High angiopoietin-2 levels associate with arterial inflammation and long-term glucocorticoid requirement in polymyalgia rheumatica

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High angiopoietin-2 levels associate with arterial inflammation and long-term glucocorticoid requirement in polymyalgia rheumatica

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Abstract

Objectives. PMR frequently co-occurs with GCA. So far, a simple biomarker for detecting concomitant arterial inflammation in PMR patients is lacking. Furthermore, biomarkers predicting disease course in PMR are awaited. We here investigated the diagnostic and prognostic value of acute-phase markers (ESR, CRP, IL-6, serum amyloid A) and angiogenesis markers (VEGF, soluble Tie2, angiopoietin-1, angiopoietin-2) in isolated PMR and PMR/GCA overlap patients.

Methods. We prospectively included 39 treatment-naïve PMR patients, of whom 10 patients also showed evidence of large vessel GCA by PET-CT. Age-matched healthy controls ($n = 32$) and infection controls ($n = 13$) were included for comparison. Serum marker levels were measured by an ELISA or Luminex assay. Receiver operating characteristic and Kaplan–Meier analyses were used to asses diagnostic and prognostic accuracy, respectively.

Results. All acute-phase and angiogenesis markers, except angiopoietin-1, were higher in isolated PMR patients than in healthy controls. Angiopoietin-2, ESR and soluble Tie-2 were significantly higher in patients with PMR/GCA overlap than in isolated PMR patients. Angiopoeietin-2, but not soluble Tie2, outperformed ESR and CRP in discriminating patients with and without overlapping GCA (area under the curve: 0.90; sensitivity: 100%; specificity: 76%). Moreover, high angiopoietin-2 levels were associated with long-term glucocorticoid requirement.

Conclusion. Assessment of angiopoietin-2 at baseline may assist diagnosis of concomitant vasculitis in PMR. Moreover, high levels of angiopoietin-2 were associated with an unfavourable disease course in isolated PMR patients. These findings imply that angiopoietin-2 is an interesting diagnostic and prognostic biomarker in PMR.

Key words: PMR, GCA, vasculitis, angiogenesis, biomarkers

Rheumatology key messages

- High serum angiopoietin-2 is a robust marker of concomitant arterial inflammation in PMR patients.
- High serum angiopoietin-2 predicts an unfavourable disease course in PMR patients without arterial inflammation.

Introduction

PMR is the most common inflammatory rheumatic disease in the elderly [1]. It is characterized by (peri-)articular inflammation, which is typically accompanied by a strong acute-phase response [1]. Symptoms of PMR include pain and morning stiffness of shoulders, proximal limbs, neck and hip girdle. The main treatment strategy of PMR is long-term glucocorticoids (GCs), which are associated with severe side effects such as diabetes and infections [2, 3].

A key question for every physician dealing with a PMR patient is whether or not the patient also has inflammation of medium and large arteries (i.e. GCA) [4, 5]. The frequency of GCA among PMR patients has been reported to range from 16% to 21% [1]. Arterial inflammation in PMR is likely underdiagnosed since symptoms of GCA can be non-specific [4, 6]. As GCA patients require higher daily GC dosages than PMR patients in order to prevent ischaemic complications such as vision loss, timely diagnosis of GCA is essential [6]. Diagnostic

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CLINICAL SCIENCE

workup for GCA includes imaging and/or a temporal artery biopsy (TAB). These techniques are costly and/or not readily available to every physician. To identify GCA in patients presenting with PMR, sensitive biomarkers reflecting arterial inflammation are needed.

In addition, better prognostic biomarkers at baseline are awaited in PMR. The best-studied biomarker in this regard is ESR, which was associated with a worse disease course (i.e. longer GC requirement) [7]. However, multiple studies have failed to confirm this finding [8, 9]. Another report indicated that an elevated plasma viscosity at baseline is associated with a lower probability of stopping GCs within 5 years [10].

Little is known about the pathogenesis of PMR. In the blood, PMR shows overlap with GCA, as both diseases are characterized by a strong IL-6-dependent acute-phase response as well as altered leucocyte subset counts and functionality [11–13]. Our prior work has shown that markers of angiogenesis, including VEGF, are elevated in serum of GCA patients [14]. Angiogenesis is considered an important process in amplifying arterial inflammation. Interestingly, PMR patients may also show elevated levels of VEGF [15, 16], whereas little is known about other angiogenesis markers in PMR.

