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B Cell Therapies, Approved and Emerging: a Review of Infectious Risk and Prevention During Use

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Abstract The development of B cell-targeted biologics represents a major advance in the treatment of autoimmune rheumatic diseases. As with other immunosuppressive agents, risk of infection is a key clinical concern. This review summarises safety data from 15 years of experience of rituximab in autoimmune diseases with a particular focus on opportunistic infection and class-specific complications and infection risk. Rarely, cases of progressive multifocal leucoencephalopathy in rituximab-treated patients (5/100 000) have accumulated over time although no proven causal association has yet been shown. With repeat cycles of therapy, hypogammaglobulinaemia has been observed in a larger proportion of patients and is associated with increased risk of serious infections. The infection profile of the newer B cell-targeted agent, belimumab, in patients with active systemic lupus erythematosus is also discussed. Data from registries are needed to extend insights further and also to evaluate for any impact with the difference in mode of action of belimumab and infection risk in this population.

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Introduction

The development of biological disease-modifying anti-rheumatic drugs (bDMARDs) including B cell-targeted therapies represents a major advance in the treatment of autoimmune rheumatic diseases such as rheumatoid arthritis (RA), systemic lupus erythematous (SLE) and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). These therapies have been shown to provide effective therapeutic options with improved quality of life for patients with inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs). However, the immunomodulatory properties of bDMARDs including rituximab have naturally raised safety concerns prompting careful evaluation in clinical trials and intensive post-marketing surveillance. Observations from these also provide insight into pathogenic basis of infectious diseases.

The aim of this report is to review infectious risk associated with currently licensed and emerging B cell therapies, the nature of reported infection and prevention strategies employed to minimise any risk with the use of B cell-targeted therapies in autoimmune rheumatic diseases. In particular, we will focus on data from (open-label) long-term extension (LTE) studies and registry cohorts. We will conclude with our expert opinion on future direction of these agents and recommendation with relation to safety.

Overview of B Cell Therapies Currently Available and Emerging

Various therapeutic strategies for B cell blockade have been investigated including B cell depletion, inhibition of B cell survival factors, inhibition of B cell receptor signalling,

development of B cell tolerogens and targeting of plasma cells. These have been met with varying degrees of success in clinical trials [1].

Rituximab, a chimeric anti-CD20 mAb, was the first licensed treatment for B cell non-Hodgkin's lymphoma in 1997. In autoimmune disease, it is licensed for moderately to severely active patients with RA who have had an inadequate response to one or more tumour necrosis factor inhibitor (TNFi) and remission induction in severe, active granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). Despite two negative randomised controlled trials in SLE [2, 3], rituximab is still widely used for highly resistant cases based on strong open-label evidence [4, 5]. The advantage of targeting CD20 molecule, which is expressed on the surface of B cells, is that it spares progenitor cells (allowing B cell regeneration) as well as long-lived plasma cells (preventing excessive reduction of normal immunoglobulin levels, at least with initial therapy). However, plasma cell numbers may fall if B cell depletion is prolonged with multiple cycles of therapy.

Belimumab is a fully humanised mAb that specifically binds to and neutralises the soluble cytokine, B cell activating factor of TNF family (BAFF), thus preventing it from binding to its receptors on the surface of B cells. BAFF and its homologue, a proliferation inducing ligand (APRIL), are responsible for B cell survival, maturation and differentiation. Following the success of two randomised controlled trials [6, 7], belimumab is the first and only therapy in over 50 years that has gained approval from the United States Food and Drug Administration (US FDA) and European Medicines Agency (EMA) for the treatment of active, autoantibody-positive SLE.

Other emerging B cell-targeted therapies under evaluation include 2nd generation anti-CD20 monoclonal antibody (mAb) (where the IgG1 is humanised or fully human to reduce immunogenicity, but with an unmodified Fc region) such as ofatumumab and veltuzumab and 3rd generation anti-CD20 mAb (humanised and with an engineered Fc region to improve therapeutic performance by adapting the effector functions) such as obinutuzumab. Another strategy for B cell depletion and inhibition is by targeting the CD22 molecule, which is responsible for regulation of B cell function and is a component of the B cell activation complex. Epratuzumab, an anti-CD22 humanised mAb, has recently completed recruitment for two phase III trials in SLE for which the results will be published later in 2015. Lastly, in terms of BAFF/APRIL blockade, a trial of atacicept in extra-renal lupus is ongoing. The results for atacicept in RA were negative [8] while another two in renal lupus were stopped prematurely due to increased therapy-associated severe infections [9, 10].

