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1 **The laboratory of clinical virology in monitoring the patients undergoing**
2 **monoclonal antibody therapy**

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18

19 **Abstract**

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

26

27 **Keywords**

28 Monoclonal antibodies; herpesviruses; polyomaviruses; hepatitis viruses; monitoring.

29

30 **Introduction**

31 The treatment of several medical conditions, such as cancer and autoimmune diseases,
32 has been revolutionized following the introduction of biologic therapies targeting specific
33 components of pathways involved in the pathogenic mechanisms. These agents are
34 prevalently monoclonal antibodies (mAbs). Immunotherapy developed with the discovery
35 of antibodies structure and the introduction of hybridoma technology, which provided the
36 first source of mAbs [1]. Initially, murine mAbs (suffix *-omab*) were burdened by major
37 problems due to immune complex formation and inadequate recruitment of host effector
38 functions. To overcome this, murine molecules were engineered to remove immunogenic
39 content and to increase the immunomodulant efficiency; this was achieved by the
40 production of chimeric (composed of murine variable regions fused onto human constant
41 regions, ~65% human component; suffix *-ximab*) and humanized (produced by grafting
42 murine hypervariable aminoacid domain into human antibodies, ~95% human component;
43 suffix *-zumab*) antibodies. Extensive researches are currently conducted to originate
44 mAbs for several diseases, such as rheumatoid arthritis, multiple sclerosis, inflammatory
45 bowel diseases, and many types of neoplasms. However, susceptibility to infections
46 remains a major concern, as the target of these mAbs are molecules or cells involved in
47 immune anti-infectious pathways. The severity of these infections can be influenced by the
48 protocol utilized (dosage, frequency, and route of administration). Considering the most
49 used mAbs in clinical practice, the reported infectious complications remain low and limit
50 particularly the utilization of mAbs targeting antigens such as CD52, CD20, tumor necrosis
51 factor (TNF)- α and the integrin very late antigen (VLA)-4 [2]. Beside bacterial and fungal
52 infections, viral infections/reactivations represent important factors limiting the utilization of
53 biological agents (Table 1).

54

55 **Anti-CD52: alemtuzumab**

56 Alemtuzumab is a humanized anti-CD52 antibody (Campath®), that is mainly expressed
57 on the surface of peripheral B- and T-cells, both normal and malignant, monocytes,
58 thymocytes, natural killer cells and macrophages, whereas it is not expressed on
59 erythrocytes or platelets. This mechanism of action makes alemtuzumab indicated for the
60 treatment of chronic lymphocytic leukemia, non-Hodgkin lymphomas, post-transplantation
61 and graft-versus-host disease. Treatment results in lymphoid ablation. In this context,
62 reactivation of cytomegalovirus (CMV) is an important problem, having been reported in 6-
63 66% of patients [3]. The wide range of reported incidence might be a result of differences
64 in study design, population, and viral detection modes; moreover, earlier studies might
65 have underreported the incidence of CMV reactivation, because CMV was not routinely
66 monitored. Nevertheless, the benefit/risk ratio favors its utilization associated to a close
67 virological monitoring for early detection of reactivation, as pre-emptive treatment prevents
68 the occurrence of potentially life-threatening disease and the initiation of anti-CMV
69 treatment avoids the interruption of alemtuzumab. Cytomegalovirus reactivation is typically
70 observed between 4 and 6 weeks after the initiation of treatment [4]. Usually, given the
71 high background of CMV-seropositivity, reactivation is monitored weekly by a sensitive
72 detection method (CMV-DNAemia). In clinical trials, among the exclusion criteria for the
73 recruitment, CMV-DNAemia positivity at screening makes the patient not eligible.
74 Treatment to reduce viral load to a non-detectable level is required and study entry is
75 possible once the infection has been treated. Among exclusion criteria, there are active or
76 prior viral hepatitis B or C or positivity for hepatitis B serology. Patients with hepatitis B
77 surface antibodies (HBsAb) with documented history of prior hepatitis B immunization are

78 eligible if other criteria are met (i.e. negativity for HBsAg, HBcAb, and anti-HCV). Patients
79 with HIV-infection are excluded. In Figure 1, an algorithm for the evaluation of viral
80 infections in relation to the administration of alemtuzumab is reported.

