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Narrative Review

ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (agents targeting lymphoid cells surface antigens [I]: CD19, CD20 and CD52)

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ABSTRACT

Background: The present review is part of the ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies.
Aims: To review, from an Infectious Diseases perspective, the safety profile of agents targeting CD19, CD20 and CD52 and to suggest preventive recommendations.
Sources: Computer-based MEDLINE searches with MeSH terms pertaining to each agent or therapeutic family.
Content: Although CD19-targeted agents (blinatumomab or inebilizumab) are not associated with an increased risk of infection, they may cause IgG hypogammaglobulinaemia and neutropenia. The requirement for prolonged intravenous infusion of blinatumomab may increase the risk of catheter-associated bloodstream infections. Infection remains the most common non-haematological adverse effect of anti-CD20 monoclonal antibodies, including severe respiratory tract infection, hepatitis B virus (HBV) reactivation and varicella-zoster virus infection. Screening for chronic or resolved HBV infection is recommended for patients receiving anti-CD20 monoclonal antibodies. Antiviral prophylaxis should be offered for 12–18 months to hepatitis B surface antigen (HBsAg)-positive and HBsAg-negative/anti-hepatitis B core antibody (HBc)-positive patients. Anti-*Pneumocystis* prophylaxis should be considered in patients receiving concomitant chemotherapy, particularly steroids. Alemtuzumab (anti-CD52) increases the risk of infections, in particular among leukaemia and solid organ transplant patients. These populations benefit from anti-*Pneumocystis* prophylaxis, prevention strategies for cytomegalovirus infection, and screening for HBV, hepatitis C virus and tuberculosis. Antiviral prophylaxis for at least 6–12 months should be provided for HBsAg-positive patients.
Implications: As there are limited clinical data for many of the reviewed agents, special attention must be given to promptly detect and report emerging infectious complications. **M. Mikulska, Clin Microbiol Infect 2018;▪:1**

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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 is aimed at analysing, 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 participants. 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. The present section is focused on the risk of infection entailed by the use of monoclonal antibodies and antibody constructs targeting CD19, CD20 and CD52. The effects of chimeric antigen receptor-modified T-cell therapy are beyond the scope of this review. Agents targeted at other lymphoid cell surface antigens (such as CD22, CD30, CD33, CD38, SLAMF7 or CCR4) and also used in patients with haematological malignancies are covered in a separate section of the document.

In the last two decades there has been an increasing interest in developing monoclonal antibodies targeting different surface proteins on lymphoid cells, mainly clusters of differentiation (CDs), for the treatment of leukaemia and lymphoma. Although most of these newer drugs are used in combination with traditional chemotherapeutic agents, they can also be prescribed as salvage or maintenance monotherapy in selected cases. Additionally, some agents (e.g. anti-CD20 or, more recently, anti-CD52 antibodies) are also used in patients with autoimmune or immune-mediated conditions, such as haemolytic anaemia, rheumatoid arthritis or multiple sclerosis. For these indications they are usually used as monotherapy, and the cumulative dosage is usually lower than in haematological malignancies.

The development status, therapeutic indications and potential impact on the infectious risk of the reviewed agents are summarized in Table 1. The available data on infectious complications extracted from studies that included a control group are outlined in Table 2. Characteristics of different anti-CD20 agents are shown in Table 3. Finally, the suggested strategies for the prevention of infection in patients treated with these agents are depicted in Table 4.

CD19-directed agents: blinatumomab, inebilizumab and combotox

Mechanism of action, approved indications and off-label uses

Blinatumomab (Blincyto®; Amgen, Thousand Oaks, CA, USA) is a bispecific T-cell engager antibody construct designed to direct CD3-expressing cytotoxic T cells to CD19-expressing B cells (Fig. 1) [2]. It is approved in monotherapy by the FDA and the EMA for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL). In July 2017, blinatumomab was also approved by the FDA for Philadelphia chromosome-positive forms of the disease. A single cycle of treatment consists of 4 weeks of continuous intravenous infusion followed by a 2-week treatment-free interval, and a treatment course consists of up to a total of five cycles (Table 1).

Inebilizumab (previously known as MEDI-551, MedImmune; AstraZeneca, Cambridge, UK) is a humanized, afucosylated IgG1 κ monoclonal antibody that depletes CD19-expressing B cells by means of antibody-dependent cell-mediated cytotoxicity. Currently, this agent is in phase 3 studies for neuromyelitis optica, a condition for which inebilizumab received in 2017 the status of orphan drug from the EMA, and in earlier clinical testing phases for chronic lymphocytic leukaemia (CLL), B-cell lymphoma, multiple sclerosis, systemic scleroderma and multiple myeloma.

Combotox is a 1:1 mixture of two immunotoxins (HD37-dgRTA and RFB4-dgRTA) obtained from coupling IgG1 monoclonal antibodies targeted against CD19 and CD22 and a deglycosylated ricin A chain (dgRTA, previously called dgA). CD19 is present on virtually every malignant lymphoblast in patients with B-lineage ALL, whereas the CD22 epitope is expressed on about 80% of the blast population. Therefore, B-cell ALL and B-cell lymphoma are the main therapeutic targets of combotox [3]. The dosage of combotox is still to be standardized, and repeated cycles and escalation are permitted in the absence of grade 3–4 toxicity or development of specific antibodies [3].

Chimeric antigen receptor T cells have been also developed for the treatment of ALL and other CD19-positive malignancies [4], but their performance and safety are beyond the scope of this document. Infectious complications associated with their use have been recently reviewed [5].

Expected impact on the infection risk

The expression of CD19, which is almost exclusively restricted to B cells, commences during early development stages of the cell such as pro-B, pre-B and other immature cells, germinal centre, naive and memory B cells, as well as in the majority of plasma cells located in secondary lymphoid organs (such as spleen and tonsils). All peripheral blood plasma cells and more than 50% of plasma cells in bone marrow also express CD19 on their surface. Compared with CD20, it is expressed at earlier development stages of B lymphocytes. Of note, CD19 is also present in the majority of B precursor ALL blasts, hence its main indication.

