Life-Threatening Complications of Biological Therapies

23

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Abstract The last decade was characterized by the successive introduction of several biological agents for the treatment of autoimmune rheumatic diseases (ARD). Randomized controlled trials (RCT) proved them to have globally acceptable safety and tolerability profiles. However, life-threatening complications are rare events and RCT are underpowered to detect them. As these drugs became more widely prescribed in clinical practice, and particularly, having the information from multiple national biologics registries available, serious adverse events became perceptible. Infection remains the major concern, but other serious and life-threatening complications have emerged, such as malignancies, congestive heart failure, demyelinating disorders, and drug-induced autoimmune syndromes. Several of these are correlated with either the underlying disease or concomitant immunosuppressive medication. Most of them can be avoided by the adoption of preventive measures and an early proper management might significantly change the outcome. Awareness of the possible serious side effects is of utmost importance for a safer use of biological agents.

In this chapter, we aim to describe the most commonly reported life-threatening complications of biological therapies in the literature – including those with antitumor necrosis factor agents, rituximab, abatacept, tocilizumab, and anakinra. Risk groups are identified and strategies for the prevention and initial management are included.

Key words Autoimmune diseases • Biologics • Complications • Demyelinating disorders • Drug-induced autoimmune syndromes • Heart failure • Infections • Malignancies • Management • Prevention

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23.1 Introduction

Improved understanding of the immunopathology of various autoimmune rheumatic diseases (ARD), combined with biopharmaceutical development, has led to the introduction of biological therapeutics. These agents target specific components of the immune response (e.g., cytokines, immune cells) that are central to the etiology of the disease process. Biological therapy has brought a paradigm shift in the management of several ARD decreasing the disability and improving quality of life and health outcomes. Biological agents include those that interfere with cytokine function (antitumor necrosis factor-α agents [anti-TNF-α], Tocilizumab, Anakinra); deplete B cells (Rituximab); and downregulate T-cell stimulation (Abatacept) (Table 23.1).[1] The most widely used are TNF-α antagonists.

These therapies have demonstrated acceptable safety and tolerability profiles during randomized controlled trials (RCT). However, RCT are underpowered to detect specific risks (particularly rare events) due to short duration of follow-up, relatively small number of patients studied, and exclusion of those with risk factors for complications. During post-approval surveillance, increased risks of serious infections (including opportunistic), malignancies, congestive heart failure, demyelinating disorders, and drug-induced autoimmune syndromes have been reported.[2-4] Nonetheless, these findings have been inconsistent and the reported risks and frequencies differ widely (Table 23.2).[5-11] Recognized limitations of the different sources of safety data (post-marketing surveillance reports, national registries and meta-analyses), such as lack of a control group and channeling or confounding by indication bias, underlie this variability.[12,13] Different mechanisms of drug action and their diverse pharmacokinetics and pharmacodynamics characteristics influence their safety profile, including the risk of serious adverse events (SAE) (Table 23.1). Patients with ARD have a higher mortality compared to general population, due to increased susceptibility to infections, malignancy, and cardiovascular disorders.[14-17] The underlying immune deregulation of these diseases, the concomitant immunosuppression by conventional disease-modifying antirheumatic drugs (DMARD) and steroids, and the frequent existence of comorbidities are recognized as major factors. These complex interactions make it difficult to ascribe complications solely to biological agents.

Infection remains the major concern of biological therapy, but other – some unexpected – serious complications have emerged as these agents became more widely prescribed. Overall, SAE appear to be rare (Table 23.2), but some are life-threatening, requiring judicious selection of candidates, pretreatment screening and eventual prophylactic measures, close observation during therapy, and careful attention to patient education.

23.2 Life-Threatening Complications of Biological Therapies

In safety reports of biological agents, complications that threaten life or function of a patient are often not specifically analyzed and rather are included in a broader category of SAE, i.e., those that require admission to hospital, are fatal or life-threatening, or result

Table 23.1 Biological therapies most used in autoimmune rheumatic diseases

Biologic agent	Target/affinity	Immune actions	Half-life	Administration	Approved indications[a]
Etanercept (humanized fusion protein)	TNF[b]-α, lymphotoxin-α (TNF-β). Soluble TNF-α	Decreases circulating TNF-α; partial blockade; no lysis of TNF-expressing cells	4 days	Subcutaneous injection of 25 mg/kg twice per week or 50 mg/kg once a week	RA[c], JIA[d], PsA[e], AS[f], plaque psoriasis
Infliximab (chimeric mAb[g])	TNF-α. Soluble and membrane TNF-α	Monocyte and T-cell apoptosis; lysis of TNF-expressing cells	9 days	Infusion of 3–5 mg/kg at 0, 2, 6 weeks and then every 6–8 weeks	RA, AS, PsA, Crohn's disease, ulcerative colitis, plaque psoriasis
Adalimumab (humanized mAb)	TNF-α. Soluble and membrane TNF-α	Lysis of TNF-expressing cells; possible effects on apoptosis, monocytes, and natural killer cells	14 days	Subcutaneous injection of 40 mg every 2 week	RA, PsA, AS, Crohn's disease
Rituximab (chimeric mAb)	CD20-positive B cells	Lysis of CD20-expressing pre-B lymphocytes and mature B lymphocytes; potential modulation of T-cell immunity	3.5–17 days	Two infusions (1 gr) with 2 week-interval	RA
Abatacept (humanized fusion protein)	Selective modulation of CD80/86:CD28 costimulatory signal required for full T-cell activation	Modulates T-cell activation, by inhibiting the "second signal" between T cells and APC[h]	8–25 days	Infusion of 8–10 mg/kg at 0, 2, 4 weeks and then every 4 weeks	RA
Tocilizumab (humanized mAb)	IL-6 receptor	Competitive blocking of IL-6 receptor	5–10 days	Infusion of 4 or 8 mg/kg every 4 weeks	RA; in Japan also: polyarticular or systemic-onset JIA, multicentric Castleman's disease

(continued)

Table 23.1 (continued)

Biologic agent	Target/affinity	Immune actions	Half-life	Administration	Approved indications[a]
Anakinra (recombinant human protein)	IL-1 receptor	Competitive blocking of IL-1 receptor; signal blockade	4–6 h	Daily subcutaneous injection	RA, JIA, Adult-onset Still's disease, CAPS[i]

[a]Approved indications for autoimmune diseases as defined by United States Food and Drug Administration (FDA) and European Medicines Agency (EMEA)
[b]Tumor necrosis factor
[c]Rheumatoid arthritis
[d]Juvenile idiopathic arthritis
[e]Psoriatic arthritis
[f]Ankylosing spondylitis
[g]Monoclonal antibody
[h]Antigen-presenting cells
[i]Cryopyrin-associated periodic syndromes

Table 23.2 Serious adverse events of biological agents as estimated in selected studies