Associated Infection and Serious Infection Events

Data regarding serious infection event (SIE) from randomised controlled trials (RCTs), long-term extension (LTE) studies and registries are summarised in Table 1. The more detailed data from RA are further discussed below.

The rate of rituximab-associated SIE differs with different treatment stages. When rituximab was evaluated in patients with RA and TNF-inadequate response (TNF-IR), numerically higher rates of SIEs were seen in the rituximab 2×1000 mg group compared to placebo, 4.7 versus 3.2/100 patient-years, respectively, in the DANCER trial [11] and 5.2 versus 3.7/100 patient-years in the REFLEX trial [12]. On the other hand, the rate of SIE was lower in the two rituximab dosage groups (1000 and 500 mg) compared with placebo (3.74, 4.61 and 6.09/100 patient-years, respectively) when rituximab was evaluated in methotrexate-naive patients (IMAGE trial) [13]. An increased risk of SIE in patients treated with rituximab compared with placebo was not observed in the short term from a meta-analysis of three RCTs [14].

The 2011 Cochrane meta-analysis of use of biological therapies in RCTs in RA showed that of all the biologics studied, rituximab was associated with the lowest numerical odds for SIEs compared with control treatment (OR 0.26, 95 % CI 0.03 to 2.16) albeit not statistically significant. When rituximab was compared indirectly with other TNFis, anakinra, abatacept and tocilizumab, odds for SIEs remained lower in the rituximab group and were statistically significantly lower compared to certolizumab and anakinra [15].

The long-term safety data of patients with RA treated and maintained with repeat cycles of rituximab in combination with methotrexate (MTX) have been pooled from eight RCTs and two LTE studies (total follow-up 11,962 patient-years). This showed that the infection and SIE rates remained stable over time and with multiple courses of rituximab. Careful interpretation of data is needed as LTE studies sub-select patients with sustained response and do not include those who withdraw treatment due to intolerance. The SIE rate was 3.94/100 patient-years in the all exposure rituximab group (3.26/100 patient-years in patients observed for >5 years) and was comparable with the placebo+methotrexate group (3.79/100 patient-years). The commonest infections (>5 % patients) reported in the rituximab group were upper respiratory tract infections, nasopharyngitis, urinary tract infections, bronchitis, sinusitis, diarrhoea, influenza and gastroenteritis [16••]. This SIE rate is similar to data from long-term follow-up with other bDMARDs used in RA (ranging from 3.0 to 5.2/100 patient-years) [17–19].

The RCTs of ocrelizumab (OCR), a humanised anti-CD20 mAb in RA [20, 21] and SLE [22], were suspended due to increased SIE and opportunistic infections. In post-hoc analysis, OCR500+MTX group demonstrated improvement in clinical response included radiographic outcome, but this dose

Table 1 Summary of data pertaining to serious infection, opportunistic infection and risk factors for infection of autoimmune rheumatic disease patients treated with either rituximab or belimumab from randomised controlled trials (RCTs), pooled data [comprising RCTs and open-label long-term extension (LTE) studies of RCTs] and registries