CD19-targeted agents deplete normal B cells with the consequent reduction in IgG levels. In a phase 3 RCT the presence of IgG hypogammaglobulinaemia (HGG) occurred in 6% of patients in the blinatumomab arm compared with 0.9% of those treated with conventional chemotherapy [6]. The rate of neutropenia with blinatumomab was lower than with chemotherapy (38% versus 58%, respectively) [6]. The length of HGG is difficult to establish and may depend on the number of doses of blinatumomab. In a follow-up report on six individuals with ALL from a phase 2 study with blinatumomab, only one exhibited normal serum IgG levels at approximately 2 years from the initiation of treatment, whereas none of them recovered IgA levels, even though half of them had normal IgA serum levels at the initiation of therapy [7]. Since CD19, but not CD20, is expressed on plasmablasts, CD19-targeted agents are expected to induce a more profound decrease in serum immunoglobulin levels than CD20-targeted agents [7]. Finally, B-cell-dependent activation of T cells may be also affected by CD19-targeted agents, as reported with anti-CD20 monoclonal antibodies.

Available clinical data

Trials performed within the clinical development programme for blinatumomab found no significant differences in the incidence

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Table 1
Description of the main agents targeting surface antigens on lymphoid cells

Agent	Mechanism of action	Status of development (year of approval)	Approved indications	Off-label or experimental uses	Use as single agent	Use as first-line treatment	Cellular expression	Type of immunity impairment
Blinatumomab	Bispecific CD19-directed $CD3^+$ T-cell engager	Approved, EMA (2015), FDA (2014)	Ph-negative and Ph-positive relapsed or refractory B-cell precursor ALL	DLBCL	Yes	No	B cells (including earlier stages), follicular dendritic cells	B cells, HGG, impaired B-cell-dependent T-cell activation
Inebilizumab (previously MEDI-551)	Anti-CD19 monoclonal antibody	Phase 2 and 3 studies in NMO; phase 2 in CLL, SS, B-cell lymphoma and MS; phase 1 in MM	NA	NA	Yes	No		
Combotox	Immunotoxins targeting CD22 and CD19	Phase 2 studies in ALL ongoing	NA	NA	Yes	No	See CD19 and CD 22 agents	See CD19 and CD22 agents
Rituximab	Anti-CD20 monoclonal antibody	Approved, EMA and FDA (1998)	DLCBL, low-grade NHL or follicular lymphoma, CLL, RA, Wegener granulomatosis, microscopic polyangiitis	MS, GvHD, ITP, SLE, PTLD, autoimmune neuropathies or cytopenias, Rasmussen encephalitis, pemphigus vulgaris	Yes	Yes	B cells excluding plasma cells and B-cell precursors	T- and B-cell subsets
Obinutuzumab (previously afutuzumab)	Anti-CD20 monoclonal antibody	Approved, EMA (2014), FDA (2013)	CLL, relapsed or refractory or treatment-naive follicular lymphoma	ODD for marginal zone lymphoma	Yes	Yes	Same as other CD20-targeted agents	Potentially T- and B-cell subsets (no long-term data available)
Ofatumumab	Anti-CD20 monoclonal antibody	Approved, EMA (2010), FDA (2009)	Relapsed or refractory or recurrent CLL	No	Yes (second line in CLL)	Yes	Same as other CD20-targeted agents	T- and B-cell subsets
Ocrelizumab	Anti-CD20 monoclonal antibody	Approved, FDA (2017), EMA marketing authorization (2018)	Relapsed or progressive MS	NHL, RA, SLE (trial discontinued in 2017 due to infections)	Yes	No	Same as other CD20-targeted agents	Potentially T- and B-cell subsets (no long-term data available)
Veltuzumab	Anti-CD20 monoclonal antibody	Phase 1 and 2 trials in ITP, NHL and CLL; phase 2 in NHL; effective in refractory NHL in association with milatuzumab (anti-CD74)	NA	ODD for CLL by EMA and for ITP, CLL, pemphigus vulgaris and superficial pemphigus by FDA	Potentially yes	NA	Same as other CD20-targeted agents	Potentially T- and B-cell subsets (no long-term data available)
Ublituximab	Anti-CD20 monoclonal antibody	Phase 2 terminated, phase 3 ongoing in CLL and DLBCL; phase 2 in MS	NA	ODD for DLBCL, marginal zone lymphoma, CLL, NMO spectrum disorder	Potentially yes (ongoing trials)	NA	Same as other CD20-targeted agents	Potentially T- and B-cell subsets (no long-term data available)
Ocaratuzumab	Anti-CD20 monoclonal antibody	Phase 1 and 2 trials in haematological malignancies; phase 3 in pemphigus	NA	No	Potentially yes	NA	Same as other CD20-targeted agents	Potentially T- and B-cell subsets (no long-term data available)
^{90}Y-ibritumomab tiuxetan	Anti-CD20 monoclonal antibody, delivery of radioactive isotope	Approved (2002)	Relapsed low-grade NHL or follicular lymphoma, consolidation therapy in follicular lymphoma	No	Yes	No	Same as other CD20-targeted agents	T- and B-cell subsets and granulocytes (proximal radio-toxicity)
Alemtuzumab (MabCampath®)	Anti-CD52 monoclonal antibody	Approved, FDA (2001), EMA (2001, withdrawn in 2011)	CLL	MS, GvHD, conditioning regimens	Yes	No	Mature lymphocytes (not plasma cells)	Thymocytes, lymphocytes (not plasma cells), monocytes, macrophages and epithelial cells
Alemtuzumab (Lemtrada®)	Anti-CD52 monoclonal antibody	Approved, EMA (2013), FDA (2014)	MS	No	Yes	No		

ALL, acute lymphoblastic leukaemia; CLL, chronic lymphocytic leukaemia; DLBCL, diffuse large B-cell lymphoma; EMA, European Medicines Agency; FDA, Food and Drug Administration; GvHD, graft versus host disease; HGG, hypogammaglobulinaemia; ITP, immune thrombocytopenic purpura; MS, multiple sclerosis; MTX, methotrexate; NHL, non-Hodgkin's lymphoma; NMO, neuromyelitis optica; ODD, orphan drug designation; Ph, Philadelphia chromosome; PTLD, post-transplant lymphoproliferative disorder; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS, systemic sclerosis.

