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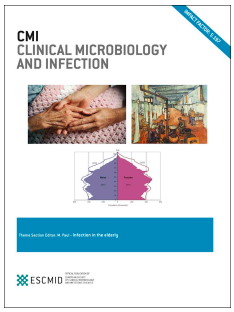

ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the Safety of targeted and biological therapies: an Infectious Diseases perspective (Introduction)

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Review paper

Title page

Complete title: ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the Safety of targeted and biological therapies: an Infectious Diseases perspective (Introduction)

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Abstract (250 words)

Background: The field of new biological agents is increasing exponentially over the past years, thus making prevention and management of associated infectious complications a challenge for non-specialized clinicians.

Aims: The present Consensus Document is an initiative of the ESCMID Study Group for Infections in Compromised Hosts (ESGICH) aimed at analyzing, from an Infectious Diseases perspective, the safety of targeted and biological therapies.

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

Content: The document is structured in 8 different sections according to the targeted site of action of each drug class: pro-inflammatory cytokines; interleukins, immunoglobulins and other soluble immune mediators; cell surface receptors and associated signaling pathways; intracellular signaling pathways; lymphoma and leukemia cells surface antigens; and other targeted therapies. A common outline was followed for each agent: (a) summary of mechanism of action, approved indications and common off-label uses; (b) expected impact on the host's susceptibility to infection; (c) available clinical evidence (i.e., pivotal clinical trials, post-marketing studies, case series and case reports); and (d) suggested prevention and risk minimization strategies. In this introductory section, the methodological and practical difficulties of assessing the specific risk posed by a given agent is also discussed.

Implications: This ESGICH Consensus Document constitutes not only a comprehensive overview of the molecular rationale and clinical experience on the risk of infection associated to approved targeted therapies, but also an attempt to propose a series of recommendations with the purpose of guiding physicians from different disciplines into this emerging framework.

Keywords: targeted therapies; biological therapies; infection; monoclonal antibodies; small-molecule inhibitors; recommendations; review.

Purpose, scope and methodology of the document

The Consensus Document contained in the present Supplement issue represents an official initiative of the ESCMID (European Society of Clinical Microbiology and Infectious Diseases) Study Group for Infections in Compromised Hosts (ESGICH) specifically aimed at analyzing, from an Infectious Diseases (ID) perspective, the safety profile of biological and targeted therapies. We aimed at a comprehensive overview of the clinical experience on this topic and its underlying molecular rationale, and at proposing a series of recommendations based on the best available evidence with the ultimate aim of reducing the incidence of infectious complications among the growing population of patients receiving these novel therapeutics.

In September 2016 a Scientific Committee was set up under the direction of the current and past chairs of the ESGICH with the tasks of selecting the drug classes to be reviewed and choosing a group of experts (including, but not restricted to, ID specialists, hematologists, oncologists and rheumatologists) with both clinical experience and scientific background. This committee drew up an overall document design split into 8 different sections [1-7], each of them under the responsibility of a scientific coordinator who was given freedom to decide how to divide the workload among the remaining co-authors. After contacting these coordinators to confirm their availability and willingness to participate in the project, in November 2016 a formal Invitation Letter was issued to the chosen experts explaining the aims and scope of the document, the class of targeted agents that was invited to be reviewed, the proposed methodology, and the deadline to submit their contributions.

A set of computer-based MEDLINE (National Library of Medicine, Bethesda, MD) searches with no temporal or language restrictions was carried out by using the MeSH terms appropriate for each agent (always including “infection” or “infectious complications”) to identify literature pertaining to the subject. Particular attention was given to the safety data reported across pivotal randomized controlled trials (RCTs). The bibliographies of the selected articles were also scrutinized for additional relevant references. In addition, the authors reviewed package information and boxed warning alerts from main regulatory agencies (European Medicines Agency [EMA] and US Food and Drug Administration [FDA]). For each agent (or class of agents) reviewed, a common outline was proposed as follows: (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 coming from the clinical use of that agent (i.e., RCTs, post-marketing studies, case series and single case reports); and (d) suggested prevention and risk minimization strategies. Although authors were encouraged to ideally formulate these recommendations on high-quality evidence, the members of the Scientific Committee acknowledged that the absence of supporting information for certain clinical scenarios would force them to mostly provide experts' opinion sustained by their own experience. These recommendations were jointly discussed in an ESGICH meeting held at the 27th European Congress of Clinical Microbiology and Infectious Diseases (Vienna, April 22, 2017), and latter disseminated among the remaining authors of the document.

Due to their selective impact on the functionality of immune system and, presumably, host-pathogen interactions, the scope of the present Consensus Document was restricted to those agents exclusively (or mainly) used to treat malignant or (auto)inflammatory diseases. Therefore, a number of compounds that have been approved (or are currently in an advanced stage of development) for other indications, from cardiovascular conditions to prevention of allograft rejection, was not covered in the document (**Table 1**). With the exception of punctual cases with particular historical interest, currently withdrawn drugs due to lack of efficacy, unfavorable safety profile or budgetary reasons were not included either.

