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Assessing the safety of biologic agents in patients with rheumatoid arthritis

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Abstract

Biologic treatments—including five TNF-α inhibitors, the IL-1 receptor antagonist anakinra, the IL-6 receptor inhibitor tocilizumab, the selective inhibitor of T-cell co-stimulation abatacept and the B-cell-directed mAb rituximab—have provided effective therapeutic options for patients with RA with inadequate response to conventional DMARDs. However, the fact that these agents are immune modulators has raised safety concerns, prompting careful evaluation in clinical trials and intensive post-marketing surveillance. Serious infections may arise, and diagnosis may be delayed by an atypical spectrum of signs and symptoms. Patients may experience reactivation of latent tuberculosis, hepatitis B or C or opportunistic infections. RA is a risk factor for cancer, and biologic therapy may modestly increase the risk of lymphoma and some solid tumours beyond background. During biologic therapy, demyelinating disorders of the CNS have been noted, and pre-existing disease manifestations may be aggravated. Hepatic transaminase levels may increase, although these elevations are usually mild to moderate, transient and without clinical consequence. Hyperlipidaemia, which is responsive to lipid-lowering therapy, may develop, and patients with congestive heart failure may experience symptom exacerbation. Safe use of biologic agents requires thorough risk assessment of potential candidates for treatment and careful monitoring during and after therapy.

Key words: abatacept, adalimumab, anakinra, etanercept, infliximab, methotrexate, rituximab, tocilizumab, tumour necrosis factor-α inhibitor.

Introduction

Guidelines for the treatment of RA recommend early aggressive therapy with one or more DMARDs to prevent joint destruction, disability and loss of work capacity [1–3]. Conventional DMARDs are usually considered the standard of care for most patients [1, 4]. The emergence of biologic agents has provided effective therapeutic options for patients with inadequate response to conventional DMARDs.

Despite the efficacy of biologic agents, their immunomodulatory properties have raised many safety concerns, prompting careful evaluation in clinical trials and intensive post-marketing surveillance. This article will discuss the safety of currently available biologic agents in patients with RA and will present potential methods by which the safety of these drugs can be monitored and addressed.

Co-morbidity in RA

Patients with RA are at increased risk for several disorders, including cancer, infection and cardiovascular disease (CVD). Rates of haematological malignancies (i.e. lymphomas, myeloid leukaemia) [5], non-melanoma skin cancer (NMSC) and lung cancer are elevated in this patient population [6]. Another frequent finding in RA is an atherogenic pattern of dyslipidaemia [low total and high-density lipoprotein cholesterol (HDL-C) levels and elevated levels of triglyceride lipoprotein(a), low-density lipoprotein cholesterol (LDL-C) and free fatty acids] [7]. Compared with the general population, persons with RA have up to a three-fold increased risk for cardiovascular events [8], and CVD mortality is increased by ~50% [9]. There are also reports of progressive multifocal leucoencephalopathy (PML), a rare, often fatal demyelinating disease caused by JC virus reactivation, in patients with RA [10].

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Safety of biologic agents

Currently approved biologic agents for RA treatment include several TNF-α inhibitors (i.e. infliximab, etanercept, adalimumab, certolizumab and golimumab), anakinra, tocilizumab, abatacept and rituximab.

TNF-α inhibitors

Inhibition of TNF-α, a pro-inflammatory cytokine found in high concentrations in joints affected by RA [11], is a major avenue of RA treatment. TNF-α plays a key role in the cytokine cascade, stimulating the production of other inflammatory mediators and the further recruitment of immune and inflammatory cells into the joint [11].

Differentiating the safety profiles of individual TNF-α inhibitors is difficult because of the lack of head-to-head trials and differences between studies in patient populations, adverse events (AEs) enumerated and stringency of exclusion criteria. AEs commonly associated with TNF-α inhibitors include acute infusion reactions (AIRs) and infections with infliximab [12, 13] and injection site reactions (ISRs), upper respiratory tract infection (URTI), headache, rash and nausea with the other TNF-α inhibitors [12, 14–17]. Extended post-treatment monitoring is required for TNF-α inhibitors after an increased rate of sepsis was observed recently in patients who stopped TNF-α inhibitors, most often because of previous infectious complications [18]. Of note, times for drug elimination are $\leqslant$300 h for etanercept [19], $\leqslant$5 months for adalimumab, certolizumab and golimumab [20–22] and $\leqslant$6 months for infliximab [23].