Table 2
Summary of infectious events in patients treated with CD19-, CD20- and CD52-targeted agents across randomized controlled trials and observational studies that included a control group

Agent	Type of study	Treatment arms	No. of participants	Rate of infection (novel agent versus comparator)	Specific infections reported in the literature
Blinatumomab	Multicentre phase 3 RCT for ALL [6]	Blinatumomab vs standard-of-care chemotherapy	376 (267 vs 109)	Overall infection: 34% vs 52%; URTI: 7% vs 1%; CRBSI: 6% vs 5.5%; pneumonia: 6% vs 14.7%; oral herpes: 5.6% vs 8.3%; sepsis: 5.2% vs 7.3%; febrile neutropenia: 24% vs 39%	IFI, CMV infection, viral respiratory tract infection, enteroviral encephalitis, PCP, PML
Inebilizumab	Multicentre phase 1 RCT for limited or diffuse cutaneous SS [11]	Inebilizumab vs placebo	28	Overall infection: 45.8% vs 50%	
Rituximab	Meta-analysis of RCTs for malignant lymphomas [44]	17 RCTs (2 as first-line treatment)	5259	Overall infection: RR 1.00 (95% CI 0.87–1.14; p 0.9); infection-related mortality: RR 1.60 (95% CI 0.68–3.75; p 0.3); febrile neutropenia: RR 1.14 (95% CI 0.80–1.63; p 0.5); neutropenia: RR 1.07 (95% CI 1.02–1.12; p 0.008)	Respiratory tract infection, fatal reactivation of chronic or occult HBV, HCV or HEV exacerbation, enteroviral infection, PCP, PML
	Pooled safety data for moderate to severe RA treated with rituximab plus methotrexate	8 RCTs, 2 long-term open-label extension studies, 1 open-label prospective study	3595 vs 818 placebo	Overall infection rate: 75.70 (95% CI 74.31–77.11) vs 90.39 (95% CI 84.96–96.17) per 100 patient-years Serious infection rate: 3.76 (95% CI 3.46–4.09) vs 3.79 (95% CI 3.49–4.12)	
Ofatumumab	Multicentre phase 3 RCT for relapsed CLL [60]	Ofatumumab	474 (238 vs 236)	Severe infection: 13% vs 8%	
Obinutuzumab	Phase 3 RCT for refractory NHL [62]	Obinutuzumab plus bendamustine vs bendamustine	194 vs 202	Neutropenia: 35% vs 29% URTI: 13% vs 9% Sinusitis: 12% vs 5%	
	Phase 3 RCT as first-line therapy for follicular lymphoma [63]	Obinutuzumab plus CHOP or CVP or bendamustine vs rituximab plus CHOP or bedamustine	595 vs 597	Overall infection (in association with bendamustine [338 patients per arm]): • Induction: 8% vs 7.7% • Maintenance: 16.7 vs 12.8% • Follow-up: 9.3% vs 2.3%	
Ocrelizumab	Pooled data form 2 phase 3 RCTs for relapsing MS [65]	Ocrelizumab vs IFN-β1a	821 vs 825	URTI: 40% vs 33%; LRTI: 8% vs 5%	
	Phase 3 RCT for primary progressive MS [64]	Ocrelizumab vs. placebo	732	URTI: 49% vs 43%; LRTI: 10% vs 9%; HSV: 5% vs 4%	
Alemtuzumab	Systematic review of RCTs for NHL [72]	Alemtuzumab 90 mg/week for 12 weeks plus chemotherapy vs chemotherapy	175 vs 175	CMV infection: 6% vs 0%	CMV, HSV and VZV infection, PCP
	2 multicentre phase 2 to 4 RCTs for SOT recipients [73,74]	Alemtuzumab 30 mg once vs basiliximab 20 mg (plus long-term tacrolimus and MMF in both arms)	760 vs 766	Overall infection: 73% vs 75%; serious infection: 32% vs 32%; CMV infection[a]: 9.6% vs 9.5%; BKV infection: 7 vs 5%, IFI: 1% vs 1%	
	3 phase 2/3 RCTs for MS [75–77][a]	Alemtuzumab (12 mg/day for 5 days) vs IFN-β	1180 vs 496	Overall infection: 73% vs 58%; serious infection: 3% vs 1%; CMV infection: 0% vs 0%; HSV: 10% vs. 2%; VZV: 5% vs 1%	HSV, VZV, HPV infection, TB, listeriosis, mucosal candidiasis (mainly oral or vaginal)
	Case series, case reports [78–81]	NA	NA	PCP, invasive aspergillosis, nocardiosis, listeriosis, PML; mycobacterial, BKV, CMV, VZV and HSV infections; HBV reactivation	

ALL, acute lymphoblastic leukaemia; CLL, chronic lymphocytic leukaemia; CMV, cytomegalovirus; CRBSI, catheter-related bloodstream infection; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HPV human papillomavirus; HSV herpes simplex virus; IFI invasive fungal infection; IFN interferon; LRTI, lower respiratory tract infection; MMF, mycophenolate mofetil; MS, multiple sclerosis; NA, not applicable; NHL, non-Hodgkin's lymphoma; PCP, *Pneumocystis jirovecii* pneumonia; PML, progressive multifocal encephalopathy; RA, rheumatoid arthritis; RCT, randomized control trial; RR, relative risk; SOT, solid organ transplantation; SS, systemic sclerosis; TB, active tuberculosis; URTI, upper respiratory tract infection; VZV, varicella-zoster virus.
[a] Pooled data for trials with different alemtuzumab dose regimens.

of infection between study groups (Table 2). In a phase 3 RCT in 376 individuals with ALL, the rate of infection was 34% within the blinatumomab group compared with 52% within the conventional chemotherapy group that mainly received FLAG regimen (fludarabine, high-dose cytosine arabinoside and granulocyte colony-stimulating factor with or without anthracycline), although the occurrence of upper respiratory tract infection and intravascular catheter-related bloodstream infection was higher among patients receiving blinatumomab [6]. Overall, phase 2 studies with blinatumomab reported infections typically present in patients with ALL [8,9], but higher rates of catheter-related bloodstream infection (11% in one study and ranging from 3% to 11% for patients aged >65 years in a second study) [9,10]. This finding could be explained by the mode of administration of blinatumomab, requiring continuous intravenous infusion for various numbers of weeks.

