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Management of infection in systemic lupus erythematosus.

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Abstract

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterised by abnormal autoantibody production and clearance. This immunological background has been suggested to play a role in the susceptibility of SLE patients to infection. Moreover, drugs (most of them immunosuppressive or immunomodulating agents) used in the treatment of moderate and severe lupus give rise to a tendency for infections, including opportunistic ones. Infections may mimic the exacerbations of SLE, leading to confusion over the diagnosis and appropriate treatment. Despite increased awareness of this problem, infections remain a major source of morbidity and mortality in SLE. There are various strategies which can be applied to try and reduce the risk of infection in SLE patients. Options include vaccinations, antibiotic/antiviral prophylaxis and intravenous immunoglobulins.

Keywords

Bacterial viral fungal flare; Vaccination; Vaccine antibiotic prophylaxis; Immunoglobulin

Abbreviations

ANA anti-nuclear antibody

C1q complement factor 1q

C3 complement factor 3

CMV cytomegalovirus

CRP C-reactive protein

CVID common variable immunodeficiency

DNA deoxyribonucleic acid

ESR erythrocyte sedimentation rate

EULAR European League against Rheumatism

H1N1 haemagglutinin 1, neuraminidase 1

HIV human immunodeficiency virus

HPV human papilloma virus

iC3b inactive C3b

IVIg intravenous immunoglobulin

MBL mannose binding lectin

MMR mumps, measles, rubella

PCR polymerase chain reaction

PJP *Pneumocystis jiroveci pneumonia*

SLE systemic lupus erythematosus

Sm Smith

SLEDAI Systemic Lupus Erythematosus Disease Activity Index

Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterised by abnormal autoantibody production and clearance. This immunological background has been suggested to play a role in the susceptibility of SLE patients to infections [1]. Moreover, drugs (most of them immunosuppressive or immunomodulating agents) used in the treatment of moderate and severe lupus give rise to a tendency for infections, including opportunistic ones.

Infections may mimic the exacerbations of SLE, leading to confusion over the diagnosis and appropriate treatment. Despite increased awareness of this problem, infections remain a major source of morbidity and mortality in SLE. Infectious diseases are still the most frequent causes of death in SLE in the first year after onset [2]. The increase in SLE deaths associated with infection, especially pneumonia and septicemia, is worrisome, especially in some areas of the globe [3]. Indeed, survival rates for SLE patients in developing countries are comparatively lower than those reported in industrialised countries, with early death from infection and active disease [4].

In this review, we aim to review infections in SLE and appropriate prevention strategies.

Characteristics of infection in SLE

Infections are known to be a major cause of morbidity and mortality in SLE [1]. Several studies evaluated the characteristics of major infections in SLE patients requiring hospitalisation [5], [6] and [7]. According to these studies, infections that SLE patients developed were attributed to the same pathogens as in the general population and included community-acquired pneumonia, urinary tract infection and vaginal infection, and some patients may develop tuberculosis. However, despite the pathogens often being the same as in the general population, the clinical manifestations of the infections can be atypical, due to an abnormal immunological response or due to ongoing treatment. Careful inspection and monitoring and timely collection of the specimens for bacterial culture are warranted to avoid misdiagnosis.

Some patients also develop viral, fungal and protozoan infections. Rarely, multiple organisms can be found [8]. Usually, in an outpatient setting, infections are non-life-threatening ones. Zonana-Nacach et al. reported that in this scenario, infections are associated with disease activity only, independently of socio-demographic and therapeutic factors [5]. However, it is noteworthy that infection in SLE can require hospitalisation, especially when concomitant with a flare (mainly involving the kidney or central nervous system) or when therapy with steroids or cyclophosphamide is ongoing [1].

Predictors of major infections in SLE

Several studies have analysed the prevalence and associated clinical and laboratory features of infection in SLE [8], [9], [10] and [11]. Common themes are medications, including use of steroids and/or cyclophosphamide or high-disease activity as measured by the SLE Disease Activity Index [12].

Recently, Ruiz-Irastorza and co-workers [13] in a nested case–control study design used within the prospective Lupus-Cruces cohort analysing 249 patients found that the risk of major infections in patients with SLE is mostly influenced by treatment. Prednisone treatment, even at moderate doses, increases the risk, whilst antimalarials have a protective effect [13]. In detail, it was shown that the prednisone dose at the time of the event had a facilitating effect on infections, in agreement with previous studies [9], [10] and [11]. Moreover, it is worthy of note that the median dose of patients with major infections was only 7.5 mg day⁻¹, with an 11-times higher risk of suffering a serious infection for each increase of 10-mg day⁻¹ prednisone.

SLE, infections and mortality

When the frequency, characteristics of the main causes and prognostic significance for morbidity and mortality in 1000 patients with SLE during a 5-year period were analysed, the most frequent causes of death were active SLE, infections and thromboses [14]. In the long-term follow-up of the same study, infection was the present in 36% of the 1000 patients and most frequent causes of death were confirmed to be similarly divided among active SLE (26.5%), thromboses (26.5%) and infections (25%). A survival probability of 92% at 10 years was found [15].

In a retrospective study performed to describe the characteristics associated with a poor outcome in SLE patients admitted to hospital during a 1-year period, infection was found to be the second cause of hospitalisation after clinical flare of SLE [16].

Infections according to nature of microbe

Bacterial infections

A wide variety of infectious pathogens have been recognised in SLE. The most frequent types of infections are respiratory, urinary tract and soft-tissue infections [12]. Most infections are caused by common pathogens and include *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli* and *Pseudomonas aeruginosa*. Indeed, common pathogens that often behave more aggressively than in the healthy population. *[12] and *[17] An increased incidence of *Salmonella* infection and pneumococcal sepsis is also observed [18].

S. pneumoniae

S. pneumoniae is a Gram-positive bacterium, which is a common cause of community-acquired pneumonia, meningitis and septicaemia. Several studies indicate that patients with SLE have an increased frequency and severity of *S. pneumoniae* infections, accounting for 6–18% of all bacterial infections in these patients *[17] and [20]. It has been suggested that some defective mechanisms in SLE patients can underpin this increased susceptibility to *S. pneumoniae* infections. Recently, Goldblatt et al. [20] reported that opsonisation of *S. pneumoniae* with complement factor 3b/inactive C3b (C3b/iC3b) was significantly reduced in serum from patients with SLE compared with patients with non-SLE rheumatic disease and healthy controls, suggesting that a failure to appropriately activate the immune system via complement may contribute to the increased susceptibility of SLE subjects to infections and may correlate with a risk of pneumonia in a subgroup of SLE patients.

Salmonella

Infection with *Salmonella* species is recognised to be more common in SLE patients than the normal population and may be due to splenic dysfunction or to a defect in opsonisation as previously described [19] and [20]. The risk factors of mortality for *Salmonella* infection have been recently analysed in a cohort of SLE patients hospitalised in a medical centre in Taiwan [21]. Patients with *Salmonella* infection associated with lupus flare or re-infection with *Salmonella* species have been found to be the strongest factor associated with a higher risk of mortality [21]. In another study, retrospectively reviewing 50 SLE patients diagnosed with bacteriologically proven non-typhoidal salmonellosis over a 20-year period, it was found that most episodes were bacteraemic without a localising focus, and some patients were afebrile. Mortality in general occurred from concomitant septic shock and major organ failure from active lupus (mainly renal) [22]. It is noteworthy that osteomyelitis of the long bones due to *salmonella* can occur in SLE patients [23]. Active SLE or co-existent underlying systemic disease, chronic renal failure, and immunosuppressive agents were shown as main predisposing factors [23]. Recently, Navarra et al. [24] described the spectrum of *Salmonella* infections among Filipino patients with SLE, with typhoid fever and septic arthritis as the most common presentation. Atypical involvement included soft-tissue abscess and meningitis, with the worst prognosis noted in those with sepsis syndrome.

Klebsiella

Some studies showed that *Klebsiella* was one of the leading causes of Gram-negative bacteraemia in the general population [25]. SLE patients infected with *Klebsiella* were found to have lower probabilities of 14-day survival [26] in a study analysing the short-term survival of patients with SLE after bacteraemia episodes.

It is noteworthy that sera from patients with *Klebsiella pneumoniae* were found to contain high titres of the common anti-DNA idotype [27]. However, the presence of autoantibodies in the serum of patients with *Klebsiella* infections may be the result of non-specific stimulation due to bacterial polyclonal activation. However, there might also be a specific stimulus triggered by idiotypic cross-reaction between autoantibodies and anti-*Klebsiella* antibodies [28].

