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NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Monoclonal Antibodies. [Updated 2019 Apr 12].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Monoclonal Antibodies

Updated: April 12, 2019.

OVERVIEW

Monoclonal antibodies are antibodies that have a high degree of specificity (mono-specificity) for an antigen or epitope. Monoclonal antibodies are typically derived from a clonal expansion of antibody producing malignant human plasma cells. The initial monoclonal antibodies were created by fusing spleen cells from an immunized mouse with human or mouse myeloma cells (malignant self-perpetuating antibody producing cells), and selecting out and cloning the hybrid cells (hybridomas) that produced the desired antibody reactivity. These initial monoclonal products were mouse antibodies and were very valuable in laboratory and animal research and diagnostic assays, but were problematic as therapeutic agents because of immune reactions to the foreign mouse protein. Subsequently, production of chimeric mouse-human monoclonal antibodies and means of further "humanizing" them and producing fully human recombinant monoclonal antibodies were developed. The conventions used in nomenclature of monoclonal antibodies indicate whether they are mouse (-omab), chimeric (-ximab), humanized (-zumab) or fully human (-umab).

Monoclonal antibodies have broad clinical and experimental medical uses. Many of the initial monoclonal antibodies used in clinical medicine were immunomodulatory agents with activity against specific immune cells, such as CD4 or CD3 lymphocytes, which are important in the pathogenesis of rejection after solid organ transplantation. Subsequently, monoclonal antibodies were prepared against specific cytokines (anti-cytokines), which were believed to play a role in cell and tissue damage in immunologically mediated diseases such as rheumatoid arthritis, alkylosing spondylitis, inflammatory bowel disease, multiple sclerosis and psoriasis, among others. In addition, therapeutic monoclonal antibodies were developed, aimed at blocking or inhibiting the activity of specific enzymes, cell surface transporters or signaling molecules and have been used in cancer chemotherapy and to treat severe viral infections. Use of monoclonal antibodies is currently broadening to therapy of other severe, nonmalignant conditions including asthma, atopic dermatitis, migraine headaches, hypercholesterolemia, osteoporosis and viral or bacterial infections. Thus, the therapeutic monoclonal antibodies do not fall into a single class and have broad therapeutic uses. As of 2018, more than 60 therapeutic monoclonal antibodies are approved and in use in the United States.

Monoclonal antibodies are generally well tolerated. Because they are large proteins (typically 150-200,000 daltons in size) they require parenteral, often intravenous, administration. Circulating proteins are metabolized by many cells, but particularly by hepatocytes. Proteins undergo hepatic uptake by endocytosis and are either degraded or recycled to the cell surface for secretion. The hepatic metabolism of antibodies often determines their half-life. Proteins are broken down by cellular proteases into small peptides and amino acids that can used to synthesize other proteins. Metabolism of proteins does not generate toxic intermediates and, therefore, monoclonal antibodies are unlikely to induce drug induced liver injury via production of toxic metabolites. On the other hand, the peptides that are generated by the metabolism of the exogenously administered protein may ultimately be presented as foreign epitopes and generate an immune response. In addition, the primary effect of

the monoclonal antibody may generate a response, either immune or otherwise, that leads to an immune mediate hepatic injury. Finally, monoclonal antibodies that suppress the immune system may cause reactivation of latent infections, including tuberculosis and hepatitis B.

Among the monoclonal antibodies that have been used in clinical medicine, only a few have been linked to drug induced liver injury and, in many situations, the cause of the hepatic adverse event is often unclear. The monoclonal antibodies most clearly linked to drug induced liver injury include the antibodies to tumor necrosis factor (anti-TNF such as infliximab, adalimumab, certolizumab and golimumab), to antibodies to checkpoint proteins (anti-CTLA4 such as ipilimumab; anti-PD1 such as nivolumab, pembrolizumab and cemiplimab; and anti- PD-L1 such as atezolizumab, avelumab and durvalumab) and to antibodies to B cell markers and activation signals (anti-CD20 such as rituximab, ofatumumab and tositumomab). The liver injury caused by these products is usually attributed to induction of autoimmunity or to immune modulation and reactivation of hepatitis B.

Because of their fine specificity, monoclonal antibodies can also be used to direct more conventional therapeutic agents to specific organs, tissues or cells. Several monoclonal antibody conjugates have been developed, largely in the therapy of cancer, the conjugated drug being an antineoplastic or cytotoxic agent. Five such agents are gemtuzumab ozogamicin, brentuximab vedotin, trastuzumab emtansine, inotuzumab ozogamicin and moxetumomab pasudotox. These products combine a monoclonal antibody (anti-CD33, anti-CD30, anti-HER2, anti-CD22) to a microtubule inhibitor (ozogamicin, vedotin, emtansine, pasudotox). These agents have been associated with serum enzyme elevations during therapy, and several have been linked to hepatic vascular damage, sinusoidal obstruction syndrome and nodular regenerative hyperplasia. These forms of hepatotoxicity are likely due to the conjugate (the "payload") rather than the monoclonal antibody (the targeting vehicle).