In phase 1 and 2 trials, therapy with inebilizumab resulted in lower serum levels of immunoglobulins [11], with no apparent

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Table 3
Main characteristics of different CD20-targeted agents

Generation	Drug	Type	Terminal half life	Clinical phase
First generation: murine or chimeric (human-mouse) antibodies	Rituximab	Chimeric	18–32 days depending on scheduling	Approved
	^{90}Y-ibritumomab	Murine, conjugated with a radioactive isotope	30 hours	Approved
Second generation: humanized or fully human antibodies developed with the purpose of reducing immunogenicity and improving efficacy	Ofatumumab[a]	Fully human	14 days	Approved
	Ocrelizumab	Humanized	26 days	Approved
	Veltuzumab	Humanized	10–15 days	Phase 2
	^{131}I-tositumomab	Fully human, conjugated with a radioactive isotope		Discontinued in 2013
Third generation: antibodies with an engineered Fc region to boost CDC and ADCC	Obinutuzumab	Humanized	28 days	Approved
	Ocaratuzumab	Humanized	19 days	Phase 3
	Ublituximab	Chimeric	6 days	Phase 2

ADCC, antibody-dependent cell-mediated cytotoxicity; CDC, complement-dependent cytotoxicity; Fc, crystallizable fraction.
[a] Induces cell lysis regardless of the level of expression of CD20, as well as rituximab-resistant CD20-positive cells.

increase in the incidence of infectious complications [11,12]. No specific data on infection were reported in an RCT of inebilizumab plus bendamustine versus rituximab plus bendamustine in 147 patients with relapsed or refractory CLL [13].

No clinical data on infections associated with combotox are currently available because of the absence so far of controlled studies [3,14].

Conclusions and suggested prevention strategies

- In view of available data, which are currently limited to blinatumomab, therapy with CD19-targeted agents is not associated with a meaningful increase in the risk of infection compared with conventional chemotherapy, with overall rates comparable to those expected in patients undergoing treatment for relapsed or refractory ALL.
- The need for continuous 4-week intravenous infusion is probably responsible for a non-negligible rate of catheter-associated infection among patients treated with blinatumomab. Careful management of intravenous lines is therefore warranted to minimize risk.
- Clinicians caring for patients receiving such therapy should be aware of the increased risk of HGG and neutropenia, which are associated with a well-known pattern of infectious complications. In case of severe IgG HGG, immunoglobulin replacement therapy according to local guidelines could be considered, particularly in case of recurrent infections.

CD20-directed agents: rituximab, ofatumumab, ocrelizumab, veltuzumab, ^{90}Y-ibritumomab tiuxetan, ^{131}I-tositumomab, obinutuzumab, ocaratuzumab and ublituximab

Mechanism of action, approved indications and off-label uses

Anti-CD20 monoclonal antibodies constitute a family of targeted agents mainly used in the treatment of CD20-positive B-cell malignancies, as well as an increasing number of aggressive and/or orphan autoimmune diseases. According to their molecular structure, which conditions in turn the different cell-death pathways triggered, anti-CD20 monoclonal antibodies are divided into three distinct generations whose main characteristics are detailed in Table 3. At present, there are five agents approved by the FDA and EMA for different clinical uses: rituximab (Mabthera®; Roche, Basel, Switzerland), ^{90}Y-ibritumomab tiuxetan (Zevalin®; Spectrum Pharmaceuticals, Henderson, NV), ofatumumab (Arzerra®; Novartis Pharmaceuticals, Basel, Switzerland), obinutuzumab (Gazyvaro® in Europe, Gazyva® in the USA, Roche) and ocrelizumab (Ocrevus®, Roche). Three other agents are currently in phase 2 (veltuzumab) or phase 3 (ocaratuzumab and ublituximab) trials. Iodine (^{131}I)-tositumomab (Bexxar®; GlaxoSmithKline, Brentford, UK) was approved by FDA and received Orphan Drug Designation by EMA in 2003, but its production and distribution were discontinued by the manufacturer in 2014 (Table 1). Rituximab was the first anti-CD20 monoclonal antibody approved for clinical use in 1998. It represented a cornerstone in the therapeutic approaches to CD20-positive malignancies, and has been more recently approved for various autoimmune conditions. It is foreseeable that its use will further increase due to the reduced cost of biosimilar drugs and its well-known safety profile (which allows for risk stratification of patients), even in combination with other drugs.

Expected impact on the infection risk

CD20 is mainly expressed on normal and malignant B cells, beginning at the pre-B phase and progressively increasing in concentration until the mature stage. As neither B-cell precursors nor plasma cells express CD20, the action of anti-CD20 monoclonal antibodies does not immediately impair immunoglobulin production [15]. However, HGG may subsequently occur with increasing courses of therapy, which are generally required in relapsing–remitting diseases. The development of HGG after CD20-targeted therapy has been reported in patients with underlying T-cell dysfunction, in children and in patients treated for autoimmune diseases [16]. In particular, a clinical study including a total of 1039 patients with rheumatoid arthritis reported that serum IgM levels fall more rapidly than either IgG or IgA levels [17]. Remarkably, in patients with autoimmune conditions, such as systemic lupus erythematosus and thrombotic thrombocytopenic purpura, the depletion of CD20-positive B cells following rituximab administration may induce a selective effect on autoantibody secretion, resulting in the remission of the disease while preserving humoral immunity [18,19].

The clinical impact in humans of HGG induced by CD20-targeted therapy remains unclear. However, animal models suggest that the resulting B-cell depletion may lead to a strong reduction in the primary antibody response to neoantigens, even though memory B and plasma cells are resistant to these agents. Recent clinical studies highlight that after multiple courses of anti-CD20 monoclonal antibodies, individuals with autoimmune diseases may develop a clinical condition similar to common variable immunodeficiency, with the degree of HGG being directly associated with infection rates, although severe infections are generally infrequent [20]. Severe long-lasting HGG has also been reported [21].

