Current evidence for therapeutic interventions and prognostic factors in polymyalgia rheumatica: a systematic literature review informing the 2015 European League Against Rheumatism/American College of Rheumatology recommendations for the management of polymyalgia rheumatica

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ABSTRACT

To summarise evidence on therapeutic interventions and prognostic factors in polymyalgia rheumatica (PMR). A systematic literature review was conducted using Ovid Medline, Embase, PubMed, CINAHL, Web of Science and the Cochrane Library (1970 through April 2014). Quality of evidence (QoE) of identified studies was appraised by Grading of Recommendations Assessment, Development and Evaluation (GRADE) (interventions) and the Quality In Prognosis Studies (QUIPS) methodologies (prognostic factors). Out of 10 931 titles identified, 52 articles were finally selected. A single study indicated that an initial prednisone dose of 20 mg/day is associated with a lower short-term relapse rate than 10 mg/day but at the cost of a higher rate of adverse events. Another study suggested a comparable efficacy of intramuscular methylprednisolone and oral glucocorticoids (GCs) with lower cumulative GC doses and less weight gain in the former group. Moderate to high QoE (1–2 studies) indicated a benefit of methotrexate in remission rates and cumulative GC doses in early PMR. Anti-tumour necrosis factor α agents are ineffective for PMR treatment. Among prognostic factors, female sex, high erythrocyte sedimentation rate (ESR) and peripheral arthritis were associated in some studies with a higher relapse risk. Women and patients with high ESR also appeared to have a longer duration of treatment. Several studies of varying quality, however, failed to prove these associations. In PMR, evidence for initial GC doses and subsequent tapering regimens is limited. Intramuscular methylprednisolone and methotrexate may be effective GC sparing agents. Female sex, high ESR and peripheral arthritis at disease outset are potential risk factors for a worse prognosis.

INTRODUCTION

There is still a wide heterogeneity in the methods used to treat polymyalgia rheumatica (PMR) that may be subject to personal experience, the setting in which it is managed (ie, primary or specialty care) and to the existence and implementation of national guidelines.[1–4] Treatment tailored to the individual is desirable but is hampered by the absence of reliable predictors of long-term disease outcomes.

The objective of this work was to summarise evidence on therapeutic interventions and prognostic factors in PMR informing the panel developing new European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) recommendations for the management of PMR.[4a 4b]

METHODS

See online supplementary file S1 for full details.

In brief, we used Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology as a framework.[5] The key questions were framed in the PICO (Population, Intervention, Comparator, Outcome) format (box 1). Outcomes were retrieved from a survey among rheumatologists, general practitioners and patients (see online supplementary box S1). A sensitive systematic literature search was conducted by two investigators (CD, YPS) using Ovid MEDLINE, Embase, PubMed, CINAHL, Web of Science and the Cochrane Library databases (from January 1970 until April 2014), applying the thesaurus of PMR, text words, abbreviations and truncated text words (see online supplementary box S2 for key words used for Ovid Medline). The grey literature and clinical trial registries were reviewed and tracked to determine whether additional peer-reviewed articles not identified by the primary search had been published. We excluded all articles that did not report original data, did not study patients with PMR, or that considered patients with PMR and giant cell arteritis (GCA) as a single group. We also excluded all studies on prognostic factors investigating tests that were not routinely available and/or with a <6 months' follow-up. Quality appraisal of interventional and prognostic studies was performed using GRADE[6 7] and the Quality in Prognostic Studies (QUIPS) tool,[8] respectively. We attempted to perform meta-analyses (fixed effect methods) for interventional studies whenever possible, whereas for prognostic studies, meta-analysis was impossible because of the large heterogeneity in study design, PMR case definition, measurements and definitions of prognostic factors and outcomes as well as study quality.

Box 1 PICO (=Population, Intervention, Comparator, Outcome) questions

PICO questions on interventions

1. In polymyalgia rheumatica (PMR) (P), what is the effect of non-steroidal anti-inflammatory drugs and/or analgesics (I) on outcome (O) compared with glucocorticoids (C)?
2. In PMR (P), what is the effect of short duration of glucocorticoid therapy (I) on outcome (O) compared with long duration of glucocorticoid therapy (C)?
3. In PMR (P), what is the effect of low-dose oral glucocorticoids (≤7.5 mg/day of prednisone equivalent) (I) on outcome (O) compared with medium dose of glucocorticoids (> 7.5 mg/day but ≤30 mg/day of prednisone equivalent) (C)?
4. In PMR (P), what is the effect of medium-dose oral glucocorticoids (>7.5 mg/day but ≤30 mg/day of prednisone equivalent) (I) on outcome (O) compared with high dose of glucocorticoids (> 30 mg/day but ≤100 mg/day of prednisone equivalent) (C)?
5. In PMR (P), what is the effect of an oral glucocorticoid dose of ≥10 mg/day but ≤20 mg/day prednisone equivalent (I) on outcome (O) compared with a dose of >20 mg but ≤30 mg/day of prednisone equivalent (C)?
6. In PMR (P), what is the effect of rapid taper of glucocorticoids (I) on outcome (O) compared with slow taper of glucocorticoids (C)?
7. In PMR (P), what is the effect of intramuscular injection of glucocorticoids (I) on outcome (O) compared with oral glucocorticoids (C)?
8. In PMR (P), what is the effect of administration of oral glucocorticoid therapy in divided doses (morning plus evening) (I) on outcome (O) compared with a single dose (morning only) (C)?
9. In PMR (P), what is the effect of glucocorticoids plus non-biological disease modifying antirheumatic drugs (I) on outcome (O) compared with glucocorticoids alone (C)?
10. In PMR (P), what is the effect of glucocorticoids plus biological agents (I) on outcome (O) compared with glucocorticoids alone (C)?
11. In PMR (P), what is the effect of biological agents (I) on outcome (O) compared with glucocorticoids alone (C).
12. In PMR (P), what is the effect of glucocorticoids plus non-pharmacological interventions (I) on outcome (O) compared with glucocorticoids alone (C)?