Source of data	Disease group (number of patients treated with B cell agent)	Duration of follow-up	Treatment schedule	Serious infection event (SIE)	Opportunistic infections	Risk factors for infection
RITUXIMAB						
Pooled data (RCT+LTE)						
8 RCTs+2 LTE study [16••]	RA (n=3194)	11,962 PY	Rituximab (either 2×1000 mg or 2×500 mg given 2 weeks apart in RCTs and for maintenance in OLEs) 2428 (76 %) were retreated with RTX	3.94/100 PY (3.26/100 PY in patients observed >5 years) in RTX group versus 3.79/100 PY in placebo+MTX group	Pulmonary TB reactivation (n=2) Rate of other OIs: 0.06/100 PY (atypical pneumonia, n=2; Candida, n=1; pharyngeal abscess, n=1; Scedosporium lung infection, n=1; Pneumocystis jirovecii pneumonia, n=1; and JC virus, n=1) Rate of herpes zoster in RTX group (9/100 PY) versus (11.7/100 PY in placebo+MTX group	SIE rates were similar before and during/after low IgG, but both rates were significantly higher than in patients who never developed low IgG Baseline risk factors for development of low IgG: older, longer disease duration, lower mean CD19+count, lower mean IgG levels and had received more csDMARDs
RCT						
RAVE [76]	AAV (n=99)	18 months	Single-course RTX (375 mg/m² body surface area weekly for 4 weeks) for remission induction	Rate of SIE was similar: 7 and 12 % at 6 and 18 months in RTX monotherapy group versus 7 and 11 % in CyC+AZA maintenance group	None in RTX group but 3× fatal infections in CyC+AZA maintenance group (i) Enterococcus/Escherichia coli sepsis (ii) Pseudomonas aeruginosa sepsis and (iii) Pneumocystis jirovecii pneumonia with secondary Staphylococcus aureus/Escherichia coli sepsis in a patient not compliant with prophylaxis	No risk factors identified
RITUXVAS [77]	AAV (n=33)	2 years	Single-course RTX (375 mg/m² body surface area weekly for 4 weeks) for remission induction	Rate of SIE similar: 0.25/PY in RTX monotherapy group versus CyC+AZA maintenance group	2 cytomegalovirus infections reported in RTX group and none in the CyC+AZA maintenance group	RTX-treated patients had higher VDI at baseline (median, IQR: 2 (0–3)) compared to CyC+AZA maintenance (1 (0–2))
EXPLORER [2]	SLE (n=169)	78 weeks	Single-course RTX (2×1000 mg)	Higher rate of SIE in the placebo+csDMARDs group versus RTX+csDMARDs group; 17 and 9.5 %, respectively	More herpes zoster infection in RTX+csDMARDs Group; 16 (9.5 %) than Placebo+csDMARDs Group 3 (3.4 %)	None reported
LUNAR [3]	SLE (n=72)	78 weeks	Single-course RTX (2×1000 mg)	4 SIEs reported in each RTX+csDMARDs (16.6/100 PY) and placebo+csDMARDs (19.9/100PY)	3 OIs in RTX+csDMARDs group: colitis, histoplasmosis and cryptococcal pneumonia plus fungal sepsis, respectively, versus 1 OI in placebo+csDMARDs group: cytomegaloviral pneumonitis	None reported
Registry data						
French Registry (AIR) [24•]	RA (n=1303)	1629 PY	Most patients had RTX 2×1000 mg dose (96 %) 712 (55 %) were retreated with RTX	92 SIEs in 88 patients (5/100 PY)	2 OIs: fungal septic arthritis and varicella zoster virus	Chronic lung disease and/or cardiac insufficiency, RA-related extra-articular involvement and low IgG level before RTX were associated with an increased risk of SIEs after RTX infusions in multivariate analysis

Table 1 (continued)

Source of data	Disease group (number of patients treated with B cell agent)	Duration of follow-up	Treatment schedule	Serious infection event (SIE)	Opportunistic infections	Risk factors for infection
German Registry (GRAID) [78•]	Total patients (n=370) including: SLE (n=85) AAV (n=58) Primary Sjogren's (n=6)	299 PY	Most patients had RTX 2×1000 mg dose (86 %) 18.6 % were retreated with RTX	5.3/100 PY	5 OIs in SLE patients: *Salmonella typhimurium* (n=1), meningococcal meningitis (n=1), *Listeria meningitis* (n=1), oesophageal candidiasis (n=1) and Herpes zoster infection (n=1) 2 OIs in AAV and pemphigus patients; both were due to herpes zoster reactivation	There was a significant relationship between multiple repeat doses of RTX and a reduced rate of infections in the Poisson regression analysis
Spanish Registry (BIOBADASER 2.0) [27•]	Total patients (n=135) including the following: RA (n=75) Other CTD (n=60) However, total TNFi-treated patients studied (n=3166)	245 PY	RTX dose and number of cycles were not reported	Higher rate of SIE was reported in RTX group than TNFi group for RA (17.1 and 7.6/100 PY, respectively) and CTD group (11.0 and 3.1/100 PY, respectively)	4 OIs in RTX Group: *Mycobacterium abscessus* (n=1), Candida albicans (n=1) and JC Virus (n=1) versus 76 OIs (predominantly mycobacterium infections) in the TNFi group	In multivariate analysis, increased SIE was associated with the use of rituximab in CTD patients, many of which have other risk factors for infections included lung and renal problems and co-treatments such as corticosteroids
BELIMUMAB Pooled data						
One RCT+LTE study of belimumab in SLE [47••]	SLE (n=449)	1746 PY	Belimumab (either 1 or 10 mg/kg in RCT) 10 mg/kg dose in LTE	The rate of SIE peaked in year 1 (8.3/100 PY) and declined in years 2–7 (6.0–3.6/100 PY)	2 OIs: *coccidioidomycosis* in an endemic area of Arizona (not-related to the drug) and another was fatal cytomegalovirus pneumonia	None reported

