Accepted Manuscript

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)

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PII: S1198-743X(18)30150-2
DOI: 10.1016/j.cmi.2018.02.002
Reference: CMI 1202

To appear in: Clinical Microbiology and Infection

Received Date: 10 November 2017
Revised Date: 31 January 2018
Accepted Date: 3 February 2018


This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
Revised manuscript (CLM-17-12784.R1) [for AA publication]

Review paper

Title page

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• **Word length** (excluding title page, figure legends and references): 11,348

• **Number of figures**: 2

• **Number of tables**: 3

• **Number of references**: 272

• **Funding sources**: This research was partially supported by Plan Nacional de I+D+I 2013-2016 and Instituto de Salud Carlos III, Subdirección General de Redes y Centros de Investigación Cooperativa, Spanish Ministry of Economy and Competitiveness, Spanish Network for Research in Infectious Diseases (REIPI RD16/0016/0002) - co-financed by the European Development Regional Fund (EDRF) "A way to achieve Europe". M.F.R. holds a clinical research contract “Juan Rodés” (JR14/00036) from the Instituto de Salud Carlos III, Spanish Ministry of Economy and Competitiveness.

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Abstract (250 words)

Background: The present review is part of the ESCMID Study Group for Infections in Compromised Hosts (ESGtICH) Consensus Document on the safety of targeted and biological therapies.

Aims: To review, from an Infectious Diseases perspective, the safety profile of agents targeting interleukins, immunoglobulins and complement factors and to suggest preventive recommendations.

Sources: Computer-based MEDLINE searches with MeSH terms pertaining to each agent or therapeutic family.

Content: Patients receiving interleukin (IL)-1-targeted (anakinra, canakinumab or rilonacept) or IL-5-targeted agents (mepolizumab) have a moderate risk of infection and no specific prevention strategies are recommended. The use of IL-6/IL-6 receptor-targeted agents (tocilizumab and siltuximab) is associated to a risk increase similar to that observed with anti-tumor necrosis factor (TNF)-α agents. IL-12/23-targeted agents (ustekinumab) do not seem to pose a meaningful risk of infection, although screening for latent tuberculosis infection may be considered and antiviral prophylaxis should be given to hepatitis B surface antigen (HBsAg)-positive patients. Therapy with IL-17-targeted agents (secukinumab, brodalumab and ixekizumab) may result in the development of mild-to-moderate mucocutaneous candidiasis. Pre-treatment screening for Strongyloides stercoralis and other geohelminths should be considered in patients coming from endemic areas receiving IgE-targeted agents (omalizumab). C5-targeted agents (eculizumab) are associated with a markedly increased risk of infection due to encapsulated bacteria, particularly Neisseria spp. Meningococcal vaccination and chemoprophylaxis must be administered 2-4 weeks before initiating eculizumab. Patients with high-risk behaviors and their partners should be also screened for gonococcal infection.

Implications: Preventive strategies are particularly encouraged to minimize the occurrence of neisserial infection associated to eculizumab.

Keywords: anakinra; canakinumab; rilonacept; tocilizumab; secukinumab; brodalumab; ixekizumab; eculizumab; infection; prevention.
Introduction

The present review paper is part of a larger effort launched by the ESCMID (European Society of Clinical Microbiology and Infectious Diseases) Study Group for Infections in Compromised Hosts (ESGICH) and aimed at analyzing, from an Infectious Diseases perspective, the safety profile of biological and targeted therapies. By means of a set of unrestricted computer-based MEDLINE (National Library of Medicine, Bethesda, MD) searches based on the MeSH terms appropriate for each agent or therapeutic family, we identified literature pertaining to the subject. In addition, package information and boxed warning alerts from regulatory agencies (European Medicines Agency [EMA] and US Food and Drug Administration [FDA]) were reviewed. Methodological details are provided in the Introduction section of the present Supplement issue [1]. For each agent (or class of agents), a common outline is offered: (a) summary of mechanism of action, approved indications and most common off-label uses; (b) theoretically expected impact on the host’s susceptibility to infection; (c) available evidence emerging from the clinical use of that agent (i.e., randomized clinical trials [RCTs], post-marketing studies, case series and single case reports); and (d) suggested preventive and risk minimization strategies. This section is the second one specifically focused on the risk of infection entailed by the use of agents targeting soluble immune effector molecules, such as interleukins, immunoglobulins and complement factors (Table 1).

Interleukin (IL)-1-targeted agents: anakinra, canakinumab, gevokizumab and rilonacept

Mechanism of action, approved indications and off-label uses

The interleukin (IL)-1 family comprises a total of 11 closely related members involved in the inflammatory response. IL-1α and IL-1β, the most extensively studied components, act as strong pro-inflammatory cytokines upon binding to the IL-1 receptor (IL-1R) and an accessory protein (IL-1RαcP) to initiate a complex intracellular signaling cascade. IL-1R activation ultimately results in the transcription of nuclear factor kappa B (NF-κB), leading to neutrophil recruitment, production of pro-inflammatory mediators and appearance of fever. IL-1 receptor antagonist (IL-1Ra), also a member of the IL-1 family, acts as a competitive inhibitor as it binds to IL-1R with similar affinity as IL-1α and IL-1β. However, IL-1Ra lacks agonist activity, thus contributing to the endogenous signaling regulation [2,3]. The therapeutic blockade of IL-1 has been subject of clinical development since decades in view of the implication of the IL-1 family
(particularly IL-1β) in the pathogenesis of autoimmune and autoinflammatory disorders, as well as in crystal deposition diseases (Figure 1) [3,4].

Anakinra (Kineret®, Sobi) is a recombinant, nonglycosylated IL-1 receptor antagonist that only differs from the native IL-1Ra in the presence of an extra methionine residue at the aminoterminal end. It is manufactured by using the Escherichia coli expression system and inhibits the binding of IL-1α and IL-1β to IL-1R by mirroring the mode action of its endogenous counterpart. Canakinumab (Ilaris®, Novartis Pharmaceuticals) is a fully human IgG1 monoclonal antibody and gevokizumab (XOMA Corporation) is a potent humanized allosteric-modulating monoclonal antibody, both targeting IL-1β. Rilonacept (Arcalyst®, Regeneron Pharmaceuticals) is a fusion protein composed of the ligand-binding domains of the extracellular portions of IL-1R1 and IL-1RAcP linked to the fragment crystallizable (Fc) portion of human IgG1, which acts as a soluble decoy receptor, inhibiting the binding of IL-1α and IL-1β to IL-1R.

Anakinra was approved by the EMA in 2002 for the treatment of rheumatoid arthritis (RA) in combination with methotrexate in patients with inadequate response to methotrexate alone. One year earlier the FDA had given a similar indication (moderately to severely active RA in adult patients that have failed to one or more disease-modifying antirheumatic drugs [DMARDs]). In addition, anakinra is FDA-approved for the treatment of the neonatal-onset multisystem inflammatory disease (NOMID), which is part of the cryopyrin-associated periodic syndromes (CAPS). Anakinra is given daily by subcutaneous injection of 100 mg and 1-2 mg/Kg for pediatric and adult patients, respectively.

Rilonacept was approved by the EMA for the treatment of CAPS in 2009, but was voluntarily withdrawn from the European market in 2012 by Regeneron on commercial grounds. It has been approved by the FDA for the treatment of CAPS, including familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS) in adults and children 12 years of age and older. After a loading dose of 320 mg, it is administered by weekly subcutaneous injection of 160 mg (2.2 mg/Kg for children).

Canakinumab has been approved by the EMA for the treatment of patients aged of 2 years and older with CAPS (including MWS, NOMID, chronic infantile neurological cutaneous articular syndrome [CINCA], and severe forms of FCAS and familial cold urticaria [FCU]), tumor necrosis factor receptor-associated periodic syndrome (TRAPS), hyper-IgD syndrome/mevalonate
kinase deficiency (MKD), familial mediterranean fever (FMF), adult-onset Still’s disease and
systemic juvenile idiopathic arthritis refractory to non-steroidal anti-inflammatory drugs
(NSAIDs) and systemic corticosteroids. It has also been approved for the treatment of adult
patients with frequent gouty arthritis attack in whom colchicine and NSAIDs are contraindicated,
not tolerated or do not provide an adequate response and in whom corticosteroids are not
appropriate. Canakinumab has been approved by the FDA for the treatment of CAPS (including
FCAS and MWS in adults and children of 4 years and older), TRAPS, hyper-IgD
syndrome/MKD, FMF in adult and pediatric patients, and systemic juvenile idiopathic arthritis in
patients aged 2 years and older. Canakinumab is administered subcutaneously every 4 or 8
weeks depending on the indication and patient’s weight.
To date, the use of gevokizumab has not been approved by the EMA or the FDA.
In addition, these agents are often used for off-label indications if another IL-1-targeted agent
has been agency-approved for that given indication, especially across autoinflammatory
diseases [5]. Other off-label uses include the treatment of crystal deposition diseases different
than gout (like pseudogout) [6], Behçet’s disease [7], idiopathic uveitis, refractory pericarditis [8]
and neutrophilic dermatoses [9]. Recently, the efficacy and safety of canakinumab as secondary
prophylaxis to prevent atherosclerotic events or cardiovascular death in patients with previous
myocardial infarction and an elevated baseline C-reactive protein (CRP) level have been tested
in a large RCT [10].

Expected impact on the infection risk
The IL-1 family of cytokines are key components of the innate immune system. The precursor of
IL-1α is expressed in many cells types in healthy subjects, but the synthesis of the inactive
precursor form of IL-1β (pro-IL-1β) is mainly restricted to monocytes, macrophages and
dendritic cells (DCs) [11]. The synthesis of pro-IL-1β via NF-κB is stimulated in response to
microbial products and other inflammatory cytokines. Pro-IL-1β is cleaved into its biologically
active form IL-1β by caspase-1, which is in turn activated by recruitment to a large molecular
platform termed the inflammasome [12]. To date, several inflammasomes have been identified.
The formation of inflammasomes can be triggered by various stimuli usually involving pattern
recognition receptors (PRR), which recognize highly conserved molecular patterns of microbes
(pathogens-associated molecular patterns [PAMPs]), endogenous stress signals or
environmental stimuli (damage-associated molecular patterns [DAMPs]) [13]. Myriad of PAMPs, which are components of bacteria, viruses and fungus, have been reported to activate PRRs and initiate an immune response against specific pathogens [14-16].

