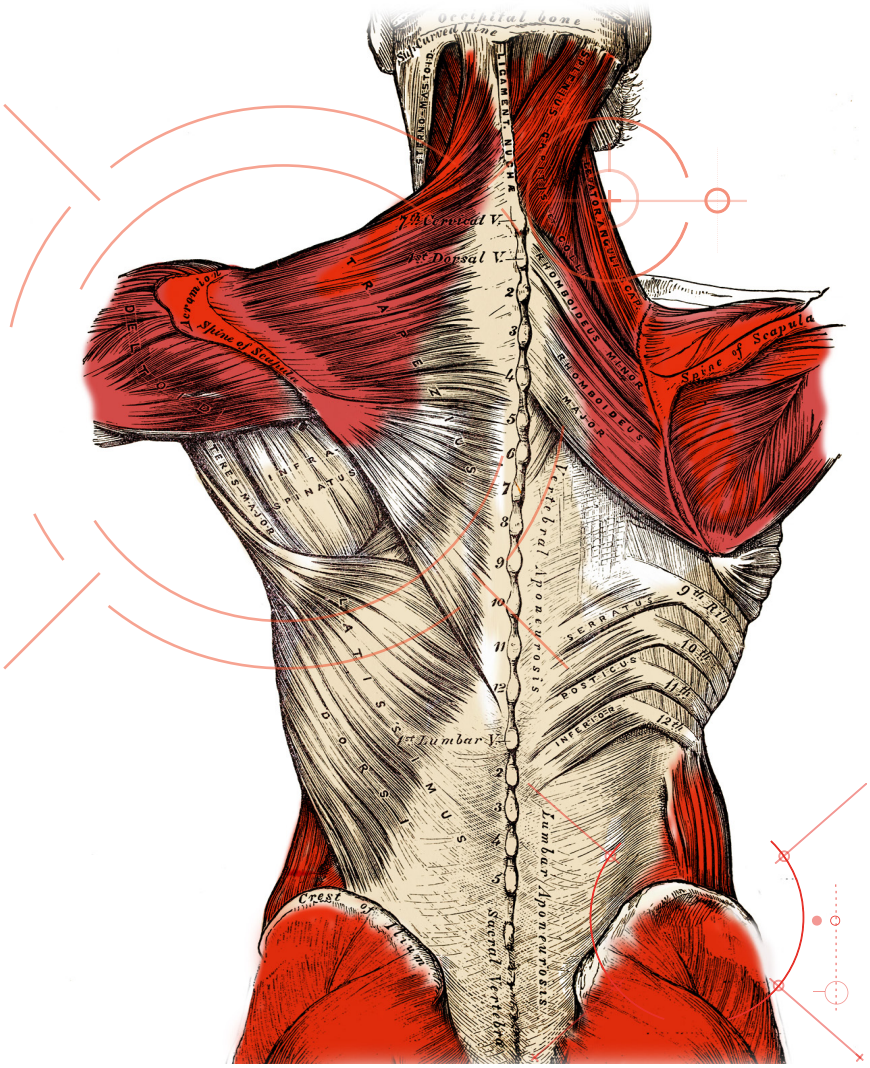
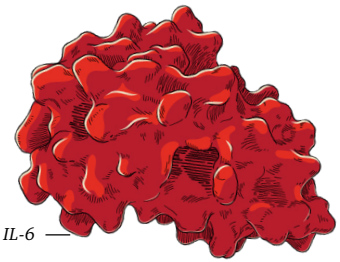
# UNDERSTANDING PMR




Key hallmarks associated with polymyalgia rheumatica (PMR), such as painful inflammation, can be attributed, in part, to certain immune cells and cytokines, such as interleukin-6 (IL-6).[1,2]

Current guidelines establish glucocorticoids (GCs) as the standard of care; however, challenges remain such as time on therapy, relapses, and risks with the increase of GC-related toxicities.[3-6]

Many patients may need a PMR treatment strategy that minimizes the use of GCs.[5]

