Safety of biologics in rheumatoid arthritis

Placebo-controlled trials of biological therapies in the treatment of rheumatoid arthritis have demonstrated significant efficacy with acceptable safety profiles. Nevertheless, while biologic treatment is well established, toxicity concerns remain an area of focus; both inter- and intra-class differences in targeted drugs are associated with different safety issues. Understanding these is important to guide therapy choice in the context of disease characteristics and comorbidity. Long-term safety data for the earliest introduced biologics (TNF-α inhibitors; infliximab, etanercept and adalimumab) are becoming available from large observational cohorts, such as national registries, and will be discussed in this review. For the more recently available treatments (certolizumab pegol, golimumab, rituximab, tocilizumab and abatacept), data from long-term extension studies of trials will be examined.

KEYWORDS: abatacept ■ biologic ■ rheumatoid arthritis ■ rituximab ■ safety ■ tocilizumab ■ TNFi ■ TNF inhibitor

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Learning objectives

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

- Analyze the risk of serious bacterial infections associated with biological therapies
- Distinguish biological therapies with the strongest association with tuberculosis
- Evaluate the use of biological therapies among patients with chronic viral hepatitis
- Assess the association between biological therapies and the risk of cancer

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Biologic therapy has transformed the management of rheumatoid arthritis (RA). Placebo-controlled trials have demonstrated marked efficacy of biologics in ameliorating signs and symptoms of RA on the background of acceptable safety profiles, enabling their introduction into clinical practice. Table 1 illustrates adverse event and serious adverse event rates amongst randomized controlled trials (RCTs) in patients with an inadequate response to previous disease-modifying antirheumatic drug (DMARD) therapy; the number of patients with adverse events appears similar in biologic and placebo groups within these studies [1–12].

Nevertheless, safety remains an important issue with the implications of the various targeted agents not fully elucidated. There are now several biologic agents licensed for the treatment of RA worldwide. Specific toxicity and prescribing concerns exist with different classes of agent, as well as with specific drugs within the same class. Differences in structure and mechanism of action have important implications for issues of safety, with differences emerging even amongst biologics directed against the same cytokine, the TNF-α inhibitors (TNFi). Infection remains a central concern, a risk clearly linked to the nature of the various biologic therapies (as are other adverse events, for example infusion and injection-site reactions). However, association with malignancy remains unclear in the context of an established risk of malignancy with rheumatoid disease itself. Additional adverse events have also been reported, with data often from case series. This review will focus on the main safety concerns utilizing evidence from meta-analyses of RCTs and, for assessment of long-term safety, from large observational cohorts such as national registries. For more recently available biologics, data from long-term extension studies of trials will be examined. With regard to more uncommon adverse events, case reports and case series will be considered.

Infection

While use of biologic therapies is effective in achieving disease control in RA, interference in pathways within the innate or adaptive immune systems poses an increased risk of infection and potential reactivation of latent infection. This remains one of the main concerns, in terms of safety, of these therapies. RCT data provide some information regarding infection risk, although duration of follow-up is short and those at greatest risk are often excluded. Data from registries, extension studies and postmarketing surveillance have provided longer-term information on larger number of patients (Table 2).

Serious bacterial infections

TNFi: infliximab, etanercept & adalimumab

With increasing use of the established TNFi (infliximab, etanercept and adalimumab), information regarding serious bacterial infections is well documented in several large registries and databases (Table 2). Increased risk with all three TNFi has been noted [13–17], in particular within the first 6 months of treatment initiation (adjusted hazards ratio [HR]: 1.8; 95% CI: 1.3–2.6) [17]. Increased rates of pneumonia have been seen, within the first 6 months again posing the window of greatest risk [13,14,17]. Serious skin and soft tissue infections have

Table 1. Number of patients experiencing at least one adverse event in randomized controlled trials of biologic therapy in rheumatoid arthritis patients who have failed prior disease-modifying antirheumatic drug therapy†.

Biologic (study)	Patients with adverse event(s), n (%)			Patients with serious adverse event(s), n (%)			Ref.
	Placebo (± DMARD)	*Biologic monotherapy*	*Biologic plus DMARD*	*Placebo (± DMARD)*	*Biologic monotherapy*	*Biologic plus DMARD*	
Etanercept (TEMPO)	185/228 (81)	192/223 (86)	187/231 (81)	37/228 (16)	35/223 (16)	29/231 (13)	[1]
Infliximab (ATTRACT)	(94)	N/A	(95)‡	18/86 (21)	N/A	10/88 (11)	[2]
Adalimumab (Van de Putte *et al.*)	105/110 (96)	429/434 (99)‡	N/A	16/110 (15)	13/113 (12)	N/A	[3]
Certolizumab pegol							[4,5]
(RAPID 2)	66/125 (53)	N/A	139/248 (56)	4/125 (3)	N/A	18/248 (7)	
(FAST4WARD)	63/109 (58)	84/111 (76)§	N/A	3/109 (3)	33/111 (30)	N/A	
Golimumab (GO-FORWARD)	81/133 (61)	84/133 (63)¶	61/89 (69)	3/133 (2)	5/133 (4)	5/89 (6)	[6]
Rituximab (DANCER)	105/149 (70)	N/A	164/192 (85)	4/149 (3)	N/A	13/192 (7)	[7]
Abatacept							[8,9]
(AIM)	184/219 (84)	N/A	378/433 (87)	26/219 (12)	N/A	65/433 (15)	
(Kremer *et al.*)	NR	N/A	NR	19/119 (16)	N/A	14/115 (12)	
Tocilizumab							[10–12]
(CHARISMA)	23/49 (47)	31/52 (60)	27/50 (54)	0/49 (0)	0/52 (0)	3/50 (6)	
(OPTION)	129/204 (63)	N/A	143/206 (69)	12/204 (6)	N/A	13/206 (6)	
(TOWARD)	253/414 (61)	N/A	584/802 (73)	18/414 (4)	N/A	54/802 (7)	

†*Patients receiving biologic in licensed doses unless otherwise stated.*
‡*Pooled data for all dose groups including licensed dose.*
§*Certolizumab pegol 400 mg every 4 weeks.*
¶*Golimumab 100 mg every 4 weeks.*
DMARD: Disease-modifying antirheumatic drug; N/A: Not applicable.

also been recorded [18]. No significant difference between infliximab, etanercept and adalimumab has been noted [17].

Analysis of retrospective data within a US multi-institutional collaboration found no overall increased risk of hospitalization for serious infections in patients initiated with TNFi compared with those on nonbiologic regimes [19]. However, infliximab was associated with a significantly increased infection risk compared with etanercept (adjusted HR: 1.26; 95% CI: 1.07–1.47) and adalimumab (adjusted HR: 1.23; 95% CI: 1.02–1.48) [19,20]. The risk was further increased with glucocorticoid use and the presence of certain baseline characteristics, including chronic obstructive pulmonary disease and Type 2 diabetes mellitus. Health Assessment Questionnaire Disability Index, older age, comorbidity and past hospitalization have also been found to predict subsequent hospitalization for infection [14].

Other TNFi

Information on risk of infection with the newer TNFi (certolizumab pegol and golimumab) is more limited and mainly derived from RCTs.

In the FAST4WARD trial, rates of serious infections were documented in zero versus four cases per 100 patient-years in the placebo and certolizumab pegol groups, respectively [5]. In RAPID 1 this was 2.2 per 100 patient-years in the placebo group versus 5.3 and 7.3 per 100 patient-years in the certolizumab 200 and 400 mg groups, respectively [21]. In RAPID 2 serious infections occurred in 0, 3.2 and 2.4% in the placebo, certolizumab pegol 200 and 400 mg groups, respectively [4]. A meta-analysis of the RCT data confirms this increased risk [22].

In the GO-AFTER study, infection rates were similar between the three groups and serious infections were uncommon (placebo 3 out of 155 [2%] patients versus golimumab 4 out of 304 [1%] patients) [23]. However, other RCTs have reported a higher occurrence in the patients receiving golimumab with one study reporting several cases of pneumonia, one complicated by septic shock [24]. In the GO-BEFORE study more patients receiving methotrexate (MTX) and golimumab 100 mg subcutaneous had serious infections (7 out of 159 [4.4%]) compared with MTX and placebo (3 out of 160 [1.9%]), golimumab

Table 2. Relative risk of infections in patients receiving biologic therapies.