General overview of biological therapies

A long journey has been traveled since the pioneer research of Paul Ehrlich in the transition from 19th to 20th centuries [8] and the approval of rituximab and imatinib for the treatment of hematological malignancies in 1997 and 2001, respectively [9,10]. At current time, the number of biological therapies used in hematology, rheumatology, dermatology or gastroenterology is rapidly increasing, and there are more new molecules in the pipeline or at different stages of clinical development.

The classification of biological therapies can be made on the basis of their mode of action, targeted site, or structural properties. The two later classifications may not be useful in clinical practice, but they are still important for research purposes [11]. Three main categories can be established:

1. *Biological response modifiers,* which are agents that do not directly target cancer cells but rather exert a stimulating effect that boosts the immune system to fight against them.

Biological response modifiers include exogenous interferons, interleukins (ILs) or colony-stimulating factors, as well as nonspecific immunomodulating agents (such as the bacille Calmette-Guérin [BCG] or levamisole).

2. *Gene therapies,* which constitute a separate entity since genes can be manipulated through different ways [12]: replacing the defective gene with a normal gene (this approach mainly works against non-malign disorders with a single-gene aberration [13]), simulating the immune response against cancer cells [14], sensitizing cancer tissues to conventional chemotherapy and radiotherapy [15], delivering genes that change drugs from an inactive prodrug to the active form to cancer cells [16], blocking processes that protect cancer cells such as anti-apoptotic mechanisms [17], using altered viruses (oncolytic virus therapy) to kill cancer cells directly [18], or by means of DNA or RNA oligonucleotide therapies [19].
3. *Targeted therapies,* which are the most common biological approach not only to malignancies, but also to inflammatory disorders. They have the advantage of directly targeting the cells or pathways involved in disease pathophysiology, thus sparing normal tissues and minimizing the occurrence of treatment-related adverse events. These therapeutics may act on a virtually endless number of targets, from cell surface receptors to cytokines, immunoglobulins, intracellular enzymes or even bacterial toxins. The present document is focused on these therapies, which may be categorized into two main pharmacological classes: therapeutic monoclonal antibodies (mAbs) and small-molecules enzyme inhibitors. Although not exactly encompassed in the aforementioned groups, specific sections are also devoted to proteasome inhibitors and mammalian target of rapamycin (mTOR) inhibitors (**Table 2**).

Monoclonal antibodies and related agents

Since more than 30 years, the use of mAbs has been established as a standard component of therapy for cancer and an increasing number of rheumatological and inflammatory diseases [20]. The first agents in this class to be used in clinical practice were murine mAbs. However, the inherent limitations associated with administering mouse immunoglobulins to humans (development of alloimmune responses leading to its rapid clearance and suboptimal induction of host's immune response against the targeted cells) soon became evident. A crucial step forward was achieved when techniques of genetic engineering were developed, allowing for the

sequential replacement of mouse-derived amino acids by human sequences. Chimerization process, in which the murine constant regions are replaced by human constant regions, were the first engineered improvement [21]. Nevertheless, chimeric mouse-human mAbs still pose a significant risk of eliciting alloimmune responses since a significant portion of the antibody remains nonhuman. The humanization process constituted the next development, in which only complementarity determining regions (CDRs) of the variable regions remain of mouse origin [22]. “Fully human” mAbs represent the current state of the art, where antigen specificity is selected either *in vivo* by the use of transgenic mice containing human immunoglobulin genes or through antibody engineering processes combined with screening in recombinant human antibody libraries (**Figure 1**). Humanized and fully human mAbs exhibit a lower immunogenicity than mouse or chimeric antibodies [23].

Since the early 1990s, a consistent nomenclature scheme fixed by the WHO International Nonproprietary Names (INN) Programme has been used for mAbs (with the exception of the anti-CD3 agent muromonab-CD3). Each INN for a given mAb is composed by a random/fantasy prefix, a substem A indicating the target (molecule, cell or organ) class, by a substem B indicating the species on which the immunoglobulin sequence is based (*-i-* primate, *-o-* mouse, *-xi-* chimeric, *-xizu-* chimeric-humanized, *-zu-* humanized, and *-u-* fully human), and by the stem *-mab*. This scheme has been recently revised [24].

From a structural and functional point of view, all these constructs mirror naturally occurring human IgG. The use of IgG-based agents has a number of advantages. The serum half-lives of IgG1, IgG2 and IgG4 subclasses are considerably longer (approximately 23 days) than those of other immunoglobulin classes (which ranges from 2 to 7 days), thus facilitating in most cases the therapeutic administration in a weekly or monthly basis. The interaction between the IgG fragment crystallizable (Fc) region and immune cell receptors such as Fcγ receptors (FcγRs) or complement protein C1q leads to efficient cell lysis through mechanisms of complement-dependant cytotoxicity (CDC), antibody-dependant cell-mediated cytotoxicity (ADCC) and antibody-dependent cell-mediated phagocytosis (ADCP), as well as to enhanced antigen presentation to dendritic cells [25]. In addition, the high diffusion coefficient of IgG results in the rapid distribution of mAbs to the extravascular compartment and in the persistence within tumor environment for long periods of time. In opposition to the full-length mAbs, certolizumab (a new-

generation tumour necrosis factor [TNF]-α-targeted agent) does not contain the IgG Fc region and, therefore, lacks *in vitro* CDC or ADCC effector activity (**Figure 2**).