PICO questions on prognostic factors

13. In PMR (P), what is the effect of older age at diagnosis (I) on outcome (O) compared with younger age (C)?
14. In PMR (P), what is the effect of female sex (I) on outcome (O) compared with male sex (C)?
15. In PMR (P), what is the effect of high levels of inflammatory markers (ie, erythrocyte sedimentation rate and/or C-reactive protein) at diagnosis (I) on outcome (O) compared with low levels of inflammatory markers (C)?
16. In PMR (P), what is the effect of more active/severe disease at diagnosis (I) on outcome (O) compared with lower disease activity/severity (C)?
17. In PMR (P), what is the effect of the presence of peripheral arthritis at diagnosis (I) on outcome (O) compared with the absence of peripheral arthritis (C)?
18. In PMR (P), what is the effect of longer symptom duration at diagnosis (I) on outcome (O) compared with shorter symptom duration (C)?
19. In PMR (P), what is the effect of concomitant conditions (including cardiovascular disease, cerebrovascular disease, peripheral vascular disease, osteoporosis, hyperlipidaemia, diabetes, hypertension, infection, cataract, glaucoma, peptic ulcer, skin disorders, adiposity, mood disturbances, cognitive disorder) at diagnosis that might be exaggerated by PMR and/or glucocorticoid therapy (I) on outcome (O) compared with the absence of these conditions (C)?
20. In PMR (P), what is the effect of rapid response to glucocorticoids (I) on outcome (O) compared with delayed response?
21. In PMR (P), what is the effect of shared patients' management by primary and secondary care (I) on outcome (O) compared with management in primary care only?
22. In PMR (P), what is the effect of optimal control management of patients (I) on outcome (O) compared with conventional management (C)?

RESULTS

Our initial and update searches yielded n=10 078 and 853 articles, respectively (figure 1). The characteristics of the 52 included studies are given in table 1 (interventions) and table 2 (prognostic factors).

No study was found describing the effect of short versus long duration of glucocorticoid (GC) therapy (PICO 2), the effect of administration of GCs in divided doses (PICO 8), the prognostic value of shared patients' management by primary and secondary care (PICO 21) and the relevance of optimal control management of patients compared with conventional management (PICO 22).

The full GRADE profile on interventions and evidence tables on prognostic factors are shown in online supplementary tables S1 and S2, respectively.

Evidence for therapeutic interventions (PICOs 1–12)

#### Non-steroidal anti-inflammatory drugs compared with GCs (PICO 1)

Two retrospective studies (n=364) reported a lower rate of vertebral fractures (RR=0.05 (CI 0 to 0.78)) among non-steroidal anti-inflammatory drug (NSAID) users than among GCs users, whereas no difference was found in hip and radius fractures. In addition, there was a trend towards a higher rate of cardiovascular events (HR=1.64 (0.99 to 2.70)) and hypertension (RR=1.72 (0.94 to 3.13)) in the NSAID group.[17 20] The quality of evidence (QoE) for all reported outcomes was very low.

High versus low initial GC doses (PICOs 3–5)

A single randomised controlled trial (RCT) with 39 patients with PMR investigated starting doses of 20 mg and 10 mg oral prednisone.[22] We also identified seven retrospective studies with comparisons between >7.5 mg/day and ≤7.5 mg/day,[9 20 26] >15 mg/day and ≤15 mg/day[12 24–26] and >30 mg/day and ≤30 mg/day oral prednisone.[18 26]

The RCT demonstrated a lower relapse rate at 2 months in the higher-dose group than in the lower-dose group (RR=0.16 (0.04 to 0.62), moderate QoE),[22] whereas the retrospective studies showed contradictory results (all with very low QoE). Patients in