In view of the major role played by the IL-1 pathway in the protection against pathogens, there are theoretical concerns about an increased risk of serious or opportunistic infections among patients subjected to IL-1 blockade, especially with long-term treatments and in pediatric individuals who frequently encounter pathogens for the first time with no adaptive immunity. In addition, animal models suggest that IL-1-targeted therapy would lead to a higher susceptibility to active tuberculosis (TB) [17] [18]. Indeed, IL1-β production has been demonstrated in lung granulomas from patients with active pulmonary TB, as well as an increased ratio of IL-1β to IL-1R. Certain single nucleotide polymorphisms (SNPs) in the IL1B gene may influence risk of extrapulmonary TB in the general population [19,20] or invasive fungal infection in solid organ transplant recipients [21].

Available clinical data

Short-course therapy with IL-1 inhibitors (anakinra, canakinumab or rilonacept) for acute flares of gouty arthritis are usually well tolerated in the setting of RCTs, with no significant increase in the incidence of infectious events [22-24]. Various larger placebo-controlled RCTs (overall including more than 5,000 participants) have assessed the safety of long-term treatment with anakinra for RA [25-32] and canakinumab and rilonacept for gout [33-35]. In this adult population, usually suffering from preexisting conditions or concomitantly treated with other immunosuppressive drugs, an increase in the incidence of infection was observed compared to placebo. Infections were usually mild to moderate and rarely lead to permanent drug discontinuation. The most frequently observed events were upper respiratory and urinary tract infection. The cumulative rate of serious infection among 1,346 RA patients treated with anakinra for 3 years was 5.4 episodes per 100 patient-years, similar to those reported for other biological DMARDs such as tocilizumab, and remained constant across consecutive years of therapy [27].

Auto-inflammatory diseases are rare conditions mainly affecting children. Current evidence mostly derived from observational studies (prospective and retrospective), open-label studies and small-size RCTs [36-39]. As patients suffering from auto-inflammatory disorders are usually
treated for many years, long-term assessment of drug safety is of paramount importance in this particular population. Maximum follow-up periods in published studies extended up to 5 years [40,41]. The similar profile was close to that observed for the adult population, with an increased infection rate, usually involving the respiratory tract. Some episodes of varicella-zoster virus (VZV) infection [42], influenza [36,43] and orolabial herpes [44] have been reported. However, IL-1 blockade was usually well tolerated, and the most frequent adverse event was local reaction at the injection site. Drug discontinuation was rarely needed. For example, in an open-label clinical cohort study involving 43 patients diagnosed with CAPS, the cumulative incidence rates for urinary tract infection and pneumonia after a median anakinra exposure of 4.9 years were 14.0% and 11.6%, respectively. Only one out of 273 infectious events (a serious cellulitis) required temporary drug discontinuation [45]. Moreover, disease flares during infection were commonly observed, raising the concern that an abrupt withdrawal of IL-1 blockade would exert a deleterious impact on the course of the underlying inflammatory disorder. Two hospitalized patients with acute gouty arthritis were successfully treated with anakinra despite being on antibiotic therapy for the previous occurrence of severe infection (pneumonia and sepsis), with no exacerbation of intercurrent infections [46]. Only 3 participants in RCTs or open-label extension studies died while on therapy with IL-1-targeted agents (due to *Staphylococcus aureus* bacteremia, pneumococcal meningitis and macrophage activation syndrome [30,43,47]. A recently published RCT recruited (the CANTOS trial) more than 10,000 patients (median age of 61 years) with previous myocardial infarction and elevated CRP levels to receive different doses of canakinumab or placebo during a 48-month period [10]. In addition to the largest sample ever recruited for a trial with IL-1-targeted agents, this study has the advantage to include patients with a priori low baseline risk of infection (as opposed to those with autoimmune and autoinflammatory disorders), a circumstance that would allow to more accurately define the contributing role of canakinumab to infection susceptibility. Neutropenia was more frequent among patients treated with canakinumab, with a significant dose-dependent increase across treatment groups. The incidence of fatal infection or sepsis was also significantly higher with canakinumab than placebo (0.31 versus 0.18 episodes per 100 patient-years; *P*-value = 0.03), as was the incidence of pseudomembranous colitis. The patients dying from infection tended to be older and more likely to have diabetes. On the other hand, no
differences were found in the rates of opportunistic infection between canakinumab- and placebo-treated individuals [10].

Opportunistic infections have been rarely reported. Cases consisted of infection due to nontuberculous mycobacteria (NTM), histoplasmosis and *Candida* esophagitis [27]. A child with juvenile idiopathic arthritis and living in an endemic zone developed visceral leishmaniasis after 6 months of treatment with anakinra, with successful response to therapy [48]. Some pediatric patients with CAPS developed macrophage activation syndrome while on IL-1 blockade, although such event also occurred in the placebo group [40,47]. Only a few episodes of TB have been reported in published RCTs (mostly restricted to the CANTOS trial [10]), which is in contrast with the evidence accumulated for anti-tumor necrosis factor (TNF)-α agents. Such apparent minor risk is especially relevant for patients suffering from Behçet's disease, who frequently live in high-endemic areas [49,50]. There are two isolated case reports of RA patients treated with anakinra developing pulmonary TB reactivation and tuberculous pyomyositis, respectively [31,32]. However, it should be noted that most RCTs with IL-1-targeted agents were carried out in low-prevalence areas and, therefore, the real risk of TB might have been underestimated.

Very limited experience has been gained with the use of IL-1-targeted agents in patients with latent tuberculosis infection (LTBI), although no progression to active TB was noted even with uncompleted courses of anti-tuberculous therapy [51-53]. Finally, antibody responses following the administration of non-adjuvanted influenza and serogroup C meningococcal conjugate vaccines were not affected by canakinumab [54].

A summary of the infectious events reported among patients treated with IL-1-targeted agents across RCTs and observational studies is detailed in Table S1 of Supplementary Material.

*Conclusions and suggested prevention strategies*

- In view of available data, therapy with IL-1-targeted agents is associated with a moderate increase in the risk of infection, usually mild to moderate in severity, among children and adult patients with autoimmune and autoinflammatory disorders.
- However, the risk of serious and life-threatening infection seems to be increased among older patients with previous comorbidities (such as diabetes) receiving IL-1-targeted agents, with such evidence stemming from a single large RCT with canakinumab.
• Patients receiving IL-1-targeted agents should be carefully monitored for the occurrence of infection. The decision of whether to discontinue therapy in case of active infection should be taken on a case-by-case basis by an experienced physician, as abrupt withdrawal can induce a flare of the underlying autoinflammatory disorder.

• In view of the theoretical increased risk of active TB associated to IL-1 blockade and occasional cases of active TB reported in RCTs, screening for LTBI should be considered before starting treatment with IL-1-targeted agents (followed by appropriate therapy if needed).

• Age-appropriate antiviral vaccinations should be strongly encouraged (including pneumococcal and *Haemophilus influenzae* type b [Hib]), especially for young children on long-term treatment with IL-1-targeted agents [55,56]. However, it should be noted that live-virus vaccines (i.e., VZV, yellow fever or measles-mumps-rubella [MMR]) may be contraindicated due to underlying diseases.

• Since certain primary immunodeficiencies (e.g., common variable immunodeficiency) may clinically manifest as autoimmune or autoinflammatory phenomena, it seems advisable to perform a basic evaluation of immune status (i.e., quantification of lymphocyte subpopulations and measurement of serum immunoglobulin levels and complement activity) before initiating IL-1-targeted agents.

**Interleukin (IL)-5-targeted agents: mepolizumab and reslizumab**

*Mechanism of action, approved indications and off-label uses*

Formerly called eosinophil differentiation factor, IL-5 is a homodimeric glycoprotein characterized by its ability to support the growth and differentiation of eosinophils and, to lesser extent, B-cells [57]. Its effects are exerted via heterodimeric receptors comprising an IL-5-specific receptor α subunit (IL-5RA) and a common receptor β subunit (shared with IL-3 and granulocyte-macrophage colony-stimulating factor), which acts as downstream signal-transducing molecule [58]. Its distinctive role as potent growth factor and chemoattractant for eosinophils is thought to be critical in the etiopathogenesis of allergic disorders and eosinophil-mediated conditions [59].

Mepolizumab (Nucala®, GlaxoSmithKline) is a humanized IgG1 monoclonal antibody targeted at IL-5 with high affinity and specificity. By blocking the binding of IL-5 to the α subunit (IL-5RA) of
the receptor complex on the eosinophil cell surface, mepolizumab inhibits IL-5 signaling and renders eosinophils less responsive to chemoattractant factors such as eotaxins [60]. Mepolizumab has been FDA- and EMA-approved as an add-on treatment for severe refractory eosinophilic asthma in adult patients [61]. In addition, mepolizumab has been used for various off-label indications, including eosinophilic granulomatosis with polyangiitis [62], chronic obstructive pulmonary disease (COPD) with an eosinophilic phenotype [63], allergic bronchopulmonary aspergillosis [64], primary hypereosinophilic syndrome [65,66], atopic dermatitis [67], severe nasal polyposis [68] or eosinophilic esophagitis [69]. The recommended dose is 100 mg administered subcutaneously every 4 weeks.

Reslizumab (Cinqaero®, Teva Pharmaceuticals) is a humanized IgG4 monoclonal antibody also targeting IL-5, with a mode of action comparable to mepolizumab. Its use has been approved by both the FDA and EMA as add-on therapy for severe eosinophilic asthma in adult patients inadequately controlled despite conventional therapy [70]. Reslizumab is administered by intravenous (IV) infusion at 4-week intervals.

**Expected impact on the infection risk**

Eosinophilia is a distinctive feature of some parasitic infections, particularly those produced by tissue-invasive helminths (such as *Schistosoma* spp, *Trichinella spiralis* or filarial nematodes), or during the lung migration phase of the life cycle of geohelminths (Löffler syndrome). In addition, some protozoa (i.e., *Dientamoeba fragilis*) can also induce peripheral blood eosinophilia [71]. As strong inducers of Th2 polarization of naïve T-cells, these parasites trigger robust Th2-type cytokine responses involving IL-5, among others [72]. Similarly to the potential effect latter discussed for IgE-targeted agents (omalizumab), the critical role displayed by IL-5 in eosinophil survival and functionality would represent an at least theoretical concern about the eventual risk of parasitic infections among patients receiving mepolizumab or reslizumab. Nevertheless, the so-called “hygiene hypothesis” postulates an inverse association between the development of allergic or autoimmune disorders and chronic infections [73]. Baseline helminthic infections, therefore, would be a priori unlikely among those patients suffering from conditions for which IL-5-targeted agents are currently approved.

