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Review article

Is there a real risk of bacterial infection in patients receiving targeted and biological therapies?

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ABSTRACT

Over the past decades, the advent of targeted and biological therapies has revolutionized the management of cancer and autoimmune, hematological and inflammatory conditions. Although a large amount of information is now available on the risk of opportunistic infections associated with some of these agents, the evidence regarding the susceptibility to bacterial infections is more limited. Biological agents have been shown to entail a variable risk of bacterial infections in pivotal randomized clinical trials and post-marketing studies. Recommendations on risk minimization strategies and therapeutic interventions are therefore scarce and often based on expert opinion, with only a few clear statements for some particular agents (i.e. meningococcal vaccination for patients receiving eculizumab). In the present review the available information regarding the incidence of and risk factors for bacterial infection associated with the use of different groups of biological agents is summarized according to their mechanisms of action, and recommendations based on this evidence are provided. Additional information coming from clinical research and real-world studies is required to address unmet questions in this emerging field.

¿Existe un riesgo real de infección bacteriana en pacientes que reciben terapias biológicas?

Palabras clave:
Infección bacteriana
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RESUMEN

La introducción de terapias dirigidas y biológicas ha revolucionado a lo largo de las últimas décadas el tratamiento del cáncer y de las enfermedades autoinmunes, hematológicas e inflamatorias. Si bien existe abundante información acerca del exceso de riesgo de infección oportunista vinculado a algunos de estos agentes, la evidencia disponible sobre el riesgo de infección bacteriana específicamente es más limitada. En el marco de los ensayos clínicos pivotales y de estudios poscomercialización se ha demostrado un riesgo variable de infección bacteriana asociada al uso de terapias biológicas. Por ese motivo las recomendaciones para su minimización y abordaje terapéutico son escasas, y a menudo basadas en la opinión de expertos, con tan solo algunos escenarios de alto riesgo claramente establecidos para ciertos agentes (como la recomendación de vacunación anti-meningocócica en pacientes tratados con eculizumab). En la presente revisión se actualiza la información disponible respecto a la incidencia de infección bacteriana relacionada con las diferentes familias terapéuticas según su mecanismo de acción y sus factores de riesgo, aportándose igualmente algunas recomendaciones basadas en esta evidencia. Se requieren más estudios de investigación clínica en vida real para aclarar las preguntas sin resolver en este novedoso campo.

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Introduction

Over the last twenty years, the introduction of targeted and biological therapies has revolutionized the treatment of solid cancer and hematological and inflammatory diseases. The increasing experience with these agents has allowed to estimate the associated risk of developing opportunistic infections, such as invasive aspergillosis, shingles or *Pneumocystis jirovecii* pneumonia.[1] Targeted and biologic therapies produce different blockages in the immune pathways involved in both the innate and adaptive responses related to the host-bacteria interaction, which could increase the susceptibility to severe bacterial infections.[2] Nevertheless, this specific risk has not yet been completely elucidated, and recommendations are mainly based on expert opinions.

The present review summarizes the information concerning the risk and management of bacterial infection in patients receiving targeted and biological therapies. We performed a computer-based MEDLINE (National Library of Medicine, Bethesda, MD) search with no temporal or language restrictions, using the MeSH terms appropriate for each agent (always including "infection" or "infectious complications") to capture the literature pertaining to the subject. Particular attention was given to the safety data reported across pivotal randomized controlled trials (RCTs) and relevant post-marketing surveillance studies. The references of selected articles were also examined for additional related references. We have also collected information from the recommendations issued by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Infections in Compromised Hosts (ESGICH).[2–9]

Which factors related to bacterial infections have to be considered before the initiation of targeted and biological therapies?

First, we should consider that many autoimmune and inflammatory diseases intrinsically confer an increased baseline susceptibility to bacterial pathogens. Therefore, those patients with severe underlying conditions could be at additional risk once the therapy is initiated.[10] Table 1 depicts some risk factors that could increase concomitantly the risk of bacterial infection in patients with rheumatic diseases receiving targeted therapies.[11,12] The presence of previous debilitating chronic disorders (e.g. chronic obstructive pulmonary disease, interstitial lung disease or chronic kidney disease),[11,12] the previous occurrence of serious infections, and high cumulative doses of corticosteroids also act as contributing factors. Despite the paucity of supporting data, numerous guidelines recommend not to initiate any biological therapy in patients with a concomitant severe active infection (which is usually defined as that requiring intravenous treatment or hospitalization).[11]

Table 1
Risk factors for the occurrence of bacterial infections in patients with rheumatic diseases receiving biological therapy.

Specific syndromes	Risk factors
Upper or lower respiratory infections	Advanced age COPD/asthma Diabetes mellitus Heart disease Smoking
Urinary tract infections	Age ≥ 65 years Concomitant therapy with corticosteroid (daily prednisone dose > 5–10 mg or equivalent) or DMARDs Disease duration > 10 years Diabetes mellitus Heart disease Chronic renal disease Recurrent infections Charlson comorbidity index ≥ 2 Hypogamaglobulinemia (in patients treated with anti-CD-20 agents) COPD/asthma Smoking
Skin and skin structure infections	Advanced age Diabetes mellitus History of previous skin and skin structure infections Corticosteroid therapy (daily prednisone dose > 10 mg or equivalent)
Osteoarticular infections	Advanced age Prosthesis Opportunistic infections Corticosteroid therapy (daily prednisone dose > 10 mg or equivalent) Existence of extra-articular RA manifestations B-cell depletion
Disseminated infection	Advanced age Longstanding rheumatic disease History of previous infections Concomitant therapy with DMARDs and glucocorticoids

Adapted from Teixeira L et al.[11]
COPD: chronic obstructive pulmonary disease, DMARDs: disease modifying anti-rheumatic drugs, RA: rheumatoid arthritis.

What is the risk of developing a bacterial infection with the different targeted and biological agents?

We have reviewed the existing experience by classifying the biological agents into six large categories according to their intimate mechanism of action (Table 2).

Soluble immune effector molecules and pro-inflammatory cytokines: anti-TNF-α agents

Most relevant data related to the specific risk of bacterial infection in patients receiving targeted and biological agents are derived from the experience with the therapeutic blockade of tumor necrosis factor (TNF)-α in rheumatoid arthritis (RA) and inflammatory bowel disease (IBD). This theoretical background is often extensible to other indications with a more limited clinical experience. Curtis et al. analyzed the incidence of common bacterial infections with anti-TNF-α agents (abatacept, rituximab, infliximab, etanercept and adalimumab) in a large cohort ($n = 3111$) of RA patients from the US Veterans Health Administration between 1998 and 2011, reporting high rates for pneumonia (37%), cellulitis and soft tissue infection (22%), and urinary tract infection (9%). In this study, the use of abatacept was associated with a higher rate of bacterial infection-related hospitalization, although the multivariate analysis revealed no differences across different agents. The risk of infection was greater among patients receiving corticosteroids (daily prednisone dose > 7.5 mg or equivalent) and for those in the highest quartile of C-reactive protein levels and erythrocyte sedimentation rate (as compared to the lowest quartile).[12] More recently, Carrara et al. estimated in an Italian cohort of RA patients ($n = 4656$) incidence rates for pneumonia, bloodstream infection, cellulitis and septic arthritis of 2.95, 2.51, 1.30 and 1.06 episodes per 1000 patient-years, respectively. Abatacept seemed to be protective for severe infection-related hospitalization as compared to etanercept, while the use of other agents was not shown to increase the infection risk compared with this anti-TNF-α agent. Additional risk factors included the occurrence of severe infection within the previous year and high corticosteroid doses.[13] A Japanese cohort found a higher incidence of pulmonary infection among patients receiving adalimumab, with no differences between different biological agents in the overall risk of infection. These authors also found a significantly increased risk related to older age, RA severity, low body mass index, and presence of chronic comorbidities such as diabetes.[14] A network meta-analysis for severe infection

Table 2
Bacterial infection risk associated to different families of targeted and biological agents and proposed prevention strategies.

Therapeutic group	Specific targeted agents	Bacterial infection risk	Prevention strategies
Agents targeting pro-inflammatory cytokines	TNF-α-targeted agents	Moderate to high[a]	Pneumococcal vaccination
Agents targeting interleukins, immunoglobulins and complement factors	IL-1-targeted agents	Moderate	Pneumococcal vaccination
	IL-5-targeted agents	Not increased	
	IL-6/IL-6R-targeted agents	Moderate to high	Pneumococcal vaccination
	IL-12/23 p40-targeted agents	Not increased	
	IL-17-targeted agents	Mild	Not defined
	IgE-targeted agents	Not increased	
	C5-targeted agents	High to specific bacteria	Menigococcal, pneumococcal and Hib vaccination
Cell surface receptors and associated signaling pathways	VEGF-targeted agents	Moderate	Not defined
	VEGFR tyrosine kinase inhibitors	Moderate	Not defined
	EGFR -targeted agents	High	Doxycycline prophylaxis
	HER2/neu-targeted agents Inhibitors of ErbB tyrosine kinase family	Mild	Not defined
Intracellular signaling pathways (tyrosine kinase and mTOR inhibitors)	BRAF inhibitors	Not increased	
	MEK inhibitors	Not increased	
	PI3K inhibitors	Not increased	
	mTOR inhibitors	High[b]	Pneumococcal vaccination
	Janus kinase (JAK) inhibitors	High	Pneumococcal vaccination
	BCR/ABL tyrosine kinase inhibitors	Not increased	
	Antiapoptotic protein Bcl-2- targeted agents	Not established	
	Bruton's tyrosine kinase inhibitors	High	Pneumococcal vaccination
Agents targeting lymphoid or myeloid cells surface antigens	CD19-targeted agents	Moderate (CRBSI)	Not defined
	CD20-targeted agents	Moderate	Pneumococcal vaccination
	CD22-targeted agents	Not increased	
	CD30-targeted agents	Not increased	
	CD33-targeted agents	Not established	
	CD38-targeted agents	Mild	Not defined
	CD40-targeted agents	Mild	Not defined
	SLAMF7-targeted agents	Moderate	Not defined
	CD52-targeted agents	Moderate	Not defined
	CCR4-targeted agents	Not increased	Not defined
Immune checkpoint inhibitors, cell adhesion inhibitors, sphingosine-1-phosphate receptor modulators, and proteasome inhibitors	PD-1/PD-L1-targeted agents	Not increased[c]	Related to additional immunosuppression
	CTLA-4-targeted agents	Not increased[c]	
	α4-integrins-targeted agents	Moderate[d]	Not defined
	Proteasome inhibitors	Moderate	Pneumococcal vaccination
	LFA-3-targeted agents	Not increased	
	Sphingosine-1-phosphate receptor	Not increased	