Modern mAb technology offers the possibility of generating a virtually unlimited quantity of recombinant human IgG with predetermined specificities and properties [26]. Since the discovery of the anti-CD20 specific antibody B1 (later renamed tositumomab) in 1981 [27] and the Food and Drug Administration (FDA) approval of rituximab for the treatment of indolent lymphoma in 1997 [10], the history of clinical development of CD20-targeted antibodies well illustrates the improvements attained over the last decades in the engineering of therapeutic mAbs [28]. Upon binding to CD20, rituximab and ofatumumab (two type I anti-CD20 mAbs of first and second generation, respectively) rapidly induce the translocation of the antibody-antigen complex to lipid rafts (membrane microdomains rich in cholesterol and sphingolipids) within the cell membrane. Lipid rafts serve as a setting for signal transduction, leading to strong CDC through the recruitment of C1q, but only to weak direct cytotoxicity. Ofatumumab (a second-generation mAb) differs from rituximab in the binding site at the CD20 protein, resulting in superior binding affinity and more potent CDC activity. Variations in lipid raft composition may contribute to the emergence of resistance to these type I mAbs. Type II anti-CD20 mAbs such as obinutuzumab or ocaratuzumab do not localize the antibody-antigen complex into lipid rafts and, therefore, induce 10- to 100-fold weaker CDC than rituximab or ofatumumab. However, reduced FcγR-mediated CD20 internalization increases the capacity of these agents to bind and activate natural killer (NK) and other FcγR-expressing cells (e.g., granulocytes or macrophages), which ultimately leads to enhanced ADCC and ADCP [29].

The covalent attachment of a polyethylene glycol (PEG) molecule (PEGylation) constitutes a refinement in the building of therapeutic mAbs. PEGylation improves pharmacokinetics and enhances therapeutic efficacy of the conjugate by increasing its hydrophilicity and serum half-life and reducing the rate of glomerular filtration [30]. Such strategy is particularly useful when the fragment antigen-binding (Fab) region of the mAb (which lacks the Fc region) is used as therapeutic agent, since its clinical applicability would be limited by short serum half-life. Second-generation site-specific PEGylation techniques result in well-defined conjugated products with improved features as compared to those obtained by non-specific random conjugations. Certolizumab pegol exemplifies an approved application of this technology [31].

A further achievement in the development of targeted agents resulted from the construction of antibody-drug conjugates (ADCs), which are mAbs covalently attached to biologically active drugs by means of specialized chemical linkers [32]. This approach allows for delivering and releasing potent cytotoxic agents at the precise tumor site thanks to the specific affinity of the antibody for the targeted antigen expressed on the surface of malignant cells. Therefore, surrounding non-malignant tissues are spared and the risk of systemic exposure and toxicity is notably reduced. The attached drug can be a cytotoxin that induces DNA or microtubule damage (i.e., auristatins or calicheamicins) or a bacterial toxin (i.e., *Pseudomonas* exotoxin A [PE]). At the current time, noncleavable linkers are the most commonly used since they require proteolytic degradation of the antibody part within the lysosome of the targeted cell to release the cytotoxic molecule, minimizing the amount of free circulating drug into the bloodstream. Examples of ADCs include CD22-targeted (moxetumomab pasudotox or inotuzumab ozogamicin), CD30-targeted (brentuximab vedotin) or CD33-targeted agents (gemtuzumab ozogamicin) [33].

In a similar way to ADCs, therapeutic MAbs also represents an excellent platform to deliver radioisotopes directly to tumor cells, therefore minimizing the systemic toxicity of conventional radiotherapy. Due to the wide availability of specific target antigens and its relative radiosensitivity, lymphoma cells are particularly amenable for treatment with radioimmunoconjugates. Two CD20-targeted agents, ibritumomab tiuxetan and tositumomab, which are conjugated to different isotopes (^{90}Y and ^{131}I respectively), have been FDA-approved for the treatment of patients with low-grade or follicular non-Hodgkin's lymphoma [33].

Bispecific T-cell engagers (BiTEs) are constructs obtained through an innovative technology that fuses the antigen-binding variable regions of two different mAbs (**Figure 3**). One of these two arms targets a surface antigen expressed on cytotoxic T-cells, whereas the other is designed to bind to an antigen primarily found on malignant cells. Thus, the BiTE antibody forms a stable bridge between the immune and the tumor cell, enabling antigen recognition and the targeted deployment of cytotoxic mechanisms (i.e., degranulation of granzyme B and perforin) [34]. Blinatumomab, a CD19-targeted agent, is the first-in-class and so far only approved BiTE antibody in clinical use [35].

Decoy receptors are other therapeutic products derived from the mAb technology. These genetically engineered agents consist of the extracellular ligand-binding domains of naturally occurring receptors fused to the Fc region of an human immunoglobulin (usually IgG1). The resulting chimeric protein is able to trap the targeted soluble mediator (e.g. a cytokine or a growth factor), thus preventing its biological action. The Fc region partner contributes to improve the pharmacokinetic property of the recombinant fusion protein (prolonging its serum half-life) and facilitates large-scale production through processes similar to those applied for the production of therapeutic mAbs (i.e., expression in mammalian cells, secretion into culture supernatants and subsequent affinity-based purification). Etanercept, aflibercept, rilonacept and olamkicept are examples of decoy receptors targeting TNF-α, vascular endothelium growth factor (VEGF), interleukin (IL)-1 and IL-6, respectively. Anakinra, other IL-1-targeted agent, is designed on a therapeutic principle analogue to decoy receptors. It is a recombinant form of the native IL-1 receptor antagonist (IL-1Ra), which acts as a competitive inhibitor by binding to IL-1α and IL-1β. Since it does not possess the Fc region, anakinra has to be administered on a daily basis following a loading dose due to its short half-life.

