Systemic lupus erythematosus and infections: clinical importance of conventional and upcoming biomarkers.

SYSTEMIC LUPUS ERYTHEMATOSUS AND INFECTIONS: CLINICAL IMPORTANCE OF CONVENTIONAL AND UPCOMING BIOMARKERS

Sciascia S.[1,2], Ceberio L.[3], Garcia-Fernandez C.[4], Roccatello D.[2], Karim Y.[5], Cuadrado M.[5]

[1] Lupus Research Unit, The Rayne Institute, Division of Women's Health, King's College London, UK

2 Dipartimento di Malattie Rare, Immunologiche, Ematologiche ed Immunoematologiche, Centro di Ricerche di Immunopatologia e Documentazione su Malattie Rare (CMID), Ospedale Torino Nord Emergenza San G. Bosco ed Università di Torino, Turin, Italy

3 Medicina Interna, Txagorritxu Hospital, Vitoria Gasteiz, Spain

4 Medicina Interna. Complejo Hospitalario Carlos Haya. Málaga, Spain

5.Louise Coote Lupus Unit, Guy's and St Thomas' NHS Foundation Trust, St Thomas' Hospital, London, UK

Correspondence: Maria Cuadrado.

Mail: mjcuadrado@yahoo.com

Louise Coote Lupus Unit, Guy's and St Thomas' NHS Foundation Trust, St Thomas' Hospital, London, UK

Tel: +44 02071883569 Fax: +44 02076202658

Running Title:

Biomarkers for Systemic Lupus Erythematosus and Infection

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Highlights

- Infection is a common problem and has become one of the leading causes of mortality in patients with systemic lupus erythematosus. It can be notoriously difficult to differentiate between infection and disease flare in some cases.
- hsCRP levels and ESR/CRP rate, in contrast to other autoimmune systemic diseases (e.g. rheumatoid arthritis), seem to be a good marker to differentiate SLE activity from infection. However, the presence of arthritis and serositis has to be taken into account when using these parameters to help to assess the likelihood of infection.
- CD64 expression in patients with inflammatory diseases has been reported to differ significantly from those with systemic infections, suggesting CD64 as an attractive candidate to distinguish patients who have an acute flare of their autoimmune disease from those who have systemic bacterial infections

Abstract

Infection is a common problem and has become one of the leading causes of morbidity and morbidity and mortality in patients with systemic lupus erythematosus (SLE). The reasons for the high incidence of infection are immunosuppressive therapy and immune disturbances of lupus itself.

Infections may mimic exacerbations of SLE, leading to confusion over the diagnosis and appropriate treatment. It can be notoriously difficult to differentiate between infection and disease flare in some cases. Indeed they may co-exist.

Along with the conventional biomarkers of lupus flares as hypocomplementemia, anti-double-stranded-DNA antibodies and erythrocyte sedimentation rate, other biomarkers as procalcitonin, and autoantibodies against complement fraction C1q, have been investigated to distinguish infections from other inflammatory processes.

Recent research has provided data about new potential biomarkers to assist clinical decision-making in the management of SLE patients (e.g. percentage of circulating CD27 high plasma cells from the peripheral blood, 25′-oligoadenylate synthetase isoforms, soluble triggering receptor expressed on myeloid cells-1 and pentraxin 3), but only some of them are supported by convincing evidence, such as CD 64-Fc receptor expression.

We reviewed the literature on the available tests to discriminate between SLE activity and infections, focusing on conventional and upcoming biomarkers.

INTRODUCTION

Infection is a common problem and has become one of the leading causes of mortality in patients with systemic lupus erythematosus (SLE). The reasons for the high incidence of infection are immunosuppressive therapy and immune disturbances of lupus itself [1].

Immunological abnormalities may play an important role in the susceptibility of SLE patients to infections [2]. Furthermore, immunosuppressive agents used in the treatment of moderate and severe lupus increase the risk of infections including by opportunistic agents. Infections may mimic exacerbations of SLE, leading to confusion over the diagnosis and appropriate treatment. It can be notoriously difficult to differentiate between infection and disease flare in some cases. Moreover, some infections may produce a systemic infection mimicking SLE, either superimposed or trigger a flare [3, 4].

