Review

Laboratory investigations useful in giant cell arteritis and Takayasu's arteritis

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ABSTRACT

A raised erythrocyte sedimentation rate (ESR) is considered a hallmark for the diagnosis of giant cell arteritis (GCA). The American College of Rheumatology 1990 criteria for GCA include ESR greater than or equal to 50 mm/h as one of the five criteria. Although the presence of a normal ESR made GCA less likely, the results of a population-based study showed that the occurrence of a low /normal value in GCA at diagnosis is not rare. Pre-treatment ESR may be a prognostic indicator for duration of treatment. C-reactive protein (CRP) and interleukin-6 (IL-6) may be more sensitive indicators of disease activity than ESR in GCApatients. However, it is unclear whether the use in clinical practice of CRP and IL-6 has some apparent advantage over ESR.

ESR is the most often used tool to assess disease activity in Takayasu's arteritis (TA). However, some studies have found that ESR and CRPare not able to differentiate patients with clinically active and inactive TA. Furthermore, histopathological studies have shown that over 40% of patients thought to be in clinical remission with normal acute phase reactants have active arteritis. IL-6 could be a promising marker of disease activity in TA; however, further studies are required to confirm its usefulness in clinical practice.

Other laboratory investigations could be useful in the diagnosis or follow-up of GCA and TA, but more studies are required.

Giant cell arteritis

Erythrocyte sedimentation rate

A highly elevated erythrocyte sedimentation rate (ESR) is considered a hallmark for the diagnosis of giant cell arteritis (GCA) (1). The American College of Rheumatology (ACR) 1990 criteria for GCAinclude ESR greater than or equal to 50 mm/h as one of the five criteria (2). Table I shows the upper limit of normal for ESR in men and women. ESR is higher in women than in men and higher in older persons. Although the choice of an upper limit of normal is arbitrary, 20 and 30 mm/h may be considered the upper limit of normal for males and females over the age of 50, respectively (3).

Smetana *et al.* have evaluated the accuracy of the ESR for the diagnosis of GCA (4). They reviewed 21 studies with the purpose of determining the value of clinical features and ESR in predicting the likelihood of a positive temporal artery biopsy among patients with a clinical suspicion of GCA. The most useful finding was a normal ESR, which made GCAmuch less likely (LR 0.2, 95% CI: 0.08 – 0.51).

However, GCAmay be present despite a normal ESR. Several reports have described cases with a low ESR level at the time of diagnosis (5-14). The frequency , however, has varied in different reports and ranged from 0 to 22.5% (Table II). Factors that may explain these variations include case selection, previous glucocorticoid treatment, and differences in the cut-off value of ESR considered discriminant for an elevation of the ESR.

Table I. Upper limit of normal ESR in men and women*.

	Upper limit of normal (mm/h)
Age < 50 years	
Male	15
Female	20
Age > 50 years	
Male	20
Female	30

*Bottiger and Svedberg, *Br Med J* 1967 (3).

Table II. Frequency of a normal ESR at diagnosis in different clinical series of patients with GCA.

Authors (reference)	Study design	No. of patients	% with normal ESR	ESR cut-off value (mm/h)
Huston *et al*. (5)	Retrospective, population-based study	42	0%	Not defined
Ellis & Ralston (6)	Retrospective	80	22.5%	≤ 30
Kyle *et al*. (7)	Prospective	74	0%	≤ 30
Olsson *et al*. (11)	Prospective	49	4.1%	≤ 30
Branum *et al*. (8)	Retrospective	62	3.2%	< 40
Jundt & Mock (9)	Retrospective	46	15%	< 40
Wise *et al*. (10)	Retrospective	30	16.6%	< 50
Martínez-Taboada *et al*. (12)	Retrospective	248	4.0%	< 50
von Blotzeim & Borruat (13)	Retrospective	47	15%	< 50
Salvarani *et al*. (14)	Retrospective, population-based	128	2.3% 3.9% 7.8%	≤ 30 < 40 < 50

The results of a population-based study showed that the occurrence of a low or normal value of ESR in GCA at diagnosis is not rare (14). Using the level of ≤ 30 mm/h as a cutoff, 3.6% fit this category. 5.4% of the patients had values < 40 mm/h and 10.8% <50 mm/h (the cutoff for the 1990 ACR criteria for GCA).