Figure 1 Study flow diagram detailing the literature search. PICO, Population, Intervention, Comparator, Outcome; PMR, polymyalgia rheumatica.
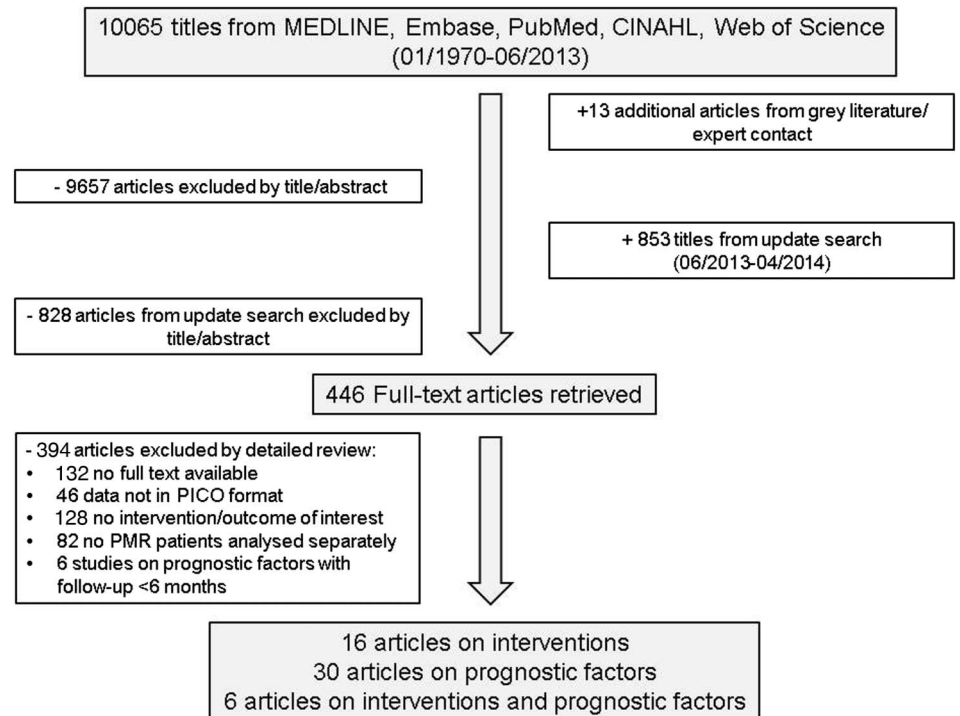
the high-dose groups, however, appeared to be at a higher risk for GC-related adverse events according to one prospective (RR=11.55 (0.68 to 195.63), very low QoE) and one retrospective study (RR=6.73 (1.84 to 24.56), very low QoE).[12 22]

Rapid versus slow tapering of glucocorticoids (PICO 6)
A single retrospective study (low QoE, n=364) analysed the effect of fast versus slow GC tapering on relapse risk using statistically modelled 'tapering constants'. Compared with slow tapering, medium and fast GC dose reduction were linked with a 2.4- and 5.3-fold increased risk, respectively for a first relapse.[20]

Intramuscular versus oral glucocorticoid therapy (PICO 7)
A single multicentre RCT (12 weeks double-blinded plus 84 weeks open-label) on 60 patients with PMR was identified.[13 14] The authors reported a similar efficacy of intramuscular (IM) and oral GCs for remission rates at weeks 12, 48 and 96; however, the QoE decreased from moderate at first to very low at the last visit because of a lack of blinding and increasing imprecision after week 12.

The trial reported a lower cumulative GC dose (mean difference (MD) of 1.1 g and 1.5 g at weeks 24 and 96, respectively; moderate QoE) and less weight at week 96 (MD −2.6 kg) in the IM group compared with the oral GC group. Other GC-related side effects, however, did not differ between the groups.

Conventional synthetic disease-modifying antirheumatic drugs (PICO 9)
We identified four RCTs and one retrospective study testing the use of methotrexate (MTX) at doses of 7.5–10 mg/week.[10 11 15 24 27 29] In addition, a retrospective analysis on the use of hydroxychloroquine was found.[24]

We found moderate to high QoE from one to two studies indicating a benefit of MTX for remission at week 44 (RR=5.22 (1.28 to 21.29)),[27] relapse rate at week 76 (RR=0.64 (0.42 to 0.98)),[10] discontinuation of GCs at weeks 48 (RR=1.74 (1.15 to 2.64)) and 76 (RR=1.64 (1.15 to 2.35))[10] as well as cumulative GC doses at 12 months (meta-analysed effect of two

studies: MD 0.51 g (0.6–0.43 g) prednisone).[15 27] Additionally, Caporali et al[10] reported median cumulative prednisone doses of 2.1 g (IQR=1.96–2.9) and 2.97 g (2.17–3.65) in MTX and control groups, respectively, at week 76.