Infections can be diagnosed by clinical features and positive cultures and/or response to antibiotic therapy. When cultures of bacterial isolates are negative or not available, diagnosis of infection rely on clinical findings which can be quite similar to symptoms of active SLE. Clinicians have to make treatment decisions based on clinical judgment because no other laboratory parameters are totally reliable to distinguish between active disease and infection. In some patients both situations can co-exist being the diagnosis and therapeutic approach a real challenge.

We reviewed the literature on the available tests to discriminate between SLE activity and infections, mainly focusing on evidence about new potential biomarkers to assist clinical decision-making. The relevant and most recent studies chosen from a MEDLINE search from February 2002 until February 2012 are reviewed in this article.

CONVENTIONAL BIOMARKERS FOR DISEASE ACTIVITY

Conventional biomarkers for the assessment of disease activity include anti-dsDNA antibodies, serum complement levels (C3 and C4), erythrocyte sedimentation rate (ESR), and autoantibodies against complement fraction C1q.

Their value to predict disease flares and efficacy of therapeutics has been broadly evaluated under different clinical and experimental settings [5] [6] [7].

Nevertheless, even taken together, the "classical" markers of activity are not specific and lack diagnostic accuracy in differentiate between flares and infections. In fact, their increase can be attenuated by immunosuppressive medications, especially glucocorticoids [8]. Conversely, persistently high levels of anti-dsDNA antibodies or low levels of complement (C3 and C4) can be found in some patients with low SLE disease activity [9]. (Figure 1)

Overall, traditional activity biomarkers alone are not always adequate in evaluating disease activity versus infections and potential new biomarkers are required to discriminate between these two conditions.

CONVENTIONAL BIOMARKERS FOR INFECTION

C-reactive protein

C-reactive protein (CRP) is a very well known marker of inflammatory and infectious processes.

In SLE, unlike in other inflammatory diseases where robust increase in levels has been seen, CRP level changes have been less frequently found during flares [10]. IL-6 decrease has been described in SLE patients. This cytokine is clearly related to production of CRP in the

inflammatory cascade [11]. During infection, in contrast, CRP increases are seen and it is proposed to be a good marker to differentiate between infection and flare.

Recently, Kim at al. [12] retrospectively evaluated the clinical significance of CRP as a marker of infections in SLE, in comparison to procalcitonin and phagocyte-specific S100A8/A9 protein levels. Evaluating 34 SLE patients with bacterial infection and 39 with flares, they concluded that CRP is a more sensitive and specific marker for diagnosing bacterial infections in SLE compared to the other biomarkers (specificity and sensitivity for infection 90% and 100%, respectively).

Nevertheless, the use of CRP alone as a marker of infections can present some limits. First, most of the studies investing the role of CRP mainly focused only on bacterial infections and very few data are available about the clinical role of CRP during viral or fungal infections. Secondly, significant elevation on CRP levels have been found in SLE during serositis, polyarthritis and nephritis flares [13],[14]. Amezcua-Guerra and al [15] recently demonstrated that in patients with SLE, acute-phase proteins behave differently depending on the kind of organ damage evaluated and that CRP was determined the best in patients with arthritis. Thirdly, elevation of CRP levels has been found with age, and although not significant, increases are also seen with gender (male), Body Mass Index, oral contraceptives and renal failure. Treatment with statins, antimalarials and steroids have been related to reduction of CRP levels [16].

ESR/CRP ratio has also been found to be useful in distinguishing between flare and infection. In a series of 53 patients, ratios higher than 15 very significantly correlated to flare in 95% of patients presented and ratios above 2 correlated to infection in all patients presented [17].

ESR levels are well known to be raised not only with infection, but also with disease activity [10]. Interestingly, Villa et al reported that it can be used to assess disease activity more accurately than to evaluate infection [18]

In recent years more sensitive CRP (high sensitivity CRP, hsCRP) tests have been developed and it is now possible to detect values as low as 0.2 mg /l. When hsCRP is above 6mg/dl specificity and sensitivity for infection are as high as 84% and 55% respectively [10].

