Title: Approach to vaccination in systemic lupus erythematosus on biologic 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 remains 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 biologic era in rheumatology, relatively little data have been published investigating these parameters in those receiving biologic agents, therefore no definitive consensus about a vaccination policy for SLE patients is currently available. In this review, we aim to address what is established about vaccinating systemic lupus erythematosus patients on biologic agents and discuss potential problems.

INTRODUCTION

Infections remain the leading cause of mortality and morbidity in patients with SLE.[1] 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 hypocomplementemia, and abnormal neutrophil and macrophage response to pathogens.[2] 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.[2]

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.[3] This approach has concomitantly raised the importance of prevention of infectious complications triggered by these agents in SLE patients.

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.[4-8] In this regard, the evidence based 2019 update of The European Alliance of

Associations for Rheumatology (EULAR) recommendation has highlighted that SLE patients should be strongly encouraged to have pneumococcal and influenza vaccination.[9] Despite these recommendations, immunisation rates remain suboptimal among SLE patients, with only 42-64% for receiving influenza vaccine and 60-67% for a pneumococcal vaccine.[10] This inadequate rate of vaccination may be explained by several factors including lack of medical prescription and misconceptions about efficacy and safety issues in autoimmune diseases.[10] In the biologic era over the last 20 years, the exponential increase in the use of these agents in many patients including those with SLE, has led to questions about their impact on vaccine responses and long-term efficacy. Research on this topic has been accumulated but conclusive recommendations remain elusive.

Here we review the latest data in the field of vaccinations in SLE patients focusing on the perspective of biologic treatment (notably rituximab and belimumab), addressing the impact of the vaccinations, and drawing attention to potential problems when vaccinating this specific population (Table-1).

PNEUMOCOCCAL VACCINATION

Background

Respiratory infections are one of the most common causes of infection in the SLE population, with Streptococcus pneumoniae being the most frequent pathogen associated with mortality and morbidity.[11] In a population-based study, SLE patients were found to have a 13 times higher risk of invasive pneumococcal infection compared with a healthy population (201 versus 15.6 per 100.000 patient-years).[12,13] In this study, streptococcus pneumoniae was seen to be responsible for 8.3% of all serious infections.[12] Schurder et al. have reported that hypogammaglobulinemia (<5 g/L) and past medical history of lupus nephritis are significant risk factors for development of pneumococcal infection in SLE. Moreover, they have found that either steroid and/or immunosuppressive drug use increase infection severity in this group. [14] To date, several studies have demonstrated that pneumococcal vaccination is well-tolerated in SLE, but the antibody response to pneumococcal vaccination in this group is relatively insufficient, leading to potential long-term concerns.[4 5] More encouragingly, Alyasin et al reported an adequate immune response in 78% of children with SLE.[15] 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 SLE patients. Based on the recent CDC recommendations, stepwise pneumococcal vaccination, a PCV13 prime-PPSV23 boost which was the previous recommended strategy for young children, adults above 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 one year later.[16] The evidence regarding the combination of pneumococcal vaccines in autoimmune inflammatory rheumatic disease (AIIRD) patients is insufficient. However, in a randomized 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[4 8 17-20], 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.[21] Few studies evaluating the pneumococcal vaccinations in SLE patients receiving RTX treatment have been published, which all investigated antibody responses only.[17] Bingham et al reported a decreased antibody response with the addition of RTX (57% in RTX plus MTX versus 82% in MTX alone) in patients with rheumatoid arthritis (RA).[8] In terms of monitoring long-term vaccine efficacy, no data have been published so far in SLE patients, whereas Broyde and colleagues showed that the efficacy of the PPSV23 vaccination appears to be preserved in patients with RA, spondylarthritis (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.[22] 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 hypogammaglobulinemia (<5 g/l), are associated with failure to sustain immune protection at 12 months.[23] 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.[24] 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 (BLyS) from binding to its receptor on B cells, is currently one of only two biologic treatments approved for SLE by the Food and Drug Administration (FDA) in the United States of America (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).[25]