# PMR is the second most common inflammatory rheumatic disease after rheumatoid arthritis (RA)[4]

**The residual lifetime risk of developing PMR in both men and women[7]**

**>**

**IS GREATER THAN**

**The risk of developing RA, as well as other inflammatory rheumatic diseases in individuals age 60 or older[7]**

**The lifetime risk of PMR in the US[8]**

**2.4%**
**FOR WOMEN**

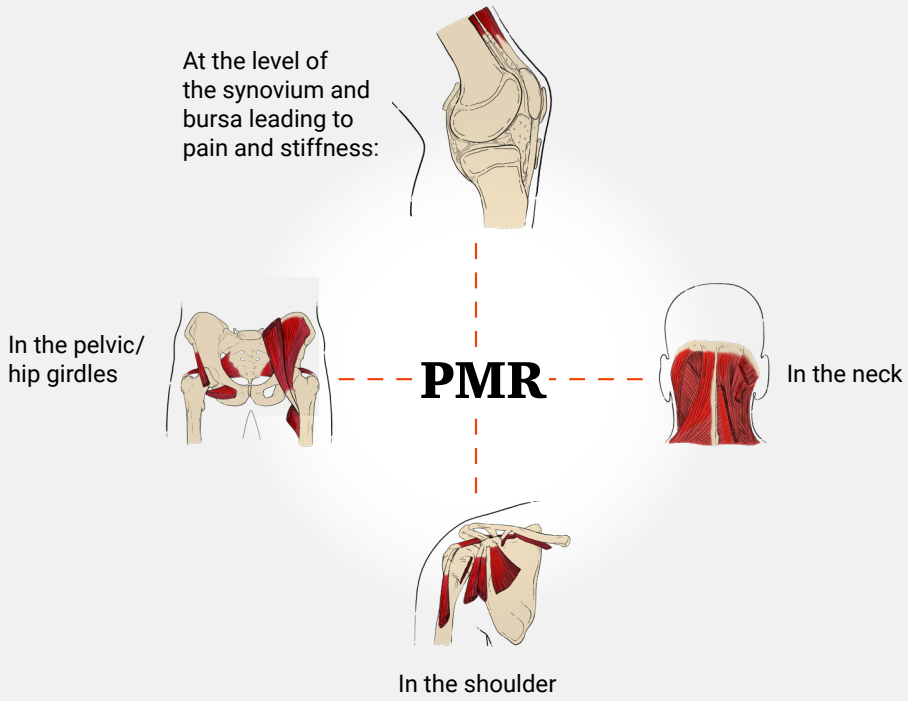
**1.7%**
**FOR MEN**

*I work out regularly, I thought it was muscle pain. I tried heat, I tried ice, I went to the chiropractor. I asked my PCP to send me to physical therapy. Finally, I was sent to a rheumatologist.*

– Patient living with PMR

# PMR is characterized not only by inflammation and stiffness, but also by significant pain[1,9]

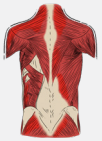
## PMR symptoms have a typical distribution pattern of inflammation[10]



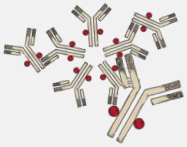

**PMR pain can be distinguished from mechanical because inflammatory pain from PMR can improve with physical activity[1,9]**

# Diagnosing PMR has its challenges[11]

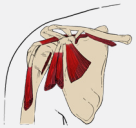
The American College of Rheumatology and the European Alliance of Associations for Rheumatology propose classification criteria for diagnosing PMR as people aged ≥50 years with bilateral shoulder aching and abnormal C-reactive protein concentrations or ESR, plus at least 4 points (without ultrasound) or 5 points or more (with ultrasound) from[1]:



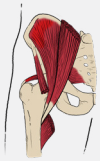
Morning stiffness lasting >45 minutes (2 points)



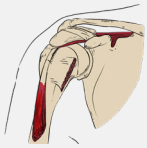
Absence of RF or ACPAs (2 points)



Absence of other joint involvement (1 point)



Hip pain or restricted range of motion (1 point)



Ultrasound findings of bilateral shoulder abnormalities (subdeltoid bursitis, biceps tenosynovitis, or glenohumeral synovitis) or abnormalities in 1 shoulder and hip (hip synovitis, trochanteric bursitis) (1 point)

*My rheumatologist asked me to get up and down out of my chair, lift my arms. He said this looks like classic PMR, we'll run blood work and start prednisone.*

– Patient living with PMR

ACPA=anti-citrullinated protein antibody; ESR=erythrocyte sedimentation rate; RF=rheumatoid factor.