Author (reference)	Biological agent	Disease/number of patients included (*n*)	Serious adverse events
Leombruno et al.[5]	Anti-TNF[a]-α agents	RA[b]; *n* = 5,759 (meta-analysis of 18 RCT[c])	13.9% (anti-TNF at recommended doses) vs 11.8% (control group); OR[d] 1.11 (95% CI[e], 0.94–1.32); RR[f] 0.94 (95% CI, 0.77–1.15)
Dixon et al.[6]	Anti-TNF-α agents	RA; *n* = 7,664	53.2 per 1,000 patient-years (anti-TNF) vs 41.4 per 1,000 person-years (DMARD); adjusted* IRR[g] 1.03 (95% CI, 0.68–1.57)
Cohen et al.[7]	Rituximab	RA; *n* = 520	7% – 5.3 per 100 patient-years (1 g dose) vs 10% (control group)
Keystone et al.[8]	Rituximab (additional courses)	RA; *n* = 1,039 (course 1), 571 (course 2), 191 (course 3), 40 (course 4)	1.5 (0.5–2.9), 1.2 (0.5–2.4), 1.1(0.2–8.0) and 8.0(1.1–56.8)** per 100 patient-years during courses 1,2,3 and 4 (respectively) (95% CI)
Sibilia and Westhovens et al.[9]	Abatacept	RA; *n* = 1,955	14% (10 mg/kg dosage) vs 12.5% (control group)
Emery et al.[10]	Tocilizumab	RA; *n* = 499	6.3% (8 mg/kg dose group), 7.4% (4 mg/kg dose group) vs 11.3% (control group)
Fleischmann et al.[11]	Anakinra	RA; *n* = 1,346	26.5–27.7 per 100 patient-years (3 years) vs 22.3 per 100 person-years (placebo)

[a]Tumour necrosis factor
[b]Rheumatoid arthritis
[c]Randomized controlled trials
[d]Odds ratio
[e]Confidence interval
[f]Risk ratio
[g]Psoriatic arthritis
[h]Incidence rate ratio
*Adjusted for age, sex, disease severity, comorbidity, extraarticular manifestations, steroid use, and smoking
**Rates for course 4 were based on a limited number of patients (12.5 patient-years), and the amount of follow-up was considered by the authors of the study to be insufficient to provide meaningful data and reliably estimate a serious adverse event rate

in persistent or significant disability. Causes of mortality are also frequently not specified. Thus, detailed analysis on life-threatening events is restricted.

Most of the data on SAE of biologics refer to anti-TNF agents and less to Rituximab; so, we focus on these here, with references to other biological agents (Abatacept, Tocilizumab and Anakinra) as appropriate. With respect to ARD, most safety reports refer to patients with rheumatoid arthritis (RA), with less focus on other diseases.

Table 23.3 Potential life-threatening complications of biological therapy

Infections Serious and life-threatening infections Postoperative infectious complications Opportunistic infections Tuberculosis Nontuberculous mycobacteria infections Invasive fungal infections Other granulomatous infections Viral infections Reactivation of chronic viral infections
Malignancies (melanoma)
Anaphylactic reactions Serum-sickness-like reactions
Cardiovascular complications
Autoimmune diseases induced by biological agents Vasculitis Systemic lupus erythematosus Interstitial lung disease
Demyelinating disorders
Other serious complications Cytopenias Hepatotoxicity Pulmonary complications Gastrointestinal perforation

Most frequent life-threatening complications can be included in six broad categories (Table 23.3). Other less frequent potentially fatal adverse events have also been described.

23.2.1 Infections

Infection remains one of the leading causes of morbidity and mortality in autoimmune diseases, particularly RA and systemic lupus erythematosus (SLE), and these patients appear to have increased baseline susceptibility for infection, including serious and opportunistic infections.[14-17] In patients with RA, a twofold increased incidence of infections was estimated in the prebiologics era.[14,18] In SLE, infection is responsible for approximately 25% of all deaths. The prevalence of life-threatening infections appears to be highest within the first 5 years of the disease onset.[15-17] Immunosuppressive therapy, including steroids, also plays a key role.[15,16]

The potential from biological therapies to increase infection risk has been a major concern. They have been associated with a widely variable increased incidence of severe and non-severe infections. An increased incidence of TB and opportunistic infections associated with biologic treatments is evident, and some are fatal. Likewise, new infections or reactivation of latent viral infections resulting in serious complications or death are also

concerning. Concomitance of ARD and chronic viral diseases can be a major problem when additional immunosuppression is added. However, screening strategies and prophylactic measures are effective in reducing these potentially life-threatening complications.

23.2.1.1 Serious and Life-Threatening Infections

Life-threatening infections are included in a broader category of "serious infections," i.e., those fulfilling the criteria for SAE or requiring intravenous antibiotics. Incidence rates of serious infection vary among the studies, and no firm conclusion exists about the overall increased risk of infection in patients on biologics (Table 23.4).[5-7,10,18-26]

An increased risk for serious infections is apparent in patients on anti-TNF therapy (with odds ratios (OR) varying from 1.22 to 2.16), particularly in the first 3 months of treatment and at specific sites of infection (notably the lower respiratory tract and skin/soft tissue) (Table 23.4). Common pathogens prevail (most frequently *Streptococcus pneumoniae* and *Staphylococcus aureus*, respectively). This risk appears to be somewhat higher with anti-TNF monoclonal antibodies (particularly Infliximab), compared to Etanercept, although not all studies agree.[6,20] The large induction dose of Infliximab, Etanercept's lower half-life, and different mechanistic properties between the two anti-TNF antibodies might account for these differences.[6,18,22,26] Life-threatening infections are more common in patients with risk factors (Table 23.5)[18,26] and usually result from disseminated disease and/or severe pulmonary infections progressing to respiratory failure. A common feature in fatal cases is the paucity of signs or symptoms indicating the severity of developing infections. Pneumococcal pneumonias can rapidly progress to fatal acute respiratory distress syndrome (ARDS) and septic shock. Atypical clinical presentation poses a problem in the differential diagnosis with a flare of the underlying disease, as clinical and laboratory signs of infection might be "blunted" in patients on anti-TNF therapy (e.g., absence of fever and elevated acute inflammatory markers). Occasionally, both problems are present. Distinguishing pneumonia and interstitial lung disease secondary to lung involvement and infectious meningitis/encephalitis and central nervous system (CNS) involvement of the diseases can be hard. Estimated death rates attributed to serious infections are generally not available, as these are generally calculated for total SAE. The risk for perioperative infections has rarely been addressed: Two studies showed that therapy interruptions before surgery did not significantly decrease the risk for infectious complications, though a recent study suggested that this risk was twofold lower in patients who stopped the drug for 28 days pre-surgery.[27-29]

Few studies have analyzed rates of serious infections in patients treated with other biologic agents. Results from major RCT in patients with RA[7,8,30,31] and other ARD[32] treated with Rituximab did not show a significant increase in serious infections. Infections of the lower respiratory tract seem more frequent, but are rarely severe. Even the presence of hypogammaglobulinemia (which only occurs with repeated cycles of Rituximab) does not correlate with a significant increase in serious infections. However, levels of the immunoglobulin (Ig) of the IgG isotype below 500 mg/dL are a concern (particularly if sustained for long periods).[33,34] In case reports of patients with severe pneumonia, concomitant immunosuppressives are invariably being taken. Nonetheless, the biologic effects post-Rituximab on memory B cells and Ig levels, with the concomitant modulation of T-cell immunity, require further investigation.[34]

Table 23.4 Rates of serious (including life-threatening) infections in patients with autoimmune rheumatic diseases according to selected published studies and meta-analyses