We hypothesized that markers of angiogenesis may mirror arterial inflammation in PMR patients with concomitant GCA, and that their diagnostic accuracy for concomitant GCA outperforms the acute-phase response markers. In addition, we investigated the prognostic value of acute-phase markers and angiogenic markers in PMR. To that end we performed a comprehensive analysis of acute-phase markers (CRP, ESR, serum amyloid A (SAA)), IL-6 and angiogenic markers (VEGF, soluble Tie2 (sTie2), angiopoietin-1, angiopoietin-2) in our prospective cohort of treatment-naïve isolated PMR patients and PMR/GCA overlap patients.

Methods

Patient characteristics

Twenty-nine newly diagnosed and treatment-naïve (GCs or DMARDs) PMR patients participated in this study. Diagnosis of PMR was based on clinical signs and symptoms, acute-phase markers and imaging by ^{18}F-fluorodeoxyglucose PET-CT. Five isolated PMR patients did not fulfil the Chuang criteria [17] due to a low ESR. In these five cases, patients had elevated CRP (>10 mg/L) and/or were diagnosed based on imaging. In 26 isolated PMR patients no evidence of GCA was found, i.e. by TAB ($n = 6$), vascular ultrasound ($n = 8$) and/or PET-CT scan ($n = 24$, see Table 1). In the other three isolated PMR patients, no additional testing for GCA was performed due to lack of symptoms. In addition, we included 10 newly diagnosed, treatment-naïve PMR patients who all had a positive PET-CT for GCA. Thirty-three age- and sex-matched healthy controls and 13 age-matched infection controls were included. Volunteers in both control groups were excluded in cases of past and current morbidities and immunomodulatory drug use. Hospitalized infection controls all had either pneumonia or urinary tract infection. Patients and controls started participation (as a consecutive series) in our cohort between 2010 and 2018 and were all seen by a rheumatologist at the University Medical Centre Groningen (UMCG). Written informed consent was obtained from all study participants. All procedures were in compliance with the Declaration of Helsinki. The study was approved by the institutional review board of the UMCG (METc2010/222 and METc2012/375).

Treatment

PMR patients were initially treated with 15 mg prednisolone daily (median; range 15–30 mg), whereas PMR/GCA overlap patients started with 40–60 mg prednisolone daily. When remission was achieved, GCs were tapered in accordance with the British Society for Rheumatology guidelines [18, 19]. Tapering was done when clinical signs and symptoms of disease activity were absent, preferably with normalization of the CRP and ESR. In cases of relapse, GC dose was increased and/or a conventional synthetic DMARD was added. Relapse was defined as return of disease-specific clinical signs and symptoms. Upon remission, GCs were tapered until GC-free remission was achieved. GC-free remission was defined as an absence of signs and symptoms, no GC use and no return of active disease within at least 6 months of follow-up.

Serum marker measurements

Blood samples were drawn at the Rheumatology and Clinical Immunology outpatient clinic of the UMCG, and were stored at −20°C. CRP and ESR were measured in the context of standard medical care. Levels of serum IL-6 (standard curve range 4.8–1154; sensitivity 1.7 pg/ml), VEGF (0.55–2250; 2.1 pg/ml), sTie2 (614–149 166; 211 pg/ml), angiopoietin-1 (114–27 610; 9.43 pg/ml) and angiopoietin-2 (90.5–22 000; 17.1 pg/ml) were determined with the Human premix Magnetic Luminex screening assay kit (R&D Systems, Abingdon, UK) according to the manufacturer's instructions and read on a Luminex Magpix instrument (Luminex, Austin, TX, USA). Data analysis was performed with xPONENT 4.2 software (Luminex). Levels of SAA (standard curve range 1.7–219; detection level 1.6 ng/ml) were measured by in-house ELISA [20]. Clinical information was blinded to the performers of the measurements.

Statistics

Data were analysed by non-parametric testing. Differences in serum marker levels between study populations were tested by Kruskal–Wallis and Mann–Whitney *U* tests. Spearman's rank correlation coefficient was used to assess the strength of correlations between markers. To assess which marker independently associated with vasculitis in PMR patients, multiple regression analysis was performed. Receiver operating characteristic analysis with area under the curve (AUC) was used to evaluate the markers' discriminatory performance. To identify optimal cut-off points, the maximum of the sum of sensitivity and specificity was assessed, according to the Youden index. To compare time to GC-free remission, Kaplan–Meier

Table 1 Baseline characteristics of newly diagnosed, treatment-naïve patients with isolated PMR and PMR/GCA overlap

