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Infections in the management of rheumatic diseases: An update

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Patients with inflammatory rheumatic conditions have an increased risk of infection. While this could be the result of the underlying disease, it may also be caused by the use of immunosuppressive therapies, which are needed to treat these disorders. An increasing number of patients with rheumatoid arthritis or other rheumatic diseases are using biologic therapies (biologics) in addition to the synthetic disease-modifying anti-rheumatic drugs. The side-effects and complications of these relatively new agents are unknown to many specialists (outside of rheumatology) and general practitioners. This article highlights updates on the most important infections encountered in the daily management of patients with rheumatic diseases and discusses how these may be prevented.

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Viral infections

Patients with inflammatory rheumatic conditions have an increased risk of infection, including viral infections.[1] Rheumatological manifestations, such as arthritis, are also relatively common occurrences with viral infections.

Hepatitis B

The prevalence of hepatitis B virus (HBV) in rheumatic patients has recently been reported at ~3% in a large cross-sectional study on comorbidities, which included almost 4 000 rheumatoid arthritis (RA) patients at 17 centres worldwide.[2] The prevalence differed according to geographical area – more infections in Asia and fewer in Europe and the USA. However, it demonstrates this common problem in daily rheumatological practice owing to the risk of hepatitis B reactivation through immunosuppressive therapy.

According to the American College of Rheumatology (ACR) guidelines and the views of experts, RA patients should be screened for HBV before initiation of methotrexate, leflunomide and biologic therapies.[3] Patients with chronic hepatitis B should receive treatment with oral antivirals before starting therapy. Those with significant liver damage should, however, not receive these immunosuppressive drugs.

There are no guidelines with regard to the use of synthetic disease-modifying anti-rheumatic drugs (sDMARDs) and biologics in patients with a history of hepatitis B infection (hepatitis B core antibody positive). A significant population of those who were exposed to HBV, have cleared the virus. Depending on the prevalence of chronic HBV infection, the prevalence of past HBV infection varies between 5% and 80% worldwide. In the literature on haematology (lymphomas), rituximab-containing chemotherapy regimens lead to reactivation in 3 - 25% of patients with past HBV infection.[4] As data are limited, it is not clear if pre-emptive antiviral prophylaxis is needed in a rheumatological setting, but recently a large prospective study in >1 200 RA patients demonstrated a risk of reactivation in cases of previous HBV infection (15%) treated with biologics.[5] The majority were treated with anti-tumour necrosis factor (anti-TNF), but rituximab and other biologics were also used. It was reassuring that there were no observed cases of HBV reactivation during biologic treatment. This confirms the results of previous studies that the risk of HBV reactivation in patients with rheumatic diseases and a history of HBV infection treated with anti-TNF and rituximab is very low.[6] However, more studies should be done to assess the need for pre-emptive antiviral prophylaxis in patients with past HBV infection. In practice, regular monitoring for viral reactivation during therapy, particularly in patients lacking evidence of immunity (HBsAb negative), is necessary. If the transaminase levels are increased, HBV DNA should be checked and antiviral therapy initiated if reactivation occurs.

Hepatitis C

Hepatitis C virus (HCV) infection is a major global health problem, with a prevalence of 2.8%. Universal screening for individuals between the ages of 45 and 65 years is recommended by the US Centers for Disease Control and Prevention (CDC).[7] HCV can be associated with rheumatic syndromes, such as the potentially serious rheumatic complication of HCV-associated cryoglobulinaemic vasculitis (CV).

To treat HCV, interferon alpha (IFNα)-based regimens can achieve viral clearance in about 50% of patients, but it has many side-effects (e.g. cytopenias, depression, flu-like symptoms) and renal impairment is a contraindication. New oral direct-acting antivirals (DAAs) are being introduced into clinical practice. A prospective cohort study on treatment with a combination of first-generation DAAs with PegIFNα and ribavirin in 30 patients with severe refractory CV, who were not responding to standard treatment with antiviral therapy, was published recently.[8] After 1 year of treatment, 67% of these patients showed a clinical response, with total clearance of the virus. However, there were many side-effects, such as cytopenias and infections.

Fortunately, the newer DAAs, which target specific proteins such as non-structural protein 3b/4A/5A, will it is hoped signal the end of interferon use in HCV patients in the future.[9,10] These new drugs could possibly cure the disease in >90% of patients, with fewer side-effects. They are extremely expensive and only administered to patients with the highest risk of complications, such as those with CV with end-organ manifestations.[11] Despite the high cost, they are considered to be cost-effective.[12] Data on these new drugs in patients with rheumatic diseases are confined to a few case reports, but several trials are currently underway.

