Adalimumab

'*Adalimumab*, sold under the trade names **Humira** among others, is a medication used for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, moderate to severe chronic psoriasis, moderate to severe hidradenitis suppurativa, and juvenile idiopathic arthritis. In rheumatoid arthritis, adalimumab has a response rate similar to methotrexate, and in combination nearly doubles the response rate of methotrexate alone.[1]

Adalimumab is a TNF inhibiting anti-inflammatory biologic medication. Adalimumab binds to tumor necrosis factor-alpha (TNFα). TNFα normally binds to TNFα receptors, which leads to the inflammatory response of autoimmune diseases. By binding to TNFα, adalimumab reduces this inflammatory response. Because TNFα is also part of the immune system that protects the body from infection, treatment with adalimumab may increase the risk of infections. Adalimumab was the first fully human monoclonal antibody drug approved by the FDA. It was derived from phage display,[2] and was discovered through a collaboration between BASF Bioresearch Corporation (Worcester, Massachusetts, a unit of BASF) and Cambridge Antibody Technology as D2E7,[3] then further manufactured at BASF Bioresearch Corporation and developed by BASF Knoll (BASF Pharma) and, ultimately, manufactured and marketed by Abbott Laboratories after the acquisition of BASF Pharma by Abbott. On January 1, 2013 Abbott split into two companies, one retaining the Abbott name and the other named AbbVie. Humira is now owned by AbbVie.

Humira costs approximately $3,100 per month, like the TNF-alpha inhibitor etanercept. In 2012 to 2014 Humira topped the top selling pharmaceutical product sales lists and in 2014, Humira had $13.0 billion of sales globally.[4] Also in 2014, in India the first adalimumab biosimilar at a price of $200 a dose came to market. Humira's U.S. patent will expire in 2016.[5] In 2016, another Indian drugmaker Torrent Pharmaceuticals launched a biosimilar to adalimumab.[6]

1 Medical uses

Adalimumab, like other TNF inhibitors, infliximab, etanercept, certolizumab pegol and golimumab, may be used in the treatment of several conditions where the suppression of the immune response is desired. Not all the listed applications have been approved worldwide. It is administered by subcutaneous injection.[7] For most indications the maintenance treatment is an injection every other week.[7]

1.1 Rheumatoid arthritis

Adalimumab has been shown to reduce the signs and symptoms of moderate-to-severe rheumatoid arthritis (RA) in adults. It has also been shown to have efficacy in moderate to severe polyarticular juvenile idiopathic arthritis (JIA) in children 4 years of age and older, and is approved for use in the treatment of that condition. In RA it can be used alone or with methotrexate or similar medicines. In the US since 2002[8][9]

1.2 Psoriatic arthritis

Adalimumab is (since 2003) undergoing trials for use in treating psoriasis and psoriatic arthritis.[10]

1.3 Ankylosing spondylitis

Adalimumab has been shown to reduce the signs and symptoms of, and is approved for treatment of, ankylosing spondylitis (AS) in adults.[11]

1.4 Crohn's disease

Adalimumab has been shown to reduce the signs and symptoms[12] of, and is approved for treatment of, moderate to severe Crohn's disease since 2009 in the UK.[13]

1.5 Ulcerative colitis

Adalimumab may be effective and well tolerated in Ulcerative colitis. It has been approved by the FDA for treatment of moderate-to-severe cases in adults.[14]

1.6 Plaque psoriasis

Adalimumab has been shown to treat moderate to severe chronic plaque psoriasis (Ps) in adults who have the condition in many areas of their body and who may benefit from taking injections or pills (systemic therapy) or phototherapy (treatment using ultraviolet light alone or

with pills).[15] Adalimumab has been shown to be effective therapy when used either continuously or intermittently in patients with moderate to severe psoriasis.

1.7 Juvenile idiopathic arthritis

Adalimumab has been shown to reduce the signs and symptoms of moderate to severe polyarticular juvenile idiopathic arthritis (JIA) in children four years of age and older. For patients 15 kg (33 lbs) to 30 kg (66 lbs) administer 20 mg subcutaneously every other week. For patients weighing more than 30 kg (66 lbs) administer 40 mg subcutaneously every other week.[16]

2 Side effects

Components of a Humira autoinjector pen. See file details for explanation of parts.

Because adalimumab suppresses TNF, which is part of the immune system, latent infections, such as tuberculosis, can be reactivated, and the immune system may be unable to fight new infections. This has led to fatal infections.[17]

According to the product labeling, after a number of studies and reports of adverse events in patients receiving adalimumab, including serious and sometimes fatal blood disorders, serious infections including tuberculosis (TB) and infections caused by viruses, fungi, or bacteria, rare reports of lymphoma[18] and solid tissue cancers, rare reports of serious liver injury, rare reports of demyelinating central nervous system disorders, rare reports of cardiac failure, the U.S. Food and Drug Administration issued a black box warning to doctors which appears in the product labeling of adalimumab and the other TNF drugs instructing them to screen and monitor potential patients more carefully.[16] Anaphylaxis or serious allergic reactions may occur.[16]

3 History

Adalimumab was discovered as a result of the collaboration between BASF Bioresearch Corporation (Worcester, Massachusetts, a unit of BASF) and Cambridge Antibody Technology which began in 1993.[19]

It was the third TNF inhibitor, after infliximab and etanercept, to be approved in the United States. It was constructed from a fully human monoclonal antibody, while infliximab is a mouse-human chimeric antibody and etanercept is a TNF receptor-IgG fusion protein.