To summarize, CRP levels and ESR/ CRP rate, in contrast to other systemic diseases, seem to be a good marker to differentiate SLE activity from infection. Age and the presence of arthritis and serositis have to be taken into account when using these parameters to make a diagnosis.

Procalcitonin

Procalcitonin (PCT) measurement has been claimed to be a marker of bacterial infection, useful to distinguish from other noninfectious diseases. It can be used to anticipate treatment with antibiotics as well as to control treatment duration. It seemed to be more accurate than the traditional markers (CRP and ESR). Newer research, though, has showed controversial results. Procalcitonin appeared to be a promising marker in the management of respiratory infection [19] but shows low specificity and sensitivity to differentiate between sepsis and other noninfectious diseases such as autoimmune diseases in critical patients [20].

Different studies are now trying to investigate factors which could interfere with PCT values such as inflammatory diseases, trauma or non-bacterial infectious agents. PCT levels in SLE patients have been analyzed in several studies [21]. Two retrospective studies did not find modification in PCT levels in lupus flare [22] .There are some discrepancies regarding changes during infection. In the first study by Lanoix et al [22], including 60 hospitalized lupus patients, there were no significant PCT changes during flare or during infection. In contrast, Quintana et al [23] retrospectively analyzed 56 patients with SLE. They found that high levels of PCT suggest the presence of concurrent infection. In a more recent prospective case control study investigating

the effects of SLE activity on PCT levels, Quintana at al [23] compared the serum PCT levels in 2 groups of patients with SLE: group 1 (*n*=21 patients with no significant lupus activity), and group 2 (*n*=32 patients with active SLE). The only 3 patients with frankly elevated PCT levels had both active disease and pneumonia (*n*=1), renal failure (*n*=1), or urinary tract infection (*n* =1). This study suggested that SLE activity does not increase serum PCT levels and that an elevated PCT in these patients should raise a high level of suspicion of a coexisting infection. However, in this study a cohort of patients with both SLE and infection was not included [24].

Nevertheless, it is important to note that levels may be influenced by other factors. Elderly people and men have significantly higher values [22]. PCT may also be influenced by renal function. Uremia in patients with endstage renal disease seems to increase PCT levels, and the PCT levels declined after each hemodialysis session [25]. Corticosteroid therapy does not seem to affect PCT values. A retrospective study, including 79 patients with different autoimmune diseases, showed that PCT has good specificity in distinguishing acute bacterial infections from disease flare in patients with autoimmune diseases even when they were treated with steroids [26].

Overall further studies are needed to a better understanding of the role of PCT as a tool to distinguish activity from infection in SLE patients

Urinalysis

Renal involvement is known to be common in SLE, though the spectrum of severity is very wide. Since renal involvement generally occurs without symptoms (unless very severe or advanced), screening urinalyses tend to be a part of routine follow-up in SLE, in order to detect hematuria, casts, proteinuria, and/or pyuria [27-29].

On the other hand, most studies find urinary tract infection (UTI) as one of the commonest in SLE patients [30]'[31] To discriminate among UTI and SLE renal involvement might be difficult in some patients. Clearly, UTI can be diagnosed by clinical features and positive cultures and/or response to antibiotic therapy.

Urinary casts, proteinuria and renal tubular cells strongly suggest glomerular or tubular inflammatory involvement due to SLE. Hematuria or pyuria, as isolated urinary findings, may present a clinical dilemma for the treating physician. Pyuria, especially when combined with polymorphic hematuria and casts, should be regarded as an expression of glomerular inflammation, consonant with a florid nephitis, rather than a superimposed UTI. Detection of significant proteinuria (sometimes of nephrotic or sub-nephrotic range) is a rule in these cases. Moreover, repeated empirical treatment for UTI may cause false negative culture for bacterial infection.

