Review

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Mitigating infection risk with immunotherapy for rheumatoid arthritis

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The last two decades have seen major advances in the treatment of rheumatoid arthritis, with the introduction of combination of disease-modifying antirheumatic drug strategies and the advent of biologic therapies. Accordingly, with aggressive immunosuppression, rheumatologists are required to be more alert to infection risk. Even prior to immune suppression infections are more frequent in rheumatoid arthritis and are significant contributors to morbidity and mortality. The etiology is multifactorial reflecting an interaction between immunological dysfunction, disease activity and immunosuppression. There are several steps clinicians can take to mitigate against the risk of infection: these include appropriate patient selection for aggressive treatment strategies, vaccination against preventable pathogens and utilization of lower risk drugs in at-risk subjects. This review will address these aspects of immunosuppression.

Keywords: immunosuppression • infection • rheumatoid arthritis • vaccination

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LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Describe the overall risk for infection in patients with rheumatoid arthritis, based on a review
- Describe the risk for infection associated with use of various treatments in patients with rheumatoid arthritis
- Identify strategies to reduce the risk for infection in patients with rheumatoid arthritis

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Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disorder affecting approximately 1% of the UK population. It is a disease characterized by chronic inflammation within joints, resulting in pain and progressive disability. Compared to the general population, people who suffer with RA have an increased mortality, with a reduction in life expectancy by approximately 10 years [1]. The reasons for this are multifactorial; however, one key contributor to both mortality and morbidity in RA is an increased infection burden [2].

Control of inflammation in RA with a target of disease remission is associated with the best clinical outcomes [3–7]. Current national guidelines advocate a treat to target approach, with a combination of disease-modifying antirheumatic drugs (DMARDs), escalating to biologic therapies until disease control is achieved [8]. It is estimated that RA costs the National Health Service between £3.8 and £4.75 billion per annum [9]. Biologic agents cost circa £10,000/year per patient and complications of therapy such as infection add to the costs incurred due to morbidity, mortality and loss of productivity. Interruption in drug treatment during periods of infection also has cost implications as this may be associated with reduction in drug efficacy. Accordingly, the financial consequences of reducing infection are important.

The burden of infection in RA

The etiology of increased infection risk in RA is multifactorial and reflects an interaction between immunological dysfunction, disease activity and immunosuppression. There is evidence from immunological studies that even prior to immune suppression, patients with RA have aberrant immune systems with impairment of innate and adaptive responses to infection. Irrespective of treatments, disease activity is also an independent risk factor for infection. Au *et al.* [10] reported for every 0.6 unit increment of Disease Activity Score 28 (DAS28), the risk of hospitalization with infection was increased by 25%.

Prospective observational studies have shown that the absolute rate of infection in RA patients treated with nonbiologic DMARDs is approximately 3% with increased risk if medicated with biologic agents [11]. A retrospective longitudinal cohort study by Doran *et al.* compared the frequency of infection in patients with RA compared with age and sex-matched healthy controls [12]. Doran reported on 609 RA patients with over 7700 patient years cumulative follow-up, during which the infection rate was 70–80% higher in RA subjects compared with controls. Hazards ratios (HR) for objectively confirmed infections, infections requiring hospitalization and any documented infection in patients with RA were 1.70 (95% CI: 1.42–2.03), 1.83 (95% CI: 1.52–2.21) and 1.45 (95% CI: 1.29–1.64). All types of infections were increased in patients with RA compared with controls, with the commonest foci being the soft tissue, urinary and respiratory tract. The sites of infection in RA patients with the greatest relative risk compared with the general population were osteomyelitis (rate ratio: 10.63; CI: 3.39–126.81), septic arthritis (rate ratio: 14.89; CI: 6.12–73.71), skin (rate ratio: 3.28; CI: 2.67–4.07) and respiratory tract (rate ratio: 1.88; CI: 1.41–2.53). Similar findings have been observed in subsequent retrospective and prospective cohort studies [13,14]. Population studies linking in-patient admission data to national death registry data have confirmed an increased standardized mortality ratio in RA patients (males 1.8 [95% CI: 1.6–2.0];

females 2.1 [95% CI: 1.9–2.3]) due to respiratory tract infections [15].

Infection risk & RA treatments

Treatments for RA also contribute to infection risk. In general, individual clinical trial data are underpowered to study infection risks and the nature of selective recruitment to clinical trials limits their validity. Much of the research around infection risk is drawn from observational cohorts. It is important to acknowledge a substantial challenge of channeling bias in observational studies. Channeling bias describes the scenario where the reasons that lead a clinician to prescribe a particular therapy are also associated with the outcome of interest. In the setting of infections with RA, disease severity predicts treatment choices and also predicts infections. If an association is observed between treatment and infection this may simply reflect the underlying relationship between treatment and disease severity.

Nonbiologic DMARDs, steroids & infections

Lacaille *et al.* presented findings of infection risk with nonbiologic DMARDs from a total of 27,710 individuals with RA providing 162,710 person years of follow-up collected from a retrospective population-based study [16]. In patients prescribed DMARDs, the overall rate of infection per person year of follow-up was 1.31 (95% CI: 1.28–1.31) compared with 1.30 (95% CI: 1.29–1.31) with no DMARD therapy. The risk of serious infection (i.e., those requiring hospitalization, intravenous antibiotics or resulting in death) was increased in patients receiving DMARD therapy compared with those not on DMARD therapy; although statistically significant the clinical significance was questionable (risk difference: 0.3%). An important observation was that corticosteroid exposure was an important confounder in the analyses and was a significant independent predictor of infection (the relative risk [RR] of serious infection 60% in DMARD users additionally on steroid).