AAV anti-neutrophil cytoplasmic antibody-associated vasculitis, *AZA* azathioprine, *CyC* cyclophosphamide, *csDMARDs* conventional disease-modifying anti-rheumatic drugs, *CTD* connective tissue diease, *LTE* long-term extension, *MTX* methotrexate, *OI* opportunistic infection, *RCT* randomised controlled trial, *PY* patient-year, *RTX* rituximab, *SIE* serious infection event, *SLE* systemic lupus erythematosus, *TB* tuberculosis, *TNFi* tumour necrosis factor inhibitor, *VDI* Vasculitis Damage Index

was associated with an increased incidence of SIEs. In contrast, OCR200+MTX group did not show superior efficacy compared with existing therapies, but was safe and well tolerated [23••]. OCR was also investigated in renal lupus but with higher doses, 400 and 1000 mg. Despite enhanced B cell depletion was achieved in the OCR groups, the trial was halted due to increased SIE and opportunistic infections; some of which were fatal in the OCR+standard of care groups [22].

Risk Factors for Serious Infection

Low Immunoglobulin Prior to and After Therapy

Registry data in RA show that low IgG level (<6 g/L) before a cycle of rituximab was associated with SIE, particularly in the 3 months following rituximab infusion, 16.2 versus 3.9 % without low IgG [24•]. In RCTs and LTE studies in RA, however, low IgM and IgG were exclusion criteria for trial entry. In these studies, a similar increase in SIE rate was seen following rituximab both before and after the development of low IgG compared with patients who never developed low IgG [16••]. This might attribute SIE to other pre-existing demographic or clinical risk factors rather than the low IgG itself. Careful interpretation is needed, as the number of patients with low IgG post-therapy was low, 3.5 %. More data from registries are needed to assess the effect of secondary low IgG with the risk of SIE after repeat cycles of rituximab.

IgM tends to decline following therapy. Levels of IgM were lower in patients receiving 2×1000 mg rituximab versus those receiving 2×500 mg [25••]. In the RCTs+LTE studies, 22.4 % of patients developed low IgM [16••]. Low IgM prior to and post-rituximab has not been associated with SIE [16••, 24•], although this analysis may have been limited by the low incidence of SIE. The development of low IgA post-rituximab is uncommon (1.1 %) and, thus, does not appear to be associated with SIE [16••].

In AAV, remission induction with cyclophosphamide has led to a decline in all immunoglobulin classes at 6 months post-therapy and remained below the baseline levels up to 36 months. Following a relapse, a single cycle of rituximab further aggravated the decline in IgM and IgG levels [26].

Concomitant Glucocorticoid and csDMARDs

Glucocorticoids impair phagocyte function and suppress cell-mediated immunity and, thus, may increase the risk of infection. Registry data (AIR and BIOBADASER 2.0) shows an increased risk of SIE with concomitant glucocorticoid [24•, 27•]. A similar finding has been shown for TNFi in RA [28].

The co-prescription of csDMARD appears safe. A phase II RCT showed no increase in SIE rates using combination methotrexate or cyclophosphamide with rituximab [29]. Data

from the CERERRA study showed no significant difference in infection rate when rituximab was used either in combination with leflunomide, methotrexate or as monotherapy; rates were 6.2, 6.6 and 7.4 %, respectively [30]. Although the incidence of infection was higher in the rituximab and MTX group compared to rituximab monotherapy in the GISEA registry (33.6/100 patient-years and 9.3/100 patient-years, respectively), the rate of SIE was similar (3.6 and 3.3 %, respectively) [31].

