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Risk of Herpes Zoster and Opportunistic Infections with Treatments for Autoimmune Rheumatic Disease

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Abstract

Purpose of review New advances in the treatments of autoimmune rheumatic diseases have altered the landscape of opportunistic infection risk, including infections such as herpes zoster, tuberculosis and *pneumocystis jirovecii* pneumonia. Recommendations for preventative strategies, including vaccination and prophylaxis, have also evolved in response to availability of new vaccines and decreased reliance on glucocorticoid therapy.

Recent findings The newest treatment options, including Janus Kinase (JAK) inhibitors and the type 1 interferon receptor inhibitor, anifrolumab, have been associated with an increased risk of herpes zoster compared to other existing immunosuppressive agents in rheumatology, beyond the already high baseline risk. The adjuvanted zoster virus has allowed safe immunization of rheumatology patients in attempt to reduce the incidence of herpes zoster albeit with recent population based studies demonstrating less effectiveness than in immunocompetent patients.

Summary Infection risk assessment requires stratification of host, disease and treatment factors. Despite advances in immunosuppressive therapy, glucocorticoid use is still substantial and contributes to risk of opportunistic infections. Introduction of Shingrix, a non-live vaccine has made immunization for HZ more straight forward for immunocompromised patients. It is important to assess risk for other opportunistic infections, like *pneumocystis jirovecii* and tuberculosis, and prescribe prophylaxis.

Keywords Herpes zoster · Opportunistic infections · Tuberculosis · Biologicals · JAK inhibitors · Immunization

Introduction

Treatments for autoimmune rheumatic diseases have continued to evolve in the last several years. From glucocorticoids (GC) and conventional disease modifying antirheumatic drugs (cDMARDs) like methotrexate to biologics and small molecule inhibitors. Most recently, chimeric antigen receptor therapies have shown early signs of sustained remission for severe manifestations of connective tissue diseases such as systemic sclerosis (SS) and systemic lupus erythematosus(SLE) [1]. With these new advances, opportunistic infections, especially viral are of concern. This article aims to highlight specific risks regarding opportunistic infections for common immunosuppressive classes used in rheumatology and strategies to reduce this risk.

Host and Disease Considerations

Prior to considering treatment effects, it is important to understand the impact of host and disease on risk of opportunistic infections. For example, viral immunity relies on both innate and adaptive immune systems with T cell immunity in particular playing a vital role in control of viral infections [2]. With advancing age and reducing adaptive immune function, the incidence of reactivation of latent viruses increases. Underlying conditions that impact the body's immune system also increases this risk, for example, diabetes and autoimmune diseases (AID) [3]. While it is difficult to tease out the impact of treatment on risk, SLE in

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particular appears to have two to 10-fold higher incidence of herpes zoster compared to healthy young controls [3, 4]. Rheumatoid arthritis (RA) has an estimated two fold increased risk compared to age-matched controls [4]. There is also this difference between other opportunistic infections in rheumatology cohorts with *pneumocystis jirovecii* incidence higher in patients with dermatomyositis, SS, SLE and Sjogren's syndrome compared to RA [5].

Glucocorticoids

GCs have been a big part of rheumatic disease management for their rapid anti-inflammatory effects since its discovery [6]. The impact of GC on the host is broad with a number of off-target manifestations, such as diabetes, osteoporosis and mood disturbances [7]. Long term infection risk continues to remain a major concern for patients on GC with studies demonstrating this even at 5 mg prednisolone per day [8]. There is a dose related effect for prednisolone on infection with low doses (< 5 mg/day) associated with an adjusted rate of hospitalized pneumonia of 1.32–1.4 which increased to 2.4–2.98 for patients on > 10 mg/day [9, 10]. GC alone and in combination with other immunosuppressive agents also increase the risk of a variety of opportunistic infections [7].

Herpes Zoster and other Herpesviruses

Varicella zoster (VZV), a DNA virus, is part of the Herpesviridae family. These viruses cause lifelong infection, remaining inactive unless changes in the host's immune system lead to immune escape and reactivation. Herpes zoster (HZ), also known as shingles, is a common condition with a Lifetime risk of 30% and up to 50% for individuals Living to 85 [11, 12]. Whilst most cases are self-limiting, up to 30% can have post herpetic neuralgia with other more severe complications including secondary bacterial infection, zoster ophthalmica and disseminated zoster infection [13].