As part of the BLISS-76 study, SLE patients with a history of prior pneumococcus, tetanus, and influenza vaccination were assessed for antibody titers 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.[26] A small subpopulation 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.[26] A randomized, open-label study with 79 SLE patients compared those who were vaccinated with the pneumococcal (23-valent pneumococcal polysaccharide) vaccine 4 weeks before belimumab (pre-belimumab 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 pre-belimumab cohort versus 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 SLE patients 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 SLE patients were on conventional DMARD, with 11 of those being added belimumab, and 32 patients were concomitantly on prednisolone. The antibody response post-vaccination was found to be lower compared to 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 administrating 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.[9] 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 SLE patients. In a real-life cohort study, SLE patients vaccinated against influenza showed a lower hospitalization rate [(HR) 0.82], fewer admissions to the Intensive Care Unit [HR 0.55], to hospital for septicaemia, bacteraemia or viremia [HR 0.48] and lower predisposition to death [HR 0.41].[30] In this study, lack of data regarding immunosuppressive agents used is one of the major limitations while analysing this conclusion**.** Influenza vaccination in SLE patients, 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 SLE patients, 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 SLE patients, 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.[34] In a prospective study of 1668 adult autoimmune rheumatic disease (ARD) patients, 572 with SLE , after immunisation with non-adjuvant influenza A (H1N1) vaccine seroprotection rate (titre $\geq$ 1:40) and seroconversion rate were found to be significantly lower compared to 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 titer 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 SLE patients, 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 SLE patients.[32] 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 SLE patients receiving seasonal influenza vaccination.[41]

Rituximab

The impact of RTX treatment on influenza vaccination has not been reported in SLE patients. In contrast data from RA subjects showed that humoral response is impaired by RTX administration.[8 42-44] More encouragingly, a study by Arad et al reported that cellular immunity remained preserved in RA patients treated with RTX.[45] Westra et al, showed that an in-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 to 10 months after RTX treatment, but there was no change in the IgM response.[46]

Belimumab

Eighty-nine SLE patients 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 to placebo, the majority of patients reached adequate titers (which was accepted as $\geq$ 1:10) to reduce the risk of infection. Four patients among those receiving belimumab 1 mg/kg did not reach adequate titer levels against the two strains. In both belimumab groups, a total of 10 influenza cases were reported, all of which were mild to moderate. Utilization of the same influenza strain for the subsequent seasons and different vaccination timepoints in pre-study and on-study are major limitations that may lead to variable belimumab response.[26]

Recommendation

Despite lower seroprotection or seroconversion rates compared to healthy population, inactivated influenza vaccination still offers some protection, therefore it should be strongly recommended to all SLE patients annually .[9] Although there has been some evidence that a booster for influenza increases the immunogenicity in SLE patients, 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.[9] 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, albeit limited, have not shown any alterations in antibody responses, therefore routine vaccination should be undertaken until proven otherwise.

SARS-CoV2 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.[47-49] 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 autoimmune rheumatic disease (AIRD)(n=686) and was compared with the general population (n=121).[21] 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 one 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 study[53] 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 autoimmune rheumatic diseases (20 ANCA-associated vasculitis, six each with RA, Sjögren's syndrome, SLE, four with systemic sclerosis and IgG4-related disease, and one had an IgA vasculitis) recruited in this study. More than half were on immunosuppressive co-medication. Anti-spike IgG antibodies were detected in nearly half of the patients (49%) compared to 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 UI/mL (IQR 0·27–1·01) in healthy controls versus 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 56–78] for the time since last anti-CD20 therapy, 67% [55–80] for peripheral CD19+ count, and 66% [54–79] 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 co-existing immunosuppressive medication were the only determinants that affected vaccine-elicited cell-mediated immune responses ($p<0·001$).[53] In contrast, Simon et al.[54] reported that T cell responses against the spike S1 and nucleocapsid proteins were unaffected after B-cell depleting therapy in vaccinated patients.[51] Another study focussed 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-pre-treatment group compared to the RTX-pre-treated group (78.8% vs 18.2%, $p<0.0001$). T-cell responses showed notable increase in the RTX-treated 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, anti-cytokine biologic 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, $p\leq0.0001$). 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 COVİD-19 infected and/or vaccinated against SARS-CoV2. However, in a recently published study by Yuzaiful 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, Maini and colleagues have reported that replication-transcription complex (RTC)-epitope-specific T cells that cross-recognized human seasonal coronavirus (HCoV variants), specifically RNA polymerase, increase in vivo to abort viral infection. This data highlight the potential role of novel vaccines targeting RTC specific T-cells.[58]

In a meta-analysis of 23 studies [59] comprising 1342 patients with SLE, RA, non-Hodgkin lymphoma (NHL), and ANCA-associated vasculitis (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) versus 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 SLE patients prospectively assessed the immune response of SARS-CoV2 vaccination in belimumab (n=30) and non-belimumab (n=20) treated patients. Most received a mRNA-based vaccine (92%), and a small proportion of patients were immunized with a vector-based vaccine (8%). Among 30 patients in the belimumab group, only two 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 SLE patients on belimumab and 13 healthy controls. Although average antibody titers were significantly lower compared to controls, 94% of belimumab-treated patients produced antibodies against SARS-Cov2. 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 is 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 SLE patients taking rituximab after tetanus/diphtheria vaccination. Battafarano et al[5] reported that a protective level of antibody response to tetanus toxoid developed in the majority of SLE patients (90%). A diminishing trend

in antibody response was seen, particularly in active patients treated with immunosuppressive agents, but did not reach statistical significance.[5]