All analyses from one to four prospective and retrospective studies reporting no benefit of MTX for these outcomes were of very low quality:[15 24 27 29] Van der Veen's study, for example,[29] reported no difference in remission and relapse rates between MTX and control groups; however, this trial was limited by a very high drop-out rate (ie, study bias) of 48% (withdrawals for several reasons) and imprecision about the outcomes of interest. The (meta-analysed effect of the) two randomised studies by Ferraccioli et al[15] and Nazarinia et al[27] reporting no difference between groups in the relapse rate at 12 months were limited by lack of blinding, heterogeneity, indirectness (because different GC doses and relapse criteria were used) and imprecision. Additionally, the intervention and control groups in Ferraccioli's trial received different prednisone starting doses (25 mg in the MTX group and 15 mg in the control arm).[15]

For the reduction of GC side effects, one trial reported a better dual energy X-ray absorptiometry result during follow-up in the MTX group than in the control group (MD of bone mineral density 2.7% (CI 3.9% to 1.5%), moderate QoE);[15] however, the rate of osteoporotic fractures was similar in both groups according to four studies.[10 11 15 29] None of the other GC-related adverse events tested was reduced by MTX treatment.[10 11 15 29] The QoE of these results was very low mainly because of study limitations and (serious) imprecision. None of the studies was adequately powered to detect differences in GC-related adverse events.

Hydroxychloroquine was ineffective for reducing relapses as indicated by a single very low QoE retrospective study.[24]

Biological agents (PICO 10 and 11)
A single 52-week RCT examined the efficacy of infliximab (3 mg/kg body weight) versus placebo in 53 patients with PMR.[28] The trial failed to show a benefit of infliximab for primary and secondary efficacy endpoints.

Table 1 Characteristics of studies on interventions

Study ID	PICO	Design	Duration	Follow-up	PMR criteria	Intervention	Control	No pt.	No female patients (%)	No patients with complete follow-up (%)	Outcomes (time point)
1991 Catoggio[9]	3	Case–control (retro.)	7 y	NR	Descript.	OP 10–15 mg	OP 7.5 mg	36	18 (50)	36 (100)	Relapse (>3 m)
2004 Caporali[10] 2008 Cimmino[11]	9	R, DB, Mul.+Obs. (prosp.)		76 w 59 m†	Chuang	MTX 10 mg+OP 25 mg	OP 25 mg	72	48 (67)	62 (86)	Relapse (244876 w) Disc GC (244876 w) GC-sides (76 w)
1988 Delecoeuillerie[12]	5	Case–control (retro.)	10 y	NR	Descript.	OP 15–30 mg	OP 7–12 mg	132	NR	132 (100)	Relapse (varT) Disc. GC (varT) Devel. GCA (varT) GC-sides (varT)
1998 Dasgupta[13] **1997 Dolan[14]**	7	R, DB, Mul.+ Obs. (prosp.)		12 w 84 w	Jones	IMP 120 mg/3 w (starting dose)	OP 15 mg (starting dose)	60£	43 (72)	49 (82)	Remission (124896 w) Disc GC (96 w) GC-sides (61224 m) Cumul GC (24, 52, 96 w) Mortality (96 w)
1996 Ferraccioli[15]	9	R, Mul.		12 m	Descript.	MTX 10 mg+OP 25 mg	OP 15 mg	24	22 (92)	24 (100)	Relapse (12 m) Disc GC (12 m) GC-sides (12 m) Cumul GC (6,12 m) ESR/CRP (12 m) GC-dose <5 mg (12 m)
2007 Fu[16]	12	R		12 w	Descript.	Yanghe+OP 20 mg	OP 20 mg	61	43 (71)	61 (100)	Remission (12 w) GC-sides (12 w) ESR (4812 w) Morning stiff (12 w)
1997 Gabriel[17] &	1	Case–control (retro.)	22 y	8 y‡	Descript.	NSAIDs	OP	181	163 (89)	181 (100)	GC-sides (varT)
1986 Kanemaru[18]	4	Case–control (retro.)	9 y	NR	Hamrin	OP 60 mg	OP >10 mg and ≤30 mg	6	3 (50)	6 (100)	Relapse (after taper)
2010 Kreiner[19]	11	R, DB		14 d	Chuang	ETN 25 mg 2×/week	Placebo	22	NR	20 (91)	PMR-AS (2 w)
2005 Kremers[20] &	3 6	Case–control (retro.)	30 y	5 y‡	Descript.	OP >10 mg GC fast tapering	OP <5 mg GC slow tapering	121 163	NR	12 (10) 42 (26)	Hazard 1st relapse
2007 Kremers[21] *	1	Case–control (retro.)	30 y	8 y‡	Descript.	NSAIDs	OP	364	244 (67)	NR	GC-sides (varT)
1989 Kyle[22,23]	5	R+Obs. (prosp.)	NR	2 m 12–177 w	Jones	OP 20 mg	OP 10 mg	39	NR	39 (100)	Relapse (2 m) GC-sides (varT)
2013 Lee[24]	5 9	Case–control (retro.)	NR	114 wt†	Bird	OP >15 mg OP+HCQ OP+MTX	OP ≤15 mg OP OP	39 24 12	NR	39 (100) 24 (100) 12 (100)	Relapse (varT)
2010 Mackie[25]	5	Case–control (retro.)	NR	5 y	Bird	OP >15 mg	OP ≤15 mg	171	124 (73)	164 (96)	Relapse (5 y) Dur. GC therapy Devel. GCA (5 y)
2001 Myklebust[26]	3 4 5	Case–control (retro.)	8 y	NR	Bird/ Hamrin	OP >10 mg and ≤30 mg OP >30 mg OP >15 mg and ≤30 mg	OP ≤10 mg OP >10 mg and ≤30 mg OP ≤15 mg	175 206 175	124 (71) 139 (68) 120 (69)	157 (90) 188 (91) 157 (90)	Disc GC (1, 2 y)