GC use in RA has been consistently shown to increase the risk of HZ irrespective of other disease modifying agents [14–16]. This risk has been demonstrated in a dose dependent fashion with the RABBIT study from Germany showing an adjusted hazards ratio of 1.47 (95% CI 1.17 to 1.85, $p = 0.0008$) for 5-10 mg prednisolone vs. 0 mg and 4.42 (95% CI 2.50 to 7.83, p = < 0.0001) for > 10 mg/day [17]. GC use > 30 mg in SLE had a crude odds ratio of 3.8 for HZ [18]. A cohort study in Canada had 82/422 (30.5%) patient reported HZ events with 71.9% reporting being on prednisolone at the time of diagnosis [19].

GC is first line for the treatment of giant cell arteritis (GCA), a disease affecting individuals > 50 years. Interestingly, there was no increased risk of HZ compared to the general population in the first 6 months in this retrospective cohort study of 204 GCA patients with matched controls [20]. This potentially highlights the importance of the underlying disease with risk for HZ.

Other clinically relevant herpesviruses at risk of reactivation include herpes simplex (HSV) and cytomegalovirus (CMV). HSV 1 and 2 cause oral and genital ulcers, which can be recurrent and in a minority of cases, progress to disseminated disease. Prednisolone use > 7.5 mg in SLE patients increases risk of HSV episodes [21]. CMV reactivation can present in many different ways from asymptomatic viraemia to severe organ threatening involvement. Most of the literature with steroids and CMV reactivation is in the hematological and solid organ transplant cohorts where steroids have been shown to increase risk of reactivation [22]. Two studies were identified in a recent systematic review in SLE patients and both reported higher GC doses with CMV disease though these patients were not on GC monotherapy reflecting also the impact of disease severity and potentially other concurrent immunosuppressive medications [23]. In general, there is a paucity of literature regarding risk of reactivation in AID with steroid monotherapy for HSV or CMV potentially highlighting a reduced burden in this cohort compared to HZ.

Hepatitis B

Hepatitis B is a blood borne DNA virus found in high prevalence in southeast Asia, Africa and parts of South America. Once exposed, individuals will either clear the infection, also called resolved infection, (hepatitis B cAb positive, sAg negative) or develop chronic infection (hepatitis B sAg positive). Individuals with chronic infection are at increased risk for hepatic complications and require close monitoring and if commencing immunosuppression, prophylactic treatment [24]. For immunocompromised patients with resolved hepatitis B infection, discussion regarding risk of reactivation is required [25].

Prednisolone use > 10 mg/day for 4 weeks has moderate risk of reactivation (1–10%) [26, 27]. The recommendation is to consider hepatitis B prophylaxis at the discretion of the physician as well as patient risk and preferences [25].

Pneumocystis Jiroveci Pneumonia

Pneumocystis jiroveci pneumonia (PJP) is an opportunistic fungal pulmonary infection that without prompt treatment is associated with high mortality. Besides underlying host factors, one of the main risks for the development of PJP pneumonia has been ongoing corticosteroid use, either alone or in combination with other immunosuppressive agents [5,

28]. Incidence of PJP in a non-transplant non-HIV cohort has been less easy to define, especially with new emerging treatment options [29]. Nevertheless, currently, prophylaxis is recommended for individuals who remain on moderate to high doses of prednisolone for greater than 4 weeks [30].

Mycobacterial Infections

Tuberculosis(TB) remains one of the leading causes of death in the world from infection [31]. Reactivation of TB can occur with GC and other immunosuppressive agents [32–34]. The development of extrapulmonary TB is also higher in patients who are immunocompromised [35]. In regions with moderate to high TB prevalence, like Taiwan, chronic GC can increase risk of incident TB irrespective of the underlying treating condition [36].

