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The laboratory of clinical virology in monitoring patients undergoing monoclonal antibody therapy

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Abstract

The relevant efficacy of monoclonal antibodies (mAbs) has resulted in the successful treatment of several diseases, although susceptibility to infections remains a major problem. This review summarizes aspects of the literature regarding viral infections and mAbs, specifically addressing the risk of infection/reactivation, the measures that can reduce this risk, and the role played by the laboratory of clinical virology in monitoring patients undergoing mAb therapy.

Keywords: Hepatitis viruses, herpesviruses, monitoring, monoclonal antibodies, polyomaviruses
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Introduction

The treatment of several medical conditions, such as cancer and autoimmune diseases, has been revolutionized following the introduction of biological therapies targeting specific components of pathways involved in the pathogenic mechanisms. These agents are mainly monoclonal antibodies (mAbs). Immunotherapy developed with the discovery of antibody structure and the introduction of hybridoma technology, which provided the first source of mAbs [1]. Initially, murine mAbs (suffix *-omab*) suffered from major problems resulting from immune complex formation and inadequate recruitment of host effector functions. To overcome this, murine molecules were engineered to remove immunogenic content and to increase the immunomodulant efficiency; this was achieved by the production of chimeric (composed of murine variable regions fused onto human constant regions, *c.* 65% human component; suffix *-ximab*) and humanized (produced by grafting murine hypervariable amino acid domains into human antibodies, *c.* 95% human component; suffix *-zumab*) antibodies. Extensive research is currently being conducted to produce mAbs for several diseases, such as rheumatoid arthritis, multiple sclerosis, inflammatory bowel diseases, and many types of neoplasm. However, susceptibility to infections remains a major concern, as the targets of these mAbs are molecules or cells involved in immune anti-infectious pathways. The severity of these infections can be influenced by the protocol utilized (dosage, frequency, and route of administration). Considering the most used mAbs in clinical practice, the reported infectious complications remain low in frequency, and are limited mainly to mAbs targeting antigens such as CD52, CD20, tumour necrosis factor (TNF)-α, and the integrin very late antigen (VLA)-4 [2]. Besides bacterial and fungal infections, viral infections/reactivations are important factors limiting the utilization of biological agents (Table 1).

Anti-CD52: Alemtuzumab

Alemtuzumab is a humanized anti-CD52 antibody (Campath) that is mainly expressed on the surface of peripheral B-cells and T-cells, both normal and malignant, monocytes, thymocytes, natural killer cells, and macrophages; it is not expressed on erythrocytes or platelets. This mechanism of action makes alemtuzumab indicated for the treatment of chronic lymphocytic leukaemia, non-Hodgkin lymphomas, post-transplantation patients, and graft-versus-host disease. Treatment results in

TABLE 1. Main viral infections/reactivations in patients undergoing monoclonal antibody therapy and monitoring or recommendations

	Anti-CD52 (alentuzumab)	Anti-CD20 (rituximab)	TNF-α antagonists (infliximab, etanercept, adalimumab, certolizumab pegol)	Anti-integrin VLA-4 (natalizumab)
CMV	6–66% reactivation within 4–6 weeks, close monitoring [3,4]	Few cases, close monitoring [5]	Poorly known [22–26]	
HBV	Active and prior infection as exclusion criteria in clinical trials	20–55%, close monitoring [5–10]	Case reports, close monitoring, exclusion criteria in clinical trials, but consider occult infection [18–21]	
HCV	Active and prior infection as exclusion criteria in clinical trials		Poorly known, close monitoring [14,15]	
VZV		Few cases [5]	Poorly known [28]	
JCV		57 cases [11,12]		30 cases [12]
EBV	Up to 40% reactivation, <1% risk of PTLD [33]		Poorly known [27]	
HPV			Poorly known [29]	

CMV, cytomegalovirus; EBV, Epstein–Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papillomavirus; JCV, JC virus; PTLD, post-transplantation lymphoproliferative disorder; TNF, tumour necrosis factor; VLA, very late antigen; VZV, varicella-zoster virus.

lymphoid ablation. In this context, reactivation of cytomegalovirus (CMV) is an important problem, having been reported in 6–66% of patients [3]. The wide range of reported incidence might be a result of differences in study design, population, and viral detection modes; moreover, earlier studies might have under-reported the incidence of CMV reactivation, because CMV was not routinely monitored. Nevertheless, the benefit/risk ratio favours its utilization with close virological monitoring for early detection of reactivation, as pre-emptive treatment prevents the occurrence of potentially life-threatening disease, and the initiation of anti-CMV treatment avoids the interruption of alemtuzumab. CMV reactivation is typically observed between 4 and 6 weeks after the initiation of treatment [4]. Usually, given the high background of CMV seropositivity, reactivation is monitored weekly with a sensitive detection method (CMV-DNAemia). In clinical trials, among the exclusion criteria for recruitment, CMV-DNAemia positivity at screening makes the patient not eligible. Treatment to reduce the viral load to a non-detectable level is required, and study entry is possible once the infection has been treated. Among exclusion criteria are active or prior viral hepatitis B or C or positivity for hepatitis B serology. Patients with hepatitis B surface antibodies (HBsAbs) with a documented history of prior hepatitis B immunization are eligible if other criteria are met (i.e. negativity for hepatitis B surface antigen (HBsAg), hepatitis B core antibody, and anti-hepatitis C virus (HCV) antibody). Patients with human immunodeficiency virus (HIV) infection are excluded. In Fig. 1, an algorithm for the evaluation of viral infections in relation to the administration of alemtuzumab is given.

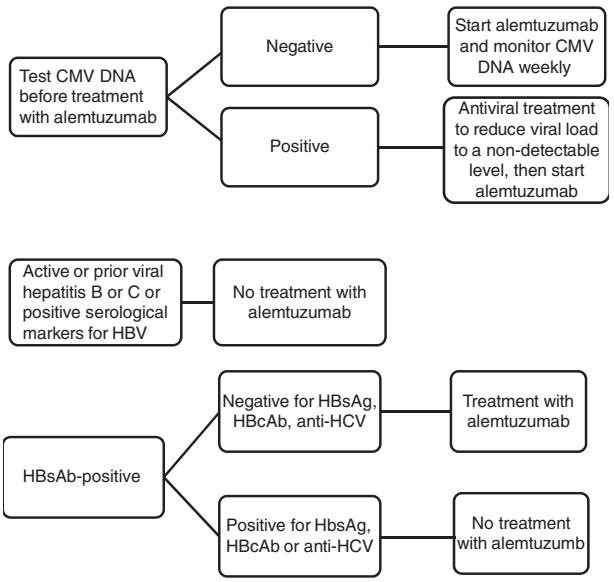

FIG. 1. Algorithm for the evaluation of viral infections in relation to the administration of alemtuzumab. CMV, cytomegalovirus; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus.

Anti-CD20: rituximab

Rituximab (Mabthera or Rituxan) is a chimeric mAb targeting the CD20 molecule, and is expressed on the normal B-cell lineage (from pre-B stage to memory stage) as well as on abnormal B-lymphocytes. Rituximab has been approved for the treatment of indolent CD20, B-cell non-Hodgkin lymphomas, chronic lymphocytic leukaemia, and moderate-to-severe rheumatoid arthritis. Several viral infections related to rituximab have been reported. In a meta-analysis [5], 64 cases of serious viral infection after rituximab treatment were found, in particular hepatitis B virus (HBV) reactivation in patients with chronic lymphocytic leukaemia and lymphomas [5–9]; CMV infection, varicella-zoster virus infection and other infections were also found. Close monitoring for viral infec-