Continued

Table 1 Continued

Study ID	PICO	Design	PMR criteria	Duration	Follow-up	Intervention	Control	No pt.	No female patients (%)	No patients with complete follow-up (%)	Outcomes (time point)
2013 Nazarina[27]	9	R	Chuang		44 w	MTX 10 mg+OP 15 mg	OP 15 mg	58	30 (52)	47 (81)	Remission (44 w) Relapse (44 w) Cumul GC (44 w)
2007 Salvarani[28]	10	R, DB, Mul.	Healey		52 w	IFX 3 mg/kg+OP 15 mg	OP 15 mg	51	31 (61)	47 (92)	Relapse (22, 52 w) Disc GC (22, 52 w) GC-sides (52 w)
1996 van der Veen[29]	9	R, DB, Mul.	Descript.		2 y	MTX 7.5 mg+OP 20 mg	OP 20 mg	40	30 (75)	21 (53)	Remission (104 w) Relapse (24 m) GC-sides (24 m)
2009 Wang[30]	12	R	Bird		12 w	Biqi+OP 10 mg	OP 10 mg	39	28 (72)	NR	Response (12 w)

Articles containing both data on interventions and prognostic factors are shown in bold.
Studies are listed in alphabetical order; †mean, ‡median; #, & or ¥ multiple papers on partially the same cohort; *patients with first relapse analysed; †mean, ‡median; #, days; DB, double blind; Descript., description of symptoms and laboratory criteria defining PMR (no formal criteria used); Devel., GCA, development of giant cell arteritis during follow-up; dur., total duration of study; ESR, erythrocyte sedimentation rate; ETN, etanercept; Follow-up, length of follow-up; GC, glucocorticoid; GC-sides, glucocorticoid-related side effects; HCQ, hydroxychloroquine; HealthC, healthcare resource use; IFX, infliximab; IMP, intramuscular methylprednisone; inc., increased; m, months; MTX, methotrexate; Mul., multicenter; No pt., number of patients; No, number of; NR, not reported; NSAIDs; non-steroidal anti-inflammatory drugs; Obs. (prosp), observational prospective follow-up; OP, oral prednisone (equivalent); Outcome (time points), outcomes (out of the list of critical outcomes listed in online supplementary table S1) addressed in the corresponding study and the time points at which the outcome was investigated in parentheses); PICO, Population, Intervention, Comparator, Outcome (number of PICO question); PMR, polymyalgia rheumatica; PMR-AS, PMR activity score; PV, plasma viscosity; R, randomised; RS3PE, remitting seronegative symmetrical synovitis with pitting oedema; SF-36, short form 36 questionnaire; stiff, stiffness; Study ID, study identifier; sympt. Dur., symptom duration; varT, variable time point/no exact date reported; w, weeks; y, years.

Case–control (retro.), Case–control study with retrospective design; Control, control treatment; CRP, C-reactive protein; Cumul, cumulative; d, days; of patients as reported in the study of Dasgupta *et al.*

Another RCT compared etanercept with placebo in patients with newly diagnosed PMR not receiving GCs.[19] This trial failed to show a greater reduction of the PMR activity score at week 2 with etanercept than with placebo (primary endpoint) (low QoE).

Non-pharmacological interventions (PICO 12) and herbal preparations

No clinical trials on non-pharmacological interventions were found.

For herbal preparations, we identified two randomised studies testing Chinese Yanghe herb decoction and Chinese Biqi capsules.[16 30] Treatment with Chinese Yanghe resulted in a lower degree of morning stiffness and a lower erythrocyte sedimentation rate (ESR) at week 12 (low and moderate QoE, respectively).[16] For Biqi capsules there was low QoE, indicating a higher response rate at week 12 using a new (not validated) clinical composite score (RR=1.4 (1.0 to 2.0)).[30]

Evidence for prognostic factors (PICOs 13–22)
Older versus younger age (PICO 13)

Four studies (n=480, low risk of bias (LoB) in three to six out of eight QUIPS+two categories) examined the prognostic relevance of age.[20 39 47 52] In one study, older age was associated with lower healthcare resource use (n=364, LoB 6/8).[47]

Female versus male sex (PICO 14)

The prognostic impact of sex was investigated by 21 studies (n=1811) with varying quality (LoB in 3–6/8).[14 18 20 24 25 31 32 34 36–39 41 42 44 47 51–53 57 58] A higher number of relapses in women was found in one study (n=80, LoB 5/8),[37] whereas eight studies (n=693, LoB ranging from 3 to 6/8) showed no such association.[18 20 24 34 41 51 52 57] One study each reported a lower discontinuation rate of GCs after 2 years (n=50, LoB 4/8),[14] a longer duration of GC therapy (n=183, LoB 3/8),[32] a higher risk of developing GCA (n=176, LoB 5/8)[25] and a higher cumulative GC dose (n=80, LoB 4/8).[37] Additionally, GC side effects were generally more common among women than men (three studies, total n=196, LoB 2–4/8).[31 36 37]

Higher versus lower acute phase reactants (PICO 15)

Acute phase reactants were examined by 16 studies (n=2067).[4 20 24 26 32 33 39 40 43 44 47 48 50 54 56 57] The parameter most commonly investigated was ESR, whereas C-reactive protein (six studies, n=722),[4 24 32 33 39 57] interleukin 6 (one study, n=94)[57] and plasma viscosity (one study, n=183)[32] were less frequently tested. For this report, we focused on ESR as results for other acute phase reactants were comparable.