Data on the use of biologics in patients with hepatitis C infections are scarce. Biologics are contraindicated in cases of acute or chronic HCV infection with significant liver damage, as progression of HCV has been described in such patients who receive biologics. In RA patients with chronic HCV infection without significant liver damage, rituximab and anti-TNF (the ACR suggests etanercept as the preferred anti-TNF) may be used, but monitoring of serum transaminases is advised.

Herpes zoster

Reactivation of the latent varicella zoster virus causes herpes zoster (HZ), a painful vesicular skin rash that could be complicated by chronic pain and post-herpetic neuralgia. In patients with rheumatic disease, the incidence of HZ is almost 12 times higher in RA, 20 times higher in systemic lupus erythematosus (SLE) and 45 times higher in Wegener's granulomatosus.[13] This increased risk of HZ is caused by the underlying disease, especially in those receiving immunosuppressive therapy.[14] A recent review showed that there was some increased risk with the use of biologics (anti-TNF) and sDMARDs,[15] but that high-dose corticosteroids and cyclophosphamide led to the highest increase in risk.

HIV

HIV can cause several rheumatological manifestations, including an inflammatory polyarthritis mimicking RA. Therefore, an HIV test may be useful in patients presenting with inflammatory arthritis. HIV can also result in several challenges in the management of patients with rheumatic diseases, who are also HIV-positive, especially if not on antiretroviral treatment. Data on the safety of immunosuppressive drugs in HIV-positive patients are limited, but there have been reports on the use of sDMARDs and TNF-α inhibitors to treat RA or other inflammatory conditions in HIV infection.[16,17] In general, these reports suggest that DMARDs such as methotrexate and anti-TNF are tolerated well by HIV-positive patients, provided that the patients are on an effective antiretroviral regimen before the start of therapy.

Vaccinations

According to the latest recommendations by the CDC, immunocompromised patients such as those with rheumatic diseases should receive killed (pneumococcal, annual intramuscular influenza and hepatitis B) and recombinant (human papillomavirus (HPV)) vaccines before starting an sDMARD or a biologic.[18] It also recommends that, if not previously done, vaccination with pneumococcal, intramuscular influenza, HBV and HPV vaccines should be done in patients already taking an sDMARD or a biologic. All vaccines should be given based on age and risk, and physicians should refer to vaccine instructions and CDC recommendations for details about dosing and timing. Importantly, both the pneumococcal polysaccharide vaccine (PPSV23) and the 13-valent conjugate pneumococcal vaccine (PCV13) should be given. In non-immunised patients, one should start with the PCV13, then wait for 2 months, and thereafter administer the PPSV23 vaccine. In patients <65 years of age, a repeat dose of the PPSV23 should be given after 5 years. Live virus vaccines (such as the live attenuated influenza vaccine; measles, mumps, rubella) should not be administered to immunosuppressed patients with rheumatic diseases.

The COMORA study showed how often patients with rheumatic diseases were being vaccinated.[2,19] This study was performed at 17 centres worldwide, where 25% of RA patients had received an influenza vaccination in the past year, 17% a pneumococcal vaccination in the past 5 years, and only 10% both vaccinations. It is not known how often South African (SA) patients with rheumatic diseases are vaccinated, but this shows that clinicians, especially rheumatologists, must do more to ensure adequate vaccination in these patients.

Efficacy and safety of the HZ vaccine

In immunocompetent individuals the risk of HZ can be reduced by 50 - 70% with a live attenuated vaccine.[20] According to the ACR guidelines, the live HZ vaccine may be given to all patients with rheumatic diseases before starting immunosuppressive therapy.[3] Once on such therapy, patients may receive the vaccine if treated with sDMARDs (mono- or combination therapy), but it is contraindicated in those receiving biologics or high-dose steroids (prednisone >20 mg/day) owing to a concern of developing a varicella infection from the vaccine virus strain.

Recently a study on the association between HZ vaccination and the risk of HZ infection in patients with immune-mediated diseases such as RA, psoriatic arthritis and ankylosing spondylitis was published.[21] Of the 465 000 patients, <5% were vaccinated against HZ. The vaccine, however, showed a similar efficacy in healthy individuals, with a decreased risk of HZ (adjusted hazard ratio (HR) 0.61) and an 80% decrease in post-herpetic neuralgia. Interestingly, in the 633 patients who were treated with biologics (87% on anti-TNF), there were no cases of varicella or HZ. The ACR published an update suggesting that it may be reasonable to discontinue a biologic for a period, administer the HZ vaccine and then resume the biologic after 30 days.