**Available clinical data**
The clinical development program for mepolizumab in severe eosinophilic asthma has not demonstrated significant differences in the incidence of infection between study groups. Mepolizumab was generally well tolerated, with rates of adverse events (mostly mild-to-moderate) comparable to those reported with placebo [74-77]. Only two mepolizumab-treated patients recruited in two separate trials developed herpes zoster (HZ) during respective study periods [74,77]. A meta-analysis published in 2013 with 7 RCTs (total n = 1,131) found that mepolizumab significantly reduced eosinophil counts in blood and sputum, as well as the rate of exacerbations compared with placebo. Upper respiratory tract infections were predominant [78]. A long-term open-label extension study in patients who had received mepolizumab or placebo reported similar rates of upper respiratory tract infection and pneumonia for both groups [79]. An indirect treatment comparison between mepolizumab and omalizumab for severe asthma found comparable safety profiles across both agents [80].

Various recently published trials for off-label indications have confirmed the lack of an apparent increase in the risk of infection resulting from IL-5 blockade. Two phase 3 RCTs comparing mepolizumab for 52 weeks with placebo in patients with COPD with previous history of moderate or severe exacerbations while on triple inhaled therapy with high-dose corticosteroids reported similar incidences of infection across study groups. There was only one case of TB in a patient receiving mepolizumab at 300 mg every 4 weeks [63]. Likewise, a RCT recruiting 136 patients diagnosed with eosinophilic granulomatosis with polyangiitis found that infectious complications occurred at similar rates with mepolizumab or placebo, being upper respiratory tract infection (21% and 16%, respectively) the most commonly reported event. Of note, most patients in both groups were receiving immunosuppressive therapy (mainly systemic corticosteroids) at baseline [62]. No serious adverse events during mepolizumab therapy were reported in a RCT for severe nasal polyposis [68].

Existing safety data for reslizumab are more limited, although this agent seems to be also well tolerated across RCTs performed for different conditions [81-84], with upper respiratory tract infection as common adverse events [85].

Finally, and despite the theoretical increase in helminth-specific susceptibility, no cases of parasitic infection have been reported to date in patients receiving IL-5-targeted agents.

Conclusions and suggested prevention strategies
Although an increased susceptibility to helminth infection could be theoretically expected from its mode of action, therapy with IL-5-targeted agents does not increase the risk of infection in view of available clinical data.

No specific prevention strategies are recommended for patients receiving IL-5-targeted agents, although continuous clinical surveillance is advisable since rare adverse events may have been missed given the limited drug exposure so far.

Interleukin (IL)-6-targeted agents: tocilizumab and siltuximab

Mechanism of action, approved indications and off-label uses

Interleukin-6 was discovered over three decades ago as a pivotal and pleomorphic cytokine involved in inflammation, immune regulation and tissue regeneration [86]. To date, two IL-6-targeted agents (tocilizumab and siltuximab) have been approved for the treatment of various autoimmune disorders (Figure 2). In addition, several agents targeting IL-6 or its receptor (IL-6R), such as sirukumab, olokizumab, clazakizumab or sarilumab, are in varying stages of clinical development, as well as a novel sgp130-Fc fusion protein (olamkicept) [86].

Tocilizumab (RoActemra®, Roche) is a humanized IgG1 monoclonal antibody that selectively neutralizes both the soluble and membrane-bound forms of IL-6R. It has been approved (in combination with methotrexate or as sole agent) by the FDA and EMA for the treatment of RA and polyarticular and systemic juvenile idiopathic arthritis [86]. Moreover, tocilizumab has been recently FDA-approved for patients with giant cell arteritis [87]. In adults the drug is administered either as IV infusion of 4 or 8 mg/Kg at 4-week intervals, or subcutaneously at a dose of 162 mg weekly or biweekly depending on patient’s weight and clinical response.

Siltuximab (Sylvant®, Janssen Cilag) is a chimeric (human-murine) IgG1 monoclonal antibody targeting IL-6 that has been approved for the treatment of multicentric Castleman’s disease in human immunodeficiency virus (HIV)- and human herpesvirus (HHV)-8-seronegative patients [88]. Apart from its impact on infection susceptibility discussed below, tocilizumab and the other IL-6- or IL-6R-targeted agents share a number of common class-related adverse events, including alteration of liver function tests, elevation of total and low-density lipoprotein (LDL) cholesterol levels, and lower gastrointestinal tract perforation [89]. Tocilizumab shows a rapid onset of action leading to reductions of inflammatory markers, particularly CRP levels, within the first 1-2 weeks of therapy. This prompt suppression of inflammation has been linked with the
description of serious and even life-threatening episodes of bacterial infection with minimal clinical (fever) or laboratory markers (raised CRP levels) in some case reports [90-92].

Expected impact on the infection risk

Critical to the understanding of the mode of action of tocilizumab and other IL-6- or IL-6R-targeted agents is the recognition that this pleiotropic cytokine has a characteristic signaling pathway, also shared by other members of the so-called IL-6-type or gp130 group of cytokines [93] (Figure 2). All of them exhibit structural similarity and use the protein gp130 as a common signal transducer [86]. There are two distinct forms of IL-6R, soluble and membrane-bound, although the latter is limited to hematopoietic cells, hepatocytes and certain epithelial cells [92]. Binding of IL-6 to its cognate ligand (i.e., IL-6R on a constitutively expressing cell) is not sufficient for generating an activation signal, since the ubiquitously expressed gp130 must be also recruited for successful signal transduction. Dimerization of this second receptor subunit initiates intracellular signaling cascades. This route is referred as classical (or cis-signaling) and is only observed on cells that constitutively express IL-6R [86]. More widespread is signaling via the interaction of IL-6 with the circulating soluble form of IL-6R, which is produced after cleavage of the membrane-bound counterpart in a process likely involving an ADAM family metalloprotease. The resulting cytokine-receptor complex is able to activate cells that only express gp130 (virtually all nucleated cells) but lack membrane-bound IL-6R [86]. This is referred as trans-signaling. Although the interplay between both signaling modalities is complex, it is believed that cis-signaling has primarily housekeeping or physiological functions (including plasma cell differentiation and acute phase response) whereas trans-signaling is a stress pathway. On the basis of animal models, it has been hypothesized that agents primarily targeting the trans-signaling may be more physiological and less prone to induce drug-related complications, including eventually infections [86].

Ex vivo research and genetically manipulated models support the role of IL-6 in generating immunocompetent responses to bacterial, viral or fungal pathogens [90,94]. Of particular importance are the lessons from primary immunodeficiency disorders due to naturally occurring antibodies against IL-6 [86], which involve increased susceptibility to microorganisms such as *Escherichia coli*, *S. aureus* and *Streptococcus intermedius* [90]. Other clinical model highlighting the role of IL-6 in host defense comes from defects in the downstream IL-6 signaling pathways,
namely the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway. Patients with autosomal dominant hyper-IgE syndrome (also known as Job's syndrome) suffer from a disruption in STAT3 that leads to a well-established immunodeficiency phenotype characterized by eczematosid dermatitis, recurrent skin and soft tissue infections (cold abscesses due to \textit{S. aureus} or chronic mucocutaneous candidiasis) and, less frequently, \textit{Aspergillus} bronchiectasis [95].

\textit{Available clinical data}

Both pivotal RCTs and real world experience with tocilizumab suggest that this compound increases the risk of opportunistic and serious bacterial infection to a similar extent as other biological DMARDs also targeting pro-inflammatory cytokines, such as anti-TNF-\(\alpha\) agents. Detailed information is still scarce for other IL-6- or IL-6R-targeted agents in clinical development, although phase 2 and 3 trials with sarilumab, sirukumab, olokizumab or clazakizumab have reported rates of serious infection (0-6\% after 12-24 weeks of exposure) similar than those observed with other biological agents in RA patients [96-102].

A 2011 meta-analysis of data from the tocilizumab development program reported a rate of serious infection of 4.9 per 100 patient-years among participants receiving doses of 8 mg/Kg, and lower for those receiving placebo or tocilizumab at 4 mg/Kg (3.5 per 100 patient-years) [89]. The distribution of infection types was typical of an RA population, with pneumonia, urinary tract infections and cellulitis being most common. In certain age strata the incidence rates were higher, reaching 8.5 episodes per 100 patient-years in those 65 years of age or older. In addition, prior anti-TNF-\(\alpha\) therapy increases the incidence of infection. In a phase 3b trial evaluating tocilizumab at 8 mg/Kg in 1,681 patients, the observed incidence of serious infection was also higher among subjects previously exposed to anti-TNF-\(\alpha\) agents (6.8 episodes per 100 patient-years) compared to those without such therapy (4.2 per 100 patient-years) [103]. Risk factors for tocilizumab-related infection appear similar to those for RA patients with other biological DMARDs, including older age, underlying lung disease and chronic corticosteroid therapy [89]. Using data from 13 RCTs of tocilizumab, Strand et al. estimated an incidence of serious infection of 5.25 per 100 patient-years of exposure, with a relative risk of 1.82 when compared to placebo among those who had previously failed to non-biological DMARDs [104].
Neutropenia occurs more frequently with tocilizumab and the remaining IL-6 or IL-6R-targeted agents as compared to other biological agents. The underlying mechanism is uncertain, although it is thought to be related to neutrophil compartment redistribution. The functional consequences of this decline in the absolute neutrophil count are not clear, and no association between neutropenia and the occurrence of serious infection has been observed in the setting of RCTs [89].

Real world studies on tocilizumab include both open-label multi-center registries and large cohorts of RA patients derived from population-based sources like claims data. An open-label study in Germany reported an incidence of serious infection of 4.4 episodes per 100 patient-years over 52 weeks of tocilizumab exposure, a rate comparable to that reported from RCTs [105]. A similar post-marketing study among biological DMARD-naïve RA patients in Japan (n = 839) found an incidence of 5.84 episodes per 100 patient-years. Importantly, this study documented the role of tocilizumab as a corticosteroid-sparing agent (since 34% of prednisone users discontinued such therapy throughout the 52 weeks of study) [106].

Higher rates of infection have been reported in population-based studies. Within a Japanese tocilizumab cohort of 7,901 users, the incidence of serious infection reached 9.0 episodes per 100 patient-years during the first 28 weeks of therapy [107]. In a US registry based on Medicare claims data, investigators observed an incidence of infection requiring hospitalization of 14.9 episodes per 100 patient-years. These relatively higher estimates likely reflected the older age of this population, as well as the fact that all tocilizumab users included had been previously treated with anti-TNF-α agents. After multivariate adjustment, the relative risk of hospitalization due to infection was not significantly different between tocilizumab and other biological DMARDs [108]. Analyses of US claims data also highlighted the risk of gastrointestinal tract perforation with tocilizumab (1.5-2.5 episodes per 100 patient-years), with more than a two-fold risk increase compared to users of anti-TNF-α therapy. Although not necessarily implying infectious etiologies, such events can be further complicated by the subsequent occurrence of bacteremia and/or sepsis [109].