The association between corticosteroid use and infection, even at low doses (below 7.5 mg prednisolone daily) is well established, having been the subject of a recent systematic review [17]. There is no true definition of what constitutes low dose steroid although consensus opinion from the British Society of Rheumatology (BSR) suggests doses below 10 mg daily would be a sensible compromise. While steroids remain an important therapeutic option, the extensively documented potential side effects have led to caution with long-term use. Results from another prospective cohort study found a much higher increase in the rate of infection, with a greater than sixfold rate of hospitalized infection in patients treated with prednisolone compared with no prednisolone [10]. These results are concordant with Smitten *et al.* who found an increased infection rate with steroids with increased risk in a dose-dependent manner [13]. Meta-analysis of observational studies conducted by Dixon *et al.* has shown that corticosteroid therapy is associated with an increased risk of all-site serious infection (RR: 1.89; 95% CI: 1.60–2.24), lower respiratory tract infections (RR: 2.10; 95% CI: 1.52–2.91), tuberculosis (TB) (RR: 1.74; 95% CI: 1.09–2.76) and herpes zoster (RR: 1.74; 95% CI: 1.28–2.36) with a dose-related increase in risk of infection [17]. Serious infections only represent the 'tip of the iceberg' when considering infection risk. Mild infection may not come to the attention of healthcare providers despite contributing to the morbidity associated with steroid therapy.

Randomized controlled trial (RCT) meta-analysis did not show an association between glucocorticoid therapy and infection risk (RR: 0.97; 95% CI: 0.69–1.36) in contrast to the observational data. The reasons for this are likely multifactorial but include underestimation of risk in clinical trials through a narrow selection criteria.

Biologic agents

The major advance in antirheumatic care in recent years has been the advent of highly targeted biologic immune modulators. Available therapies modulate specific components of the host immune defense systems (e.g., TNF-α, B cells and T cells) and through their specific mode of action leave patients at potential risk of infection. To what extent these agents expose a person to infections has been the subject of a great many publications. The key findings from the available literature will be summarized.

TNF-α is a cytokine secreted by macrophages and is released in response to inflammatory stimuli and is involved in immune regulation, inflammation, sepsis, apoptotic cell death and cancer. It has been identified as being a key pro-inflammatory cytokine in RA pathophysiology. There are currently five anti-TNF agents commercially available. Several intracellular and opportunistic infections have been reported as complications of anti-TNF therapy, with the commonest foci of infection being the respiratory tract, skin and soft tissues and the urinary tract. A meta-analysis by Leombruno *et al.* to quantify the adverse events associated with anti-TNF therapies did not find a significant increase in severe infection risk with anti-TNF therapy at recommended doses, quoting an odds ratio of 1.21 (95% CI: 0.89–1.63; p = 0.24) [18]. In contrast, data from national registries that have monitored the safety and effectiveness of biologic treatments over a

long-term period have suggested a small but significant increase in infection risk with biologic agents [11]. Reporting on 11,798 RA patients treated with anti-TNF agents comparing them to 3598 nonbiologic DMARD-treated controls, the BSR biologics registry reported the adjusted HR for serious infection in the anti-TNF-treated patients was 1.2 (95% CI: 1.1–1.5), similar to the point estimate of Leombruno *et al.* The BSR biologics register had access to 36,228 patient years follow-up compared with 7846 patient years of follow up in Leombruno's analysis. The risk of infection was highest during the first 6 months of therapy, HR 1.8 (95% CI: 1.3–2.6). Data from Dutch, Italian and German groups support the findings of increased infection risk with anti-TNF use that diminishes over time [19–21]. Once patients had been on therapy for 2 years, the increased risk of infection with anti-TNF was no longer apparent. This may be due to an improvement in overall disease activity, reduced steroid exposure and third possibly due to healthy user effect.

Overall, anti-TNF biologics appear to increase the risk of infection by a small but significant amount (~20% increase in risk) [11]. When considering the absolute risks, assuming a baseline infection risk of 3% in RA patients, the number needed to harm (i.e., the number of patients that would need to be treated to observe one additional infection attributable to anti-TNF therapy) is 166. This calculation makes the assumption that all patients have the same baseline infection risk. As described by Doran, important predictors of infection aside from steroid use include significant comorbidity (chronic lung disease, alcoholism, organic brain disease and diabetes mellitus), increasing age, presence of extra-articular manifestations of disease and leucopenia. A history of previous severe infection has also been found to predict future infection [10–21]. If these variables are considered, the infection risk can be markedly different between patients. Clinicians therefore need to modify therapy according to individual risk factors in order to mitigate against infection. This can be achieved in part through minimizing steroid exposure and choosing drugs with the best safety profiles.

Considering anti-TNF agents, these do not appear equal in terms of their associated infection risk with registry data suggesting reduced risk of tuberculosis (TB) and opportunistic infection with etanercept (ETN) compared with infliximab (IFX) and adalimumab (ADA) [22,23]. These findings have led to a preference to consider ETN in patients who may be at high risk of developing TB or re-activation of latent TB. Although there is a signal of concern for reactivation of TB with newer anti-TNF agents certolizumab pegol (CZP) and golimumab (GOL), data from observational studies are currently lacking. Meta-analysis has, however, shown a statistically higher odds of serious infections with CZP compared with abatacept (ABA), ADA, ETN, GOL and rituximab (RTX) [24]. There are limitations to the CZP data, including the duration of follow-up which is not comparable to other trials as well as the issue that a substantial amount of information on infection was derived from two trials which utilized corticosteroid and CZP in combination. Infections were more common, but it is unclear if this was driven by steroid therapy or CZP [25,26].