Mycobacterium tuberculosis

The reported prevalence of *M. tuberculosis* infection in SLE patients ranges widely from 5% to 30% [29] and [30]. The higher prevalence of tuberculous infections in SLE is attributed to multiple immune abnormalities observed in these patients and to the immunosuppressant therapy [31]. The clinical presentation of *M. tuberculosis* infection seems to be different in SLE patients when compared with the general population; in fact, more frequent extrapulmonary involvement as well as more extensive pulmonary involvement and a high relapse rate even if treated with prophylactic isoniazid have been reported [30] and [32]. Mycobacterial infection and SLE may have a similar presentation and may mimic each other. In an individual patient, the differential diagnosis is crucial. In a retrospective analysis involving more than 3000 SLE patients, Hou et al. [33] documented 19 lupus patients with 21 episodes, 10 of which were pulmonary while the other 11 episodes were extrapulmonary (joint, cutaneous or visceral-organ involvement). Fever and cough were found to be the most common manifestations of tuberculosis. However, Sayarlioglu et al. [34], comparing lupus patients without and with tuberculosis, found that arthritis and renal disease were significantly higher in the latter group, underlining the importance of an accurate diagnostic approach.

Opportunistic infections

Increasing evidence indicates that opportunistic infections contribute to the infectious mortality in SLE, as stated before. The burden of opportunistic infections in SLE is complex; often, they are under-reported due to difficulties in diagnosis, as they can mimic or be superimposed upon active lupus. Listeriosis, nocardiosis, candidiasis, cryptococcal meningitis, *Pneumocystis jirovecii* pneumonia (PJP) and invasive aspergillosis are described in patients with SLE [1]. Sometimes, even more rare infections are reported to occur in SLE, such as haemotrophic mycoplasma [35].

Cases of SLE with fungaemia or invasive fungal infection are rare but life-threatening conditions in SLE [36]. Severe *Candida* infection is the most frequently identified opportunistic fungal infection in several SLE series, associated with steroid and cytotoxic drug therapy [37]. Nocardial infections have been also described in steroid-treated SLE patients, and pneumonia and brain abscess are the most frequent clinical presentations [38] and [39]. Taken together, all the studies stressed that active lupus disease (SLEDAI > 7) is probably the main risk factor for opportunistic infection. It is noteworthy to remember that low prednisolone doses before fungal infection or high prednisolone doses following fungal infection are associated with higher mortality [37].

Viral infections

The most commonly reported viral infections in patients who have SLE are parvovirus B19 (HPV-B19) (there are more than 30 reports of primary B19 infection reported as lupus-like syndrome) [37] and cytomegalovirus (CMV) (predominantly presenting in severely immunosuppressed patients). It is not among the purposes of this review to analysis the causative role of virus in the pathogenesis of SLE. Herewith, we focus on the clinical settings when the two conditions, SLE and viral infection, co-exist.

Ramos-Casals et al. [40] described the largest series of acute viral infections in SLE patients. Among 25 patients diagnosed with new-onset SLE, HPV-B-19, CMV, Epstein–Barr virus and hepatitis A were concomitantly detected. In patients already diagnosed with SLE, symptoms related to infection mimicked a lupus flare due to disseminated viral infection and a severe, multi-organ process similar to that described in catastrophic antiphospholipid syndrome was reported. Mortality was high, with 12 patients dying due to infection.

Parvovirus B19

The occurrence of HPV-B19 infection has been documented in patients with SLE, in particular in relation to disease onset. The main reported clinical manifestations were fever, articular involvement, cutaneous lesions, lymphadenopathy, hepato and/or splenomegaly, serositis, renal involvement and cerebral impairment. Cytopenia was also frequently observed. Thus, the differential diagnosis between HPV-B19 infection and SLE flare is a real challenge, also because HPV-B19 infection may induce a serological profile mimicking a flare. Elevated titres of double-stranded DNA, Sm (Smith), nuclear ribonucleoprotein, Ro-SSA, La-SSB, cardiolipin and/or beta2-glycoprotein I antibodies were reported in concomitant to B19 infection [41]. The B19 infection

has usually a self-limiting course; nevertheless, in immunocompromised SLE patients symptoms may persist several months after the viral infection and induce severe clinical settings.

CMV

Sekigawa et al. [42], reporting SLE patients with spatially related SLE and CMV, emphasised the main features of the complex relationship between SLE and viral infection: a) CMV infection and SLE exacerbation may be impossible or difficult to distinguish, b) the development of SLE may be triggered by a CMV infection and 3) existing SLE may undergo an exacerbation following a CMV infection. Notably, CMV infection can be considered as an opportunistic infection, when affecting SLE patients on chronic steroids and/or immunosuppressive agents. Among the possible CMV-related manifestations, retinitis has to be kept in mind, especially when ongoing therapy includes both azathioprine and low-dose corticosteroid [43].

HIV

Interestingly, SLE has a lower incidence in the human immunodeficiency virus (HIV)-infected population when compared to the general population [44]. It has also been suggested that SLE may be influenced by HIV infection. It has been suggested that the immunosuppression resulting from HIV infection can prevent the emergence of SLE, as the immunosuppressive effect of HIV may inhibit the development of autoimmune diathesis [45]. To date, several cases of concomitant association between the two diseases have been reported, but the diagnosis was simultaneous in very few of those. Very recently, Carugati et al., reporting two cases and review of the literature, concluded that SLE could occur despite the loss of immunocompetence caused by HIV infection. Moreover, they stated that SLE and HIV infection might influence each other possibly through immunologic mechanisms determining awkward manifestations [46].

Serological markers of infection in SLE

Conventional biomarkers of lupus flares are hypocomplementaemia, anti-double-stranded-DNA antibodies and erythrocyte sedimentation rate. Their value to predict disease flares and efficacy of therapeutics has been proven; however, even taken together, they are not specific and lack diagnostic accuracy in differentiating between flares and infections [47]. In SLE, unlike in other rheumatic diseases where increase in levels has been observed, changes in C-reactive protein (CRP) level have been less frequently observed during disease flares, proposing this marker as a valid tool to discriminate infection and lupus activity [48]. Albeit with some limitations (such as the presence of arthritis and serositis), to date CRP levels and erythrocyte sedimentation rate/C-reactive protein (ESR/CRP) ratio seem to be the best marker to differentiate SLE activity from infection. Other biomarkers such as procalcitonin, and autoantibodies against complement fraction C1q, have been investigated to distinguish infections from other inflammatory processes but further studies are warranted.

Prevention of infection in SLE

As illustrated in the first part of this article, predisposition to infection with microbial agents is a major problem in SLE. If patients develop either atypical or recurrent infections, then this is a challenge to the clinician. There is a range of predisposing factors which may be present in SLE patients (see Table 1). There are various strategies which can be applied to try to reduce the risk of infection in SLE patients. Options include vaccinations, antibiotic/antiviral prophylaxis and intravenous immunoglobulins (IVIg).

Vaccinations

Patients with SLE are at an increased risk of infection, especially if they are taking immunosuppressive medication. Vaccination can be considered as a possible strategy. The history of vaccination in SLE patients has been controversial. This is because in certain cases, vaccination can trigger a flare of the disease. However, a number of reviews have recently been undertaken and seem to be in favour of vaccination, that is, the risk benefit is for vaccination to reduce infection risk compared with the risk of flare [49]. In their own practice, the authors opt for vaccination unless there is a previous history of vaccination-related disease flare. If possible,

vaccination should be administered before commencing immunosuppressive medication, as once this is started then live vaccines are contraindicated, and responses to non-live vaccines may be suboptimal. Non-live (inactivated/killed or subunit) vaccines can be used in patients on immunosuppressant therapy [49]. It is also best to vaccinate, if possible, when the lupus is quiescent [50].

The major questions with respect to vaccination in SLE and other autoimmune rheumatic diseases are as follows:

1. Are they safe?
2. Do they trigger disease flares?
3. Do they work?
4. Which vaccines are important?

Are they safe?

Killed or subunit vaccines are safe to administer to SLE patients on immunosuppression. However, live vaccines are contraindicated in patients on immunosuppressive medications according to expert opinion from European League against Rheumatism (EULAR). Expert opinion from EULAR also suggests that vaccines should be administered while disease activity is quiescent [50]. Abu-Shakra also suggested avoiding vaccines when lupus is very active [51].

Do they trigger disease flares?

Vaccines may trigger the generation of autoantibodies, which are usually of short term and of little clinical significance. Hence, more commonly, induction of autoantibodies but not autoimmune disease may occur. For example, induction of cardiolipin antibodies, but not β 2-glycoprotein-I antibodies, was seen in SLE patients and healthy controls [52]. However, in individual cases vaccines may cause SLE flares. No specific clinical or laboratory variables have been shown to be predictive of flare of systemic lupus erythematosus following vaccination [51].

Do they work?

Vaccinations, if possible, could be administered before commencing immunosuppressive medication as vaccination responses may be blunted in patients receiving high-dose corticosteroids or immunosuppressive medication. If possible, the authors suggest vaccination before starting immunosuppressive therapy or biologics. For example, rituximab, as a B-cell-depleting medication, has a significant effect on vaccine responses. It is best to administer vaccines either 4 weeks before or 6 months after rituximab treatment [50].

O'Neill and Isenberg (2006) commented that the majority of SLE patients have an appropriate response to vaccination, but a significant minority do not [49]. Response to hepatitis-B vaccination may be impaired and serological responses should be assessed post vaccination. They speculated that disease activity or immunosuppressive drugs were risk factors of poor response, rather than intrinsic abnormalities of immune function in SLE.

Response to influenza vaccination was lower in those SLE patients with haematologic criteria, or on prednisolone or of European American ancestry. After vaccination, low respondents were more likely to have disease flares and to have increased titres of anti-nuclear antibodies (ANAs) [53]. Azathioprine impaired response after influenza vaccination, though most patients still developed protective responses [54] and [55].

Which vaccines are important?

Pneumococcus

Respiratory infections are common in patients with SLE. Vaccination against the *Pneumococcus* bacterium should be with Pneumovax 23, the 23-valent polysaccharide vaccine, as the first line, to give the broadest coverage. If the patient does not respond to Pneumovax 23, then Prevenar 13, the 13-valent conjugated

vaccine, can be considered. Where possible, it is important to ensure that patients are responding to vaccinations by checking pre- and post-vaccination antibody levels. This is routinely possible for *Pneumococcus*, and serology is also available for other organisms such as *Haemophilus influenzae*, *Meningococcus*, diphtheria and tetanus toxoids and mumps, measles and rubella viruses.

The duration of protective antibody status may be shorter in patients on immunosuppressive therapy. Hence, the standard advice of a 5-year interval for pneumococcal vaccination may not hold true. Measurement of antibody levels, namely serotype-specific pneumococcal antibodies, may help guide vaccination frequency. Elkayam et al. showed that most patients did respond to the pneumococcal vaccine, but five (20.8%) of 24 patients with SLE responded to either none or only one of the seven serotypes tested [56].

Tuberculosis

Bacillus Calmette–Guérin (BCG) is not recommended because most cases are related to reactivation, not de novo infection; BCG is not always protective against tuberculosis in adults; there is a risk of BCGosis in patients on immunosuppressive therapy. In Western countries, there is not a need for anti-tuberculosis prophylaxis. However, in areas where tuberculosis is common, for example, India, or in patients of certain ethnic origins, there may be a case for anti-tuberculosis prophylaxis [57].

Influenza

One should consider vaccination with seasonal influenza annually and with the H1N1 influenza A strain. Studies suggest that patients do mount an immune response but perhaps less than healthy controls. Wiesik-Szewczyk et al. (2010) showed a lower seroprotection rate after inactivated influenza vaccine in SLE patients compared with healthy controls [58]. There were one severe and six mild-to-moderate flares observed in 62 SLE patients. Mathian et al. showed that impaired efficacy of H1N1 influenza A vaccine was associated with immunosuppressive medication or lymphopaenia [59].

Another possible good reason for antimalarials is the following: Borba et al. showed reduced response to influenza A/H1N1 in patients taking >20 mg day⁻¹ prednisolone, or on immunosuppressive medication or receiving both [60]. The group of patients taking chloroquine had a non-significant difference in seroconversion compared to the SLE no-therapy group. However, these findings would need to be corroborated in larger studies.

Azathioprine impaired the response after influenza vaccination in SLE but most patients managed to develop protective antibody levels [54] and [55].

Human papilloma virus

Cervical smear abnormalities are common in SLE, which may progress to cervical cancer. It may therefore be worth considering the use of the quadrivalent HPV vaccination, Gardasil [61]. Mok et al. reported the Gardasil vaccine to be safe and reasonably effective in a group of 50 SLE patients [62].

Thrombo-embolic events after Gardasil vaccination have been reported. Of the 31 reported cases, 90% had a risk factor, in fact antiphospholipid syndrome in two cases [63]. It is important to be aware of antiphospholipid antibody status in SLE patients so that appropriate measures can be taken.

Herpes zoster

There are separate varicella zoster (VZV; e.g., Varivax) and herpes zoster (e.g., Zostavax) vaccines. Licenced herpes zoster vaccine is a lyophilised preparation of a live, attenuated strain of VZV, which is the same strain used in the varicella vaccines. However, its minimum potency is at least 14-times higher than the potency of a single-antigen varicella vaccine. Although live vaccines are to be avoided in general for patients receiving immunosuppressive therapy, the Advisory Committee on Immunization Practices (ACIP) has made recommendations for the herpes zoster vaccine. [64] The committee has proposed that the dose of immunosuppressive makes a difference, for example, patients could receive the herpes zoster vaccine if taking

<0.4 mg kg⁻¹ week⁻¹ methotrexate, <3.0 mg kg⁻¹ azathioprine and a moderate dose of corticosteroids <20 mg day⁻¹. Varicella vaccine has been administered without subsequent infection in HIV-infected children with a CD4 percentage ≥15% or a CD4 count ≥200 mm⁻³ [65]. Varicella vaccine has also been administered to HIV-infected subjects with CD4 ≥400 cells μl⁻¹, but was only modestly immunogenic [66]. There are unpublished studies for the herpes zoster vaccine in adult HIV patients with a CD4 count ≥200 mm⁻³ (<http://www.clinicaltrials.gov/ct2/show/NCT00851786?term=zostavax+hiv&rank=1>) and in older patients on treatment with prednisone 5–20 mg day⁻¹ (<http://www.clinicaltrials.gov/ct2/show/NCT00546819?term=zostavax+corticosteroid&rank=1>). Specialist advice should be sought from a consultant virologist, when considering live vaccinations in patients receiving immunosuppression.

Measles, mumps and rubella

Measles, mumps and rubella (MMR) is a live vaccine, and most individuals in the UK would have received the MMR vaccine as part of their standard childhood immunisation schedule. It is possible to check antibody levels to mumps, measles and rubella. Theoretically, as a live vaccine, MMR is contraindicated in patients on immunosuppressive therapy. However, the MMR vaccine has been administered without subsequent infection to paediatric patients 2 years after bone marrow transplantation [67].

EULAR points out that MMR, varicella and herpes zoster vaccine might be exceptions to this rule and may be considered in mildly immunosuppressed patients with autoimmune rheumatic disease on a case-by-case basis. The authors believe that this is a grey area, and that individual decisions should be made between the rheumatologist, clinical immunologist and virologist.

Antibiotic prophylaxis

No great deal of evidence exists as a basis for antibiotic prophylaxis, though in certain cases use of such an approach makes common sense. For example, in patients who develop recurrent infections with a particular organism, it may be worth considering prophylactic antimicrobials, at least while they remain on immunosuppressant medication. For example, a patient with recurrent herpes zoster infection could be considered for prophylaxis with valaciclovir. The herpes zoster vaccine (Zostavax) is live and hence cannot be considered in patients receiving a certain level of immunosuppression. A patient developing CMV retinitis on azathioprine could be considered for the following:

- checking thiopurine methyltransferase levels,
- an alternative immunosuppressant and
- prophylaxis with valganciclovir.

Gilliland and Tsokos (2002) suggested antimicrobial prophylaxis in cohorts of patients with increased prevalence of certain infections, those who receive heavy doses of immunosuppressive agents or those undergoing procedures associated with temporary bacteraemia [68].

Endocarditis

Zysset et al. (1987) recommended that patients with SLE who have valvular abnormalities should receive endocarditis prophylaxis before invasive dental or genitourinary procedures [69].

Tuberculosis

Prophylactic treatment against tuberculosis should be considered in certain ethnic groups of patients with SLE, and in certain parts of the world where tuberculosis is common [57]. It is not required in low-risk patients in the Western world.

CMV

CMV infection is an uncommon but potentially fatal opportunistic infection in SLE. Yoon et al. suggested more active CMV vigilance and consideration of polymerase chain reaction (PCR)-based CMV prophylaxis in CMV PCR-positive patients with SLE undergoing intensive immunosuppressive therapy [70].

PJP

Gupta et al. reviewed the occurrence of PJP in SLE. They found a low frequency of PJP in SLE patients on cyclophosphamide of 0.1588% [71]. They did not recommend routine use of trimethoprim–sulphamethoxazole for PJP prophylaxis in SLE patients on cyclophosphamide, except in those with elevated risk, that is, with severe leucopenia, lymphopaenia, high-dose corticosteroids, hypocomplementaemia, active renal disease and higher mean Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score [71] and [72].

Splenectomy and complement

Patients may have had splenectomy as part of SLE management, such as for thrombocytopaenia. In these cases, vaccination with encapsulated bacteria is essential. This should include *S. pneumoniae*, *H. influenzae* type b and *Neisseria meningitidis* (A, C, W135 and Y). They should also receive antibiotic prophylaxis with penicillin V. In addition, there is evidence of splenic dysfunction in SLE [73], with defective clearance of immune complexes, which could include microbial antigens. Low complement levels and acquired reduction of complement receptor type 1 on red cell membranes reduce immune complex delivery to the spleen [74].

Hepburn and Davies (2002) stress the important relationship between hypocomplementaemia, splenic dysfunction and infection in SLE [74]. Infection with *S. pneumoniae* and *N. meningitidis* appears to be especially important. They have recommended antibiotic prophylaxis in SLE patients with chronic acquired hypocomplementaemia, as well as in the very rare genetic complement deficiencies with SLE. With respect to the latter, 13 out of 41 patients with C1q deficiency had recurrent bacterial infections, including meningitis and pneumonia [75].

Intravenous immunoglobulin

Replacement therapy with IVIg is appropriate for primary immune deficiency and can also be very helpful in patients with secondary immune deficiency. There are a number of different humoral defects which have been described in SLE patients. For example, common variable immune deficiency (CVID), drug-induced hypogammaglobulinaemia, hypogammaglobulinaemia related to nephrotic syndrome and specific antibody deficiency are all reported [76]. In some cases, the patient may be well though the immunoglobulin levels may be low. In these cases, a wait-and-see policy may be appropriate. For example, immunoglobulin levels in patients with drug-induced or nephrotic syndrome-related hypogammaglobulinaemia may improve over time. Treatment of the nephrotic syndrome should improve the hypogammaglobulinaemia. Drugs implicated in causation of hypogammaglobulinaemia include cyclophosphamide and rituximab. The latter does not tend to cause hypogammaglobulinaemia after the initial course but only after repeated cycles. Venhoff et al. recommended surveying patients post cyclophosphamide and rituximab treatment for serum immunoglobulin levels and persisting hypogammaglobulinaemia [77]. In some patients, hypogammaglobulinaemia may be associated with an increased risk of infection, particularly of the respiratory tract. Some patients may have specific antibody deficiency: that is, normal immunoglobulins but an inability to mount an antibody response to specific bacteria, even after vaccinations.

Therefore, criteria for replacement IVIg therapy in SLE patients should be the presence of hypogammaglobulinaemia or specific antibody deficiency, together with a history of recurrent infection. In specific antibody deficiency, an additional condition should be that they have not responded to treatment with antibiotic prophylaxis.

The approach to IVIg in these situations would be to administer a replacement dose, rather than the high-dose immunomodulatory approach used for suppressing autoimmunity. Immunoglobulin infusions can be administered every 3–4 weeks at a dose of approximately 0.4 g/kg weight–1 month–1. Treatment for these patients should be supervised by a consultant clinical immunologist.

Monitoring for IVIg consists of measurement of the trough immunoglobulin G (IgG) level, obtained immediately prior to an infusion. The target trough level should be 5–10 g l⁻¹, but towards 10 g l⁻¹ if there is established respiratory disease such as bronchiectasis. Additional monitoring has traditionally been full blood count (FBC), liver function tests (LFTs), hepatitis B surface antigen and hepatitis-C PCR. However, there have been no cases of IVIg-acquired viral hepatitis since the mid-1990s, and hence the hepatitis monitoring may become superfluous.

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Table 1.

Risk factors for infection.

Leukopenia
Acquired hypocomplementaemia
Genetic complement deficiency
MBL deficiency
Hypogammaglobulinaemia
Splenectomy
Functional hyposplenism
Prednisolone dose
Immunosuppressive medication
Biologics e.g., rituximab

MBL = mannose binding lectin.