with high risk of glucocorticoid-related side effects, severe or relapsing disease, or poor or ill sustained response to glucocorticoids. The response to standardized therapy is hetero- geneous, and a significant proportion of patients do not respond completely. Introduction Polymyalgia rheumatica (PMR), a common inflammatory condi- tion of older persons, is characterized by bilateral proximal

pain and morning stiffness and an acute phase response of elevated erythro- cyte sedimentation rate (ESR) and/or C-reactive protein (CRP). The condition is subject to variations of practice in primary and secondary care, and is a common indication for long-term gluco- corticoid use in the community. Accurate diagnosis and assessment of disease activity are crit- ical to balance the benefits of glucocorticoids against the increased risk of adverse outcomes such as diabetic complications and glucocorticoid-related fractures. The diagnosis of polymyalgia rheumatica is often uncertain be- cause numerous common mimicking conditions can present with a polymyalgic syndrome. There is no gold standard test. An inter- national initiative to address this diagnostic conundrum has led to classification criteria for the polymyalgic syndrome and definition of a meaningful clinical response. Clinicians often consider that rapid resolution of symptoms with glucocorticoid therapy is a diagnostic hallmark, but there is little evidence for this belief because many mimicking conditions may also seem to respond to this therapy. Furthermore, incomplete response to glucocorticoid therapy is not uncommon, even in patients with confirmed polymyalgia rheumatica. Clinical manifestations have variable severity, and half of patients have one or more relapses in the first year of disease. The median duration of glucocorticoid treatment is typically around 2–3 years. Epidemiology The epidemiology and population burden of polymyalgia rheumatica is documented in few studies. Incidence varies markedly according to geographical region, with much higher rates in countries in the northern latitudes. In northern United States, the average annual age- and sex-adjusted incidence of polymyalgia rheumatica per 100 000 population 50 years of age or over is estimated at 58.7, with a significantly higher incidence in women (69.8) than in men (44.8). Similar incidence estimates have been reported from Denmark (68.3/100 000) and Norway (112/100 000), but lower figures in Göteborg, Sweden (28/100 000), Reggio Emilia, Italy (12.7/100 000) and Lugo, Spain (18.7/100 000).

section 19 Rheumatological disorders 4586 Clinical features Difficulties in diagnosing and classifying patients with polymyalgia rheumatica are inherent to accepted definitions of the condition. The proximal pain and stiffness syndrome, the commonly accepted phenotype of polymyalgia rheumatica, can occur at presentation in many other rheumatological and inflammatory illnesses, es- pecially in older people. Polymyalgia is also associated with giant cell arteritis in 10–30% of cases. For all these reasons, recent guide- lines on polymyalgia rheumatica opt for a safe and specific ap- proach, preferring a relative underdiagnosis to an overdiagnosis of polymyalgia rheumatica. In an international initiative sponsored by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR), candidate classification criteria for polymyalgia rheumatica were defined through systematic literature review, a three-phase consensus process, and a wider survey. These criteria were then evaluated in a 6 month prospective cohort study of 125 patients with new-onset polymyalgia rheumatica and 169 nonpolymyalgia rheumatica comparison subjects with conditions mimicking the disease. Potential criteria were assessed for their ability to discriminate polymyalgia rheumatica from other condi-tions and a scoring algorithm was developed. New-onset bilateral shoulder pain in subjects aged 50 years or older and elevation of C-reactive protein and/or erythrocyte sedi- mentation rate are regarded as essential items for classification as polymyalgia rheumatica (Table 19.11.11.1). The clinical scoring algorithm is based on morning stiffness in excess of 45 minutes (2 points), hip pain/limited range of motion (1 point), absent rheuma- toid factor (RF) and/or anti-citrullinated protein antibody (ACPA) (2 points), and absence of peripheral joint pain (1 point). A score of 4 or more has 68% sensitivity and 78% specificity for discriminating all comparison subjects from polymyalgia rheumatica. The spe- cificity is higher (88%) for discriminating shoulder conditions