	Healthy controls	Isolated PMR	PMR/GCA overlap	Infection controls	*P*-value		
					Isolated PMR *vs* healthy controls	Isolated PMR *vs* PMR/GCA overlap	Isolated PMR *vs* infection controls
n	33	29	10	13	—	—	—
Age, mean (range), years	68 (50–83)	72 (54–84)	70 (56–81)	73 (47–97)	NS	NS	NS
Females, *n* (%)	22 (67)	18 (62)	8 (80)	4 (31)	NS	NS	NS
PET-CT positive for PMR, *n* (%)	NA	24 (83)	10 (100)	NA	—	—	—
PET-CT for GCA, positive/negative/not done, *n*	NA	0/24/5	10/0/0	NA	—	—	—
TAB, positive/negative/not done, *n*	NA	0/6/23	1/6/3	NA	—	—	—
Ultrasound for GCA, positive/negative/not done, *n*	NA	0/8/21	2/4/4	NA	—	—	—
Follow-up time, median (range), months	NA	46 (0–76)	34 (3–69)	NA	—	—	—
Symptoms at baseline, *n* (%)							
New headache	NA	5 (17)[a]	4 (40)	NA	—	NS	—
Jaw claudication	NA	3 (10)[a]	2 (20)	NA	—	NS	—
Temporal artery abnormal	NA	1 (3)[a]	0 (0)	NA	—	NS	—
Amaurosis fugax	NA	0 (0)	3 (30)	NA	—	0.013	—
Vision loss	NA	0 (0)	1 (10)	NA	—	NS	—
Fever (>38°C)	NA	6 (21)	3 (30)	NA	—	NS	—
Weight loss (>2 kg)	NA	15 (51)	10 (100)	NA	—	0.007	—
Malaise	NA	26 (90)	7 (70)	NA	—	NS	—
Night sweats	NA	11 (38)	5 (50)	NA	—	NS	—
Biomarker levels, median (range)							
CRP, mg/l	**3** (0.2–7)	**42** (3.2–186)	**50** (25–215)	**71** (10–339)	<0.0001	NS	NS
ESR, mm/h	**8** (1–30)	**57** (8–109)	**94** (43–117)	NA	<0.0001	0.014	—
SAA, μg/ml	**2.1** (0.9–14)	**74** (3.1–515)	**102** (1.0–540)	**120** (9.0–395)	<0.0001	NS	NS
IL-6, pg/ml	**1.5** (0.6–4.1)	**19.8** (2.0–117)	**15.1** (2.0–233)	**22.1** (0.9–152)	<0.0001	NS	NS
VEGF, pg/ml	**75** (24–606)	**190** (47–536)	**100** (14–548)	**161** (35–345)	0.0001	NS	NS
sTie-2, ng/ml	**9.88** (3.87–14.4)	**12.1** (2.94–30.8)	**18.4** (4.31–32.6)	**12.6** (8.50–23.1)	0.016	0.026	NS
Angiopoietin-1, ng/ml	**48** (3.5–111)	**48** (29–87)	**52** (4–88)	**64** (39–96)	NS	NS	NS
Angiopoietin-2, pg/ml	**952** (288–6411)	**1848** (535–8350)	**5222** (3220–16 622)	**4417** (775–14 404)	<0.0001	<0.0001	0.018
Angpt-2/angpt-1 ratio	**0.017** (0.005–0.52)	**0.038** (0.010–0.29)	**0.13** (0.054–0.89)	**0.055** (0.015–0.24)	0.0025	0.0002	NS

Differences in sex and symptoms at baseline between the groups were tested by the Fisher's exact test. Differences in age and biomarker levels were tested with the Mann–Whitney *U* test. The bold values represent the median. [a]All isolated PMR patients with cranial symptoms suggestive of GCA were PET-CT negative for GCA and had either a negative ultrasound or negative biopsy. NA: not applicable; NS: non-significant; SAA: serum-amyloid A; sTie2: soluble Tie2.