Rituximab

In a controlled trial including 103 RA patients by Bingham and colleagues, [13] recall responses to the T-cell-dependent tetanus vaccine did not differ with the addition of RTX treatment to MTX compared to those on MTX alone (39.1% vs 42.3%).[8] In contrast, in a multicentre cohort study including 284 patients with RA, axial SpA/PsA, Behcet's disease, and ANCA-associated vasculitis, 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 to 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 titers $\geq$ 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.[26]

Recommendation

Based on limited data and EULAR recommendation, SLE patients, if indicated, should receive tetanus vaccine prior to starting rituximab treatment.[9] 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 autoimmune inflammatory rheumatic disease (AIIRD) patients 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 biologic 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 SLE patients (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 SLE patients receiving biologic treatment. In a phase 1 conducted study including 80 adults with hematologic malignancy receiving anti-CD20 monoclonal antibodies, the efficacy of inactivated zoster vaccine (ZV_{IN}) 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 ZV_{IN}). 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 European Medicines Agency (EMA), no data are available in assessing the use of RZV in ARD patients.[69] From the perspective of SLE, the impact of biologic agents, particularly rituximab and belimumab, has not been tested yet.

OTHER NON-LIVE VACCINATION

Data monitoring the effect of biologic 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 SLE patients is still an area of investigation. In a study including 47 RA patients of whom eight 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-HBS level of over 10 IU/ml.[70]

In a study by Mertoglu et al, conducting the immunogenicity of inactivated hepatitis A vaccination in childhood systemic lupus erythematosus patients, two were on rituximab treatment. One was reported to achieve seropositivity after vaccination.[71] Although no study is available to investigate the rituximab impact on inactivate polio vaccination in SLE patients, 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.[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 biologic treatment.[73]

Recommendation

As there is insufficient data investigating the impact of biologic drugs on other non-live vaccinations in SLE patients, 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 two weeks after vaccination.[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 SLE patients

and inactivated vaccines appear to be safe. However, in this biologic era, further studies are warranted to monitor the efficacy of vaccines in SLE patients, especially those on immunosuppressive medication. It should be also kept in mind that the concomitant use of other immunosuppressive agents with biologic 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.

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Table-1: Vaccination recommendations for SLE patients on biologic agents

Vaccine type	**Specific recommendations/comments**
Pneumococcus	*Rituximab*: vaccinate before starting rituximab, or as long as possible after the last dose (ideally ≥6 months) and 4 weeks before the next dose[*] *Belimumab*: no specific statement is available; vaccination should be performed according to general population[+]
Influenza	*Rituximab*: vaccination should ideally be administered before initiating rituximab, or as long after the last dose of rituximab and 2–4 weeks before the next dose [*] *Belimumab*: no specific statement is available; vaccination should be performed according to general population[+]
SARS-CoV2	*Rituximab*: as long as possible after the last dose, 2–4 weeks before the next dose[&] (However, if B-cell repopulation can be monitored, the optimal time for vaccination can be determined according to the results[**]) *Belimumab*: no specific statement is available; vaccination should be performed according to general population[+]
Varicella zoster	*Rituximab*: recommendation is conditional. Patients with high risk profile for zoster infection[*] (Age >50); before starting rituximab, or as long as possible after the last dose (ideally ≥6 months) and 4 weeks before the next dose[&] *Belimumab*: no data is available, the decision for vaccination should be carefully assessed especially based on patients with high risk profile for VZV infection complications[+]
Tetanus	*Rituximab*: vaccinate before starting rituximab[*] *Belimumab*: No specific statement is available; vaccination should be performed according to general population[+]
Other non-live vaccinations	*Rituximab:* deferring vaccination until the next RTX dose is due, give RTX at least two weeks following vaccination***

[*]2019 European League Against Rheumatism recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases[9]

** 2022 European League Against Rheumatism recommendations for the management and vaccination of people with rheumatic and musculoskeletal diseases in the context of SARS-CoV-2[63]

*** 2022 American College of Rheumatology Guideline for Vaccinations in Patients With Rheumatic and Musculoskeletal Diseases[29]

& American College of rheumatology guidance for COVID-19 vaccination in patients with rheumatic and musculoskeletal diseases: version 1[62]

+ Authors' recommendations based on timely available evidence.