Age and Comorbidity

An increasing number of elderly patients, who have more comorbidity, are diagnosed with autoimmune rheumatic diseases. These patients are at increased risk of SIE after rituximab [24•, 27•]. Comorbidities investigated included chronic obstructive pulmonary disease (COPD), interstitial lung disease, renal failure, hypertension and cardiac insufficiency.

Rituximab-Associated Neutropaenia

Neutropaenia is recognised as a complication of rituximab for B cell malignancies with an incidence of 3–27 % [32]. Data in autoimmune rheumatic diseases are more limited, and the optimal management of these patients has not been defined. Data from large cohort studies suggested an incidence of 2.5–3.0 % in RA, increased to 20 % in AAV [33, 34]. In most cases, neutropaenia recovered promptly, but counts $<0.5\times10^9$/L were associated with severe infection requiring treatment with intravenous antibiotic and granulocyte colony-stimulating factor (GCSF). Current data suggests retreatment with monitoring is appropriate, with additional caution needed only in severely neutropaenic patients [34]. The mechanism of rituximab-associated neutropaenia remains unclear.

Opportunistic Infections

The immunomodulatory effect of bDMARDs has raised concerns with regard to the risk of opportunistic infections including fungal, viral, tuberculosis and other mycobacterial infections. A recent meta-analysis of bDMARDs in RA trials showed that although the overall incidence was low, there was an increased risk of opportunistic infections with bDMARDs (OR 1.79; 95 % CI, 1.17–2.74; I^2=3 %), resulting in 1.7 excess infections/1000 patients treated (number needed to harm, NNH=582) compared to control [35]. Risk of individual agents can be linked to their targets (e.g. cytokine, T cell modulation, B cell).

Tuberculosis

Two cases of pulmonary tuberculosis (TB), both treated with anti-TB chemoprophylaxis, occurred in the 'all exposure' population in the long-term data from RCTs and LTE studies in RA [16••]. No cases of extra-pulmonary TB or multidrug-resistant TB were observed over a long period of time and in other rituximab indications. This is in contrast to reactivation of latent tuberculosis with the use of TNFi, particularly the monoclonal antibody type. TNF-α plays a major role in the formation and maintenance of granulomas that confine mycobacterial infections by stimulating phagocytosis and enhances mycobacterial killing in concert with interferon gamma (IFN-γ), which cannot otherwise be eradicated by the host defence mechanisms [36, 37]. Inhibition of TNF-α leads to loss of ability to control primary infection, breakdown of granulomas, release of mycobacteria and rapid progression to activation of latent TB. Rituximab has been administered to seven RA patients with latent TB and six patients with TNFi-associated TB. Over the following year, no patient developed active TB or had QuantiFERON-TB-Gold In-Tube (QFT-GIT) conversion [38]. Rare cases of non-tuberculosis mycobacterium, *Mycobacterium avium pleuritis* and *disseminated Mycobacterium kansasii*, have been reported in rituximab-treated myositis [39]. Three other atypical *mycobacterium* were reported in a survey carried out in the USA and Canada [40].

Four cases of TB (two serious pulmonary latent TB, one extra-pulmonary TB and one non-serious latent TB) have been reported in LTE studies of belimumab in SLE. Two non-serious cases of non-tuberculosis mycobacterial infections have been reported [41].

Hepatitis B and C

Experience from oncology has demonstrated hepatitis B virus (HBV) reactivation (sometimes fatal) in rituximab-treated patients [15, 42]. A series of case reports ($n=7$) have shown HBV reactivation following rituximab in RA patients with chronic hepatitis B infection (only one received antiviral treatment) [43•]. Interestingly, however, a recent small prospective study showed no viral reactivation in any of the vaccinated group ($n=4$), resolved HBV infection ($n=12$) or chronic HBV infection ($n=2$; they received lamivudine and entecavir, respectively) and no significant change in protective anti-HBs titres during rituximab treatment [44].