In addition to designing immunologically efficient and pharmacokinetically optimized mAbs, the choice of the targeted antigens is also critical. For cancer therapy, factors such as the density and consistency of expression on malignant cells of that targeted molecule, its limited expression on non-tumor tissues, the lack of high-level soluble forms and the limited tendency of antigen-negative escape tumor variants to emerge must be taken into account. For inflammatory diseases, the pathophysiological role displayed by certain cytokines, ILs or soluble immune mediators in each specific condition guides the selection of targeted molecules.

Small-molecule enzyme inhibitors

An entirely different concept of targeted therapy is embodied by the so-called “small-molecule inhibitors”, whose development has been fueled by the continuous discovery of key oncogenic mutations involved in tumorigenesis and by the precise characterization of the critical role played by angiogenesis in tumor cell survival and metastatic dissemination. Since the approval in 2001 of imatinib for the treatment of Philadelphia chromosome (Ph)-positive chronic myeloid leukemia [36], a large number of kinase inhibitors have been designed over the past decades. In most cases, these agents block initial steps of intracellular downstream signaling cascades

that are overexpressed in tumor cells due to point mutations (i.e., V600 mutations in the B-type Raf kinase *(BRAF)* oncogene in melanoma [37]) or chromosomal rearrangements (i.e., the BCR-ABL fusion tyrosine kinase resulting from the [9;22] translocation in Ph-positive leukemias [38]). The Ras/phosphatidylinositol-3-kinase (PI3K)/Akt/mTOR cascade and the Ras/Raf/MEK/ERK cascade (also known as MAPK/ERK) are two crucial pathways implied in the delicate control of cell survival, differentiation and proliferation in response to extracellular stimuli. Thus, various drug classes are targeted to inhibit some steps of both that are overexpressed in tumor cells, including BRAF inhibitors (such as vemurafenib) [39], PI3K δ isoform inhibitors (idelalisib) [40], MEK inhibitors (trametinib or cobimetinib) [41] or mTOR inhibitors (everolimus or temsirolimus) [42]. While some small-molecule inhibitors exert a selective action on the tyrosine kinase domains integrated into the cytoplasmic tails of certain cell surface receptors (i.e., epidermal growth factor receptor [EGFR] or vascular endothelium growth factor receptor [VEGFR]), others indirectly block receptors that lack intrinsic enzymatic activity and rely on unspecific kinases to initiate the intracellular signaling pathway (i.e., type I and II cytokine receptors and the Janus family of tyrosine kinases) [43]. However, it should be noted that some degree of off-target inhibition results unavoidable even with the more specific agents. As an example, imatinib has a large number of indications beyond Ph-positive leukemias, including c-Kit-positive gastrointestinal stromal tumor (GIST), myelodysplastic syndromes, systemic mastocytosis or dermatofibrosarcoma protuberans. This concept is particularly evident for the multikinase inhibitors such as sorafenib or sunitinib, which in addition to VEGFR act on a large array of receptors (such as BRAF, c-Kit, platelet-derived growth factor receptor [PDGFR] or *fms*-like tyrosine kinase-3 [FLT3]) [44].

As compared to therapeutic mAbs and related agents, small-molecule inhibitors have pharmacokinetic advantages: good oral bioavailability, rapid absorption (reaching peak plasma levels within the first hours from administration), extensive tissue distribution (with good central nervous system penetration in some cases), and high protein bound [45]. However, they are not extent from drug-to-drug interactions since most of them are metabolized through the cytochrome P450 (CYP) 3A4 isoform (with other CYP-enzymes playing a secondary role) and are substrate of efflux transporters such as the ATP-binding cassette transporter family [46].

Assessment of the risk of infection: from molecule to bedside

Targeted agents are directed towards cytokines, immune soluble mediators, cell surface molecules and receptors, and components of intracellular signaling cascades involved in the pathophysiology of cancer, autoimmune or inflammatory diseases. However, these targeted sites are often also key elements of physiological processes such as normal immune homeostasis or cell cycle control. The blockade of pathways controlling immune or inflammatory responses may result in an impaired immune function, with the consequent risk of infection [47]. Both innate and adaptive immunity may be targeted. Long-term immunological memory relies on CD4+ and CD8+ memory T-cells. Acquired immunity to extracellular and intracellular microorganisms depends on a network of Th17 and Th1 cells, cytotoxic CD8+ T-cells, and B-cells [48]. Targeted therapies may therefore affect responses to acute infection exposures as well as control of latent or chronic infections.