In countries where the prevalence of tuberculosis is low, there is an increased incidence of nontuberculous mycobacterial (NTM) infections, particularly amongst the RA cohort [37, 38]. Immunocompromised patients are at increased risk of extrapulmonary involvement with their NTM [39]. Diagnosis in these patients can be challenging and delayed. Chronic GC use is a big risk factor for the development of NTM [40]. Table 1 summarizes the infection risk for GC and other drugs.

Conventional Disease Modifying Anti-rheumatic Agents (cDMARDs)

The following medications are included in the category of cDMARDs – methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, azathioprine and mycophenolate. In general, these medications have a low risk of opportunistic infections, including HZ, with some exceptions.

Methotrexate

Methotrexate use, particularly in RA does not appear to significantly increase the risk of HZ [41, 42]. From the point of view of other viral opportunistic infections, there are case reports of CMV and HSV however these are rare, and typically in combination with other immunosuppressive agents [43–45]. To date there are no case reports of PJP with methotrexate monotherapy in rheumatology patients with reported literature of low dose methotrexate causing PJP in combination with low dose prednisolone [46]. The risk of reactivation of TB is thought to be low with methotrexate with potentially a slight increase when patients are >65 years and most recent guidance recommends a personalized approach for high risk individuals when it comes to screening prior to methotrexate initiation [30, 47].

Mycophenolate

Mycophenolate mofetil (MMF) inhibits inosine-5'-monophosphate with immunosuppressive effects on both T and B cells. In a nested case-control study looking at risk of opportunistic infection in SLE patients, MMF was associated with an adjusted odds ratio of 2.13 (95% CI 1.31–3.46) compared to non-MMF users [48]. This included HZ (Adjusted OR 2.85 (1.32–6.15)), TB (adjusted OR 2.22 (0.99–4.99)), and systemic mycosis (2.13 (1.21–3.73)) with odds increasing in a dose dependent fashion. After prednisolone, MMF was associated with the highest risk of PJP in a Taiwanese cohort with an adjusted hazards ratio of 7.14 (95% CI 4.21–12.13) [5]. NTM risk is less well documented, there is some evidence that combination immunosuppression most likely adds to the risk, but GC and TNF inhibitors remain the main risk factors as discussed elsewhere [49].

Cyclophosphamide

Prior to the introduction of biologics and targeted small molecule inhibitors, cyclophosphamide (CYC), an alkylating agent, was used for life threatening organ manifestations of connective tissue diseases. It still has a role in rheumatology patients, for example, SLE with organ-threatening or life-threatening disease [50]. CYC increases the risk of severe infection compared to GC monotherapy in patients with ANCA vasculitis [51]. The use of CYC has been associated with increased risk HZ [52, 53]. CMV infection appears to be at increased risk in patients who are on CYC and GC with over 80% of patients in this cohort found to be on CYC at the time of their CMV diagnosis [54]. There is a paucity of data in the rheumatology cohort regarding the risk of TB reactivation with CYC, however in oncology patients receiving cytotoxic chemotherapy, there was no increased risk of TB reactivation [55]. In a systematic review, PJP risk with cyclophosphamide had a pooled odds ratio of 3.72 (95% CI 2.66–5.39) [56]. Hepatitis B reactivation in the setting of resolved infection is low with CYC (1.9%) and was not associated with seroconversion in multivariate analysis [57].

Biologicals

Tumor Necrosis Factor Inhibitors

TNF inhibitors were the first biological agent approved for rheumatoid arthritis (RA). They are also used in several other rheumatic diseases, such as but not limited to psoriatic arthritis, ankylosing spondylitis and sarcoidosis. There are

Table 1 Summary of reporting infection risk in patients with autoimmune disease based on class of drug