Tuberculosis

The 2012 ACR guidelines recommend screening for latent tuberculosis (TB) infection (LTBI) in all patients with rheumatic diseases being considered for biologic therapy, regardless of the presence of risk factors.[3] Doctors should assess the patient's medical history to identify other risk factors (such as smoking and corticosteroid use) for TB and perform the tuberculin skin test (TST) or interferon-gamma-release assays (IGRAs) initially in all patients starting biologic agents. Patients should have a chest radiograph and, if suggestive of active TB, a sputum examination should be done to test for the presence of active TB. In a high-prevalence TB setting such as SA, these screening tests are not always reliable and there is little consensus on the most appropriate test,[22] but a TST and/or an IGRA (if deemed appropriate by the clinician) may be performed. If both tests are used, they should be done at the same time, as TST could boost IGRA responses, which may confound the interpretation of the results.

Chemoprophylactic drugs for LTBI may be either isoniazid (INH) for 9 months or rifampicin combined with INH for 3 months. Treatment with biologic agents can be initiated or resumed after 1 month of LTBI treatment and after completion of the treatment of active TB. Some experts and studies suggest that non-TNF biologic therapies, such as rituximab and abatacept, are safer and better choices as first-line biologics in patients in high-burden settings.[23]

It remains uncertain how to manage RA patients with a negative initial screening for TST or IGRA on chronic biologic therapy. In low-prevalence TB settings patients may not need further evaluation in the absence of risk factors and/or clinical suspicion for TB. However, patients may have false-negative TST or IGRA results owing to immunosuppression. Therefore, a negative TST or IGRA does not exclude the possibility that a patient has LTBI. An updated consensus statement by the ACR recommends that repeat screening should be considered in areas of high TB risk populations or in the case of potential TB exposure. Recent studies, however, have shown that TB conversions may occur during anti-TNF therapy in ~10% of RA patients.[24] It is unclear

if these conversions always represent 'true conversions'. More data are needed to make recommendations regarding rescreening in the absence of definite TB exposure.

Serious infections in RA

It is not well understood why patients with RA have an increased prevalence of other serious infections, particularly pulmonary, urinary tract, skin, and joint infections. Factors that may contribute include immunosuppression by the disease, treatment of the disease, presence of inflammatory lung disease, or factors associated with disability and immobility. Compared with the increased risk of infection associated with the use of corticosteroids and biologics, the sDMARDs do not appear to be associated with such a risk.

Biologics have been used in RA for almost 15 years and rheumatologists have gained much experience with these drugs. A large number of randomised controlled trials have been published on their efficacy and safety, and data exist from national registries worldwide. An important question that often arises with regard to a patient taking these drugs is: 'What is the risk of a serious infection when on biologic therapy compared with being on sDMARDs?'

A number of meta-analyses have assessed this risk.[25-27] Recently, the largest meta-analysis to date (>42 000 patients) assessed the rate of serious infection in RA.[28] The authors found that if the rate of serious infection on standard doses of biologic therapy (with or without sDMARDs) is compared with that of sDMARD monotherapy, the risk is increased by 30% (odds ratio 1.31). It is important to understand what this means in absolute numbers. The absolute annual risk for serious infections when using sDMARD monotherapy is 2%. Therefore, 2% of the RA population on sDMARDs experience a serious infection every year. The risk was increased by 30% when using biologic therapy, resulting in an absolute risk of 2.6%. The absolute increase in the number of serious infections compared with traditional DMARDs was 6/1 000 patients per year for standard-dose biologic therapy with or without traditional DMARDs. One would therefore have to treat 1 000 RA patients with biologic therapy to cause 6 more serious infections compared with traditional DMARDs.

Serious infections in SLE

The risk of serious infections in cases of SLE was reviewed recently.[29] In SLE, 20 - 30% of deaths are caused by infections. In a US study, the rate of serious infections in SLE was ~10.8/100 patient-years, which is approximately 5 times higher than in RA patients.[30] In lupus nephritis (LN) this risk was almost 12 times higher than in RA patients, i.e. 23.9/100 patient-years. Men and black patients with SLE were found to have an increased risk of serious infection. In this study, traditional immunosuppressive therapy in SLE, such as azathioprine, mycophenolate mofetil and cyclophosphamide, showed a 10% increased risk (HR 1.11), but not in the LN group (HR 0.92). With the use of corticosteroids there was an increased risk of >50% (HR 1.51) in SLE and almost 25% in LN patients (HR 1.23). Interestingly, the rate of serious infections was decreased by almost 30% in SLE and 20% in LN when using chloroquine. The most common serious infections in SLE are bacterial, such as pneumonia, urinary tract infection, opportunistic infection, sepsis and skin infections.[31] These studies confirm the importance of limiting the dose of corticosteroids in SLE patients.

Conclusion

Patients with rheumatic diseases have an increased risk of infections owing to their condition and immunosuppressive therapies. This article highlights the latest research findings with regard to the most important infections encountered in the daily management of patients with rheumatic diseases. This knowledge can be used when balancing the potential harm and the clinically important benefits of sDMARDs and biologics and will assist patients and their physicians to make evidence-based decisions.

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