Common bacterial infections including pulmonary and soft tissue infection are increased with anti-TNF therapy; however, clinicians need to be alert to opportunistic infection. Meta-analysis of RCT data of opportunistic infections associated with biologic therapy has found a small but significantly increased risk compared with placebo or DMARDs, with an odds ratio (OR) of 1.79 (95% CI: 1.17–2.74) and a number needed to harm of 552. There was a significant risk for mycobacterial (OR: 3.73; 95% CI: 1.72–8.13) and viral (OR: 1.9; 95% CI: 1.02–3.58) infections [27]. No significant increased risk was found for superficial or invasive fungal disease, pneumocystis or varicella zoster infection. The relationship between anti-TNF and varicella zoster has been discordant across studies. The authors commented that in the meta-analysis, there was a suggestion that anti-TNF therapies were associated with an increased risk of shingles (although not thought to be clinically significant) [28]. It is important to acknowledge that patients with RA have a significantly higher rate of shingles than the general population [29].

RTX is a genetically engineered chimeric monoclonal antibody that targets CD20-positive B cells. RTX depletes subpopulations of B cells that are involved in the initiation and maintenance of inflammatory cascades in RA. The meta-analysis of RTX from the RCTs did not show an increased risk of infection compared with placebo (OR: 1.45; 95% CI: 0.56–3.73) [30]. Evaluation of the long-term safety of RTX using pooled case-analysis of patients with moderate-to-severe RA in a global clinical trial program has not identified any new safety concerns with prolonged and repeated courses of treatment [31]. The overall serious infection event rate was 3.94 per 100 patient years (3.26/100 patient years in patients observed for more than 5 years) which was comparable with placebo with Methotrexate (3.79/100 patient years). Acknowledging the important limitations of safety analyses in long-term extension studies (where the healthy user effect is often substantial) further stated analyses from observational data sets will help define the safety of RTX. Important caveats regarding the infection profile of

RTX relate to the risk of hypogammaglobulinemia [32]. Some patients can develop profound and persistent low immunoglobulin (Ig) levels. Baseline low IgG levels also predict infection in patients commencing RTX. Accordingly, monitoring of Ig levels serially in patients requiring repeated courses should be undertaken.

Although the overall increase in infection risk seems to be limited, RTX has been associated with the rare complication of progressive multifocal leukoencephalopathy, an irreversible inflammatory demyelinating disorder caused by JC virus infection with high mortality. An insignificant increase in the rate of progressive multifocal leukoencephalopathy was reported by the Swedish registry in RA patients relative to the general population (1.0/100,000 person years vs 0.3/100,000 person years) [33].

There are concerns regarding the risk of reactivation of occult hepatitis B (surface antigen negative, core antibody positive) with RTX therapy. Hepatitis B reactivation has been described in the oncology literature with reports of fulminant liver failure in patients with lymphoproliferative disease [34]. It is recommended that all patients are screened for latent infection and treated with prophylactic agents during the course of treatment.

Tocilizumab (TOC), another licensed second-line agent for RA works by binding to the IL-6 receptor and blocks the action of IL-6 cytokine. IL-6 is produced from a wide range of innate and adaptive immune cells to drive an inflammatory response, in particular causing production of C-reactive protein within the liver, a marker of infection and inflammation. TOC is a highly effective treatment in RA with a head-to-head trial showing superior efficacy versus anti-TNF [35]. Cochrane systematic review has not shown a significant increased risk of infection with TOC compared with placebo [36]. In contrast a cohort study reported a markedly higher infection rate compared with clinical trial data [37]. Reporting on 112 TOC-treated subjects over a 2-year follow-up period, 26 patients developed infections, 18 were classified as mild to moderate and 8 severe bacterial infections. Factors associated with mild-to-moderate infections included use of Leflunomide and Prednisone, elevated disease activity scores and patients who had previously been treated with RTX. Longer disease duration and exposure to multiple DMARDs (more than three) were associated with severe infections. More detail from observational cohorts is required to gain information regarding the real life safety of TOC.

Specific caution needs to be given with prescription of TOC in patients with diverticular disease due to an increased incidence of intestinal perforation in this population. Reporting of results of pooled data from five core Phase III trials, two extension trials and one clinical pharmacology study, Schiff *et al.* reported a diverticular perforation rate of 0.28/100 patient years in TOC exposed patients compared with 0.2/100 patient years in the all-control groups (patients in control groups for all five randomized controled trials) [38] Systematic review of the risk of diverticular perforation with TOC was found to be higher than with other anti-TNF therapies but lower than with corticosteroids and nonsteroidal anti-inflammatories [39]. As TOC inhibits IL-6 production, patients may not mount an expected inflammatory response to pathogens leading them to be more susceptible to infection. This is an important consideration when evaluating TOC-treated patients.

ABA, a selective T-cell co-stimulation inhibitor inhibits T-cell activation by binding to CD80 and CD86, blocking interaction with CD28. This interaction is required for full activation of T lymphocytes that are implicated in the pathogenesis of RA. ABA has a favorable infection risk profile compared with other biologics with incidence rates of hospitalized infection being comparable to nonbiologic DMARD cohorts, with similar findings for hospitalized pneumonia and the incidence of TB [40]. Cochrane meta-analysis has confirmed its safety compared with other biologics making it an attractive choice in patients deemed to be at high risk of infection [24]. Head-to-head comparison between ABA with ADA has showed similar efficacy between the two agents but fewer discontinuations of ABA due to serious infection compared with ADA [41]. The mechanism of action suggests ABA has a more immunomodulatory rather than immunosuppressive method of action providing biological plausibility for its better infection profile. A number of biologic treatment pathways reflect this and suggest use of ABA in high-risk patients.