	Herpes Zoster	CMV	Resolved hepatitis B	PJP	Mycobacterial infections
Glucocorticoids	HR 1.47-4.42(17) in RA Dose dependent risk	Increased in combination with other IS(23, 87) No evidence for monotherapy	Moderate (1-10%)(25-27)	Dose dependent risk(5, 28)	Increased risk for NTM and incident TB(36, 39) Dose dependent risk for TB reactivation(33, 34)
Conventional DMARDs	Rare MMF – slight increase(48)	Rare	Rare	Rare MMF – moderate aHR 7.14 (95% CI 4.21-12.13)(5)	Rare
Cyclophosphamide	Increased HR 4.05(52)	Low (54)	Low 1.9%(57)	Increased OR 3.72(56)	Low(55)
Biologicals					
TNFi	Mildly increased Pooled RR 1.61(65)	Rare Case reports(68)	Low <1% (25)	Low, but possible in combination 0-0.56/1000 PY (69)	High(37, 38)
IL-6i	Similar to TNFi(72)	Rare Case reports	Low to moderate 3%(77)	Low 0.37/100 PY(76)	Low risk reactivation(112) Similar incident risk of TB as TNFi(74, 75)
CTLA-4 ligand	Similar to other biologics 1.7-1.87/100 PY	Rare	Moderate Higher than TNFi but lower than B cell depletion 9.4/1000 PY(82)	Low	Low Risk present in endemic areas(81)
B cell depletion	Similar to TNFi(86)	Rare (87)	High risk: up to 31%(85, 91) 1 study 3/6 reactivated (50%)(89)	Moderate 0.15-7.93/100 PY(29, 94)	Low(73)
Interferon alpha I	Higher than TNFi 6.8/100 PY(100)	No current long term data			
Small molecule inhibitors					
JAK inhibitors	Higher than TNF 1.1-12.3/100 PY (109)	Low (0.3%)(109)	Low-moderate (1-3%)(115-117)	Low (113)	Higher risk in endemic areas 0.21/100 PY (113)
Avacopan	Minimal reported in phase III trials, no current long term data				
CAR T cell therapy	High in first 3 months. For prophylaxis	No reported cases	No reported cases	High in first 3 months. For prophylaxis	No reported cases

Legend

No data — Lower risk — Higher risk

now five (infliximab, adalimumab, etanercept, golimumab, certolizumab) on the market. The risk for reactivation of TB was identified very early on with infliximab and subsequently other TNF inhibitors [37, 58, 59]. Screening and treatment for latent tuberculosis has substantially reduced reactivation for this cohort [60]. Patients who live in areas of high prevalence remain at increased risk of acquiring TB infection and a low threshold for investigating if they present with symptoms suggestive of TB should be undertaken. TNFi increases the risk of all mycobacterial infections, with a higher rate of extrapulmonary manifestations also identified [61]. Most recently, NTM incidence appears to also be prevalent in TB endemic countries for patients on TNFi and should remain a differential in the appropriate clinical scenario [62].

Data for risk for HZ reactivation with TNFi is conflicting. One large study in the US showed no increased risk compared to non-biologic treatments in patients with RA [63]. Further cohort studies found the incident rate of HZ at 1.6–2.5/100 person years with no significant difference between mode of action for biologics [64]. The RABBIT registry found a total event rate per 1000 person years for RA patients to be 8.9

(95% CI 8.2–9.6) with the adjusted hazards ratio for TNF inhibitors (monoclonal and soluble TNF receptor fusion protein) between 1.45 and 1.73 compared to cDMARDs [17]. This increased risk was supported in a meta-analysis with a pooled risk ratio of 1.61 (95% CI 1.16–2.23, $p=0.004$) [65]. Other herpesvirus infections can theoretically reactivate with TNFi, but there have been no clear cohort studies demonstrating a clear association. Herpes simplex infections can occur but only small numbers of severe infection have been published [66, 67]. There are more case reports with CMV infection, however this was more common in the inflammatory bowel disease cohort than a rheumatology cohort and most patients were on multiple immunosuppressive agents at the time of their diagnosis [68].

PJP infection in patients on TNFi are low, and determining the real risk from TNFi has been hard to estimate with incidences in population-based cohort studies ranging from 0 to 0.56 cases per 1000 person years [69]. Risk factors for PJP included age greater than 65, pre-existing pulmonary disease and GC use [70]. TNFi have a low risk of reactivation of resolved hepatitis B infection and prophylaxis is not routinely recommended [25].