In some of the patients with low ESR levels, the low acute phase response seemed to be related to a intrinsic decreased ability to respond to a phlogistic stimulus. These patients had a number of ESR determinations in their lives that were always lower than 40 mm/h, even during inflammatory events different from GCA. In these patients a genetically determined inhibition in the initiation of the cellular and cytokine cascades involved in the process of acute phase response may be hypothesized (15). In this population-based study systemic symptoms/signs were more frequent in patients with high ESR compared to those with low ESR, while visual symptoms, in particular blindness, were similarly distributed.

In a study from Spain the presence of a strong acute-phase response (fever and weight loss, ESR ≥ 85 mm/h, Hb < 11 gm/dl) at diagnosis defined a subgroup of patients at very low risk of developing cranial ischemic events (in particular visual loss) (16). However, the results of other studies were conflicting. Liozon *et al*. reported a correlation between cranial ischemic complications and both lower mean ESR and higher mean hemoglobin levels, but no correlation with fever or weight loss (17). Gonzàlez-Gay *et al*. showed an association between the absence of fever and weight loss and permanent visual loss, but no correlation with anemia or the mean ESR (18). Nesher *et al*. did not identify a correlation between cranial ischemic complications and either of these parameters (19). Therefore, the clinical usefulness of this observation, although of pathophysiologic relevance, must be accurately tested.

Hernandez-Rodriguez *et al*. reported that GCA patients with a strong initial systemic inflammatory reaction (defined by the presence of at least 3 of these 4 parameters: fever and weight loss, ESR ≥ 85 mm/h, Hb < 11 gm/dl) have higher and more prolonged corticosteroid requirements and experience more disease flares during corticosteroid therapy than patients with a weak systemic acute phase response (20). Some studies have suggested that pre-treatment ESR is a prognostic indicator for the duration of treatment in polymyalgia rheumatica (PMR)/GCA patients (21-23); however, other studies did not confirm this observation (24). Furthermore, PMR/GCApatients with a low or normal ESR at diagnosis do not seem to have a different disease course with respect to the corticosteroid dosage and duration, and the percentage of relapse/ recurrence (12, 25-27). Therefore, the prognostic role of pre-treatment ESR value remains to be defined.

Table III. Advantages and disadvantages of ESR and CRPdeterminations*.

ESR	CRP
Advantages - Inexpensive - Much clinical information available	Advantages - Rapid response to inflammatory stimulus - Reflects value of a single acute-phase protein - Unaffected by age and gender - Quantitation is precise and reproducible
Disadvantages - Affected by age and gender, red blood cell morphology, anemia and polycythemia - Reflects levels of many plasma proteins - Responds slowly to inflammatory stimulus	Disadvantages - Less clinical information available - Relatively more expensive

*Sox and Liang, *Ann Intern Med* 1986 (28); Gabay &Kushner, *N Engl J Med* 1999 (29)

C-reactive protein and interleukin-6

In Table III are listed the advantages and disadvantages of ESR and C-reactive protein (CRP) determination (28, 29). ESR has many disadvantages: it is influenced by age and gender, red blood cell morphology, anemia and polycythemia; it reflects levels of many plasma proteins; and it responds slowly to inflammatory stimulus. CRP has many advantages: it shows a rapid response to inflammatory stimulus; it reflects value of a single acute-phase protein; it is unaffected by age and gender; and its quantitation is precise and

reproducible. Therefore, CRP determination may be preferred in many instances over the traditional strategy of measuring the ESR rate in GCA patients.

CRP was elevated in 10 of 11 patients with biopsy-proven GCA before treatment (30). A positive correlation with ESR was found; however, CRP was a more sensitive indicator of disease activity than ESR during corticosteroid therapy. Hayreh *et al*. ascertained the sensitivity and specificity of signs/ symptoms and ESR and CRP for the early diagnosis of GCA (31). They found that CRP was more sensitive (100%) than ESR (92%) for the early diagnosis of GCA; ESR combined with CRPgave the best specificity (97%).

