Infections and Biological Therapy in Patients with Rheumatic Diseases

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ABSTRACT: Long-term extension studies and observational drug registers have revealed an increased risk of serious infections in patients treated with anti-tumor necrosis factor agents, particularly infliximab, etanercept and adalimumab. The same may be true for the newer biological drugs rituximab, tocilizumab and abatacept, although this has yet to be confirmed by long-term observational studies. We review the risk of tuberculosis, herpes zoster and other opportunistic infections, and the recommendations for screening for tuberculosis and hepatitis B and C infections in patients with rheumatoid arthritis, with the aim of informing patients and encouraging greater awareness among physicians.

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Ten biological therapies for rheumatoid arthritis (RA) are currently licensed to induce disease control and/or remission and improve patients' quality of life, but there are still concerns regarding the risk of serious adverse events [1,2]. A number of studies have shown that treatment with biological drugs can lead to the development of serious infections necessitating hospitalization and intravenous antibiotics, and might even result in death [3].

Since anti-tumor necrosis factor (TNF) drugs were introduced at the start of the century, registries have significantly improved our understanding of the risks associated with these drugs [4]. The registries contain data relating to thousands of patients with disabilities and co-morbidities, as well as patients who would be considered ineligible for randomized controlled trials (RCTs). Registries have consistently reported a slightly increased risk of severe infections (SIs), particularly lower respiratory tract, skin and soft tissue infections, during the first 6 months of anti-TNF treatment in older patients, those with highly active disease, those taking concomitant corticosteroids, and those receiving monoclonal antibodies other than etanercept [3-10]. They have also revealed that the time-dependent decrease in risk can be attributed to high risk patients discontinuing anti-TNF treatment because of death, inefficacy, side effects, or loss to follow-up, and to improvements in functional status and lower corticosteroid doses [8].

A Cochrane Review of the anti-TNF drugs used for different indications found that infliximab and certolizumab had the highest odds ratio (OR) of SIs as compared to control treatments: 1.41, 95% confidence interval (CI) 0.75–2.62, and 4.75, 95%CI 1.52–18.5 respectively [11]. Furthermore, exposure to more than one anti-TNF drug during therapy was shown to result in a twofold risk of developing an SI [12].

ANTI-TNF DRUGS

TUBERCULOSIS

Tuberculosis (TB), mainly caused by the reactivation of latent tuberculous foci as a result of a destabilized balance between host immunity and pathogen virulence [12], is the opportunistic infection most frequently associated with anti-TNF drugs and is highly likely to lead to widespread, complicated extra-pulmonary infection [13,14].

A recent meta-analysis of RCTs and long-term extension studies of RA patients found 31 cases of TB occurring during anti-TNF treatment (OR 1.92, 95%CI 0.91–4.03, $P = 0.085$). The incidence was higher in those treated with anti-TNF monoclonal antibodies (OR 307.71, 95%CI 184.79–454.93) than in those treated with etanercept (OR 67.58, 95%CI 12.1–163.94), and higher in countries where TB is more frequent [15]. RTCs of certolizumab pegol and golimumab have shown significantly higher rates of TB than observed with earlier anti-TNF drugs, but these were conducted in countries with higher rates of TB [16-18]. Consequently, all candidates for anti-TNF drugs should be screened for TB (history, physical examination, purified protein derivative, chest X-ray), and it

is strongly recommended that those with latent TB start TB treatment before starting anti-TNF drugs [19], particularly in endemic areas. The diagnosis of latent TB is based mainly on the patient's medical history and the findings on physical examination, tuberculin skin test (TST) or interferon-gamma release assays (IGRAs), and chest X-ray. The main disadvantages of TSTs (such as the need for training to interpret the results, the time required for the reaction, and the effect of Koch bacillus vaccination on the findings) [20] have been partially overcome by the use of IGRAs, although only limited data are available for some populations, such as patients recently exposed to TB, children aged < 5 years, and immunocompromised subjects (including patients with rheumatic diseases). Effective screening and prophylaxis have decreased the risk of TB [21].

BACTERIAL, VIRAL AND FUNGAL INFECTIONS

The most frequently encountered infections in anti-TNF-treated patients are due to bacteria and viruses, and the most frequently affected sites are the respiratory system, cutaneous and soft tissue, and the urinary tract. According to Dixon et al. [5], there is a fourfold increased risk of skin and soft tissue infections in anti-TNF-treated patients, which suggests that TNF plays a greater role in host defense, particularly in the skin and soft tissues than in other tissue.

Cryptococcosis, histoplasmosis and coccidioidomycosis have all been associated with anti-TNF drugs in endemic areas [22], which indicates that anti-TNF treatment should be started cautiously in patients living in or visiting regions with endemic mycoses. Patients receiving anti-TNF drugs may also be at increased risk of developing *Pneumocystis jiroveci* and *Nocardia* infection [22-24].

The British Society for Rheumatology Biologics Register (BSRBR) has shown that RA patients receiving anti-TNF are twice as likely to develop septic arthritis as those treated with non-biological disease-modifying anti-rheumatic drugs (DMARDs); furthermore, since this could affect the healing of a surgical wound [25,26], some guidelines suggest discontinuing biological treatment before surgery. RA flares upon discontinuing treatment are more likely in patients with established disease than in those with early disease; therefore, TNF blockers need to be resumed promptly after surgery in order to avoid this risk [24]. Berthold et al. [27] found a higher rate of total perioperative surgical site infections (SSIs) after elective orthopedic or hand surgery in patients continuing anti-TNF drugs, although this was probably related to the infrequency of this complication in patients who discontinued the drugs. No particular medical treatment (including anti-TNF drugs) was significantly associated with the risk of SSIs, but there was a trend towards a higher risk in patients treated with methotrexate. On the basis of their findings and other available evidence, the authors concluded that their center would continue the routine perioperative use of anti-TNF drugs [27]. The almost universal policy of discontinu-

ing anti-TNF drugs is therefore based on the principle of caution and expert opinion.

