# Vedolizumab

**Vedolizumab** (trade name **Entyvio**) is a monoclonal antibody developed by Millennium Pharmaceuticals, Inc (a subsidiary of Takeda Pharmaceuticals) for the treatment of ulcerative colitis and Crohn's disease.[1] It binds to integrin $\alpha_4\beta_7$ (LPAM-1, lymphocyte Peyer's patch adhesion molecule 1).[1][2] Blocking the $\alpha_4\beta_7$ integrin results in gut-selective anti-inflammatory activity.[3] It is marketed under the trade name Entyvio.

## 1 Current Medical uses

### 1.1 Ulcerative colitis

Vedolizumab has been investigated in one main study in adult patients. Patients with moderate to severe active disease in whom conventional therapy or TNF-alpha antagonists were ineffective or could not be tolerated received either vedolizumab or placebo. The main measure of effectiveness was the proportion of patients whose symptoms improved after 6 weeks of treatment. Vedolizumab was shown to be more effective than placebo: 47% (106 out of 225) of patients who received vedolizumab showed an improvement in symptoms, compared with 26% (38 out of 149) of patients who received placebo. The study also showed that vedolizumab maintained the effect up to 52 weeks more effectively than placebo.[4]

### 1.2 Crohn's disease

In one main study in adult patients with moderate to severe active Crohn's disease in whom conventional therapy or TNF-alpha antagonists were ineffective or could not be tolerated vedolizumab was shown to be more effective than placebo: 15% (32 out of 220) of patients receiving vedolizumab showed improved symptoms after 6 weeks of treatment, compared with 7% (10 out of 148) of patients on placebo. The maintenance of the effect up to 52 weeks was more effective with vedolizumab than with placebo.[4]

## 2 Potential Future Medical Uses

### 2.1 HIV infection

On October 13 2016, Scientists from Emory, led by Aftab Ansari, PhD and National Institute of Allergy and Infectious Diseases (NIAID) published a paper which claimed that they applied daily ART of 90 days followed by simianized (rhesus macaques)anti alpha4beta7 antibody on SIV+ rhesus macaques for 23 weeks. 23 months after stopping both ART and anti alpha4beta7 antibody treatment, the in vivo SIV level still remain undetectable. Therefore, treating HIV+ people with ART and anti alpha4beta7 simultaneously can be a new therapy that can potentially lead to an HIV infection cure.[5] Phase 1 clinical trial of that therapy has been initialized by NIAID since May 2016. For each of the participants, they will get Vedolizumab infusions every 4 weeks for 30 weeks. Before 23rd week of Vedolizumab infusions, cART is kept. During the 30 weeks, blood draws are repeated for baseline tests. after the 22-week-cART is stopped, both viral load and CD4 count will be monitored biweekly. If HIV viral load goes high or their CD4 cell counts decreases by too much during Vedolizumab is used alone, cART will be brought back on the participants. [6]

## 3 History

The cell line used to develop vedolizumab was created by physician scientists at the Massachusetts General Hospital in Boston, Massachusetts, as a result of work executed at Dr. Robert B. Colvin's lab, from the Department of Pathology. An antibody was isolated that reacted with long term activated antigen-specific (tetanus toxoid) T lymphocytes originally isolated from blood lymphocytes. The cell lines were created in Dr. Jim T. Kurnick's lab. Although the antibody did not block primary activation of T lymphocytes, it appeared late after activation with a number of lymphocytic stimuli, and was named "Act-1" because it was the first activation marker identified by this group of investigators. Dr. Andrew Lazarovits, a post-doctoral fellow in the laboratory, discovered the murine homologue of MLN0002,[7][8] chiefly published the original key papers, and up until the late 90's, coordinated, and led the studies for its development and application for Crohn's Disease and Ulcerative Colitis. Dr. Lynn Baird's group showed the antibody reacted with a single protein band of 63Kd, and Dr. Atul Bhan's group showed that it stained tissue lymphocytes but did not react with non-lymphoid tissues. Although Act-1 had limited efficacy in its ability to prevent kidney rejection in a sub-human

primate transplantation model, Dr. Lazarovits continued to investigate the activities of Act-1 when he returned to Canada to become the Director of Transplantation at the University of Western Ontario.[8]

It was later determined that the Act-1 monoclonal antibody reacted with an alpha-4/beta-7 integrin that was subsequently shown to interact with a gut-associated addressin, MadCAM. Early work with Yacyshyn showed differential expression in inflammatory bowel disease (5). Dr. Lazarovits isolated the antibody to produce the murine homologue MLN002 which he licensed with the Massachusetts General Hospital to Millennium Pharmaceuticals of Boston for further development.[7] Scientists at LeukoSite realized the potential of this antibody to treat inflammatory bowel disease, and this company was eventually acquired by Millennium which took an exclusive license to the cell line from Massachusetts General Hospital. In vivo proof of concept ultimately led to the decision to humanize the antibody and move it into clinical trials as "Vedolizumab." In addition to its reactivity to gut-associated lymphoid tissues, Act-1 antibody also stains large numbers of lymphocytes in rheumatoid synovium, and has been shown by Dr. A. A. Ansari of Emory University to prevent or delay onset of AIDS in a monkey-model of Simian Immunodeficiency Virus-induced AIDS. Thus, reactivity with this antibody may show widespread applicability in inflammatory processes of diverse etiologies.

# 4 Approval status

Takeda has filed a Marketing Authorization Application (MAA) in the European Union on March 7, 2013[9] and a Biologic License Application (BLA) with the U.S. Food and Drug Administration on June 21, 2013 for both Crohn's Disease and Ulcerative Colitis.[10] On September 4, 2013, Vedolizumab was given a Priority Review Status, which functions to expedite potential acceptance to market.[11]

On December 9, 2013, the Gastrointestinal Drugs Advisory Committee (GIDAC) & Drug Safety and Risk Management Advisory Committee (DSaRM) discussed the Vedolizumab application for approval for both UC and CD under the trade name Entyvio.[12] The voting went as follows: 1. Safety and efficacy data outweigh potential risks 21-0 2. In favour of UC treatment 21-0 3. In favour for CD treatment 20-1.[13][14] Although GIDAC/DSaRM were a non-binding advisory committee, their opinions as field experts represent one of the last steps towards drug acceptance.

On 20 March 2014, the Committee for Medicinal Products for Human Use (CHMP, the committee advising the European Commission) adopted a positive opinion, recommending the granting of a marketing authorization for Vedolizumab (brand name Entyvio).[15]

On 20 May 2014, vedolizumab (Entyvio) was approved by the FDA for treatment of both moderate-to-severe ulcerative colitis and moderate-to-severe Crohn's disease.[16] On May 27, 2014, Entyvio was approved for the treatment of both ulcerative colitis and Crohn's disease in the 28 European Union states as well as Norway, Iceland and Lichtenstein. On April 28, 2015 Health Canada approved Entyvio.[17]

# 5 Research

Vedolizumab eventually completed a number of phase 3 clinical trials[18][19] for Crohn's Disease and Ulcerative Colitis (GEMINI I,[20] GEMINI II,[21] and GEMINI III[22]) that demonstrate that vedolizumab is an effective and well tolerated drug.[23][24] The results of the GEMINI 1 and GEMINI 2 randomized, placebo controlled multicenter trials of induction and maintenance therapy in Crohn's disease and ulcerative colitis have been published.[25][26] An additional clinical trial, GEMINI LTS (Long-term Safety), is still being run.[27]

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