From a theoretical point of view, the potential of these agents to predispose to specific infectious complications or to overall increase infection risk mainly depend on their site of action (i.e., the targeted soluble immune mediator, cell surface antigen of intracellular signal transducer) and the subsequent impact on the functionality of the immune system [49]. Interestingly, the action some mAbs mirrors the immune defects that underlie the pathogenesis of well-defined primary immunodeficiencies, as is the case of CD40-targeted agents (lucatumumab or dacetuzumab) and the hyper-IgM syndrome [50,51], or IL-17-targeted agents (secukinumab or brodalumab) and chronic mucocutaneous candidiasis [52].

However, in clinical practice such associations are far from deterministic, since they are modulated by a plethora of factors such as the nature and stage of the underling condition, the prior or concurrent receipt of other immunosuppressive agents, the duration of therapy or the accumulative exposure to the agent. This concept is well exemplified by the notable differences in the rates of infection observed with the use of the anti-CD52 mAb alemuzumb according to the indication of therapy, multiple sclerosis or B-cell malignancy (since the corresponding maximum annual doses vary from 36 to 1,080 mg, respectively) [53,54]. In the case of immune checkpoint inhibitors targeting inhibitory T-cell receptors, such as nivolumab or ipilimumab, the risk is not driven by the use of the agent itself, but by the subsequent requirement of additional immunosuppression therapy to manage the immune-related adverse effects emerging from the upregulation of immune response [55]. The underlying inflammatory state present in certain

conditions may predispose to the activation of some pathogens (e.g., cytomegalovirus [CMV] via TNF-α). Thus, control of inflammation by targeted therapies would reduce the predisposition to infection intrinsically related to the disease [47]. In fact, a decline in the absolute risk of infection over time can be observed in some cohorts of patients under TNF-α-targeted agents due to the improvement in their clinical status and disease activity [56]. In addition, and despite its allegedly specific mode of action, some of these drugs do exert an off-target action on different cellular sites, further hampering the precise characterization of its impact on the host's susceptibility. As above mentioned, this should be anticipated when assessing the risk posed by the multikinase inhibitors like dasatinib, which has been recently associated to an increases incidence of CMV infection [57]. On the other hand, the abrupt discontinuation of therapy may lead to a paradoxical aggravation of the ongoing infection caused by the onset of immune reconstitution inflammatory syndrome (IRIS) or the aggravation of underlying disease, as observed in children with auto-inflammatory diseases receiving IL-1-targeted agents. Finally, immunosenescence, an emergent concept of immune degradation over time, is also a matter of concern because of its implications in the risk of infection. With chronic inflammation inducing continuous immune activation, accelerated T-cell senescence is unavoidable. The contraction of the immune repertoire may also determine the degree of susceptibility to new pathogens [58].

Moreover, the assessment of the infection risk associated to the use of targeted therapies is challenged by a number of methodological and practical difficulties. Pivotal RCTs that justify the approval by regulatory agencies are usually performed in patients with relapsed or refractory forms of disease, thus making it difficult to delineate the incremental risk of infection conferred by a certain agent from the background effect of previous lines of therapy. Caution must be exerted even if pivotal studies do not report an increased occurrence of infection, since most of the data on relatively uncommon complications has only emerged from the wide-scale use of a marketed agent, either in form of case series or data from large post-marketing observational studies, such was the case of active tuberculosis with TNF-α-targeted agents [59] or progressive multifocal leukoencephalopathy (PML) with natalizumab or brentuximab vedotin [60,61]. Unfortunately, post-marketing observational studies usually lack an adequate control group, leaving open to interpretation whether events are associated with the therapeutic agent or with the disease itself [62]. On the other hand, most RCTs do not provide detailed data on the

clinical syndromes or causative agents in observed episodes of infection. The reported rates of infection for a given agent may substantially differ across different trials according to the geographic origin of the recruited patients (e.g., disparate incidence of active tuberculosis in low- or high-endemicity areas), the stringency of exclusion criteria (e.g., chronic infection with hepatitis virus), or the screening and prophylaxis strategies required per study protocol. Finally, since trials are usually designed to measure drug efficacy rather than detect rare adverse effects, the follow-up period may not be large enough to allow infections with protracted courses or long incubation periods (such as tuberculosis or certain endemic mycoses) to clinically emerge [62].

In view of the aforementioned limitations, the evaluation of the risk of infection for each targeted agent is far more complex than simply evaluating its efficacy or defining the expected safety profile within a given drug class. Although the majority of serious infections under these therapies are similar to those observed in the general population, it is clear that some specific events are much more likely to occur with certain agents or to evolve into a more severe course. While pathogens that exclusively cause disease among immunocompromised hosts can clearly be designated as “opportunistic”, for most infections such concept is elusive. This is partly due to the lack of a formal definition in the context of targeted therapies, unlike other types of immunosuppression [63]. Prior attempts to define opportunistic infections associated with the use of targeted agents have been inconsistent, resulting in wide-ranging risk estimates across studies [64]. However, a multidisciplinary committee has recently reached an agreement upon a consensus definition for the reporting of each pathogen, recommending these criteria to be used in future studies to facilitate comparison between different agents [63].

Conclusion

The field of targeted and biological agents is now increasing exponentially, with dozens of agents approved over the few past years. The prevention and management of infectious complications associated with these therapies constitute a clinical challenge. In addition, our scientific understanding of the mechanisms leading to an increased susceptibility to infection in this setting is ever-changing. The present ESGICH Consensus Document is an attempt to update the potential risk of infection posed by currently approved targeted therapies and to guide physicians from different disciplines in this emerging framework.