The presence of isolated pyuria justifies a search for a infectious aetiology. The presence of leukocytosis on repeated urine analysis may indeed warrant a search for atypical infections, particularly if the patient in question has risk factors The need to rule out mycobacterial infections must be considered, particularly for at risk ethnic groups and geographic regions. If infectious etiology cannot be proven, then a renal biopsy may be indicated. Persistent isolated hematuria and isolated pyuria should not be considred as a `benign' urinary finding in patients with SLE until the possibility of inflammatory renal involvement has been excluded.

Moreover, tubulointerstitial nephritis or interstitial cystitis could be considered especially when SLE occurs in association with Sjögren's síndrome [32].

NEW MARKERS

Common screening laboratory tests employed to diagnose infections, such as leukocyte number, presence of immature forms, CRP and ESR, may have poor sensitivity and specificity, as previously described.

Culture results are often viewed as confirmatory test for infection, especially bacterial ones, but in daily practice they cannot be used in immediate treatment decisions because of their relatively slow turnaround times of up to 72 hours or more [33]. Virological examination including detection of viral antigens and antibodies, and less commonly the isolation of viruses and the detection of viral nucleic acids can help to assess the likelihood of infection – these can be quickly available in some centres. Nevertheless, some of these investigations are carried out only by some specialist virology centres and turnaround times and accuracy of the results can widely vary [34].

A range of soluble biomarkers and quantitative cellular measurements have been proposed as candidates to help with the dilemma of disease activity versus infection.

Among quantitative cellular measurements, such candidates would be Fc receptors [35], and the percentage of circulating CD27 high plasma cells in the peripheral blood [36, 37]. They have the advantage of timely and early evaluation of the patient (within four to six hours after the contact with microbial surface agents) but flow-cytometry is a resource consuming technique and these tests could not be available as a routinely tested approach in all laboratories.

Soluble biomarkers include the triggering receptor expressed on myeloid cells-1 (sTREM-1) and pentraxin 3 (PTX3)[38], phagocyte-specific S100A8/A9 protein levels [12] and CXC ligand 13 protein (CXCL13) serum levels [39]. These tests have the advantage of being tested by enzyme-linked immunosorbent assay (ELISA), which makes them cheaper and faster to detect than analyses performed by flow cytometry or real-time PCR.

25′-oligoadenylate synthetase isoforms (OAS) [40] are tested by real-time PCR. Unless stronger evidence is available, as the involved technology is sophisticated, the costs and time to test make it less attractive to be routinely used. These markers are summarised in Table 1.

CELL BIOMARKERS

CD64 expression

One of the Fc receptor for IgG is the Fc γ receptor I (Fc γ RI or CD64). Several studies have assessed the diagnostic utility of neutrophil CD64 expression [35],[41, 42].

Normally, CD64 is present on the surface of less than 5% circulating polymorphonuclear leukocytes (PMN), but neutrophil CD64 expression rapidly increases as a physiological response to microbial wall components, complement split products and some proinflammatory cytokines. This occurs within four to six hours after the contact with microbial surface agents [42, 43]. Hoffmeyer et al proposed CD64 as an attractive biomarker to distinguish patients who have an acute flare of their autoimmune disease from those who have systemic bacterial infections. However, this study did not compare the usefulness of CD64 with standard laboratory markers such as ESR and CRP as these data were not collected in all patients. In a subsequent study, Allen and co-workers [41] reported that CD64 expression in patients with inflammatory diseases differed significantly from those with systemic infections. These preliminary data make CD64 an attractive candidate to distinguish patients who have an acute flare of their autoimmune disease from those who have systemic bacterial infections.

Hussein et al [35] using receiver operator characteristic (ROC) curve evaluation, found a level of CD64 (≥43.5% of neutrophil) to be both sensitive and specific (94.4%, 88.9% respectively) for detection of infection and to differentiate it from active (rheumatoid arthritis and SLE) patients

who expressed lower level of CD64 (<43.5%). In this study, expression of CD64 was significantly more prevalent in patients with both infections and underlying inflammatory disease than in patients with active disease alone. Of note, the use of immunosuppressive drugs did not seem to have a significant impact on CD64 expression. A significant positive correlation was also found between CD64 expression and SLEDAI. This study was limited by the restricted number of enrolled patients and the focusing both on RA and SLE patients without further sub-classification.