Regarding the development of opportunistic infection, the above mentioned meta-analysis found 22 cases over 9,000 person-years of tocilizumab exposure (0.23 episodes per 100 patient-years). Most of these infections occurred in patients receiving doses of 8 mg/Kg, and included
active TB, infection due to NTM, invasive candidiasis, *Pneumocystis jiroveci* pneumonia (PCP) and cryptococcosis [89]. As for the “real world” experience, few population-based data have evaluated this issue. A Japanese post-marketing registry suggested that the risk of TB is similar to that observed with anti-TNF-α agents, whereas incidence rates for infection due to NTM and PCP were sensibly higher [107]. The rate of HZ is estimated in about 2.2 episodes per 100 patient-years. In the US, the only large population-based study comparing the risk of opportunistic infection with tocilizumab to other biological DMARDs was recently conducted using US Medicare data. The incidence of HZ was 2.15 episodes per 100 patient-years among patients starting tocilizumab, with no differences compared to other biologicals [110]. In the setting of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, the safety of tocilizumab is largely unknown. Such patients were excluded from RCTs, and only several case reports or series have been published in the literature. These reports include two HBV patients (who received concomitant anti-viral therapy) and one HCV patient. All of them were successfully treated with tocilizumab [111-113]. In addition, several small case-series reported that 2 out of 25 patients with prior HBV exposure had self-limited viremia during tocilizumab therapy [114-116]. In the registry-based Japanese post-marketing surveillance noted above, no hepatobiliary disorders due to HBV or HCV reactivation were observed throughout the 28 weeks following the initiation of therapy. This experience included 52 patients with “prior exposure to HBV,” although their serologic status was not detailed and it is unclear whether they were at high (i.e., HBsAg-positive) or low risk for reactivation (i.e., anti-HBc positive and HBsAg-negative) [107].

**Conclusions and suggested prevention strategies**

- In view of available data, therapy with IL-6- or IL-6R-targeted agents is associated with an increase in the risk of infection similar to that observed with other biological DMARDs (namely anti-TNF-α agents), although it should be noted that most experience is restricted to tocilizumab.
- Therefore, it seems advisable to implement the prevention strategies suggested for patients receiving anti-TNF-α therapy, including screening for LTBI and chronic HBV infection (followed by appropriate prophylaxis or therapy if needed).
- Age-appropriate inactivated vaccination (i.e., trivalent inactivated influenza, pneumococcal or Hib vaccines) should be administered [55,56]. Some live-virus vaccines (i.e., VZV or
MMR) may be contraindicated in patients receiving IL-6- or IL-6R-targeted agents, although additional data are needed before definitive recommendations can be made.

• Since certain primary immunodeficiencies (e.g., common variable immunodeficiency) may clinically manifest as autoimmune phenomena, it seems advisable to perform a basic evaluation of immune status (i.e., quantification of lymphocyte subpopulations and measurement of serum immunoglobulin levels and complement activity) before initiating IL-6 or IL-6R-targeted agents.

• Continuous clinical surveillance in patients under IL-6 blockade is advisable since the underlying mechanisms of infection susceptibility are still poorly understood and rare infections may have been missed given the limited drug exposure so far.

Interleukin (IL)-12/23 p40-targeted agents: ustekinumab

Mechanism of action, approved indications and off-label uses

Ustekinumab (Stelara®, Janssen Cilag) is a fully human IgG1 monoclonal antibody that targets the 40-kDa common cytokine receptor-like subunit p40 shared by IL-12 and IL-23. The receptor of both cytokines—which is expressed on T-cells, among others—is a heterotrimeric protein complex that also shares a common β1 chain (IL-12R1β1). By preventing p40 from binding to IL-12R1β1, ustekinumab inhibits the biologic functions of IL-12 and IL-23 [117]. Ustekinumab was first approved by the EMA and FDA for the treatment of moderate to severe plaque psoriasis or active psoriatic arthritis (alone or in combination with methotrexate). In addition, both agencies also approved in 2016 the use of ustekinumab for adult patients with moderately to severely active Crohn’s disease who have failed or are intolerant to either conventional or TNF-α-targeted therapies or that have contraindications to such therapies [117,118]. In addition, this agent has been used for various off-label indications, including pityriasis rubra pilaris [119], SAPHO syndrome [120], pyoderma gangrenosum [121] or hidradenitis suppurativa [122].

Ustekinumab is given subcutaneously in patients with psoriasis and psoriatic arthritis (first dose of 45-90 mg repeated 4 weeks later and at 12-week intervals thereafter), whereas the regimen for Crohn’s disease comprises a single initial IV dose followed by 90 mg subcutaneous administration after 8 weeks and at 12-week intervals [117,118].

Expected impact on the infection risk
Both IL-12 and IL-23 are mainly produced by macrophages and dendritic cells (DCs) and exert relevant roles in mounting innate and adaptive responses [123]. The cytotoxic activity of natural killer (NK) cells is enhanced in response to IL-12, which dramatically increases the production of interferon (IFN)-γ (particularly by the CD56\textsuperscript{bright} NK cell subset) [124,125]. In addition, IL-12 is crucial in inducing Th1 polarization of CD4\textsuperscript{+} T-cells [126]. Thus, ustekinumab-induced abrogation of the effector functions of IL-12 is expected to confer increased susceptibility to intracellular pathogens. This is well exemplified by a rare condition termed mendelian susceptibility to mycobacterial disease (MSMD), a collection of monogenic disorders in different genes resulting in impaired IL-12-dependent IFN-γ immunity [127]. In detail, mutations in the gene \textit{IL12RB1}, encoding the common receptor chain whose interaction with IL-12 and IL-23 is inhibited by ustekinumab, has been observed in children with severe TB [128]. On the other hand, IL-23 is responsible for the differentiation and maintenance of the Th17 cell population [129]. Therefore, a theoretical risk of fungal infection might be hypothesized in patients treated with ustekinumab by analogy with those suffering from inherited defects in the IL-23/IL-17 axis (chronic mucocutaneous candidiasis) [130] or receiving IL-17-targeted agents [131].

\textit{Available clinical data}

Pivotal RCTs across different indications (psoriasis [132-137], psoriatic arthritis [138,139] and Crohn's disease [140]) and dose regimens did not identify a significant increase in the incidence of infection within the ustekinumab arms. In comparative trials with other biological agents, the overall rate of infectious events (including candidiasis) among participants receiving ustekinumab was lower than or similar to those observed for brodalumab [136], secukinumab [137] or etanercept [133]. Most infections were limited to the upper respiratory tract. Opportunistic infection was only occasionally observed in some of these studies (including \textit{Listeria monocytogenes} meningitis [140], \textit{Candida} esophagitis [140], disseminated histoplasmosis [140], VZV reactivation [132] and oral herpes [137]), although most of the episodes occurred in patients receiving concomitant immunosuppressive drugs (i.e., long-term corticosteroids). Of note, only two cases of active TB were specifically reported (one of them diagnosed 10 months after a single IV ustekinumab dose) [134,140], although it should be noted that most trials were carried out in low-endemic countries and that the requirement of screening for LTBI at enrollment with subsequent treatment if needed was mandatory for some
(but not all) studies [134,139]. The safety profile through up to 3 years of exposure was confirmed in a pooled data analysis from 4 psoriasis trials, in which rates of overall and serious infections among ustekinumab-treated patients were found to be consistent with those expected for psoriasis patients under conventional systemic agents [141].

Post-marketing surveillance based on real-life practices across 93 institutions from different areas (including TB high-endemic countries) showed a cumulative incidence rate of serious infections for ustekinumab-treated psoriasis patients (0.83 per 100 patient-years) that were lower than those observed for patients receiving anti-TNF-α agents or conventional therapies (methotrexate) [142]. A retrospective analysis found an incidence of HZ of 2.5% within the first year of initiating ustekinumab [143], although the specific impact of this agent on the risk of zoster remains controversial [144]. In this regard, the occurrence of multidermatomal HZ [145] and VVZ meningitis [146] has been also reported. Some studies have evaluated the safety of ustekinumab therapy in patients with chronic HBV and HCV infection [147,148]. No episodes of HBV reactivation occurred among HBsAg-positive patients under antiviral prophylaxis or among those at risk of occult HBV infection (i.e., HBsAg-negative, HBc-positive patients) [147]. Finally, no cases of progressive multifocal leukoencephalopathy (PML) have been reported to date.

Conclusions and suggested prevention strategies

• In view of available data, therapy with ustekinumab seems not to be associated with a meaningful increase in the risk of infection.

• Screening for LTBI may be considered before starting treatment with ustekinumab (followed by appropriate therapy if needed), in view of the theoretical increased risk of active TB associated to this agent.

• In addition, screening for chronic HBV infection should be performed before initiating ustekinumab therapy and antiviral prophylaxis given to HBsAg-positive patients for preventing HBV reactivation. There is no sufficient evidence to recommend periodic screening for reactivation of occult HBV infection among HBsAg-negative anti-HBc-positive patients receiving ustekinumab.

• Age-appropriate inactivated vaccination (i.e., trivalent inactivated influenza, pneumococcal or Hib vaccines) should be administered [55,56]. Some live-virus vaccines (i.e., VZV or
MMR) may be contraindicated in patients receiving ustekinumab, although additional data are needed before definitive recommendations can be made.

**Interleukin (IL)-17-targeted agents: secukinumab, ixekizumab and brodalumab**

*Mechanism of action, approved indications and off-label uses*

The discovery in 2005 of the Th17 subset of CD4+ T-cells constituted a notable advance in the understanding of the pathogenesis of immune-mediated inflammatory diseases [149]. IL-17A belongs to a cytokine family comprised of other five members (IL-17B through IL-17F) with varying degrees of sequence homology. Although Th17 cells produce both IL-17A and IL-17F, the former is 10 to 30-fold more potent and, therefore, is considered as the main effector cytokine for this T-cell subset. In addition, both cytokines may form a heterodimer complex (IL-17A/F). The IL-17 receptor (IL-17R) family includes five different subunits (A through E), although both IL-17A and IL-17F signal through the same receptor subunits, IL-17RA and IL-17RC [150].

The presence of IL-17A at high levels at sites of skin and joint disease, such as synoviocytes in patients with RA, fueled interest in developing IL-17A-targeted therapeutic agents. Apart from its pro-inflammatory effects, IL-17A plays a central role in the expression of psoriasis signature genes resulting in keratinocyte activation, which in turn produces cell proliferation, chemokine expression and further immune cell recruitment [151]. In the RA setting, IL-17A (and, to a lesser extent, IL-17F) enhance the expression of cytokine receptors by synovial cells and contribute to cell migration, chemokine gene expression and synoviocyte invasiveness [152].