# The pathogenesis of PMR is multifaceted[10]

## It involves both innate and adaptive immune systems[10]:

- These are in response to unknown triggers[10]
- Inflammation experienced by patients with PMR suggests that cytokines such as IL-6, IL-1, IL-17, IL-10, and TNFα play a role in the pathogenesis[10,12]

## PMR could occur simultaneously with giant cell arteritis (GCA), a systemic vasculitis affecting the large arteries[1]:

- GCA is diagnosed in an estimated 10% to 30% of patients with PMR[1]
- According to published data, 40% to 50% of patients with GCA have PMR manifestations[1]

## It mimics other conditions:

- Diagnosis of PMR involves recognizing clinical symptoms of PMR and excluding other conditions that may have a similar clinical presentation[9]

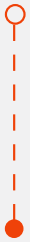
**There are no diagnostic tests specific to the condition, therefore careful consideration and exclusion of conditions that may mimic PMR are important[11]**

TNFα=tumor necrosis factor alpha.

# In PMR, IL-6 is a major driver of acute-phase response and systemic inflammation[1,13]

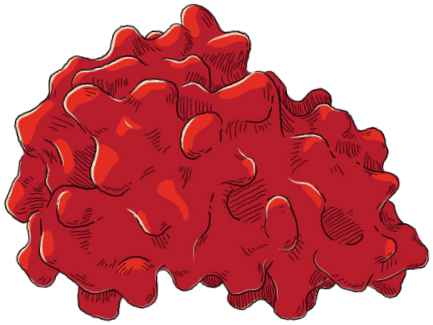
## IL-6 stimulates increases in[10]:

Erythrocyte sedimentation rate (ESR)



C-reactive protein (CRP)

And plays an important role in pain, **independent from inflammation.**[14]

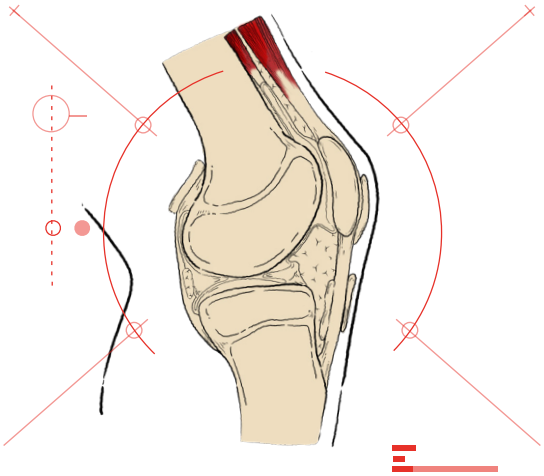


## IL-6 levels also correlate with PMR disease activity[2]

- Elevated concentrations of plasma IL-6 are a characteristic feature in patients with PMR vs healthy controls[2]
- A study of patients with PMR demonstrated that muscle pain and stiffness concurrently developed when IL-6 plasma concentrations were increased[2]
- Synovitis observed in PMR is a type of inflammation accompanied by increased levels of IL-6 in the synovial fluid[15-17]

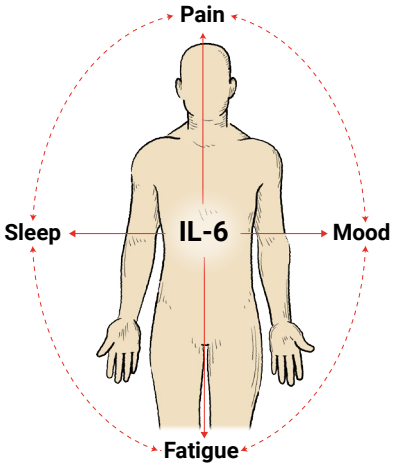
**In certain instances, the degree of IL-6 elevation appears to correlate with the magnitude of pain[14]**

# IL-6 is central to the pathogenesis of PMR[18]



- IL-6 concentrations (along with sIL-6R) are increased with PMR[2,19]
- The increase of IL-6 is associated with fatigue, impaired sleep, and mood disorders, particularly anxiety and depression[4,20]

> *[PMR feels like] when you spill coffee—it's unexpected and it touches everything. Everything you are doing.*
>
> – Patient living with PMR

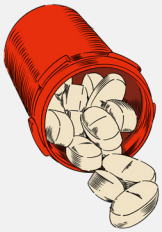



sIL-6R=soluble interleukin-6 receptor.