However, Kyle *et al*. and Park *et al*. (7, 32) showed that ESR correlated better than CRPwith disease activity in PMR/ GCA patients, both at presentation and during relapses. In a recent study CRP was a more sensitive indicator of current disease activity than the ESR in PMR/GCA patients (25). However, ESR at diagnosis was a superior predictor of relapse than CRP.

IL-6 appears to be a potentially useful biologic marker of disease activity in GCA. IL-6 is the chief stimulator of the production of most acute-phase proteins. IL-6 is one of the cytokines released in GCA vascular lesions and its concentrations are highly elevated in untreated GCApatients (33-35). Serum levels rapidly respond to immunosuppression with corticosteroid and closely correlate with the clinical manifestations of GCA (34-36). IL-6 may also have a protective role by inducing angiogenesis in the development of ischemic events in GCA(37).

Some studies have shown that plasma IL-6 is more sensitive than ESR for indicating disease activity in treated and untreated GCA patients (36). ESR was elevated in 76% of untreated GCA patients, as was the plasma IL-6 level in 92%. ESR was elevated in 58% of disease flares, as were the plasma IL-6 levels in 89%. Furthermore, plasma IL-6 levels may also have a prognostic value; elevated levels of IL-6 after one month of treatment characterized PMR patients who required a higher initial corticosteroid dose and corticosteroids for a longer period of time (23).

In conclusion, CRP and IL-6 levels appear to be sensitive indicators of disease activity in GCA. However, whether the determination in clinical practice of these two markers of inflammation has some apparent advantage over ESR is unclear at the moment. Future studies will clarify if these markers of inflammation can substitute ESR and can be routinely used to monitor disease activity and to gauge the rate of reduction in the corticosteroid dose.

Other laboratory investigations

Other laboratory investigations have been found to be abnormal in GCA patients. Abnormal liver function tests, in particular elevation of serum alkaline phosphatase, are present in approximately one third to half of patients (38). The elevation is usually modest and returns to normal after treatment.

Serum levels of von Willebrand factor (vWF), a marker of endothelial dysfunction, have been found to be elevated in patients with GCA (39). Unlike the acute phase proteins, levels of vWF do not rapidly decrease with corticosteroid therapy, therefore they are not useful in monitoring disease activity.

Elevated levels of antiphospholipid antibodies are frequently present in PMR/GCA(40). They are not related to ischemic events.

In a preliminary study, serum amyloid A concentrations seem to be more sensitive than CRP in determining disease activity and more specific than ESR in the determination of inactive disease (41). However these results must be confirmed.

Some studies reported a reduced percentage or number of circulating CD8+ cells in patients with active PMR/GCA, however these findings were not confirmed by other studies (42,43).

Plasma viscosity may offer advantages over ESR in diagnosing and monitoring GCA, however only 31 patients were investigated (44).

In patients suspected of having GCA a marked thrombocytosis seems to be a useful but perhaps less specific marker of a positive temporal artery biopsy (45).

Circulating cytokines and related molecules (sICAM-1, sIL-2 receptors, MCP-1, endothelin-1) have been found to be increased in untreated patients with PMR/GCA (46-49). However, these laboratory investigations do not have any proven clinical usefulness.

In conclusion, most patients with GCA can be followed by either the ESR or CRP, keeping in mind that the CRP is somewhat more sensitive and reliable as a laboratory test. IL-6 is perhaps the most sensitive test, but may not be available as a routine laboratory test in most clinics.

Takayasu's arteritis

Erythrocyte sedimentation rate

Acute phase reactants are a less reliable indicator of the state of vascular inflammation in Takayasu's arteritis (TA). The "gold standard" for determining the presence of active vasculitis in TA is the histopathological evaluation of involved vessels, whose specimens are usually obtained during vascular surgery. Histopathological studies have found that over ≈ 40% of patients thought to be in clinical remission with normal acute phase reactants at the time of vascular surgery procedures have active arteritis in the vessels operated on (50, 51).