Author (reference)	Biological agent	Population studied	Number of patients included (*n*)	Serious infections
Bongartz et al.[19]	Anti-TNF-α[a] antibodies (Infliximab and Adalimumab)	RA[b]	*n* = 5,014 with 3–12 months of follow-up; meta-analysis of 9 RCT[c]	OR[d] 2.0 (95% CI[e], 1.3–3.1) in patients treated with anti-TNF antibodies compared to RA controls
Leombruno et al.[5]	Anti-TNF agents (all)	RA	*n* = 8,808 with 7,846 years of follow-up; meta-analysis of 18 RCT	In patients treated with anti-TNF antibodies compared to RA controls: at recommended doses: OR 1.21 (95% CI, 0.89–1.63); at higher doses: OR 2.07 (95% CI, 1.31–3.26)
Listing et al. [20]	Anti-TNF-α agents (Infliximab and Etanercept)	RA	*n* = 858 with a median follow-up < 1 year	In patients treated with anti-TNF antibodies compared to RA controls: adjusted RR[f]: 2.31 (95% CI, 1.4–3.9) for Etanercept vs 3.01 (95% CI, 1.8–5.2) for Infliximab
Dixon et al. [6]	Anti-TNF-α agents (all)	RA	*n* = 8,973 (7,664 in the anti-TNF cohort); median follow-up 1.26 years	Overall serious infections: IRR[g] 1.03 (95%CI, 0.68–1.57) Severe skin/soft tissue infection: IRR 4.28 (95% CI, 1.06–17.17) compared to RA control group
Dixon et al. [21]	Anti-TNF-α agents (all)	RA	*n* = 10,755 (8,659 in the anti-TNF cohort, 2096 in the control group)	*According to* "*at-risk*" *period*: for the whole treatment period – adjusted IRR 1.22 (95% CI, 0.88–1.69); first 90 days after starting the treatment – adjusted IRR 4.6 (95% CI, 1.8–11.9) *According to the anti-TNF agent*: for Infliximab: 95.4/1,000 person-years (95% CI, 75.0–119.2), for adalimumab: 59.9/1,000 person-years (95% CI, 39.8–85.9), for Etanercept: 60.0/1,000 person-years (95% CI, 45.5–77.4)
Askling et al.[22]	Anti-TNF-α agents (all)	RA	*n* = 44,946 (4,167 in the anti-TNF cohort); 7,776 person-years of follow-up	*Rate of hospitalization (anti-TNF cohort vs RA controls) according to period of treatment:* first year – adjusted RR 1.43 (95% CI, 1.18–1.73); second year – adjusted IRR 1.15 (95% CI, 0.88–1.51); after 2 or more years: 0.82 (95% CI, 0.62–1.08)
Curtis et al. [23]	Anti-TNF-α agents (Etanercept and Infliximab)	RA	*n* = 5,195 (Infliximab-treated 850, Etanercept-treated 1,412, control group 2,933)	*According to the anti-TNF agent:* adjusted IRR 2.4 (95% CI, 1.23–4.68) vs 1.61 (95% CI, 0.75–3.47) for Infliximab versus Etanercept (respectively)

Lichtenstein et al.[24]	Anti-TNF-α agent (Infliximab)	Crohn's disease	*n* = 6,290 patients; follow-up 10,000 patient-years; mean follow-up 1.9 years	No increased risk for serious infection (OR, 0.99; 95% CI, 0.64–1.54) Annualized incidence rate within the first 3 months: 1.3% vs 0.7% during the rest of the time
Salliot et al. [25]	Rituximab	RA	*n* = 1,143 (745 treated with Rituximab, 398 in the control group) (meta-analysis of 3 RCT)	2.3% (Rituximab) vs 1.5% (control group); pooled OR 1.45 (95% CI, 0.56–3.73)
Cohen et al. [7]	Rituximab	RA	*n* = 520 (311 treated with Rituximab, 209 in the control group)	Incidence rate: 5.2 (Rituximab) vs 3.7 (control group) per 100 patient-years
Emery et al. [10]	Tocilizumab	RA	*n* = 499	6.3% (Tocilizumab 8 mg/kg), 7.4% (Tocilizumab 4 mg/kg) vs 11.3% (control group)
Salliot et al.[25]	Abatacept	RA	*n* = 2,945 (1,960 treated patients, 985 in the control) (meta-analysis of 5 RCT)	2.5% (Abatacept) vs 1.8% (control group); pooled OR 1.35 (95% CI, 0.78–2.32)
Salliot et al.[25]	Anakinra	RA	*n* = 2,791 (2,062 treated patients, 729 in the control group) (meta-analysis of 4 RCT)	1.4% (Anakinra) vs 0.5% (control group); pooled OR 2.75 (95% CI, 0.90–8.35)

[a]Tumour necrosis factor
[b]Rheumatoid arthritis
[c]Randomized controlled trials
[d]Odds ratio
[e]Confidence interval
[f]Rate ratio
[g]Incidence rate ratio

Table 23.5 Risk factors associated with serious infections in patients treated with biological therapy

Type of serious infections	Risk factors
Common infections	– Comorbidities (e.g., diabetes mellitus, chronic lung disease, chronic renal failure) – Previous splenectomy – Concomitant immunosuppressive medication (particularly steroids) – Immunodeficiency (primary or acquired) – Hypogammaglobulinemia (primary or acquired – e.g., Rituximab) severe (IgG[a] < 500 mg/dL) or prolonged – Elderly – Active underlying autoimmune disease
Opportunistic infections (global risks for all opportunistic infections)	– Immunosuppression: primary or acquired (e.g., exposure to immunosuppressive medication – particularly steroids, HIV[b] infection, transplanted persons) – Comorbidities (chronic renal failure, diabetes mellitus, chronic heart failure, chronic lung disease)
– Tuberculosis	– Birth or extended living in high-endemic country for TB[c] – Risk contacts for TB (recent contact with an active case, history of substance abuse, incarceration, living in homeless shelter or nursing home or contact with persons in these conditions; recent travel in endemic areas) – Occupational exposure to TB (employment in health care system) – Chest radiograph abnormalities (chronic lung disease – particularly silicosis, signs suggestive of previous TB)
– Nontuberculous mycobacteria infections	– Risk exposure (e.g., fishing)
– Invasive fungal infections	– Colonization with pathogenic fungi – History of invasive aspergillosis or other mold infections – Environmental exposure – High-risk travel in endemic area (e.g., histoplasmosis, coccidioidomycosis) – High-risk outdoor activities (e.g., spelunking, cleaning chicken coops, disturbing soil beneath bird-roosting sites) – Occupational exposure (e.g., construction) – Chronic neutropenia and renal dysfunction
– Other granulomatous infections	– Elderly, children, pregnant women, and presence of lymphocytopenia (for *Listeria*) – Exposure to air-conditioning devices (for *Legionella*) – Risky dietary habits (e.g., unpasteurized dairy products, raw eggs or meat, precooked meats, soft cheeses) (for *Salmonella* and *Listeria*)
– Viral infections	– $CD4^+$ T lymphopenia (particularly if <200 cells/mm^3)

[a]Immunoglobulin isotype G
[b]Human immunodeficiency virus
[c]Tuberculosis

Data published on Abatacept indicate an increased risk of serious infection limited to subsets of patients treated concomitantly with another biologic.[35] However, a slightly increased risk for hospitalization with infection was found in a large cohort of patients treated with Abatacept compared to biologic-naïve RA cohorts.[36]

A recent meta-analysis (from 12 RCT performed with Rituximab, Abatacept and Anakinra) did not show an increase of serious infections with Rituximab or Abatacept. Anakinra's increased risk was correlated to the presence of comorbidities.[25]

Studies on Tocilizumab safety did not report an increase in serious infections compared to biologic-naïve RA controls.[10]

Prevention and management: Immunization against *Pneumococcus* is recommended before (2–3 weeks) the initiation of anti-TNF treatment. Exclusion of hypogammaglobulinemia is warranted for candidates to biological therapy (particularly Rituximab) and the evaluation should be repeated before additional courses or in the event of an active infection. A high level of suspicion for infection is necessary, particularly in patients with baseline risk factors (Table 23.5).[18,26] Once symptoms become clinically overt, severe sepsis must be anticipated and immediate discontinuation of the biological therapy (anti-TNF agents) is essential as well as prompt evaluation. Appropriate preemptive antibiotic therapy should be initiated until infection is definitely ruled out. Support treatment with intravenous Ig (IVIg) might be provided as an individual case decision and according to other risk factors.[33]

23.2.2 Opportunistic Infections

As set out above, patients with ARD are inherently prone to infections with opportunistic agents, including mycobacteria, atypical bacteria, virus, fungi, and parasites. The risk increases with biological therapy (Table 23.6).