Rituximab-related hepatitis C virus (HCV) progression has been reported in patients with RA [45]. A recent retrospective study was conducted in Taiwan and compared HCV progression in patients with RA and HCV infection treated with either TNFi or rituximab without concomitant antiviral therapy. After a median follow-up of more than 2 years, no patient developed worsening of clinical HCV. Nevertheless, although the liver transaminases remained stable, viral load was significantly increased in the rituximab group compared to the TNFi, $p=0.003$ [45]. This suggests a potential safety concern in patients with HCV infection, without antiviral therapy. There are no data to inform on exposure to belimumab in patients with a history of current hepatitis B or C infection.

Herpes Zoster

Data from RCTs and LTE studies in 3194 patients with RA reported 108 cases of herpes zoster in 100 patients (including two cases of ophthalmic herpes zoster and five SAEs) in the all exposure group compared to 13 cases in the placebo+ MTX group, rates of 9/1000 and 11.7/1000 patient-years, respectively [16••]. This is comparable to the rate in the general RA population, 11.5/1000 patient-years [46].

There were no herpes zoster cases reported in the RCTs and LTE study of belimumab in SLE [47••], but one severe case in the phase II trial was observed [48].

JC Virus Reactivation (Progressive Multifocal Leucoencephalopathy)

Progressive multifocal leucoencephalopathy (PML) is a rare, progressive, demyelinating disease of the central nervous system, caused by the reactivation of the JC virus. This virus is present in up to 80 % of healthy adults, typically only causing PML in immunocompromised patients. Thirty-four confirmed cases of PML in the context of autoimmune rheumatic diseases have been reported (RA=10, SLE=17, vasculitis=4 and dermatomyositis=3). Of these, 14 were treated with rituximab (RA=6, SLE=5, cryoglubulinaemic vasculitis=2 and dermatomyositis=1) [49•]. This is equivalent to an incidence rate of 5/100,000 exposed patients which is lower than treatment for Crohn's and multiple sclerosis with natalizumab (1/1000) [50] and for psoriasis with efalizumab (1/400) [51]. Of the nine outcomes known, six resulted in deaths. No definite conclusion can yet be derived on the causal link of PML in this series due to the small number of cases, background risk associated with disease and comorbidity, and concomitant immunosuppressant. Two cases of PML have been reported recently in patients with SLE treated with belimumab [52, 53].

Other Intracellular Organisms (Bacterial, Viral or Fungal)

A small number of infections with intracellular organisms have been reported in the setting of rituximab therapy. Pooled data from RCTs and LTE studies in RA reported two cases of atypical pneumonia (no organisms isolated) and one case each of *Candida* septicaemia, pharyngeal abscess (organism unspecified), *Scedosporium* lung infection and *Pneumocystis jirovecii* pneumonia which equated to rate of 0.06/100

patient-years [16••]. The incidence of *P. jirovecii* pneumonia following rituximab in AAV was reported as increased to 1.2 % [54]. In LUNAR trial (SLE), three patients had colitis, histoplasmosis, and *cryptococcal pneumonia* plus fungal sepsis, respectively [3].

Sepsis caused by *Acinetobacter baumannii* was reported in the 10 mg/kg belimumab group in the phase III trial [7] while two other added cases of opportunistic infections were reported in the long-term RCTs and LTE study of belimumab in SLE, *coccidioidomycosis* in an endemic area of Arizona (not-related to the drug) and another was fatal cytomegalovirus (CMV) pneumonia [55].

Use in Patients With Human Immunodeficiency Virus

There is a limited experience on the use of rituximab in patients with autoimmune rheumatic disease and human immunodeficiency virus (HIV) [56]. Rituximab has been widely used in the treatment of HIV-associated Castleman's disease and lymphoma and seems to be well tolerated, but with a particular risk of reactivation of Kaposi's sarcoma [57].

Measures to Minimise Infection Risk When Administering Rituximab

Initiating B Cell-Targeted Therapy

Prior to commencing treatment, an individual therapeutic goal should be agreed between the patient and the treating rheumatologist [25••, 58] including discussion of the risks of their autoimmune diseases, and benefits and risks of therapies.

Patients should be reviewed for infection risk factors, taking into account the intensity and duration of immunosuppression that is likely to be needed.