IL-6 Inhibitors

Tocilizumab is used in a number of rheumatological conditions, including RA, giant cell arteritis and Adult onset Still's disease. Sarilumab has recently been approved for treatment of polymyalgia rheumatica [71]. In a large cohort study using claims from the US, tocilizumab had More serious bacterial infections than TNFi, but the rates of opportunistic infections were similar with an incidence rate of 0.11 per 100 person years for HZ for both [72]. Previous clinical trial cohort studies in areas where this is low prevalence of TB have shown little risk for TB reactivation with tocilizumab [32, 73]. However recent studies out of South Korea and Japan have an incident rate of TB comparable to TNFi users [74, 75]. Incidence rate for PJP in a post marketing study was 0.37 per 100 patient years [76]. Routine PJP prophylaxis is not recommended for tocilizumab monotherapy. Patients who are hepatitis B cAb positive, sAg negative have a risk of reactivation up to 3% but no evidence of hepatitis flare [77–79]. Although these studies found it difficult to differentiate the effect of other immunosuppressive agents on this risk. The presence of hepatitis B surface antibody (sAb) also influences risk with these patients less likely to reactivate compared to somebody lacking sAb [78]. Given this uncertainty recent guidelines highlight the importance of shared decision making [25]. Close monitoring with 3 monthly hepatitis B viral load and liver function tests or commencement of an antiviral with a high barrier to resistance can both be considered.

Cytotoxic T Lymphocyte antigen (CTLA)–4 Ligand

Abatacept inhibits the co-stimulation of T cells. The rate of opportunistic infections is overall lower than TNFi [80] and similar rates to placebo-treated patients [81]. The most common opportunistic infection found was TB and occurred in endemic areas [81]. HZ rates were comparable to other biologics at 1.7–1.87 per 100 person years [64, 81]. Interestingly, abatacept has a higher risk of hepatitis B reactivation than TNFi but lower than rituximab with an adjusted HR of 15.39 (95% CI 3.08–77.04 [82]. The risk for reactivation was higher in patients on other immunosuppressive agents at commencement of their biologic and with undetectable Hep BsAb [83]. Similar to IL-6 inhibitors, close biochemical monitoring or prophylaxis with an antiviral can be suggested for individuals thought at higher risk [25].

B cell Depleting Therapy

Rituximab is now used in a number of autoimmune rheumatic diseases including but not limited to RA, SLE and ANCA-associated vasculitis. The impact of this drug on risk of opportunistic infections needs to take into consideration the underlying host and the disease. In recent observational studies, rituximab has been associated with an increased severe infection rate compared to etanercept [84] and an overall serious infection rate of between 2.2 and 9.8 cases per 100 person years [85]. HZ incidence is similar to TNFi [86]. CMV reactivation has occurred with rituximab use, but was not found to be significant in a multivariate analysis [87]. TB reactivation with rituximab use remains low [73, 88].

It is well established that reactivation of hepatitis B is the highest risk with rituximab compared to other biologic agents [82]. Prophylaxis with an antiviral, e.g. entecavir, is routinely recommended in this cohort of patients and should continue for at least 12–18 months post cessation due to the concerns of delayed reactivation [25, 57]. A recent study in Taiwan found 3 out of 6 rheumatology patients who did not receive prophylaxis had HBV reactivation with a time to activation between 7 and 48 months [89]. This incidence is higher than other studies which demonstrated reactivation rates of 0–31% with lower rates in non-Asian populations [82, 85, 90–93]. Further studies looking at host factors and virus genotype differences may help explain these differences in more detail.

Data is also mixed regarding risk of PJP infection with rituximab use with incidence rates ranging from 0.15 to 7.93 cases per 100 patient years [29, 94]. However, in the study from Park et al., 10 out of the 11 patients who developed PJP were also on concomitant GC therapy, reflecting potentially the effect of combination immunosuppression on the development of PJP [94]. ANCA- associated vasculitis (AAV) is a disease where rituximab induction has been practice changing

and using less GC has been pursued, meaning that the risk profile for these patients has changed with the incidence of PJP decreasing [29]. However, peripheral B cells remain important in T cell protective immune responses against pneumocystis [95]. Patients with SLE who receive rituximab appear to have a higher risk of PJP with an IR of 6.1 per 100 PYs albeit with no PJP prophylaxis and concomitant GC use [96].