23.2.2.1 Tuberculosis

For patients with RA, in the prebiologics era, estimated increased risks of Tuberculosis (TB) vary among the studies (between two and up to ninefold)[18,37] and mirror the background prevalence in different countries. In some, where tuberculosis is endemic, the incidence of infection among SLE patients exceeds 5% and commonly it presents in the miliary form with high mortality.[38] Immunosuppressive therapy and notably steroids are known to be associated with miliary or disseminated TB.

TB remains the most frequent opportunistic infection associated with the use of biological therapy, particularly with TNF-α inhibitors (Table 23.7).[37,40-43] TNF is essential to immune defense playing a major role in the recruitment of inflammatory cells to the site of infection and in the granuloma formation and maintenance, which is necessary for containment of intracellular infections. Being born in a TB-endemic country is a major risk factor, which may be elevated up to ~10-fold (OR 10.35; 95% CI, 2.40–44.55).[43] Other frequent

Table 23.6 Most commonly reported opportunistic infections and etiologic agents complicating the use of biological therapy

Opportunistic infections	Etiologic agents (most common)
Tuberculosis infection	*Mycobacterium tuberculosis*
Nontuberculous mycobacteria infections	Nontuberculous mycobacteria (*M. avium species*, *M. chelonae*, *M. marinum*, *M. abscessus*)
Invasive fungal infections	*Histoplasma capsulatum* (endemic areas)[a] *Aspergillus* species *Candida* species *Pneumocystis jirovecii* *Cryptococcus neoformans* *Coccidioides* species (endemic areas)[a] *Zygomycetes* species
Other granulomatous infections (atypical and intracellular bacteria)	*Listeria monocytogenes* *Nocardia* species *Salmonella* species *Legionella* species
Viral infections (disseminated cytomegalovirus infection, herpes zoster, primary varicella-zoster infection)	Cytomegalovirus Varicella-zoster virus
Progressive multifocal leukoencephalopathy	JC virus

[a]Regions in the Ohio and Mississippi River valleys (interior central states of United States of America)

risk factors include older age and concomitant use of corticosteroids (Table 23.5).[40,43] The clinical presentation can be atypical and is dominated by extrapulmonary disease, occurring in 60–70% of cases, with a significant percentage (>25%) of these presenting disseminated TB. Unusual sites of infection (e.g., meningoencephalitis, gastrointestinal, spondylodiscitis) are also more commonly seen. Most cases of TB occur soon after the initiation of treatment, especially with Infliximab. However, a significant number of disseminated TB cases in patients treated with Adalimumab occurred after therapy has been stopped (>3 months).[43]

Whether the risk of TB infection is a class effect of the anti-TNF agents is still debated, although most studies conclude that treatment with anti-TNF monoclonal antibodies confers a higher risk of this complication (up to three- to fourfold in most reports) (Table 23.7).[37,40,44] Different drug pharmacokinetics/pharmacodynamics and mechanisms of action (e.g., antibodies' apoptosis-inducing activity, different avidities of the agents for soluble *versus* transmembrane TNF, and the irreversibly high and fast binding to TNF exhibited by Infliximab compared with Etanercept) potentially explain the dissimilar risks of TB development.[44] A dissimilar action of the two types of anti-TNF agents on specific effector T cells and Treg cells has also been suggested.[43] In addition, differences in the time to develop TB are apparent. For Infliximab, most cases occur sooner after the treatment (first 90 days) than for Adalimumab and Etanercept (median interval above 1 year). These

Table 23.7 Risk of tuberculosis associated with antitumor necrosis factor α agents according to selected studies

Author (reference)	Source of data	Estimated risk of tuberculosis
Wolfe et al.[39]	United States of America national database	Latent TB[a] (before and post-introduction of Infliximab): 6.2 cases per 100,000 RA[b] patients *versus* 52.5 cases per 100,000 patient-years (respectively)
Dixon et al.[40]	BSRBR[c]	For Adalimumab: 144 events/100,000 person-years (pyrs); for Infliximab: 136/100,000 pyrs; for Etanercept: 39/100,000 pyrs. Compared to Etanercept: adjusted IRR[d] 3.1 (95% CI[e], 1.0–9.5) for Infliximab and 4.2 (95% CI, 1.4–12.4) for Adalimumab.
Gomez-Reino et al.[41]	Spanish national database (BIOBADASER[f])	Risk ratio of TB: 90.1 (95% CI, 58.8–146.0) for Infliximab-treated RA patients *versus* the general population and 19.9 (95% CI, 16.2–24.8) *versus* patients with RA treated with non-biologic therapy
Seong et al.[42]	Korean cohort	Adjusted RR[g] for TB of 30.1 (95% CI, 7.4–122.3) compared with the general population
Tubach et al.[43]	French national biologics registry (RATIO[h])	For all anti-TNF[i] agents: SIR[j] 12.2 (95% CI, 9.7–15.5) in patients with various autoimmune diseases For Infliximab: SIR 18.6 [95% CI, 13.4–25.8] and Adalimumab: SIR 29.3 [95% CI, 20.3–42.4] *versus* SIR 1.8 [95% CI, 0.7–4.3], for Etanercept
Askling et al.[37]	Swedish biologics register (ARTIS[k])	For Infliximab: 145 per 100 patient-years (95% CI, 58–129) *versus* Etanercept: 80 per 100 patient-years (95% CI, 16–232)

[a]Tuberculosis
[b]Rheumatoid arthritis
[c]British Society for Rheumatology Biologics Register
[d]Incidence rate ratio
[e]Confidence interval
[f]Spanish Society for Rheumatology Biologic Products Database ('*Base de Datos de Productos Biológicos de la Sociedad Española de Reumatología*')
[g]Rate ratio
[h]French Research Axed on Tolerance of Biotherapies registry,
[i]Tumor necrosis factor
[j]Standardized incidence ratio
[k]Antirheumatic Treatment in Sweden

differences suggest that Infliximab-related TB cases are particularly related to reactivation of latent TB, whereas the linearity of the TB infection curve until late phases of treatment with Etanercept is related to reactivation and probably to new infections.[44] Screening procedures for the diagnosis and proper treatment of latent TB before initiating anti-TNF therapy reduce significantly the incidence of the infection.[45,46] However, cutaneous anergy

is more common in RA patients. Indeed, studies from the French registry report that two-thirds of TB cases during anti-TNF therapy occurred in patients with negative tuberculin skin testing (TST) at screening.[43]

The frequent atypical presentations, the potential false-negative screening tests, and the occurrence of TB after discontinuation of anti-TNF therapy warrant a high level of suspicion for the possibility of this infection, when using these drugs, particularly monoclonal antibodies.