Hib: Haemophilus influenzae type b; CRBSI: Catheter related bloodsttream infection.
[a] Conflicting data.
[b] Dose-dependent (higher for cancer patients that for solid organ transplant recipients.
[c] Risk may be increased due to additional immunosuppression used to treat immune-related adverse events.
[d] Specifically vedolizumab.

in RA patients found that standard- (odds ratio [OR]: 1.31; 95% confidence interval [CI]: 1.09–1.58) and high-dose (OR: 1.90; 95% CI: 1.50–2.39) therapy with biological agents were both associated with a higher risk for severe infection, although such difference was not significant for methotrexate (MTX) *naïve* and anti-TNF-α experienced patients.[15] In a meta-analysis of IBD patients receiving different anti-TNF-α agents and other therapies (vedolizumab or natalizumab), the incidence of serious infection was not significantly increased as compared to placebo (OR: 0.89; 95% CI: 0.71–1.12). Nevertheless, the overall risk of infection was higher in those patients on biologic agents (OR: 1.19; 95% CI: 1.10–1.29).[16] In summary, there is limited evidence suggesting an increase in the risk of bacterial infection with the use of anti-TNF-α agents. Of note, infections occur most frequently within the first year since the initiation of therapy.[17]

Agents targeting interleukins, immunoglobulins and complement factors

Therapy with interleukin (IL)-1-targeted agents has been shown to be associated with a moderate increase in the risk of bacterial infection, mainly in form of respiratory, urinary tract and skin and skin structure infections.[18,19] The reported incidence of serious infection is 5.4 episodes per 100 patient-years and seems to be increased among older patients with previous chronic diseases.[20] IL-6/IL-6R-targeted agents are associated with an increase in the

risk of bacterial infection comparable to that observed with anti-TNF-α therapies, with pneumonia, urinary tract infection and cellulitis as the most commonly reported events.[21,22] The pooled estimate for serious infection in phase 3 and extension RCTs is 4.9 episodes per 100 patient-years,[23] with higher rates in population-based studies (9.0 episodes per 100 patient-years).[24] It is important to note that most of the available experience with IL-6 blockade is restricted to tocilizumab, with limited data for sarilumab or siltuximab.

Phase 2 and 3 RCTs evaluating the use of IL-17-targeted agents in patients with psoriasis, ankylosing spondylitis and psoriatic arthritis showed a minor increase in the risk of bacterial infection (2.4 episodes of serious infection per 100 patient-years), usually mild to moderate in severity. Upper respiratory and urinary tract infections were the most common syndromes, whereas cellulitis was the predominant serious infection.[25,26] IL-12/23-targeted agents have not been associated with a significant increase in the risk of bacterial infection.[27]

Eculizumab, a humanized monoclonal antibody targeting and preventing cleavage of the terminal complement component C5, notably predisposes to infections due to *Neisseria* spp., with a 10,000-fold increased risk for meningococcal infection. In addition, this agent has been associated with a significant increase in the risk of respiratory tract infection as compared to placebo.[4]

Cell-surface receptors and associated signaling pathways

A large meta-analysis pooling data from 41 RCTs and more than 30,000 patients with various cancer types (mostly colorectal carcinoma) that received vascular endothelial growth factor (VEGF)-targeted agents[28] concluded that the use of bevacizumab significantly increased the incidence of infection of any grade (relative risk [RR]: 1.45; 95% CI: 1.27–1.66) and serious infection (RR: 1.59; 95% CI: 1.42–1.79). In this meta-analysis, the infection risk associated to bevacizumab seemed to be mostly linked to the occurrence of febrile neutropenia, fistulae or abscesses, and pneumonia, but not sepsis or colitis.[28]

Therapy with VEGF tyrosine kinase inhibitors does not increase the risk of infection.[29] The use of anti-VEGFR2 monoclonal antibodies (ramucirumab) is likely associated with a risk increase similar to that observed for VEGF-targeted agents, including the role of drug-induced neutropenia and gastrointestinal perforation as contributing factors.[30,31]