from polymyalgia rheumatica and lower (65%) for discriminating rheumatoid arthritis from polymyalgia rheumatica. Differential diagnosis The presence of headache, visual symptoms, and jaw claudication should be recognized as giant cell arteritis. About 40% of patients with giant cell arteritis have polymyalgia at onset. The presence of arm or leg claudication and prominence of systemic symp- toms would suggest a large-vessel vasculitis. See Chapter 19.11.6 for further discussion of giant cell arteritis and other large-vessel vasculitides. Inflammatory arthropathies and connective tissue diseases may have polymyalgic onset in older people. Negative rheumatoid serology is part of the polymyalgia rheumatica classification criteria algorithm, and all patients with the condition should be monitored for peripheral joint involvement at follow up visits. ANCA-associated vasculitis can also present with the polymyalgic syndrome, and the clinician should enquire about symptoms of mesenteric ischaemia, nasal polyps, crusting, epistaxis, sinusitis, and late-onset asthma. Dipstick urinalysis is essential: the presence of significant proteinuria and/or haematuria is not explained by a diagnosis of polymyalgia rheumatica. A chronic onset of symptoms also indicates an alternative diag- nosis. Patients with fibromyalgia can sometimes be mistaken as having polymyalgia rheumatica due to pain and tiredness, but these patients do not describe true inflammatory stiffness and have a prominence of depressive symptoms and poor sleep patterns with multiple trigger points on examination. Such patients often appear to initially respond to a trial of glucocorticoids. The clinical examination should be focused on the differential diagnoses. All peripheral joints must be assessed for synovitis. The spine should be assessed for tenderness suggestive of fractures/me- tastases/osteomyelitis/discitis and to check the range of movement for a spondyloarthropathy. Sacroiliitis should be considered when hip symptoms dominate the clinical picture. Painless muscle weakness might suggest an inflammatory polymyositis. Features of Cushing’s syndrome should be obvious on inspection of the patient. Discoid or photosensitive rashes might suggest systemic lupus erythematosus. The absence of peripheral pulses, difference in bilateral blood pressures, or presence of arterial bruits suggests a large-vessel vasculitis. The heart, lungs, and ab- domen should be examined routinely looking for signs of infection or malignancy. Neurological examination may reveal Parkinsonism, the only common noninflammatory condition to produce true stiffness. The presence of a sensory or motor neuropathy in the arms points towards a local disorder affecting the neck or back, such as disc protrusion or discitis. The absence of systemic and lower limb symp- toms indicates local shoulder pathology, such as bilateral adhesive capsulitis or osteoarthritis. Table 19.11.11.1 Polymyalgia rheumatica classification criteria: scoring algorithm. Required criteria: age≥50 years, bilateral shoulder aching, and abnormal C-reactive protein and/or erythrocyte sedimentation ratea Points without US 0–6 Points with USb 0–8 Morning stiffness >45 minutes 2 2 Hip pain or limited range of motion 1 1 Normal RF or ACPA 2 2 Absence of other joint involvement 1 1 At least one shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) AND at least one hip with synovitis and/or trochanteric bursitis Not applicable 1 Both shoulders with subdeltoid bursitis, biceps tenosynovitis, or glenohumeral synovitis Not applicable 1 ACPA, anti-citrullinated protein antibody; CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; US, ultrasound. a A score of 4 or more is categorized as polymyalgia rheumatica in the algorithm without US and a score of 5 or more is categorized as polymyalgia rheumatica in the algorithm with US. b Optional ultrasound criteria.

19.11.11 Polymyalgia rheumatica 4587 Clinical investigation At baseline evaluation, all patients with suspected polymyalgia rheumatica should have full blood count, urea, and electrolytes, liver function tests, bone profile, C-reactive protein, creatine kinase, thy- roid function tests,

immunoglobulins, and electrophoresis, basic urin- alysis, urinary Bence Jones protein, and chest radiograph checked. Other investigations should be tailored to the individual symp- toms and patient, and may include serum cortisol, prostate-specific antigen (in men), antinuclear antibody, rheumatoid factor, anti- cyclic citrullinated peptide antibodies, antineutrophil cytoplasmic antibodies, computed tomography of the chest/abdomen/pelvis, spinal radiographs, magnetic resonance imaging of the spine and sacroiliac joints, echocardiogram, and fluorodeoxyglucose positron emission tomography CT scan. Musculoskeletal and vascular ultrasound examination should be considered and performed at first presentation. Patients may have features which are a mix of bursitis, tenosynovitis, synovitis, and large-vessel vasculitis on imaging. Ultrasound Ultrasound depicts characteristic pathologic findings of shoulders and hips that can aid in distinguishing polymyalgia rheumatica from other diseases that may mimic it. Typical findings include subdeltoid bursitis and biceps tendon tenosynovitis at the shoulder, and less fre- quently synovitis of the glenohumoral joint. In the hips, ultrasound often reveals synovitis and trochanteric bursitis. Inflammatory shoulder lesions may be observed even in patients with normal erythrocyte sedimentation rate values, and it has been suggested that ultrasound may facilitate the correct diagnosis in patients with the typical proximal symptoms of polymyalgia rheumatica who also have a normal erythrocyte sedimentation rate. Magnetic resonance imaging Although more expensive than ultrasound, magnetic reson- ance imaging (MRI) scanning also reveals features of subdeltoid/ subacromial bursitis in patients with polymyalgia rheumatica. Fluorodeoxyglucose positron emission tomography A significant percentage of patients with polymyalgia rheumatica have increased vascular uptake on fluorodeoxyglucose-positron emission tomography, or FDG-PET scans suggestive of large-vessel vasculitis. In our experience the following situations justify a FDG- PET scan in the setting of either polymyalgia rheumatica or giant cell arteritis: unexplained constitutional symptoms, limb claudica- tion, and persistent incomplete response to glucocorticoids. Management The 2015 EULAR American College of Rheumatology guidelines were developed after a survey of quality of evidence using GRADE methodology, followed by consensus-based decisions which also ad- dressed values and preferences, benefits versus side effects, resource use, and extrapolation from external evidence. The guidelines rec- ommend these overarching principles of care:

1. Establish the diagnosis by ruling out mimics, considering clues to a nonpolymyalgia rheumatica diagnosis, and assessing any overlap with inflammatory arthritis or large-vessel vasculitis. A thorough history, examination, and review of blood results are essential prior to prescription of glucocorticoids. A pain diagram indicating the site of pain may be useful in improving accuracy of polymyalgia rheumatica diagnosis in primary care. Clues to a nonpolymyalgia rheumatica diagnosis include younger age, chronic onset, periph- eral arthritis, spinal involvement, pronounced systemic symptoms, either very high or normal C-reactive protein/erythrocyte sedi- mentation rate, and poor response to low-dose glucocorticoids.
2. Assess the severity of the condition (based on intensity of pain, stiffness, disability, inflammatory markers)
3. Assess comorbidities which may be relevant to choice of glucocorticoid dose.
4. Make an individualized choice of glucocorticoid dose and other therapy based on these assessments and the patient’s preferences.
5. Provide education on the condition, its treatment, and potential complications, precautions, and monitoring requirements.

6. Provide advice on range of motion exercises for the shoulder and pelvic girdle muscles. Initial treatment An empirical trial of glucocorticoids should not be used as an alter- native to diligent clinical evaluation of polymyalgia rheumatica. The EULAR American College of Rheumatology guidelines build on the British Society for Rheumatology polymyalgia rheumatica guide- lines and recommend using the minimum effective glucocorticoid dose within a range of 12.5–25 mg prednisone equivalent daily as initial treatment (Fig. 19.11.11.1). Starting doses greater than 30 mg daily or less than 7.5 mg daily are not recommended. Dose tapering schedules in polymyalgia rheumatica should be individualized, with regular monitoring of disease activity, laboratory markers, and side effects. Although uncommonly used, intramuscular methylprednisolone may be an option in milder cases and where a lower cumulative glucocorticoid dose is desirable. The initial dose is 120 mg intramuscularly repeated at 3–4-week intervals. The dose is then reduced by 20 mg every 2–3 months and given monthly. An early adjunct use of methotrexate may be considered in pa- tients with a high risk for relapses, glucocorticoid-induced adverse events, or incomplete or ill sustained response to glucocorticoids. A 70% improvement in patient-reported global stiffness and inflam- matory markers by four weeks indicates a complete response. Reports show that 3–4 weeks after starting prednisolone 15 mg daily only 55% showed a complete response to therapy. If the initial response to treat- ment is not complete, alternate diagnoses should be reconsidered. Long-term management Low-dose glucocorticoids with gradual tapering over one to two years after disease control is achieved are the principal therapy for polymyalgia rheumatica. However, owing to heterogeneity in gluco- corticoid response between patients, treatment should be tailored according to individual patient needs. The clinical response should be significant (i.e. >70% global response), with lack of response throwing doubt on the veracity of the diagnosis.