Serious infections and tuberculosis

Patients taking TNF-α inhibitors are at increased risk for serious infectious events, including tuberculosis and infections caused by opportunistic pathogens [12, 14–17]. The incidence of serious bacterial infections is as high as 0.07–0.09/patient-year (PY) in patients receiving a TNF-α inhibitor *vs* 0.01–0.06/PY for treatment with other DMARDs [24]. Infection risk is highest in the skin, soft tissues and joints during the first 6 months of treatment and in patients receiving multiple biologic agents [24]. Histoplasmosis [12, 14–17, 25, 26], coccidioidomycosis [12, 14–17, 27–29] and *Pneumocystis* pneumonia are the most frequent opportunistic infections [12, 14–17]; therapy must be initiated with caution in patients who have lived in or travelled to regions with endemic mycoses [23]. Antigen and antibody test results may be negative in patients with fungal infection [12, 14–17], and disseminated disease is not uncommon [12, 14–17, 25, 26, 28, 29]. Although rare, PML has been reported in patients receiving TNF-α inhibitors [30, 31].

TNF-α regulates host defences against mycobacterial infection [32]; therefore patients receiving TNF-α inhibitors are at increased risk for new-onset tuberculosis and tuberculosis reactivation [12, 14–17]. Disseminated or extrapulmonary disease is not uncommon, and some cases have been fatal [12, 14–17, 23]. In clinical trials, tuberculosis incidence was 0.4% with infliximab [12], 0.01% with etanercept [14], 2% with certolizumab [16], 0.26/100 PYs with adalimumab [15] and 0.23/100 PYs with golimumab [17] (using local country guidelines for tuberculosis skin test eligibility). Of note, initial trials with TNF inhibitors did not include screening procedures for latent tuberculosis. Re-activation risk may be lower with etanercept than with mAbs targeted against TNF-α [14]. Given that tuberculosis has been observed in patients with negative results on pre-screening for latent tuberculosis, vigilance is required [33].

Infusion reactions, ISRs and immunogenicity

In clinical trials, ~20% of infliximab-treated patients had AIRs, and patients who developed anti-infliximab antibodies were two to three times more likely to experience reactions, including anaphylactic-like reactions [23]. Infusion reactions may lead to discontinuation of infliximab therapy [13]. ISR rates are 36% for etanercept [19], 15% for adalimumab [20], 6.4% for certolizumab [21] and 5.8% for golimumab [22].

Induction of autoimmune disease

Proportions of patients who developed ANAs in clinical trials that did not compare individual TNF-α inhibitors were as follows: infliximab 8% (placebo not reported); etanercept 11% *vs* placebo 5%; adalimumab 11.9% *vs* placebo 8.1%; certolizumab 16.7% *vs* placebo 12.0% and golimumab 4.0% *vs* controls 2.6% [19–23]. In comparative studies the incidence of ANA positivity was higher with infliximab than with etanercept [34, 35]. TNF-α deficiency also may induce autoimmune disorders (e.g. lupus-like syndrome, autoimmune hepatitis) [19–23, 36–38], new-onset psoriasis or psoriasis exacerbations [39–42] and drug-induced vasculitis [43, 44]. Pulmonary granulomatous reaction [45] and new-onset uveitis [46] have been reported with etanercept treatment. Symptoms of autoimmune disease usually improve when TNF-α inhibitor therapy is discontinued [36, 37, 39–42, 47–50], but rare cases of persistent or fatal vasculitis have been reported [43].

Malignancies

Clinical trial data suggest a link between TNF-α inhibitor treatment and cancer [19–21, 23]. In infliximab-treated and placebo patients, respectively, incidence rates were 0.09% compared with 0% for lymphoma and 0.4% compared with 0.06% for other malignancies [23]. For patients treated with etanercept for up to 6 years, the malignancy incidence was 3%, consistent with that generally seen in patients with RA, but additional cases of lymphoma and breast and lung carcinoma were reported during the post-marketing period [19]. In adalimumab and control groups, respectively, event rates per 1000 PYs were 8.8 *vs* 2.6 for NMSC, 0.8 *vs* 0.9 for lymphoma and 5.9 *vs* 4.3 for other malignancies [20]. In certolizumab-treated patients, event rates per 100 PYs were 0.07 for lymphoma and 0.02 for melanoma [21]. Event rates per 100 PYs in golimumab-treated and placebo patients, respectively, were 0.10 *vs* 0 for lymphoma, 0.72 *vs* 1.51 for NMSC and 0.51 *vs* 0.60 for other malignancies [22].