The use of epidermal growth factor receptor (EGFR)-targeted agents is associated with a meaningful increase in the risk of infection, mainly as a result of neutropenia and secondary infection in cases of severe papulopustular rash, with *Staphylococcus aureus* as a remarkable causative microorganism in skin and skin structure infections.[32,33]

Therapy with monoclonal antibodies targeting the human epidermal growth factor receptor 2 (ErbB2/HER2) might be associated with a minor increase in the risk of infection. However, the biologic rationale and clinical evidence supporting this association are weak.[34] Finally, ErbB receptor tyrosine kinase-targeted agents (including either selective EGFR/HER1 and/or ErbB2/HER2 inhibitors or pan-ErbB inhibitors) does not meaningfully increase the rate of bacterial infection.[5]

Intracellular signaling pathways (tyrosine kinase and mTOR inhibitors)

With some exceptions, this family of biologic agents does not show a significant increase in the susceptibility to bacterial pathogens.[6] Ibrutinib (a Bruton's tyrosine kinase [BTK] inhibitor) exhibited a modest increase in the risk of bacterial infection. Pneumonia is observed mainly in the presence of neutropenia, whereas about 10% of patients developed urinary tract infections.[35,36] The risk is influenced by other factors like additional immunosuppressive drugs or previous immune disorders related to the underlying B-cell malignancies.

Janus kinase (JAK) inhibitors are associated with a considerable increase in the risk of infection. Indeed, urinary tract infection, pneumonia, and septic shock were described for patients on ruxolitinib (a potent oral JAK1/JAK2 inhibitor) in rates of 24.6%, 13.1% and 7.9%, respectively, in one pivotal RCT for the treatment of myelofibrosis. Surprisingly, the long-term follow-up revealed a decrease in the incidence of infection, presumably resulting from the stabilization of the underlying disease with resolution of cytopenias.[37]

A meta-analysis evaluating the use of mammalian target of rapamycin (mTOR) inhibitors in 4,097 cancer patients from 12 RCTs (8 with everolimus and 3 with temsirolimus) reported an increased risk of infection (overall incidence of all-grade infection of 25.0%; 95% CI: 16.7–35.9%), including fatal outcomes due to sepsis and pneumonia. Sub-group analysis revealed heterogeneity across different tumor types, with lower risks for patients with giant cell astrocytoma, breast cancer and angiomyolipoma, and higher risks for those with renal cell carcinoma, lymphomas or neuroendocrine tumors.[38] The variations in dose regimens are relevant in explaining these findings as compared to the more favorable safety profile observed among solid organ transplant recipients.[6]

BCR-ABL tyrosine kinase inhibitors, BRAF/MEK kinase inhibitors, and PI3K inhibitors do not seem to increase the risk of serious bacterial infection, whereas limited information is still available for BCL-2 inhibitors.[6]

Agents targeting lymphoid or myeloid cells surface antigens

In pivotal RCTs, mostly limited to blinatumomab, therapy with CD19-targeted agents does not show a significant increase in the risk of bacterial infection compared with conventional chemotherapy, with overall rates comparable to those expected in patients undergoing treatment for relapsed or refractory acute lymphoblastic leukemia.[39] Of note, the need for continuous intravenous infusion for 4 weeks in the blinatumomab regimen explains the elevated rate of catheter-associated bloodstream infection in the RCTs evaluating this first-in-class bispecific T-cell engager, with rates ranging from 2.2% to 11%.[40,41] Careful management of intravenous lines is therefore warranted to minimize this risk. Clinicians caring for patients receiving such therapy should be also aware of the associated risk of hypogammaglobulinemia (HGG), which is associated with a well-established increased susceptibility to encapsulated bacteria such as *Streptococcus pneumoniae*.[42]

Infection prevails as the most common non-hematological adverse effects of anti-CD20 monoclonal antibodies, including severe respiratory tract infection. Separate meta-analysis in lymphoma and RA do not show a significant increase in the risk of bacterial infection.[43,44] Nevertheless, in a French cohort of patients with immune thrombocytopenia, the incidence of serious bacterial infections was 6.3 episodes per 100 patient-years, and as high as 100.5 episodes per 100 patient-years for non-serious infections. Pneumonia was the most frequently reported syndrome (42.8%), with gastrointestinal and urinary tract infections as other common infections.[45] Second- and third-generation anti-CD20 monoclonal antibodies could also increase the risk of bacterial infection, although this risk is determined by the presence of concomitant comorbidities, previous and concomitant immunosuppressive therapies, and the long-term occurrence of sever HGG.[7]

The use of alemtuzumab (CD52-targeted agent) for different diseases shows a variable risk of bacterial infection explained in part by differences in dose regiments and the presence of previous immunosuppression. Overall, bacterial infections are higher in

some scenarios such as cutaneous lymphoma, with an incidence rate of 23.3 episodes per 100 patient-years.[46]

Immune checkpoint inhibitors, cell adhesion inhibitors, sphingosine-1-phosphate receptor modulators, and proteasome inhibitors