Study (year)	Biological DMARD group (n)	Comparator group (n)	Serious infections IRR (95% CI)	Hospitalization for serious infections aHR (95% CI)	Lower respiratory tract infections/ pneumonia IRR (95% CI)	Hospitalization for pneumonia IRR (95% CI)	Skin and soft tissue infections IRR (95% CI)	Ref.
Wolfe *et al.* (2006) (US registry)	TNF inhibitors: Infliximab Adalimumab Etanercept	(16,788)	–	–	–	HR 1.1† (0.9–1.4) 1.1† (0.6–1.9) 0.8† (0.6–1.1)	–	[15]
Dixon *et al.* (2006) (UK registry)	TNF inhibitors (7664)	Non-TNF RA (354)	1.03† (0.68–1.57)	–	0.77† (0.46–1.31)	–	4.28† (1.06–17.17)	[18]
Dixon *et al.* (2007) (UK registry)	TNF inhibitors (8659)	Nonbiologic DMARDs (2170)	4.6† (1.8–11.9)‡ 1.22† (0.88–1.69)§	–	–	–	–	[16]
Curtis *et al.* (2007) (US healthcare)	TNF inhibitors (2393)	Methotrexate (2933)	HR: 4.2 (2.0–8.8)¶ 1.9(1.3–2.8)§	–	–	–	–	[13]
Askling *et al.* (2007) (Swedish Biologics register)	TNF inhibitors (2692)	RA inpatient register (44,956)	1.43† (1.18–1.73)# 1.15† (0.88–1.51)†† 0.82† (0.62–1.08)‡‡	–	1.24† (0.92–1.68)#	–	0.57† (0.21–1.57)#	[14]
Galloway *et al.* (2011) (UK registry)	TNF inhibitors (11,798): Infliximab Adalimumab Etanercept	Nonbiologic DMARDs (3598)	aHR 1.2 (1.1–1.5) 1.3 (1.1–1.6) 1.3 (1.1–1.5) 1.2 (1.0–1.4)	–	–	–	–	[17]
Grijalva *et al.* (2011) (US multi-institutional collaboration)	TNF inhibitors (RA; 10,484): Infliximab vs etanercept Infliximab vs adalimumab	Nonbiologic regimens (10,484)	–	1.05 (0.91–1.21) 1.26 (1.07–1.47) 1.23 (1.02–1.48)	–	–	–	[19]

†*Adjusted IRR.*
‡*First 90 days of treatment.*
§*Entire study time period.*
¶*Within 6 month of treatment start.*
#*First year of treatment.*
††*Second year of treatment.*
‡‡*Third year of treatment.*
§§*Standardized for age, sex and corticosteroid use.*
aHR: Adjusted hazard ratio; CCT: Controlled clinical trial; DMARD: Disease-modifying antirheumatic drug; HR: Hazard ratio; IRR: Incidence rate ratio; OLE: Open-label extension studies; OR: Odds ratio; RA: Rheumatoid arthritis; RCT: Randomized controlled trial.

Table 2. Relative risk of infections in patients receiving biologic therapies (cont.).

Study (year)	Biological DMARD group (n)	Comparator group (n)	Serious infections IRR (95% CI)	Hospitalization for serious infections aHR (95% CI)	Lower respiratory tract infections/ pneumonia IRR (95% CI)	Hospitalization for pneumonia IRR (95% CI)	Skin and soft tissue infections IRR (95% CI)	Ref.
Curtis *et al.* (2011) (US healthcare)	Biologics (7847): Adalimumab vs infliximab Etanercept vs infliximab Abatacept vs infliximab Rituximab vs infliximab	–	–	 0.52 (0.39–0.71) 0.64 (0.49–0.84) 0.68 (0.48–0.96) 0.81 (0.55–1.20)	–	–	–	[20]
Salliot *et al.* (2009) (RCT meta-analysis)	 Rituximab (745) Abatacept (1960)	 Placebo (398) Placebo (985)	Pooled OR: 1.45 (0.56–3.73) 1.35 (0.78–2.32)	–	–	–	–	[30]
Singh *et al.* (2011) (Meta-analysis of RCTs, CCTs and OLE [n = 70 studies; 21,853 participants])	 Abatacept (3543) Adalimumab (7016) Anakinra (3821) Certolizumab pegol (1929) Etanercept (7334) Golimumab (2895) Infliximab (6242) Rituximab (4485) Tocilizumab (4485) All biologics (41,036)	Control	Pooled OR 0.97 (0.40–2.31) 1.23 (0.65–2.40) 4.05 (1.22–16.84) 4.75 (1.52–18.45) 1.29 (0.72–2.45) 1.11 (0.45–2.59) 1.41 (0.75–2.62) 0.26 (0.03–2.16) 0.84 (0.20–3.56) 1.37 (1.04–1.82)	–	–	–	–	[22]
Hoshi *et al.* (2011) (Clinical trials and extension studies)	Tocilizumab (601)	Nontocilizumab RA (601)	–	–	–	2.35[§§] (1.66–3.24)	–	[41]

[†]*Adjusted IRR.*
[‡]*First 90 days of treatment.*
[§]*Entire study time period.*
[¶]*Within 6 month of treatment start.*
[#]*First year of treatment.*
[††]*Second year of treatment.*
[‡‡]*Third year of treatment.*
[§§]*Standardized for age, sex and corticosteroid use.*
aHR: Adjusted hazard ratio; CCT: Controlled clinical trial; DMARD: Disease-modifying antirheumatic drug; HR: Hazard ratio; IRR: Incidence rate ratio; OLE: Open-label extension studies; OR: Odds ratio; RA: Rheumatoid arthritis; RCT: Randomized controlled trial.

100 mg and placebo (2 out of 157 [1.3%]) or golimumab 50 mg and MTX (2 out of 158 [1.3%]) [25]. Similarly, in the 52-week GO-FORWARD study of MTX inadequate-responder RA, patients receiving MTX and golimumab 100 mg appeared to have an increased risk of serious infections [26]. These were also more common with intravenous golimumab (2 and 4 mg/kg) than MTX and placebo (23 of 626 patients [4%] and two of 129 patients [2%], respectively) [27].

Rituximab

Although two clinical trials on patients with RA reported numerically higher rates of serious infection [7,28], a subsequent RCT showed the converse [29]. A meta-analysis that included three RCTs also demonstrated no overall increased risk of severe infections in RA patients treated with rituximab compared with placebo [30].

Pooled analysis of safety data of patients treated with rituximab in combination with MTX (n = 2578) in a global clinical trial program revealed an overall serious infection rate of 4.31 per 100 patient-years (95% CI: 3.77–4.92) [31]. Rates of infections, including serious infections, remained stable over time across five courses at 4–6 events per 100 patient-years. Pneumonia was the most common serious infection, affecting 27 patients (1%).

The French AutoImmunity and Rituximab registry also found the risk of serious infection to be increased with rituximab use (5.0 per 100 patient-years) with approximately 80% of severe infections occurring in the first 6 months of treatment. Bronchopulmonary infections formed the greatest proportion of infections (41.5%). Lung and cardiac comorbidities, extra-articular involvement and low IgG levels (<6 g/l) were documented predisposing factors [32,33].

Low immunoglobulin levels have been documented with rituximab therapy [31] and, as with the AutoImmunity and Rituximab registry, low IgG levels in particular have been associated with an increased risk of serious infection (odds ratio [OR]: 1.99; 95% CI: 1.2–3.3; p = 0.008) [34]. Hypogammaglobulinemia after rituximab was associated with older age, history of cancer and serious or recurrent infections. Low total gammaglobulin levels and IgM levels, on the other hand, have not resulted in increased infection risk.

Abatacept

From a meta-analysis of the five abatacept RCTs, the pooled ORs for serious infections at all doses of abatacept versus placebo did not reveal any statistically significant increased risk (OR: 1.35; 95% CI: 0.78–2.32) [30].

An integrated summary analysis (from eight trials) included 4149 patients treated with abatacept, with 12,132 patient-years of exposure. Of these patients, 1165 (28%) had ≥5 years of exposure at the time of data analysis [35]. The incidence rate (IR) of serious infections in patients treated with abatacept was consistent in the short-term, long-term and cumulative periods, and similar to patients treated with nonbiologic DMARDs. The most common serious infections were pneumonia, urinary tract infection and cellulitis. An IR (events per 100 patient-years) of infections requiring hospitalization of 2.72 (95% CI: 2.37–3.10) has been reported for 4134 abatacept patients compared with 1.41–3.92 (range) for 94,000 DMARD-treated patients. The corresponding rate for pneumonia requiring hospitalization for abatacept was 0.65 (95% CI: 0.47–0.82) and for DMARDs was 0.27–1.31 [36].

In a preliminary analysis of data for the first 682 patients in the French Orencia and Rheumatoid Arthritis registry (mean follow-up: 8.0 months/353 patient-years) 16 severe infections were documented corresponding to 4.5 severe infections per 100 patient-years [32].

Tocilizumab

From a meta-analysis of RCTs evaluating tocilizumab an increased risk of serious infections has been documented (OR: 1.58; 95% CI: 0.85–2.94) [22], in particular in the 8 mg/kg combination group compared with controls (OR: 1.30; 95% CI: 1.07–1.58) [37]. An integrated summary analysis of over 4000 patients receiving tocilizumab reported an overall infection rate of 103.7 (95% CI: 101.9–105.5) per 100 patient-years; rate of serious infection remained stable over time (reported over 12 month periods from year 1 to 4) [38]. The most common serious infections with tocilizumab were cellulitis and pneumonia [39].

