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**RESEARCH ARTICLE**

# ALEMTUZUMAB: PHARMACOLOGY, SAFETY AND NEW POSSIBLE APPLICATIONS

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**ABSTRACT**

**Introduction**: Alemtuzumab is a new generation monoclonal antibody with anti-CD52 action and with specific indication for relapsing-remitting multiple sclerosis. In recent years, however, "off-label" applications in the immunological field have begun, such as immunosuppression in transplants or the treatment of other dysimmune diseases. The purpose of this article is, starting from its characteristics, to describe these uses and the tolerability profile. **Materials and methods**: A computerized search was carried out for the articles inserted through the use of international databases such as pubmed, scopus, researchgate, google scholar, selecting articles about alemtuzumab with particular regard to pharmacovigilance and new off-label applications. The research was carried out by selecting recent articles, obviously also including those relating to authorized uses. We also use the AIFA site and some books for the chapter on pharmacovigilance together with the "codifa" site to evaluate the technical data sheet. **Discussion and Conclusion**: Alemtuzumab is an interesting drug, very potent and usable for both inducing and maintaining remission from highly active forms of multiple sclerosis. However, induced immuno-reconstitution has prompted researchers to test its use both in the transplant field, especially for the immunosuppression induction regimen in the immediate post-surgical period, and for immuno-manipulation in the management of autoimmune diseases such as some rheumatic forms. refractory to conventional treatments. However, it must be said that safety is not always favorable, as it is associated with two important risks; severe opportunistic infections (including PML) and induction of secondary autoimmunity, particularly on the thyroid gland.



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# INTRODUCTION

Alemtuzumab is an highly potent biotech drug classified as a selective-acting immunosuppressant, available as a 12 milligram concentrate for solution for infusion (codifa). [1] It is a humanized monoclonal antibody, of the IgG1 class, with a variable human structure, constant regions and regions that determine complementarity obtained from a mouse monoclonal antibody, produced by recombinant DNA technology in a suspension culture of cells of mammalian origin (Chinese hamster ovary) and indicated as single disease-modifying therapy in adults with relapsing-remitting multiple sclerosis. (RRMS) for the following patient groups:

- Patients with highly active disease despite a complete and adequate course of treatment with at least one disease-modifying therapy (DMT);
- Patients with rapidly evolving severe relapsing-remitting multiple sclerosis, defined by 2 or more disabling relapses in one year and with 1 or more gadolinium-enhancing lesions on brain MRI or with a significant increase in T2 lesion load compared to recent previous MRI[2]

In MS patients it is administered by venous infusion at a particular dosage, 12 mg/day, administered by intravenous infusion for 2 initial treatment courses, with up to 2 additional courses as needed[3].

The initial treatment for 5 consecutive days can be followed by a second cycle of more reduced, 12 mg/day for only 3 days and administrable after at least 12 months after the first treatment cycle. It's possible then consider up to two additional courses of treatment as needed, always only 3 days and never before a year apart. [4] Such a regimen can stabilize the patient from the disease up to more than 5 years after the last infusion.[5] It is recommended that patients be pre-treated with corticosteroids immediately prior to drug administration on each of the first 3 days of each treatment cycle, usually with methylprednisolone or with antihistamines and / or antipyretics. Oral prophylaxis for herpetic infections should be administered to all patients starting with the first day of each treatment cycle and for at least 1 month after alemtuzumab treatment. In addition to these official indications, alemtuzumab has been tested in other medical conditions other than MS and in particular:

- Randomized controlled trials had demonstrated low levels of rejection in renal transplant recipients compared with other induction agents, albeit mainly in the early months following transplantation.[6] Studies have shown that alemtuzumab enables the use of lower calcineurin inhibitor (CNI) maintenance drugs; however, this reduction in nephrotoxic immunosuppression has not consistently been matched by an improvement in renal function
- In diseases such as rheumatoid arthritis, vasculitis and other refractory systemic rheumatism, as a third line of intervention[7]
- In the treatment of IVIG-dependent dysimmune peripheral neuropathies such as CIDP

The purpose of this article is to evaluate these possible applications in light of the pharmacological basis and the possible adverse reactions (ADRs) in the short and long term.[8]

# MATERIALS AND METHODS

A computerized search was carried out for the articles inserted through the use of international databases such as pubmed, scopus, researchgate, google scholar, selecting articles about alemtuzumab with particular regard to pharmacovigilance and new off-label applications. The research was carried out by selecting recent articles, obviously also including those relating to authorized uses. We also use the AIFA site and some books for the chapter on pharmacovigilance together with the "codifa" site to evaluate the technical data sheet.