The available data from pivotal RCTs suggest that CTLA-4 (ipilimumab or tremelimumab) or PD-1/PD-L1 blockade (nivolumab or atezolizumab) is not intrinsically associated with an increase in the risk of infection.[47–51] Nevertheless, cancer patients receiving immune checkpoint inhibitors may develop immune-related adverse events that may entail additional immunosuppressive therapy (such as corticosteroids or anti-TNF-α agents) impacting the susceptibility to bacterial pathogens (9). A systematic review in IBD found that patients treated with vedolizumab (an α4-integrin-targeted monoclonal antibody) experienced a moderate increase in the incidence of serious bacterial infections and surgical site infections compared to placebo.[52]

Pneumonia is a common bacterial infection among patients with multiple myeloma (MM) treated with proteasome inhibitors (PIs), but data do not seem to support a higher risk weighed with comparator therapies. Of note, untreated MM patients already face an increased incidence of respiratory tract infections (including pneumonia) due to the underlying impairment of humoral immune responses. However, this susceptibility seems to be influenced by the use of PIs in the induction regimen.[53]

Should biologic therapies be discontinued while treating a bacterial infection? When should they be reintroduced?

Currently, studies evaluating these questions are lacking, and there is no clear evidence to guide the optimal management of bacterial infections in patients receiving biologic agents. Nevertheless, most guidelines concur on the need of discontinuing therapy in the presence of serious bacterial infection, to be reintroduced only once the infection has completely resolved. The decision should ideally be taken on a case-by-case basis by an experienced physician since, in some situations, the abrupt withdrawal of therapy can induce a flare of the underlying autoinflammatory disorder[11] or negatively impact the prognosis of the underlying disease. Indeed, it has been reported an increased risk of progression among patients with chronic lymphocytic leukemia in which the BTK inhibitor ibrutinib has to be discontinued.[54]

Should asymptomatic bacteriuria be treated in patients receiving biological therapies?

No studies have addressed whether patients receiving biologic therapies should be systematically screened and treated for asymptomatic bacteriuria. A case–control study performed in women with autoimmune rheumatic diseases reported no differences in the incidence of either asymptomatic or symptomatic urinary tract infection compared with the control group.[55] More data are needed to establish the management in this population, although systematic treatment would not be indicated, in line with other clinical scenarios in which no apparent benefit from this strategy has been demonstrated.[56,57]

What prevention strategies are required to prevent bacterial infections in patients receiving biological therapies?

Clear recommendations aimed at minimizing the risk of bacterial infection linked to the use of the different families of biological and targeted agents are mostly lacking, except for some specific agents. As mentioned above, in view of the increased risk of *N. meningitidis* infection with eculizumab use, meningococcal vaccination must be assured before the initiation of therapy.[4] Vaccination against pneumococcal disease and *Haemophylus influenzae* type B should be provided according to current guidelines, and are recommended for various biologic targeted agents mentioned previously[3,11] (Table 2). In other specific scenarios, antibiotic prophylaxis is recommended, as occurs in patients on EGFR targeted-agents who should receive oral doxycycline to prevent skin infections.[6] However, it should be emphasized that there is no clear evidence to support such practices, and any potential benefit must be always balanced against the well-defined risk of inducing antimicrobial resistance, as observed in neutropenic patients.

Conclusion

Bacterial infections in patients on targeted and biologic therapies have a variable incidence depending on the agent used, with this risk being influenced by contributing factors such as previous comorbidities, the activity of the underlying condition, or the receipt of additional immunosuppressive therapy. There are few specific recommendations concerning the management and prevention of bacterial infections in these patient populations. The proven risk of invasive infections due to encapsulated bacteria clearly supports meningococcal and pneumococcal vaccination among patients treated with eculizumab and anti-CD20 agents. Nonetheless, evidence is mostly lacking for therapies involving interleukins and other soluble mediators, and no guidance may be provided for newer agents even in the presence of a theoretical infection risk (such as that potentially resulting from the blockade of the pro-inflammatory cytokines IL-1β or IL-6). In addition, no risk thresholds have been established to define in which patient subgroups interventions should be implemented. Multicenter post-marketing surveillance with granular information on the type and severity of infection, open-label extension studies and other sources of real-world data are necessary to elucidate the safety profile of these therapies, with the ultimate aim to define specific interventions if significant risk signals emerge.

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Conflict of interest

The authors have no conflicts of interests to disclose.

References

1. Singh H, Nugent Z, Demers AA, Bernstein CN. Screening for cervical and breast cancer among women with inflammatory bowel disease: a population-based study. Inflamm Bowel Dis. 2011;17:1741–50.
2. Fernández-Ruiz M, Meije Y, Manuel O, Akan H, Carratalà J, Aguado JM, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the Safety of targeted and biological therapies: an Infectious Diseases perspective (Introduction). Clin Microbiol Infect. 2018;24 Suppl. 2:S2–9, http://dx.doi.org/10.1016/j.cmi.2018.01.029.
3. Baddley JW, Cantini F, Goletti D, Gómez-Reino JJ, Mylonakis E, San-Juan R, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an

Infectious Diseases perspective (Soluble immune effector molecules [I]: anti-tumor necrosis factor-α agents). Clin Microbiol Infect. 2018;24 Suppl. 2:S10–20, http://dx.doi.org/10.1016/j.cmi.2017.12.025.
4. Winthrop KL, Mariette X, Silva JT, Benamu E, Calabrese LH, Dumusc A, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an Infectious Diseases perspective (Soluble immune effector molecules [II]: agents targeting interleukins, immunoglobulins and complement factors). Clin Microbiol Infect. 2018;24 Suppl. 2:S21–40, http://dx.doi.org/10.1016/j.cmi.2018.02.002.
5. Aguilar-Company J, Fernández-Ruiz M, García-Campelo R, Garrido-Castro AC, Ruiz-Camps I. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an Infectious Diseases perspective (Cell surface receptors and associated signaling pathways). Clin Microbiol Infect. 2018;24 Suppl. 2:S41–52, http://dx.doi.org/10.1016/j.cmi.2017.12.027.
6. Reinwald M, Silva JT, Mueller NJ, Fortún J, Garzoni C, de Fijter JW, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an Infectious Diseases perspective (Intracellular signaling pathways: tyrosine kinase and mTOR inhibitors). Clin Microbiol Infect. 2018;24 Suppl. 2:S53–70, http://dx.doi.org/10.1016/j.cmi.2018.02.009.
7. Mikulska M, Lanini S, Gudiol C, Drgona L, Ippolito G, Fernández-Ruiz M, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an Infectious Diseases perspective (Agents targeting lymphoid cells surface antigens [I]: CD19, CD20 and CD52). Clin Microbiol Infect. 2018;24 Suppl. 2:S71–82, http://dx.doi.org/10.1016/j.cmi.2018.02.003.
8. Drgona L, Gudiol C, Lanini S, Salzberger B, Ippolito G, Mikulska M. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Agents targeting lymphoid or myeloid cells surface antigens [II]: CD22, CD30, CD33, CD38, CD40, SLAMF-7 and CCR4). Clin Microbiol Infect. 2018;24 Suppl. 2:S83–94, http://dx.doi.org/10.1016/j.cmi.2018.03.022.
9. Redelman-Sidi G, Michielin O, Cervera C, Ribi C, Aguado JM, Fernández-Ruiz M, et al. ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an Infectious Diseases perspective (Immune checkpoint inhibitors, cell adhesion inhibitors, sphingosine-1-phosphate receptor modulators and proteasome inhibitors). Clin Microbiol Infect. 2018;24 Suppl. 2:S95–107, http://dx.doi.org/10.1016/j.cmi.2018.01.030.
10. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum. 2002;46:2287–93.
11. Teixeira L, Fonseca AR, Eugénio G, Rodrigues M, Khmelinskii N, Fernandes S, et al. management of infections in rheumatic patients receiving biological therapies. The Portuguese Society of rheumatology recommendations. Acta Reumatol Port. 2016;2016:287–304.
12. Curtis JR, Yang S, Patkar NM, Chen L, Singh JA, Cannon GW, et al. risk of hospitalized bacterial infections associated with biologic treatment among US veterans with rheumatoid arthritis. Arthritis Care Res. 2014;66:990–7.
13. Carrara G, Bortoluzzi A, Sakellariou G, Govoni M, Scirè CA. Risk of hospitalization for serious bacterial infections in patients with rheumatoid arthritis treated with biologics. Analysis from the record study of the Italian society for rheumatology. Clin Exp Rheumatol. 2019;37:60–6.
14. Mori S, Yoshitama T, Hidaka T, Sakai F, Hasegawa M, Hashiba Y, et al. Comparative risk of hospitalized infection between biological agents in rheumatoid arthritis patients: a multicenter retrospective cohort study in Japan. PLOS ONE. 2017;12:1–16, http://dx.doi.org/10.1371/journal.pone.0179179.
15. Singh JA, Cameron C, Noorbaloochi S, Cullis T, Tucker M, Christensen R, et al. Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. Lancet. 2015;386:258–65.
16. Bonovas S, Fiorino G, Allocca M, et al. Biologic therapies and risk of infection and malignancy in patients with inflammatory bowel disease: a systematic review and network meta-analysis. Clin Gastroenterol Hepatol. 2016;14:1385–97, http://dx.doi.org/10.1016/j.cgh.2016.04.039, e10.
17. Askling J, Fored CM, Brandt L, Baecklund E, Bertilsson L, Feltelius N, et al. Time-dependent increase in risk of hospitalisation with infection among Swedish RA patients treated with TNF antagonists. Ann Rheum Dis. 2007;66:1339–44.
18. Fleischmann RM, Schechtman J, Bennett R, Handel ML, Burmester GR, Tesser J, et al. Anakinra, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis: a large, international, multicenter, placebo-controlled trial. Arthritis Rheum. 2003;48:927–34.
19. Den Broeder AA, De Jong E, Franssen MJAM, Jeurissen MEC, Flendrie M, Van Den Hoogen FHJ. Observational study on efficacy, safety, and drug survival of anakinra in rheumatoid arthritis patients in clinical practice. Ann Rheum Dis. 2006;65:760–2.
20. Fleischmann R, Tesser J, Schiff MH, Schechtman J, Burmester GR, Bennett R, et al. Safety of extended treatment with anakinra in patients with rheumatoid arthritis. Ann Rheum Dis. 2006;65:1006–12.
21. Burmester GR, Lin Y, Patel R, Van Adelsberg J, Mangan EK, Graham NMH, et al. Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group phase III trial. Ann Rheum Dis. 2017;76:840–7.