CVD

Findings of elevated TNF-α levels in patients with congestive heart failure (CHF) [51] suggested that TNF-α inhibitor therapy might be effective in these patients. However, new-onset or worsening CHF and increased CHF mortality have been reported in patients administered some TNF-α inhibitors [19–23]. Clinical trials of TNF-α inhibitor therapy in patients with chronic heart failure have shown an increased risk of adverse clinical events with infliximab [52] but not with etanercept [53]. With the exception of etanercept, TNF-α inhibitor therapy is contraindicated in patients with class III/IV heart failure [20–23], and these agents should be used cautiously in patients with less severe CHF [20–23]. It is recommended that treatment be discontinued if new or worsening symptoms develop [20–23].

Lipid levels

During clinical trials, rates of dyslipidaemia (or lipids increased) were reported as uncommon (0.1 to <1%) with certolizumab [21] and golimumab [22] and very common (>10%) with adalimumab [20], but have not been reported for infliximab and etanercept. The reason for the apparent increased rate of dyslipidaemia with adalimumab was unclear; however, the results were observed in separate clinical trials and could not be compared directly because the outcome parameters might have varied.

Hepatic effects

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels may increase during TNF-α inhibitor therapy [20–23, 54]. Elevations are usually mild to moderate [$<3\times$ upper limit of normal (ULN)], but severe elevations ($\geqslant 5\times$ ULN) have been reported in $\leqslant$0.9% of patients [22, 23]. The most frequent elevations are seen with infliximab followed by adalimumab [55]. Transaminase elevations are usually asymptomatic, resolving spontaneously or after medication adjustment or discontinuation [20, 22, 23]. Reactivation or worsening of HBV and HCV infections may occur and may be associated with increased mortality [19–23, 56]. Risk factors for HBV or HCV infection should be evaluated before commencing anti-TNF therapy, and carriers should be monitored for active infection during and after treatment [19–23]. In HCV-infected patients, outcomes have been favourable with anti-TNF therapy without anti-viral therapy [57, 58] or with ciclosporin [59, 60], whereas concomitant antiviral therapy may be required in HBV-infected patients receiving anti-TNF agents.

Demyelinating disease

Recent evidence has suggested that biologic agents, most notably TNF-α inhibitors, are associated with the development of demyelinating disease. A database analysis in patients with RA exposed to various biologic agents noted a trend towards an increased incidence of demyelinating diseases after treatment with TNF-α inhibitors [61], suggesting caution in their use in patients at high risk for demyelinating disease.

Anakinra

Anakinra, an IL-1 receptor inhibitor [62], is regarded as less effective than TNF-α inhibitors in reducing symptoms associated with RA, even though a direct comparative trial has not been conducted [24]. Anakinra is used by <5% of patients with RA [63]. AEs associated with its use include ISRs, URTIs, headache, nausea and diarrhoea [64].

The favourable AE profile of anakinra may be due in part to its markedly shorter half-life (4–6 h) compared with other biologic agents, which preserves the anti-infective activity of IL-1 [62, 65]. IL-1 may also play a reduced role in host defence mechanisms, so that IL-1 inhibition may render patients less susceptible to AEs than TNF-α inhibition [65].

Serious infections and tuberculosis

In controlled trials, rates of serious infection remained stable over 3 years, and no infection-related deaths were reported with anakinra [62]. Rare cases of fungal, mycobacterial, bacterial and viral opportunistic infection have occurred. Concurrent use of anakinra and a TNF-α inhibitor should be avoided because the combination increases the risk for infection without improving efficacy [62]. In contrast to TNF-α inhibitors, no link has been observed between anakinra therapy and tuberculosis development or reactivation [24, 65].

Infusion reactions, ISRs and immunogenicity

ISR was the most frequently reported AE and the most common reason for clinical trial discontinuation [62]; rates were 71% with anakinra and 28% with placebo [62]. ISRs frequently occur within 4 weeks after initiating treatment and are most frequent in patients with previous ISRs [62].