Mitigating against infection risk in RA

Formal assessment for infection risk should be undertaken before commencing any immunosuppression. Important predictors of infection risk include increasing age, disease severity, and disability. The infection risk associated with steroids has been discussed above and is a predictor of infection risk but perhaps most importantly, a history of prior infection predicts future infection; patients with a history of prior hospitalized infection have an increased risk of hospitalization with bacterial infection when exposed to anti-TNF [42]. In patients warranting biologic agents, those who have had recurrent episodes of severe sepsis, chronic or localized infection, active hepatitis B, untreated hepatitis C infection and retroviral disease may not be eligible. Hepatitis B serology (including core antibody testing), Hepatitis C and HIV tests are routine pre-screening

investigations. Additionally, patients with demyelinating disease and malignancy (active or malignancy within 10 years) would be excluded from anti-TNF therapy but may warrant alternative biologic use.

Hepatitis B reactivation has been reported in patients undergoing chemotherapy for solid organ and hematological malignancies although limited data are available examining the safety of TNF blockade on the course of hepatitis B infection. Caporali *et al.* prospectively evaluated the safety of anti-TNF therapies in patients with occult hepatitis B infection (surface antigen negative, core antigen positive) and inflammatory arthritis [43]. Sixty-seven patients (comprising 59 with RA, 4 psoriatic arthritis and 4 ankylosing spondylitis) were treated with IFX (25/67), ETA (23/67) and ADA (19/67). The mean ± SD follow-up was 42.5 ± 22.3 months. There were no cases of hepatitis B reactivation reported and in particular, no patients presented with appearance of hepatitis B surface antigen or increases in viral load, suggesting TNF-α blockade appears safe in patients with occult infection. These results are supported by Biondo *et al.* who prospectively followed 20 patients with occult hepatitis B infection treated with anti-TNF for inflammatory arthropathies and found no cases of hepatitis B reactivation during a restricted follow-up period of 4 years [44]. Current clinical practice advises that in patients warranting biologic treatment with occult hepatitis B infection, consideration should be given to use of concurrent antiviral therapy (e.g., lamivudine or entecavir), although this may be associated with the development of resistant viral strains. The safety of anti-TNF therapy for active RA in the setting of concurrent hepatitis C infection was investigated by Ferri *et al.* [45]. In 31 patients with active RA treated with IFX, ETA and ADA, anti-TNF treatments were associated with significant improvements in clinical (DAS28 and patient assessment of global health scores) and serological (ESR reduction) parameters at evaluation 3 months post biologic commencement. No significant variations in hepatic transaminases or viral load were seen. Despite the small study numbers, the authors suggested the results supported the safety of TNF blockade in patients with active RA and hepatitis C infection, *en proviso* close monitoring of clinical and virological data. In complex patients requiring biologic therapy, the opinion of a hepatologist is advised.

HIV infection is a significant public health concern, although the advent of effective antiretroviral agents has been associated with an increased survival. Clinicians need to be aware of the rheumatic manifestations of HIV infection in addition to the implications of drug therapy and drug interactions, especially in those with comorbid diseases that require immunosuppressive treatment. Data are limited regarding the safety of DMARDs in RA with concurrent HIV infection, with the majority of the evidence base yielded from case series. Sulfasalazine and hydroxychloroquine appear to be safe and effective treatments; however, methotrexate has been associated with unfavorable outcomes although data were derived from studies when effective antiretroviral treatments were not available. There are no reports of leflunomide use in RA patients with HIV [46]. Anti-TNF drugs may have a theoretical beneficial effect in patients with HIV because TNF has been reported to modulate the replication of HIV. There is limited evidence on the safety of anti-TNF in HIV infection. Although ETN, IFX and ADA have been used safely in patients with HIV with no worsening of immunological or virological parameters, the potential risk of polymicrobial infection must be considered carefully and thus would not be suitable in patients with high infection risk or poorly controlled HIV. Nonetheless, close liaison with sexual health physicians and rheumatologists is required in patients requiring immunomodulatory treatment [46].

Due to potential concerns relating to reactivation of mycobacterial infection with biologic agents, prescreening investigations are required though local policy will dictate methodology, either tuberculin skin testing or IFN-γ release assay (IGRA). In IGRA, the advantage of reduced risk of false positives due to cross reactivity with BCG vaccination and a reduced risk of false negatives due to background immunosuppression. A chest x-ray is recommended as routine. In patients with evidence of latent TB, prophylaxis has been shown to be effective [47]. A formal risk assessment score has been developed and validated to allow risk stratification of patients. The tool helps to estimate the probability of serious infection within 12 months of commencing treatment. The 'RABBIT' tool [48] was developed with data from over 5000 patients with RA who were recruited to the German biologics registry with validation in a subsequent cohort of nearly 3000 patients (Figure 1) [21,49]. High agreement between observed and predicted infections was demonstrated and although it does not replace clinical judgement, it serves as an aide to help clinicians make informed decisions when balancing treatment versus infection risk. A risk of more than 10% of serious infection within 12 months is thought to represent a 'high risk' patient, though the discretion and judgement of the treating clinician is key in interpreting the score in context of the individual patient. A strength of the RABBIT risk calculator is that it accommodates for time varying factors such as infections within previous 12 months.