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Table 4
Summary of risk of infectious complications and possible management strategies for the reviewed targeted agents

Group	Agent	Risk of neutropenia	Risk of HSV and VZV (anti-herpesvirus prophylaxis warranted)	Risk of PCP (anti-*Pneumocystis* prophylaxis warranted)	Risk of HBV reactivation (prophylaxis warranted for $HBsAg^{+}$/$HBsAg^{-}$ anti-HBc^{+})	Risk of CMV infection (monitoring warranted)	Other infections to be considered
CD19-targeted agents	Blinatumomab	No	Yes	Yes	Yes/yes	ND	Immunoglobulin replacement therapy if severe HGG
	Inebilizumab	ND	ND (probably in haematological malignancies)	ND	Probably yes/yes	ND	Immunoglobulin replacement therapy if severe HGG
CD20-targeted agents	Rituximab	Yes	ND (consider in haematological malignancies depending and concomitant therapy)	Possible (consider if concomitant corticosteroid therapy)	Yes/yes	ND, symptom-based approach in haematological malignancies	PML, HCV, enteroviral infections
	Obinutuzumab	Potentially yes	ND (consider depending on underlying disease and concomitant therapy)	ND, consider depending on underlying disease and concomitant therapy	ND, probably yes/yes	ND, symptom-based approach in haematological malignancies	Enteroviral infections
	Ofatumumab	Yes	ND (consider depending on underlying disease and concomitant therapy)	ND, consider depending on underlying disease and concomitant therapy	Yes/yes	ND, symptom-based approach in haematological malignancies	
	Veltuzumab	Potentially yes	ND (consider if haematological malignancies depending and concomitant therapy)	ND, possibly as rituximab	ND, probably yes/yes	ND, symptom-based approach in haematological malignancies	
	Ocrelizumab	Potentially yes	No	ND (consider depending on underlying disease or concomitant therapies)	ND, probably yes/yes	No	PML (consider based on data with rituximab and previous treatment with natalizumab)
CD52-targeted agents	Alemtuzumab (MabCampath®)	Yes	Yes	Yes	Yes/prophylaxis or monitoring	Yes	IFI, BK and JC polyomaviruses reactivation
	Alemtuzumab (Lemtrada®)	No	Yes	No (lower dose, no need of additional immunosuppression)	Probably yes/prophylaxis or monitoring	No	HPV, TB, listeriosis, candidiasis

CMV, cytomegalovirus; HBc, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papillomavirus; HSV, herpes simplex virus; IFI, invasive fungal infection; ND, no data available; PCP, *Pneumocystis jirovecii* pneumonia; PML, progressive multifocal encephalopathy; TB, active tuberculosis; VZV, varicella-zoster virus.

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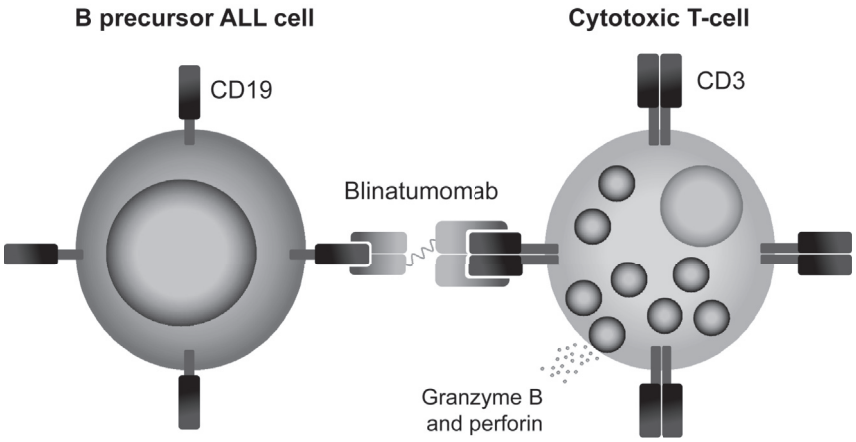

Fig. 1. Mode of action of blinatumomab, a first-in-class bispecific T-cell engager (BiTE) engineered using a diabody approach. This agent results from combining two variable regions (VH and VL) of normal antibodies with different specificities. One of these region binds to CD3 on the surface of cytotoxic T cells, while the other binds to CD19, which is largely expressed on the majority of B precursor acute lymphoblastic leukaemia blasts. The elimination of the constant regions of these antibodies allows for close approximation of both cells, thereby facilitating T-cell-mediated killing of the bound malignant B cells.

Anti-CD20 monoclonal antibodies impact immune response by modulating B-/T-cell interactions rather than directly affecting humoral immunity. In addition to antibody production, B cells play a pivotal role in activating T cells through antigen presentation and cytokine release. A significant amount of evidence suggests that B-cell depletion exerts a deleterious impact on the induction, maintenance and activation of cell-mediated immunity [22], and *in vivo* studies suggest that rituximab therapy induces a decrease in inflammatory cytokines among patients with autoimmune disorders [23]. Moreover, there are post-marketing reports of patients treated with anti-CD20 monoclonal antibodies who strongly associated with impaired cellular immunity [24], such as progressive multifocal leucoencephalopathy [25], *Pneumocystis jirovecii* pneumonia (PCP) [26], hepatitis C virus (HCV) reactivation [27] and disseminated varicella-zoster virus (VZV) infection [24,28,29]. Disseminated and/or severe enteroviral infections, probably associated with HGG, have also been reported [30–32].

A recent animal model study proved that B cells do not affect secondary T-cell responses against viral pathogens (i.e. once memory T cells are already established). However, B-cell depletion before or during primary viral infection significantly impairs cytokine production and generation of new memory $CD4^+$ T cells, thus increasing the risk of systemic primary infections [33].

In addition to the B-cell-dependent mechanism, CD20-targeted agents can directly affect cell-mediated immunity by targeting T cells. In particular, rituximab has been used for treating graft rejection after kidney transplantation and graft-versus-host disease following allogenic haematopoietic stem cell transplantation. Moreover, it has been recently discovered that about 3%–5% of human T cells express CD20 ($CD3^+$ $CD20^+$ T cells). These cells are widely represented in primary and secondary lymphatic tissues, blood and central nervous system, and are selectively depleted by CD20-targeted agents. The natural function of this T-cell subset is currently unclear. However, their depletion seems to have a central role in the remission of multiple sclerosis in patients treated with anti-CD20 monoclonal antibodies [34].