A higher ESR was associated with a higher relapse rate in three studies (n=208, LoB 4–5/8),[24 33 56] a lower probability of GC discontinuation after 1 and 2 years in one study (n=199, LoB 5/8),[26] a longer duration of GC therapy in two studies (n=381, LoB 2–5/8)[32 40] and a lower physical and mental quality of life after 1 year (one study, n=129, LoB 8/8).[4] A lack of association between baseline ESR levels and relapse rate (3 studies, n=427, LoB 4–6/8),[48 54 57] discontinuation of GCs (1 study, n=20, LoB 5/8)[44] and duration of GC therapy (2 studies, n=278, LoB 5–6/8)[33 48] was also reported.

More active versus less active/severe disease (PICO 16)

A single high-quality study (n=129) examined the prognostic impact of morning stiffness on patients' reported outcomes,

Table 2 Characteristics of studies on prognostic factors

Study ID	PICO	Design	Dur.	Follow-up	PMR criteria	Prognostic factor	No pt.	No female (%)	No pt. with complete follow-up (%)	Outcomes (time point)
1985 Ayoub[31]	14	Case–control (retro.)	8 y	NR	Descript.	Sex	76	42 (55)	76 (100)	GC-sides (varT)
2008 Barraclough[32]	14	Case–control (retro.)	10 y	2 y	Clinical	Sex	183	138 (75)	183 (100)	Longer duration GC therapy
	15					ESR, CRP, PV	180	138 (77)	180 (100)	
2000 Cantini[33] ¥	15	Obs. (prosp.)	5 y	37 m‡	Descript.	ESR	177	117 (66)	177 (100)	Duration GC therapy
1996 Caplanne [34]	14	Obs. (prosp.)	NR	NR	Bird	Sex	20	15 (75)	20 (100)	Relapse (varT)
2006 Ceccato[35]	17	Case–control (retro.)	13 y	40 m‡	Chuang	Arthritis	74	56 (76)	74 (100)	Relapse (varT)
1994 Cimmino[36] #	14	Obs. (prosp.)	NR	19 m†	Jones & Hazleman	Sex	40	24 (60)	38 (95)	GC-sides (varT)
2006 Cimmino[37] #	14	Obs. (prosp.)	NR	15 m†	Chuang	Sex	80	52 (65)	80 (100)	Number of relapses (varT), Cumul GC (varT), GC-sides (varT)
2011 Cimmino[38] #	14	Obs. (prosp.)	18 m	6 m	Bird	Sex	60	35 (58)	60 (100)	Response (1 m)
	17					Arthritis				Response (1 m)
	20					Rapid response				Relapse (6 m)
1997 Dolan[14]	14	Obs. (prosp.)	NR	96 w	Jones	Sex	50	36 (72)	50 (100)	Disc GC (2 y)
2013 Do-Nguyen[39]	13	Case–control (retro.)	11 y	1 y‡	NR	Age	100	71 (71)	100 (100)	Remission on and off therapy (1 y)
	14					Sex				
	15					ESR				
	18					sympt. dur.				
1997 Gonzalez-Gay[40]	15	Case–control (retro.)	NR	27/32 m†	Descript.	ESR	201	121 (60)	191 (95)	Duration GC therapy
1999 Gonzalez-Gay[41]	14	Case–control (retro.)	NR	≥12 m	Descrip.	Sex	134	85 (63)	NR	Relapse (varT)
2001 Gran[42]	14	Case–control (retro.)	11 y	64 m†	Bird	Sex	274	183 (67)	NR	Mortality (varT)
1996 Helfgott[43]	15	Case–control (retro.)	5 y	NR	Jones	ESR	117	89 (76)	117 (100)	Time to response
2007 Hutchings[4]	15	Obs. (prosp.)	2 y	12 m	Jones	ESR	129	77 (60)	122 (95)	HAQ (12 m), SF36-PCS/MCS (12 m)
	16					Morning stiffness				HAQ (12 m), SF36-PCS/MCS (12 m)
	20					Rapid response				Relapse (12 m)
1986 Kanemaru[18]	14	Case–control (retro.)	9 y	NR	Hamrin	Sex	6	3 (50)	6 (100)	Relapse (varT)
	20					Rapid response				
1997 Kanik[44]	14	Case–control (retro.)	NR	33–38 m†	Descript.	Sex	20	16 (80)	20 (100)	Disc GC (varT)
	15					ESR				
2012 Kim[45]	17	Case–control (retro.)	NR	28 m†	Bird	Arthritis	51	36 (71)	41 (80)	Remission (varT)
	19					comorbidities				
2012 Kimura[46]	17	Case–control (retro.)	10 y	26 m†	Hunder	RS3PE	151	78 (52)	136 (90)	Relapse (varT), GC-sides (varT), duration GC therapy
2005 Kremers[20] &	13	Case–control (retro.)	30 y	5 y‡	Descript.	Age	364	244 (67)	163* (100)	Hazard 1st relapse
	14					Sex				
	15					ESR				
2005 Kremers[47] &	13	Case–control (retro.)	30 y	5y‡	Descript.	Age	364	244 (67)	364 (100)	HealthC (6 m, ever)
	14					Sex				HealthC (1 m, 6 m, ever)
	15					ESR				HealthC (6 m, ever)