In a postmarketing surveillance programme in Japan, pneumonia was found to be the most common serious infection (47 events in 44 out of 3881 patients; 2.62 per 100 patient-years) [40]. A history of respiratory disorders, prednisolone dose at baseline ≥5 mg/day and age ≥65 years were risk factors for the development of serious infections.

The risk of serious respiratory infections in 601 RA patients enrolled in clinical trials assessing tocilizumab and their extension studies was approximately double that of age- and sex-matched RA patients treated in daily clinical practice at Tokyo Women's Medical University (Japan). The calculated standardized incidence

ratio (SIR) of serious respiratory infection with tocilizumab was 2.35 (95% CI: 1.66–3.24) standardized for age, sex and corticosteroid use; 1.85 (95% CI: 1.30–2.55) standardized for age, sex and pre-existing pulmonary involvement; and 2.41 (95% CI: 1.68–3.34) standardized for age, sex and disease activity [41].

Summary

In summary, the overall risk of serious bacterial infection has been found to be increased with the use of all the biologics, although possibly less so with abatacept. A recent Cochrane review has suggested an increased infection rate with certolizumab pegol; differences in study design between the trials included in this review may, however, have contributed to this observation [22]. A zero event rate was often reported in the control group of the certolizumab studies, which may account for the disproportionately high infection rate noted compared with other biologics. For the TNFi and rituximab this risk appears greater within the first 6 months of treatment. Pneumonia was one of the most common serious infections documented. Age, associated comorbidity and concomitant glucocorticoid use increase the risk of infection, with low IgG levels noted to be a particular risk for those receiving rituximab. Monitoring of IgG levels in patients treated with rituximab is recommended, particularly in those who demonstrate low baseline levels and in higher risk patient groups, such as the older patient, those with comorbidities and those using concomitant glucorticoids [42].

Tuberculosis

A serious side effect associated with immunosuppression is the reactivation of latent infections including tuberculosis (TB).

A Cochrane meta-analysis of RCTs and open-label extension studies has shown an overall increased risk of reactivation of latent TB compared with controls (OR: 4.68 [95% CI: 1.18–18.60]) [22]. Data on individual classes of therapies will also be examined (Table 3).

TNFi: infliximab, etanercept & adalimumab

TNF plays a critical role in immunity to *Mycobacterium tuberculosis* and other intracellular bacterial and fungal pathogens. In addition to being essential for immune control of TB, it has also been implicated in its immunopathology [43]. Initial reports of TB reactivation provided further insights for work on animal models into the role of TNF and granuloma stabilization [44].

Several large registries [45–49] and retrospective studies [50] have confirmed the increased incidence of TB with TNFi compared with the general population and with patients with RA not receiving TNFi. Older age, a past history of pulmonary TB, Felty's syndrome and corticosteroid use have also been documented as independent variables associated with an increased risk of active TB [50].

Furthermore, a differential risk within the class of TNFi has been observed; several registries [32,51,52] have shown the risk of TB to be higher with the monoclonal antibody TNFi (OR: 13.3; 95% CI: 2.6–69.0) versus etanercept (OR: 17.1; 95% CI: 3.6–80.6) [32].

Other TNFi

Five patients in the RAPID 1 study [21] developed TB after 1.5–9 months of treatment, three of whom were purified protein derivative (PPD) positive at baseline (5-mm reaction), but had previous Bacillus Calmette–Guérin vaccination and negative findings on chest x-ray. One patient (PPD negative) was a worker in a TB clinic. In the RAPID 2 study, there were also five cases of TB after 2–6 months of therapy. Two of the five had PPD reactions of 4–5 mm with normal chest x-ray findings at screen. One of the patients with a PPD reaction (6 mm) had abnormal chest x-ray findings at baseline but was deemed not clinically significant by local investigators [4]. No cases of TB were reported in the FAST4WARD study [5].

A Cochrane meta-analysis of the golimumab RCTs found no significant differences between golimumab and placebo for the development of TB [22]. A case of TB of the spine was reported 1 month after golimumab therapy in the GO-BEFORE study [25] and two cases of TB in patients, who initially tested negative at screening, between 6 and 12 months of IV golimumab therapy [27].

The introduction of screening measures and prophylaxis for those with latent TB infection before the start of TNFi therapy has been successful in reducing the risk of TB reactivation [51] and is advocated in clinical practice in all patients prior to starting TNFi. Later trials with the newer biologics also required TB screening and prophylaxis or excluded patients with evidence of previous TB exposure; hence reporting much lower TB IRs.

Abatacept

A few opportunistic infections have been reported during the cumulative study period with abatacept use (IR: 0.36 per 100 patient-years

Table 3. Relative risk of tuberculosis in patients receiving TNF inhibitors.

Study (year)	Comparator groups	Incidence per 100,000 person-years (95% CI)	RR (95% CI)	Ref.
Gomez-Reino *et al.* (2003) (Spanish registry)	General population RA nonbiologic RA infliximab	21 in 2000 95 1893 in 2000 and 1113 in 2001	1 4.13 (2.59–6.83) 53 (35.4–89) in 2001† 11.7 (9.5–14.6) in 2001‡	[45]
Wolfe *et al.* (2004) (US registry)	General population RA RA infliximab	6.4 6.2 (1.6–34.4) 52.5 (14.3–134.4)	1 1 8	[46]
Askling (EULAR 2007) (Swedish registry)	General population RA non-TNF RA TNF	 110 (690–1600)	1 2.5 (1.8–3.6) 31 (18–51)	[47]
Seong *et al.* (2007) (Korean registry)	General population RA non-TNF RA infliximab RA etanercept	67.2 257 2558 0	1 8.9 (4.60–17.2) 30.1 (7.40–122.3)	[48]
Gomez-Reino *et al.* (2007) (Spanish registry)	 General population RA TNF (before March 2002) RA TNF (after March 2002–January 2006) RA TNF 100% compliance† RA TNF <100% compliance† RA infliximab RA etanercept RA adalimumab	 472 (284–642) 172 (103–285) 43 (11–175) 311 (181–536) 383 (159–921) 114 (28–459) 176 (24–1254)	IRR: 1 19 (11–32) 7 (3–13) 1.8 (0.28–7.1) 13 (6–25)	[51]
Dixon *et al.* (ACR 2008) (UK registry)	 RA DMARD RA TNF RA infliximab RA etanercept RA adalimumab	 0 111 (77–154) 131 (68–228) 50 (20–103) 196 (112–319)	IRR: 2.8 (1.2–7.1) Referent 2.8 (1.6–9.1)	[52]
Tubach *et al.* (EULAR 2008) (French registry)	General population TNF (RA, PsA, Crohn's disease, TA and Behcet's disease) Infliximab/adalimumab Etanercept	8.7 39.2 71.5 6.00		[49]
Tam *et al.* (2010) (Hong Kong and China – retrospective case controlled study)	 General population RA TNF-naive RA TNF		SIR: 2.35 (1.17–4.67) 34.9 (8.89–137.20)	[50]
Mariette *et al.* (2011) (French registry)	 Infliximab vs etanercept Adalimumab vs etanercept		OR: 13.3 (2.6–69.0) 17.1 (3.6–80.6)	[32]

†*Compared to the general population.*
‡*Compared to RA nonbiologic.*
ACR: American College of Rheumatology; DMARD: Disease-modifying antirheumatic drug; EULAR: European League Against Rheumatism; IRR: Incidence rate ratio; OR: Odds ratio; PsA: Psoriatic arthritis; RA: Rheumatoid arthritis; RR: Relative risk; SIR: Standardized incidence ratio; TA: Takayasu's arteritis.

[95% CI: 0.27–0.49]), with eight cases of TB (IR: 0.07 per 100 patient-years [95% CI: 0.03–0.13]) observed overall [35].

Rituximab

In the RA clinical trials on rituximab, patients who did not respond to TNFi treatment were prescreened for the presence of active or latent TB before TNFi, and in other trials patients with active TB were excluded (although no screening for latent TB was performed). There is no evidence of an increased frequency of TB in patients with lymphoma treated with rituximab [53]. Two cases of pulmonary TB have been reported from the rituximab clinical trial safety database; these appear to have been *de novo*

infections (information from Roche, Basel, Switzerland) [41]. From a survey carried out in the USA and Canada, three cases of TB and five cases of nontuberculous mycobacterial infections were reported in RA patients on rituximab [54]. However a few case reports, have described the use of rituximab in patients with a history of active TB without TB reactivation [55,56].

Tocilizumab

Eight reports of TB have been documented during long-term follow-up of patients (n = 4009) who received at least one dose of tocilizumab (mean treatment duration: 2.4 years [39]) during either one of five RCTs [11,39,57,58], two extension trials and a clinical pharmacology study [38,59]. None had a relevant medical history, history of TB or previous known exposure to TB. Pulmonary TB was reported in four patients, TB pleurisy in three, and TB (not otherwise specified) in one. No cases of TB were reported in the control group.