Studies designed to answer the question whether there is an acceptable serological marker of TA disease activity did not include vessel histopathology as a standard for the presence of active disease. Therefore, the absence of an acceptable standard for differentiating active and inactive disease is the main limitation of all these studies.

ESR is the tool most often used to assess disease activity in TA. In the Mayo Clinic series ESR was elevated in 78% of patients and a reduction in ESR values followed the start of corticosteroid therapy, paralleling the improvement of systemic features (52). In a recent series of 104 Italian patients with TA, about 80% of patients had elevated ESR at diagnosis. In this study a multivariate analysis showed that an ESR at onset ≤ 30 mm/h was associated to a higher probability of a delay in diagnosis ≥ 2 years (53). In the series of patients studied at National Institute of

Health (NIH) ESR was an unreliable marker of disease activity (50). ESR was elevated in 72% of patients with active disease and in 56% of patients in remission.

In a series of Japanese patients with TA ESR, the presence of complications and the pattern of the past clinical course were the best predictors of long-term outcome (54).

Differently from the GCA criteria, an elevated ESR was not included in the 1990 ACR criteria for TA(55).

C-reactive protein and interleukin-6

In one study CRP values, similarly to ESR, were not able to differentiate patients with clinically active and inactive TA (56). Furthermore, significant differences in CRP values were not observed between TA patients and healthy controls. The conclusions of this study were that CRP and ESR are not a reliable guide to disease activity in TA. However, this study included only 7 patients with active disease.

Seko *et al*. evaluated the expression of cytokine genes in aortic tissue from 4 patients with TA and found strong expression for IL-6 in all patients (57). These authors suggested that this cytokine is locally produced at the site of inflammation in TA. An Italian study has evaluated IL-6 serum levels in TA with active and inactive disease (58). Furthermore, some of the patients with active disease underwent long-term follow-up to evaluate the possible role of IL-6 in the longitudinal monitoring of disease activity. All patients with active disease had higher serum levels of IL-6 than healthy controls, while patients in remission had values comparable to the healthy controls. In the 4 patients with active TA who went in remission, the improvement in clinical signs/symptoms was associated with a marked reduction in serum IL-6 compared with the values recorded during active disease. Moreover, a positive correlation was found between IL-6 levels and the disease activity score, while the correlation between CRPlevels and disease activity score was not significant. Therefore, the authors concluded that monitoring IL-6 in serum may help the clinicians to find adequate treatment adjustments in individual patients and that IL-6 may offer a more precise index of disease activity than CRP. However, a larger sample size and additional studies are required to confirm these promising results.

In conclusion, although IL-6 seems to be a promising marker of disease activity in TA, further studies are needed to establish its usefulness in clinical practice.

Other laboratory investigations

RANTES serum levels were higher in patients with active TA than in healthy controls, they tended to normalize in remission, but values remained higher than those of healthy controls (58). Like IL-6, a positive correlation was also found between RANTES serum levels and disease activity score. However, further studies must be performed to confirm if the determination of serum RANTES levels is a sensitive measure of disease activity in TA. IL-1β serum levels were below the detection of ELISA in all patients with TA and in healthy controls as well (58).

In a study multiple serological tests (including tissue factor, vWF, thrombomodulin, tissue plasminogen activator, ICAM-1, VCAM-1, E-selectin and PECAM-1) were performed in patients with active and inactive TA (56). No test was reliably able to distinguish between healthy control and patients with active TA.

Another study confirmed that ICAM-1 plasma levels are not increased in the serum of patients with TA, but VCAM-1 levels were significantly higher in TA compared with controls (59). However, the patients with TA were not differentiated according to disease activity state.

Akazawa *et al*. studied plasma levels of molecular markers for platelet activity (platelet factor 4, β-thromboglobulin), thrombotic status (thrombin-antithrombin III complex, fibrinopeptide A), fibrinolytic status (plasmin-β2-plasmin inhibitor complex, D-dimer) and endothelial injury (vWF, thrombomodulin) in patients with active and inactive TAand in healthy controls (60).