Therefore, though future studies are needed to confirm these results, CD64 could be useful in the acute treatment decisions to differentiate between disease activity and infection. At the moment, the added value of CD64 testing could be the timely and early evaluation of the patient: because of the up-regulation of CD64 expression on the PMN and the normal 6-hour half-life of the blood PMN, determination of the PMN CD64 expression should provide a true indication of the presence of bacterial infection.

CD27 ^{high} plasma cells

Among cell markers, previous studies have also focused on the frequency of CD27 ^{high} plasma cells [36, 37]. It has been described that CD27^{high} plasma cell frequency is high in SLE patients and that it correlates with SLE disease activity index (SLEDAI) and some ENA antibodies [36, 37]. However, the percentage of circulating CD27^{high} plasma cells is also increased in non-SLE patients with bacterial infection [44].

Yang at al [45] demonstrated that in SLE patients *with or without* infection, a significantly increased percentage of CD27^{high} plasma cells from the peripheral blood can be found. Moreover, higher percentages of CD27 ^{high} plasma cells were found among SLE patients with infection, and lower percentages of CD27 ^{high} plasma cells (though higher than that in controls) were more prevalent in SLE patients with active disease.

Thus, the percentage of CD27 ^{high} plasma cells from peripheral blood may be considered a potential biomarker for evaluating disease activity in SLE patients who do not have infection; its role as a potential parameter for distinguishing a lupus flare-up from infection therefore still needs further evaluation.

SOLUBLE BIOMARKERS

2′5′-Oligoadenylate synthetase

Measurement of 2′5′-Oligoadenylate synthetase (OAS) has described in SLE more than 20 years ago [46]. Recently, OAS was rediscovered to be a part of interferon signature(s), which plays an important role in the pathogenesis of SLE by several microarray gene expression studies [47], [48]. These studies have identified three isoforms of OAS, i.e., OAS1, OAS2, and OASL. Expression of OAS was reported to be up-regulated in a newly diagnosed active lupus cohort. It was then postulated that the patterns of OAS isoforms may provide useful information to distinguish disease flare from infection in SLE [40]. In that study, though a correlation between SLEDAI and OAS isoforms in active SLE had not been observed, the expression pattern of OAS isoforms, OASL in particular, was proposed to be of value to differentiate infection from disease flares in lupus. Of note, the majority of the infective subjects had invasive bacterial infections (not enough to cover the whole infection spectrum in SLE) and the paucity of fungal and viral infections may represent a limit for that study.

These data can be considered preliminary and at the moment considering costs and time to test (as OAS are tested by PCR), OAS seems far from being part of routine standard laboratory testing.

Soluble triggering receptor expressed on myeloid cells-1 and pentraxin 3

The role of serum levels of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) and pentraxin 3 (PTX3) as markers of infection in patients with SLE [38] has been also investigated. Tracing back the data, only serum sTREM-1 levels were significantly higher in the infection group than in active SLE patients. Of note, this study was focused only on febrile SLE patients.

This approach has the advantage of being measured by ELISA, a technique used in most laboratories. It would be cheaper and/or faster than flow cytometry or real-time PCR but till now the results are scanty and further studies are necessary.

Phagocyte-specific S100A8/A9 protein

Phagocyte-specific S100A8/A9 protein levels have also been under investigation [12, 49]. High levels of S100A8/A9 were found in some inflammatory diseases as rheumatoid arthritis and juvenile rheumatoid arthritis and they correlate with active stages of the diseases [49, 50]

Soyfoo and co-workers [49] investigated the level of this marker in SLE patients. They reported that serum levels of S100A8/A9 were are significantly raised in SLE versus primary Sjogren's Syndrome patients and healthy controls and could be correlated to a disease activity index (SLEDAI).