Figure legends

Figure 1. Schematic representation of different types of therapeutic mAbs according to their progressive humanization. Regions of human and murine origin are shown in grey and black, respectively. CDRs: complementarity-determining regions.

Figure 2. Applications of engineered mAb technology. Fab fragment (50,000 daltons) is a monovalent fragment consisting of the VH, CH1, VL and CL domains linked by an intramolecular disulfide bond. Fab' fragment (55,000 daltons), which may be obtained from a divalent $F(ab')_2$ fragment, contains a free sulfhydryl group that may be alkylated or utilized in conjugation with an enzyme, toxin or other partner. Diabody is a noncovalent dimer formed by two single-chain variable regions (scFv), each consisting of the VH and VL domains connected by a small peptide linker. Triabody has three scFv heads, each consisting of the VH domain from one polypeptide paired with the VL domain from a neighboring polypeptide. Bispecific T-cell engagers (BiTEs) are composed of a single polypeptide chain that consists of two VL and VH pairs (i.e., two tandem scFv regions), each with a unique antigen specificity (one recognizes CD3 and the other recognizes an antigen on tumor cell surface). Constant regions (CH and CL) are shown in dark grey, variable regions (VH and VL) in clear grey.

Table 1. Examples of targeted agents not covered by the present ESGICH Consensus Document.

Targeted molecule	Agent	Approved or intended use
Platelet glycoprotein IIb/IIIa receptor	Abciximab	Platelet aggregation inhibitor
Dabigatran	Idarucizumab	Reversal of anticoagulant effects of dabigatran
Human cardiac myosin	^{111}In-imciromab	Cardiac imaging
Proprotein convertase subtilisin kexin type 9 (PCSK9)	Atezolizumab, evolocumab	Primary hypercholesterolemia or mixed dyslipidemia
IL-2 receptor chain α (CD25)	Basiliximab, daclizumab	Prevention of rejection in solid organ transplantation
Vascular endothelial growth factor (VEGF)	Ranibizumab	Age-related macular degeneration
Receptor activator of nuclear factor Kappa-B ligand (RANKL)	Denosumab	Osteoporosis
Bacillus anthracis protective antigen	Obiltoxaximab	Inhalational anthrax
Respiratory syncytial virus (RSV) F protein	Palivizumab	Prevention of RSV infection
Clostridium difficile toxin B	Bezlotoxumab	*Clostridium difficile* infection
Fungal heat shock protein 90 (Hsp90)	Efungumab	Invasive fungal disease

Table 2. Targeted and biological agents reviewed in the present ESGICH Consensus Document.

Section of the document (ref)	Targeted molecule	Agents reviewed
2 [1]	TNF-α	Infliximab, adalimumab, golimumab, certolizumab pegol, etanercept
3 [2]	IL-1	Canakinumab, anakinra, rilonacept, gevokizumab
	IL-5	Mepolizumab, reslizumab
	IL-6	Tocilizumab, siltuxumab
	IL-12/23 common p40 subunit	Ustekinumab
	IL-17	Secukinumab, ixekizumab, brodalumab
	IgE	Omalizumab
	Complement factor C5	Eculizumab
4 [3]	VEGF	Bevacizumab, aflibercept
	VEFGR	Sorafenib, sunitinib, axitinib, pazopanib, regorafenib, vandetanib, cabozantinib, ramucirumab
	EGFR	Cetuximab, panitumumab
	ErbB2/HER2	Trastuzumab, pertuzumab
	ErbB receptor tyrosine kinases	Erlotinib, gefitinib, afatinib, osimertinib, lapatinib, neratinib
5 [4]	BCR-ABL tyrosine kinase	Imatinib, dasatinib, nilotinib, bosutinib, ponatinib
	BRAF/MEK kinases	Vemurafenib, dabrafenib, trametinib, cobimetinib, selumetinib, encorafenib
	Bruton's tyrosine kinase	Ibrutinib, acalabrutinib
	PI3K	Idelalisib, buparlisib, rigosertib, duvelisib
	Bcl-2	venetoclax
	Janus kinases	Ruxolitinib, tofacitinib, baricitinib
	mTOR	Everolimus, temsirolimus
6 [5]	CD19	Blinatumomab, inebilizumab, combotox
	CD20	Rituximab, ^{90}Y-ibritumomab tiuxetan, ofatumumab, ocrelizumab, veltuzumab, ^{131}I-tositumomab, obinutuzumab, ocaratuzumab, ublituximab

	CD52	Alemtuzumab
7 [6]	CD22	Epratuzumab, inotuzumab ozogamicin, moxetumomab pasedotox, combotox
	CD30	Brentuximab vedotin
	CD33	Gemtuzumab ozogamicin
	CD38	Daratumumab, isatuxumab
	CD40	Dacetuzumab, lucatumumab
	CD319 (SLAMF7)	Elotuzumab
	CCR4	Mogamulizumab
8 [7]	CTLA-4	Ipilimumab, tremelimumab
	PD-1 and PD1L	Nivolumab, pembrolizumab, atezolizumab
	LFA-3	Alefacept
	α4-integrins, LFA-1	Natalizumab, vedolizumab, efalizumab
	Sphingosine-1-phosphate receptor	Fingolimod
	Proteosome	Bortezomib, carfilzomib, ixazomib