Prevention and management: Screening for latent TB is mandatory before initiation of anti-TNF therapy. Careful assessment of risk factors is required (Table 23.5). The threshold for considering latent TB should be lowered in high-risk patients (considering as positive an induration ≥5 mm in the TST). Blood-based diagnostic assays, such as QuantiFERON-TB or T-Spot TB, have greater specificity and are preferred in patients previously vaccinated with bacille Calmette-Guérin (BCG), as false-negative TST results are more common among them. A diagnosis of latent TB warrants the exclusion of active infection before initiation of prophylactic medication. The optimal interval between initiation of preventive treatment and starting TNF blockers is unknown, but observational data suggest that initiating anti-TNF therapy after 1 month of prophylactic treatment for latent TB substantially decreases the risk of reactivation. Likewise, the lag period between initiation of treatment of active TB and starting anti-TNF agents is not defined, but this appears safe after 2 months of treatment for TB.[1] Precise guidelines on re-testing patients are not defined, but latest recommendations suggest that in areas of high TB prevalence, or in the event of potential TB exposure, repeat testing should be considered.

Few cases of TB infection associated with treatment with other biologic agents (Rituximab, Abatacept and Tocilizumab) have been described, and most studies report the absence of TB infections subsequently.[7,8,18,30,47,48] Most patients included had already been screened for latent TB for previous biological therapy (anti-TNF agents) and those with latent infection were excluded in most major RCT with newer biologics; this fact helps to explain the difference in incidence rates compared to anti-TNF agents. However, some studies included patients without previous screening for latent TB and the results have not shown an increased incidence of TB infection. Differences in the mechanism of action between these new agents and anti-TNF drugs might also cause variance in the risk. Screening for TB is now recommended before initiating treatment with Abatacept and Tocilizumab but not with Rituximab.[1]

23.2.2.2 Other Opportunistic Infections

Increasing incidence of other opportunistic serious infections has been seen in patients on biological therapy. Some carry high rates of mortality. Particularly, important high risk factors are inherent impairment in cellular immunity, especially $CD4^+$ T-cell lymphopenia, and prolonged immunosuppression, most notably with steroids.

Many pathogens causing opportunistic infections have been reported in patients receiving biological therapies (Table 23.6).[3,18,26] The most common are infections by mycobacteria other than TB, invasive fungal infections, and other granulomatous infectious diseases and viral infections.

Nontuberculous Mycobacteria (NTM)

Recent reports on NTM infections in patients receiving mostly anti-TNF agents, but also B-cell depletion therapy, have increased substantially.[18,49] These pathogens most frequently cause a serious infection, with nearly half of the patients presenting with extrapulmonary or disseminated disease. Admission to hospital is often needed, and relatively high mortality rates (9–15%) have been seen. In patients without disseminated disease, the most commonly affected organ is the lung, particularly in those with previous pulmonary disease. *Mycobacterium avium* is the most commonly reported pathogen. TNF inhibitors, and especially Infliximab, are the agents most frequently implicated agents. Unlike TB infection, much longer median periods (18–43 weeks) between the start of drug use and infection diagnosis are described. Whether this is due to newly acquired infections during biological therapy or to reactivation of pretreatment undiagnosed pulmonary infection, remains unclear. Most of the existing studies on NTM infections are based on data from spontaneous reporting; thus, the actual number of cases is likely to be underestimated.

Invasive Fungal Infections (IFI)

These opportunistic infections in patients on biological therapy have been reported increasingly in recent years.[4,18,26,44,50,51] Published information is limited mainly to case reports and case series, and most data are derived from voluntary reporting systems; so, the true incidence is unknown. The most common IFI is histoplasmosis, followed by aspergillosis, candidiasis, and pneumocystosis. Histoplasmosis and coccidioidomycosis occur mainly in patients living in, or coming from, high-endemic geographic regions in the Ohio and Mississippi River valleys (interior central states of United States of America). *Aspergillus* species are ubiquitous worldwide in the environment. Serious *Pneumocystis jirovecii* (formerly *Pneumocystis carinii*) infections have been linked to anti-TNF agents and more recently to B-cell depletion.[9,26] Concomitant immunosuppressive therapy is an additional major factor in nearly all cases of IFI.

Most of these infections involve the lung or present as disseminated disease. The clinical course, in patients on TNF blockers, is often serious or fulminant and the diagnosis might be challenging due to a paucity of early signs and symptoms of infection (a consistent feature of the descriptions) and the similarity of presentation of some cases to flares of underlying diseases. High rates of mortality are reported in patients receiving biologic treatment diagnosed with IFI, particularly with respect to aspergillosis, disseminated candidiasis, and cryptococcosis (ranging from 50% to 100%), and somewhat less with histoplasmosis (20%).[50,51] The time for recognition and treatment appears to influence significantly the clinical course and outcome. Host conditions (e.g., neutropenia, environmental exposure) are also determinant factors in the severity of IFI.[51] Infliximab is the biologic agent most commonly reported (an estimated increased risk of granulomatous infections 3.25-fold higher with Infliximab *versus* Etanercept is reported[26]), but all anti-TNF agents and the other biologic agents may be implicated. Most infections occurred soon after the start of treatment, particularly with Infliximab (median: ≤3 infusions).[26,50,51]

Close surveillance, a high level of suspicion, and prompt treatment of these life-threatening complications are essential, particularly in high-risk populations (Table 23.5).

Prevention and management: To date, there is no reliable method to screen patients before starting anti-TNF therapy, to predict their risk for IFI, partially because most of them are *de novo* infections. Screening for risk factors is essential (Table 23.5). Patients on treatment are recommended to avoid high-risk activities associated with the endemic mycosis in their geographic areas (Table 23.5).[50,51] Physicians should maintain a high level of suspicion for the possibility of IFI, particularly when patients present with respiratory and/or atypical symptoms. Discontinuation of TNF antagonists is warranted and targeted anti-fungal therapy should be started promptly in a patient with signs of serious infection, not improving while on appropriate antibiotics for common infections, particularly if no pathogen is isolated. Uncertainty remains about when the high-risk period abates after TNF blockade, and thus the question of when it is safe to restart these drugs (if at all) cannot be answered easily.

Other Granulomatous Infections

Intracellular bacteria, such as *Listeria*, *Salmonella Nocardia*, and *Legionella* species (among others), have been linked to disseminated life-threatening infections in patients treated with anti-TNF therapy.[4,18,26,47] *Listeria* infection was found to occur at a higher incidence among patients on this therapy when compared to healthy and biologic-naïve RA populations in Spain. Estimated rate ratio (RR) for acquiring *Legionella* pneumonia in patients treated with TNF antagonists was between 16.5 and 21.0 in a recent French study.[18] For most other pathogens, however, there are no studies comparing frequencies of infection in patients receiving biologics to those given conventional DMARD.