# DISCUSSION

Alemtuzumab has a very particular action profile as it binds to CD52 (cluster of differentiation), an expressed surface glycoprotein antigen present in high concentrations on T (CD3 +) and B (CD19+) lymphocytes and, in lower concentrations, on natural killer (NK) cells, monocytes and macrophages.[9] CD52 is detectable in low concentrations (or undetectable) on neutrophils, plasma cells or bone marrow cells. Alemtuzumab acts by antibody-dependent cell cytolysis and complement mediated lysis following the binding of the cell surface to T and B lymphocytes.[10] The mechanism by which it exerts its therapeutic effect on MS is not yet fully understood. [11] However, research indicates that with lymphocyte depletion and repopulation there are immunomodulatory effects, which include (Image 1):

- Change in the number, percentages and properties of some subgroups of lymphocytes after treatment
- Increased presence of subgroups of regulatory T cells
- Increased presence of memory T and B lymphocytes
- Transient effects on components of innate immunity (e.g., neutrophils, macrophages, NK cells) The decrease in the concentration of circulating B and T cells, and the consequent repopulation, they can decrease the potential for relapse, without substantially delaying the progression of the disease.[12]

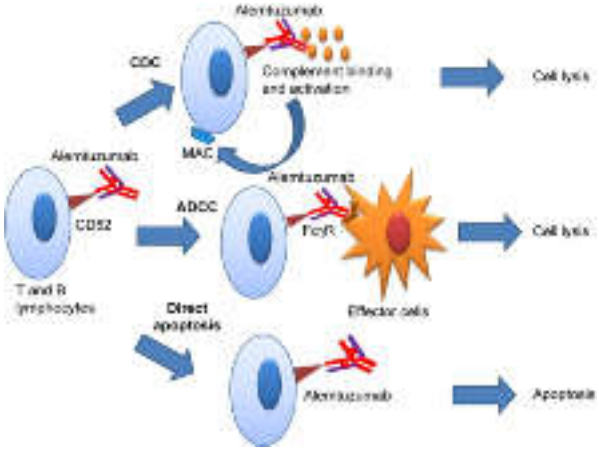


**Image 1. Alemtuzumab-mediated cytolysis and apoptosis of T-and B-lymphocytes. Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; CDC, complement-dependent cytotoxicity;**

*MAC, membrane attack complex; FcγR, Fc-gamma receptor. From: Intractable and highly active relapsing multiple sclerosis – Role of alemtuzumab (DOI:10.2147/NDT.S90473)*

Specifically, alemtuzumab A depletes circulating T and B lymphocytes after each treatment cycle, reaching the lowest values low 1 month after a course of treatment. Lymphocytes repopulate over time with B cell recovery usually completed within 6 months. CD3 + and CD4 + lymphocyte counts reach normal values more slowly, but do not generally return to baseline within 12 months after treatment.[13,14] Approximately 40% of patients had total lymphocyte counts reaching the lower limit of normal range (LLN) within 6 months after each cycle of treatment and approximately 80% of patients had total lymphocyte counts reaching the LLN within 12 months after each cycle. Neutrophils, monocytes, eosinophils, basophils and natural killer cells were only transiently affected by use.[15]

**Focus on: alemtuzumab and lymphopenia**

Lymphopenia is the reduction in the absolute count of lymphocytes in the blood count, which can be classified according to the number of lymphocytes per cubic millimeter (mm3) in 4 different degrees:

Grade 1 (mild lymphopenia) ALC<lower limit of normal to 800/mm3

Grade 2 (moderate lymphopenia) ALC<800–500/mm3

Grade 3 (severe lymphopenia) ALC<500–200/mm3

Grade 4<200/mm3

[16]It should be borne in mind that, in peripheral blood, approximately 75% of lymphocytes are T