Bcl-2: B-cell lymphoma 2; CTLA-4: cytotoxic T-lymphocyte-associated antigen 4; EGFR: epidermal growth factor receptor; HER: human epidermal growth factor receptor; IgE: immunoglobulin E; IL: interleukin; LFA: lymphocyte function-associated antigen; mTOR: mammalian target of rapamycin; PD: programed death; PI3K: phosphatidylinositol-3-kinase; SLAMF7: signaling lymphocytic activation molecule F7; TNF: tumour necrosis factor; VEGF: vascular endothelium growth factor; VEGFR: VEGF receptor.

Transparency declaration

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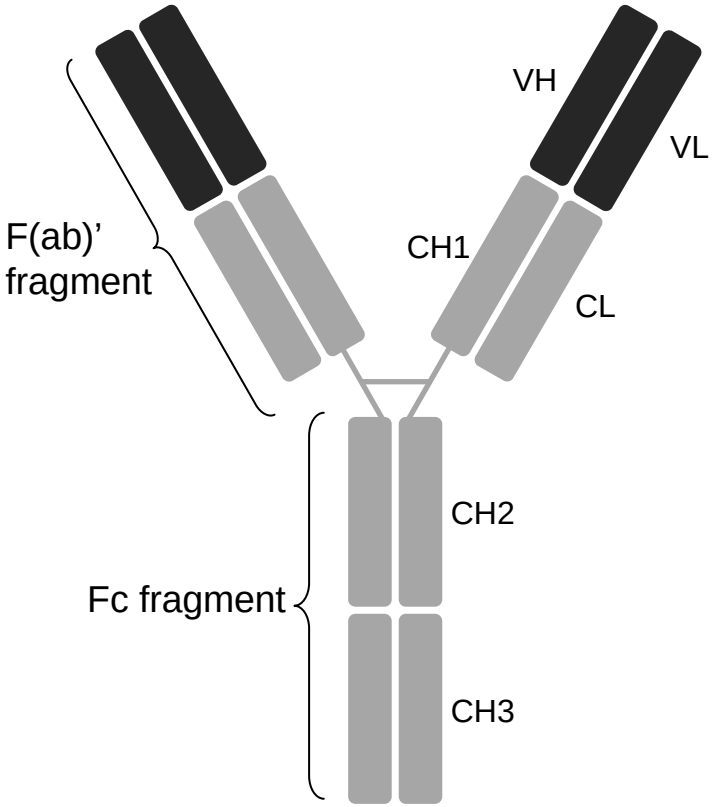

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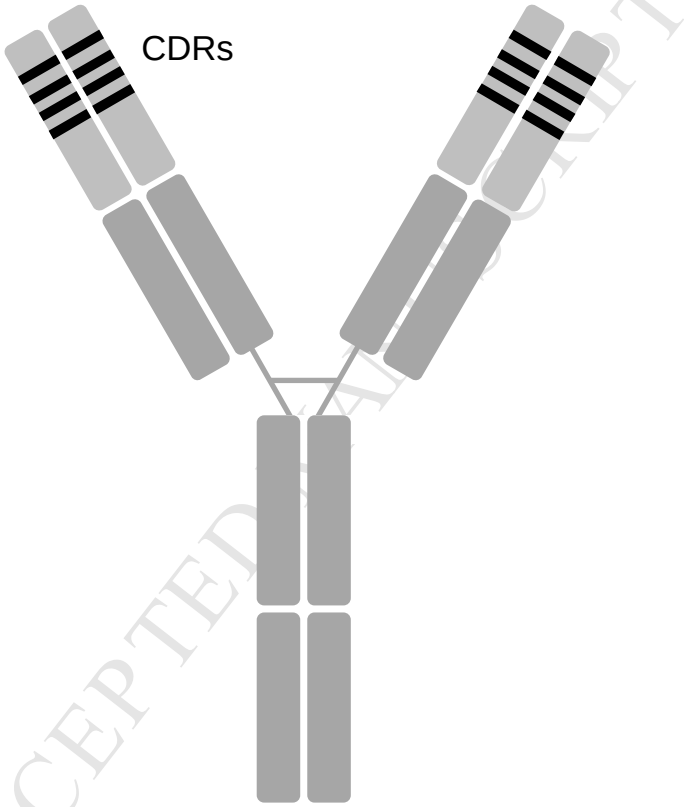