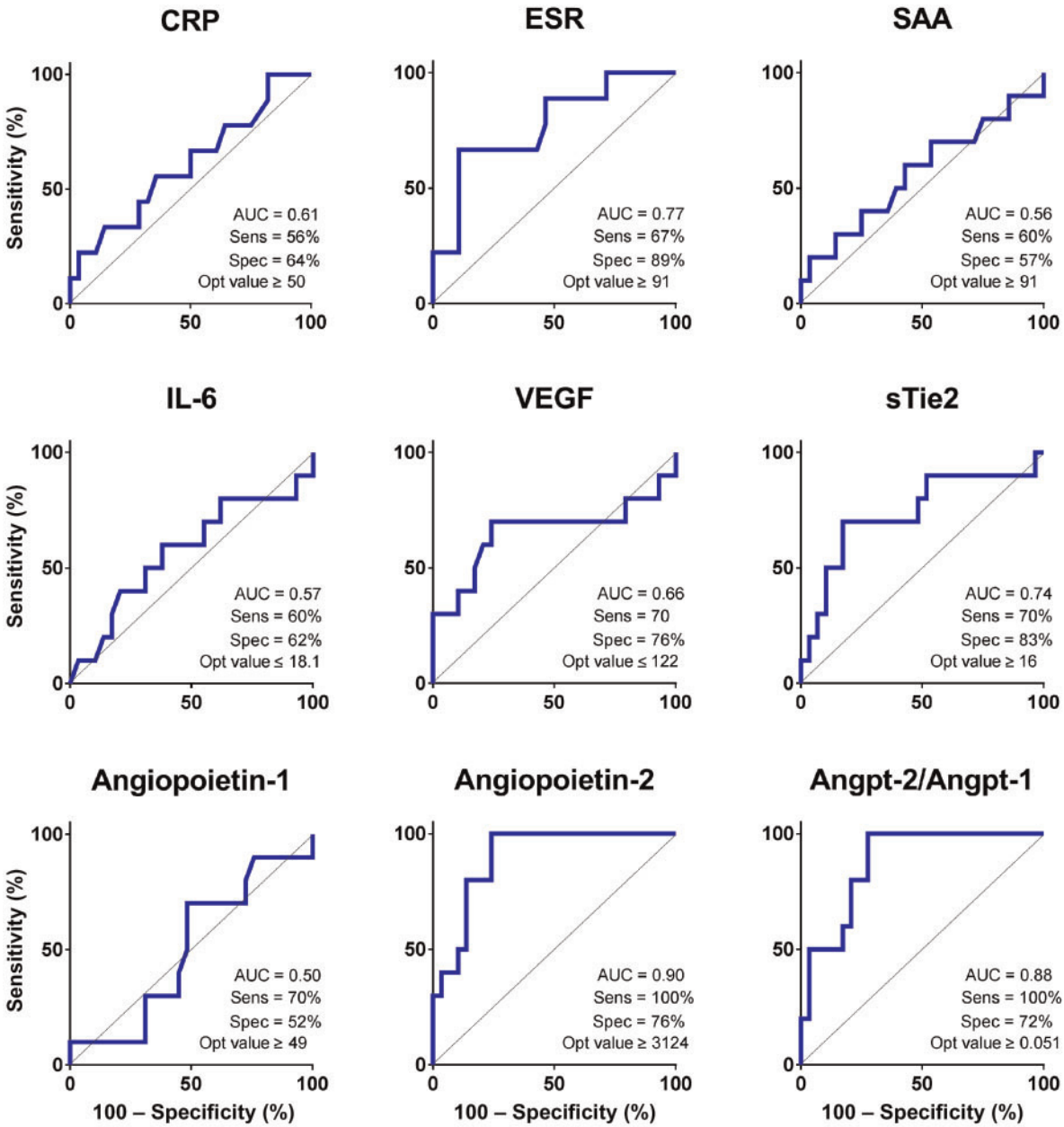
analysis and log rank tests were used. Analyses were performed with IBM SPSS Statistics 23 (IBM corp., Armonk, NY, USA) and Prism 7.02 (GraphPad Software, Inc., La Jolla, CA, USA) software.

Results

Baseline characteristics of patient groups

Baseline characteristics of patients with isolated PMR, PMR/GCA overlap patients, healthy controls and infection controls are displayed in Table 1. Age and sex were not significantly different between isolated PMR patients and the other groups. At baseline, significantly more amaurosis fugax (P = 0.013) and weight loss (P = 0.007) was found in PMR/GCA overlap patients compared with isolated PMR patients. Isolated PMR and PMR/GCA overlap patients were followed for a median of 46 (range 0–76) and 34 (range 3–69) months, respectively. Two patients with isolated PMR developed GCA later in the disease course.

Fig. 1 High angiopoietin-2 levels discriminate between PMR/GCA overlap patients and isolated PMR patients



ROC curves reflect the ability of each acute-phase marker and angiogenesis marker to detect arterial inflammation in PMR patients. The optimal sensitivity, specificity and cut-off value are identified according to the Youden index. AUC, sensitivity, specificity and optimal cut-off value for each marker are depicted on the graphs. AUC: area under the curve; opt: optimal; ROC: receiver operating characteristic; SAA: serum-amyloid A; sens: sensitivity; spec: specificity; sTie2: soluble Tie2.