Interestingly, therapeutic blockade of IL-17A has been proven to be ineffective in Crohn’s disease, with a proof-of-concept placebo-controlled trial being prematurely stopped due to futility [153]. The unexpected higher rate of disease worsening among treated patients suggests some degree of tissue-specificity in the clinical effect of monoclonal antibodies, despite sharing a common mode of action at the molecular level [154].

Secukinumab (Cosentyx®, Novartis) is a fully human IgG1κ monoclonal antibody that selectively targets to IL-17A. By blocking the binding of the IL-17A ligand with the IL-17RA receptor subunit, secukinumab inhibits the downstream release of pro-inflammatory cytokines and chemokines that contribute to autoimmune and inflammatory diseases [149]. Secukinumab was the first IL-17A-targeted agent approved for the treatment of moderate-to-severe plaque
psoriasis in 2015 [155]. In 2016, the FDA announced the approval of secukinumab to treat adults with active ankylosing spondylitis and psoriatic arthritis [156]. All these indications have been also granted by the EMA. Importantly, secukinumab has no apparent effect on IL-17F or on other functions exerted by Th17 cells [149]. Ixekizumab (Taltz®, Eli Lilly) is a humanized IgG4 monoclonal antibody targeting IL-17A [157], which has been also approved in 2016 for moderate-to-severe plaque psoriasis [158]. Brodalumab (Siliq®, or Kyntheum®, Valeant Pharmaceuticals) is a fully human IgG2 monoclonal antibody targeting IL-17RA [159]. Contrary to secukinumab and ixekizumab, brodalumab does not target the ligand but the receptor of the IL-17 signaling pathway. Therefore, this agent also blocks the activity of IL-17F, IL-17E (also known as IL-25) and the IL-17A/F heterodimer [159]. In 2017, the FDA and EMA approved the use of brodalumab for the treatment of moderate to severe plaque psoriasis in adult patients who had failed to respond or had lost response to other systemic therapies [160].

Expected impact on the infection risk

In addition to its nature as signature cytokine of the Th17 cell subset, other sources of IL-17A also include CD8+ and γδ T-cells, natural killer (NK) cells, mast cells and neutrophils [161]. Multiple roles have been described for IL-17A, such as neutrophil granulopoiesis and chemotaxis through upregulated expression of ELR-positive chemokines, antimicrobial peptide expression (namely β-defensin-2), and macrophage stimulation [149]. The clinical implications of the therapeutic IL-17A blockade can be anticipated from the phenotype observed in certain primary immunodeficiencies that result from nonsense mutations in genes coding for IL-17A, IL-17F or IL-17RA, or from the development of anti-IL-17 autoantibodies (i.e., autoimmune polyendocrinopathy syndrome type 1). These patients have increased susceptibility to Candida infections of the mucosal, nail and skin surfaces, which may exhibit a persistent or recurrent course (chronic mucocutaneous candidiasis). Disseminated or invasive forms of candidiasis rarely occur. No mutations in the IL17A gene have been associated to systemic immunodeficiency to date [162]. Therefore, it appears that IL-17A does not play a significant role in systemic immunity, contrary to tumor necrosis factor alpha (TNF)-α [161-163]. Moreover, the role displayed by IL-17 cytokines against other pathogens seems to be largely redundant [162]. It has been recently demonstrated that the use of secukinumab has no in vitro effect on
Mycobacterium tuberculosis dormancy within granulomas, as opposite than anti-TNF-α agents [164].

Available clinical data

Several phase 2 and 3 RCTs evaluating the safety and efficacy of secukinumab have been performed. A recent pooled analysis of 10 of these studies, encompassing 3,993 patients with moderate to severe plaque psoriasis treated with secukinumab at various doses or etanercept, found that upper respiratory tract infections were the most common infectious events [165]. The requirement for oral or IV antimicrobial therapy was similar between the secukinumab and the etanercept group. There were no significant differences in the exposure-adjusted incidence rate of adverse events across both groups. As expected, the incidence of candidiasis was higher among patients receiving secukinumab, with a dose-cumulative gradient (incidence rates of 3.55, 1.85 and 1.37 episodes per 100 patient-years for secukinumab 300 mg or 150 mg and etanercept, respectively). However, all these events were non-serious mucosal or cutaneous candidiasis (with no cases of chronic or systemic infection), responsive to standard antifungal treatment, and not leading to drug discontinuation. No disseminated VZV infection was reported. Grade 3 neutropenia was uncommon (0.5% of patients receiving secukinumab) and was not associated with serious infections [165]. Similar results were reported from a phase 3 trial with 606 patients diagnosed with psoriatic arthritis and treated with secukinumab, with upper respiratory tract infection as the most common adverse event during the entire safety-data period [166]. Although Candida infections were more frequent among patients receiving secukinumab, all the cases responded to oral therapy and the patients continued in the study [166]. No serious opportunistic infections were observed. Finally, a RCT with 30 patients with ankylosing spondylitis randomly assigned to receive secukinumab or placebo reported only one serious infection (a subcutaneous abscess due to S. aureus). Although some cases of leucopenia and neutropenia were reported, all of them were considered as grade 1 and did not show any apparent temporal association with the occurrence of infection [167].

A systematic review of three major phase 3 RCTs of brodalumab for plaque psoriasis reported that upper respiratory tract infections were among the most common adverse events [168]. All cases of neutropenia were mild and transient, with no associated infections. Infections produced by Candida spp. were also more common among patients treated with brodalumab than in
those receiving placebo, but again were mild to moderate and did not require drug discontinuation [168]. Recently, a systematic review and meta-analysis of the safety and efficacy of brodalumab for plaque psoriasis, which included in the final analysis 6 RCTs with more than 4,000 patients, found no statistically significant differences in terms of serious adverse events or infection in the short term. Unfortunately, there was not sufficient data to confirm such safety profile for longer exposure periods [169].

A pooled analysis of 7 controlled and uncontrolled ixekizumab psoriasis trials, with approximately 4,200 patients followed for a median of 507 days, has been recently published [170]. Although the overall rate of infection was significantly higher for ixekizumab than for the comparator during the induction (weeks 0 to 12) period of therapy (118.4 versus 100.5 episodes per 100 patient-years, respectively), the incidence of serious infections was low and similar between active treatment groups (2.4 and 1.8 episodes per 100 patient-years for ixekizumab and etanercept). Upper respiratory and urinary tract infections were the most commonly reported syndromes, whereas cellulitis was the predominant serious infection. Candida infections were more frequently diagnosed in the ixekizumab group (4.8 episodes per 100 patient-years), particularly oral and vulvovaginal candidiasis. None of the cases of Candida infection (including the 8 episodes of esophageal candidiasis) required discontinuation of ixekizumab [170]. Only 2 patients developed non-serious VZV infection within the ixekizumab-treated group. There were no cases of TB, although it should be noted that most patients were recruited from low-endemic countries and that LTBI screening was usually mandatory. Likewise, no HBV or HCV reactivation was reported either, with most RCTs requiring screening for chronic infection before initiating the study drug [170].

Finally, a recent systematic review of 13 RCTs of IL-17-targeted agents for psoriasis or psoriatic arthritis found that Candida infection occurred in 4.0%, 1.7% and 3.3% of patients treated with brodalumab, secukinumab and ixekizumab (compared to 0.3%, 2.3% and 0.8% for those receiving placebo, ustekinumab or etanercept, respectively) [171].

**Conclusions and suggested prevention strategies**

- In view of available data, therapy with IL-17-targeted agents is associated with a minor increase in the risk of infection, usually mild to moderate in severity.
Clinicians caring for patients receiving IL-17-targeted agents should be aware of the increased risk of Candida infections (which seems to be slightly higher for brodalumab and ixekizumab than secukinumab). Most of these cases are limited to mild to moderate mucocutaneous involvement, respond to oral or topical antifungal therapy, and do not require drug discontinuation.

Screening for LTBI should be considered before starting treatment with IL-17-targeted agents (followed by appropriate therapy if needed), although the risk of progression to active TB associated with IL-17 blockade seems to be low.

Immunoglobulin (Ig) E-targeted agents: omalizumab

Mechanism of action, approved indications and off-label uses

Omalizumab (Xolair®, Novartis Pharmaceuticals) is a recombinant humanized IgG1 monoclonal antibody targeted at the third constant (Cε3) domain of the Fc portion of the circulating IgE. The Cε3 portion of the IgE molecule electrostatically binds to the α2 subunit of the high-affinity IgE receptor (FcεRI). By inhibiting the binding of free IgE to its receptor on the surface of mast cells and basophils, omalizumab reduces mediator release at the start of allergic responses [172] and subsequently induces the internalization of FcεRI on these effector cells [173]. Omalizumab has been approved by the EMA and FDA for the treatment of severe persistent allergic asthma in adults and children with a positive skin test or in vitro reactivity to a perennial aeroallergen in presence of reduced pulmonary function, frequent symptoms and multiple severe exacerbations despite conventional therapy [174]. In 2014, omalizumab received an additional EMA approval as add-on therapy for patients with chronic spontaneous urticaria with inadequate response to H₁ antihistamine treatment [175]. In addition, omalizumab has been used for various off-label indications, including intrinsic asthma lacking IgE-specific sensitization [176], atopic dermatitis [177], allergic bronchopulmonary aspergillosis (ABPA) [178,179], and a large spectrum of IgE-mediated conditions (i.e., drug allergy, angioedema, allergic rhinitis, systemic mastocytosis or Churg-Strauss syndrome) [180]. The dose and frequency of administration must be individualized according to baseline IgE levels and body weight (with a maximum recommended dose of 600 mg subcutaneously every two weeks).

Expected impact on the infection risk

25
The role played by IgE in the immune response against parasites raises theoretical concerns about the potentially increased susceptibility to parasitic infections in patients receiving omalizumab. Particular attention has been focused on the so-called geohelminths (or soil-transmitted helminths), which comprise Ascaris lumbricoides, Trichuris trichiura, hookworms (Ancylostoma duodenale and Necator americanus), and Strongyloides stercoralis [181]. Antigens from both larval and adult forms of these parasites are strong inducers of Th2 responses, mainly orchestrated through the effector functions of IL-4 and IL-13 [72]. This results in the activation and expansion of CD4+ Th2 cells, IgE-secreting plasma cells, eosinophils, mast cells and basophils, all of which may produce various Th2-type cytokines. Persistent exposure to helminths has been shown to be associated with increased serum levels of IgE, suggesting the physiological nature of this response [182]. Helminth antigens cross-link IgE-FcεRI complexes on the surface of mast cells to trigger their activation and degranulation [183].