From observational postmarketing surveillance data in Japan of 3881 RA patients receiving tocilizumab, four patients developed TB (0.22 per 100 patient-years) [40]. None had a previous history of TB. Two cases developed 1 and 2.5 months after beginning tocilizumab treatment and the other two after more than 4 months of treatment. All cases improved with appropriate treatment.

Summary

Evidence from the literature therefore confirms an increased risk of TB reactivation with biologic therapy, predominantly the TNFi. This risk appears to be higher for the monoclonal antibody TNFi compared with the soluble-receptor inhibitors. Screening for TB and the use of TB prophylaxis for cases of latent TB has been shown to reduce the risk of reactivation. Fewer data are available for the newer biologics, although case reports have been documented; guidelines advocate screening according to local practice before initiating any biologic therapy [60].

Viral infections

Herpes zoster

Patients with RA have been documented to be at greater risk of herpes zoster compared with those without RA. Within a cohort of RA patients, retrospective studies of two large USA and UK databases found that use of biologics (infliximab, etanercept and anakinra) was also associated with herpes zoster (OR: 1.54; 95% CI: 1.04–2.29). Traditional DMARDs and oral corticosteroids were other associated factors [61].

From the German biologics register RABBIT (n = 5040 on TNFi with 5.5-years follow-up) the IR of herpes zoster was 10.1 per 1000 patient-years in the TNFi group versus 5.6 per 1000 patient-years with DMARDs; with an incidence of serious herpes zoster (multidermatomal or ophthalmic) of 2.5 per 1000 patient-years versus 0.9 per 1000 patient-years with DMARDs [62]. The risk was increased with the monoclonal antibodies (adjusted HR: 1.82; 95% CI: 1.05–3.15) compared with etanercept (adjusted HR: 1.36; 95% CI: 0.73–2.55) [62]. Similar findings were documented in the French RATIO registry. In addition, this risk was found mainly at the start of TNFi therapy [63].

The risk of hospitalization for shingles or chickenpox was also higher in those receiving TNFi [64]. From the Spanish BIOBODASER registry and national hospital discharge database, the estimated IR (cases per 100,000 patient-years) of hospitalization due to shingles in patients exposed to TNFi was 32 (95% CI: 14–78) and the expected rate in the general population was 3.4 (95% CI: 3.2–3.5), the SIR 9 (95% CI: 3–20) and the standardized incidence difference 26 (95% CI: 14–37). The estimated IR (cases per 100,000) of hospitalization due to chickenpox was 26 (95% CI: 10–69), the expected rate was 1.9 (95% CI: 1.8–2.0), the SIR 19 (95% CI: 5–47) and the standardized incidence difference 33 (95% CI: 21–45).

In the long-term pooled safety analysis of rituximab in RA, herpes zoster was documented in 2% of RA patients on rituximab a calculated rate of 0.98 events per 100 patient-years [31]; an incidence similar to that seen with TNF inhibitors [62].

Herpes zoster has also been reported in clinical practice with tocilizumab [65,66]. Published IRs appear to be the same as with the TNFi [62], including a pooled analysis of safety data from five RCTs [11,39,57,58]. In the SAMURAI study, the incidence was 0.6% in the tocilizumab group [67] and in the extension STREAM study, the rate of serious herpes infections was 1.1 per 100 patient years [68].

Data from the literature therefore demonstrate an increased risk of herpes zoster with the use of biologic therapies. This incidence appears similar for all agents for which data is available.

Hepatitis B

As with TB, hepatitis B virus (HBV) can avoid initial eradication and enter a latent state. Affecting

up to 400 million people worldwide [69], both the acute eradication and the chronic containment of the virus are dependent on an intact immune system. Immune suppression has been associated with HBV reactivation in chronic carriers, and patients with resolved HBV infection may develop recurrent hepatitis B infection that leads to fulminant hepatic failure and death [70,71].

TNF inhibitor

Case reports of fatal outcome have been described due to HBV reactivation following infliximab administration in patients with chronic HBV (hepatitis B surface antigen-[HBsAg]-positive) [72–75]. Case reports of HBV reactivation have also been documented with etanercept and adalimumab [76].

A systematic literature review on the use of TNFi in HBsAg-positive patients identified 35 cases where TNFi was used with HBsAg-positivity known before TNFi initiation [77]. Infliximab was used in 17 cases, etanercept in 12 cases and adalimumab in six. All six (17%) cases of clinically symptomatic hepatitis were associated with infliximab. The two deaths reported occurred with infliximab. Infliximab was also associated with a greater than twofold increase in alanine aminotransferase in six out of nine cases and greater than 1000-fold increase in HBV DNA load in three out of four cases.

Several case reports and studies have documented the use of combination therapy with TNFi and oral antiviral therapy in patients with chronic HBV infection. Use of prophylactic antivirals was associated with good outcomes and was effective in preventing significant elevations in alanine aminotransferase levels and liver decompensation [78–81].

Concerns have also been raised regarding the recurrence of HBV in patients with past infection. One prospective study showed recurrent HBV in patients with resolved HBV infection (HBsAg-negative, hepatitis B core antibody [HBcAb]-positive) who were followed-up for 1 year, with HBV recurrence reported in six (16%) out of 38 patients treated with etanercept [82]. While several case reports and a retrospective case series of 88 Korean patients followed over 6.5 years suggested occasional clinical evidence of HBV recurrence [83], two recent prospective cohort studies comprising 88 European patients [78,84] and case reports including 21 patients with past HBV infection [75] reported no cases of recurrent HBV. In a study including 19 patients with resolved HBV who received etanercept for several years, HBV DNA was not detected [80]. A large-scale postmarketing surveillance study carried out in Japan to determine the safety profile of infliximab in 5000 RA patients showed no cases of *de novo* hepatitis B [85]. Therefore, in patients with past history of HBV infection the risk of HBV reactivation appears low with TNFi [86].

In patients who have developed an immune response to HBV, a few studies have reported a reduction in HBsAb titers with TNFi [75,78]. In one study this was particularly noted in those with low or moderate titers with TNFi [75]. As a decrease in HBsAb titer has been shown to precede HBV reactivation in patients treated for hematological cancer or following immunosuppressive therapy [87], closer follow-up of patients, particularly with low baseline HBsAb titers, for evidence of HBV reactivation has been suggested [75]. Vaccination should be considered in patients who have not previously been infected with hepatitis B.

Rituximab

HBV reactivation in patients receiving rituximab is widely documented in the oncology literature in patients with serological evidence of past HBV infection (HBsAg-negative and HBcAb-positive) [88,89]. Recent case reports have also shown the occurrence of HBV reactivation in HBV carriers with rituximab [90].

Tocilizumab

To date a few case reports, all of Japanese patients chronically infected with HBV who were subsequently treated with tocilizumab, have been published [91,92]. One received an anti-HBV agent (entecavir) when the HBV was diagnosed and the other recieved lamivudine prophylaxis prior to commencement of tocilizumab therapy.

Summary

Overall, therefore, concerns exist with regards to hepatitis B activation, particularly with rituximab. However, the literature also suggests that chronic HBV infection need not preclude biologic therapy. Use of a TNFi and biologics may generally be considered with careful counseling, collaboration with hepatologists and intensive monitoring [79].

A consensus statement from the European League Against Rheumatism recommends that patients be screened for HBV infection prior to starting biologic therapy [60]. The rituximab consensus statement also advises prescreening and subsequent management if indicated with expert gastroenterology/hepatology consultation [42]. The American College of Rheumatology (ACR) stated in 2008 that biologics were contraindicated

in patients with HBV infection who had Child–Pugh class B or C liver disease regardless of the concomitant use of antiviral agents [93].

In patients with chronic hepatitis B, or HBV carriers (HBsAg-positive), undergoing biologic therapy, anti-HBV treatment or prophylaxis prior to biologic initiation should be considered to prevent hepatitis reactivation. Close monitoring for any clinical or serological evidence of hepatitis and HBV DNA is also recommended [77,94,95]. It has been suggested that such patients remain on antiviral therapy for 6 months after ceasing biologic therapy as immune reconstitution may lead to a flare of HBV [86,96]. In those with a past history of HBV, (HBsAg-negative and HBcAb-positive) on the other hand routine antiviral prophylaxis is not recommended, but close clinical and serologic follow-up is deemed prudent [84,86,95].

The effect of long-term biologic therapy on the risk of hepatic fibrosis, cirrhosis and hepatocellular carcinoma remains to be seen.

Hepatitis C

Many patients exposed to hepatitis C virus (HCV), an RNA virus transmitted primarily parenterally, develop chronic infection. HCV infection has been documented in 1–3% among different geographical areas, and in up to 20% in undeveloped countries [97].

TNF inhibitor

A systematic literature review addressing the safety of TNFi in patients affected by chronic hepatitis C (January 1990–October 2010) found 37 publications with data on 153 patients [98]. The mean TNFi treatment duration was 11.9 months. Ninety-one patients had RA, 22 had psoriasis, six had Crohn's disease and 14 patients had other chronic inflammatory diseases. Only one confirmed case of worsening of liver disease (with hepatic improvement after withdrawal of etanercept) and one suspected case (treated with infliximab) was described. In five other patients, increases in the levels of transaminases did not correspond to increased viral loads and vice versa and liver biopsies were not executed. There were no data for certolizumab pegol or golimumab.