Malignancies

During clinical trials, overall cancer incidence was the same in anakinra-treated and placebo patients and did not differ from that in the general population [62]. Lymphoma incidence was consistent with that reported in patients with RA [62].

Tocilizumab

Tocilizumab is a humanized mAb against the human IL-6 receptor that inhibits signalling via both soluble and membrane-bound human IL-6 receptors [66, 67]. Commonly reported AEs in patients who received tocilizumab 8 mg/kg monotherapy in clinical trials were URTI, nasopharyngitis, headache, hypertension and increased ALT [66]. A meta-analysis of AEs from six randomized controlled trials of tocilizumab with or without MTX showed a higher risk for infection with the 8 mg/kg combination group compared with controls (odds ratio 1.30), but no increased risk for malignancy, tuberculosis reactivation or hepatitis [68]. The safety profile of tocilizumab in an open-label clinical practice study was similar to that noted in randomized controlled trials [69].

A pooled analysis of 4009 patients enrolled in five phase 3 clinical trials, a phase 1 study and two ongoing open-label extension studies has provided extensive safety and tolerability data for an all-exposed population

that included patients who received at least one dose of tocilizumab [70]. Comprehensive safety data from this analysis following total exposure to tocilizumab of 8580 PYs and observation to 9414 PYs have been published [70]. Longer-term data encompassing 3.6 years of follow-up and a total treatment exposure of 12 293 PYs were presented recently [71]. These analyses have demonstrated that the long-term safety profile of tocilizumab is consistent with that observed in phase 3 studies.

Serious infections and tuberculosis

In the all-exposed population, rates of serious infection/100 PYs were 3.5, 3.5 and 4.9 in the control, tocilizumab 4 mg/kg and tocilizumab 8 mg/kg groups, respectively [70]. The overall rate of serious infection after 3.6 years of treatment was 4.6/100 PYs [71]; the rate remained stable with continued exposure to tocilizumab, but increased with age [70]. The most common serious infections in tocilizumab-treated patients are pneumonia, gastroenteritis and cellulitis. A report from Japan noted a three-fold higher rate of serious respiratory infections among RA patients treated with tocilizumab in clinical trials compared with those in clinical practice (1.77/100 *vs* 0.53/100 PYs) [72]. The death rate from serious infection has been estimated at 0.13/100 PYs [73]. One report of leucoencephalopathy has been associated with tocilizumab treatment [74]. No cases of HBV reactivation have been observed in clinical trials, but it is noteworthy that patients screening positive for hepatitis B or C were excluded [75].

In the pooled analysis, seven patients in the all-exposed population developed tuberculosis, all in the tocilizumab 8 mg/kg group [70]. Six cases of tuberculosis were reported in the worldwide tocilizumab RA clinical trials database based on >10 000 PYs of exposure [76]. Experience with tocilizumab therapy in patients with latent tuberculosis is limited.

Infusion reactions, ISRs and immunogenicity

During randomized controlled trials, 6.9% of the tocilizumab 8 mg/kg plus DMARD group and 5.1% of the placebo plus DMARD group experienced AIRs [66]. In the all-exposed population, eight anaphylactic events occurred, requiring treatment discontinuation with median 2.6 years treatment [70]. Of 2876 tested patients in randomized controlled trials, 46 (1.6%) developed anti-tocilizumab antibodies and 6 had medically significant hypersensitivity reactions. Thirty patients (1.1%) developed neutralizing antibodies [66]. Recently, a post-marketing case of fatal anaphylaxis was reported with tocilizumab in a patient with RA who had experienced a reaction to a previous infusion [77].

Malignancies

In the all-exposed population, overall rates of malignancy with median 2.6 years treatment were 0.7/100, 1.4/100 and 0.7/100 PYs in the control, tocilizumab 4 mg/kg plus DMARD and tocilizumab 8 mg/kg plus DMARD groups, respectively [70]. The overall malignancy rate of 1.1/100 PYs remained stable over time, and the standardized incidence ratio for all cancer types was comparable with that for the general population [70].

CVD

During randomized controlled trials, tocilizumab-treated patients had durable CRP reductions to within normal ranges as early as week 2 and experienced rapid ESR reductions [66]. After a median 3.6 years of follow-up, rates of myocardial infarction and stroke were 0.3/100 and 0.2/100 PYs, respectively [71]. Rates remained stable over time and did not exceed expected rates in the RA population [71].