Monoclonal antibodies available for clinical use in the United States are listed below with the type of monoclonal and specific antigen targeted in parentheses, followed by the year of approval and major use. Those monoclonal antibodies with specific discussions of their hepatotoxicity in LiverTox are underlined and have a link to the corresponding record.

MONOCLONAL ANTIBODIES

Underlined Generic Names link to a LiverTox record.

CANCER				
Generic Name **Brand Name**	**Type** **Antigenic Target**	**Approval**	**Likelihood Score†**	**Major Uses**
Alemtuzumab Campath	Humanized CD52	2001	E	Chronic lymphocytic leukemia
Atezolizumab Tecentriq	Humanized PD-L1	2016	D	Urothelial carcinoma Non-small cell lung cancer
Avelumab Bavencio	Human PD-L1	2017	E*	Merkel cell carcinoma Urothelial carcinoma
Bevacizumab Avastin	Humanized VEGF	2004 2006 2009 2018	E	Colorectal cancer Non-small cell lung cancer Macular degeneration (off lbl) Renal cancer Ovarian cancer
Blinatumomab Blincyto	Mouse CD3, CD19	2014	E	Acute lymphoblastic leukemia
Brentuximab Adcetris	Chimeric CD30	2011 2018	E	Hodgkin lymphoma Peripheral T-cell lymphoma

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Cemiplimab Libtayo	Human PD-1	2018	C	Squamous cell carcinoma
Cetuximab Erbitux	Chimeric EGFR	2004	E	Head and neck cancer Colorectal cancer
Daratumumab Darzalex	Human CD38	2015	E	Multiple myeloma
Dinutuximab Unituxin	Chimeric GD2	2015	E*	Neuroblastoma
Durvalumab Imfinzi	Human PD-L1	2017	C	Urothelial carcinoma
Elotuzumab Empliciti	Humanized SLAMF7	2015	D	Multiple myeloma
Gemtuzumab Mylotarg	Humanized CD33	2000 2017	A	Acute myelogenous leukemia
Inotuzumab Besponsa	Humanized CD22	2017	B	Acute lymphoblastic leukemia
Ipilimumab Yervoy	Human CTLA4	2011	A	Malignant melanoma
Mogamulizumab Poteligeo	Humanized CCR4	2018	C	Mycosis fungoides Sézary syndrome
Moxetumomab Lumoxiti	Mouse CD22	2018	E*	Hairy cell leukemia
Necitumumab Portrazza	Human EGFR	2015	E	Non-small cell lung cancer
Nivolumab Opdivo	Human PD-1	2015 2018	E*	Malignant melanoma Metastatic small cell lung cancer
Ofatumumab Arzerra	Human CD20	2009	E	Chronic lymphocytic leukemia
Olaratumab Lartruvo	Human PDGF	2016	E*	Soft tissue sarcoma
Panitumumab Vectibix	Human EGFR	2006	E*	Colorectal cancer
Pembrolizumab Keytruda	Humanized PD-1	2014 2015 2018	E*	Malignant melanoma Non-small cell lung cancer Advanced cervical cancer
Pertuzumab Perjeta	Humanized HER2	2012	E*	Breast cancer
Ramucirumab Cyramza	Human VEGF	2014 2015	E*	Gastric, non-small cell lung cancer Colorectal cancer
Rituximab Rituxan	Chimeric CD20	1997	A	Chronic lymphocytic leukemia Non-Hodgkin lymphoma Rheumatoid arthritis
Tositumomab Bexxar	Mouse CD20	2003	C	Non-Hodgkin lymphoma
Trastuzumab Herceptin	Humanized HER2	1998	C	Breast and gastric cancer