22. Iking-Konert C, Von Hinüber U, Richter C, Schwenke H, Gürtler I, Kästner P, et al. ROUTINE-a prospective, multicentre, non-interventional, observational study to evaluate the safety and effectiveness of intravenous tocilizumab for the treatment of active rheumatoid arthritis in daily practice in Germany. Rheumatology (United Kingdom). 2016;55:624–35.
23. Schiff MH, Kremer JM, Jahreis A, Vernon E, Isaacs JD, van Vollenhoven RF. Integrated safety in tocilizumab clinical trials. Arthritis Res Ther. 2011;13.
24. Koike T, Harigai M, Inokuma S, Ishiguro N, Ryu J, Takeuchi T, et al. Effectiveness and safety of tocilizumab: postmarketing surveillance of 7901 patients with rheumatoid arthritis in Japan. J Rheumatol. 2014;41:15–23.
25. Van De Kerkhof PCM, Griffiths CEM, Reich K, Leonardi CL, Blauvelt A, Tsai TF, et al. Secukinumab long-term safety experience: a pooled analysis of 10 phase II and III clinical studies in patients with moderate to severe plaque psoriasis. J Am Acad Dermatol. 2016;75:83–98, http://dx.doi.org/10.1016/j.jaad.2016.03.024, e4.
26. Papp KA, Bachelez H, Blauvelt A, Winthrop KL, Romiti R, Ohtsuki M, et al. Infections from 7 clinical trials of Ixekizumab an anti-interleukin-17A monoclonal antibody in patients with moderate-to-severe psoriasis. Br J Dermatol. 2017;167:1537–51.
27. Kalb RE, Fiorentino DF, Lebwohl MG, Toole J, Poulin Y, Cohen AD, et al. Risk of serious infection with biologic and systemic treatment of psoriasis: results from the psoriasis longitudinal assessment and registry (PSOLAR). JAMA Dermatology. 2015;151:961–9.
28. Qi WX, Fu S, Zhang Q, Guo XM. Bevacizumab increases the risk of infections in cancer patients: a systematic review and pooled analysis of 41 randomized controlled trials. Crit Rev Oncol Hematol. 2015;94:323–36, http://dx.doi.org/10.1016/j.critrevonc.2015.02.007.
29. Hansen CR, Grimm D, Bauer J, Wehland M, Magnusson NE. Effects and side effects of using sorafenib and sunitinib in the treatment of metastatic renal cell carcinoma. Int J Mol Sci. 2017;18:E461.
30. Garon EB, Ciuleanu TE, Arrieta O, Prabhash K, Syrigos KN, Goksel T, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet. 2014;384:665–73.
31. Arnold D, Fuchs CS, Tabernero J, Ohtsu A, Zhu AX, Garon EB, et al. Meta-analysis of individual patient safety data from six randomized, placebo-controlled trials with the antiangiogenic VEGFR2-binding monoclonal antibody ramucirumab. Ann Oncol. 2017;28:2932–42.
32. Funakoshi T, Suzuki M, Tamura K. Infectious complications in cancer patients treated with anti-EGFR monoclonal antibodies cetuximab and panitumumab: a systematic review and meta-analysis. Cancer Treat Rev. 2014;40:1221–9, http://dx.doi.org/10.1016/j.ctrv.2014.09.002.
33. Qi WX, Fu S, Zhang Q, Guo XM. Incidence and risk of severe infections associated with anti-epidermal growth factor receptor monoclonal antibodies in cancer patients: a systematic review and meta-analysis. BMC Med. 2014;12:1–12.
34. Funakoshi T, Suzuki M, Muss HB. Infection risk in breast cancer patients treated with trastuzumab: a systematic review and meta-analysis. Breast Cancer Res Treat. 2015;149:321–30.
35. Byrd JC, Furman RR, Coutre SE, Flinn IW, Burger JA, Blum KA, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med. 2013;369:32–42.
36. Wang ML, Rule S, Martin P, Goy A, Auer R, Kahl BS, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2013;369:507–16.
37. Cervantes F, Vannucchi AM, Kiladjian J-J, Al-Ali HK, Sirulnik A, et al. Three-year efficacy, safety, and survival findings from COMFORT-II, a phase 3 study comparing ruxolitinib with best available therapy for myelofibrosis. Blood. 2013;122:4047–53.
38. Garcia CA, Wu S. Attributable risk of infection to mTOR inhibitors everolimus and temsirolimus in the treatment of cancer. Cancer Invest. 2016;34:521–30.
39. Kantarjian H, Stein A, Gökbuget N, Fielding AK, Schuh AC, Ribera J-M, et al. Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia. N Engl J Med. 2017;376:836–47.
40. Kantarjian HM, Stein AS, Bargou RC, Grande Garcia C, Larson RA, Stelljes M, et al. Blinatumomab treatment of older adults with relapsed/refractory B-precursor acute lymphoblastic leukemia: results from 2 phase 2 studies. Cancer. 2016;122:2178–85.
41. Martinelli G, Boisel N, Chevalier P, Ottman o, Gükbuget N, Topp MS, et al. Complete hematologic and molecular response in adult patients with relapsed/refractory philadelphia chromosome-positive B-precursor acute lymphoblastic leukemia following treatment with blinatumomab: results from a phase II, single-arm, multicenter study. J Clin Oncol. 2017;35:1795–802.
42. Schiopu E, Chatterjee S, Hsu V, Flor A, Cimbora D, Patra K, et al. Safety and tolerability of an anti-CD19 monoclonal antibody, MEDI-551, in subjects with systemic sclerosis: a phase I, randomized, placebo-controlled, escalating single-dose study. Arthritis Res Ther. 2016;18:1–14, http://dx.doi.org/10.1186/s13075-016-1021-2.
43. Lanini S, Molloy AC, Fine PE, Prentice AG, Ippolito G, Kibbler CC. Risk of infection in patients with lymphoma receiving rituximab: systematic review and meta-analysis. BMC Med. 2011;9:36, http://dx.doi.org/10.1186/1741-7015-9-36.
44. Van Vollenhoven RF, Fleischmann RM, Furst DE, Lacey S, Lehane PB. Longterm safety of rituximab: Final report of the rheumatoid arthritis global clinical trial program over 11 years. J Rheumatol. 2015;42:1761–6.
45. Moulis G, Lapeyre-Mestre M, Palmaro A, Sailler L. Infections in non-splenectomized persistent or chronic primary immune thrombocytopenia adults: risk factors and vaccination effect. J Thromb Haemost. 2016;15:785–91.
46. Thursky KA, Worth LJ, Seymour JF, Miles Prince H, Slavin MA. Spectrum of infection, risk and recommendations for prophylaxis and screening among patients