As part of pre-bDMARD screening prior to initiating a new therapy, in addition to the routine laboratory tests, baseline immunoglobulin levels (IgM, IgA and IgG) should be determined [25••].

As long-term data have not shown evidence of an increased frequency of reactivation of TB in autoimmune patients treated with rituximab, screening patients systematically for TB prior to rituximab is not necessarily recommended at the present time. A past history of TB was not an exclusion criterion for the BLISS-52 and 72 trials of belimumab in SLE, but prior TB is an exclusion criterion in a new trial of belimumab in myositis (NCT02347891). Due to reactivation of TB cases reported recently [41], screening for TB prior to use may be warranted in this disease group.

Patients should be screened for hepatitis B (HBsAg and anti-HBs), hepatitis B core antibody (anti-HBc) and hepatitis

C. If antibody against anti-HBc antigen is positive, HBV DNA should be checked. If this viral load is negative, therapy with rituximab may be initiated with regular check of viral load. If the viral load is positive, then antiviral therapy is recommended (see "Antiviral Therapies and Monitoring for Patients With Hepatitis B" section later). The individual risk–benefit ratio of rituximab for this group of patient with chronic HBV and/or chronic HCV infections should be discussed with the patient, and expert gastroenterologist/hepatologist input is recommended in this setting. The risk of HBV or HCV reactivation is unknown for belimumab.

Vaccination

Observational studies and a RCT showed that humoral responses to vaccination of influenza and pneumococcal polysaccharide (T cell-independent antigens) were impaired after rituximab, but not to tetanus (T cell-dependent antigen) [59–61]. The low rate of infection among B cell-depleted patients may be explained by the preservation of cellular immunity. Following B cell repopulation, responses to influenza and pneumococcal polysaccharide were restored. For this reason, any patient considered for rituximab therapy is recommended for any indicated vaccines (hepatitis B for at-risk population, pneumococcus, tetanus toxoid every 10 years, influenza annually) either 4 weeks before the first (or next planned) course or at least 6 months after the last course [62]. In a small number of patients with SLE who were treated with belimumab, they were able to mount a protective response to pneumococcal, tetanus or influenza vaccines [41].

Herpes zoster vaccination (HZV) is a live, attenuated virus vaccine containing a lyophilized preparation of a strain of varicella zoster virus. Previous recommendations avoid the HZV in patients actively receiving TNFi, as well as abatacept, rituximab and anakinra [25••, 62]. Recent safety data looks promising, reporting that, of the 110 patients receiving biologics via intravenous infusion (included rituximab) and 42 patients via subcutaneous injection, no patient in either group developed herpes zoster within the 6 weeks post vaccination. Only two patients who were vaccinated since 2012 in the infusion group developed herpes zoster at 16 and 20 months [63]. More rituximab-treated patients receiving HZV and longer-term data are needed before firmer treatment recommendations can be made.

Antiviral Therapies and Monitoring for Patients With Hepatitis B

For patients with HBsAg positivity, antiviral therapy should be initiated prior to rituximab. The choice of anti-viral mainly depends on the duration of the scheduled therapy and on HBV serology status (chronic hepatitis B versus inactive carrier) [64]. Patients receiving long-term immunosuppression (i.e.

>12 months) and/or suffering from chronic hepatitis B are usually treated with newer 2nd generation anti-viral such as entecavir or tenofovir [43•]. Rituximab should not be started until the HBV DNA levels become undetectable. Thus, frequent monitoring of HBV DNA and liver function tests (after 1 month, then every 3–6 months) are mandatory [65, 66].

The management of occult/resolved HBV infection with anti-HBc positivity alone remains unclear. Additional risk factors should be taken into account including HBV DNA positivity, presence of anti-HBs (which should protect against reactivation, although this effect is controversial with rituximab) and the degree of immunosuppression [25••, 67]. For this group of patient, HBV DNA could be determined and then prophylactic therapy considered; if not undertaken, close follow-up to detect a rise in HBV DNA is recommended.

If HBV is reactivated and HBV DNA becomes detectable, further rituximab should be avoided and antiviral therapy must be promptly initiated to mitigate against hepatocellular damage. If HBV DNA becomes positive during lamivudine therapy, switching to the tenofovir is recommended as cross-resistance has been reported between lamivudine and the other 2nd generation anti-viral, entecavir.