Lipid levels

In the all-exposed population, total, LDL-C, HDL-C and triglyceride levels increased in tocilizumab-treated patients but stabilized with continued treatment with a median 2.6 years of treatment; 456 patients began lipid-lowering therapy during treatment [70]. Of note, elevated levels of lipoprotein(a), which reflect an independent cardiovascular risk factor, decreased during 3 months of tocilizumab treatment [78].

Hepatic effects

In the all-exposed population, tocilizumab (median 2.6 years of treatment) often resulted in mild to moderate (>1 to 3 × ULN) ALT/AST increases in patients with normal baseline levels, which often occurred during concomitant DMARD therapy. Rates of elevations of ALT and AST >3 × ULN were 9.5 and 3.1%, respectively, in the all-exposed population and led to dose reduction or temporary interruption of treatment in 9.3% of patients; rates remained stable and were not associated with clinical sequelae [70].

Haematological abnormalities

In some patients treated with tocilizumab 8 mg/kg plus MTX in randomized controlled trials, neutrophil and platelet counts decreased [66]. In the all-exposed population, common toxicity criteria (CTC) grade 3 neutropenia [absolute neutrophil count (ANC) 0.5 to $<1.0 \times 10^9$/l) was reported in 4.1% of patients (165/3992) and CTC grade 4 (ANC $<0.5 \times 10^9$/l) neutropenia in 0.6% (24/3992) [70] with a median 2.6 years of treatment. There was no temporal association of grade 4 neutropenia with serious infection.

Gastrointestinal perforations

After 3.6 years, 29 patients experienced gastrointestinal perforation (0.24/100 PYs) [71]. Seventeen (59%) of 29 events were colonic diverticular perforations [71]. Tocilizumab should be used cautiously in patients with a previous history of intestinal ulceration or diverticulitis [66].

Abatacept

Abatacept, an inhibitor of T-cell co-stimulation, is a fusion construct of human cytotoxic T-lymphocyte-associated antigen 4 and the modified Fc portion of human IgG1 [24, 79]. Common AEs associated with abatacept include headache, nasopharyngitis, dizziness, cough, back pain, hypertension, dyspepsia and urinary tract infection [80].

Safety data from an integrated analysis of five RA trials of s.c. abatacept have been reported recently [81, 82]. These analyses included 1879 patients with 3086 PYs of exposure to abatacept with mean exposure of 20 months (range 2–56 months). The pooled safety data with up to 4.5 years of exposure showed that long-term treatment with s.c. abatacept did not increase rates of AEs of concern with biologic therapy and were generally consistent with observations from i.v. therapy [82]. Another safety analysis from clinical trials in different patient populations showed lower rates of AEs, serious AEs, serious infections and malignancies in previously untreated or MTX-treated patients compared with TNF inhibitor-treated patients, suggesting a more favourable safety profile of abatacept in patients with early RA [83].

Serious infections and tuberculosis

Serious infections with abatacept, including sepsis and pneumonia, have been reported and some have been fatal [84]. In a recent integrated analysis of safety from short- and long-term periods of five abatacept clinical trials, serious infections occurred at a rate of 1.94/100 PYs in 59 (3.1%) patients, with pneumonia, urinary tract infections and gastroenteritis being the most frequent infections. The incidence rate (IR) was highest during the first 6 months and declined thereafter [81]. For patients treated with i.v. abatacept, the reported IR for serious infections was 2.87 in 332 patients [82].

Infections often develop during concomitant immunosuppression therapy, and concurrent TNF-α inhibitor therapy is not recommended [84]. In placebo-controlled studies, no increased tuberculosis incidence was observed; however, screening for latent tuberculosis is recommended [84].

Infusion reactions, ISRs and immunogenicity

In clinical trials, AIRs occurred in 9.8% of abatacept-treated and 6.7% of placebo patients, and anti-abatacept antibodies developed in 2.8% of patients treated with abatacept for $\leqslant$3 years [84]. No correlation between antibody development and clinical response or AEs was observed [84]. The integrated safety summary for s.c. ISRs reported an IR of 2.22, the majority of which were mild and occurred during the first 6 months [81].