# The standard of care for PMR starts with GCs[3-6]

## To manage PMR, EULAR/ACR strongly recommends:

- Using GCs instead of NSAIDs, with the exception of possible short-term NSAIDs and/or analgesics in patients with pain related to other conditions[21]
- Using a minimum effective individualized duration of GC therapy[21]
- Against the use of anti-TNFα agents[21]



## Treating PMR varies by rheumatologist[21]

- GC dose-tapering strategies[21]
- Use of disease-modifying antirheumatic drugs (DMARDs)[21]
- Duration of treatment[21]

GC

## GCs typically lead to a dramatic improvement in symptoms within the first few days[22,23]

- Once symptoms resolution is stable, the tapering process may start[22,23]
- However, not all patients are able to taper off steroids[22,23]
- Stopping steroids or tapering can be challenging due to potential of relapse[22,23]

NSAIDs=nonsteroidal anti-inflammatory drugs.

# Although there is a standard of care, challenges still remain[3-6]

Time on therapy

Variable efficacy

Increased risk of GC-related toxicities

## GCs may not be appropriate for all patients

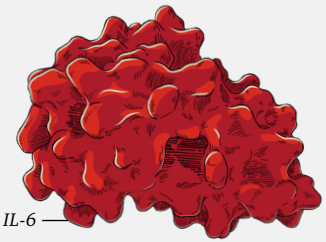
- As much as 43% of patients taking GCs relapse within 1 year[5]
- The risk of GC-related complications exists even at low doses of long-term GC use in patients with rheumatic diseases like PMR[24]
- Use of GCs leads to risk of medication-related complications such as cardiovascular disease, osteoporosis, and diabetes[21]
- Patients with comorbidities that are commonly seen in older adults—osteoporosis, uncontrolled hyperglycemia, diabetes mellitus, glaucoma, joint infection, and uncontrolled hypertension—should consider using GCs with caution[25]
- Some patients may not achieve adequate management of symptoms with GCs and thus have limited treatment options[3]

**GCs do not always address the underlying mechanisms of PMR[2]**

# There's a need for advancement

**The residual lifetime risk of developing PMR is higher in both men and women than the risk of developing RA, as well as other inflammatory rheumatic diseases in individuals age 60 or older.[7]**

**PMR is characterized by inflammation, stiffness, and significant pain.[1,9]**




- Key hallmarks associated with PMR can be attributed in part to certain immune cells and cytokines such as IL-6[1,2,26]
- In PMR, IL-6 is a major driver of acute-phase response and systemic inflammation[1,13]
- IL-6 plays an important role in peripherally induced pain, and in some instances, the degree of IL-6 elevation appears to correlate with the magnitude of pain[14]