Cells, 20% B cells, and 5% natural killer cells. Normal lymphocyte counts in adults are 1000-4800/ mcl but different laboratories may have slightly different normal values. Almost 65% of the T cells in the blood are CD4 + (helper) T cells. Thus, most patients with lymphocytopenia have a reduction in the absolute number of T cells, particularly in the number of CD4 + T cells. The mean number of CD4 + T cells in the blood of adult individuals is 1100 / mcL (range, 300-1300 / mcL [1.1 × 109 / L with a range of 0.3 to 1.3 × 109 / L]) and the mean number of cells of the other large subgroup of T cells, those CD8 + (suppressors), is 600 / mcL (range, 100-900 / mcL).17 Deficiencies in particular lymphocyte subgroups (eg, CD4 +, CD8 +, B, natural killer cells) may not be reflected in blood lymphocyte counts but can cause functional lymphocytopenia. It is also important to note that lymphocytes in the blood represent only a small percentage of the total pool. Lymphocytopenia itself typically does not cause symptoms. However, signs of an associated disorder may be found such as:

- Absent or small tonsils or lymph nodes, indicative of cellular immunodeficiency
- Skin abnormalities (eg, alopecia, eczema, pyoderma, or telangiectasia)
- Findings of hematologic disease (eg, paleness, petechiae, jaundice, or oral ulcers)
- Generalized lymphadenopathy with splenomegaly18

CD4+T cells displayed a longer-lasting depletion (only 10–20% of patients with CD4+cells above the LLN by month 12). In addition to the reduction in lymphocytes, in 16% of the alemtuzumab-treated patients mild neutropenia could be observed, whereas severe neutropenia occurred in 0.6%. 20

Patients with lymphocytopenia have recurrent infections or develop infections with atypical microorganisms. Pneumocystis jirovecii pneumonia, cytomegalovirus, measles and chickenpox are frequently fatal. Lymphocytopenia is also a risk factor for the development of cancer and for autoimmune diseases. Alemtuzumab infusion results in a substantial and sustained depletion of circulating lymphocytes (grades 3 and 4 lymphopenia: 99.9% of patients). Immune reconstitution varies for lymphocyte subpopulations. After each treatment cycle, approximately 40% and 80% of patients reached lymphocytes at the lower limit of normal (LLN) by 6 and 12 months, respectively.[19] While the repopulation of B cell counts (CD19+) occurred early (LLN in≥85% by 6 months), CD8+T cells showed similar repopulation kinetics as compared with the ALC, while. In the neurological field, off-label, alemtuzumab has been tested in patients with peripheral demyelinating neuropathies refractory to conventional treatment. Chronic inflammatory demyelinating polyneuropathy (CIDP) is an idiopathic immune mediated neuropathy causing demyelination and conduction block thought to occur as the result of an aberrant autoimmune response resulting in peripheral nerve inflammation mediated by T cells and humoral factors. Diagnosis commonly prompts initial treatment with steroids or intravenous immunoglobulin (IVIG) on which 5–35% subsequently become dependent to maintain function.[21] Despite a number of small scale trials, the role for alternative long-term immunosuppression remains unclear. In a study, a single intravenous infusion results in rapid and profound lymphopoenia lasting >12 months.

We report its use and clinical outcome in a small series of patients with severe IVIG-dependent CIDP. Seven patients (4 Males; 3 Females) who had failed to respond to conventional immunosuppression were treated in 5 centres receiving 9 courses of alemtuzumab (dose range 60–150 mg).

Following treatment, mean monthly IVIG use fell 26% from 202 to 149 g and IVIG administration frequency from 22 to 136 days. [22]Two patients had prolonged remission, two patients had a partial response and no clear benefit was observed in the remaining three patients (2 Males, 1 Females). Responding patients had a younger age at onset (19.5 years) and shorter disease duration than non-responders. Three patients developed autoimmune disease following treatment. Alemtuzumab may offer an alternative treatment for a subset of early onset IVIG dependent CIDP patients failing conventional immunosuppressive agents, but concerns about toxicity may limit its use.In a case report (image 2), a patient with intravenous immunoglobulin (IVIg) dependent relapsing chronic inflammatory demyelinating polyneuropathy (CIDP), unresponsive to steroids or conventional immunosuppressive agents, had a remission following treatment with alemtuzumab. After several relapses with standard therapy, the infusion of the drug allowed to obtain clinically considerable benefits, even if followed by further relapses but of lower severity.[23]

