**Biological Drug Therapy in Rheumatology ©**

**ANTI-TUMOUR NECROSIS FACTOR ALPHA (ANTI-TNF-α) ©**

* **FDA Approved Medications**
* Etanercept (Enbrel)
* Infliximab (Remicade)
* Adalimumab (Humira)
* **Other new (not yet approved) medications 🗹:**
* Cimzia.
* Golimumab.
* ***Both drugs have the advantage of less frequent SC injection needed.***
* **Structure**
* Etanercept is a recombinant, dimeric fusion protein consisting of the soluble human p75 TNF receptor coupled to the Fc fragment of human IgG1 lacking the CH1 domain ©. It binds soluble form of TNFα 🗹.
* Infliximab is a "humanized" monoclonal antibody in which the antigen-binding regions of a mouse anti-TNF monoclonal antibody have been placed in the framework of a human IgG1 kappa antibody.
* Adalimumab is a recombinant, fully human monoclonal IgG1 kappa antibody.
* **Mechanism of Action**
* TNF-α and TNF-β are cytokines that regulate a wide array of biological functions necessary for normal inflammatory and immune responses.
* TNF-α, through its binding to membrane-bound TNF receptors, mediates many of the proinflammatory processes implicated in inflammatory arthritis.
* Etanercept binds soluble TNF- α and TNF-β and prevents their association with cell-surface receptors.
* Both infliximab and adalimumab bind soluble as well as membrane-bound TNF-α and block cell signaling through TNF receptor pathways.
* **Pharmacokinetics**
* Bioavailability: Etanercept (subcutaneous) 60%, adalimumab (subcutaneous) 64%. Infliximab is administered intravenously.
* Average half-life: Etanercept 4.25 days; infliximab 8–12 days; adalimumab 14 days.
* Clearance: The exact mechanisms of clearance for etanercept, infliximab, and adalimumab have not been definitively determined, although the reticuloendothelial system may play a role. No formal studies have been done to determine the effects of hepatic or renal impairment on clearance.
* **Uses in Rheumatic Disease**
* ***Rheumatoid Arthritis***
* Etanercept has been studied in diverse populations of adult patients with active RA, including patients with active RA despite previous therapy with at least one DMARD and DMARD-naíve patients with early RA. Etanercept is superior to placebo as either monotherapy or add-on therapy with methotrexate in relieving many of the signs and symptoms associated with RA.
* In patients with active RA despite treatment with methotrexate, infliximab is superior to placebo in reducing the signs and symptoms of disease when given in concert with methotrexate.
* