Approach to vaccination in systemic lupus erythematosus on biological treatment

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ABSTRACT
In recent years, treat-to-target strategy and early intervention strategies with immunosuppressive agents have attempted to improve the prognosis and outcome in patients with autoimmune inflammatory rheumatic diseases. However, infectious complications due to side effects of medication remain a major concern in routine practice. In this regard, vaccine immunity and vaccination programmes are of the utmost importance in patients with systemic lupus erythematosus (SLE) in terms of morbidity and mortality. Encouragingly, research investigations have increased exponentially, both in monitoring the vaccines efficacy, and in determining the immune response while patients are on immunosuppression. However, in this biological era in rheumatology, relatively little data have been published investigating these parameters in those receiving biological agents, therefore, no definitive consensus about a vaccination policy for patients with SLE is currently available. In this review, we aim to address what is established about vaccinating patients with SLE on biological agents and discuss potential problems.

INTRODUCTION
Infections remain the leading cause of mortality and morbidity in patients with systemic lupus erythematosus (SLE). This susceptibility can be attributed to two main causes: disease related and medication induced. SLE carries an increased risk due to altered host immune status notably hypocomplementaemia, and abnormal neutrophil and macrophage response to pathogens. A mainstay of treatment in SLE, immunosuppressive drugs such as corticosteroids and cytotoxic agents, may impair the immune response to viral and bacterial pathogens, contributing to the increased risk.

Since the disease may cause life-threatening organ damage, utilisation of immunosuppression even in the early stages of the disease has been identified in the context of a 'treat-to-target' strategy as a primary goal in management. This approach has concomitantly raised the importance of prevention of infectious complications triggered by these agents in patients with SLE.

Vaccines are the cornerstone in the prevention of certain infections by inducing and/or enhancing immune system components. Despite possibly impaired antibody responses to vaccination and/or the theoretical risk of disease flare following vaccination, the available evidence suggests that vaccines are well tolerated and effective in this population, without any potential risk for increased disease flares. More encouragingly, Alyasîn et al reported an adequate immune response in 78% of children with SLE. The 23-valent pneumococcal polysaccharide vaccine (PPSV23) and the 13-valent pneumococcal conjugate vaccine (PCV13) are currently available pneumococcal vaccines. Although the immunogenicity of conjugate vaccines is higher than polysaccharide vaccines in the child population, no data are so far available to compare the immunogenicity.
of PCV13 and PPSV23 in adult patients with SLE. Based on the recent Centre for Disease Control and Prevention (CDC) recommendations, stepwise pneumococcal vaccination, a PCV13 prime-PPSV23 boost which was the previous recommended strategy for young children, adults aged 65 years old and patients at risk for pneumococcal disease has been revised. The advisory committee currently recommends one dose of PCV (either PCV20 or PCV15) for adults aged ≥65 years who PCV-naive or whose previous vaccination history is unknown. For adults aged 18–69 years with underlying conditions, who were PCV-naive or unknown vaccination history, one dose of PCV (either PCV20 or PCV15) is recommended. If PCV15 is used as the first-line vaccination, a dose of PPSV23 should be administered 1 year later. The evidence regarding the combination of pneumococcal vaccines in autoimmune inflammatory rheumatic disease (AIIRD) patients is insufficient. However, in a randomised trial, no difference in terms of immunogenicity was found between sequential administration of PCV7, followed by PPSV23 in comparison with PPSV23 alone.17

**Rituximab**

The impact of concomitant immunosuppressive therapy on the immunogenicity of pneumococcal vaccinations remains an area of uncertainty. While no apparent effect was reported in an early study, based on recent studies and meta-analysis, antibody responses appear to diminish in the setting of immunosuppressive therapy. Rituximab, as an anti-CD20 agent, depletes B-cells, with a variable reconstitution period of 6–9 months following infusion. Few studies evaluating the pneumococcal vaccinations in patients with SLE receiving RTX treatment have been published, which all investigated antibody responses only. Bingham et al reported a decreased antibody response with the addition of RTX (77% in RTX plus MTX vs 82% in MTX alone) in patients with rheumatoid arthritis (RA). In terms of monitoring long-term vaccine efficacy, no data have been published so far in patients with SLE, whereas Broyd et al showed that the efficacy of the PPSV23 vaccine appears to be preserved in patients with RA, spondyloarthritis (SpA), psoriatic arthritis (PsA) and inflammatory bowel disease (IBD) over the long term (for at least 10 years), and not affected by biologics. However, the biologics assessed in this study were TNF-inhibitors and tocilizumab. Sacre et al reported that some factors including exposure to immunosuppressive agent, a lymphopenia (<1000/mL), a B-cell lymphopenia notably in the naive and transitional subsets and a hypogammaglobulinaemia (<5 g/L), are associated with failure to sustain immune protection at 12 months. Accordingly, in a systematic review and meta-analysis, some predictive factors for poor immunogenicity have been identified namely including high erythrocyte sedimentation rate (ESR), older age, earlier SLE onset, high disease activity and concurrent immunosuppressive therapy. However, the heterogeneity of the data reviewed in this analysis necessitates caution when addressing risk factors based on these authors’ conclusions.

**Belimumab**

Belimumab, a human immunoglobulin monoclonal antibody that blocks a soluble B lymphocyte stimulator protein from binding to its receptor on B cells, is currently one of only two biological treatments approved for SLE by the Food and Drug Administration (FDA) in the USA (anifrolumab being the other). In 2020 and 2021, belimumab was approved for the treatment of adults with active lupus nephritis, by FDA and by European Medicines Agency (EMA). As part of the BLISS-76 study, patients with SLE with a history of prior pneumococcus, tetanus and influenza vaccination were assessed for antibody titres before and after treatment with belimumab plus standard therapy (ST) or placebo plus ST. No difference was found among treatment groups, implying that belimumab did not affect pre-existing antibody response to pneumococcal vaccines. A small subgroup of BLISS-76 trial who received pneumococcal vaccination during study (n=7) was also assessed. No difference was found in the immune response between the belimumab and non-belimumab groups, but the number of patients studied is a major limitation when drawing conclusions. Encouragingly, no serious or severe pneumococcal pneumoniae were seen in all groups. A randomised, open-label study with 79 patients with SLE compared those
who were vaccinated with the pneumococcal (PPSV23) vaccine 4 weeks before belimumab (prebelimumab cohort), and those vaccinated 24 weeks after belimumab (belimumab-concurrent cohort). The vaccine response rate 4 weeks after vaccination was similar in the two groups (97% in prebelimumab cohort vs 97.6% in belimumab-concurrent cohort). This study supports the view that belimumab treated patients receiving a pneumococcal vaccination have no change in immune response.27

In the study by Nagel et al, 47 patients with SLE and 21 healthy controls who were vaccinated with 13-valent conjugated pneumococcal vaccine, were compared in terms efficacy, the impact of disease-modifying antirheumatic drugs (DMARD) and addition of belimumab. Forty patients with SLE were on conventional DMARD, with 11 of those being added belimumab, and 32 patients were concomitantly on prednisolone. The antibody response postvaccination was found to be lower compared with healthy controls (p=0.02). The addition of belimumab to patients previously on conventional DMARD or prednisolone did not alter the antibody response to pneumococcal vaccination.28

Recommendation
According to EULAR, pneumococcal vaccinations are strongly recommended for patients with rheumatic disease taking DMARD therapy, preferably administering PCV13 followed by a dose of PPSV23 at least 8 weeks later, with a booster of PPSV23 given 5 years later.9 In contrast, recently published ACR guideline recommends pneumococcal vaccination in patients with rheumatic and musculoskeletal disease aged <65 years who are receiving immunosuppressive drugs. The task force also refers to CDC guidelines when choosing a strategy of which specific pneumococcal vaccination should be performed.29 This strategy, despite improving the pneumococcal vaccination responses in patients treated with conventional synthetic DMARD, remains inadequate for those on rituximab. The first dose should be ideally implemented before initiating DMARD therapy. Patients on rituximab should be vaccinated at least 2 weeks (ideally 4 weeks) before their next dose of rituximab is due.30 In terms of belimumab, although no consensus has been reached, pneumococcal vaccination should be administered as in the general population until proved otherwise.

INFLUENZA VACCINATION

Background
Influenza is an important infectious pathogen in morbidity and mortality of patients with SLE. In a real-life cohort study, patients with SLE vaccinated against influenza showed a lower hospitalisation rate (HR 0.82), fewer admissions to the intensive care unit (HR 0.53), to hospital for septicemia, bacteremia or viraemia (HR 0.48) and lower predisposition to death (HR 0.41).31 In this study, lack of data regarding immunosuppressive agents used is one of the major limitations while analysing this conclusion. Influenza vaccination in patients with SLE, despite early concerns regarding potential risks for disease flares, has not been found to affect disease activity.31–33 Subsequently, studies have reported similar, adequate responses to influenza vaccination in patients with SLE, although some reports described relatively lower humoral responses. Importantly, all of these reports suggested that influenza vaccine is well tolerated in patients with SLE.6 7 34–37 The difference in vaccine immunogenicity appears to be viral-strain specific. In a study of 24 patients with SLE, the response rates to the A/Beijing/262/95 (H1N1), A/Sydney/05/97 (H3N2) and B/Harbin/07/94 components were found to be 58%, 63% and 38%, respectively, which are lower than in the general population.14 In a prospective study of 1668 patients with adult autoimmune rheumatic disease (ARD), 572 with SLE, after immunisation with non-adjuvant influenza A (H1N1) vaccine seroprotection rate (titre>1:40) and seroconversion rate were found to be significantly lower compared with healthy controls (64.9% vs 82.9% for seroprotection rate; p<0.0001 and 60.5% vs 76.9% for seroconversion rate; p<0.0001, respectively). Moreover, geometric mean titre increase in antibody response were also blunted in comparison to healthy controls (7.9 vs 13.2, p<0.0001).38 In a meta-analysis, seroprotection and seroconversion rates were notably reduced in patients with SLE, particularly in those given the A/H1N1 and A/H3N2 vaccines, but not influenza B.39 Another systematic review reported similar results with lower immune responses to influenza A strains, in contrast to preserved seroprotection against influenza B in patients with SLE.40 Importantly, immunosuppressive drugs were found to impair the vaccine response.40 A second booster dose of vaccine to improve immunogenicity, given 3–4 weeks after the first, was successfully noted in patients with SLE receiving seasonal influenza vaccination.11

Rituximab
The impact of RTX treatment on influenza vaccination has not been reported in patients with SLE. In contrast data from RA subjects showed that humoral response is impaired by RTX administration.42–44 More encouragingly, a study by Arad et al reported that cellular immunity remained preserved in patients with RA treated with RTX.45 Westra et al showed that an incremental increase in IgM and IgG (IgG1 and IgG3) antibodies against both influenza strains was inadequate in the RTX treated group. IgG restoration was observed 6–10 months after RTX treatment, but there was no change in the IgM response.46

Belimumab
Eighty-nine patients with SLE from the BLISS-76 trial were vaccinated against influenza during this study.26 Although the antibody response was lower in patients on belimumab (1 mg/kg and 10 mg/kg) compared with placebo, the majority of patients reached adequate titres (which were accepted as >1:10) to reduce the risk of infection. Four patients among those receiving belimumab 1 mg/kg did not reach adequate titre levels against the two strains. In both belimumab groups, a total of 10 influenza cases were reported, all of which were mild to moderate. Utilisation of the same influenza strain for the subsequent seasons and different vaccination timepoints in prestudy and on-study are major limitations that may lead to variable belimumab response.26

Recommendation
Despite lower seroprotection or seroconversion rates compared with healthy population, inactivated influenza vaccination still offers some protection, therefore, it should be strongly recommended to all patients with SLE annually.7 Although there has been some evidence that a booster for influenza increases the immunogenicity in patients with SLE, more studies are needed to make a general statement. According to EULAR guideline, in case of RTX use, influenza vaccine should ideally be administered before initiating rituximab, or as long after the last dose of rituximab and 2–4 weeks before the next dose.11 In contrast, the recent ACR guideline recommends a conditional influenza vaccination rather than cancelling vaccination in RTX users.29 No specific statement for influenza vaccination is available.
for patients treated with belimumab. Data from belimumab, although limited, have not shown any alterations in antibody responses, therefore, routine vaccination should be undertaken until proven otherwise.

**SARS-CoV-2 Vaccination**

**Background**

There was a concern during the first phase of the COVID-19 pandemic that patients with immune-mediated inflammatory diseases (IMID) were at high risk for SARS-CoV-2 infection and COVID-19-related severe outcomes. Despite conflicting results, a meta-analysis indicated that patients with autoimmune diseases did have a significantly higher risk of COVID-19 than in the healthy population.47,48 Furthermore, certain medications notably glucocorticoids and B-cell-depleting therapy were found to be associated with severe COVID-19 outcomes.47,50 Early reports on SARS-CoV-2 vaccination in this specific population showed that vaccines are well tolerated, but humoral immune response rates to SARS-CoV2 vaccination were reduced with the use of methotrexate, mycophenolate, glucocorticoids, abatacept and especially in those receiving B-cell depleting agents.21,51,52

**Rituximab**

In a multicentre observational study by Furer et al, the immunogenicity and safety of the two-dose regimen BNT162b2 mRNA vaccine were investigated in adult patients with ARD (n=686) and was compared with the general population (n=121). In this study, 101 out of 686 patients had SLE and CD20-depleting agents were used in 87 patients (86 RTX and 1 ocrelizumab), of whom 28 were treated with monotherapy and 14 were combined with MTX. Vaccine immunogenicity was significantly impaired in RTX users, who had the lowest seropositivity rate of 39% (p<0.001). Vaccine immunogenicity was significantly affected by the time interval between the administration of RTX and when BNT162b2 vaccination was given. The seropositivity rate in vaccinated patients showed increasing trends: below 20% within 6 months to about 50% in 1 year after RTX treatment. The impact of anti-CD20 treatment on immunogenicity was sustained regardless of the concomitant use of other DMARDs.21

The RituxiVac study53 showed that nearly a quarter of RTX receiving patients were positive both for anti-SARS-CoV-2 spike IgG and cell-mediated responses, compared with the majority (88%) of healthy controls (p<0.001). Ninety-six patients with a history of anti-CD20 treatment had ARDs (20 ANCA-associated vasculitis (AAV), 6 each with RA, Sjögren’s syndrome, SLE, 4 with systemic sclerosis and IgG4-related disease and 1 had an IgA vasculitis) recruited in this study. More than half were on immunosuppressive comedication. Anti-spike IgG antibodies were detected in nearly half of the patients (49%) compared with healthy controls (100%) after the second vaccine dose implementation (p<0.001). SARS-CoV-2-specific IFNγ release was found to be significantly different among the groups (0.62 U/mL (IQR 0.27–1.01) in healthy controls vs 0.04 (0.01–0.21) in the patients (p<0.001)). The time since the last anti-CD20 therapy (>7.6 months), peripheral CD19+ cell count (>27 cells per μL) and CD4+ lymphocyte count (>653 cells per μL) were predictive of humoral vaccine response (area under the curve (AUC) 67% (95% CI 56% to 78%) for the time since last anti-CD20 therapy, 67% (95% CI 55% to 80%) for peripheral CD19+ count, and 66% (95% CI 54% to 79%) for CD4+ count).

Interestingly, there was no association between total serum IgG concentrations and humoral vaccine responses, but the low cumulative dose of CD20-depleting therapy and the longer time since the last treatment were found to be independent predictors of vaccine-induced humoral immune responses (p<0.001). Furthermore, peripheral CD19+ cell counts, and coexisting immunosuppressive medication were the only determinants that affected vaccine-elicited cell-mediated immune responses (p<0.001).53 In contrast, Simon et al54 reported that T cell responses against the spike S1 and nucleocapsid proteins were unaffected after B-cell depleting therapy in vaccinated patients. Another study focused on humoral and cell-mediated responses to SARS-CoV-2 vaccination in patients with immune-mediated inflammatory diseases who failed to seroconvert after two doses of SARS-CoV2 vaccine and were exposed to a third vaccination with either mRNA or vector-based vaccines. The seroconversion rates were significantly higher in the non-RTX-pretreatment group compared with the RTX-pretreated group (78.8% vs 18.2%, p<0.0001). T-cell responses showed notable increase in the RTX-pretreated group after the third dose of the vaccine, regardless of the type.55 Similarly, a recent study showed that the humoral response was fully restored after the third dose in all patients treated with MTX, anticytokine biological agents, abatacept and JAK inhibitors, whereas only 30% of RTX users achieved these targets, carrying a 16.1-fold increased risk for a negative humoral response (OR 0.062 (95% CI 0.017 to 0.224, p≤0.0001). No change in the cellular immune response was seen in RTX-treated patients following the third vaccine.56 The role of B cell in humoral immune response and the impact of B-cell depletion drugs have been well understood in COVID-19 infected and/or vaccinated against SARS-CoV2. However, in a recently published study by Md Yusof et al, rituximab dose, time to vaccination since last rituximab dose, vaccine type and peripheral B-cell depletion were not found to lead moderate-to-severe COVID-19 outcomes.57 Encouragingly, Swadling et al have reported that replication-transcription complex (RTC)-epitope-specific T cells that cross-recognised human seasonal coronavirus (HCoV variants), specifically RNA polymerase, increase in vivo to abort viral infection. These data highlight the potential role of novel vaccines targeting RTC-specific T-cells.58

In a meta-analysis of 23 studies59 comprising 1342 patients with SLE, RA, non-Hodgkin’s lymphoma and AAV diagnoses, the overall rate (proportions of responders) for humoral response and cell-mediated responses were found to be 0.40 (40%) (95% CI 0.35% to 0.47%) and 0.71 (71%) (95% CI 0.57% to 0.87%), respectively. Humoral response rates were higher in patients whose last anti-CD20 therapy administration exceeded 6 months when compared those who received anti-CD20 within last 6 months (0.63 (95% CI 0.53 to 0.72) vs 0.2 (95% CI 0.03 to 0.43); p≤0.01). The humoral response rates were positively correlated with the presence of circulating B-cells.59

**Belimumab**

A recent study of 50 patients with SLE prospectively assessed the immune response of SARS-CoV-2 vaccination in belimumab (n=30) and non-belimumab (n=20) treated patients. Most received an mRNA-based vaccine (92%), and a small proportion of patients were immunised with a vector-based vaccine (8%). Among 30 patients in the belimumab group, only 2 failed to produce antibodies against SARS-CoV2 even after three doses. Notably, these patients had been previously treated with RTX. No statistically significant difference was found between the two groups.60 Despite promising results, no data are available about the prevention of infections. This observation was consistent with a previous study by Fabris et al, which enrolled 17 patients with SLE on belimumab and 13 healthy controls. Although average
antibody titres were significantly lower compared with controls, 94% of belimumab-treated patients produced antibodies against SARS-CoV-2. No difference in T-cell response was seen between the groups.61

Recommendation
While an ACR guideline recommended a time frame of as long as possible after the last dose and 2–4 weeks before the next dose for RTX,62 the recent EULAR task force suggested monitoring the B-cell repopulation to decide who will or will not respond to vaccination, however, there is an absence of good evidence to support this. Thus, the guideline also adds that no more specific recommendation can be made with the level of current evidence.63 For those planned to have or to be treated with belimumab, it appears that vaccination against SARS-CoV2 is safe and effective, but data are still limited.

TETANUS/DIPHTHERIA VACCINATION

Background
Data investigating antibody responses after tetanus/diphtheria vaccination in ARD are relatively limited in comparison to pneumococcal, influenza and recently SARS-CoV2 vaccinations.5 8 64 To date, there are no published data regarding the antibody response in patients with SLE taking rituximab after tetanus/diphtheria vaccination. Battafarano et al5 reported that a protective level of antibody response to tetanus toxoid developed in the majority of patients with SLE (90%). A diminishing trend in antibody response was seen, particularly in active patients treated with immunosuppressive agents, but did not reach statistical significance.6

Rituximab
In a controlled trial including 103 patients with RA by Bingham et al, (13) recall responses to the T-cell-dependent tetanus vaccine did not differ with the addition of RTX treatment to MTX compared with those on MTX alone (39.1% vs 42.3%).5 In contrast, in a multicentre cohort study including 284 patients with RA, axial SpA/PsA, Behcet’s disease and AAV, response rates in SpA/PsA patients were significantly higher than RA and vasculitis patients.64 Tetanus booster vaccination seems to be safe and immunogenic in patients with rheumatic diseases, when compared with diphtheria vaccination, which is less immunogenic. More importantly, rituximab was found to be the only factor diminishing tetanus immunogenicity but had no impact on diphtheria vaccine responses.64 This discrepancy between both studies might be explained by the differences in study populations, with the latter consisting of relatively heterogeneous disease groups, age distributions and low numbers of patients who had diphtheria vaccination given RTX treatment.

Belimumab
BLISS-76 study has demonstrated that antibody responses against tetanus in a previously vaccinated group did not differ after starting belimumab, with titres ≥0.50 IU/mL at week 52. This observation was similar to a study in a population of those who were vaccinated after belimumab infusion. However, there were few patients on belimumab in this group (3 out of 5), and further investigations are needed.66

Recommendation
Based on limited data and EULAR recommendation, patients with SLE, if indicated, should receive tetanus vaccine prior to starting rituximab treatment.5 For patients treated with belimumab, routine tetanus vaccination can be recommended according to available data suggesting no alterations in antibody response, but further studies still are warranted.