AUTOIMMUNE DISEASES				
Generic Name Brand Name	**Type Antigenic Target**	**Approval**	**Likelihood Score†**	**Major Uses**
Adalimumab Humira	Human TNFα	2002	B	Inflammatory bowel disease Rheumatoid, psoriatic arthritis Severe psoriasis
Belimumab Benlysta	Human B cell activity factor	2011	E	Systemic lupus erythematosus
Brodalumab Siliq	Human IL-17A	2017	E	Plaque psoriasis
Canakinumab Ilaris	Human IL1β	2009	E	Autoinflammatory diseases
Certolizumab Cimzia	Humanized TNFα	2008	E*	Inflammatory bowel disease Rheumatoid arthritis
Daclizumab Zinbryta	Humanized CD25	2016	C	Multiple sclerosis
Dupilumab Dupixent	Human IL-4α	2017	E	Atopic dermatitis
Efalizumab Raptiva	Humanized CD11a	2003 Withdrawn	D	Plaque psoriasis
Golimumab Simponi	Human TNFα	2009	E*	Inflammatory bowel disease Rheumatoid, psoriatic arthritis
Guselkumab Tremfya	Human IL-23	2017	E*	Plaque psoriasis
Infliximab Remicade	Chimeric TNFα	1998	A	Inflammatory bowel disease Rheumatoid arthritis Severe psoriasis
Ixekizumab Taltz	Humanized IL-17A	2016	E	Plaque psoriasis Psoriatic arthritis
Ocrelizumab Ocrevus	Humanized CD20	2017	E*	Multiple sclerosis
Rituximab Rituxan	Chimeric CD20	1997	A	Chronic lymphocytic leukemia Non-Hodgkin lymphoma Rheumatoid arthritis
Sarilumab Kevzara	Human IL6R	2017	E*	Rheumatoid arthritis
Secukinumab Cosentyx	Human IL-17A	2015	E	Plaque psoriasis Psoriatic arthritis
Siltuximab Sylvant	Chimeric IL6	2014	E	Castleman disease
Tildrakizumab Ilumya	Humanized IL-23	2018	E*	Plaque psoriasis
Tocilizumab Actemra	Humanized IL6R	2010	D	Rheumatoid arthritis
Ustekinumab Stelara	Human IL-12, IL-23	2010	E*	Plaque psoriasis Psoriatic arthritis

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Vedolizumab Entyvio	Humanized Integrin α4β7	2014	E*	Inflammatory bowel disease

LIVER TRANSPLANTATION				
Generic Name Brand Name	**Type Antigenic Target**	**Approval**	**Likelihood Score†**	**Major Uses**
Basiliximab Simulect	Chimeric IL-2Rα	1998	E	Prevention of transplant rejection
Daclizumab Zenapax	Humanized IL-2	1997 Withdrawn	E	Prevention of transplant rejection
Muromonab-CD3 OKT3	Mouse CD3 T cells	1986	E	Prevention of transplant rejection

MISCELLANEOUS				
Generic Name Brand Name	**Type Antigenic Target**	**Approval**	**Likelihood Score†**	**Major Uses**
Abciximab Reopro	Chimeric GpIIb/IIIa	1993		Inhibition of platelet aggregation
Alirocumab Praluent	Human PCSK9	2015	E	Hypercholesterolemia
Benralizumab Fasenra	Humanized IL5	2017	E	Eosinophilic asthma
Bezlotoxumab Zinplava	Human C. difficile toxin B	2016	E*	Prevention of recurrence of C. difficile infection
Burosumab Crysvita	Human FGF 23	2018	E	X-linked Hypophosphatemia
Denosumab Prolia, Zgeva	Human RANKL	2010	E	Osteoporosis Bone metastases
Eculizumab Soliris	Humanized C5	2007 2011	D	Paroxysmal nocturnal hemoglobinuria
Emapalumab Gamifant	Human Interferon Gamma	2018	E	Hemophagocytic lymphohistiocytosis
Emicizumab Hemlibra	Humanized Factor IXa & X	2017	E	Hemophilia A
Erenumab Aimovig	Human CGRP	2018	E	Migraine headache
Evolocumab Repatha	Human PCSK9	2015	E	Hypercholesterolemia
Fremanezumab Ajovy	Humanized CGRP	2018	E	Migraine headache
Galcanezumab Emgality	Humanized CGRP	2018	E	Migraine headache
Ibalizumab Trogarzo	Humanized CD4	2018	E	HIV infection
Lanadelumab Takhzyro	Human Kallikrein	2018	E	Hereditary angioneurotic edema

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Mepolizumab Nucala	Humanized IL15	2015	E	Eosinophilic asthma Hypereosinophilic syndrome
Natalizumab Tysabri	Humanized Integrin α4β7	2004	C	Multiple sclerosis Inflammatory bowel disease
Obiltoxaximab Anthim	Chimeric Anthrax toxin	2016	E	Inhalational anthrax
Omalizumab Xolair	Humanized IgE	2003	E	Eosinophilic asthma
Palivizumab Synagis	Humanized RSV fusion protein	1998	E	Respiratory syncytial virus infection
Ranibizumab Lucentis	Humanized VEGF-A	2006	E	Macular degeneration
Ravulizumab Ultomiris	Humanized Complement C5	2018	E*	Paroxysmal noctural hemoglobinuria
Raxibacumab	Human Anthrax toxin	2012	E	Inhalational anthrax
Reslizumab Cinqair	Humanized IL5	2016	E	Eosinophilic asthma

† Likelihood Score indicates the likelihood of association with drug induced liver injury, based upon the known potential of the drug to cause such injury.

Updated: February 3, 2019