# Alemtuzumab

**Alemtuzumab** is a drug used in the treatment of chronic lymphocytic leukemia (CLL), cutaneous T-cell lymphoma (CTCL) and T-cell lymphoma under the trade names **Campath**, **MabCampath** and **Campath-1H**, and in the treatment of multiple sclerosis as **Lemtrada**. It is also used in some conditioning regimens for bone marrow transplantation, kidney transplantation and islet cell transplantation.

It is a monoclonal antibody that binds to CD52, a protein present on the surface of mature lymphocytes, but not on the stem cells from which these lymphocytes are derived. After treatment with alemtuzumab, these CD52-bearing lymphocytes are targeted for destruction.

Alemtuzumab is used as second-line therapy for CLL. It was approved by the US Food and Drug Administration for CLL patients who have been treated with alkylating agents and who have failed fludarabine therapy. It has been approved by Health Canada for the same indication, and additionally for CLL patients who have not had any previous therapies.

(Mab)Campath was withdrawn from the markets in the US and Europe in 2012 to prepare for a higher-priced relaunch of Lemtrada aimed at multiple sclerosis.[1]

A complication of therapy with alemtuzumab is that it significantly increases the risk for opportunistic infections, in particular, reactivation of cytomegalovirus.

## 1 Medical uses

### 1.1 Chronic lymphocytic leukemia

Alemtuzumab is indicated for the treatment of B-cell chronic lymphocytic leukemia (B-CLL) in patients who have been treated with alkylating agents and who have failed fludarabine therapy. It is an unconjugated antibody, thought to work via the activation of antibody-dependent cell-mediated cytotoxicity (ADCC).[2]

### 1.2 Multiple sclerosis

In 2008 early tests at Cambridge University suggest that alemtuzumab might be useful in treating and even reversing the effects of multiple sclerosis.[3] Promising results were reported in 2011 from a phase III trial against interferon beta 1a.

In September 2013 alemtuzumab was approved for first-line use in the EU.

In November 2013, the US FDA issued a comprehensive briefing on alemtuzumab for an agency review meeting. The document highlighted numerous serious safety and efficacy concerns, including substantial doubts about the adequacy of relevant clinical trials.[4] In December 2013, the US FDA indicated that the Lemtrada application is not ready for approval, due to lack of evidence from "adequate and well-controlled studies" that demonstrate that the benefits of the drug outweigh the risks.[5] The CEO of Genzyme, David Meeker, strongly disagreed with this decision and indicated that the company would file an appeal.

In November 2014, Alemtuzumab was finally approved by the FDA[6]

On December 1, 2014 the first treatments with Lemtrada (or alemtuzumab) were administered to the first patients outside clinical trials. Dr. Christopher LaGanke was the attending physician and was also instrumental in having the FDA reconsider the approval.[7]

## 2 Contraindications

Alemtuzumab is contraindicated in patients who have active systemic infections, underlying immunodeficiency (e.g., seropositive for HIV), or known Type I hypersensitivity or anaphylactic reactions to the substance.

## 3 Adverse effects

Alemtuzumab has been associated with infusion-related events including hypotension, rigors, fever, shortness of breath, bronchospasm, chills, and/or rash. In post-marketing reports, the following serious infusion-related events were reported: syncope, pulmonary infiltrates, ARDS, respiratory arrest, cardiac arrhythmias and myocardial infarction.

It can also precipitate autoimmune disease through the suppression of suppressor T cell populations and/or the emergence of autoreactive B-cells.[8][9]

# 4 Biochemical properties

Alemtuzumab is a recombinant DNA-derived humanized IgG1 kappa monoclonal antibody that is directed against the 21–28 kDa cell surface glycoprotein CD52.[10]

## 4.1 Antiviral properties

In an in-vitro experiment, it has been shown that Alemtuzumab has antiviral properties against HIV-1[11]

# 5 History

The origins of alemtuzumab date back to *Campath-1* which was derived from the rat antibodies raised against human lymphocyte proteins by Herman Waldmann and colleagues in 1983.[12] The name "Campath" derives from the *path*ology department of *Cam*bridge University.

Initially, Campath-1 was not ideal for therapy because patients could, in theory, react against the foreign rat protein determinants of the antibody. To circumvent this problem, Greg Winter and his colleagues humanised Campath-1, by extracting the hypervariable loops that had specificity for CD52 and grafting them onto a human antibody framework. This became known as Campath-1H and serves as the basis for alemtuzumab.[13]

While alemtuzumab started life as a laboratory tool for understanding the immune system, within a short time it was clinically investigated for use to improve the success of bone marrow transplants and as a treatment for leukaemia, lymphoma, vasculitis, organ transplants, rheumatoid arthritis and multiple sclerosis.[14]

Campath as medication was first approved for B-cell chronic lymphocytic leukemia in 2001. It is marketed by Genzyme, which acquired the world-wide rights from Bayer AG in 2009. Genzyme was bought by Sanofi in 2011. In August/September 2012 Campath was withdrawn from the markets in the US and Europe. This was done to prevent off-label use of the drug to treat multiple sclerosis and to prepare for a relaunch under the trade name *Lemtrada*, with a different dosage aimed at multiple sclerosis treatment, this is expected to be much higher-priced.[1]

Bayer reserves the right to co promote Lemtrada for 5 years, with the option to renew for an additional five years.