However, the precise contribution of helminth-specific IgE to the development and maintenance of protective anti-parasite immunity has not been fully elucidated, particularly in view of the multiplicity of innate and adaptive immune mechanisms elicited by these pathogens [183]. On the other hand, omalizumab does not significantly alter the intracellular expression pattern of Th1 or proinflammatory cytokines in circulating T-cells, which would indicate a minor impact on the immunity against intracellular opportunistic pathogens [184].

Available clinical data

Pivotal RCTs performed within the clinical development program for omalizumab found no significant differences in the incidence of infection between study groups. This safety profile was consistent across different indications, such as severe persistent asthma [185-191], chronic urticaria [192], or seasonal allergic rhinitis [189,193-195]. Most events in the omalizumab arm were upper or lower respiratory tract infections. Only one single trial found a higher incidence of upper respiratory tract infection among patients with chronic idiopathic/spontaneous urticaria receiving omalizumab compared to placebo (7.1% versus 2.4%, respectively) [196]. In addition, long-term post-marketing surveillance has shown that omalizumab therapy is not associated with an increased risk of other potentially immunosuppression-related adverse events, such as malignancy [197].
The incidence of helminth infection in pivotal trials with omalizumab was low, with one case of *Enterobius vermicularis* infection and a further unspecified parasite infection (accounting for less than 1 case per 1,000 treated patients) [198]. Nevertheless, it should be noted that most studies did not describe whether specific parasitic disease surveillance was applied at screening or throughout the study period. In addition, the exclusion of patients with documented infection at the baseline evaluation was rarely stated in the description of the study [193, 196, 199]. Thus, some degree of underreporting should not be ruled out, particularly for mild to moderate helminth infections.

Few studies have specifically assessed the incidence of parasitic infection among patients receiving omalizumab [200, 201]. Cruz et al. conducted a randomized trial in Brazil that recruited 137 patients diagnosed with allergic asthma and either a concurrent geohelminth infection or that were considered at high risk for such a condition (prior documented history of infection, household member with geohelminth infection within the previous year, or positive assay for *Ascaris*-specific IgE at the pretreatment screening). All the participants received broad-spectrum anthelmintic drugs (albendazole, ivermectin and praziquantel in the presence of schistosomiasis) before initiating a 52-week course of omalizumab or placebo. Stool examination was centrally performed every 4 weeks during the treatment and follow-up periods. By using this rigorous approach, the authors found that 50.0% of patients receiving omalizumab had at least one episode of geohelminth infection (mostly due to *A. lumbricoides*) compared with 40.6% of those receiving placebo. After adjusting for baseline active infection status, there was a nearly significant trend towards increased risk of geohelminth infection associated to omalizumab (odds ratio: 2.2; 95% CI: 0.94-5.15). However, no differences were observed in terms of infection severity or response to anthelmintic drugs [200]. Unfortunately, this trial is limited by small sample size and did not provide safety data regarding systemic helminth infections such as schistosomiasis. A non-comparative study in Turkey included 19 patients in which stool examination were performed at months 4 and 8 of omalizumab therapy, reporting one single case of *Giardia lamblia* infection and no episodes of geohelminth infection [201].

The development of hepatic hydatidosis due to *Echinococcus multilocularis* after two years of omalizumab therapy has been anecdotally reported in a patient from a high endemic area [202]. There are no documented cases of *S. stercoralis* hyperinfestation syndrome potentially
associated to omalizumab. Interestingly, and in accordance with its presumed lack of impact on Th1 responses [184], omalizumab has been successfully used in patients diagnosed with ABPA with no evidence of development of invasive aspergillosis [179].

Finally, it could be hypothesized that individuals with high parasite burden (i.e., microfilaremia or chronic asymptomatic strongyloidiasis) would be relatively unlikely to have an IgE-mediated condition for which omalizumab therapy is indicated, due to the suggested existence of an apparent inverse association between allergy and chronic helminth infection (the so-called “hygiene hypothesis”) [73].

Conclusions and suggested prevention strategies

- Both biological rationale and clinical evidence suggest that therapy with IgE-targeted agents may be associated with a modest increase in the risk of parasitic infection, mainly due to geohelminths, with most cases mild to moderate in nature.
- This complication is to be particularly expected among migrants from endemic areas (resource-limited countries with warm, moist climates and poor sanitation), as well as among residents of non-endemic areas that had spent long periods in endemic areas.
- In both high-risk scenarios, routine screening for geohelminths (including conventional stool examination [i.e., Kato-Katz thick smear method] and specific surveillance for S. stercoralis [i.e., Koga agar plate culture or Baermann concentration technique, ideally associated to serological testing]) should be performed at the pretreatment evaluation. In positive cases, specific antiparasitic therapy should be given before initiating omalizumab.
- For migrants coming from specific endemic areas, pretreatment screening may be further extended to certain geographically restricted systemic helminth infections (i.e., filariasis or schistosomiasis), although evidence of omalizumab-induced increased susceptibility to these conditions is lacking.
- An alternative approach could be based on the empirical administration of broad-spectrum anthelmintic drugs (albendazole plus ivermectin) for patients coming from endemic areas, although the cost-effectiveness of this strategy seems questionable and must be balanced with the risk of potential adverse events (i.e., ivermectin-induced encephalopathy in subjects with high Loa loa microfilaremia).
• Repeated screening for geohelminths during the course of omalizumab therapy is unlikely to provide further benefit, except in patients at continuous high risk for potentially severe infections (namely, strongyloidiasis) due to ongoing exposure (i.e., long-term residents in endemic areas).

• No expected benefit is expected from routine pretreatment screening among residents in non-endemic countries or individuals with short-term exposure (i.e., tourist travel to endemic areas), due to their very low risk for baseline helminth infection.

Complement component 5 (C5)-targeted agents: eculizumab

Mechanism of action, approved indications and off-label uses

Eculizumab (Soliris®, Alexion) is a recombinant humanized monoclonal IgG2/4 monoclonal antibody targeting complement protein C5. This first-in-class agent blocks the formation of the C5 convertase (C4bC2aC3b for classical and mannose-binding lectin [MBL] activation pathways and [C3b]2Bb for alternate pathway) and its subsequent cleavage into the anaphylatoxin C5a (with potent prothrombotic and proinflammatory effects) and C5b. Therefore, eculizumab prevents the formation of the terminal membrane attack complex (MAC) C5b-C9 [203]. The MAC plays a key effector role in complement mediated hemolysis and extracellular killing in pyogenic infections, especially for bacteria belonging to the genus *Neisseria* [204]. Since all three activation pathways of the complement cascade converge at the point of C5 activation, the advent of eculizumab has opened novel horizons for the treatment of a plethora of complement-mediated disorders [205].

Eculizumab was first approved for the treatment of paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS)-associated thrombotic microangiopathy (TMA) in 2007 and 2011 respectively, by both the FDA [206] and EMA [207].

Intravascular hemolysis in PNH results from a deficiency in glycosylphosphatidylinositol (GPI)-anchored proteins CD55 and CD59, which protect cells from complement-mediated destruction [203]. Eculizumab has dramatically revolutionized the management of PNH [208]. It has proven not only to reduce hemolysis and prevent thrombotic events [209-211], but also to improve anemia, renal function, quality of life [212] and patient survival [213]. The recommended eculizumab regimen for this indication consists of 4 weekly IV induction doses of 600 mg followed by lifelong maintenance with 900 mg fortnightly.
Hyperactivation of complement's alternative pathway, resulting from mutations in regulatory genes, underlies the pathogenesis of TMA associated to aHUS [203]. Eculizumab regimen for aHUS consists of 4 weekly IV doses of 900 mg, followed by fortnightly maintenance with 1,200 mg. There is no consensus on the duration of therapy, although there are reports of successful early discontinuation [214]. Eculizumab therapy decreases plasmapheresis requirements and allows to achieve sustained TMA-free status, with improvements in renal function and quality of life [215]. In addition, the proven efficacy of eculizumab includes the prevention and treatment of TMA recurrence following kidney transplantation (KT) [216-218] and of other complement-amplifying conditions associated with aHUS, such as post-partum [219], infection-induced [220,221] or drug-induced TMA [222], as well as those forms associated to autoimmune conditions such as lupus nephritis, antiphospholipid antibody syndrome, scleroderma or ulcerative colitis [223].

Following the model of aHUS, eculizumab use has been extended to the therapy of transplant associated TMA (TA-TMA) in both hematopoietic stem cell transplantation (HSCT) [224,225] and other solid organ transplants apart from kidney [226]. However, recent data suggest that benefit in TA-TMA may be limited to improvements in hematological and renal parameters, with little impact on overall survival, especially among patients with comorbidities [227].

Limited evidence suggests that eculizumab decreases glomerular inflammation and endocapillary proliferation in C3 glomerulopathies, improving proteinuria and renal function in the most inflammatory forms of disease [214,228].

Both the C3a and C5a anaphylatoxins are pivotal in ischemia-reperfusion injury leading to delayed allograft function (DGF) among KT recipients [229]. In 2014, eculizumab was granted orphan drug designation for the prevention of DGF after KT. However, a phase 2-3 RCT assessing its efficacy to reduce the occurrence of DGF among high-risk KT recipients failed to meet its primary endpoint (ClinicalTrials.gov identifier: NCT02145182). A second multicenter RCT with a similar aim is underway.

Classical activation pathway also plays a partial but key role in the complex pathogenesis of donor-specific antibody-mediated graft rejection (AMR) [230]. Nevertheless, the evidence supporting the use of eculizumab for prevention and treatment of AMR is heterogeneous and conflicting. Despite successful reports of AMR reversal in a variety of solid organ transplant
recipients [230], failure of salvage therapy with eculizumab in KT recipients has been reported [231,232]. In a small, uncontrolled trial, eculizumab reduced the incidence of AMR by 33% in crossmatch-positive live donor KT recipients [233]. However, this approach did not prevent subclinical rejection in the long-term follow-up, nor did it improve graft survival [234]. An open-label multicenter phase 2 trial also failed to show any benefit from eculizumab in the prevention of AMR (NCT01399593). Further ongoing trials are currently trying to address this gap.

The blockade of MAC formation has been explored for the treatment of a diverse array of clinical disorders, including inflammatory retinal diseases [235] and delayed or chronic hemolysis [236,237]. In asthma, control of allergen-induced responses via C5a inhibition has also been hypothesized [238]. However, the field of neurological disorders is where eculizumab shows more promise, since its efficacy and safety in the treatment of Guillain-Barre syndrome [239], neuromyelitis optica spectrum disorder [240] and refractory myasthenia gravis [241] is being investigated further in ongoing trials.

Expected impact on the infection risk

Inhibition of MAC results in defective bactericidal complement activity [204]. Nevertheless, invasive infections with encapsulated organisms like *S. pneumoniae* or *Haemophilus influenzae* type b are rarely seen during eculizumab therapy [242], likely thanks to the presence of effective upstream complement function and opsonization [204]. Therefore, the impact of deficient C5b-C9 on the risk of infection is mainly restricted to a notable increase in the susceptibility to *Neisseria* spp. [243].

Available clinical data

Patients treated with eculizumab face approximately a 10,000-fold increase in the risk of meningococcal infection, with a reported incidence of up to 1.5%. In the setting of RCTs, 4 patients developed invasive meningococcal disease while on eculizumab, despite 3 of them having being previously vaccinated [206,211,212]. This prompted the FDA to mandate eculizumab manufacturers to implement a Risk Evaluation and Mitigation Strategy.

According to recommendations from the Advisory Committee on Immunization Practices (ACIP) and EMA, patients starting eculizumab therapy should be immunized with a tetravalent meningococcal vaccine at least 2 to 4 weeks prior to treatment initiation or as soon as possible if therapy is urgent. It is preferable to use the more immunogenic conjugate vaccines.
(MenACWY), which contain either tetanus toxoid or the CRM\textsubscript{197} derivative of diphtheria toxin as the protein carrier. Two initial doses of MenACWY-D (Menactra®, Sanofi Pasteur or Nimenrix®, Pfizer) or MenACWY-CRM (Menveo®, Novartis Pharmaceuticals), separated by at least 8-12 weeks are recommended [244]. In addition, simultaneous immunization against meningococcal serogroup B (MenB), the most common one in Europe and the US, is now feasible thanks to the innovative approach of reverse vaccinology. MenB-4C (Bexsero®, Novartis Pharmaceuticals) must be administered in 2 monthly doses. MenB-fHbp (Trumenba®, Pfizer) is licensed in the US as a 3-dose series administered at 0, 2 and 6 months, but still not authorized in the European Union. Nevertheless, it should be noted that breakthrough cases have been reported despite prior vaccination (Table 2), often caused by different non-vaccine serogroups or due to the lack of protective specific antibody titers [245-251].

During the window period until protective antibody titers are achieved, antibiotic prophylaxis should be administered. All participants in pivotal RCTs who were vaccinated after initiation of the drug received 2 weeks of meningococcal chemoprophylaxis [206,252]. Nevertheless, seroprotection can be achieved as early as a month after completion of vaccination in healthy individuals. On the other hand, vaccine efficacy is expected to be similar for patients with late complement deficiency [253,254].

Serum bactericidal antibody titers are the gold standard surrogate for protection against invasive meningococcal disease and for vaccine efficacy. However, commercial assays are not available. Moreover, the utility of this biomarker in the assessment of protection is still controversial. There is some evidence suggesting that serum bactericidal antibody titers may correlate directly with serogroup-specific IgG titers, and that IgG levels greater than 2 µg/ml can be considered protective [255,256]. Of note, complement deficient patients may require higher levels (over 5 µg/ml) for effective meningococcal phagocytosis [254]. Booster doses of MenACWY should be given every 5 years if eculizumab therapy is continued. The duration of protection for MenB vaccination is less understood [257]. In a recent study, about 70% of healthy adolescents that received a single dose of MenB-4C had protective titers after 18-24 months, a rate significantly lower than those obtained after two (77-94%) or three (86-97%) vaccine doses [258].

Disseminated gonococcal infection, an uncommon form of infection due to \textit{N. gonorrhoeae}...
associated to fever, rash, migratory arthralgias, tenosynovitis and periarticular pustules, has been also reported with eculizumab [259,260]. Two young women with PNH that had being treated with eculizumab for more than a year and exhibiting high-risk sexual behavior developed gonococcemia. The first patient presented with fever and septic shock 6 days after the last drug infusion. Screening for other sexually transmitted diseases was negative, and blood cultures became negative after 7 days of antibiotic therapy [49]. The second patient developed fever and painful arthritis. Gonococcus was detected in blood and urogenital screening. Eculizumab was resumed 3 weeks after completion of a 2-week course of ceftriaxone [260]. Both patients had a favorable outcome.

Apart from neisserial infections, up to 42% of patients receiving eculizumab in the setting of RCTs developed respiratory tract infections compared to 23% of those receiving placebo [206]. Anecdotal reports of *Pseudomonas aeruginosa* bacteremia therapy have been reported, suggesting a potentially under-recognized role of terminal complement in the effective killing of Gram-negative rods [227,261-263].

There is growing evidence suggesting the contribution of the complement system to T-cell regulation [264]. In agreement with this, herpes simplex virus-1 infection (in form of acute necrotizing herpetic tonsillitis) and respiratory tract viral syndromes have been observed with eculizumab [206,265]. The recent report of a multivisceral transplant recipient treated with eculizumab for 12 months due to aHUS and subsequently diagnosed with PML raises the possibility that the blockade of MAC formation might increase susceptibility to this complication. However, it should be noted that other contributing factors (i.e., T-cell depleting agents or long-term therapy with tacrolimus) were also present in this case [266].

Finally, although fungi have a thick cell wall that resists MAC-mediated lysis, the killing of *Aspergillus* conidia partly relies on C3-dependent opsonization and C5a-mediated inflammatory response [267]. A 19-year-old female with aHUS on peritoneal dialysis that had been receiving eculizumab for 3 years developed polymicrobial peritonitis due to *A. niger*, *Escherichia coli* and *Enterococcus faecium*. She was successfully managed with voriconazole and antibiotic therapy, removal of the dialysis catheter, intraabdominal drainage and discontinuation of eculizumab [268].

The risk of infection during eculizumab therapy can be indirectly estimated via monitoring of
complement blockade and eculizumab efficacy. Soluble C5b-C9 (sCD5-C9), C5 activity and total hemolytic complement (CH50) levels have been proposed as surrogate markers of complement inhibition. In a recent study, an enzyme immunoassay for the qualitative determination of functional classical, MBL and alternative activation pathways (Wieslab® Complement system Screen kit, Euro Diagnostica) showed high sensitivity and specificity detecting C5 activity. The authors observed that terminal complement activity remained blocked in patients’ samples for up to four weeks after the last eculizumab infusion [269]. According to available literature, the most promising biomarker appears to be CH50, which negatively correlates with free eculizumab levels [270-272]. Appropriate clinical response to eculizumab is associated with complete CH50 blockade (CH50 <10%), steady eculizumab therapeutic levels and low sC5-C9 [270,271]. The clinical use of therapeutic drug monitoring for eculizumab is limited by test availability and long turnaround time.

Conclusions and suggested prevention strategies

• In view of available data, therapy with eculizumab is associated with a markedly increased risk of infection due to Neisseria spp, either in form of invasive meningococcal disease or, to a lesser extent, disseminated gonococcal infection. Therefore, eculizumab is contraindicated for patients with no adequate meningococcal vaccination.

• Meningococcal vaccination should be administered at least 2 to 4 weeks before starting eculizumab (or as soon as possible if therapy is urgent). Immunization regimen should include tetravalent conjugate vaccine (MenACWY) and serogroup B vaccine (MenB), according to the corresponding recommended schedules. In addition, booster doses of MenACWY should be given every 5 years if eculizumab therapy is maintained.

• Meningococcal chemoprophylaxis with penicillin V (250 mg every 12 hours) or ciprofloxacin (500 mg daily) should be administered for at least 4 weeks since completion of the immunization regimen or until protective antibody titers are documented (if possible).

• Continuation of chemoprophylaxis throughout the overall duration of eculizumab therapy should be strongly considered for previously immunocompromised patients (i.e., transplant recipients), in whom impaired humoral responses may confer insufficient protection following vaccination. In such cases, chemoprophylaxis discontinuation could be considered after 4 weeks from the last dose of eculizumab or, ideally, be guided by the
normalization of CH50 levels and clearance of the drug.

- The clinical utility of monitoring of serum bactericidal antibody titers as surrogate for protection against invasive meningococcal disease remains unclear, although such strategy may help to guide the requirements for vaccine booster and prolongation of chemoprophylaxis. One possible strategy is to monitor serogroup-specific bactericidal IgG titers every 6 months.

- Clinicians caring for patients receiving eculizumab should maintain close monitoring for the occurrence of symptoms or signs suggestive of neisserial infection, even among vaccinated patients, since cases of invasive meningococcal disease despite adequate prior vaccination and/or chemoprophylaxis have been reported.

- Patients with high-risk behaviors for sexually transmitted diseases and their partners should receive counseling and screening for gonococcal infection (preferably by nucleic acid testing techniques) prior to the initiation of and throughout the course of therapy with eculizumab.

- Although the risk of infection is clearly lower for other encapsulated bacteria, unvaccinated patients should be immunized against *S. pneumoniae* and *H. influenza* type b (Hib) according to current guidelines before starting eculizumab [55,56].

- Since the role of complement in the prevention and clearance of non-encapsulated bacterial, viral and fungal pathogens is poorly understood, no recommendation can be made on the potential benefit derived from the use of antiviral, anti-*Pneumocystis* or antifungal prophylaxis in patients receiving eculizumab.
Figure legends

Figure 1. Structure of different IL-1-targeted agents. Canakinumab is a fully human IgG1 monoclonal antibody and gevokizumab is a humanized monoclonal antibody, both targeting IL-1β. Anakinra is a recombinant IL-1 receptor antagonist that inhibits the binding of IL-1α and IL-1β to IL-1R by mirroring the mode action of the endogenous form (IL-1-RA). Rilonacept is a fusion protein composed of the ligand-binding domains of IL-1R1 and IL-1RAcP linked to the Fc portion of human IgG1.

Figure 2. Different signaling pathways for IL-6 and mode of action of IL-6- or IL-6R-targeted agents. The classic or cis-signaling pathway (a) is restricted to cells that constitutively express the membrane-bound form of IL-6R (mIL-6R), mainly hematopoietic cells, and is supposed to primarily exert housekeeping and physiological functions. Upon binding of IL-6 to mIL-6R, homodimerization of gp130 is induced and a functional receptor complex (IL-6/mIL-6R/gp130) is formed, thus triggering the downstream signaling cascade. On the contrary, the trans-signaling pathway (b) initiates with the binding of IL-6 to the soluble form of IL-6R (sIL-6R), produced by cleavage of mIL-6R and lacking the intracytoplasmic portion. The resulting complex (IL-6/sIL-6R) is able to activate virtually all nucleated cells, since gp130 is expressed ubiquitously in the body. This pathway has been implicated in stress signaling. Tocilizumab is a humanized IgG1 monoclonal antibody targeting both mIL-6R and mIL-6R, whereas siltuximab is a chimeric IgG1 monoclonal antibody that binds to IL-6.
Table 1. Summary of reviewed agents, mechanism of action and indications.