Monitoring After Therapy

Immunoglobulin levels should be monitored before any retreatment particularly in those who demonstrate low baseline IgG levels [25••]. Discontinuation of rituximab should be considered in patients with hypogammaglobulinaemia, but this decision should take into account other risk factors such as age, comorbidity and glucocorticoid use, as well as the risks of alternatives to rituximab in patients who are B cell depleted. Monitoring is also warranted in patients who have had SIE to identify those who may require treatment with intravenous immunoglobulin replacement (IVIG). IgG level prior to and at the time of rituximab has been shown to be correlated with the nadir IgG post-rituximab in a large cohort examining rituximab-associated hypogammaglobulinaemia in autoimmune rheumatic diseases [68].

The Role of Intravenous Immunoglobulin Replacement

Several studies have described the use of IVIG replacement in rituximab-treated patients who develop moderate to severe hypogammaglobulinaemia (IgG<5 g/L) and severe infections, ranging from 4.2 % (of 288 patients) [69•] to 21 and 14 % (both consisted of <35 AAV patients) [26, 70]. Data from a large cohort showed 6 out of 12 (50 %) continued to receive rituximab alongside IVIG replacement therapy for maintenance of disease control. Replacement with IVIG reduced the incidence and severity of infections, while allowing

recovery of IgG levels leading to cessation of IVIG replacement in two patients (after 4 and 7.5 years of treatment) [69•].

Expert Commentary

B cell targeting appears as safe, or on occasion, safer than other classes of bDMARDs used in rheumatic diseases. B cell-targeted bDMARDs have important limitations in their effects on B cell-mediated immunity. Incomplete and transient depletion of B cells and sparing of plasma cells may be one reason for the relative safety of rituximab. Prolonged rituximab therapy or more intensive B cell-depleting regimens have indicated the potential for more significant infection risk. This is an important consideration in guiding judicious use of repeat rituximab cycles. Given the lifelong nature and treatment of most autoimmune diseases, we feel that the benefits of 6-monthly retreatment may not justify risks in many patients. Importantly, once hypogammaglobulinaemia is identified, it usually persists for some time, even if B cell depletion therapy is discontinued, thus impacting on the safety of subsequent bDMARDs. Biomarkers and personalisation of therapy have shown potential in guiding the intensity of treatment required [56, 71, 72].

The safety of rituximab cannot necessarily be extrapolated to all B cell-targeted bDMARDs, as suggested by trials of OCR in SLE. Novel approaches being evaluated in clinical trials to more comprehensively inhibit B and plasma cell immunity, such as combination therapy with rituximab and belimumab or direct targeting of plasma cells with proteasome inhibitors, may bring additional problems [73].

The diseases usually treated with B cell-targeted agents by rheumatologists include the most severe multi-system autoimmune diseases. This must be considered when interpreting unusual safety signals such as the PML cases that were disproportionately observed in patients with SLE and AAV. Similarly, the risks of B cell-targeted therapies are dependent on other infection risk factors (such as age and comorbidity) and background rates of opportunistic infection (as demonstrated by the geographic distribution of opportunistic infections in OCR trials [23••]). As with many immunosuppressants, a study of B cell-targeted therapies reveals the relative risk of glucocorticoids in comparison to these more targeted immunosuppressants. The benefits of glucocorticoid-sparing effects should be considered in the judgement of risks of B cell-targeted therapies. This, as well as the immunosuppressive effect of disease activity itself, may help to explain why trials in SLE demonstrated lower rates of infection in B cell-depleted patients than those with normal B cell numbers.

As B cell-depleting therapies have raised particular questions of cumulative toxicity, adequate surveillance must be ensured. Efficacy of RCTs (and meta-analyses derived from them) is of limited value in identifying adverse events. LTE studies are not powered to and sub-select populations that tolerate therapy [74]. Long-term registry data is relatively

lacking but is needed, especially for rare and opportunistic infections.

Finally, the future therapeutic landscape that will include an expansion in biosimilar agents including rituximab biosimilars will require their own surveillance to demonstrate equivalent safety [75].

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