Elevated serum markers in newly diagnosed, treatment-naïve PMR patients

The ESR and levels of CRP, SAA, IL-6, VEGF, sTie2 and angiopoietin-2 were significantly higher in isolated PMR patients than in healthy controls (Table 1). Similar levels of these markers were found in infection controls, except for angiopoietin-2, which was significantly lower in isolated PMR (P = 0.018). Angiopoietin-2 correlated moderately with the ESR in PMR patients (rho = 0.49, $P < 0.01$), but negatively with VEGF levels (rho = −0.37, $P < 0.05$; Supplementary Fig. S1, available at Rheumatology online). Serum IL-6 levels correlated strongly with CRP and SAA, but not with the ESR.

Table 2 Baseline biomarker levels of patients in GC-free remission or on GC treatment at 24 months

Baseline biomarker	GC-free remission	On GC treatment	Cut-off value	AUC	*P*-value
CRP, mg/l	48	49	>49	0.54	0.81
ESR, mm/h	50	63	>74	0.63	0.35
SAA, μg/ml	97	120	>108	0.60	0.50
IL-6, pg/ml	21	31	>29	0.62	0.40
VEGF, pg/ml	231	141	<149	0.69	0.18
sTie2, ng/ml	12	14	>19	0.69	0.18
Angiopoietin-1, ng/ml	55	48	>71	0.53	0.84
Angiopoietin-2, pg/ml	1177	2637	>2134	**0.87**	**0.0045**
Angpt-2/angpt-1 ratio	0.029	0.048	>0.038	**0.83**	**0.013**

At 24 months after start of treatment ($n = 19$), 10 isolated PMR patients had achieved GC-free remission and nine PMR-only patients were still on GC treatment. Data are the median biomarker values at baseline (before start of treatment) in patients that were in GC-free remission ($n = 10$) and in patients that were still on GC-treatment at 24 months after start of treatment ($n = 9$). Optimal cut-off values of the ROC curves are calculated according to the Youden index. AUC values >0.8 and *P*-values < 0.05 are indicated in bold. AUC: area under curve; GC: glucocorticoids; ROC: receiver operating characteristic; SAA: serum-amyloid A; sTie2: soluble Tie2.

Angiopoietin-2 outperforms CRP and ESR in identifying patients with PMR/GCA overlap

The ESR and serum levels of angiopoietin-2 and sTie2 were lower in isolated PMR patients than in patients with PMR/GCA overlap (Table 1). Multiple logistic regression confirmed that angiopoietin-2, but not ESR and sTie2, was an independent predictor for presence of overlapping GCA in PMR patients (Supplementary Table S1, available at Rheumatology online).

Next, we further assessed the diagnostic accuracy of these markers for concomitant vasculitis in PMR. Receiver operating characteristic analyses (Fig. 1) showed poor discrimination (AUC < 0.80) between isolated PMR and PMR/GCA overlap patients for the acute-phase markers and for VEGF, angiopoietin-1 and sTie2. In contrast, angiopoietin-2 discriminated well between these patient groups, as evidenced by an AUC of 0.90, sensitivity of 100% and specificity of 76%. The angiopoietin-2/angiopoietin-1 ratio also discriminated well but did not further improve accuracy (AUC 0.88).

High baseline angiopoietin-2 predicts an unfavourable disease course in PMR patients

We determined time to GC-free remission in isolated PMR patients as a reflection of a favourable or unfavourable disease course. First, we determined optimal prognostic cut-off values for each marker based on the number of patients in GC-free remission at 24 months after start of treatment (Table 2). Baseline angiopoietin-2 levels ($P = 0.0045$) and angiopoietin-2/angiopoietin-1 ratio ($P = 0.013$) were higher in patients who were still on GC treatment at 24 months than in patients in GC-free remission at that time point. Next, we used the optimal cut-off values to assess differences in a Kaplan–Meier graph throughout the whole disease course (Fig. 2). High baseline levels of angiopoietin-2 ($P = 0.0010$), ESR ($P = 0.041$) and SAA ($P = 0.041$), or low levels of VEGF ($P = 0.031$) significantly predicted a long-term GC requirement. The angiopoietin-2/angiopoietin-1 ratio performed even better than angiopoietin-2 levels alone: $P < 0.0001$.