with lymphoproliferative disorders treated with alemtuzumab. Br J Haematol. 2006;132:3–12.
47. Wolchok JD, Neyns B, Linette G, Negrier S, Lutzky J, Thomas L, et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. Lancet Oncol. 2010;11:155–64.
48. Ramelyte E, Schindler SA, Dummer R. The safety of anti PD-1 therapeutics for the treatment of melanoma. Expert Opin Drug Saf. 2017;16:41–53, http://dx.doi.org/10.1080/14740338.2016.1248402.
49. Brahmer JR, Tykodi SS, Chow LQM, Hwu W-J, Topalian SL, Hwu P, et al. safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012;366:2455–65.
50. Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazieres J, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet. 2016;387:1837–46, http://dx.doi.org/10.1016/S0140-6736(16)00587-0.
51. Robert C, Ribas A, Wolchok JD, Hodi FS, Hamid O, Kefford R, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. Lancet. 2014;384:1109–17.
52. Bye WA, Jairath V, Travis SPL. Systematic review: the safety of vedolizumab for the treatment of inflammatory bowel disease. Aliment Pharmacol Ther. 2017;46:3–15.
53. Dimopoulos MA, Moreau P, Palumbo A, Joshua D, Pour L, Hájek R, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): and randomised, phase 3, open-label, multicentre study. Lancet Oncol. 2016;17:27–38.
54. Maddocks KJ, Ruppert AS, Lozanski G, et al. Etiology of ibrutinib therapy discontinuation and outcomes in patients with chronic lymphocytic leukemia. JAMA Oncol. 2015;1:80–7, http://dx.doi.org/10.1001/jamaoncol.2014.218.
55. Georgiadou SP, Gamaletsou MN, Mpanaka I, Vlachou A, Goules AV, Ziogas DC, et al. Asymptomatic bacteriuria in women with autoimmune rheumatic disease: prevalence, risk factors, and clinical significance. Clin Infect Dis. 2015;60:868–74.
56. Kazemier BM, Koningstein FN, Schneeberger C, Ott A, Bossuyt PM, de Miranda E, et al. Maternal and neonatal consequences of treated and untreated asymptomatic bacteriuria in pregnancy: a prospective cohort study with an embedded randomised controlled trial. Lancet Infect Dis. 2015;15:1324–33, http://dx.doi.org/10.1016/S1473-3099(15)00070-5.
57. Origüen J, López-Medrano F, Fernández-Ruiz M, Polanco N, Gutiérrez E, González E, et al. Should asymptomatic bacteriuria be systematically treated in kidney transplant recipients? Results from a randomized controlled trial. Am J Transplant. 2016;16:2943–53, http://dx.doi.org/10.1111/ajt.13829.