Tumor necrosis factor-alpha (TNF-α)

- Key component in immune response[1]
- Cytokine secreted by macrophages and other cells that signals apoptosis, activation or proliferation[1,2]
- Elevated in blood serum in an inflammatory state[2]
- Typically not detectable in aqueous nor vitreous humor[2]
- Highly present in patients with uveitis[3]

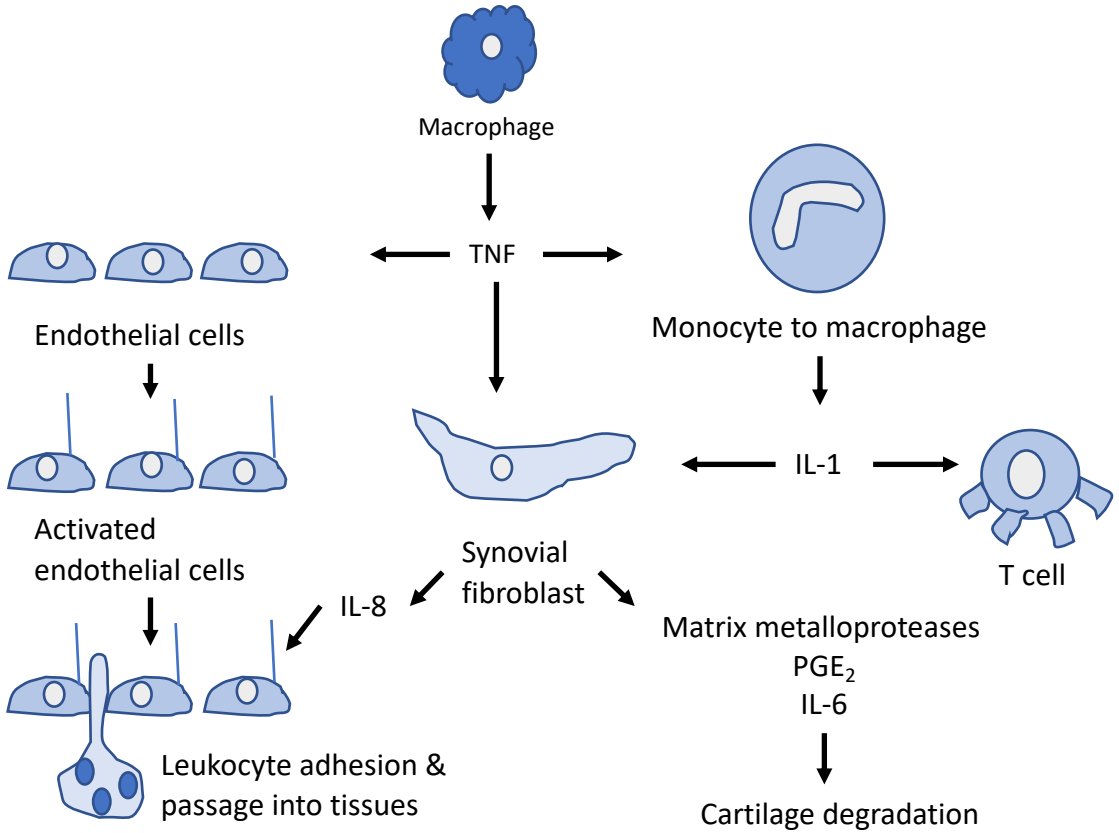

Image reference: Guzman F. Figure: Anti TNF agents molecular characteristics. Mechanism of action, indications and adverse effects of: etanercept, infliximab and adalimumab. Pharmacologycorner.com Web site 1. Lis K, et al. *Arch Med Sci*. 2014;10(6):1175-1185. 2. Steen J. *Review of Optometry*. 2018;155(5):97-104. 3. Takeuchi M. *Immunotherapy*. 2013;5(1):91-102.

TNF-α

- 2 forms of biologically active TNF: solTNF and tmTNF[1]
  - SolTNF
    - Main role is to drive the inflammatory response[1]
    - Inhibition has anti-inflammatory properties[1]
  - TmTNF
    - Important role of immune response to infections[1]
    - Inhibition causes susceptibility to infections, such as tuberculosis and listeriosis[1]

1. Lis K, et al. *Arch Med Sci*. 2014;10(6):1175-1185.

TNF-α Inhibitors

- 5 approved TNF-α inhibitors:

  infliximab, adalimumab, certolizumab, etanercept, and golimumab[1]

  ➢ Non-selective in blocking solTNF and tmTNF--may produce serious side effects[2]

  ➢ Commonly used as treatment for autoimmune diseases:

  Chron's disease, rheumatoid arthritis, ulcerative colitis, ankylosing spondylitis, juvenile arthritis, and plaque psoriasis[1]

1. Tumor Necrosis Factor (TNF) Inhibitors Market is Expected to Reach US$ 181,139.7 Million By 2026: Credence Research. Credence Research Inc. Globenewswire.com Web site. 2. Lis K, et al. *Arch Med Sci*. 2014;10(6):1175-1185.