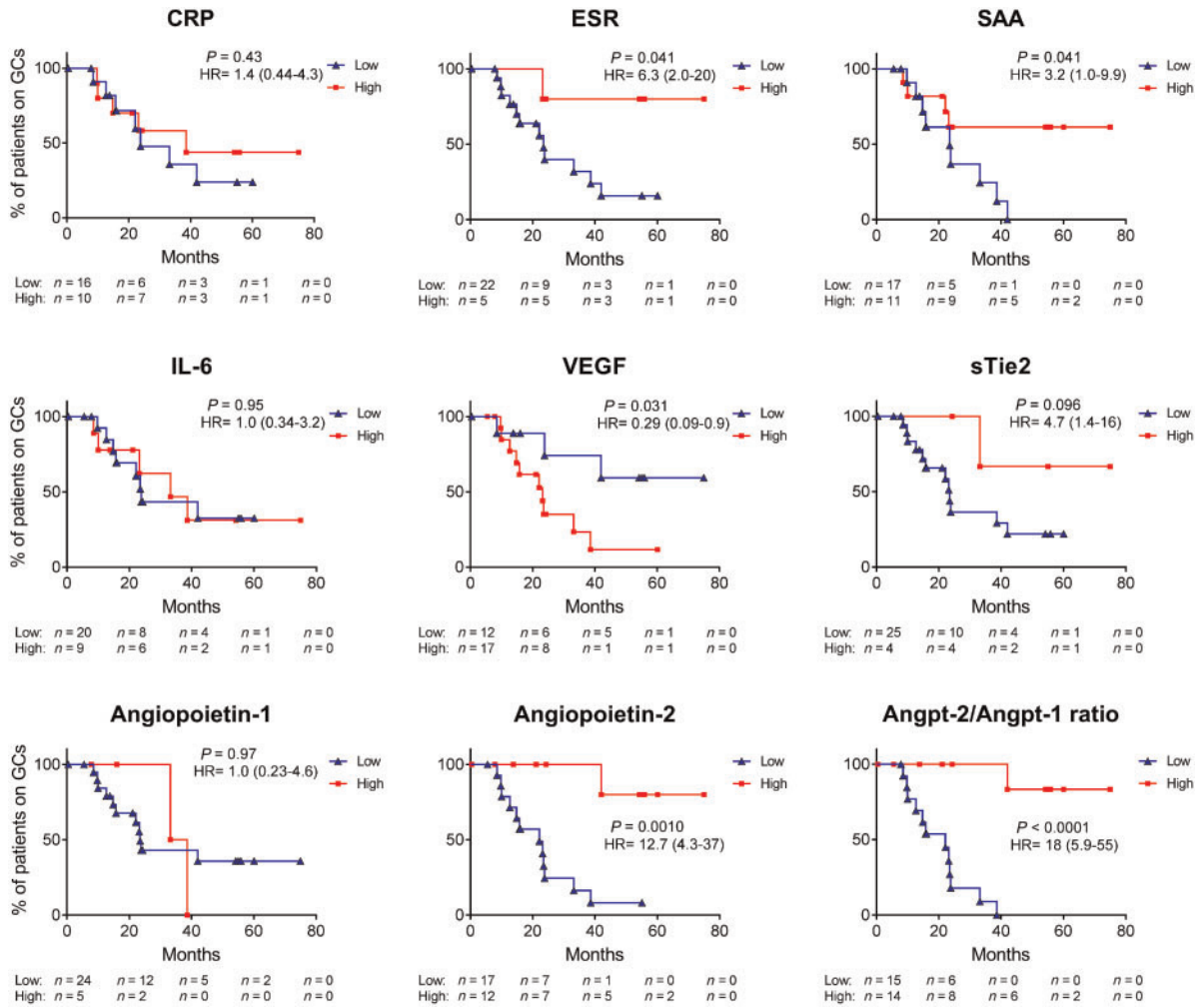
We then compared time to GC-free remission in patients with isolated PMR and patients with PMR/GCA overlap (Supplementary Fig. S2, available at Rheumatology online). Patients with isolated PMR that had high angiopoietin-2 levels at baseline and PMR/GCA overlap patients had a comparable disease course as assessed by the time to GC-free remission. In contrast, angiopoietin-2^{low} patients with isolated PMR had a shorter time to GC-free remission than patients with PMR/GCA overlap ($P = 0.017$).

Discussion

Estimating the probability of concomitant vasculitis in PMR patients is challenging [4, 6]. In addition, good prognostic markers are lacking [7]. Here we show that angiopoietin-2, a marker of angiogenesis relevant to vascular inflammation, helps to identify PMR patients with concomitant GCA. Furthermore, high levels of angiopoietin-2 at diagnosis identified PMR patients with an unfavourable long-term disease course. In Fig. 3 we propose the possible utility of angiopoietin-2 as a diagnostic and prognostic biomarker in a flow chart. In both instances, angiopoietin-2 clearly outperformed classical biomarkers CRP and ESR. To the best of our knowledge, this is the first study investigating angiogenesis markers angiopoietin-1, angiopoietin-2 and sTie2 in PMR patients.