Malignancies

In controlled trials, malignancies were reported in 1.4% of abatacept-treated and 1.1% of placebo patients [84]. In double-blind and open-label clinical trials, rates per 100 PYs were 1.41 for any malignancy, 0.74 for NMSC, 0.59 for solid malignancies and 0.12 for haematological malignancies [84]. In the integrated safety analysis, the overall IR for malignancies (excluding NMSC) was 0.68 in 21 (1.1%) patients. The most frequent malignancies were basal cell carcinoma, breast cancer and squamous cell carcinoma of the skin [81]. In the i.v. abatacept population, the IR for malignancies was 0.73 in 88 patients [82].

CVD

During long-term follow-up, rates of 3.87/100 PYs were reported for cardiac disorders following abatacept therapy [85].

Rituximab

Rituximab is a chimeric human/mouse mAb directed at the CD20 antigen expressed on mature B and pre-B cells. Peripheral B cells are temporarily depleted by treatment with rituximab but usually recover within 6–12 months [86]. Long-term safety information for rituximab has been obtained from a pooled analysis of 3194 patients (11 962 PYs) with up to 9.5 years of treatment with rituximab and MTX in clinical trials [87]. The most frequently reported AE with rituximab was AIR. Increased duration of exposure to rituximab treatment was not associated with any new safety signals.

Serious infections and tuberculosis

New, reactivated or exacerbated viral infections may occur with rituximab. Rates of serious infection remained stable following multiple courses of rituximab, and subsequent treatment with other biologic agents did not increase the risk. The safety of rituximab was similar regardless of use with another biologic agent, MTX or other DMARD and was similar among patients treated up to 24 or 48 weeks or re-treated with rituximab [88]. Given that rituximab is approved for patients who do not respond to or who are intolerant of previous TNF inhibitors, most patients will have been pre-screened for latent tuberculosis in daily practice. Pre-screening patients for the presence of latent tuberculosis was not performed for the clinical trials, and reactivation of tuberculosis was not observed.

Although assessment of peripheral B cells is not routinely recommended [89], serum immunoglobulin levels should be monitored because serious infections may occur more frequently in patients with hypogammaglobulinaemia [54]. At least 76 cases of confirmed or suspected PML have been reported in patients administered rituximab, usually those with underlying haematological malignancies such as lymphomas and those who underwent stem cell transplantation [90–93]. Patients with SLE are at particular risk for PML compared with patients with other rheumatic disease [10]. A recently published meta-analysis reported the incidence of PML was $\sim$4 based on 129 000 RA patients receiving rituximab [94]. Although no direct link between rituximab therapy and PML has been found, PML should be considered in the differential diagnosis if the neurological status of a patient changes [86]. Due to the risk for HBV reactivation, screening for HBV is recommended in at-risk patients, and anti-viral treatment should be considered in HBV carriers [95].

Infusion reaction, ISRs and immunogenicity

During clinical trials, AIRs occurred in 15% of rituximab-treated and 5% of placebo patients after the first infusion and in 2% of both groups after the second infusion [86]. In the pooled safety analysis, 23%

Table 1 Recommendations for preventing and diagnosing infections in patients receiving biologic agents [19–23, 62, 66, 84, 86]

Before starting biologic therapy
Evaluate patients for active infections before beginning therapy
Take detailed medical history
Identify possible sources of infection
Document previous and current immunosuppressive therapy
Exercise caution when considering the use of biologic therapy for a patient
With a history of recurring or chronic infections
With underlying conditions (e.g. diabetes, CHF, diverticulitis) that may predispose patients to infection
Who is receiving immunosuppressive therapy that would be continued
Who has resided in or travelled to regions where invasive fungal infections are endemic
Withhold therapy in patients with active infections until the infection is controlled
Educate patients about likely signs and symptoms of infection during biologic therapy
During biologic therapy
Remain alert so that potentially serious infections can be detected in a timely fashion
Remember that signs and symptoms of acute infection may be lessened as a consequence of biologic therapy
Instruct patients to contact their health care professional immediately if they experience signs and symptoms of infection to ensure rapid evaluation and appropriate treatment
Interrupt therapy if the patient develops a serious infection until the infection is controlled
Monitor patients with particular care when transitioning from one biologic agent to another and when they are receiving concomitant immunosuppressive therapy
After biologic therapy
Continue to monitor patients after the conclusion of treatment, at least throughout the period needed for complete drug elimination

Table 2 Recommendations for preventing and diagnosing tuberculosis in patients receiving biologic agents [19–23, 32, 63, 66]