Drugs with a shorter half-life may be considered preferable in patients with recurrent infection and high disease activity warranting biologics, although the risk-

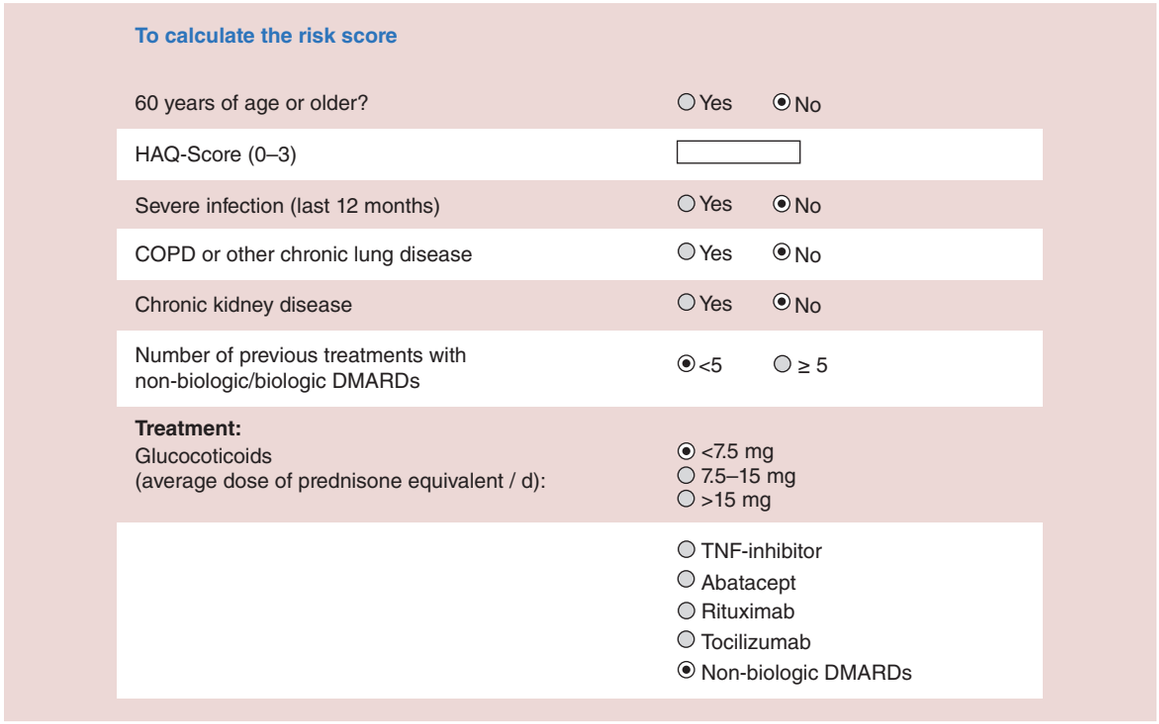

Figure 1. The 'RABBIT' risk calculator [48].

benefit ratio should be considered carefully by the clinician. Steroid therapy where possible should be avoided, accepting that in a number of patients, high disease activity warrants corticosteroids despite potential risks; in such patients, the lowest efficacious dose should be used. There may also be a preference toward ABA or ETN in patients who are considered to be at high risk of infection in accordance with the available evidence base.

Vaccinations in RA

Vaccination of preventable disease is an effective method of mitigating infection risk in RA. Vaccination programs have a direct effect on the individual by inducing protective immunity, in addition to an indirect effect of producing herd immunity on the general population [50]. In the United Kingdom., routine vaccination schedules exist for influenza and pneumococcal disease and are recommended for patients above the age of 65 and those in clinical risk groups, in other words, patients with chronic pulmonary, cardiac, renal or liver disease and patients who are immunocompromised (either due to their primary disease or due to treatment).

Despite the obvious indications for vaccination, concerns regarding general vaccine safety have arisen [51–53]. Widespread public skepticism around the safety of vaccination followed the work of Wakefield *et al.* [54]. The work received extensive media attention before the findings were found to be fraudulent and the manuscript retracted by the publishers. Nonetheless it has had a significant effect on the perception of vaccination and its subsequent uptake. While there are potentially serious side effects that exist of vaccination, it must be emphasized that these are rare but may still be of considerable concern for a healthy individual and this can affect uptake of vaccination. Immunological provocation of adults with common vaccines does not equate to a major risk factor for developing RA [55]. There is no firm evidence to suggest that vaccinations trigger autoimmune rheumatic disease. Substantial evidence in the literature supports that common vaccinations do not worsen either clinical or laboratory makers of autoimmune inflammatory diseases [56].

Despite indications for vaccination in RA patients, uptake remains poor. A national audit has shown pneumococcal vaccine uptake is poor with only 44% of eligible patients being vaccinated [Subesinghe S *et al.*, King's College Hospital audit data; unpublished data]. Particular patients at risk who were least likely to be vaccinated were young (under 65 years of age) and those without concurrent co-morbidity. Current BSR and European guidelines recommend all patients with RA receive annual influenza and single pneumococcal vaccine (Table 1) [56,57]. UK guidance is currently under review. American guidelines recently have been updated to advise repeat pneumococcal vaccination every 5 years [58]. Other vaccines may be clinically indicated depending on the clinical scenario but it is

important to note that live vaccines contraindicated in significant immunosuppression (Table 2). The shingles vaccine may be an exception, as although it is a live vaccine, a number of bodies have taken the attitude that in patients receiving low dose immunosuppression, the benefit of vaccination may outweigh the risk. The Centers for Disease Control and Prevention have advised it is safe to administer the shingles vaccine in patients on nonbiologic DMARDs including Azathioprine and Methotrexate but avoided in patients on biologic DMARDs and high-dose prednisolone (>20 mg per day) [59].