**Visit PMRandIL6.com to learn more.**

**References: 1.** Gonzalez-Gay MA, Matteson EL, Castañeda S. Polymyalgia rheumatica. *Lancet*. 2017; 390:1700-1712. **2.** Roche NE, Fulbright JW, Wagner AD, et al. Correlation of interleukin-6 production and disease activity in polymyalgia rheumatica and giant cell arteritis. *Arthritis & Rheumatism*. 1993;36(9):1286-1294. **3.** Buttgereit F, Dejaco C, Matteson EL, Dasgupta B. Polymyalgia rheumatica and giant cell arteritis: a systematic review. *JAMA*. 2016;315(22):2442-2458. **4.** Acharya S, Musa R. Polymyalgia Rheumatica. *NCBI Bookshelf*. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. **5.** Floris A, Piga M, Chessa E, et al. Long-term glucocorticoid treatment and high relapse rate remain unresolved issues in the real life management of polymyalgia rheumatica: a systematic literature review and meta-analysis. *Clinical Rheum*. 2022;41:19-31. **6.** Mazzantini M, Torre C, Miccoli M, et al. Adverse events during longterm low-dose glucocorticoid treatment of polymyalgia rheumatica: a retrospective study. *Journal Rheumatol*. 2012;39(3):552-557. **7.** Crowson CS, Matteson EL, Myasoedova E, et al. The lifetime risk of adult-onset rheumatoid arthritis and other inflammatory autoimmune rheumatic diseases. *Arthritis & Rheumatism*. 2011;63(3):633-639. **8.** Crowson CS, Matteson EL. Contemporary prevalence estimates for giant cell arteritis and polymyalgia rheumatica, 2015. *Semin Arthritis Rheum*. 2017;47(2):253-256. **9.** Mackie SL. Polymyalgia rheumatica: pathogenesis and management. *Clinical Medicine*. 2013;13(4):398-400. **10.** Guggino G, Ferrante A, Macaluso F, et al. Pathogenesis of polymyalgia rheumatica. *Reumatismo*. 2018;70(1):10-17. **11.** Kermani TA, Warrington KJ. Advances and challenges in the diagnosis and treatment of polymyalgia rheumatica. *Ther Adv Musculoskel Dis*. 2014;6(1):8-19. **12.** Martinez-Taboada VM, Alvarez L, RuizSoto M, et al. Giant cell arteritis and polymyalgia rheumatica: role of cytokines in the pathogenesis and implications for treatment. *Cytokine*. 2008;44(2):207-220. **13.** Salvarani C, Cantini F, Niccoli L, Macchioni P, Consonni D, Bajocchi G, Vinceti M, Catanoso MG, Pulsatelli L, Meliconi R, Boiardi L. Acute-phase reactants and the risk of relapse/recurrence in polymyalgia rheumatica: a prospective followup study. *Arthritis Rheum*. 2005 Feb 15;53(1):33-8. doi: 10.1002/art.20901. **14.** Sebba A. Pain: a review of interleukin-6 and its roles in the pain of rheumatoid arthritis. *Open Access Rheumatol*. 2021;13:31-43. **15.** Zen-nyoji A, Shimizu H, Ohtani K, et al. Increased RAHA titer and interleukin-6 levels in the synovial fluid in a patient with polymyalgia rheumatica. *Intern Med*. 1993;32(6):484-486. **16.** Jiemy WF, Zhang A, Boots AMH, et al. Expression of interleukin-6 in synovial tissue of patients with polymyalgia rheumatica. *Ann Rheum Dis*. 2022;0:1-2.doi:10.1136/annrheumdis-2022-222873. **17.** Lundberg IE, Sharma A, Turesson C, Mohammad AJ. An update on polymyalgia rheumatica. *J Intern Med*. 2022 Nov;292(5):717-732. doi: 10.1111/joim.13525. Epub 2022 Jun 11. **18.** Schmidt ZM, Poor G. Polymyalgia rheumatica, an age-related rheumatic disease. *OBM Geriatrics*. 2022;6(3). doi:10.21926/obm.geriatr.2203202. **19.** Mori S, Koga Y. Glucocorticoid-resistant polymyalgia rheumatica: pretreatment characteristics and tocilizumab therapy. *Clin Rheumatol*. 2016;35:1367-1375.**20.** Grygiel-Górniak B, Puszczewicz M. Fatigue and interleukin-6—a multi-faceted relationship. *Reumatologia*. 2015;53(4):207-212. **21.** Dejaco C, Singh YP, Perel P, et al. 2015 recommendations for the management of polymyalgia rheumatica: a European League Against Rheumatism/American College of Rheumatology collaborative initiative. *Ann Rheum Dis*. 2015;74:1799-1807. **22.** Bartoloni E, Pucci G, Alunno A, et al. Polymyalgia rheumatica. *The Heart in Rheumatic, Autoimmune and Inflammatory Diseases*. http://dx.doi.org/10.1016/B978-0-12-803267-1.00009-0. **23.** Hagihara K, Kawase I, Tanaka T, Kishimoto T. Tocilizumab ameliorates clinical symptoms in polymyalgia rheumatica. *J Rheumatol*. 2010;37(5):1075-1076. **24.** Gabriel S, Sunku J, Salvarani C, et al. Adverse outcomes of antiinflammatory therapy among patients with polymyalgia rheumatica. *Arthritis & Rheumatism*. 1997;40(10):1871-1878. **25.** Hodgens A, Sharman T. Corticosteroids. 2022. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. **26.** Toussirot E, Régent A, Devauchelle-Pensec V, et al. Interleukin-6: a promising target for the treatment of polymyalgia rheumatica or giant cell arteritis? *RMD Open*. 2016;2:e000305. doi:10.1136/rmdopen-2016-000305.