Finally, rituximab has been linked to progressive multifocal leukoencephalopathy (PML), an often-fatal neurological condition caused by John Cunningham virus. The pathophysiology behind the increased risk with B cell depletion is not known. It remains very rare in the rheumatology cohort with a prevalence between 2.5 and 5 cases per 100,000 patients [97, 98].

Type 1 Interferon Receptor Inhibitor

Approved in 2021, anifrolumab is used to treat SLE with a signal for herpes virus reactivation identified early on in trials [99]. HZ rates were highest in the first year (6.8 per 100 PY) and decreased over time (2.9 at year 4) [100]. While rare, cases of disseminated herpes infection have been reported, and careful monitoring and counselling of patients is important [101]. Higher rates of latent TB but not active TB were found in the long term extension study over placebo potentially reflecting improvement in cell-mediated immunity with better underlying disease control resulting in fewer indeterminate or false-negative screening interferon gamma assays [102].

Other Biologics

Other biologics used in rheumatology include BLYS, IL1, IL17, IL12/23 and IL23 inhibitors. These agents typically have less concern for opportunistic infection than other biologics [103–106]. The opportunistic infections of interest with IL-17 is oral and oropharyngeal candidiasis and oral herpes simplex virus with a reporting odds ratio compared to other biologicals of 4.22–6.04 (3.52–6.99) and 2.67 (2.33–3.06) [107].

Small Molecule Inhibitors

Janus Kinase Inhibitors

Janus kinase inhibitors have allowed more flexibility for rheumatology patients as the first effective oral treatment on par with biological agents for several inflammatory conditions. These include tofacitinib, baricitinib, upadacitinib, filgotinib and deucravacitinib with many other clinical trials underway. Compared to TNFi, JAK inhibitors are associated with a significantly increased risk of herpes zoster, and other herpesvirus reactivation [108, 109]. The exposure adjusted incidence rate (EAIR) for HZ for all JAK inhibitors ranged from 1.1 to 12.3 per 100 PY [109]. Most of these infections are single dermatomal zoster, with a small percentage being disseminated [110, 111]. Once again, concomitant GC use increases the risk of HZ [111]. Ethnicity also plays a role in risk of HZ, with incidence higher in Asian patients [110]. Recurrence of HZ with upadacitinib occurred in 6.4% (13/204) of patients at a median of 476 days [110]. These patients had low HZ vaccination rates. CMV frequency in trials was low at 0.3% [109].

As JAK inhibition means a number of cytokines are targeted, including TNF, there is also the risk of TB reactivation albeit potentially lower than TNFi especially in areas of low endemicity [112]. Most cases of TB occurred in areas of high prevalence with one study demonstrating the crude incidence rate at 0.21 per 100 patient years [113]. Current recommendations are to treat JAK inhibitors as similar risk as TNFi with TB reactivation [30, 114]. Patients should undergo screening prior to commencing and consider chemoprophylaxis.

The risk of hepatitis B reactivation for sAg negative/cAb positive patients appears moderate at around 0-3.7% [115–117]. There was a transient qualitative rise in viral DNA in 24 of the 32 patients who had a detectable viral load in the pooled data from baricitinib studies [116]. Out of those that had quantifiable viral DNA ($n=8$), only 4 went on to discontinue the drug permanently, with 3 of them also commencing antiviral therapy with no evidence of hepatitis. Recommendations for prophylaxis are therefore similar to those for tocilizumab and abatacept [25].

Avacopan

Avacopan reduces activation of the alternative complement system by inhibiting C5a and has allowed rapid reduction in GC for induction in ANCA vasculitis [118]. There is limited long term data available at the time of this review, however the phase III trials demonstrated numerically lower number of severe infections compared to prednisolone, though this wasn't statistically significant [118, 119]. In the phase III trial by Jayne et al., there was one episode of hepatitis B reactivation (who had also received rituximab) and one episode of neutropenic sepsis [118].