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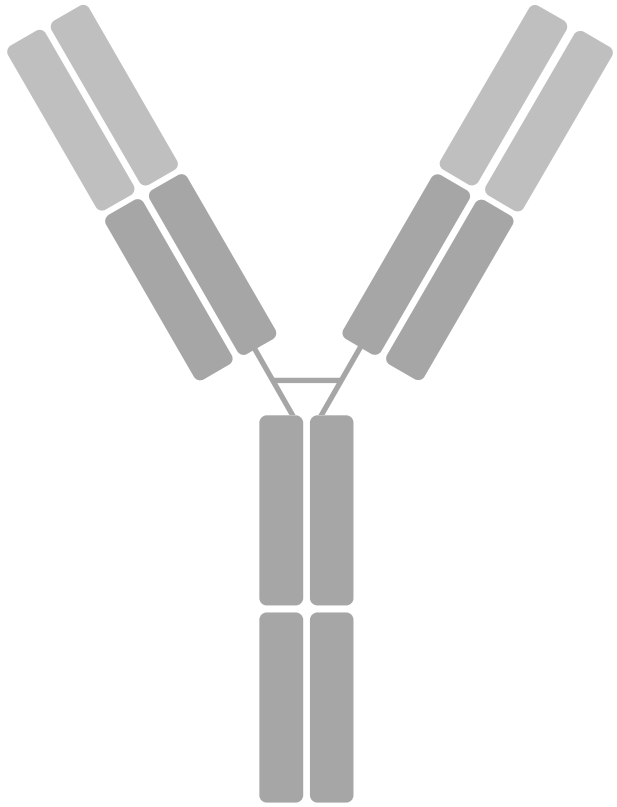

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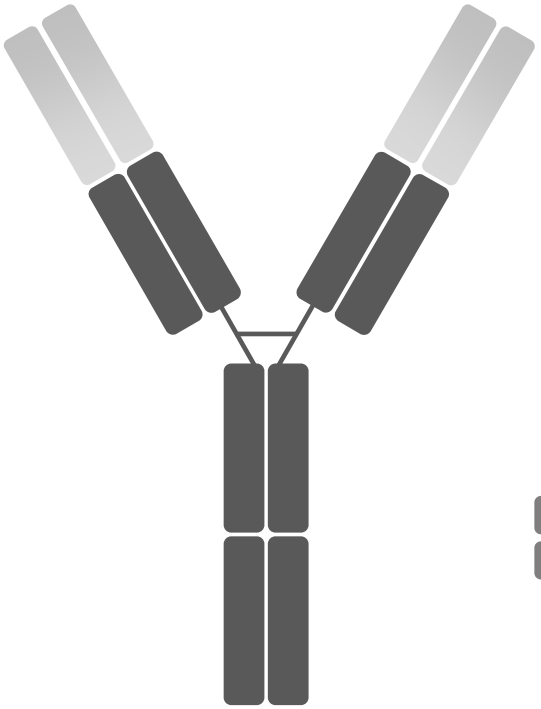

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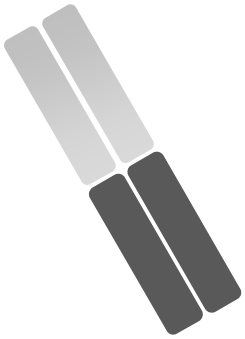

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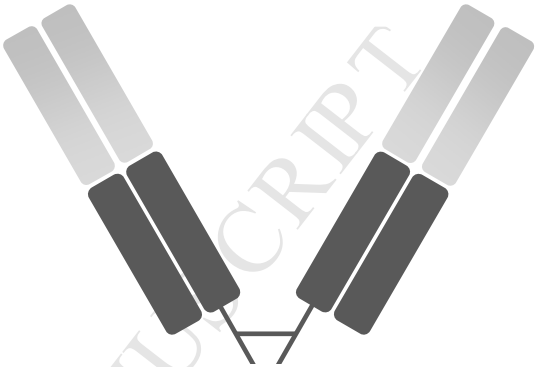

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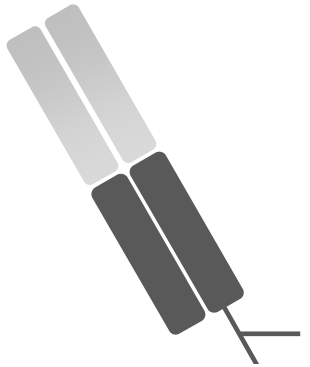

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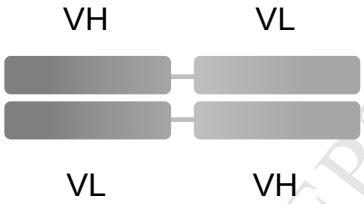

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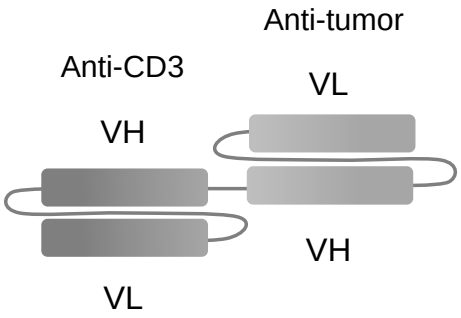

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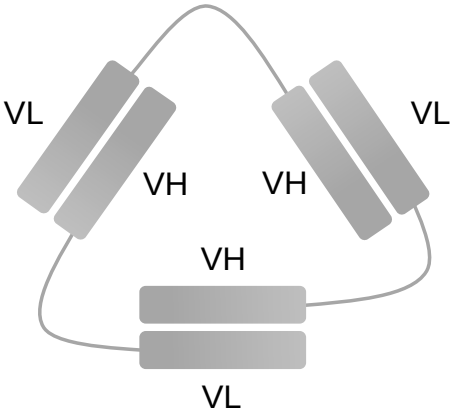

Triabody