section 19 Rheumatological disorders 4588 Some patients may benefit from a more gradual glucocorticoid taper, or a period of treatment at a stable dose, such as 5 mg pred- nisolone for three months. The dose may also require adjustment for disease severity, comorbid factors (e.g. diabetes, cardiorespiratory, or renal disease), fracture risk, patient wishes, or adverse events. It is best to avoid nonsteroidal anti-inflammatory drugs, except for short-term use for coexisting degenerative conditions. Bone protec- tion for osteoporosis prevention is advised for all patients. Relapsing polymyalgia rheumatica Speed of glucocorticoid tapering and genetic factors have been pos- tulated to influence the development of relapses, which are defined as recurrence of symptoms of polymyalgia rheumatica or onset of giant cell arteritis symptoms, such as headaches, jaw claudication, and visual symptoms, usually with a rise in erythrocyte sedimenta- tion rate/C-reactive protein. Approximately 50% of patients relapse within the first 6–12 months of treatment. Coexisting degenerative conditions such as rotator cuff disease or shoulder osteoarthritis should be noted since they may cause shoulder/hip pain. An iso- lated rise of erythrocyte sedimentation rate or C-reactive protein, if not associated with clinical features of relapse, does not require an increase of immunosuppression. Initial relapses may be treated with the previous higher dose which had controlled disease symptoms. giant cell arteritis relapse requires a high dose (40–60 mg) of prednisolone. Beyond the first relapse, steroid- sparing agents such as methotrexate or azathioprine are usually used, but leflunomide has also shown promise. Experience from completed randomized controlled trials of biological agents, such as infliximab or etanercept, is not generally encouraging. Ongoing trials of interleukin- 6 blockade in giant cell arteritis also hold promise for

refractory polymyalgia rheumatica. Trials of IL-17 and IL-1 in polymyalgia rheumatica have also shown glucocorticoid sparing potential. Monitoring Patients should be monitored for disease activity and complications, glucocorticoid-related complications, and for symptoms that may suggest an alternative diagnosis. The best measures of disease ac- tivity and treatment response in polymyalgia rheumatica appear to be patient-reported global pain, hip pain, morning stiffness, phys- ical function (modified health assessment questionnaire, MHAQ), mental function, and an inflammatory marker. Ultrasound may have utility as an outcome measure. Poorly responsive polymyalgia rheumatica, persistent raised in- flammatory markers, and constitutional symptoms may indicate large-vessel disease. Such patients may require evaluation with echocardiography, FDG-PET scanning, axillary artery ultrasound, or MRI to assess for aortitis and large-vessel disease. Bone mineral density measurement should be considered in all patients. Patient fulfilling PMR case definition (primary or secondary care)

1. Assess comorbidities, other relevant medications and other risk factors for steroid-related side effects
2. Assess possible risk factors for relapse/prolonged therapy
3. Consider specialist referral (experience or risk of side effects, relapse/prolonged therapy and/or atypical presentation)
4. Document minimal clinical and laboratory data set Increase steroid dose Clinical improvement at 2–4 wk? Re-assess Confirmation of PMR Diagnosis in question Gradual tapering of glucocorticoids Relapse Taper prednisone until discontinuation Remission yes no no yes yes no Consider MTX if at high risk for side effects/ relapse and/or prolonged therapy Diagnosis in question yes no no yes no Fig. 19.11.11.1 2015 EULAR-ACR recommendations pathway for polymyalgia rheumatica management. MTX, methotrexate; PMR, polymyalgia rheumatica. Reproduced from Dejaco C et al. (2015). Recommendations for the management of polymyalgia rheumatica: a European League Against Rheumatism/ American College of Rheumatology collaborative initiative. Annals of the Rheumatic Diseases, 74: 1799–1807, copyright 2015, with permission from BMJ Publishing Group Ltd.

19.11.11 Polymyalgia rheumatica 4589 Summary The diagnosis of polymyalgia rheumatica is clinically challenging and requires a stepwise assessment with careful consideration of both characteristic signs and symptoms and exclusion of mimicking condi- tions. There appears to be an overlap with both giant cell arteritis and large-vessel vasculitis, as well as inflammatory arthritis. While not spe- cific to polymyalgia rheumatica, subdeltoid bursitis or tenosynovitis visible on ultrasound are helpful diagnostic features. Accepted man- agement is with low-dose glucocorticoids. Meticulous monitoring for complications related to treatment and disease is required. The new EULAR/ACR classification criteria will facilitate methodologically ro- bust studies and clinical trials of novel therapies which are so urgently required for the condition (Box 19.11.11.1). The 2015 EULAR-ACR recommendations for the management of polymyalgia rheumatica emphasize risk stratification and individualized choice of gluco- corticoid treatment regimens based on demographics, comorbidities, glucocorticoid-related risk factors, and disease severity. FURTHER READING Blockmans D, et al. (2007). Repetitive 18-fluorodeoxyglucose posi- tron emission tomography in isolated polymyalgia rheumatica: a prospective study in 35 patients. Rheumatology (Oxford), 46, 672–7. Caporali R, et al. (2004). Prednisone plus methotrexate for polymyalgia rheumatica: a randomized, double-blind, placebo-controlled trial. Ann Intern Med, 141, 493–500. Dasgupta B, et al. (1998). An initially double-blind controlled 96 week trial of depot