TNF-α Inhibitors for Uveitis

Properties	Infliximab	Adalimumab
Binds to TNF-α	Yes- Membrane bound & Soluble form[1]	Yes- Membrane bound & Soluble form[1]
Composition	Chimeric monoclonal antibody[2]	Humanized monoclonal antibody[3]
Drug Administration	Intravenous[2]	Subcutaneous[3]
Typical Dosage	5 mg/kg every 8 weeks[2]	40 mg every 2 weeks[3]

1. Lis K, et al. *Arch Med Sci*. 2014;10(6):1175-1185. 2. Takeuchi M. *Immunotherapy*. 2013;5(1):91-102. 3. Pasadhika S, et al. *Biologics*. 2014;8:67-81.

Infliximab

- A chimeric monoclonal IgG antibody:
  - Composed of a mouse-derived antibody and a human antibody[1,2]
- Binds to free and membrane-bound TNF-α to inhibit the binding of TNF-α to its receptor[1,2]
- Intravenous treatment only:
  - 5 mg/kg given at 0, 2, and 6 weeks, then a maintenance dose of 5 mg/kg every 8 weeks[3]
    - Exception is the treatment of rheumatoid arthritis in which the dosage is 3 mg/kg given at 0, 2, and 6 weeks, then a maintenance dose of 3 mg/kg every 8 weeks[3]

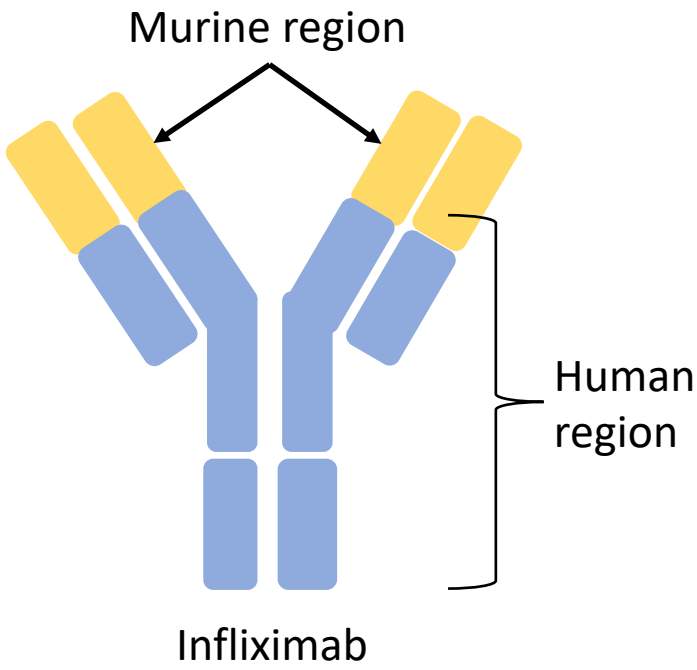

Image reference: Pasadhika S. *Rev of Ophthalmol.* 1. Pasadhika S, Rosenbaum JT. *Biologics*. 2014;8:67-81. 2. Takeuchi M. *Immunotherapy*. 2013;5(1):91-102. 3. Infliximab dosage. Cerner Multum, Inc. Drug.com Web site.

Infliximab in Trials

- In small prospective trials studying patients with uveitis secondary to Bechet's disease, treatment with infliximab revealed:

  - Complete remission of refractory uveitis in 86% of patients[1]
  - Quick resolution of cystoid macular edema in patients[1]
  - In less than 2 weeks, inflammation was controlled with infliximab[2]
    - Quicker than treatment with intravenous corticosteroid or intravitreal triamcinolone alone[2]

1. Sharma SM, et al. *Ophthalmol Ther*. 2017:1-17. 2. Steen J. *Review of Optometry*. 2018;155(5):97-104.

Infliximab in Trials

- A 2-year prospective trial of patients with refractory uveitis and various autoimmune diseases, treatment with infliximab revealed:

  - 3 in 4 patients met the initial success criteria with the loading dose[1,2]
  - Of the initial success patients, a 60% retention rate for the first year and a 60% retention rate for the second year was achieved[2]
  - Infliximab was well-tolerated and effective for 2 years or more[2]

1. Sharma SM, et al. *Ophthalmol Ther*. 2017:1-17. 2. Suhler EB, et al. *Arch Ophthalmol*. 2009;127(6):819-822.