Vaccine efficacy can be assessed through clinical parameters (i.e., disease incidence post-vaccination, hospitalization rates with immune preventable disease or mortality rates) however this requires well conducted epidemiological studies. The immunogenicity of vaccination in RA is dependent upon a number of factors including vaccine type and vaccine strain. A fourfold rise in antibody titer post-vaccination suggests successful vaccination; however, whether this is truly protective against infection is not confirmed [50]. Immunosuppressive agents can blunt the serological response to varying degrees most patients mount protective post-vaccination protective antibody titers [60–73].

Uptake of vaccination in RA

Current guidance in the U.K. advise annual influenza vaccination for patients above the age of 65 and in 'at-risk' populations (including patients with chronic diseases such as heart failure and respiratory disease) in addition to a single pneumococcal polysaccharide vaccination, which can be repeated after a 5-year interval if indicated. Patients with autoimmune rheumatic diseases may not be classified by primary care providers as having chronic disease and despite their increased susceptibility to infection, and thus may not traditionally be considered for vaccination programs.

Despite the indications and safety of vaccination, current estimates based on published audits show wide variation in the uptake of vaccinations in RA patients with uptake between 22 and 100% quoted [74–76]. National data that suggest uptake of influenza vaccination in patients above the age of 65 years according to seasonal flu vaccine data produced in January 2014 [77]. Increasing public perception of both influenza and pneumococcal infection as significant threats to health and encouraging vaccination as an effective preventive strategy may correlate with a higher uptake of vaccination. In order to increase vaccine uptake, collaborative approaches promoting vaccination between primary and secondary care are required (e.g., vaccination campaigns). Key factors that have been identified as being associated with successfully increased influenza vaccine uptake in general practice include having a lead staff member responsible for planning influenza vaccination campaigns in addition to inviting all at-risk

Table 1. Guidelines for vaccination in patients on immunosuppressive therapies.

	Recommended vaccinations	Other considerations	Ref.
UK (BSR guidelines for patients with autoimmune rheumatic disease 2011)	Annual influenza vaccination	Varicella-Zoster immunoglobulin if exposed to chicken pox or shingles	[56]
	Pneumococcal vaccination	No live vaccine administration while on immunosuppressive therapy	[57]
Europe (EULAR guidelines for patients with autoimmune rheumatic disease)	Annual influenza vaccination	Herpes zoster vaccination should be considered HPV vaccination and should be considered in selected patients	
	Pneumovax (23 valent polysaccharide vaccine)	No live vaccine administration while on immunosuppressive therapy	
USA (ACR guidelines for patients commencing/commenced on DMARDs or biologic therapy)	Annual influenza vaccination	Hepatitis B vaccination if risk factors are present	[58]
	Pneumococcal vaccination with re-vaccination after 5 years		
	Herpes zoster vaccination (unless already commenced on biologics)		

Table 2. Commercially available vaccines in the UK.

	Live vaccines	Non-live vaccines
Bacterial vaccines	BCG	Cholera (oral)
	Typhoid (oral)	Diptheria toxoid
		Hemophilus influenzae type B (Hib)
		Meningococcal Group C
		Meningococcal polysaccharide A, C, W135 and Y vaccine
		Pneumococcal
		Tetanus toxoid
		Typhoid (polysaccharide for injection)
Viral vaccines	Measles, mumps, rubella (combined vaccine)	Hepatitis A
	Poliomyelitis (oral vaccine)	Hepatitis B
	Rotavirus (oral vaccine)	Hepatitis A and B (combined vaccine)
	Varicella-Zoster	Influenza
	Yellow Fever	Poliomyelitis (injectable vaccine)
		Rabies
		Tick-borne encephalitis

Live vaccines should be given before immunosuppressive DMARD therapy (2–4 weeks prior) or 3 months after stopping DMARDs.
Live vaccines should not be given to patients on biologics. Ideally administer 4 weeks prior to commencement.

patients individually. Effective use and interrogation of electronic patient records and practice IT systems to identify eligible patients has also been found to predict higher vaccine uptake. These results are supported by a study from the USA, which suggested that effective use of electronic databases by a skilled data manager could increase the rate of influenza vaccination by over 10% [78].

Strategies in special high-risk circumstances

Clinicians are frequently faced with challenging patients who suffer from recurrent infections in the setting of active disease that requires treatment. In such situations, the potential risks and benefits of immunosuppressive treatment need to be balanced. The following are a series of pragmatic steps we use in clinical practice:

- If patients report recurrent infections, it is imperative to confirm that patients are having microbiologically proven infections and exclude mimics such as allergy. Positive culture results will help confirm diagnosis of infection. Careful examination of the patient's history of infection including sites, frequency, duration of infection as well as response to antimicrobial review of previous microbiological investigations and results. This process can help identify genuine infections and uncommon pathogens;
- Detailed review of infection history will help to identify inherent abnormalities of the immune system. For example, recurrent skin infection may suggest deficiencies in the innate immune system and prompt testing for diabetes. Viral, fungal, mycobacterial or protozoal infections suggest a T-cell defect and up-to-date HIV tests and checking of lymphocyte count should be undertaken. Patients with recurrent nasopharyngeal and respiratory tract infection should have serum Igs and IgG subclasses measured. Evaluation of a family history of recurrent infection may reveal inherited immune deficiency diseases;
- Choose the safest combination of antirheum drugs (Table 3). The data would suggest avoiding steroids as they are one of the strongest and most consistent predictors of recurrent infection. Methotrexate reduces infection risk. The drug currently felt to be safest among biologic DMARDs is ABA. Use of an infection risk calculator can help quantify individual risk. Using an infection risk calculator will help guide appropriate drug choices, avoid 'high risk' combinations and allow for more informed decision making;
- Consider additional steps to reduce infections. There are no controlled trials to prove the efficacy of antibiotic prophylaxis in patients with primary

Table 3. Selecting the safest drug in rheumatoid arthritis.