Rituximab

Although vigilance would still be advised, no major concerns have been raised with rituximab treatment in RA patients with HCV infection. Indeed, rituximab is increasingly considered for the treatment of HCV-associated cryoglobulinemic vasculitis [99]. To date, the data from short-term studies show a favorable clinical response, without significant liver toxicity [100,101], although in some case reports, mild elevation of HCV RNA levels during treatment with rituximab was noted [102].

Tocilizumab

A case report of a patient with RA and chronic HCV infection showed that short-term tocilizumab treatment did not affect the viral load or serum transaminases [103].

Abatacept

One article described the use of abatacept in two patients with RA and concomitant hepatitis C with favorable outcome [104].

Summary

Overall, the studies reviewed confirm that biologics are well tolerated, and may even be a useful therapeutic option in the setting of HCV infection associated with RA and other rheumatic diseases. As the long-term safety in chronic HCV-infected patients is not completely known, it is recommended that all patients be screened for HCV before biologic therapy initiation and monitored during the follow-up [60]. Antiviral treatment (α-interferon and ribavirin) should be considered in patients with evidence of active hepatitis C before or during biologic treatments [105]. From the ACR recommendations, biologics are contraindicated in Child–Pugh class B and C chronic hepatitis C viral infection [93]. Patients should be referred to a hepatologist for expert clinical management whenever antiviral therapy is deemed necessary or hepatitis reactivation occurs [94,95].

JC virus

The risk of progressive multifocal leukoencephalopathy (PML) has been documented as 0.4 per 100,000 in patients with RA [106]. Although rare, PML is a devastating complication. Most of the documented PML cases with RA had long-standing disease with numerous previous immunosuppressive therapies. In the few case reports of PML in RA patients, one case has been recorded with infliximab and four with rituximab. The risk with rituximab has received more attention with an incidence of less than one in 20,000 [42]; however, compared with other disease groups and monoclonal antibodies this is small (psoriasis treated with efalizumab [one in 400] and patients with Crohn's disease and multiple sclerosis treated with natalizumab [one in 1000]). Although the risk seems small, clinicians are advised to maintain vigilance [42].

Other infections

Biologic therapies have been associated with higher rates of several other infections, including herpes simplex infections [107–109] and *Legionella* [32,110]. Opportunistic infection with atypical mycobacteria, histoplasmosis [111], *Listeria* [112], *Aspergillus*, *Nocardia* and *Cytomegalovirus* [113] have also been documented. Although these will not be reviewed in depth in this article, clinicians should remain mindful of these when treating patients with biologic therapies.

Malignancy

RA is one of the many chronic inflammatory diseases associated with an increased risk of malignancy [114]. A meta-analysis of 21 observational studies revealed the rate may be increased by an estimated 5% compared with the general population when considering all cancers (SIR: 1.05; 95% CI: 1.01–1.09), but is significantly higher for the risk of lymphoma (SIR: 2.1; 95% CI: 1.8-2.4), and in particular Hodgkin's lymphoma (SIR: 3.3; 95% CI: 2.6–4.2) [115].

RCTs usually excluded patients with previous history of malignancy, possibly influencing observations and subsequent interpretation. Observational registries partly address this, although channeling bias also needs to be considered when reviewing data.

TNFi: infliximab, etanercept & adalimumab

Prescribing information for these TNFi includes the warning that in RCTs malignancies, in particular lymphoma, have been observed more frequently in patients receiving TNFi than in controls. In 2009, the US FDA issued an update to this prescribing information to report a possible association with acute and chronic leukemia, based on 147 postmarketing reports in patients using TNFi [201]. A meta-analysis of 18 RCTs reported malignancies in 0.8% of 4099 patients receiving recommended doses of infliximab, etanercept or adalimumab (3805 patient-years) in comparison with 0.6% of 2672 controls (2172 patient-years) [116]. These trials also included a number of patients treated with higher doese than the current recommended doses of adalimumab (mean dose in high-dose groups 49 mg/week) and infliximab (mean dose 1.16 mg/kg per week). Amongst these patients there was a trend towards an increased risk of all noncutaneous malignancies and melanoma ($p = 0.06$ for adjusted meta-analysis). However, it is difficult to interpret risk from such trial data; as illustrated here, follow-up time is relatively short and numbers of events are small, generating large uncertainty in risk estimates and necessitating pooling of various types of malignancies, among which risks may differ. In addition, the authors of this meta-analysis report inconsistencies between studies in the reporting of malignancies.

The French registry, RATIO, was established to be maximally inclusive of cases of lymphoma developing in patients receiving TNFi [117]. Data on use of TNFi use for any indication (including RA) has been analysed for 57,711 patient-years over a 3-year period (2004–2006): 38 validated cases of lymphoma were identified, 27 occurring in patients with RA. In comparison with the general French population, the SIR for lymphoma was 2.4 (95% CI: 1.7–3.2), and was similar in the RA sub-group (SIR: 2.3; 95% CI: 1.6–3.3). However, incidence was higher among patients receiving the monoclonal antibodies, infliximab and adalimumab, in comparison with etanercept: SIR 3.6 (95% CI: 2.3–5.6), 4.1 (95% CI: 2.3–7.1), and 0.9 (95% CI: 0.4–1.8), respectively. In a case–control analysis, with lymphoma-free controls from the registry (matched by sex, age and disease), treatment with infliximab or adalimumab in comparison with etanercept appeared to be a significant risk factor for the development of lymphoma in patients receiving TNFi (OR: 4.1; 95% CI: 1.3–17.7). This remained statistically significant amongst the RA subgroup. However, 18% of cases had received more than one TNFi therefore attributing risk to any individual agent is problematic. It must also be kept in mind that these incidence ratios, at least in part, may be explained by risk with the underlying disease.

Data from several national registries across Europe and North America have been reassuring in that no increase in the overall incidence of malignancy, or malignancy-specific rates such as the incidence of lymphoma, has been identified in comparison with RA controls not receiving biologics (Table 4) [118–127]. This is with the exception of the risk of nonmelanotic skin cancers (NMSC), which may be increased by approximately 50% with infliximab, etanercept and adalimumab compared with RA controls; a meta-analysis of prospective observational studies (including data from several national registries as shown in Table 4) calculated an overall effect size of 1.5 (95% CI: 1.2–1.8) [128]. No statistically significant risk was detected in all cancers, lymphoma or melanoma, although for these rarer malignancies the low number of cases

was reflected in wide confidence intervals; for example, the estimate of risk of melanoma was 1.8 (95% CI: 0.9–2.7). Although risk estimates may be calculated with adjustment for known risk factors such as age, and to some extent disease activity, confounding by indication (i.e., the nonrandom selection of patients for TNFi treatment) is inherent within these data. Potentially, patients most at risk may be under represented in TNFi groups, with these therapies being avoided in certain circumstances. In some studies, attempts to minimize bias have included calculation of a propensity score (quantifying the tendency for use of TNFi) in multivariate analysis [122,124]. The periods studied (up to 10 years in the instance of the US veterans cohort) is also pertinent considering the potential long latency period with some malignancies.

Data concerning the risk of recurrence in patients who have a history of malignancy are available to a lesser extent, from two registries. In 294 patients with prior malignancy (excluding NMSC) in the British Society of Rheumatology Biologics Register, for 177 patients receiving TNFi, the IR ratio for new/recurrent malignancy with TNFi was 0.6 (95% CI: 0.2–1.4) compared with controls, and 0.5 (95% CI: 0.1–2.2) after adjusting for potential confounders, including disease duration and activity [129]. The German registry, RABBIT, provides data for 122 patients with prior malignancy (67 receiving TNFi); the IR ratio for recurrence with TNFi was 1.4 (95% CI: 0.5–5.5) [125]. The mean time to recurrence was 9.5 years (standard deviation 7.8). A subanalysis of the British Society for Rheumatology Biologics Registers (BSRBR) data stratifying patients according to time from prior malignancy to start of TNFi treatment did not reveal any apparent difference in risk; adjusted IR ratio was 0.7 (95% CI: 0.2–2.8) for patients treated with TNFi within 10 years of their prior malignancy, and 0.6 (95% CI: 0.1–4.1) for those who had been free of recurrence for at least 10 years [129]. In patients with a history of malignancy, guidelines for the use of TNFi therapies recommend caution should be exercized [130], with the ACR recommending avoidance of TNFi in patients with a lymphoproliferative disorder within the preceding 5 years [93].