Many reports have also suggested an increased risk of *Listeria* infection due to foods made using unpasteurized milk, or *Salmonella* infection due to undercooked eggs or meat [4], and a BSRBR study has shown that advising patients to avoid high risk foods when starting anti-TNF drugs may reduce the risk [28].

One of the most frequently observed adverse events in clinical trials is herpes zoster (HZ), a neurocutaneous disease characterized by a painful vesicular dermatomal rash due to the reactivation of varicella zoster virus (VZV); this has been confirmed by the German RABBIT registry [29]. A recent meta-analysis of seven registries found that the pooled risk ratio for HZ was 1.61 (95%CI 1.16–2.23, $P = 0.004$), and that severe HZ occurred in 4.9–20.9% of patients treated with anti-TNF drugs as compared to 2.0–5.5% of those treated with conventional DMARDs [30]. The same meta-analysis revealed a significantly increased risk of HZ in up to 61% of patients with systemic inflammatory diseases, thus raising the question as to whether systematic prophylactic treatment should be given to those with a known history of HZ and whether previously unaffected patients should be vaccinated [30].

HEPATITIS B AND C INFECTIONS

The possible reactivation of hepatitis B virus (HBV) has been attributed to a relative lack of TNF or decreased T cell activation and interferon production. A number of reports indicate that infliximab may be associated with the reactivation of stable HBV infection [31], although the entity of the risk has not been established. HBV reactivation is related to serological status before initiation of anti-TNF drugs and is greater in HbsAg-positive than in anti-HBc-positive patients [32]. A recent systematic review and meta-analysis of 10 studies found that the prevalence of HBV reactivation was 3.9% among patients treated with etanercept and 4.6% among those treated with adalimumab [33]. Furthermore, pooled prevalence among the patients not receiving any antiviral prophylaxis was 4.0%. The rate of HBV reactivation is relatively low in anti-TNF-treated patients with rheumatic conditions, but screening is recommended with antiviral prophylaxis and early treatment with nucleoside/nucleotide analogues for patients with overt chronic HBV infection, and lamivudine prophylaxis for active and inactive HBV carriers [34]. Occult carriers (anti-HBc-positive, HbsAg-negative) requiring anti-TNF treatment do not need prophylaxis, but close observation is advised (HBsAg tests repeated every 3 months) in order to identify HBV reactivation and begin antiviral therapy as soon as possible [34]. Prophylaxis should be started at least 1 month before biotherapy and should be resumed (together with virological monitoring) for at least 6 months after its discontinuation.

There are limited data on the use of anti-TNF drugs in chronic carriers with hepatitis C virus (HCV) infections, but

all patients should be screened for HCV before starting anti-TNF treatment [35]. Preliminary data suggest that the drugs are safe in patients with chronic hepatitis C [35], but they should be administered together with antiviral therapy in those with associated hepatitis B.

NEWER BIOLOGICAL AGENTS

TUBERCULOSIS, BACTERIAL AND FUNGAL INFECTIONS

The use of the newer biological agents (abatacept, rituximab, tocilizumab) is associated with a high incidence of SIs: most of them are forms of pneumonia and pyogenic bacterial infections, but invasive aspergillosis and TB have occasionally been reported [3,36].

A meta-analysis of the tocilizumab trials conducted until 2009 did not find any increased risk of SIs in comparison with controls, though the risk nearly reached significance (hazard ratio 1.78, 95%CI 0.98–3.23) in patients receiving the higher dose (8 mg/kg) in combination with methotrexate [37]. Similarly, a meta-analysis of abatacept and rituximab (and anakinra) did not find that they increased the risk of SIs, but there was a non-significant trend towards an increased risk at the higher doses of both rituximab (1 g vs. 500 mg) and abatacept (10 vs. 2 mg/kg) [38]. A recent Bayesian network meta-analysis of 106 RCTs also found that the risk of SIs was higher at standard or high doses (OR 1.31 and 1.90 respectively), but not at low doses (OR 0.93, 95%CI 0.65–1.33), and in trials lasting 6–12 months, when biological agents were used in combination with conventional DMARDs, in patients with established RA, in studies carried out before 2004, and in patients previously treated with conventional DMARDs or anti-TNF drugs [11].

The risk of progressive multifocal leukoencephalopathy associated with rituximab has received considerable attention since the Food and Drug Administration issued a "black box warning" after two cases were reported in lupus patients, but although case reports suggest that the risk in rituximab-treated RA patients may be increased the absolute risk is extremely low [11].

Finally, HBV reactivation has been observed in rituximab-treated RA patients carrying HBsAg and in those with resolved HBV infection, but the discontinuation of immunosuppressive treatment and antiviral therapy allowed the infection to be controlled within a few months. Consequently, prophylaxis with lamivudine is recommended for rituximab-treated patients with onco-hematologic diseases, and the watchful monitoring of HBsAg/HBV DNA levels is advisable for all the other indications [39].

CONCLUSIONS

SIs are major adverse events associated with the use of biological agents but are also reported in patients treated with methotrexate, the anchor drug for treating RA. The risk of developing an SI is determined by modifiable and non-modifiable characteristics such as age, co-morbidities, the use of corticosteroids, and functional status. Pre-treatment risk scores have been developed to aid treatment decision making [11]. The RABBIT registry findings have been validated in a more contemporary cohort, and an online calculator has been developed for clinical use [40]. However, there is still a need to increase the awareness of physicians and ensure that patients are informed of the increased risk of infection.

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