This study has identified angiopoietin-2 as the most robust marker of arterial inflammation in PMR patients. In the majority of our PMR patients, concomitant vasculitis could be excluded based on low levels of angiopoietin-2. The pro-angiogenic sTie2 also distinguished isolated PMR patients from PMR/GCA overlap patients, albeit with lesser accuracy. Previously, the ESR was found to be higher in patients with PMR/GCA overlap compared with isolated PMR [21]. This was confirmed in our study,

Fig. 2 Long-term GC requirement is best predicted by baseline angiopoietin-2/angiopoietin-1 ratio



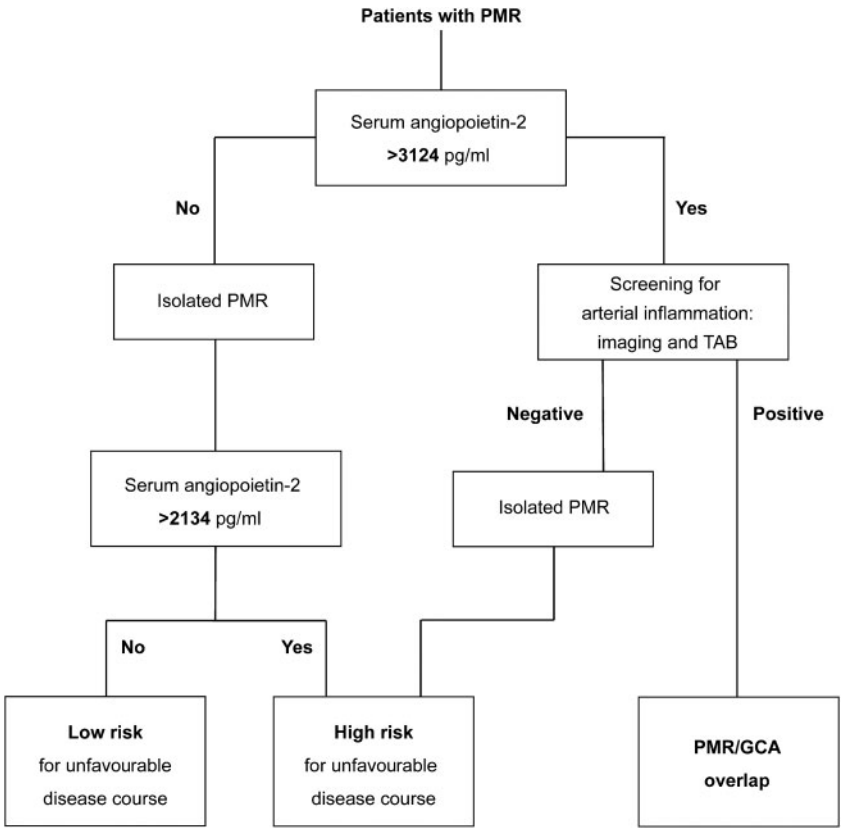
Baseline biomarker levels (or ratio) of PMR patients were split into low or high levels (based on the optimal cut-off value at 24 months after start of treatment) and were plotted in a Kaplan–Meier curve against time to GC-free remission. *P*-value and HR (including 95% CI) of the log-rank test are depicted in the graphs. GC: glucocorticoid; HR: hazard ratio; SAA: serum-amyloid A; sTie2: soluble Tie2.

whereas CRP is not different between the two disease populations. One clinical study indicated that new headache, followed by age and abnormal TAB were the best predictors of arterial inflammation in PMR patients [22]. In accordance with this study, we observed that only overlapping patients have amaurosis fugax. Moreover, we observed that all PMR/GCA overlap patients suffered from weight loss, while this symptom was noted in only half of the isolated PMR patients.

Besides aiding detection of overlapping GCA, baseline angiopoietin-2 levels may also have prognostic utility. The time to GC-free remission was significantly longer in patients with high baseline levels of angiopoietin-2. The angiopoietin-2/angiopoietin-1 ratio, commonly used to indicate a pro-angiogenic shift [23], performed even better than angiopoietin-2 levels alone. Difficult-to-treat patients require long-term GC treatment as tapering of GCs leads to return of signs and symptoms in these patients. Long-term GC requirement is detrimental for these patients, as this is associated with serious side effects such as diabetes and infections [2]. Therefore, patients with high baseline angiopoietin-2 levels could possibly benefit from starting with a GC-sparing DMARD upon diagnosis. In a prior study, PMR patients with a typical 'extracapsular' pattern of inflammation on a MRI scan were more likely to require GC treatment for >1 year [24]. Possibly, this subset of patients overlaps with our angpiopoietin-2^{high} subset of isolated PMR patients.