Continued

Review

Table 2 Continued

Study ID	PICO	Design	Dur.	Follow-up	PMR criteria	Prognostic factor	No pt.	No female (%)	No pt. with complete follow-up (%)	Outcomes (time point)
2000 Larrosa[48]	15	Case–control (retro.)	8 y	NR	Chuang	ESR	101	67 (66)	97 (96)	Relapse (varT)
2013 Lee[24]	14 15 17	Case–control (retro.)	NR	114 wt†	Bird	Sex ESR Arthritis	39	28 (72)	39 (100)	Relapse (varT)
2010 Mackie[25]	14	Obs. (prosp.)	NR	5 y	Bird	Sex	176	124 (71)	164 (93)	Earlier disc GC therapy, Devel. GCA (varT)
2012 Mazzantini[49]	19	Case–control (retro.)	39 y	NR	Bird	Osteoporosis Diabetes Dyslipidaemia	222	154 (69)	NR	Fractures (varT) Cardiovascular events (varT) Cardiovascular events (varT)
2000 Meyerhof[50]	14 20	Case–control (retro.)	NR	563 d†	Bird	ESR Fast taper	22	15 (68)	14 (64)	Response to GC (varT) Remission (varT), Relapse (varT)
2001 Myklebust[26]	15	Case–control (retro.)	8 y	NR	Bird	ESR	199	160 (80)	180 (91)	Disc GC (1, 2 y)
2000 Nagaoka[51]	14	Case–control (retro.)	12 y	5 y‡	Bird	Sex	20	10 (50)	18 (90)	Relapse (varT)
1971 Paulsen[52]	13 14	Case–control (retro.)	NR	41 m†	NR	Age Sex	16	14 (88)	16 (100)	Relapse (varT)
1999 Prickard[53]	14	Case–control (retro.)	13 y	NR	Descript.	Sex	49	40 (82)	37 (76)	Remission (2 y), Osteoporosis (varT), diabetes (varT), weight gain (varT), cataract (varT), moon face (varT), gastric complications (varT)
1999 Proven[54] &	15	Case–control (retro.)	21	5–7 y‡	Descript.	ESR	232	163 (70)	232 (100)	Remission (varT), relapse (varT)
1998 Salvarani[55] ¥	17	Obs. (prosp.)	5 y	25–41 m†	Healey	Arthritis RS3PE	177	117 (66)	177 (100)	Relapse (varT), duration GC therapy, Cumul GC (varT)
1999 Salvarani[56] ¥	15	Obs. (prosp.)	NR	44 m†	Descript.	ESR	92	69 (75)	91 (99)	Relapse (varT)
2005 Salvarani[57] ¥	14 15 17	Obs. (prosp.)	4 y	35 m‡	Descript.	Sex ESR Arthritis	94	70 (75)	94 (100)	Relapse (varT)
1995 Schaufelberger[58]	14	Case–control (retro.)	4 y	36 m†	Descript.	Sex	222	158 (71)	222 (100)	Mortality (varT)
1995 Schreiber[59]	20	Obs. (prosp.)	NR	38 m‡	Descript.	Normal CRP within 1 week	20	11 (55)	12–7$ (60–35)	Disc GC (2, 3, 4, 5 y), GC-sides (varT)

Articles containing both, data on interventions and prognostic factors are marked in bold letters.

Studies are listed in alphabetical order; †mean; ‡median; #, & or ¥ multiple papers on partially the same cohort; *patients with first relapse analysed; †mean, ‡median; $number of patients with complete follow-up data depends on the outcome, £number of patients as reported in the study of Dasgupta et al.

Case–control (retro.), Case–control study with retrospective design; Control, control treatment; CRP, C-reactive protein; Cumul, cumulative; d, days; Descript., description of symptoms and laboratory criteria defining PMR (no formal criteria used); Devel. GCA, development of giant cell arteritis during follow-up; Disc, discontinuation; dur., total duration of study; ESR, erythrocyte sedimentation rate; Follow-up, length of follow-up; GC, glucocorticoid; GC-sides, glucocorticoid-related side effects; HAQ, Health Assessment Questionnaire; HealthC, healthcare resource use; inc., increased; m, months; MCS, mental component summary score; Mul., multicenter; No pt., number of patients; No, number of; NR, not reported; NSAIDs; non-steroidal anti-inflammatory drugs; Obs. (prosp.), observational prospective follow-up; Outcome (time points), outcomes (out of the list of critical outcomes listed in online supplementary table S1) dealt with in the corresponding study and the time points at which the outcome was investigated in parentheses; PCS, physical component summary score; PICO, Population, Intervention, Comparator, Outcome (number of PICO question); PMR, polymyalgia rheumatica; R, randomised; RS3PE, remitting seronegative symmetrical synovitis with pitting oedema; SF-36, short form 36 questionnaire; stiff, stiffness; Study ID, study identifier; sympt. Dur., symptom duration; varT, variable time point/no exact date reported; w, weeks; y, years.

demonstrating that a longer duration of morning stiffness at baseline was linked with worse function and quality of life at 12 months.[4]

Presence versus absence of peripheral arthritis (PICO 17)

The prognostic value of peripheral arthritis was investigated by seven studies (n=645, LoB 2–6/8).[24 35 38 45 46 55 57] The presence of peripheral arthritis was associated with a higher risk of relapse according to one study (n=177, LoB 5/8),[55] whereas three studies (n=207, LoB 5–6/8) did not confirm this observation.[24 35 55]

Longer versus shorter symptom duration (PICO 18)

A single study (n=100, LoB 3/8) examined the prognostic impact of symptom duration before PMR diagnosis, reporting no association of this factor with later remission.[39]

Presence versus absence of conditions exaggerated by PMR and/or glucocorticoid therapy (PICO 19)

Two studies (n=273, LoB 2–4/8) investigated the prognostic impact of a total set of four concomitant conditions (depression, osteoporosis, diabetes and dyslipidaemia), reporting no significant results.[45 49]

Rapid versus delayed response to glucocorticoids (PICO 20)

A rapid response to GC therapy was dealt with by five studies (n=237, LoB 2–6/8).[4 18 38 50 59] A rapid decline of C-reactive protein was associated with a lower risk of GC side effects in a single low-quality study,[59] whereas treatment response was irrelevant for remission and relapse rates and for duration of GC therapy.[4 18 38 50 59]

DISCUSSION

One of our most intriguing observations is that fundamental treatment principles of PMR such as initial GC doses, tapering schedules and duration of treatment have not been examined by high-quality trials thus far. In contrast, we found moderate to good evidence that MTX is of benefit for patients with a new diagnosis of PMR.[10 15 27 29] Interestingly, it is clinical practice to prescribe MTX to patients with GC-resistant disease, although this approach is not supported by published evidence.[2 3] The clinical value of other conventional disease-modifying antirheumatic drugs for treatment of PMR is still unclear.

The MTX dose used in PMR trials was lower than the dose normally used in other rheumatic diseases (particularly rheumatoid arthritis);[60] and it is difficult to compare the relative efficacy of MTX between PMR and other conditions, because outcome parameters are disease specific, and disease course and concomitant treatments vary across diseases.[61] Whether higher MTX doses are more effective but still safe for treatment of PMR has to be clarified by future studies.[62]

For biological agents, evidence suggests that tumour necrosis factor α blocking agents are not effective in PMR, thus contrasting the promising results of earlier small case series.[63–66] Tocilizumab, used in a few cases thus far,[67 68] is currently being studied in a phase 2 trial (clinicaltrials.gov NCT01396317) and results of a study comparing secukinumab, canakinumab and GCs (clinicaltrials.gov NCT01364389) will be available soon.

The evidence supporting the value of prognostic factors is only fair to moderate because of methodological limitations of most studies and because the associations were not consistently reported by all authors. A single study, for example, showed a higher relapse rate in women than in men,[37] whereas eight other studies found no such association.[18 20 24 34 41 51 52 57] On the other hand, women appeared to have a longer duration of treatment,[14 32] higher cumulative GC doses[37] and more GC-related side effects.[31 36 37] Whether female patients benefit from a closer (than standard) clinical monitoring, a lower initial GC dose and a lower threshold for using MTX has to be clarified by future clinical studies.

We found one earlier systematic literature review on interventions in PMR reporting similar conclusions to our report for initial GC doses, IM methylprednisolone and the value of MTX.[69] That review, however, was limited by a less comprehensive literature search than carried out in our study (eg, Embase was not searched, non-English articles were excluded), by a lack of a priori formulated key questions and outcomes, as well as by the inclusion of studies analysing patients with GCA and PMR as a single group.[69] Additionally, the authors used the Jadad scale for quality appraisal, although this method has explicitly been discouraged for systematic literature reviews.[70 71]

In summary, moderate- to high-quality data support the use of IM GCs and MTX as GC sparing agents in PMR, whereas several treatment aspects such as initial GC doses and tapering regimen have not, or only inadequately, been investigated. Female sex, high ESR and the presence of peripheral arthritis were associated with a worse prognosis of PMR; however, a number of studies also failed to prove these associations.

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