Chimeric Antigen Receptors (CAR)

CAR T cell therapy was first developed for hematological malignancies [120]. Most recently, early studies have shown promising results for severe inflammatory autoimmune diseases such as SLE and scleroderma [1, 121, 122]. Risk of opportunistic infection is high in the 3 months post this as patients also receive lymphodepleting chemotherapy with

fludarabine and cyclophosphamide prior to the administration of the autologous CD19-CAR T cells and subsequently receive prophylaxis with acyclovir and cotrimoxazole. The Long-term safety data showed one herpes simplex infection at 3–6 months and 1 herpes zoster at 6–12 months. It is unclear if patients had received vaccination with Shingrix [1]. Hypogammaglobulinemia, a known late effect in the hematology cohort [123], does not appear to be a prominent feature in this first cohort of rheumatology patients, but further data is needed. This first cohort of patients with autoimmune disease appear to have different short-term complications compared to the hematology cohort with no high-grade cytokine release storm or immune effector cell-associated neurotoxicity syndrome (ICANS) [124].

Preventative Measures

Herpes Zoster Vaccination

Vaccination for zoster up until recently was with Live attenuated vaccine, Zostavax, which made vaccination in an immunocompromised cohort challenging though possible. This offered 50% immunity against zoster reactivation in the immunocompetent individual with reduced effectiveness in immunocompromised.

The introduction of non-live recombinant vaccine for zoster, Shingrix, has hopefully reduced reactivation in immunocompromised patients and is recommended in many countries for individuals greater than 50 years old, including immunocompromised patients [125]. There were initial concerns regarding flare of inflammatory arthritis post vaccination however recent real-world evidence does not show a significant increase flare rate [126]. Further RCTs are underway looking at vaccine safety and effectiveness in rheumatology cohorts are underway [127]. A recent population based study has found the effectiveness of Shingrix at 50% [128].

Pneumocystis Prophylaxis

Recommendations for prophylaxis for PJP reflect the high risk with GC use as well as combination therapies with evidence recommended prophylaxis if patients are on >15-30 mg prednisolone for >2–4 weeks [30]. Trimethoprim/sulfamethoxazole two-three times a week has been shown to significantly reduce the risk of PJP. There are only a limited number of cases of breakthrough when taking this. Other options include atovaquone and dapsone.

Resolved Hepatitis B Infection

Screening for hepatitis B infection should be undertaken in all patients about to be immunosuppressed. Patients who are found to be hepatitis B cAb positive and sAg negative should be monitored with regular liver function tests and HBV-DNA levels [25]. However, patients who are commencing B cell depleting therapy, rituximab, should commence on prophylaxis.

TB Preventative Therapy

Overall screening should follow national guidelines and typically includes an interferon-gamma release assay (IGRA) and chest imaging [30]. All patients planned for TNFi should be screened and offered treatment for TB preventative therapy prior to commencement.

Table 2 Preventative and prophylaxis recommendations

	Prophylaxis	Preventative therapy
Herpes Zoster	Prophylaxis may be recommended in select patients	Recombinant Zoster vaccine where available for prevention
CMV	Prophylaxis not generally recommended	N/A
Hepatitis B sAg positive	Prophylaxis recommended for biologic and small molecule inhibitor use	N/A
Isolated hepatitis B cAb positive	Prophylaxis recommended for B cell depleting therapy Other drug classes on a case-by-case basis	N/A
Tuberculosis	N/A	For patients with evidence of latent TB or epidemiological risk factrs, TB preventative therapy (treatment of latent TB to reduce risk of future reactions) frequently recommended for biologic and small molecule inhibitor use. Active TB must be ruled out in these patients
Pneumocystis Pneumonia	Prophylaxis is generally recommended for patients on long term moderate doses of prednisolone (>15 mg, >4 weeks) and other immunosuppression	N/A

Conclusions

Opportunistic infection risk assessment requires consideration of the underlying disease and the type and intensity of immunosuppressive therapy. Despite significant therapeutic advancement in the management of rheumatic diseases, glucocorticoids remain an integral part in many diseases and substantially contribute to the risk of a broad range of opportunistic infections.

Preventative strategies also seen in Table 2, including vaccination and antimicrobial prophylaxis, can reduce the incidence of infections such as herpes zoster, *pneumocystis jirovecii* pneumonia and tuberculosis. Each patient prior to further enhanced immunosuppression should undergo an individualized assessment to determine their risk and guide preventative interventions accordingly.

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Declarations

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