HERPES ZOSTER VACCINATION

Background
Immunocompromised patients have a higher incidence of HZ compared with the general population and are at increased risk for developing severe and life-threatening complications, either disease or medication related.65 However, live-attenuated vaccines remain an area of concern due to the question of tolerability and safety issues in autoimmune diseases. To date, two studies have evaluated the safety of the live-attenuated zoster vaccine in patients with AIIRD using immunosuppressive drugs have been published.66 67 The first large cohort study including 60 years and older with AIIRD did not show any increase in the incidence of herpes zoster during the first 42 days after vaccination, even with biological treatment including RTX.66 All patients recruited in this study had a diagnosis of RA, AS, PsA and IBD and the major limitation was the older age in the study population. In a small cohort of patients with SLE (n=10), followed for 12 weeks, HZ vaccination provided a measurable immune response, but lower than controls. However, these patients all had mild disease activity, were over age 50 years and taking mild to moderate immunosuppressive medications. Furthermore, the cases were specifically selected from those who were serologically positive with VZV before vaccine administration.67 Thus, it is also important to note that these results cannot be comfortably applied to younger population and clinicians should carefully approach the findings while recommendation.

Rituximab
We are unaware of any data have been published regarding HZ vaccination in patients with SLE receiving biological treatment. In a phase I conducted study including 80 adults with haematological malignancy receiving anti-CD20 monoclonal antibodies, the efficacy of inactivated zoster vaccine (ZVv3) was investigated at 28 days (postdose 4) by using interferon-c enzyme-linked immunospot (IFN-c ELISPOT). A statistically significant immune response was observed at 28 days, with an estimated geometric fold increase rate (GMFR) of 4.34 (GMFR>1.0 was accepted as sufficient for eliciting immune response against ZVv3). The vaccine seems to be well tolerated, and no major serious adverse events were reported.68

Recommendation
Currently, EULAR recommends zoster vaccination in high-risk patients, whereas no specific conditions were described in a recent ACR guideline, which suggested that VZV vaccination be given to all rheumatic patients over 18 years.9 29 Despite RZV having been approved for adults over age 18 with immunocompromised conditions by the EMA, no data are available in assessing the use of RZV in patients with ARD.69 From the perspective of SLE, the impact of biological agents, particularly rituximab and belimumab, has not been tested yet.

OTHER NON-LIVE VACCINATION

Data monitoring the effect of biological agent on other non-live vaccinations are insufficient. Rituximab treatment is well known to cause hepatitis B reactivation, but its impact on hepatitis B vaccination response in patients with SLE is still an area of investigation. In a study including 47 patients with RA of whom 8 were given RTX treatment, anti-HBS response rate was found to
be lower than other DMARDs (etanercept or infliximab, 25% vs 100%, p=0.06). Two out of eight RTX users achieved anti-IgM levels of over 10 IU/mL.\footnote{70}

In a study by Mertoglu et al, conducting the immunogenicity of inactivated hepatitis A vaccination in childhood patients with SLE, two were on rituximab treatment. One was reported to achieve seropositivity after vaccination.\footnote{71} Although no study is available to investigate the rituximab impact on inactivate polio vaccination in patients with SLE, a study including lymphoma patients which 38 patients were given rituximab-based regimen, post-treatment immune responses were found to be 89% and 97% for PV1 and PV3, respectively. Post-treatment median IgG levels were also found similar and sufficient for protection.\footnote{72} In terms of human papilloma virus vaccination, Mok et al reported lower seroconversion rate in mycophenolate mofetil users (with or without prednisolone). However, no patients in this study received any biological treatment.\footnote{73}

**Recommendation**

As there is insufficient data investigating the impact of biological drugs on other non-live vaccinations in patients with SLE, clinicians should recommend non-live vaccinations other than influenza according to the recent ACR guidelines in RTX users: deferring vaccination until the next dose is due and give RTX at least 2 weeks after vaccination.\footnote{29}

**CONCLUSION**

Vaccinations are the cornerstone of preventive medicine; their critical role having been recently confirmed during the COVID-19 pandemic. There are clear benefits to vaccinating patients with SLE and inactivated vaccines appear to be safe. However, in this biological era, further studies are warranted to monitor the efficacy of vaccines in patients with SLE, especially those on immunosuppressive medication. It should be also kept in mind that the concomitant use of other immunosuppressive agents with biological agents might alter the vaccination induced immune responses, therefore, clinicians should be cognizant of this effect. Clinicians should carefully assess the indications and discuss the risks and benefits with the patient as a part of routine cases management.

**Contributors**

DAI envisioned the article. RY drafted the initial manuscript. All authors substantially contributed to the conception and design of the work, and the acquisition, analysis or interpretation of data for the work. All authors revised the manuscript for critically important intellectual content and approve the final version for publication.

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