81

82 **Anti-CD20: rituximab**

83 Rituximab (Mabthera® or Rituxan®) is a chimeric mAb targeting the CD20 molecule, that
84 is expressed on the normal B-cell lineage (from pre-B stage to memory stage) as well as
85 on abnormal B-lymphocytes. Rituximab has been approved for the treatment of indolent
86 CD20, B-cell non-Hodgkin lymphomas, and chronic lymphocytic leukemia, as well as for
87 that of moderate-to-severe rheumatoid arthritis. Several viral infections related to rituximab
88 have been reported. In a metanalysis [5], 64 cases of serious viral infection after rituximab
89 treatment were found, in particular HBV reactivation in patients with chronic lymphocytic
90 leukemia and lymphomas [5,6-9], followed by CMV, varicella-zoster virus, and others. A
91 close monitoring for viral infections, particularly HBV and CMV, by molecular methods is
92 recommended. Periodic monitoring of HBV-DNA may predict HBV reactivation, thus being
93 advantageous in terms of costs; it is also essential in cases with HBV-DNA mutations and
94 when antibody expression is weak. The identification of HBV reactivation at an early stage
95 is important; therefore, in addition to HBV-DNA monitoring, it should be recommended to
96 evaluate changes in anti-HB titers [10]. Viral reactivation of polyomavirus JC from sites of
97 latency leading to the development of infection and destruction of the oligodendrocytes is
98 the pathogenic mechanism responsible for progressive multifocal leukoencephalopathy
99 (PML). To date, 57 PML cases have occurred in patients treated with rituximab [11,12]. A
100 high degree of awareness for PML facilitates case identification; as a definitive diagnosis
101 of PML is based on clinical, neuroimaging, histopathologic findings, as well as on the

102 detection of JCV in the brain tissue, less invasive methods based on the detection of JCV-
103 DNA in cerebrospinal fluid have been proposed. Evaluation of JCV-DNA on serum
104 specimens seems to display low operating characteristics, given the rarity of PML and the
105 high incidence of transient viremia (up to 18% in HIV-patients without PML)[13].

106

107 **Tumor necrosis factor- α antagonists**

108 Monoclonal antibodies that antagonize TNF- α (i.e. infliximab, etanercept, adalimumab,
109 certolizumab pegol) are used for several inflammatory diseases, such as Crohn's disease,
110 rheumatoid polyarthritis, psoriasis, ankylosing spondylitis, and juvenile idiopathic arthritis.
111 While the association with an increased risk of severe bacterial infections and reactivation
112 of tuberculosis has been recognized, the impact on viral infections is less known. Long-
113 term safety and efficacy in patients with chronic HBV or HCV and/or HIV infection are
114 poorly known. However, history or current active HBV, history of HCV and HIV infection
115 are exclusion criteria for enrollment in clinical trials. As regards HCV, elevated levels of
116 TNF- α are associated with chronic infection and there is a growing evidence that the
117 pathogenesis of hepatocyte destruction may be mediated by the upregulation of
118 inflammatory cytokines such as TNF- α . Therefore, TNF- α antagonists may be beneficial
119 when used in cases of HCV [14,15] and there are some reports indicating that anti-TNF- α
120 therapy in the setting of HCV appears to be safe. However, as the role of TNF- α is
121 complex, the FDA points out the possible risk of reactivation of chronic viral hepatitis.
122 Overall, data on safety and efficacy are conflicting; therefore, the presence of HCV should
123 not be an absolute contraindication, given an appropriate pretreatment screening and a
124 close monitoring. For selected patients, anti-TNF- α therapy in the setting of HCV appears
125 to be safe without apparent influence on the underlying infection. Interval monitoring of