Drug	Category	Infection risk	Special notes	Ideal choice for which patients?
Hydroxychloroquine	Nonimmunosuppressive DMARD	Considered nonimmunosuppressive	Weak antirheumatic effect	Milder disease activity. Suitable for combination of DMARDs. Safe in pregnancy
Sulfasalazine	Nonimmunosuppressive DMARD	Nil	Caution with neutropenia and drug-induced hepatitis	Safe in pregnancy
Methotrexate	Immunosuppressive DMARD	Low. Immunosuppressive action balanced by better disease control with treatment	Caution with neutropenia and drug-induced hepatitis	Anchor therapy in RA. Use in combination with other DMARDs and biologic agents. Not suitable in pregnancy
Leflunomide	Immunosuppressive DMARD	High. Increased risk of pneumonia	Not safe in pregnancy	Comparable efficacy to Methotrexate
Prednisolone	Corticosteroid	High. Increased risk of infection even at low doses. Dose-related increment in risk	No longer recommended for long-term use by European and US guidelines	Safe in pregnancy. Indicated in early arthritis. Patients with multiple DMARD intolerances
Infliximab	Biologic anti-TNF. Chimeric IgG1 anti-TNF-α antibody	High. Increased risk of serious bacterial infections and TB compared with other anti-TNF drugs. Time varying risk, highest within the first 6 months of treatment. Risk of nonserious infections also increased	Use in combination with methotrexate	Needle phobic patients unwilling to self-administer medication
Adalimumab	Biologic anti-TNF. Recombinant human IgG1 monoclonal antibody	Moderate. Increased risk of serious bacterial infections and TB compared with other anti-TNF drugs. Time varying risk, highest within the first 6 months of treatment. Risk of nonserious infections also increased	Increased risk of infection with combination therapy with corticosteroids and methotrexate	
Certolizumab Pegol	Biologic anti-TNF. Recombinant humanized Fab' fragment of a TNF- antibody coupled to polyethylene glycol	Moderate/High. Increased risk of serious bacterial infections and TB compared with other anti-TNF drugs. Time varying risk, highest within the first 6 months of treatment. Risk of nonserious infections also increased	Increased risk of infection with combination therapy with corticosteroids and methotrexate	

Table 3. Selecting the safest drug in rheumatoid arthritis (cont.).

Drug	Category	Infection risk	Special notes	Ideal choice for which patients?
Golimumab	Biologic anti-TNF. Recombinant human IgG1 monoclonal antibody specific for TNF-α	Moderate. Increased risk of serious bacterial infections and TB compared with other anti-TNF drugs. Time varying risk, highest within the first 6 months of treatment. Risk of nonserious infections is also increased	Increased risk of infection with combination therapy with corticosteroids and Methotrexate	Limited postmarketing surveillance data
Etanercept	Biologic DMARD. Soluble TNF-receptor fusion protein	Better profile with respect to TB risk, appears safest anti-TNF from infection perspective		In patients where shorter half-life required due to history of TB, infections requiring hospitalization or other co-morbidity
Rituximab	B-cell inhibitor. Chimeric monoclonal antibody targeting cells bearing CD20 surface marker	Similar risk compared with anti-TNF agents. Caution with repeated courses – hypogammaglobulinemia	More effective in seropositive patients	Patients with previous history of malignancy, interstitial lung disease, overlap syndromes or other contraindications to anti-TNF
Abatacept	T-cell costimulation inhibitor Immunoglobulin fused to the extracellular domain of cytotoxic T-lymphocyte antigen 4	Low. Similar risk to non-biologic DMARDs		In patients where shorter half-life required due to history of TB, infections requiring hospitalization or other co-morbidity
Tocilizumab	IL-6 inhibitor. Recombinant humanized antihuman IL-6 receptor monoclonal antibody of the IgG1 subclass	Moderate/high. Increased risk of infection in patients using leflunomide and corticosteroid. Severe infections related to longer disease duration, exposure to more than three previous DMARDs	No suitable if history of diverticular disease	Patients with contra-indication to anti-TNF, primary failure with anti-TNF or contraindication/ intolerance to methotrexate

immunodeficiency states, however experience with HIV patients has shown benefit of co-trimoxazole in preventing death and illness episodes in adults with both early and advanced HIV disease [79]. Prophylactic prescription of macrolide antibiotics in patients with chronic obstructive pulmonary disease have been found to be of significant benefit in reducing exacerbations [80–82]. Risks of prophylactic antibiotic use include drug resistance, potential cardiac arrhythmia, gastrointestinal morbidity and cost need to be considered. There is no evidence for prophylactic antibiotics in patients with RA who experience recurrent infection, however in the event of repeated culture positive infection, directed prophylaxis may be appropriate. In the setting of recurrent respiratory tract infection with hypogammaglobulinemia, there is a role for Ig replacement therapy. Both approaches are optimally done in collaboration with immunology and microbiology colleagues. Vaccination is a strongly advised intervention to consider.

Conclusion

Biologics have revolutionized RA care. Although they are associated with an increased risk of infection, the absolute risk is small. The vast majority of patients will never experience infection. It is essential to acknowledge their potential to suppress the immune system and understanding different infection profiles and risk mitigation strategies is essential to personalized care in RA. Key strategies to minimize risk of infection in RA include selecting the safest drug combinations based on individual risk factors, routine comprehensive assessment of infection risk (including consideration of infection history) in all patients before the commencement of immunosuppressive drugs. Finally collaborative approaches between primary and secondary care are needed to ensure vaccination in this at-risk population.