The high levels of angiopoietin-2 in both patients with PMR/GCA overlap and patients with isolated PMR requiring long-term GCs could suggest the presence of vasculitis in these angiopoietin-2^{high} PMR patients. Presence of

FIG. 3 Proposed flow chart to assess the risk for concomitant GCA or unfavourable disease course in PMR patients



This flow chart represents a proposed algorithm based on observations within our cohort. In our cohort, treatment-naïve patients presenting with PMR are at risk for overlapping GCA if serum angiopoietin-2 levels are higher than 3124 pg/ml. In absence of vasculitis, patient with serum angiopoietin levels higher than 2134 pg/ml have a high risk for an unfavourable disease course (i.e. long-term GC requirement). GC: glucocorticoid.

inflammation of large systemic arteries was precluded by ^{18}F-fluorodeoxyglucose-PET/CT in all patients with isolated PMR and high angiopoietin-2 levels. In cases of cranial symptoms, concomitant inflammation of cranial arteries was further excluded by ultrasound and/or TAB. Moreover, we observed no changes in the clinical diagnosis during the first 6 months after diagnosis. Hence, we are confident that occult vasculitis did not substantially affect our findings regarding patients with isolated PMR and high angiopoietin-2 levels. Indeed, three isolated PMR patients with low angiopoietin-2 levels had no further examination by imaging or TAB. However, the presence of concomitant vasculitis in these patients would have ameliorated rather than augmented the prognostic differences that we observed between patients with low and high angiopoeitin-2 levels. Thus, although we cannot fully exclude the possibility of undetected vasculitis in some of our isolated PMR patients, it is unlikely that such misclassification heavily influenced our findings.

Interestingly, we observed that high VEGF levels at baseline were protective against long-term GC requirement. This was also observed in GCA patients, and may thus suggest a similar protective mechanism in PMR [14]. More studies are needed to elucidate why one pro-angiogenic marker (VEGF) appears to be protective against long-term GC requirement whilst another pro-angiogenic marker (angiopoietin-2) shows the opposite effect. Moreover, we observed a moderate negative correlation between angiopoietin-2 and VEGF levels at baseline. Also high SAA and ESR levels at baseline predicted a long-term GC requirement, although statistical significance levels and hazard ratios were less convincing for these markers.

Overall, serum levels of angiopoietin-2, sTie-2 and VEGF were elevated in PMR patients when compared with healthy controls. Indeed, earlier studies also reported higher VEGF serum levels in PMR patients [15, 16]. Angiopoietin-2 instigates angiogenesis by competing with the homeostatic angiopoietin-1 for signalling by Tie2 [25]. During hypoxia and inflammation, angiopoietin-2 is released from Weibel–Palade bodies, aiding the loss of vessel integrity that leads to small vessel sprouting if VEGF is present. VEGF has been documented in synovia of PMR patients [16] but angiopoietin-2 expression has

not been assessed in PMR tissues so far. Importantly, elevated angiogenic signalling is not specific for GCA and PMR, as our infection controls show higher levels of angiogenesis markers as well. Thus, to properly interpret the diagnostic and prognostic value of these markers, the presence of infections needs to be excluded in PMR patients.

This serum marker study has strengths and limitations. It was performed in our cohort of prospectively enrolled treatment-naïve GCA and PMR patients. Patients in this cohort have gone through an intense diagnostic work-up, which provided a confident diagnosis. Specifically, overlapping vasculitis was excluded in PMR patients by a combination of clinical signs and symptoms, imaging and biopsies. Importantly, this diagnosis did not change for at least 6 months during follow-up. Another strength is the longstanding protocolized follow-up, which allowed us to determine the time to GC-free remission in most patients. Limitations are the limited number of patients that are included in the PMR/GCA overlap group. This is because only a subset of PMR patients have concomitant GCA [1]. Therefore, validation of our findings in a prognostic study is necessary before implementing these biomarkers in daily clinical practice.

In conclusion, this study provides evidence for the use of angiopoietin-2 as a diagnostic marker for concomitant vasculitis in PMR patients. When confirmed, PMR patients presenting with high angiopoietin-2 levels should be more intensively screened for the presence of arteritis. In addition, assessment of baseline angiopoietin-2 levels may help to identify a subset of PMR patients that would qualify for intensive treatment and disease-monitoring.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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