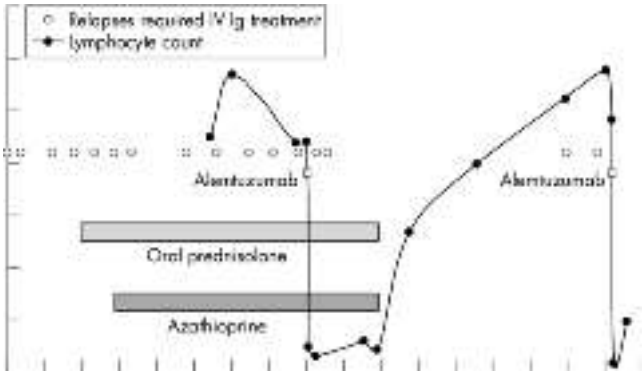


**Image 2. Relation of relapses requiring hospital admission and intravenous immunoglobulin (IVIg) to treatment with prednisolone, azathioprine, and alemtuzumab and the lymphocyte count. From: Remission of chronic inflammatory demyelinating polyneuropathy after alemtuzumab (Campath 1H) DOI: 10.1136/jnnp.2005.076869**

Another possible field of application of the drug is relapsed and refractory chronic lymphocytic leukemia (CLL), the most common indolent leukemia. Two pilot phase II studies and one larger international phase II study of single-agent intravenous alemtuzumab were conducted in the mid 1990. In one of the pilots, Osterborg and colleagues, in Europe, evaluated the overall response rate (ORR), as defined by the 1988 NCI-WG guidelines, in 29 patients who had been previously treated (not necessarily with purine analogs, including fludarabine). A total of 38% of patients achieved a partial response (PR).[24] In the second pilot, Rai and colleagues, in the USA, evaluated 24 heavily pretreated patients who had progressed after fludarabine-containing therapy. A total of 33% of these patients achieved a PR, with a median duration of response of15.4 months. The largest trial, CAM-211, was conducted at 21 different centers in Europe and the USA, and evaluated 93 heavily pretreated patients, who had relapsed after fludarabine, for ORR. A total of31 of these patients experienced a response (ORR 33%), including two CRs; 50 patients (54%) had stable disease (SD). A recent off-label application of alemtuzumab is for the prevention of rejection in kidney transplantation in particular, for which it has already been tested with interesting results. The use of this drug in post-transplant immunosuppression derives from two evidences: the very

potent cell suppression action, which is sustained for several months after a single infusion, and the fact that many of the drugs used for transplant immunosuppression they are themselves nephrotoxic, primarily cyclosporine and mTOR inhibitors. [25] Trials were conducted using alemtuzumab as an induction regimen and then continuing with other oral maintenance drugs( image 3).

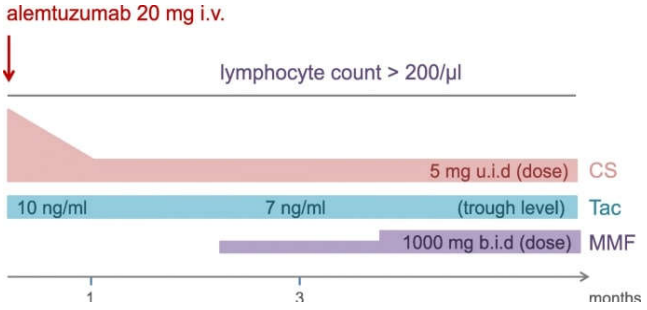


**Image 3. Induction protocol with low-dose alemtuzumab and tailored immunosuppression. Tac: tacrolimus, MMF: mycophenolate mofetil, CS: corticosteroids**

The safety of this drug has always been a significant limit to its use, especially in the long term. In fact, in addition to the classic infusion reactions (flushing, headache, urticaria, hypotension, fever and malaise), predictable and partly avoidable with the aforementioned pre-medication, the major problem are medium-long term ADRs which can be summarized in three categories:

Development of secondary autoimmunity, referable in particular to dystyroidism (up to 20-30% of treated subjects) and, less commonly, thrombotic thrombocytopenic purpura (1%) and goodpasture syndrome-like nephropathies (<1%). lymphopenia alone does not induce autoimmunity but Two important factors that play a role in this mechanism are the depletion of the regulatory T cells (Tregs) and the overproduction of interleukin (IL) -21. [26]Lymphocyte depletion is driven by levels of IL-21 that are genetically higher in patients who develop autoimmunity even before starting treatment. Thyroid autoimmune dysfunction may occur in approximately 20% –30% of the patients who receive alemtuzumab for MS, and Graves' disease is the most common presentation (60% –70%). The annual incidence of the first episode of thyroid dysfunction increases each year for 3 years, and during follow-up, the prevalence of thyroid dysfunction increased to 30%, with the onset ranging from 6 to 61months after first administration. For these reasons, many authors recommend thyroid evaluation prior to alemtuzumab and quarterly during its administration for 48months. Daniels and colleagues proposed to prolong the surveillance period of these patients up to a median time of 57.3months and a maximum of 80.6months. Graves' disease is the most common alemtuzumab-associated thyroid dysfunction (60% - 70%). There is a specific susceptibility to develop Graves' disease. In a phase 2 trial of patients with RRMS treated with alemtuzumab, positive antibodies were found in 84.7% of episodes of overt or subclinical hyperthyroidism. [27] The presence of TRAb is usually specific for Graves' syndrome, despite this can turn to Hashimoto's thyroiditis and hypothyroidism and vice versa.the infection risk, related with rapid and protracted peripheral lymphopenia. Infective adverse events were observed in more than 70% of patients in phase 2/3 RCTs, mainly of mild-to-moderate severity. JC virus (JCV)-associated diseases include a partially overlapping spectrum of entities, with pIn immunocompromised patients, JCV may cross the blood brain barrier, possibly via infected B-cells, and cause a lytic infection of oligodendrocytes, astrocytes and neurons leading to PMLrogressive multifocal leukoencephalopathy (PML) being the most well known. Natalizumab is by far the drug most frequently associated with JCV-associated complications but PML has also been observed in patients with MS treated with fingolimod, dimethyl fumarate, alemtuzumab and ocrelizumab. [28] Other types of CNS infections reported in pharmacovigilance are Herpesviruses-related diseases, including herpes simplex encephalitis (HSE), predominantly caused by reactivation of the HSV-1 virus, and Varicella zoster virus (VZV), also belong to the family of herpesviruses, has been reported to cause CNS infections, such as VZV encephalitis. Prophylactic acyclovir treatment is recommended for 1 month following initiation of each course of alemtuzumab. Other infections such as cerebral cryptococcosis and listeriosis have been reported but very rare compared to other mAbs.[29] Non-infectious adverse events like Reversible cerebral vasoconstriction syndrome (RCVS) and Primary central nervous system lymphoma (PCNSL), have also been reported as associated with alemtuzumab, especially the first. (RCVS) is believed to be caused by segmental constriction of cerebral arteries which often is spontaneously reversible within 3 months after onset, and generally presents with thunderclap headache and, less frequently, with focal neurological deficits or seizures. RCVS is associated with the posterior reversible encephalopathy syndrome (PRES) and can be complicated by stroke, subarachnoidal or intracerebral haemorrage which are reported in 39%, 34% and 20% of cases, respectively.

# CONCLUSION

Alemtuzumab has opened the way to a new possibility not only in the neurological field but also in transplant medicine and in the treatment of lymphoproliferative disorders, even if it is still off-label for these applications. Immune reconstitution therapy allows for the management of complex clinical cases with rapidly progressive disease resulting in rapid and sustained cell depletion up to several months post-infusion, allowing, in the case of MS, to arrest the progression of the disease in most cases and to increase the probabilities of transplant success allowing the establishment of immunotolerance. However, the sometimes particularly marked side effects should be noted, especially as regards the infectious risk and the development of secondary immunological self-reactivity, especially at the thyroid level, with the need for close follow-up not only during but also at the end of therapy for at least two years.

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