The effect of this therapy on non-lymphoid immune cells should also be kept in mind. Severe (grade 3–4) neutropenia is reported in 10%–33% of patients receiving any of the four approved non-conjugated anti-CD20 monoclonal antibodies. Although concomitant use of chemotherapy may have a role, post-marketing studies report that severe neutropenia is also possible in patients who receive such agents as sole therapy [35]. The occurrence of neutropenia with conjugated antibodies such as ^{90}Y-ibritumomab is much more frequent (with rates exceeding 50%) and severe than with non-conjugated compounds, in which early neutropenia is rare [36].

A peculiar condition associated with the use of anti-CD20 monoclonal antibodies is the so-called late-onset neutropenia. This entity has been largely described with rituximab [35], although preliminary studies do suggest that similar conditions might be associated with ofatumumab [37] and obinutuzumab [38]. In overall terms, late-onset neutropenia occurs between 1 and 5 months after the end of therapy in 5%–15% of patients treated with rituximab. It can persist for months and eventually resolve spontaneously, yet in some cases it evolves to have a persistent course with poor or transient response to granulocyte colony-stimulating factor therapy [39]. The mechanism of late-onset neutropenia is probably immune-mediated, and its impact on the risk of infections is unclear.

The effect of CD20-targeted therapy on vaccination has been reviewed elsewhere [40,41]. Impaired responses has been reported for influenza, *Streptococcus pneumoniae* polysaccharide and *Haemophilus influenzae* type b (Hib) conjugate vaccines, although a recent prospective study demonstrated that pneumococcal and Hib vaccines administered at least after 6 months from the rituximab infusion have high efficacy in preventing mild and severe respiratory infections in patients with immune thrombocytopenia [42]. The response to influenza vaccine was universally absent within 6 months from the last rituximab administration in patients with haematological malignancies [43].

Available clinical data

Meta-analysis and pooled data analysis of rituximab in patients with lymphoma [44] and rheumatoid arthritis [45] did not show an increase in the incidence of infections compared with placebo (Table 2). However, a large population study in patients with immune thrombocytopenia showed that the risk of serious infections (both viral and bacterial) was 2.6 times higher in participants who received rituximab compared with those who did not, whereas such increase for corticosteroids was estimated as 3.8 times [42].

It should be emphasized that the studies included in the meta-analyses did not specifically evaluate the occurrence of most frequent infectious complications, but the role of rituximab in the reactivation of both chronic and apparently resolved hepatitis B virus (HBV) infection has been extensively documented [46–48],

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with pooled odds ratio for reactivation of 5.7 compared with immunosuppressive therapy without rituximab [46], and 109 fatal cases documented in the Adverse Even reporting System [49]. For example, the rate of HBV reactivation among hepatitis B surface antigen (HBsAg)-negative/anti-hepatitis B core antibody (HBc)-positive lymphoma patients treated with rituximab-containing regimens (R-CHOP—rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) was 24% compared with no cases in those treated with chemotherapy without rituximab [50]. Antiviral prophylaxis was effective in reducing the reactivation risk and is currently recommended by various guidelines [51,52]. Antiviral prophylaxis should be offered both to HBsAg-positive and HBsAg-negative/anti-HBc-positive patients for at least 12–18 months after the last administration of anti-CD20 agent because delayed cases of HBV reactivation have been reported [53]. Monitoring for HBV reactivation should be performed for at least 12 months after the end of antiviral prophylaxis.

Lamivudine has been the most frequently used antiviral agent in this setting. Few studies on direct head-to-head comparison between lamivudine and drugs with higher genetic barrier to HBV resistance have been performed, and the benefit of the latter has been reported in HBsAg-positive lymphoma patients [50]. Nevertheless, several guidelines recommend potent antivirals, such as entecavir or tenofovir, for prophylaxis in HBsAg-positive patients receiving anti-CD20 therapy [51–53]. For HBsAg-negative/anti-HBc-positive patients, antiviral prophylaxis could be replaced by frequent (usually monthly) HBV-DNA monitoring and pre-emptive antiviral treatment in case of a positive result, but such a strategy might be more expensive and prone to poor compliance than prophylaxis [50].

Additionally, exacerbation of HCV, chronic hepatitis E virus infection and severe enterovirus infections have been reported in patients receiving rituximab therapy [30–32,54,55], as have opportunistic infections resulting from impaired cell-mediated immunity such as progressive multifocal leucoencephalopathy or *Pneumocystis jirovecii* pneumonia. A meta-analysis of 11 cohort studies suggested that the use of rituximab-containing regimens in patients with lymphoma was associated with a significantly increased risk for *Pneumocystis jirovecii* pneumonia, (with a risk ratio of 3.65). However, the incidence rate among the 942 rituximab-exposed patients was relatively low (2.97%). This risk was inversely associated with the receipt of anti-*Pneumocystis* prophylaxis [56]. However, a more recent single-centre study including 689 patients with B-cell lymphoma treated with R-CHOP concluded that the cumulative incidence of PCP until 180 days after the last cycle of therapy was low (1.5%) and below the conventional threshold for considering the use of prophylaxis [57]. Additionally, the risk of PCP has been reported to be higher among lymphoma patients receiving R-CHOP chemotherapy every 14 days compared with 21-day regimens [26]. Indeed, recent guidelines consider anti-*Pneumocystis* prophylaxis as optional only for R-CHOP-14 but not for R-CHOP-21, whereas the use of rituximab itself is not considered an indication [58]. Of note, prophylaxis should be provided to all the patients receiving steroids at the dose of 20 mg of prednisone daily (or equivalent) for at least 4 weeks [58].

Several biosimilars of rituximab are currently available. Direct comparison regarding the incidence and nature of infectious complications between rituximab and these biosimilars is lacking, but meta-analyses report similar efficacy and safety [59].

The higher rate of toxicity observed with ^{90}Y-ibritumomab tiuxetan than with rituximab is mainly due to the effect of radiation on cells surrounding the CD20-positive targets, causing severe leucopenia. Nevertheless, the spectrum of infections is similar to rituximab.

There are few data available for ofatumumab, but the rates reported for overall and severe infection ranged from 33% to 53% and 1% to 5%, respectively. Notably, no cases of active tuberculosis have been reported, even among patients coming from high-prevalence countries. A single case of fulminant HBV infection was reported in a woman concomitantly treated with methotrexate. A pivotal phase 3 open label trial assessing the efficacy and safety of ofatumumab as sole maintenance agent versus observation in 477 patients with CLL showed that progression-free survival was improved in those allocated to the ofatumumab arm. However, infections (respiratory tract and herpes simplex virus) and neutropenia were also more common in the ofatumumab group than in the control group [60].

In pivotal trials of obinutuzumab in combination with chlorambucil for CLL, severe and life-threatening cytopenias were frequent, both neutropenia (40% overall; 34% for grade 3–4) and thrombocytopenia (15% overall, 11% for grade 3–4) [61]. Similar to that reported with rituximab, cases of disseminated enterovirus infection have been described in patients treated with obinutuzumab [31,32]. Adding obinutuzumab to bendamustine in 396 patients with indolent Hodgkin's lymphoma who had failed rituximab, resulted in higher rates of neutropenia and upper respiratory tract infection compared with bendamustine monotherapy [62]. Finally, in an RCT with rituximab as comparator, the rate of infectious complications was higher in the obinutuzumab arm, particularly when used in association with bendamustine during maintenance and follow-up phases [63].

In phase 3 RCTs, ocrelizumab showed better efficacy than interferon-β or placebo in the treatment of primary progressive or relapsing multiple sclerosis, respectively [64,65]. Infection rates were overall high, exceeding 50% for both ocrelizumab and control arms, although severe infections were uncommon. Upper respiratory tract infection and oral herpes occurred more frequently among patients receiving ocrelizumab. On the other hand, ocrelizumab was marginally safer than interferon-β with regard to severe infections (1.3% versus 2.9%, respectively) [65]. Ocrelizumab therapy seems to be less safe when used in combination with other immunosuppressive agents. Clinical development of ocrelizumab as combination therapy for rheumatoid arthritis [66] and proliferative lupus nephritis [67] was terminated by the sponsor due to an increased incidence of serious infections.

Optimizing vaccine status may contribute to reduce the risk of severe infections among patients treated with anti-CD20 monoclonal antibodies. Non-live vaccines are safe and efficacious, especially if administered 4 weeks before treatment. Efficacy of non-live vaccination during or immediately after CD20-targeted therapy is more debated, and experimental and clinical data show that seroconversion is absent or severely impaired during at least 6 months after administration of rituximab [43,68]. However, population studies suggested that vaccination may improve both quality and expectancy of life, and clinical trials to optimize the vaccine scheme in patients receiving CD20-targeted therapies are ongoing. As there is no evidence on safety or efficacy of live vaccines in patients who undergo anti-CD20 therapy, they should not be administered.

Finally, it should be noted that the use of anti-CD20 monoclonal antibodies for chronic conditions (i.e. autoimmune diseases and indolent lymphomas) is increasing and, therefore, there is a need to establish best strategies for the management of late-onset complications among patients receiving multiple courses of treatment. As many of these patients might be not eligible for standard RCTs, large population and open-label extension studies or adaptive trials may help to define such preventive approaches.

Conclusions and suggested prevention strategies

- In view of available data, therapy with CD20-targeted agents (in particular the newer anti-CD20 monoclonal antibodies) is associated with at least a moderate increase in the risk of

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infection. Infection remains the most common non-haematological adverse effects of anti-CD20 monoclonal antibodies (including severe respiratory tract infection and HBV reactivation and, to a lesser extent, HCV reactivation and VZV infection).
- The increased risk of infection associated with the use of second- and third-generation anti-CD20 monoclonal antibodies should be individually evaluated in the light of patient's comorbidities and the concomitant administration of other immunosuppressive agents (in particular, this latter factor may render unacceptably high the risk of severe infections).
- There are few data on the clinical impact of cytopenias associated with the newest anti-CD20 monoclonal antibodies (such as ocrelizumab or obinutuzumab).
- Current evidence suggests that the addition of rituximab to conventional chemotherapy is not associated with an increased risk of PCP compared with chemotherapy alone, so anti-*Pneumocystis* prophylaxis in patients treated with rituximab should be considered only in those also receiving concomitant therapies which are themselves associated with an increased risk of PCP, including corticosteroids (prednisone ≥20 mg daily or equivalent dose for at least 4 weeks) [58].
- Screening for chronic or resolved HBV infection should be performed before starting treatment with CD20-targeted agents.
- Antiviral prophylaxis while on anti-CD20 therapy and for at least 12–18 months after the last dose should be administered to HBsAg-positive patients for preventing HBV reactivation. Antiviral agents with high genetic barrier to HBV resistance (e.g. entecavir) should be used. Monitoring for HBV reactivation should be performed for at least 12 months after the end of antiviral prophylaxis.
- Prophylaxis (usually with lamivudine) should be offered to HBsAg-negative/anti-HBc-positive patients to prevent the reactivation of resolved HBV infection [69].
- Age-appropriate inactivated vaccinations (e.g. influenza, pneumococcal and Hib) should be provided according to current guidelines [70]. There are no data on the safety and efficacy of live-virus vaccines (i.e. VZV or measles-mumps-rubella) in patients receiving anti-CD20 monoclonal antibodies. Therefore, such vaccines should not be provided until at least 6 months after completion of CD20-targeted therapy.