126 serum aminotransferases and HCV viral load is recommended. Elevated levels of TNF- α
127 are also seen in patients with chronic HBV and, in these patients, it may play a role in
128 clearing and controlling replication by synergizing with interferon; inhibition of TNF- α could
129 theoretically lead to enhanced viral replication [16,17]. Reports of patients with chronic
130 HBV who were treated with infliximab or etanercept, and developed a severe reactivation,
131 sometimes with fulminant hepatitis, have been published [18-21]. In most cases, patients
132 had chronic HBV with HBsAg positivity, but in others fulminant hepatitis was associated
133 with a previously unrecognized HBsAg-carrier condition. For HBsAg-negative patients with
134 a known history of HBV, the risk of reactivation is very low, but it cannot be totally
135 excluded. Patients who are persistently HBsAg-negative, but have an occult HBV infection,
136 have also been described. These patients may be at risk of developing a flare of hepatitis
137 during the course of anti-TNF- α agents as this may interrupt the suppression of viral
138 replication and gene expression typical for the occult HBV [17]. Evaluation of risk-benefit
139 profile for specific antiviral treatment with lamivudine should be performed [17]. In
140 conclusion, screening for HBV in all patients prior to treatment with anti-TNF- α agents
141 should be recommended and, if treatment has been initiated, carriers of HBV should be
142 closely monitored for laboratory and clinical signs of viral reactivation during therapy and
143 for several months following its termination.

144 Few data on the risk of reactivation of herpesvirus infections are available. Several cases
145 of CMV infection have been reported, although severe clinical manifestations are rare.
146 Authors suggested the assessment of CMV pp65-antigen levels or quantification of CMV-
147 DNA in symptomatic patients [22-26]. Limited informations are available on Epstein-Barr
148 virus reactivation, as well as JCV. Large studies with long follow-up are needed to define
149 the risk and opportunity for viral monitoring. Epstein-Barr virus is associated with

150 lymphoproliferative diseases in immunosuppressed patients and infliximab treatment has
151 been resulted in transient elevations in viral load in some patients, although at levels lower
152 than those associated to lymphoproliferative disorders [27]. Similarly, also limited data are
153 available on varicella zoster virus and screening recommendations for the presence of
154 antibodies prior to treatment or a prophylactic vaccination in non-immune patients remain
155 questionable [28].

156 Specific effects of anti-TNF- α therapy on human papillomavirus-associated diseases
157 remain unknown, with very few reports suggesting a significantly increased risk in patients
158 with inflammatory bowel diseases treated with infliximab [29].

159 HIV is considered among the relative contraindications for anti-TNF- α therapy, however its
160 safety in HIV-infected patients is unknown. Their use should be reserved for highly
161 selected patients, although further studies are needed. The potential impact of the loss of
162 HIV control needs to be determined before establishing a clear recommendation; to
163 promptly identify reactivation of HIV, close monitoring of clinical and laboratory parameters
164 in these patients is mandatory [17,30].

165 Overall, although several guidelines regarding viral infections monitoring in
166 immunocompromised patients are available, few address biological therapy. The
167 appropriate serological tests are poorly defined, although evaluation of HBV status is
168 widely supported, while HCV and HIV testing seems to be justified in high-risk patients.
169 The European Crohn's and Colitis Organisation consensus statement recommends
170 universal testing (HBsAg, anti-HBs, anti-HBc) and HBV vaccination in all the patients with
171 inflammatory bowel diseases, while no recommendations have been defined for HCV [31].
172 On the contrary, a consensus statement on pre-treatment testing in rheumatology patients

173 recommends the screening for HBV and HCV in all the patients, without a defined
174 serological strategy [32].

175

176 **Anti-integrin VLA-4**

177 Natalizumab (Tysabri®) is a selective adhesion molecule inhibitor the target of which is
178 the $\alpha 4$ subunit of VLA-4 receptor. Natalizumab binds to $\alpha 4$ -integrin expressed on the
179 surface of activated T cells and other mononuclear leukocytes, where it prevents adhesion
180 between the endothelial cell and the immune cell. This action inhibits the migration of
181 leukocytes into the central nervous system. The main indication for natalizumab treatment
182 is relapsing-remittent highly inflammatory multiple sclerosis (MS). However, the same
183 mechanism of action implies a decreased local immune surveillance, thus possibly
184 contributing to an increased risk of PML,
185 a demyelinating disease caused by lytic replication of JCV in oligodendrocytes, that is
186 observed in the setting of profound cellular immunosuppression, such as HIV patients and
187 individuals exposed to potent antilymphocyte drugs, such as natalizumab, and other
188 mAbs, such as rituximab and efalizumab.