The drug candidate was discovered initially using CAT's phage display technology and named D2E7.[3] The key components of the drug were found by guiding the selection of human antibodies from phage display repertoires to a single epitope of an antigen TNF alpha.[20] The ultimate clinical candidate, D2E7, was created and manufactured at BASF Bioresearch Corporation and taken through most of the drug development process by BASF Knoll, then further development, manufacturing and marketing by Abbott Laboratories, after Abbott acquired the pharmaceutical arm of BASF Knoll.[21]

On 2 January 2013, Abbott Laboratories separated into two independent companies, Abbott and AbbVie.[22] As a result, AbbVie is taking responsibility for the further development and marketing of Humira.[23]

As of 2008 adalimumab had been approved by the U.S. Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, moderate to severe chronic psoriasis and juvenile idiopathic arthritis. Although only approved for ulcerative colitis from late 2012 by the FDA in the disease's management, it had been used for several years in cases that have not responded to conventional treatment at standard dosing for Crohn's Disease.

3.1 Marketing

- 1999: Preliminary results of early clinical trials with the fully human anti-TNFalpha monoclonal antibody D2E7[3]

- 2001, June: Results from ARMADA, a double-blind, placebo-controlled clinical trial involving 271 patients with active rheumatoid arthritis despite treatment with methotrexate are announced. Among the results are that 50% of patients show a 50% improvement in ACR score.[24]
- 2002: Broke ground on a new state-of-the-art biologics manufacturing facility.[25]
- 2002: Adalimumab results from five separate trials show that it is effective at reducing signs and symptoms of rheumatoid arthritis. In these studies, adalimumab had a rapid onset of action and sustained efficacy. Furthermore, adalimumab was safe and effective when given alone or in combination with MTX as a subcutaneous injection.[26]
- 2002, December 31: Humira approved by the U.S. Food and Drug Administration (FDA) for treatment of rheumatoid arthritis.[25]
- 2003: Launched Humira for rheumatoid arthritis and continued clinical studies for additional indications.[25]
- 2005: Launched Humira for psoriatic arthritis. Exceeded $1 billion in annual sales for the first time.[25]
- 2005, 10 December: Eisai Submits New Drug Application for Rheumatoid Arthritis Drug Adalimumab (D2E7) in Japan.[27]
- 2006: Submitted Humira for the Crohn's disease indication and launched it for AS. Exceeded $2 billion in annual sales.[25]
- 2007: Launched Humira for Crohn's disease in the United States,[25] submitted Humira for global regulatory approval for psoriasis — the fifth new Humira disease indication at this time, achieved more than $3 billion in worldwide Humira sales.[28]
- 2007, 10 December: Abbott Opens New Biotechnology Manufacturing Facility in Puerto Rico[29]
- 2009, 10 June: Five-Year Data Demonstrate Initial Use of Humira Plus Methotrexate May Prevent Further Joint Damage in Early Rheumatoid Arthritis Patients [30]
- 2012, 16 March: Humira could be associated with a significant decrease in vascular inflammation, a major risk factor of cardiovascular disease [31]
- 2013: Due to the split of Abbott, Humira rights are now owned by AbbVie.
- 2014: Humira recognized by IMS Health as the "world's best selling drug."[32]
- 2014: In December 2014, Indian drugmaker Cadila Healthcare declared the launch of the first adalimumab biosimilar at a fifth of its U.S. price. The generic has been launched under the brand name Exemptia.[33][34]

4 Society and culture

4.1 Royalty litigation

In March 2003, British company Cambridge Antibody Technology (CAT) stated its wish to "initiate discussions regarding the applicability of the royalty offset provisions for Humira" with Abbott Laboratories in the High Court of London, UK. In November 2004, the trial began, and in December 2004, the Judge, The Hon. Mr Justice Laddie, ruled for CAT. In an unusual step, a draft of the judgement was not made available in advance.

A short version of the full statement of the proceedings was released.[35] In it Justice Laddie remarked, "Abbott was in error when it made its first royalty payment to CAT calculated on the basis that only 2% of the Net Sales was due. It should have calculated on the basis of the full royalty of just over 5% and should have paid and continued to pay CAT accordingly." Justice Laddie went on to observe "...that the construction advanced by Abbott does violence to the language of the agreements, renders them obscure and makes little or no commercial sense. For this reason CAT wins the action."[36]

Abbott was required to pay CAT US$255 million, some of which was to be passed to its partners in development.[37] Of this sum, the Medical Research Council received US$191M, and in addition, Abbott was asked to pay the MRC a further US$7.5M over five years from 2006, providing that Humira remains on the market. The MRC also is to receive a further £5.1M (sterling) in respect of past royalties.[38]

4.2 Patent litigation

On May 29, 2009, Johnson & Johnson's Centocor unit, the maker of Remicade, which is also a TNF inhibitor, won a ruling for $1.67 billion from Abbott Laboratories, the maker of Humira, for patent infringement on the process for making Humira.[39] However, in 2011 this judgment was overturned by the United States Court of Appeals for the Federal Circuit.[40]

4.3 Biosimilars

Humira stands for "human monoclonal antibody in rheumatoid arthritis".

In December 2014, Indian drugmaker Cadila Healthcare declared the launch of the first adalimumab biosimilar at

a fifth of its U.S. price. The generic has been launched under the brand name Exemptia.[5][41]

In January 2016, Indian drugmaker Torrent Pharmaceuticals launched its biosimilar for adalimumab. Torrent's Adfrar would be the second generic biosimilar of adalimumab in the world.[6]

In September 2016 the US FDA approved Amgens biosimilar adalimumab-atto sold under the brand name Amjevita.[42]

5 Similar agents

- Infliximab
- Etanercept
- Certolizumab pegol
- Golimumab

6 References

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7 External links

- Official website
  - Humira - full prescribing information
- Official website of Exemptia (adalimumab biosimilar)
- Humira Adverse Events Reported to the FDA

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