Viral Infections

Serious viral infections, including primary varicella, herpes zoster, and cytomegalovirus infections, have been reported, especially after treatment with anti-TNF monoclonal antibodies and, to a lesser extent, Rituximab. Fatal or life-threatening cases are related to disseminated disease or involvement of major internal organs (e.g., pneumonia, fulminant hepatitis).[4,48,52] Influenza can also cause serious infections in these patients and is associated with secondary bacterial infections, which may progress to sepsis.[26]

An FDA alert in 2006 about the possibility of Progressive Multifocal Leukoencephalopathy (PML) in patients with ARD receiving B-cell depletion raised an additional concern. PML is a rare, serious, and usually fatal demyelinating disease, which occurs upon reactivation of JC virus, predominantly in severely immunosuppressed populations (such as persons infected with human immunodeficiency virus (HIV)). Up to 92% of the adult population is seropositive for JC virus, without clinical disease. However, recent reviews found that immunosuppressed persons other than HIV-positive, notably those with ARD, may have an intrinsically raised risk of developing PML. It appears that SLE patients are at the highest risk.[53]

As a complication of Rituximab therapy, it was first described in oncology. More recently, five cases of PML have been reported (as of February 2010): two in patients with

SLE and one case each in other three different ARD.[54,55] Median time from last Rituximab dose to PML diagnosis was 5.5 months, and the median time to death was 2 months. The mortality rate reached 90%. $CD4^+$ T lymphopenia was associated with cases occurring sooner after the treatment and carrying higher mortality.[54] All patients were receiving concomitant immunosuppressive therapy, at varying intensities. The link between Rituximab use and the development of PML is unclear, as more than 20 patients with SLE *not* taking Rituximab have been reported to develop PML. Close surveillance remains necessary though, as early diagnosis is crucial. However, differentiating PML from the new-onset or exacerbation of CNS complications in various ARD can be difficult, such as in acute neuropsychiatric SLE or CNS vasculitis.[53,54]

Despite the possibility of underlying undiagnosed PML as the etiology of some cases of demyelinating disorders occurring in patients on anti-TNF therapy, so far, there are no reports of confirmed PML associated with these agents.[56]

Prevention and management: Influenza vaccination should be provided to candidates to anti-TNF and Rituximab therapies. $CD4^+$ T lymphopenia $<200/mm^3$ precludes B-cell depletion therapy. New-onset or aggravated neurological symptoms and signs in patients on biological therapy should raise the possibility of PML as a potential cause. Neuroimaging studies and a Neurology opinion can help in the differential diagnosis. The gold standard for the definitive diagnosis relies on brain biopsy with histological and virological examinations. However, less invasive detection of JC virus DNA (by protein chain reaction analysis) of the cerebrospinal fluid has a high specificity (though lower sensitivity), being the most commonly used test. Prompt efforts at immune reconstitution may improve survival rates, as currently available antiviral treatment appears essentially ineffective.[54,55]

23.2.3 Reactivation of Chronic Viral Infections

Hepatitis B virus (HBV) reactivation with hepatic failure or fulminant hepatitis (resulting in death or hepatic transplantation) has been reported following Rituximab and anti-TNF therapy (particularly with Infliximab).[26,47,57,58] Cases reported include patients who were inactive or occult carriers (hepatitis B surface antigen (HBsAg)-negative, HBsAg antibody-positive).[58] With Rituximab, this complication has been seen more frequently, but not exclusively, in cancer patients on concomitant chemotherapy. The median time to diagnosis of hepatitis is approximately 4 months after initiation of treatment and approximately 1 month after the last dose. In patients on anti-TNF therapy, HBV reactivation more often occurs after the second or third treatments, but surprisingly it has also been seen (though less frequently) after the discontinuation of treatment.[58] Concomitant immunosuppressives were invariably present, making a causal relationship with biologics less clear-cut.

Prevention and management: Hepatitis B virus status should be assessed before treatment with anti-TNF and Rituximab therapy. Both are usually contraindicated, if active infection is detected and should be used with caution in inactive HBsAg carriers.[1,58] These patients should be closely monitored for clinical and laboratory signs of active hepatitis, as the risk of reactivation seems to be high. Although the prophylactic treatment (specifically with lamivudine) is not agreed, much evidence suggests its efficacy in significantly

reducing this risk during both biological therapies and it probably should be given for a long time after TNF inhibitors are discontinued.[57,58]

Anti-TNF and Rituximab therapies have been both used safely for the treatment of hepatitis C virus (HCV)–induced cryoglobulinemic vasculitis (more frequently with concomitant antiviral therapy) and in HIV patients (anti-TNF agents), without complications.[26,59-61]

23.3 Malignancies

Epidemiological studies have demonstrated an increased baseline incidence of malignancies in several ARD.[14,62] In RA patients, cancer is estimated to be the second most common cause of mortality, and lymphoma has a prevalence twice as high as healthy controls. Lung and skin cancers are also more prevalent. This risk seems to be correlated with the disease severity. In SLE, the risk of lymphoma (notably non-Hodgkin lymphoma) is also significantly increased (estimated prevalence rates up to fourfold), and to a lesser extent lung cancer (though in this case, smoking appears to be a more important risk factor).[62] The relative contribution of DMARDs seems to be modest, with cyclophosphamide being the most likely "culprit."

Does biologic therapy carry a potential increased cancer risk? While earlier studies and meta-analysis of RCT[5,19,63] indicated the possibility of an increased risk of several types of cancer, and particularly of lymphoma, in patients treated with anti-TNF therapy (particularly with higher doses), observational data and posterior studies (which included larger cohorts and longer follow-up periods) have not been able to replicate these findings.[64-66] Overall and based on the results of the most reliable latest studies, the use of TNF antagonists appears to be associated with slightly increased risk only of skin malignancies (namely, non-melanotic skin cancer OR 1.5, 95% CI 1.2–1.8 and melanoma OR 2.3, 95% CI 0.9–5.4).[66] This increased risk appears to affect predominantly patients with previous history of melanoma. Patients with low risk for malignancy treated with TNF blockers do not seem to be at an increased risk for other solid cancers nor for any major further increase in the already elevated lymphoma occurrence in RA. No trend toward an increased incidence or relative risk seems to exist over time (6 years posttreatment) either.[64]

23.3.1 Prevention

At present, cancer screening in all candidates for anti-TNF therapy is essential. In those with recent history (<5 years) of treated malignancy or current diagnosed cancer, other treatment options should be considered. Vigilance during therapy for the occurrence of malignancies (including recurrence of solid tumors) remains appropriate in patients with risk factors for cancer (e.g., smokers, chronic obstructive pulmonary disease, remote history of skin cancers).[1]

There is no convincing evidence of an increased risk of malignancies in patients treated with the new biological agents (Rituximab, Abatacept, Tocilizumab).[48,67,68] Larger studies and with longer follow-up periods are needed however.

23.4 Serious Anaphylactic Reactions

Severe anaphylactic reactions are rare events during therapy with biologic agents, but if they do occur, are potentially life threatening. Most data comes from case reports and RCT. Few of the meta-analyses and post-approval studies have analyzed this problem.

Anti-TNF agents are the most frequently implicated, particularly Infliximab.[2,4] Acute severe infusion reactions are more common (up to 2–3%). They occur during the administration of the drug and usually present with symptoms of bronchospasm, hypotension, and erythematous rash, that may evolve to anaphylactic shock with respiratory failure. In such instances, therapy should be stopped and supportive or emergent care should be administered until patient stabilisation. Infliximab infusions should thus be given with trained medical personnel in attendance with access to parenteral corticosteroids, diphenhydramine, and epinephrine. Delayed hypersensitivity infusion reactions (occurring 2–12 days after infusion) are more rare (<1%) and seem to be mediated by different pathophysiological mechanisms (involving immunoglobulin E). Clinical features are similar to those described for acute reactions, but rapidly progressing interstitial lung disease with ARDS and respiratory failure seem more common. Most events occurred with the third or fourth infusion. Histologically available data revealed eosinophilic pneumonia, and human antichimeric antibodies (HACA) also appear to be common.[4] Most reports refer to patients with Crohn's disease with long treatment-free intervals, but similar reactions in patients with other autoimmune diseases treated with Infliximab are recognized. Mortality rates are not reported but fatal cases have been described and most needed admission to intensive care units. Other anti-TNF agents have not been associated with this type of life-threatening reactions.