## 5.1 Sanofi acquisition and change of license controversy

In February 2011, Sanofi-Aventis, since renamed Sanofi, acquired Genzyme, the manufacturer of alemtuzumab.[15] The acquisition was delayed by a dispute between the two companies regarding the value of alemtuzumab. The dispute was settled by the issuance of Contingent Value Rights, a type of stock warrant which pays a dividend only if alemtuzumab reaches certain sales targets. The contingent value rights (CVR) trade on the NASDAQ-GM market with the ticker symbol GCVRZ.

In August 2012, Genzyme surrendered the licence for all presentations of alemtuzumab,[16] pending regulatory approval to re-introduce it as a treatment for multiple sclerosis. Concerns[17] that Genzyme would later bring to market the same product at a much higher price proved correct.

# 6 Research and off-label use

## 6.1 Graft-versus-host disease

A 2009 retrospective study of alemtuzumab (10 mg IV weekly) in 20 patients (no controls) with severe steroid-resistant acute intestinal graft-versus-host disease after allogeneic hematopoietic stem cell transplantation (HSCT) demonstrated improvement. Overall response rate was 70%, with complete response in 35%.[18] In this study, the median survival was 280 days. Important complications following this treatment included cytomegalovirus reactivation, bacterial infection, and invasive aspergillosis infection.[18]

# 7 References


[1] McKee, Selina (21 August 2012). "Sanofi withdraws Campath in US and EU". *Pharma Times Online*. Pharma Times.

[2] "About Campath". Genzyme.

[3] Andy Coghlan (23 October 2008). "Drug reboots immune system to reverse MS". New Scientist News Service.

[4] "Alemtuzumab (BLA 103948\5139) Background Package" (PDF). *Advisory Committees*. United States: Center for Drug Evaluation and Research. 13 November 2013.

[5] "Genzyme Receives Complete Response Letter from FDA on Lemtrada (alemtuzumab) Application". BusinessWire. 30 December 2013.

[6] FDA approves Lemtrada (alemtuzumab) for the treatment of patients with relapsing forms of multiple sclerosis

[7] Newly approved multiple sclerosis drug given to first U.S. patients today in Cullman

[8] Costelloe, L; Jones J; Coles A (March 2012). "Secondary autoimmune diseases following alemtuzumab therapy for multiple sclerosis". *Expert Rev Neurother*. **12** (3): 335–41. doi:10.1586/ern.12.5. PMID 22364332.

[9] Aranha, AA; Amer S; Reda ES; Broadley SA; Davoren PM (Jun 11, 2013). "Autoimmune Thyroid Disease in the Use of Alemtuzumab for Multiple Sclerosis: A Review". *Endocrine Practice*. **19** (5): 1–25. doi:10.4158/EP13020.RA. PMID 23757618.

[10] A. Klement (7 January 2014). "Multiple-Sklerose-Behandlung". *Österreichische Apothekerzeitung* (in German) (1/2014): 24f.

[11] Ruxrungtham K, Sirivichayakul S, Buranapraditkun S, Krause W. Alemtuzumab-induced elimination of HIV-1-infected immune cells. Journal of Virus Eradication. 2016;2(1):12-18.

[12] Hale G, Bright S, Chumbley G, et al. (October 1983). "Removal of T cells from bone marrow for transplantation: a monoclonal antilymphocyte antibody that fixes human complement". *Blood*. **62** (4): 873–82. PMID 6349718.

[13] Riechmann, Lutz; Clark, Michael; Waldmann, Herman; Winter, Greg (1988). "Reshaping human antibodies for therapy". *Nature*. **332** (6162): 323–327. doi:10.1038/332323a0. ISSN 0028-0836. PMID 3127726.

[14] "The life story of a biotechnology drug: Alemtuzumab". What is Biotechnology?.

[15] Whalen, Jeanne; Spencer, Mimosa (17 February 2011). "Sanofi Buys Genzyme for over $20 billion". *The Wall Street Journal*.(subscription required)

[16] Hussein, Jasmin (Genzyme) (9 August 2012). "Discontinuation of licensed supplies of alemtuzumab (Mabcampath)" (pdf). United Kingdom: National Institute for Health and Care Excellence.

[17] "Multiple sclerosis: New drug 'most effective'". *BBC News*. 1 November 2012. Retrieved 1 November 2012.

[18] Schnitzler, Marc; Hasskarl, Jens; Egger, Matthias; et al. (August 2009). "Successful treatment of severe acute intestinal graft-versus-host resistant to systemic and topical steroids with alemtuzumab". *Bio. Blood Marrow Transplant.* **15** (8): 910–8. doi:10.1016/j.bbmt.2009.04.002.

# 8 External links

- Full Prescribing Information
- Mike Clark's Campath story
- From laboratory to clinic: the story of CAMPATH-1 (Geoff Hale and Herman Waldmann)
- Fact Sheet about Alemtuzamab (Campath) in MS treatment
- Article discussing the value of the Genzyme Contingent Value Rights (GCVRZ)

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