Other TNFi

Registry data are not yet available for the newer TNFi, certolizumab pegol and golimumab. In studies on certolizumab pegol (4065 patient-years), SIR for all malignancies was 1.2 (95% CI: 0.8–1.7) and for lymphoma was 4.1 (95% CI: 0.8–12.0) [131]. Similar results for golimumab have been reported for pooled trial data; SIR for all malignancies was 1.3 (95% CI: 0.8–2.1) amongst 2190 patient-years follow-up (recommended dose group, 50 mg every 4 weeks) [132]. There were no cases of lymphoma amongst this dose group, and incidence of NMSC was similar to that seen with other TNFi (4.1 per 1000 patient-years); however, incidence of lymphoma and NMSC appeared increased in the higher dose group (100 mg every 4 weeks) at 1.9 and 5.2 per 1000 patient-years, respectively. No trials of certolizumab pegol or golimumab have included patients with a history of malignancy.

Rituximab, abatacept & tocilizumab

Evidence for the risk of malignancy from long-term observational cohorts/registries for the above non-TNFi biologic therapies is not yet available. Again, initial insight into long-term safety (although in a clinical trial setting excluding patients with previous malignancies) is provided by pooled trial data [31,35,39]. Rates of all malignancies are shown in Table 5. There has been no signal that risk of solid malignancy or lymphoma is increased (with the exception of rituximab and individuals with T-cell deficiency in HIV infection) [133]. Again, (as discussed for TNFi above) the significant limitations of trials to assess this aspect of safety should be considered while experience of long-term use in a clinical setting is accumulating.

Injection site/infusion reactions

Various mechanisms are proposed for injection site or infusion reactions including T-cell-mediated delayed hypersensitivity [134] and type I hypersensitivity [135]. The chimeric antibodies (infliximab and rituximab) are associated with increased immunogenicity compared with humanized or fully human antibodies [136], and treatment can induce formation of human antichimeric antibodies that may, but not consistently, be associated with reduced drug efficacy and severe infusion reactions [137].

Subcutaneous TNFi

In RCTs of adalimumab and etanercept, rates of injection site reactions (including erythema, itching and pain) occurred more frequently than in placebo groups; one meta-analysis reported the percentage of patients with injection site reactions with adalimumab and

Table 4. Observational studies in rheumatoid arthritis patients assessing risk of malignancy with TNF inhibitor in comparison with biologic-naive rheumatoid arthritis patients.

Registry/ cohort (year)	Year of enrollment	Cohort size	Cancer type	Incidence in TNFi group (per 1000 patient-years)	Risk versus nonbiologic RA patients (95% CI)	Parameters included in the models for estimate of risk	Ref.
Askling *et al.* (2009) (Swedish registry)	1999–2006	n = 6366 (all receiving TNFi) Comparator cohort: 67,743 biologic naive	All	9.34	RR: 1.0 (0.9–1.2)	Age, gender, civil status, country of residence, time, duration of disease, comorbidities and in-patient care in the year preceding malignancy occurrence	[118]
	1998–2006	n = 6604 (all receiving TNFi) Comparator cohort: 67,743 biologic naive	Lymphoma	0.96	RR: 1.4 (0.8–2.1)	Age, gender, civil status, country of residence, time, comorbidities and in-patient care in the 6 months preceding lymphoma occurrence	[119]
		n = 6604 (all receiving TNFi) Comparator cohort: 67,845 biologic naive	Melanoma	Not reported	RR: 1.7 (1.0–2.9)	Age, gender, comorbidities and time since start of TNFi	[120]
			Squamous cell skin	Not reported	RR: 1.2 (0.8–2.0)		
Wolfe *et al.* (2007) (US registry)	1998–2005	n = 13,001 (5257 receiving TNFi or anakinra; anakinra in 0.3% of total cohort)	All	Not reported	OR: 1.0 (0.8–1.2)	Time of entry and exit in study period, age, gender, education, smoking, Patient Activity Score and steroid use	[121]
			Leukemia	Not reported	OR: 1.2 (0.5–3.1)		
			Lymphoma	Not reported	OR: 1.0 (0.5–2.0)		
			Melanoma	Not reported	OR: 2.3 (0.9–5.4)		
			NMSC	Not reported	OR: 1.5 (1.2–1.8)		
Amari *et al.* (2011) (US veterans cohort study)	1998–2008	n = 20,648 (4088 receiving TNFi)	NMSC	18.9	HR: 1.4 (1.2–1.6)	Propensity score (including age, comorbidities, intra-articular steroid use and orthopedic procedures) and mean number of healthcare encounters per month	[122]
Watson *et al.* (EULAR 2006) Mercer *et al.* (2012) (UK registry)	2001–2005	n = 11,875 (9998 receiving TNFi)	All	8.6	IRR: 0.7 (0.4–1.2)	Age, gender, disease severity and smoking	[123]
	2001–2008	n = 15,272 (11,757 receiving TNFi)	NMSC	4.2	HR: 1.7 (0.9–3.4)	Age, gender, disease duration, disease activity, HAQ, steroid use, number of prior DMARDs, smoking and year of registration	[124]
Strangfeld *et al.* (2010) (German registry)	2001–2006	n = 4998 (3202 receiving TNFi) Patients without prior malignancy	All	5.1	HR: 0.7 (0.4–1.1)	Age, gender, disease duration, rheumatoid factor, functional capacity, previous treatment (cyclosporin or azathioprine), comorbid conditions and disease activity	[125]
Greenberg *et al.* (ACR 2007) (North American registry)	2002–2006	n = 8804 (4651 receiving TNFi)	All	7.5	IRR: 1.1 (0.7–1.5)	Age and gender	[126]
					IRR: 0.9 (0.6–1.4)	Propensity score	
			Lymphoma	0.6	IRR: 0.7 (0.2–2.5)	Age and gender	
			Melanoma	0.3	Not reported		
			NMSC	2.7	IRR: 2.1 (1.0–4.4)		

ACR: American College of Rheumatology; DMARD: Disease-modifying antirheumatic drug; HAQ: Health assessment questionnaire; HR: Hazard ratio; IRR: Incidence rate ratio; NMSC: Nonmelanotic skin cancer; OR: Odds ratio; RA: rheumatoid arthritis RR: Risk ratio; TNFi: TNF inhibitor.

Table 4. Observational studies in rheumatoid arthritis patients assessing risk of malignancy with TNF inhibitor in comparison with biologic-naive rheumatoid arthritis patients (cont.).

Registry/ cohort (year)	Year of enrollment	Cohort size	Cancer type	Incidence in TNFi group (per 1000 patient-years)	Risk versus nonbiologic RA patients (95% CI)	Parameters included in the models for estimate of risk	Ref.
Abásolo *et al.* (ACR 2008) (Spanish Registry)	2001–2007	n = 4529 (all receiving TNFi) Comparator cohort: 789 biologic naive	All	6.0	IRR: 0.9 (0.4–2.0)	Age, gender, disease activity and disease duration	[127]

ACR: American College of Rheumatology; DMARDs: Disease-modifying antirheumatic drugs; HAQ: Health assessment questionnaire; HR: Hazards ratio; IRR: Incidence rate ratio; NMSC: Nonmelanotic skin cancer; OR: Odds ratio; RA: rheumatoid arthritis RR: Risk ratio; TNFi: TNF inhibitor.

etanercept to be 19% (95% CI: 9–29) and 25% (95% CI: 11–38), respectively [138]. In pooled data from placebo-controlled trials of certolizumab pegol in RA, rate of injection-site reactions was low and was similar to controls; 6.4% of patients developed reactions (erythema, itching, hematoma, pain, swelling or bruising) in comparison with 6.5% of controls [202]. Results of an *in vitro* study suggest the seemingly low number of observed reactions with certolizumab pegol may be due to the presence of the pegylated moiety; both certolizumab and its component part, the pegylated moiety, inhibited degranulation of mast cells cultured from stem cells, while this effect was not seen with antibody fragments alone [139]. Reaction rate also appears low in golimumab trials; in pooled data from RCTs the rate was 8% with golimumab, at the current licensed dose, compared with 3% in controls [132].

Infliximab

Infusion reactions (any adverse event occurring during or within 1 h of administration) occurred in 18% of all patients receiving infliximab in Phase III clinical trials (in comparison with 5% of controls) [203]. Most reactions were well-tolerated with only 3% of infusion reactions leading to discontinuation. Use of concomitant DMARD therapy such as MTX decreases the rate of infusion reactions and antibody production; of patients treated with infliximab (at the recommended dose for clinical practice) in combination with MTX, antibodies to infliximab were detected in 8% of patients.

Rituximab, abatacept & tocilizumab

Infusion reactions are common with rituximab, occurring in one in four patients according to pooled trial data, but are rarely serious (<1% of cases) [31]. Their frequency is reduced by the use of concomitant intravenous steroids [7,140]. In pooled data, human antichimeric antibodies were detected in 11% of patients tested. Abatacept and tocilizumab, being fully human and humanized proteins respectively, appear less immunogenic and less likely to cause infusion-related reactions. Product information reports rates of infusion reactions in RCTs to be 10% with abatacept (vs 7% in controls) and 7% with tocilizumab (vs 5% in controls), at the doses recommended for use in clinical practice [204,205]. However, serious anaphylactic reactions may occur, including rare fatal anaphylaxis occurring with tocilizumab in postmarketing surveillance [205]. Although usually occurring

during one of the first four infusions, delayed anaphylaxis with tocilizumab has been recognized with one episode of anaphylaxis occurring more than 12 h after the sixteenth infusion in one clinical study [39]. Similarly, rate of acute infusional events with abatacept decreases over time; analysis of abatacept clinical trials reveals a rate of 11.6 per 100 patient-years amongst short-term studies, decreasing to 3.9 per 100 patient-years when open-label extension periods were included (although subject withdrawal should be considered) [35].