Before initiating treatment with a biologic agent
Evaluate patients for active and latent tuberculosis
Take detailed medical history
Identify possible previous contacts with tuberculosis
Document previous and current immunosuppression therapy
Identify patients at elevated risk for latent infection (e.g. homeless persons, those who have lived in countries in which tuberculosis is highly prevalent, i.v. drug users, persons who have spent time in prison or a health care institution)
Perform appropriate screening tests
Follow local recommendations concerning the use of chest X-ray and TST
Recognize that false-negative TST results may occur because of immunosuppression; consider induration $\geqslant$5 mm as a positive response
Consider use of the QuantiFERON-TB Gold test (Cellestis Ltd, Abbotsford, Victoria, Australia) or the T-SPOT.TB (Oxford Immunotech, Abingdon, UK), if available
Withhold biologic therapy from patients with active tuberculosis
If latent tuberculosis is suspected, consult a physician with expertise in the treatment of tuberculosis
Start treatment for latent tuberculosis at least 4 weeks before initiating biologic therapy, following local recommendations
Consider administering anti-tuberculosis treatment before initiating biologic therapy for patients with:
Significant risk factors for tuberculosis
History of latent or active tuberculosis if an adequate course of treatment cannot be confirmed
Educate patients about the signs and symptoms of tuberculosis
During biologic therapy
Monitor patients closely for signs and symptoms of tuberculosis (e.g. persistent cough, wasting or weight loss, low-grade fever)
Instruct patients to seek medical advice if they experience signs or symptoms of tuberculosis

TST: tuberculin skin test.

(734/3194) of patients experienced an infusion-related reaction following the first infusion [87]. Most reactions are mild to moderate, but serious reactions have occurred [86]. Pre-treatment with methylprednisolone is recommended for reducing AIR risk and severity. Antibodies to rituximab, which developed in 9.2% of patients during clinical trials [86], may be associated with more severe infusion or allergic reactions [86].

Malignancies

In a long-term safety assessment of 2578 patients who received at least one dose of rituximab, the incidence of malignancies (excluding NMSC) was 0.84/100 PYs and was stable over multiple courses of therapy [54]. Overall, rituximab did not increase the risk for malignancies in patients with RA [54].

CVD

In the long-term safety analysis of patients receiving rituximab therapy, no notable differences in serious cardiovascular events were reported during placebo-controlled periods [54]. The overall rate of myocardial infarction of 0.41/100 PYs following long-term exposure to rituximab was consistent with rates observed in the general RA population [87].

Demyelinating disease

No data suggest an association between rituximab therapy and demyelinating disease. Interestingly, data from a phase 2 study in patients with multiple sclerosis demonstrated the efficacy of rituximab in the treatment of patients with relapsing and remitting multiple sclerosis [96].

Gastrointestinal perforations

Gastrointestinal perforations have been reported in patients receiving rituximab for the treatment of non-Hodgkin's lymphoma or post-transplantation lymphoproliferative disorder [86, 97].

Discussion

The emergence of biologic agents for the management of RA has significantly improved patient outcomes, but their use raises safety concerns, related mainly to their immunomodulatory properties. Major safety issues are serious infections (including tuberculosis), lymphoma and other malignancies, demyelinating disorders, hepatotoxicity, hyperlipidaemia, cardiotoxicity, ISRs and AIRs. Guidelines on safety assessments and monitoring during biologic therapy have been issued [63, 98]. Tables 1 [19–23, 62, 66, 84, 86] and 2 [19–23, 32, 63, 66] provide recommendations for preventing and diagnosing serious infections and tuberculosis.

To optimize patient safety, physicians should carefully screen candidates for biologic therapy, exercising special caution in patients with conditions that predispose them to adverse effects. Given that patients with co-morbidities are most often not enrolled in clinical trials, registries are crucial for the long-term assessment of safety during routine clinical practice.

Monitoring is particularly important when initiating, resuming or substantially increasing the dose of a biologic agent and for patients who are receiving multiple immunomodulators. Vigilance should continue at least through the period required for complete elimination of the drug.

Rheumatology key messages

- Development of biologic agents has significantly improved the treatment of patients with RA.
- Short- and long-term safety-related factors are critical in determining appropriate therapy for RA patients.
- Although biologic agents are clinically effective, physicians should be mindful of potential safety concerns associated with their use.

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