Plasma levels of molecular markers for platelet and coagulation activities were higher in patients with TA than in controls. However the levels of these markers were not different between the active and inactive stages of the disease. Plasma levels of vWF and thrombomodulin were similar or lower from those of healthy controls. The authors suggested that a hypercoagulable state is present in TA and contribute to vessel injury, while there is little, if any, endothelial damage.

A significant positive correlation was found between plasma endothelin-1 levels and ESR in patients with TA (61). Anti-endothelial cell antibodies are frequently present in patients with TA (62). They may play a role in the pathogenesis, but they were not tested as markers of disease activity. The presence of antiaorta-specific antibodies is debated (63).

In conclusion, the ESR, CRP, and Il-6 all reflect the inflammatory processes in most cases of untreated TA. The CRP may provide a somewhat more accurate assessment of the state of the arteritis than the ESR. However, many studies have shown that the available laboratory markers do not appear to provide an extremely accurate assessment of the activity of the disease in the chronic partially treated stage. Further studies of Il-6 in relation to active disease in surgical cases are needed to determine its usefulness as a marker in chronic disease.

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Appendix

Table I. The many possible circulating molecules that could be evaluated in large vessels vasculitis based on what is known about large vessel injury, response to injury, and cytokines and related molecules involved in tissue damage.

Mechanisms of tissue damage in large vessel vasculitis and related soluble surrogate markers

Cell source	Mediator	Pathogenic mechanism	Soluble surrogate marker
Macrophages and giant cells stimulated by interferon-α produced by Tcells	Reactive oxygen intermediates	Lipid peroxidation of cellular membranes, smooth muscle cell apoptosis and necrosis, nitration of microcapillaries	Oxygen-derived circulating free radicals and their metabolites
Macrophages and giant cells stimulated by interferon-α produced by Tcells	Metalloproteinases	Matrix degradation with mobilization of myofibroblasts, degradation of lamina elastica with aneurism formation	Circulating levels of metalloproteinases

Mechanisms of the response of arteries to immune injury in large vessel vasculitis and related soluble surrogate markers

Cell source		Consequence	Soluble surrogate marker
Macrophages and giant cells stimulated by interferon-α produced by Tcells	PDGF	Proliferation of myfibroblasts with intimal hyperplasia	Circulating PDGF
Macrophages and giant cells stimulated by interferon-α produced by Tcells	VEGF	Neoangiogenesis with perpetuation of inflammation and intimal hyperplasia	Circulating VEGF

Cytokines and related molecules involved in tissue damage in large vessel vasculitis

Cell source		Consequence	Soluble surrogate marker
Tcells	Interferon-α	Activates macrophages, induces MHC class II, ELAM-1, and ICAM-1 on endothelial cells	Interferon-α
Macrophages	TNF-α	Systemic inflammatory response	TNF-α
Macrophages/monocytes	IL-1	Systemic inflammatory response	IL-1
Tcells	IL-2	Activates T-cells	IL-2
Macrophages/monocytes	IL-6	Systemic inflammatory response	IL-6
Macrophages, dendritic cells	IL12, IL18	Induce interferon-α production	IL-12, IL-18
Endothelial cells (adventitial microvessels and neovessels within inflammatory infiltrates)	Endothelial adhesion molecules (PECAM-1, ICAM-1, ICAM-2, P-selectin, E-selectin, VCAM-1)	Leukocyte-endothelial cell interaction leading to the development of inflammatory infiltrates	PECAM-1, ICAM-1, ICAM-2, P-selectin, E-selectin, VCAM-1
Macrophages	Trasforming growth factor beta	Cell recruitment, intimal hyperplasia	TGF-β
Macrophages, Tcells, endothelial cells, dendritic cells	Inflammatory and homing chemokines	Maintenance of T-cell activation and proliferation, monocyte/lymphocyte adhesion to endothelial cells cells and recruitment within inflamed vessel wall, trapping dendritic cells in the arterial wall	CCL2, CCL5, CCL19, CCL21
Dendritic cells	Co-stimulatory molecules	Stimulation of adaptive immunity	CD86
Dendritic cells	Cell maturation-specific marker	Stimulation of adaptive immunity	CD83