189 More than 30 PML cases have been reported worldwide in patients receiving natalizumab
190 monotherapy for MS and data suggests that PML incidence increases with the number of
191 infusions (increased risk after two years of therapy). Currently, ~30,000 patients treated or
192 on treatment with natalizumab are being monitored for PML [12].

193

194 **Conclusions**

195 The elevated efficacy of mAbs is counterbalanced by an increased risk of infectious
196 complications. The complete spectrum of viral diseases complicating their administration is
197 still poorly known, although data are accumulating. Similarly, also virological screening and
198 monitoring that should be performed in these patients are still undefined and vary largely
199 depending on underlying disease, type of patients, and protocol. Particular attention is
200 required for the monitoring of herpesviruses, JCV, HBV and HCV, and data that are being
201 obtained could represent the basis to define consensus guidelines that take into account
202 the evaluation of viral status pre-treatment, as well as viral replication/reactivation during
203 therapy and following its interruption. The possible role played by the specific cellular
204 immune response in containing viral replication remains to be determined and it is likely
205 that viro-immunological monitoring could contribute to better understand the immunological
206 background underlying the occurrence of viral complications and to improve their clinical
207 management. Overall, the role played by the virology laboratory is relevant as the basal
208 evaluation of viral infection and the subsequent monitoring in patients treated with
209 biological agents could allow to start or continue a successful therapy in cases for which
210 there are few treatment options. As the benefits of these agents outweigh their risks, the
211 formulation of specific recommendations could allow to identify a small group of patients in
212 which the treatment cannot be used or must be interrupted. The aim of developing specific
213 recommendations and guidelines is becoming all the most important considering the
214 growing utilization of these agents in different clinical contexts.

215

216

217 **Conflict of interests.** None.

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303 reactivation after alemtuzumab-based conditioning for allogeneic hematopoietic stem-cell
304 transplantation. *Transplantation* 2010; 90: 564-570.

305

306 Table 1. Main viral infections/reactivations in patients undergoing monoclonal antibodies
 307 therapy and monitoring or recommendations. PTLD, post-transplantation
 308 lymphoproliferative disorders.

| | Anti-CD52 (alemtuzumab) | 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 (5,6-10) | 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 PTLD (33) | | Poorly known (27) | |
| HPV | | | Poorly known (29) | |

309

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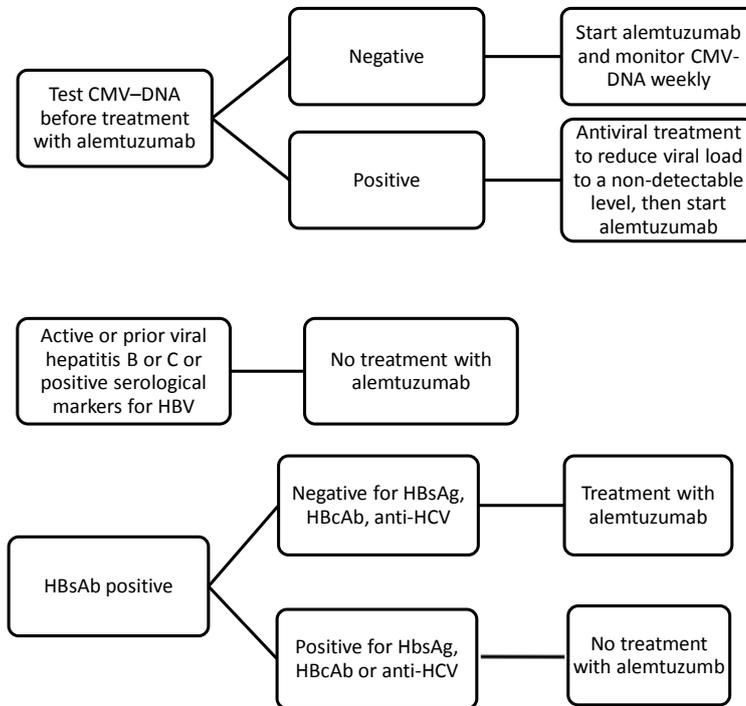
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316 Figure 1. Algorithm for the evaluation of viral infections in relation to the administration of
317 alemtuzumab.



318