CD52-targeted agents: alemtuzumab

Mechanism of action, approved indications and off-label uses

Alemtuzumab (MabCampath® or Lemtrada®; Genzyme-Sanofi, Cambridge, MA, USA) is a humanized IgG1 monoclonal antibody that binds to CD52 and leads to the lysis of targeted cells by means of complement-dependent cytotoxicity and/or antibody-dependent cell-mediated cytotoxicity. In May 2001 it was approved by the FDA for the treatment of B-cell CLL in patients who have been treated with alkylating agents and have failed on fludarabine therapy. This indication is not currently supported by the EMA. In 2013 alemtuzumab was EMA-approved, at a significantly lower dose, for the treatment of multiple sclerosis. In addition, off-label uses of alemtuzumab includes the treatment of Hodgkin's and non-Hodgkin's lymphomas, prevention (as induction therapy) or treatment of graft rejection in solid organ transplantation, and prevention or treatment of graft-versus-host disease after allogenic haematopoietic stem cell transplantation (Table 1).

The standard dose of alemtuzumab for patients with B-cell CLL is 30 mg three times weekly for up to 12 weeks (maximum dose 1080 mg per year), whereas for multiple sclerosis a two-cycle regimen of 12 mg daily for 5 days (total dose 60 mg), followed 12 months later by 12 mg daily for 3 days (total dose 36 mg) is recommended.

Expected impact on the infection risk

CD52 is expressed on most mature lymphocytes (but not plasma cells), monocytes, macrophages, epithelial cells and thymocytes. Alemtuzumab induces severe depletion of peripheral blood lymphocytes (both T and B cells, especially $CD4^+$), and this effect is more profound and long-lasting with repeated infusions. In view of the notable impact on the $CD4^+$ T-cell subset, the expected infection risk is similar to the spectrum observed in advanced human immunodeficiency virus infection, with increased incidence of classic opportunistic infections (e.g. herpesvirus infections, PCP or mycobacterial infections). Even with the lower doses of alemtuzumab used in multiple sclerosis, decreased $CD4^+$ T-cell counts (<200 cells/μL) have been reported to persist months after the completion of therapy [71].

Available clinical data

Alemtuzumab has been tested in numerous phase 3 RCTs for B-cell CLL, induction therapy in kidney transplant recipients and multiple sclerosis. Additionally, there have been phase 2 trials in rheumatoid arthritis and other conditions. Infectious complications have been reported in the setting of these phase 3 trials, as well as in a number of smaller studies, case series and case reports. The highest rates were found in patients with B-cell CLL and kidney transplant recipients, whereas the lowest were in multiple sclerosis [72–81]. Different dosing regimens, disease-related immunosuppression, and the prior or concomitant use of other agents most likely account for these differences (Table 2).

The risk of cytomegalovirus (CMV) infection was increased in non-Hodgkin's lymphoma trials, whereas herpes simplex virus and VZV were more commonly found in multiple sclerosis studies. The incidence of CMV infection was lower than one episode per 100 patient-years in pivotal multiple sclerosis trials. Anti-herpesvirus prophylaxis was the standard of care for participants in RCTs for haematological malignancies, and it was also recommended after the results of the pivotal studies in multiple sclerosis. Due to the perceived risk of PCP, standard anti-*Pneumocystis* prophylaxis has been advocated early as standard treatment. There have been case reports of HBV and HCV reactivation in patients with haematological malignancies treated with alemtuzumab. As such patients were excluded from trials in multiple sclerosis, the risk of these complications remains to be established for this particular population. Finally, a higher rate of human papillomavirus infection (2%), and single cases of listeriosis and tuberculosis have been reported in pivotal trials in multiple sclerosis. Therefore, annual human papillomavirus screening is recommended for female patients according to the FDA- and EMA-approved package insert of Lemtrada®.

Conclusions and suggested prevention strategies

- In view of available data, therapy with CD52-targeted agents (alemtuzumab) is associated with a major increase in the risk of infection, with a spectrum of syndromes and causative agents typical for severe quantitative T-cell defects (i.e. similar to advanced human immunodeficiency virus infection). This risk is clearly dependent on the dose regimen used (which depends in turn on the underlying indication), additional immunosuppressive therapies and prophylactic strategies applied.
- Anti-*Pneumocystis* prophylaxis should be administered to patients receiving alemtuzumab for haematological malignancies,

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solid organ transplantation or other off-label indications throughout the entire course of therapy. The duration of prophylaxis upon discontinuation of alemtuzumab therapy is not well established, although it seems reasonable to continue its administration for at least 2–6 months or, alternatively, until the peripheral blood $CD4^+$ T-cell count recovers to ≥200 cells/μL.

- Prevention strategies for CMV infection (antiviral prophylaxis or pre-emptive therapy guided by CMV-DNA detection or symptom-based approach) should be applied to CMV-seropositive patients receiving alemtuzumab for haematological malignancies, solid organ transplantation and other off-label indications. The election of any of these strategies may be additionally influenced by other factors (e.g. donor/recipient serostatus in solid organ transplantation and haematopoietic stem cell transplantation).
- Anti-herpesvirus (i.e. herpes simplex virus or VZV) prophylaxis should be administered to patients receiving alemtuzumab for haematological malignancies, solid organ transplantation and other off-label indications. Patients treated for multiple sclerosis should receive anti-herpesvirus prophylaxis from the first day of each treatment cycle and continue for at least 2 months or, alternatively, until the peripheral blood $CD4^+$ T-cell count recovers to ≥200 cells/μL.
- Screening for chronic or resolved HBV and for chronic HCV infection should be performed before starting treatment with alemtuzumab. Antiviral prophylaxis while on therapy and for at least 6–12 months after the last dose should be administered to HBsAg-positive patients for preventing HBV reactivation. In addition, prophylaxis with lamivudine (or, alternatively, close monitoring for HBV viral load followed by pre-emptive antiviral treatment) should be administered to HBsAg-negative/anti-HBc-positive patients to prevent the eventual reactivation of occult HBV infection [69].
- Screening for latent tuberculosis infection should be performed before starting alemtuzumab therapy, followed by appropriate therapy if needed.
- Annual human papillomavirus screening is recommended for female patients receiving alemtuzumab.
- Counselling on appropriate hygienic and food safety measures that might reduce the risk of listeriosis (e.g. to avoid unpasteurized milk and its products, certain soft cheeses like brie or feta, raw or undercooked meat) or toxoplasmosis among *Toxoplasma*-seronegative patients (e.g. avoid raw or undercooked meat and contact with cat faeces) should also be provided.

Transparency declaration

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