Rare adverse events

Interstitial lung disease

Interstitial lung disease (ILD) is the most common manifestation of lung involvement in RA, with disease-modifying treatments (MTX) also associated with lung pathology [141]. Early observations with use of TNFi, of new cases and exacerbations of ILD, focused efforts to clarify any risk associated with biologic therapies.

TNF inhibitor

Acute and occasionally fatal exacerbations of ILD have been reported in patients receiving TNFi, in particular with infliximab [142]. Analysis of 17,598 RA patients in the US National Data Bank registry was conducted to assess risk of hospitalization for ILD with various current and past DMARDs and biologic therapies; 100 hospitalizations occurred (2.6 per 1000 patient-years) and there was a temporal relationship to TNFi treatment in only one case (treated with infliximab) [143]. Approximately two-thirds of these patients had pre-existing lung disease. Past, but not current, treatment with infliximab or etanercept appeared to increase the risk of hospitalization, but risk was not significantly increased with previous adalimumab; HRs were 2.1 (95% CI: 1.1–3.8) for previous infliximab treatment, 1.7 (95% CI: 1.0–3.0) for previous etanercept and 1.1 (95% CI: 0.4–2.7) for previous adalimumab treatment. Postmarketing studies in Japan have reported similar rates of interstitial pneumonitis, occurring in the first 6 months of treatment, with infliximab and adalimumab; rates were 25 out of 5000 patients receiving infliximab (0.5%) [144] and 17 out of 3000 patients receiving adalimumab (0.6%) [145]. In patients with pre-existing ILD in the BSRBR, TNFi were associated with a trend towards higher rate of all-cause mortality (70 deaths in 299 ILD patients; 23%) compared with DMARD therapy (14 deaths in 68; 21%), which was not statistically significant (adjusted mortality rate ratio: 0.8; 95% CI: 0.4–1.7) [146]. Deaths attributed to ILD were also higher (15 deaths out of 70 patients in the TNFi group compared with one out of 14 deaths in the DMARD cohort), although reporting bias must be considered. A recent literature review searching reviews, meta-analyses, clinical studies, RCTs, case studies and series for noninfectious pulmonary adverse events with newer biologic agents did not identify any cases with certolizumab pegol and identified only one case of ILD with golimumab, which occurred in a patient taking concomitant MTX [147]. *In vitro* and animal studies provide some insight into the effect of TNF-α and TNFi on fibrosis and it has been postulated that its effect (either pro- or anti-fibrotic) may differ depending on the pathogenic stage of the disease, for example in the early inflammatory phase or in late, established fibrosis [148].

Table 5. Incidence of malignancies in patients receiving at least one dose of biologic therapy in randomized controlled trials and open-label extension analyses (pooled data).

Biologic	Pooled analysis			All malignancies (including NMSC)		All malignancies (excluding NMSC)		NMSC (incidence per 1000 patient-years	Lymphoma (incidence per 1000 patient-years	Ref.
	Number of trials	*Patients*	*Patient-years follow-up*	*Incidence per 1000 patient-years*	*SIR (95% CI)*	*Incidence per 1000 patient-years*	*SIR (95% CI)*			
Rituximab	9	2578	5013	NR	NR	8.4	1.1 (0.8–1.4)†	NR	0.2 (1 case)	[31]
Abatacept	8	4149	12,132	NR	NR	7.3	NR	0.7	0.7	[35]
Tocilizumab	8	4009	9414	11	0.80 (0.78, 0.82)†	NR	NR	NR	NR	[39]

†*In comparison with the US general population.*
NMSC: Nonmelanotic skin carcinoma; NR: Not reported; SIR: Standardized incidence rate.

Rituximab

Reports of ILD with rituximab treatment are rare. A review of 65 rituximab studies identified only one case of ILD in RA [147]; this was one of 316 patients receiving rituximab in the DANCER Phase IIb study [7]. Cases of rituximab-induced ILD have, however, been reported in use in other indications such as non-Hodgkin's lymphoma [149] and systemic lupus erythematosus [150]. In an observational study of use of rituximab in RA 48 out of 347 patients treated had pre-existing ILD; two of these patients died during follow-up, with evidence of pneumonia and possible acute deterioration of ILD as the cause of death in one [151]. An open-label study in ten patients with RA-associated advanced ILD did not demonstrate any signal for efficacy of rituximab on lung function, and rate of adverse events appeared significant with two deaths [152]. The significance of these data is difficult to determine owing to the relatively poor prognosis of this patient group (longstanding RA and concomitant lung disease) and small numbers of patients involved. Conversely, improvement and/or stabilization of lung function has been demonstrated with rituximab in case reports of its use in the treatment of ILD associated with systemic lupus erythematosus [153] and scleroderma [154].

Demyelination

TNFi

Initial data from Experimental Autoimmune Encephalitis demonstrated a clear role of TNF-α in its pathogenesis. One of the experimental TNFi, lenercept, trialed in multiple sclerosis led to an increase in disease flares and early trial termination [155]. Established TNFi have not been evaluated in the same way, although cases of the development of multiple sclerosis, optic neuritis, Guillain–Barré syndrome and other demyelinating neuropathies have been reported with therapy with TNFi [156]. The basis for the apparent contradictory outcomes remains unclear although impact of TNFi on the two different TNF receptors may be pertinent [157]. TNFi are therefore contraindicated in patients with a history of demyelinating conditions such as optic neuritis or multiple sclerosis, and treatment should be stopped if these disorders occur on treatment [158]. The role of TNFi in causality is impossible to prove. Observational registries have not signaled any rise in new cases or significant increase in incidence although channeling bias, by excluding patients with a relevant history following initial reports in 2001 [159], is probably relevant. In the Spanish registry BIODASER, demyelination was confirmed in only 15 patients receiving TNFi (optic neuritis in five, multiple sclerosis in one and other demyelinating disorders in nine) out of a total exposure to biologic therapy of 21,425 patient-years [160]. The IR of multiple sclerosis and other demyelinating disorders appeared similar to the general population, whereas for optic neuritis it appeared increased (0.23 with TNFi vs 0.05 per 1000 patient-years in the general population), although the number of cases in this study are small. A case–control study of RA patients developing a demyelinating episode in the RA cohort in Canada also suggests a trend towards increased risk of demyelination with TNFi; although this was not statistically significant high-risk patients (with a possible prior episode of demyelination) were excluded; adjusted rate ratio 1.3 (95% CI: 0.7–2.5) [161].

Cardiac failure

TNFi

Similar to data in Experimental Autoimmune Encephalitis, TNF-α is implicated in the pathogenesis of heart failure. RCTs of infliximab and etanercept were subsequently conducted in patients with non-RA-associated moderate to severe heart failure (New York Heart Association [NYHA], grade III and IV). Mortality and hospitalization for cardiac failure were increased in patients receiving high-dose infliximab (10 mg/kg at 0, 2 and 6 weeks) [162] and etanercept trials were terminated early as no beneficial effect was seen [163]. There are also reports of new-onset congestive cardiac failure and worsening of existing cardiac failure with therapy with TNFi (without other identifiable risks or precipitating factors). Observational data, including that from national registries, are limited and conflicting. A systematic literature review identified six relevant studies [164], one of which, a cohort study, indicated a statistically increased risk of heart failure with infliximab or etanercept compared with MTX use (HR: 1.7; 95% CI: 1.1–2.7) [165]. Others, including analysis of the US database [166] and a case–control study [167], suggested a significant decrease in risk of prevalent heart failure and hospitalization with heart failure, respectively, in comparison with RA patients not exposed to TNFi (including patients with no DMARD therapy). A meta-analysis was not possible owing to the heterogeneity of studies. Therapy with TNFi remains contraindicated in moderate-to-severe cardiac failure (NYHA class III or IV), however, the impact of TNFi in

heart failure is uncertain, with animal studies highlighting the complexity of the role of TNF in pathogenesis [168,169].

Rituximab

Worsening of cardiac failure has been reported with use of rituximab [170]. It is contraindicated in severe cardiac failure (NYHA class IV), but data are limited and not available in patients with mild or moderate cardiac failure. Similar to TNFi, further work is needed to improve our understanding in this area.

Lipid abnormalities

This is an important consideration in the management of RA; as cardiovascular disease has been identified as the leading cause of death, guidelines recommend a review of risk factors on at least an annual basis with attention to modifiable risk factors such as lipid profiles [171]. Proinflammatory states, including active RA, are associated with abnormal lipid profiles, with a reduction in levels of high-density lipoprotein cholesterol, and some studies also reporting a reduction in levels of low-density lipoprotein (LDL) cholesterol and total cholesterol [172]. TNFi have been shown to alter lipid profiles, with increases in these lipid fractions potentially reflecting normalization of lipid homeostasis. A systematic review reported an increase in high-density lipoprotein cholesterol of up to 79% and an increase in total cholesterol of up to 28%. Most studies were small (up to 82 RA patients) and were *post hoc* analyses. In the knowledge that IL-6 affects lipid metabolism, lipid levels have been monitored in trials of tocilizumab, providing a larger amount of prospective data; however, it is unclear whether detected changes in lipid profiles are specific to tocilizumab or may be seen with suppression of inflammatory disease with other biologics.

Tocilizumab

Tocilizumab, by suppressing the effect of IL-6 on the liver, is associated with increased lipid levels (which are usually suppressed by inflammation). For example, the TOWARD study revealed LDL cholesterol increased to over 160 mg/dl in 16% of patients compared with 3% of controls [12]. Pooled data reveal that over 104 weeks, 12% of trial patients receiving tocilizumab commenced lipid-lowering therapy, with improvement in mean LDL cholesterol (after an initial increase) to a level similar to baseline [39]. The implication for long-term cardiovascular safety is uncertain. Evidence-based guidelines recommend monitoring lipid levels after 2 months of therapy and on a 6-monthly basis thereafter [158].

Gastrointestinal perforation

Tocilizumab

In tocilizumab clinical trials (tocilizumab exposure in 4009 patients, 9414 patient-years), gastrointestinal (GI) perforation occurred in 26 patients, in comparison with none of the controls (2.8 cases per 1000 patient-years); 24 (92%) were cases of lower GI perforation (below the duodenum), the majority (17) were associated with diverticula [39]. A similar incidence was observed among six Japanese studies (five cases; 2.3 per 1000 patient-years) [173]. As a proportion of these cases occurred during open-label extension phases, a study in the USA aimed to determine risk in the general RA population to allow appreciation of any increased risk associated with tocilizumab *per se* [174]. From US databases, a cohort of 40,841 RA patients (78,384 patient-years) was identified; 37 cases of hospitalization with GI perforation were observed (0.5 per 1000 patient-years), a similar proportion (84%) to that seen with tocilizumab were perforations of the lower GI tract. Multivariate analysis suggested increased risk associated with current treatment with corticosteroids (HR: 4.7; 95% CI: 1.9–12) and previous diverticulitis (HR: 9.1; 95% CI: 3.1–26), but not with current treatment with a biologic or with MTX. Guidelines recommend caution with the use of tocilizumab in patients with a history of any GI disorder that could put them at increased risk of perforation, with those receiving concomitant corticosteroids particularly likely to be at risk [175].

Liver

TNF inhibitor

Hepatotoxicity has been rarely reported with TNFi. Infliximab, in particular, may induce immune-mediated liver disease with a clinical picture similar to autoimmune hepatitis and associated with the presence of anti-dsDNA antibodies [176]. To quantify risk, analyses of the North American registry CORRONA (3461 patients treated with TNFi out of a total 6861 RA patients in the registry) were conducted; rates of liver enzyme elevations with use of individual TNFi was compared with RA patients receiving nonbiologic therapy [177]. Elevations were uncommon (greater than the upper limit of normal in 6% and over two-times the upper limit of normal in only 0.77%). In comparison with patients treated with nonbiologic therapy, there was a higher likelihood of elevations

(greater than the upper limit of normal) with infliximab (OR: 1.6; 95% CI: 1.4–1.9) and adalimumab (OR: 1.4; 95% CI: 1.1–1.7) but not with etanercept. This remained significant when the individual TNFi used in combination with MTX were compared with MTX alone.

Tocilizumab

Tocilizumab is known to cause elevations in liver transaminases. In clinical trials, elevations above the upper limit of normal occurred with tocilizumab monotherapy at a rate similar to MTX monotherapy (~30%), with elevations above three-times the upper limit of normal in 2 and 4%, respectively [39]. Higher rates were seen with the combination of tocilizumab and DMARD therapy (46% had levels higher than normal and 6% had levels greater than three-times normal in tocilizumab 8 mg/kg dose groups). Most of these patients continued on treatment, if at a reduced dose of tocilizumab or with alteration in concomitant DMARD therapy (only 2% discontinued). Importantly, other parameters of liver function such as bilirubin, alkaline phosphatase and albumin were not affected, and no cases of severe liver injury or failure have been reported in the literature. Liver biopsies were performed at the investigators' discretion; of 11 patients biopsied, nine had evidence of steatohepatitis but most of these (seven) possessed at least one other risk factor such as diabetes.

Conclusion

Over 15 years of experience in the use of the longest established biologics (etanercept, infliximab and adalimumab) is now available, with several large patient registries providing a valuable resource for determining safety of these agents. Infection risk remains the major concern, with all currently available therapies increasing this risk, but with certain treatments associated with specific risks (e.g., role of TNFi and mycobacterial infection, B-cell depletion and hepatitis B reactivation). Insight into other concerns, for example malignancy, has generally been reassuring, although increased risk of NMSC with TNFi has emerged with recent data emphasizing the need for continued vigilance. More data and a better understanding of other inflammatory pathologies (e.g., ILD) are needed to clarify the risks associated with the different biologic treatments. As treatment is not allocated at random, confounding by indication is inherent within such data, leading to either an under- or over-estimation of specific adverse events.

Future perspective

Maintaining robust observational registries remains crucial to highlight the safety profiles of the individual biologic therapies and in particular detect rarer adverse events. Future needs include addressing the long-term exposure of the more recently introduced therapies, understanding how specific risks may be associated with targeting different molecules and clarifying whether the different biologic classes may be used safely in the context of comorbidities such as heart failure and demyelination. The challenge of interpretation of registry data with channeling bias of therapies remains and highlights the need for caution in drawing firm conclusions, but also the need for continued advances in analytical techniques (e.g., development of propensity scoring). Our increasing expectations are demanding improved safety profiles from the emerging therapeutic landscape; this, together with a better understanding of the treatments, will optimize the management and outcomes of patients with RA.

Executive summary

- All biologic therapies are associated with an increased risk of infection and must be avoided during severe, active infection.
- Certain infections may be particularly associated with interruption of specific pathways or molecules (e.g., mycobacterial infection and TNF-blockade and hepatitis B reactivation following B-cell depletion).
- The immunomodulatory effect of biologic therapies for rheumatoid arthritis and risk of solid malignancy and lymphoma has not been fully established; evidence to date is reassuring except with nonmelanotic skin cancer, which may be increased with TNF inhibitors (TNFi) infliximab, etanercept and adalimumab.
- Additional information and therefore precaution is needed for the use of biologics and:
  - Demyelinating disorders (with TNFi generally contraindicated);
  - Interstitial lung disease;
  - Congestive cardiac failure (with TNFi contraindicated in moderate and severe cardiac failure (New York Heart Association grade III and IV) and rituximab contraindicated in severe cardiac failure (New York Heart Association grade IV);
  - With tocilizumab, a history of diverticulitis (due to risk of colonic perforation) and active hepatic disease or hepatic impairment (due to risk of increased liver transaminases).
- Further data are needed to determine risk with more recently introduced biologic therapies.

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Medscape EDUCATION Safety of biologics in rheumatoid arthritis

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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. You are seeing a 50-year-old woman with rheumatoid arthritis (RA) who has not responded to treatment with methotrexate alone. She has a complicated medical history, including a history of chronic hepatitis infection and past exposure to tuberculosis (TB).

   You are concerned about the risk of adverse events associated with the initiation of biological therapy for this patient. Which of the following biological therapies is **least** likely to promote a higher rate of serious bacterial infection in this patient?

   - ☐ **A** Abatacept
   - ☐ **B** Adalimumab
   - ☐ **C** Etanercept
   - ☐ **D** Rituximab

2. Which of the following biological agents is **most** likely to promote a higher risk of TB reactivation in this patient?

- ☐ **A** Etanercept
- ☐ **B** Rituximab
- ☐ **C** Adalimumab
- ☐ **D** Abatacept

3. What should you consider regarding the patient's history of viral hepatitis prior to initiating biological therapy?

- ☐ **A** Infliximab does not appear to alter the course of chronic hepatitis B virus (HBV) infection
- ☐ **B** If she is receiving antiviral treatment, it should be continued for 6 months after discontinuation of the biological therapy
- ☐ **C** All biological therapies increase the risk of cirrhosis among patients with chronic viral hepatitis
- ☐ **D** Biological therapy is contraindicated in the setting of chronic hepatitis C virus (HCV) infection

4. The patient is concerned regarding the risk of cancer associated with biological therapy. What can you tell her is the tumor type most closely associated with this therapy?

- ☐ **A** Nonmelanotic skin cancer
- ☐ **B** Hepatocellular carcinoma
- ☐ **C** Acute lymphocytic leukemia
- ☐ **D** Non-small cell lung cancer