methylprednisolone against oral prednisolone in the treatment of polymyalgia rheumatica. Br J Rheumatol, 37, 189–95. Dasgupta B, et al. (2010). BSR and BHPR guidelines for the man- agement of polymyalgia rheumatica. Rheumatology (Oxford), 49, 186–90. Dasgupta B, et al. (2012). 2012 provisional classification criteria for polymyalgia rheumatica: a European League Against Rheumatism/ American College of Rheumatology collaborative initiative. Ann Rheum Dis, 71, 484–92. Dejaco C, et al. (2011). Definition of remission and relapse in polymyalgia rheumatica: data from a literature search compared with a Delphi-based expert consensus. Ann Rheum Dis, 70, 447–53. Dejaco C, et al. (2015). 2015 Recommendations for the management of polymyalgia rheumatica: a European league against rheumatism and American College of Rheumatology collaborative initiative. Arthritis Rheum, 67, 2569–80. Deng J, et al. (2010). Th17 and Th1 T-cell responses in giant cell arter- itis. Circulation, 121, 906–15. Doran MF, et al. (2002). Trends in the incidence of polymyalgia rheumatica over a 30 year period in Olmsted County, Minnesota USA. J Rheumatol, 29, 1694–7. Box 19.11.11.1 Future research agenda for polymyalgia rheumatica The group agreed that future studies in polymyalgia rheumatica should be multicentre and properly powered using an agreed, validated core outcome set and a robust trial design that would maximize the power of studies, facilitate regulatory approvals, and allow future meta-analysis. Specific research questions:

1. Which outcome measures—including patient-related outcomes and response, remission, and relapse criteria—should be used in polymyalgia rheumatica? What is the value of a composite score? What are the most relevant treatment targets in polymyalgia rheumatica?
2. What is the efficacy and safety of different routes of glucocorticoid administration (oral, intramuscular, intra-articular), different initial glucocorticoid doses, various tapering regimens, and different flare doses?
3. What is the efficacy and safety of disease-modifying anti-rheumatic drugs (non-TNFα biologic, conventional synthetic and conventional targeted) in polymyalgia rheumatica? What is the optimal strategy for using DMARDs in polymyalgia rheumatica: monotherapy versus combination therapy, early versus late introduction, and (particularly for biologics) use with or without GCs?
4. What is the minimal/optimal duration of therapy and which strategies for withdrawing GCs and/or DMARDs yield the best efficacy/safety profile?
5. What is the optimal strategy for shared primary and specialty care including recommendations for specialist referral? How can patients be better involved in treatment decisions, and are there any decision aids? What is the role of self-management?
6. What is the value of tight control (i.e. treat to target) versus conventional management strategies in polymyalgia rheumatica?
7. How should patients with long-standing disease and long-term low-dose GC therapy be managed?
8. What is the cost utility and effectiveness of DMARD use in polymyalgia rheumatica (versus GC use alone)?
9. What is the value of nonpharmacological therapies in polymyalgia rheumatica? Particularly, it is assumed but not yet demonstrated that physiotherapy may support preservation of function and reduce the risk of adverse events related to GC use. Patients may benefit from exercise by maintaining muscle mass and function as well as by fall prevention especially in the frail. What is the role of diet in polymyalgia rheumatica and nutrition supple- ments (e.g. fish oil) related to outcomes?

10. What is the efficacy and safety of herbal preparations in polymyalgia rheumatica?
11. What is the role of imaging (particularly ultrasound) for the assessment and monitoring of polymyalgia rheumatica, identification of overlap with other diseases (e.g. large-vessel vasculitis or inflammatory arthritis) alongside clinical and patient-reported outcomes?
12. Which biomarkers may be useful in polymyalgia rheumatica? Why do some patients do better than others? How can we identify these groups and what is the biological mechanism behind it? Should different drugs be applied to different polymyalgia rheumatica subgroups?
13. What is the morbidity and mortality of polymyalgia rheumatica patients (with a particular focus on cardiovascular risk) in long-term observational studies?
14. What is the aetiopathogenesis of polymyalgia rheumatica? Which targeted therapies could be developed based on new knowledge of disease mechanisms? Bolded points indicate the top five items of the research agenda according to the opinion of the guideline panel. Reproduced from Dejaco C et al. (2015) Recommendations for the management of polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. Annals of the Rheumatic Diseases, 74: 1799–807, copyright 2015, with permission from BMJ Publishing Group Ltd.

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