Future perspective

The last decade has seen the expansion in the therapeutic options available in RA and the current armamentarium of biologic dugs is set to expand. Through increasing understanding of the pathophysiology of RA at a molecular and cellular level, developing efficacious targeted therapies that will allow sustained (potentially) drug-free remission will be a focus. Current treatment options are all effective and therefore decisions will revolve around safety and side effect profiles. Continued pharmacovigilance will help expand knowledge around comparative safety of therapies. Infection is at the forefront of both clinician and

Executive summary

Burden of infection in rheumatoid arthritis

- Infection risk in rheumatoid arthritis (RA) is increased relative to the general population.
- The increase of infection has a multifactorial etiology due to combination of disease activity, aberrant immune systems and immunosuppression.

Infection risk & RA treatments

- Corticosteroids even at low doses increase infection risk.
- There is an increased risk of infection with anti-TNF particularly within the first 6 months of treatment.
- The respiratory tract and skin/soft tissue are common foci of infection but opportunistic infections should be considered.
- The risk of infection across anti-TNF agents is not equal.
- Abatacept is a suitable biologic choice in patients at high risk of infection.

Mitigating against infection in RA

- Formal risk assessment of infection risk is advised prior to commencing immunosuppressive agents.
- Routine screening for HIV, hepatitis B/C and TB is advised prior to commencing biologic therapies.
- Infection risk calculators can help clinicians to identify patients at highest risk of infection and select the safest drug combinations.

Vaccinations in RA

- Routine annual Influenza vaccination and a single pneumococcal vaccination are advised in all RA patients.
- Vaccinations are safe and not associated with worsening of disease activity.
- Live vaccines should be avoided in all patients on significant immunosuppression.

Strategies to reduce infection in high-risk patients

- Selection of the safest combination of drugs is advised in patients with recurrent infections.
- Corticosteroids should be avoided if possible.
- At present, there is no role for routine antibiotic prophylaxis.

Conclusion

- Clinicians must consider the potential of therapies to suppress the immune system.
- Understanding different infection profiles and risk mitigation strategies are essential to personalised care in RA.

patient's minds when prescribing although currently the absolute risks are small. Selecting the 'right therapy for the right patient' accounting for their individual characteristics, coupled with screening for infection and appropriate vaccination will help reduce risk of infection further. In the future, there is likely to be a move toward personalized care as biomarkers of response (and safety) evolve.

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Mitigating infection risk with immunotherapy for rheumatoid arthritis

To obtain credit, you should first read the journal article. After reading the article, you should be able to answer the following, related, multiple-choice questions. To complete the questions (with a minimum 75% passing score) and earn continuing medical education (CME) credit, please go to www.medscape.org/journal/ijr. Credit cannot be obtained for tests completed on paper, although you may use the worksheet below to keep a record of your answers. You must be a registered user on Medscape.org. If you are not registered onMedscape.org, please click on the "Register" link on the right hand side of the website. Only one answer is correct for each question. Once you successfully answer all post-test questions you will be able to view and/or print your certifi-cate. For questions regarding the content of this activity, contact the accredited provider, CME@medscape.net. For technical assistance, contact CME@webmd.net. American Medical Association's Physician's Recognition Award (AMA PRA) credits are accepted in the US as evidence of participation in CME activities. For further information on this award, please refer to http://www.ama-assn.org/ama/pub/about-ama/awards/ama-physicians-recognition-award.page. The AMA has determined that physicians not licensed in the US who participate in this CME activity are eligible for AMA PRA Category 1 Credits™. Through agreements that the AMA has made with agencies in some countries, AMA PRA credit may be acceptable as evidence of participation in CME activities. If you are not licensed in the US, please complete the questions online, print the AMA PRA CME credit certificate and present it to your national medical association for review.

Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.					
	1	**2**	**3**	**4**	**5**
The activity supported the learning objectives.					
The material was organized clearly for learning to occur.					
The content learned from this activity will impact my practice.					
The activity was presented objectively and free of commercial bias.					

1. Your patient is a 56-year-old woman with rheumatoid arthritis. According to the review by Subesinghe and colleagues, which of the following statements about the overall risk for infection in patients with rheumatoid arthritis is **correct**?
   - ☐ **A** Infections in persons with rheumatoid arthritis are nearly always the result of immune suppression
   - ☐ **B** Infection risk in rheumatoid arthritis is no greater than in the general population
   - ☐ **C** Increased infection burden is not a significant contributor to mortality or morbidity in persons with rheumatoid arthritis
   - ☐ **D** Causes of infection in persons with rheumatoid arthritis are multifactorial, due to a combination of disease activity, aberrant immune systems, and immunosuppression
2. According to the review by Subesinghe and colleagues, which of the following statements about the risk for infection associated with use of various treatments in patients with rheumatoid arthritis is **correct**?
   - ☐ **A** Most patients receiving biologic therapy will experience an infection during treatment
   - ☐ **B** Low-dose corticosteroids do not increase the risk for infection
   - ☐ **C** Risk for infection is increased with anti-tumor necrosis factor, particularly within the first 6 months of treatment
   - ☐ **D** The gastrointestinal tract is the most likely site of treatment-related infection
3. According to the review by Subesinghe and colleagues, which of the following statements about strategies to reduce the risk for infection in patients with rheumatoid arthritis would most likely be **correct**?
   - ☐ **A** Infection risk calculators can help clinicians identify patients at highest risk for infection and select the safest drug combinations
   - ☐ **B** Before biologic therapies are started, routine screening for HIV, Hepatitis B/C, and tuberculosis is not recommended
   - ☐ **C** Routine annual Influenza vaccination with live vaccine is advised in all patients with rheumatoid arthritis
   - ☐ **D** Routine antibiotic prophylaxis is recommended