Severe acute reactions to Rituximab have been described mainly in oncology. A cytokine release syndrome appears to be the cause, resulting in severe pulmonary and cardiovascular infusion–related events, within 24 h of the drug administration. In patients with ARD, few rare fatal cases of ARDS and cardiogenic shock have occurred, despite the administration of pre-medication.[69]

In RA patients treated with Abatacept, extremely rare cases of severe, but not fatal, infusion reactions are reported with hypotension and bronchospasm.

23.4.1 Serum-Sickness-Like Reactions

This type of delayed hypersensitivity reaction may be associated with rapidly progressing severe complications of biologics and have been reported most frequently with B-cell depletion therapy. The differential diagnosis with flares of the underlying disease can be difficult, as the clinical presentation is frequently nonspecific. In patients on anti-TNF agents (mainly Infliximab), this SAE is often associated with the development of antibodies against Infliximab.[2]

With Rituximab, the association with HACA is not as clear-cut. In SLE, HACA (with an estimated prevalence around 9%) seem important in the development of this complication

and are associated with previous low-dose treatment and absence of pre-medication. Serum-sickness reactions are particularly frequent in Rituximab-treated patients with Sjögren's syndrome (SS) (10–20%) and those with HCV-induced vasculitis also seem susceptible. Identified risk factors include prominent hypergammaglobulinemia and high baseline cryocrit. A short period (e.g., 5 days) of intermediate dose of oral steroids following the drug infusion for SS patients and plasma exchange treatment prior to infusion in HCV-induced vasculitis are suggested to prevent this complication in high-risk patients.[70,71]

23.5 Cardiovascular Complications

Cardiovascular disease plays a major role in the increased morbidity and mortality associated with ARD. It is the most common cause of death among RA patients and one of the leading causes in SLE, particularly late in the disease course.[14,17,72-74] Traditional cardiovascular risk factors (such as smoking, diabetes, hypertension, and obesity) cannot explain this increased risk, alone.[74] Although the use of corticosteroids is an important risk factor, chronic systemic inflammation is assumed to play an important role, partly through the action of pro-inflammatory cytokines. TNF-α is a mediator of endothelial dysfunction, vascular instability, and disease progression in atherosclerosis and is known to contribute to the progression of heart failure.[73,74] However, Etanercept and Infliximab treatments for severe heart failure have not been successful.[73]

The issue of prescribing anti-TNF agents to patients with diagnosis of or risk factors for heart failure is controversial. There have been several post-marketing reports of new-onset and worsening of congestive heart failure (CHF) in patients receiving anti-TNF therapy, including cases of *de novo* CHF in young patients without identifiable cardiovascular risk factors.[2,3] The median interval from the first dose of TNF antagonist to a diagnosis of new-onset or exacerbation of CHF was 3.5–4 months (ranging from 24 h to several months). In some cases, symptoms and signs of CHF disappeared completely with the discontinuation of the drug, suggesting a potential causative role for TNF antagonists. Rare fatalities were also reported.

Recent studies indicate that anti-TNF treatment in patients with RA is more likely to be beneficial than harmful with respect to the risk of CHF (through suppression of inflammation), particularly if there is no concomitant therapy with corticosteroids.[73] Furthermore, it was also shown that TNF inhibition does not increase the risk of exacerbating prevalent CHF and it may produce an early (by 6 months) reduction in myocardial infarction in those patients that respond to treatment.[73,74]

Prevention and management: In patients with history of advanced CHF (New York Heart Association (NYHA) class III or IV), consideration of other treatment options seems the best approach and anti-TNF agents should be used with caution in patients with milder CHF with close monitoring for their cardiac status during therapy, particularly if higher doses are used.[1]

Patients with preexisting cardiac arrhythmias and angina have had recurrences of these events during Rituximab infusions. Arrhythmias reported include ventricular tachycardia, supraventricular tachycardia, and trigeminy. Angina and myocardial infarction have been

rarely reported following its administration. Rare, fatal heart failure with symptomatic onset weeks after Rituximab has occurred. It remains unknown what, if any, role the drug had in these incidents. Patients with ARD who develop significant cardiopulmonary events should have Rituximab discontinued, and it should be used with caution in those with severe CHF (NYHA class IV).[1]

No significant increased short-term risk of serious cardiovascular events has been reported, so far, in association with Abatacept and Tocilizumab.[9,48]

23.6 Autoimmune Diseases Induced by Biological Therapies

Although a variety of autoantibodies have been noted to develop after the introduction of TNF-α blockers,[3,4,75,76] the appearance of clinical autoimmune syndromes is much less frequent (vasculitis up to 3.9%, lupus <0.5%). Most cases are mild diseases, which resolve after discontinuation of the drug.[2,4,75] Nevertheless, a growing number of reports of autoimmune processes related to TNF antagonists use have documented rare cases with serious, life-threatening or even fatal complications.[75] The most frequent clinical presentations consist of vasculitis – with an impressive ~25% having extracutaneous involvement (peripheral and central nervous system, renal and lung) – lupus-like syndromes and SLE (with articular, cutaneous, and constitutional symptoms, being the most common features) and interstitial lung disease (ILD). Less frequent clinical features include inflammatory myopathies, antiphospholipid syndrome, and autoimmune hepatitis.[75] The three anti-TNF agents display different risks for the diverse autoimmune disorders, with Infliximab being the most frequently implicated, except for vasculitis where Etanercept has the strongest association. The interval between administration of the drug and the appearance of the autoimmune syndrome varies between 6 and 10 months. Generally, these disorders are self-limiting after stopping anti-TNF therapy but may require corticosteroids and immunosuppressive treatment.[75,76] However, significant morbidity and mortality has also been seen. Reported causes of death were related to renal involvement of vasculitis, with rapidly progressive anti-neutrophil cytoplasmic antibodies (ANCA)-positive glomerulonephritis, and relentless progression of interstitial lung disease.[75] A case series found a significant poor prognosis in patients with induced ILD in spite of cessation of anti-TNF therapy and initiation of corticosteroids and immunosuppressives, with more than one half of patients showing no resolution and ~33% dying.[75]

Precise etiopathogenic link between these autoimmune diseases and TNF blockade remains unclear. An underlying predisposition of some patients for a second autoimmune disease (particularly in RA), given that some of them already had these autoantibodies prior to the anti-TNF therapy and the contribution or synergistic action of concomitant medication (particularly methotrexate in ILD) are confounding factors.[75,76] With respect to lupus, some authors refer to a new concept – anti-TNF-induced lupus (ATIL) – as being apparently distinct from classical drug-induced lupus (DIL) and with a phenotype more similar to idiopathic SLE (namely: cerebral and renal involvement and anti-double-stranded DNA (dsDNA) antibodies are more common, while anti-histone antibodies are less frequent, when compared to classical DIL).[76]

Prevention and management: Careful clinical and immunological screening for features suggestive of the existence of undiagnosed autoimmune disease prior to and during anti-TNF therapy is important. Screening of candidates for underlying ILD is recommended, particularly in those receiving methotrexate. Anti-TNF agents should not be used in patients with preexisting interstitial pulmonary disorders. Confirmation of an autoimmune disease induced by these agents should be followed by the drug withdrawal, unless the symptoms are very mild.[75]

The other biological therapies (Rituximab, Abatacept, Tocilizumab) have rarely been reported to induce autoantibody formation or clinical manifestations (e.g., skin vasculitis with Rituximab). Serious/life-threatening autoimmune syndromes do not appear to be associated with their use.[1,9]

23.7 Demyelinating Disorders

Concerns about potential serious neurological adverse events have been raised since the first reports on demyelinating disorders occurring in patients treated with anti-TNF antagonists a decade ago.[77] Several reports have since described the new-onset or exacerbation of both peripheral and central demyelinating disorders in small numbers of patients receiving anti-TNF therapy.[1-4] These include new-onset optic neuritis, *de novo* multiple sclerosis (MS), recurrence or flare of MS, encephalitis, myelitis, Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy, neuropathy, transverse myelitis, and leukoencephalopathy, while receiving either three of the anti-TNF agents. Etanercept has been the most often drug implicated, particularly in CNS adverse events. The mean time to symptom onset from initiation of therapy is 5 months, ranging from 1 week to 15 months.[77] Most cases show changes in magnetic resonance imaging consistent with demyelination. Other than a prior history of MS or other demyelinating diseases, no predictive factors have been identified and cases exist in patients with no history of neurological disorder.[3] In most cases, symptoms improve or resolve with cessation of therapy, but rarely neurological deficits persist. The etiopathogenesis of these demyelinating disorders occurring in patients receiving TNF inhibitors is not fully understood.