<table>
<thead>
<tr>
<th>Agents</th>
<th>Targeted molecule or pathway</th>
<th>Currently approved indications&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anakinra, cabakinumab, gevokizumab, rilonacept</td>
<td>IL-1α and/or IL-1β</td>
<td>Rheumatoid arthritis, juvenile idiopathic arthritis, CAPS, FMF, TRAPS, hyper-IgD syndrome/MKD, Still’s disease, gout</td>
</tr>
<tr>
<td>Mepolizumab, reslizumab</td>
<td>IL-5</td>
<td>Eosinophilic asthma</td>
</tr>
<tr>
<td>Tocilizumab, siltuxumab</td>
<td>IL-6</td>
<td>Rheumatoid arthritis, juvenile idiopathic arthritis, giant cell arteritis, multicentric Castleman’s disease</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>IL-12 and IL-23 (common p40 subunit)</td>
<td>Psoriasis, psoriatic arthritis, Crohn’s disease</td>
</tr>
<tr>
<td>Secukinumab, ixekizumab, brodalumab</td>
<td>IL-17</td>
<td>Psoriasis, psoriatic arthritis, ankylosing spondylitis</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>IgE</td>
<td>Allergic asthma, chronic spontaneous urticaria</td>
</tr>
<tr>
<td>Eculizumab</td>
<td>Complement component C5</td>
<td>Paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome</td>
</tr>
</tbody>
</table>


<sup>a</sup> Off-label uses are not depicted.
Table 2. Summary of case reports of invasive meningococcal disease in patients receiving eculizumab.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (years), gender</th>
<th>Underlying disorder</th>
<th>Vaccine type</th>
<th>Prophylaxis (agent)</th>
<th>Serogroup</th>
<th>Presentation</th>
<th>Infection onset after initiation of ECU or vaccination</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vicente et al. 2012 [246]</td>
<td>27, M</td>
<td>PNH</td>
<td>Men-4ps</td>
<td>No</td>
<td>X</td>
<td>Septic shock</td>
<td>NA</td>
<td>Death</td>
</tr>
<tr>
<td>Strujik et al. 2013 [247]</td>
<td>19, F</td>
<td>aHUS, KT</td>
<td>Men-4ps</td>
<td>No</td>
<td>W135</td>
<td>Septic shock</td>
<td>18 months</td>
<td>Recovery</td>
</tr>
<tr>
<td>Applegate et al. 2016 [249]</td>
<td>41, M</td>
<td>PNH</td>
<td>Men-4ps</td>
<td>No</td>
<td>NA</td>
<td>Meningitis, septic shock</td>
<td>3 years</td>
<td>Recovery</td>
</tr>
<tr>
<td>Hernando-Real et al. 2017 [250]</td>
<td>23, M</td>
<td>PNH</td>
<td>MenACWY, MenB</td>
<td>Yes, secondary (penicillin V)</td>
<td>B&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Septic shock</td>
<td>4 years after initiation of ECU, 10 months after MenB</td>
<td>Recovery</td>
</tr>
<tr>
<td>Friedl et al. 2017 [251]</td>
<td>22, M</td>
<td>SLE-TMA</td>
<td>MenB, MenC</td>
<td>Yes, primary / secondary (ciprofloxacin)</td>
<td>W135</td>
<td>WFS, septic shock</td>
<td>11 months after initiation of ECU, 3 months after MenB/C, 1 month after discontinuation of prophylaxis</td>
<td>Recovery</td>
</tr>
</tbody>
</table>

aHUS; atypical hemolytic uremic syndrome; ECU: eculizumab; F: female; KT: kidney transplantation; M: male; MenACWY: meningococcal (serogroups A, C, W-135 and Y) conjugate vaccine; MenB: meningococcal serogroup B vaccine; MenC: meningococcal serogroup C vaccine; Meb-4ps: meningococcal tetravalent polysaccharide vaccine; NA: non available; PNH: paroxysmal nocturnal hemoglobinuria; SLE: systemic lupus erythematosus; TMA: thrombotic microangiopathy; WFS: Waterhouse-Friderichsen syndrome.

<sup>a</sup> Molecular analysis demonstrated a strain with the fHbp antigen (variant 2/subfamily A) differing from the variant included in the vaccine (variant 1/subfamily B) and the same variant of the NHBA antigen (allele 1/peptide 2) present in the vaccine.
Table 3. Summary of infection risks and suggested recommendations and management strategies.

<table>
<thead>
<tr>
<th>Agents</th>
<th>Increased risk of overall infection</th>
<th>Risk of VZV / HBV infection</th>
<th>Risk of active TB</th>
<th>Observations and recommendations</th>
</tr>
</thead>
</table>
| Anakinra, cabakinumab, gevokizumab, rilonacept | Modest / major (depending on patient population) | No / no | Uncertain (theoretical risk of progression of LTBI) | • Moderate increase in the risk of mild to moderate infection in children and adults with autoimmune or autoinflammatory disorders  
• Significant increase in the risk of serious infection in older patients with previous comorbidities (evidence restricted to canakinumab)  
• Screening for LTBI before starting treatment (followed by appropriate therapy if needed)  
• Careful decision on therapy discontinuation in case of infection, as abrupt withdrawal can induce a flare of the underlying autoinflammatory disorder  
• Age-appropriate antiviral vaccinations |
| Mepolizumab, reslizumab | None | No / no | No | • No apparent increase in the risk of infection |
| Tocilizumab, siltuxumab | Modest | Yes / yes | Yes | • Risk comparable to that observed for anti-TNF-α agents (likely lower for TB)  
• Screening for chronic HBV infection before starting therapy  
• Antiviral prophylaxis while on therapy on HBsAg-positive patients  
• Monitoring for HBV viral load in anti-HBc positive, HBsAg-negative patients to assess eventual reactivation of occult HBV infection  
• Screening for LTBI before starting treatment (followed by appropriate therapy if needed)  
• Age-appropriate antiviral vaccinations |
| Ustekinumab | Minor | Yes / yes (probably low in both cases) | Uncertain (theoretical risk of progression of LTBI) | • No apparent increase in the risk of infection  
• Screening for LTBI before starting treatment (followed by appropriate therapy if needed) due to theoretical risk of active TB  
• Screening for chronic HBV infection before starting therapy (followed by antiviral prophylaxis in HBsAg-positive patients)  
• Age-appropriate antiviral vaccinations |
<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Risk Level</th>
<th>Screening for LTBI</th>
<th>Possible Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secukinumab, ixekizumab, brodalumab</td>
<td>Minor</td>
<td>No / no</td>
<td>Probably low (theoretical risk of progression of LTBI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Minor increase in the risk of mild to moderate infection</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Increased risk of mild to moderate mucocutaneous candidiasis</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(slightly higher for brodalumab and ixekizumab than secukinumab)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Screening for LTBI before starting treatment (followed by appropriate therapy if needed)</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>Minor</td>
<td>No / no</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Increased risk of mild to moderate parasitic infection (mainly due to geohelminths)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Screening for geohelminths before starting therapy in high-risk patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(migrants from endemic areas and residents of non-endemic areas with long-term stay in endemic areas), followed by specific therapy if needed</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Alternatively, empirical broad-spectrum anthelmintic drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(albendazole plus ivermectin) for migrants from endemic areas</td>
</tr>
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<td></td>
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<td></td>
<td>• Repeated screening for geohelminths during the course of therapy in patients at continuous high risk due to ongoing exposure (long-term residents in endemic areas)</td>
</tr>
<tr>
<td>Eculizumab</td>
<td>Major</td>
<td>No / no</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>(only for neisserial infections)</td>
<td></td>
<td>• Markedly increased risk of infection due to Neisseria spp.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Meningococcal vaccination (MenACWY and MenB) at least 2-4 weeks before starting eculizumab, with booster doses of MenACWY every 5 years if therapy is maintained</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Meningococcal chemoprophylaxis (penicillin V or ciprofloxacin) at least 4 weeks since completion of vaccination or until protective antibody titters are documented</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Continuation of chemoprophylaxis for immunocompromised patients, with discontinuation after 4 weeks from the last dose of eculizumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Monitoring of serum bactericidal antibody may help to guide the requirements for vaccine booster and prolongation of chemoprophylaxis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Screening for gonococcal infection in patients at high-risk for STD and their sexual partners</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Pneumococcal and Hib vaccination before starting eculizumab</td>
</tr>
</tbody>
</table>

HBV: hepatitis B virus; Hib: Haemophilus influenzae type b; IL: interleukin; Ig: immunoglobulin; LTBI: latent tuberculosis infection; MenACWY: meningococcal (serogroups A, C, W-135 and Y) conjugate vaccine; MenB: meningococcal serogroup B vaccine; STD: sexually transmitted disease; TB: tuberculosis; TNF-α: tumor necrosis factor-α; VZV: varicella zoster virus.
Transparency declaration

- **Conflict of interest disclosure:** K.W. received investigational grants and personal fees from Pfizer and BMS, as well as personal fees from Roche, Abbvie, UCB and Lilly. L.C. received personal fees from Abbvie, BMS, Jansen, GSK, Genentech, Norartis, Sanofi-Regeneron, Crescendo, UCB and Pfizer. J.S. received grants from Abbvie, Janssen, Lilly, MSD, Pfizer, Roche and Chugai, as well as personal fees from Abbvie, Amgen, Astra-Zeneca, Astro, BMS, Celgene, Celltrion, Chugai, Gilead, Glaxo, ILTOO, Janssen, Lilly, Medimmune, MSD, Novartis-Sandoz, Pfizer, Roche, Samsung, Sanofi and UCB. J.M.A. received personal fees from Pfizer, Astellas and Merck. The remaining authors declare no conflicts of interest (i.e., payment or services from a third party; relevant financial activities outside the submitted work; or patents planned, pending or issued broadly relevant to the submitted work).

- **Funding sources:** This research was partially supported by Plan Nacional de I+D+I 2013-2016 and Instituto de Salud Carlos III, Subdirección General de Redes y Centros de Investigación Cooperativa, Spanish Ministry of Economy and Competitiveness, Spanish Network for Research in Infectious Diseases (REIPI RD16/0016/0002 and 0008) - co-financed by the European Development Regional Fund (EDRF) "A way to achieve Europe". M.F.R. holds a clinical research contract “Juan Rodés” (JR14/00036) from the Instituto de Salud Carlos III, Spanish Ministry of Economy and Competitiveness.
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b) The IL-6/sIL-6R complex binds to Tocilizumab and Siltuximab, blocking downstream signaling.

Downstream signaling is blocked by the binding of Tocilizumab and Siltuximab to the IL-6/sIL-6R complex.