Recently Kim at al. [12] retrospectively evaluated the clinical significance of this marker, concluding that though useful to discriminate between flare and infections, it did not achieve better diagnostic performances than conventional biomarkers such as CRP. In the ROC analysis, the area under the curve was 0.966 [95% CI 0.925-1.007] for CRP, and 0.732 [95% CI 0.61-0.854] for S100A8/A9, respectively.

CXC ligand 13 protein

Recent studies have demonstrated that CXC ligand 13 protein (CXCL13) serum levels correlate significantly with SLE disease activity [51]. However, experimental studies show that CXCL13 production can also be induced by bacterial exposure as well as in response to inflammatory cytokines [52]. Nevertheless, Shiffer at al [39] showed that CXCL13 levels were increased in SLE patients with evidence of a bacterial infection as well as in patients with active SLE. Therefore, its value as a marker of infection seems to be limited.

NON-BACTERIAL INFECTION

Most of the available studies manly refer to bacterial infections, but these are far from enough to cover the whole infection spectrum in SLE. Only few studies focused on non-bacterial infections (viral or fungal) and data about the clinical significance of available biomarkers are elusive in this field.

Shin and coworkers demonstrated that patients with SLE and bacterial and fungal infections (n = 9) had significantly higher PCT levels than patients diagnosed with viral infection (n=3), lupus flare (n= 7), and control group (which included 11 patients with inactive SLE) [53]. Serum PCT levels tended to increase continuously in the group with non-viral infection and decreased after treatment of infection. Although this was one of the first studies to prospectively observe PCT level changes in SLE patients taking into account also non-bacterial infections, this was a limited study because of the small number of subjects. [24]

Chen et al, [54] analyzing 15 cases of invasive fungal infection in SLE patients found no statistical difference existing for markers of activity between time of SLE diagnosis and when fungal infection occurred. Moreover, taking into account mortality rate, no difference existed for disease parameters [leucocyte (WBC) count, SLEDAI, C3, C4, anti-dsDNA, 24 h urine protein,

serositis and skin rash] at fungal infection onset between deceased and surviving SLE patients. Anyway, additional case experience is required to confirm these observations, asd well as further data considering the clinical significance of further biomarkers associated with fungal infections.

The differential diagnosis between viral infections and SLE flares is a real challenge, as few studies have evaluated the impact of viral infections on the daily management of SLE patients. Ramos-Casals et al [4] analyzed the aetiology and clinical features of acute viral infections arising in patients with SLE and their influence on the diagnosis, prognosis, and treatment of SLE. The authors concluded that more proactive investigation of acute viral infections in SLE patients presenting with fever is desirable. They suggested viral serologies (EBV, CMV, herpes simplex, and B19) should be routine in SLE patients suspected for viral infections, especially in immunosuppressed patients, and should be mandatory, together with molecular tests and cultures, in patients with organ-specific features, as is already done in other immunosuppressed patients, such as transplant and hematologic patients [55]. Nevertheless, the evaluation of predictive biomarkers of viral infections was not included among the aims of that study, so no specific data analysis was provided.

CONCLUSION

Infection is a common problem and has become one of the leading causes of mortality in patients with SLE. Traditional SLE activity biomarkers alone are not always adequate in evaluating disease activity versus infections, though CRP is a useful tool. Recent research has provided data about new potential biomarkers to assist clinical decision-making in the management of SLE patients, but only some of them are supported by convincing evidence, such as CD 64-Fc receptors expression.

Further studies investigating the clinical value of new biomarkers in discriminate between flares and infections in SLE patients are desirable in order to identify a test or, more realistically, a panel of tests to be routinely performed when a patients is suspected for infection.

Several aspects as cost, time to test results, availability of the technique in daily laboratory practice, and clinical significance also in non-bacterial infections should be taken into account.

Competing interests, Funding

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Contributorship Statement

All the Authors participated in the bibliographical search, design and preparation of the manuscript.

LEGENDS

Figure 1:

Clinical behaviour of conventional biomarkers during SLE flare or infection.

CRP, C reactive protein: ERS, erythrocyte sedimentation rate; anti-C1q, antibodies against complement fraction C1q.

Table 1:

Proposed new markers to assist clinical decision-making in the management of SLE patients

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