Apart from the PML cases reported in association with Rituximab (see Sect. 23.2.2.2.4), no other serious neurological adverse events have been reported in patients on the other biological agents.

Prevention and management: Anti-TNF therapy should be avoided in patients with history of central demyelinating disorders and used with caution in those with a positive family history. Patients should be carefully monitored for the development of neurological symptoms and signs while receiving TNF antagonists and these should be discontinued when clinical signs of white matter injury appear. It is probably not safe to continue to use or readminister the drug to patients who develop significant CNS adverse reactions.[1,3,77] Some authors also recommend an evaluation for JC virus infection, when features of leukoencephalopathy predominate, although, so far, confirmed PML has not been associated with TNF blockers use.[57,78]

23.8 Other Serious Complications Associated with Biological Agents

Other, rarer but potentially life-threatening, adverse events have been reported in association with the use of biologics. Some of these were unexpected and only revealed in post-marketing surveillance reports.

23.8.1 Cytopenias

Pancytopenias or cytopenias of only one cell lineage (especially thrombocytopenia) have rarely been ascribed to all anti-TNF agents use and isolated cases of aplastic anemia were also seen with Etanercept.[1-4] A minority of these resulted in death. Cytopenias developed more frequently in few weeks after therapy initiation (but the interval time can be as long as 30 weeks) and usually resolved with discontinuation of the drug. However, some patients required corticosteroids or IVIg for treatment. The reasons linking the cytopenias and TNF blockade remain unclear and concomitant medication or other comorbidities may also be responsible.[3] Periodic monitoring (every 3–6 months) of blood cell counts is suggested as well as close surveillance for clinical features of blood dyscrasias.[2]

Severe (grade 3 or 4) cytopenias (most commonly lymphopenia) following Rituximab administration have been observed essentially in oncology, where confounding factors for the etiology (including concomitant chemotherapy and reactivation of Parvovirus B19 infection) are important.[26] However, a specific complication of this biological agent – late-onset neutropenia (LON) – has been recognized and reported in patients receiving B-cell depletion for the treatment of ARD.[79] It occurs usually 40 days (or more) after the last dose of rituximab (ranging from 2 to 6 months) and the median duration is 10 days. In some cases, it can be accompanied by serious complications, such as febrile severe neutropenia (requiring growth-factor support) or serious infections. The underlying mechanism is unknown. Some authors report that patients with autoimmune blistering skin diseases (particularly Pemphigus vulgaris) might be more susceptible.[79]

Neutropenia has been frequently reported following treatment with Tocilizumab but severe neutropenia is rare (<1%) and it has been demonstrated not to be associated with increased likelihood of developing serious infection.[1]

23.8.2 Hepatotoxicity

Rare reports of liver failure or severe hepatic toxicity have been associated with TNF inhibitors use (particularly Infliximab). The most serious include cases of acute liver failure and fulminant hepatitis, which occurred between 2 weeks and over a year after initiation of therapy and less frequently after its discontinuation.[1,2,4] Some cases were fatal or required liver transplantation.[2,4] The etiology is not clear and confounding factors or

hepatoxin exposure (e.g., sepsis, TB, isoniazid and other hepatotoxic drugs, alcohol hepatitis) may play a role. Severe or fatal reactivation of hepatitis B virus (HBV) in chronic carriers was the attributed cause in some cases (see Sect. 23.2.3).[4,57] However, in some patients, no other cause could be identified, thus suggesting a causative role for anti-TNF therapy.[2] TNF inhibitors should be stopped in patients with significant elevation of liver enzymes (>5 times the upper limit of normal).[1,4,57]

Fatal cases of fulminant hepatitis have also been reported in patients treated with Rituximab, but virtually all are associated with reactivation of HBV infection (see Sect. 23.2.3).

23.8.3 Pulmonary Complications

Rare instances of acute, severe and sometimes fatal interstitial lung disease (ILD) have been reported in patients using all TNF-α inhibitors.[1,80] Most patients had underlying previous mild or asymptomatic lung disease and/or were receiving pneumotoxic agents (e.g., methotrexate) concomitantly. However, cases without these risk factors have also been reported. Most cases occur after the second or third treatments. Histologically, usual interstitial pneumonia (UIP) has been the most frequent finding, particularly in the fatal cases[80]; less frequently, bronchiolitis obliterans organizing pneumonia (BOOP) has been found. The pathophysiology of the pulmonary insult is unknown, and in some cases, it may be autoantibody mediated. Caution and close screening before and after initiation of anti-TNF therapy is recommended, particularly in patients with previous history of lung disease and/or concomitant pneumotoxic medication. However, excluding an infectious complication (with particular focus for atypical pathogens) is mandatory before assuming any other diagnosis,[81] particularly if treatment with corticosteroids is being considered.

Cases of drug-induced lung disease have also been reported in association with Rituximab therapy and with significant mortality (18%).[69] Three "time-to-onset" patterns were documented. The most common presentation was acute/subacute hypoxemic BOOP, starting 2 weeks after the last infusion, usually resolving upon starting glucocorticoid therapy. Other cases referred to acute (within a few hours) ARDS (probably related to an infusion reaction) and delayed macronodular organizing pneumonia. The pathogenic mechanisms are not clear and most probably differ among the cases with different "time-to-onset." Monitoring during and after the Rituximab infusion is recommended, particularly in those patients with reversible "allergic-like" respiratory symptoms in previous administrations.

23.8.4 Gastrointestinal Perforation

Rare cases of upper and lower gastrointestinal perforation in patients treated with Tocilizumab have been reported. Some of these were fatal.[1,82] Risk factors are comorbidities (particularly, history of diverticulosis/diverticulitis and peptic ulcer) and concomitant medication (mostly corticosteroids and nonsteroidal anti-inflammatory drugs).

The relative risk is still not well characterized. Caution is recommended when considering the use of Tocilizumab in patients with history of diverticulitis or intestinal ulceration and, during therapy, prompt evaluation of patients with suggestive symptoms should ensue.[1,82]

23.9 Summary

Biological therapy is generally safe, particularly when compared to conventional DMARD therapy. Serious adverse events appear to be rare, but are potentially associated with life-threatening conditions. Several of these are correlated with either the underlying disease *per se* or the concomitant medication use. Most of them can be avoided by the judicious selection of candidates and adoption of preventive/prophylactic measures. The outcome may be significantly changed by close vigilance and an early proper management. Awareness of the possible serious side effects when using biological therapy is the first essential step for its safer use in patients with autoimmune diseases.

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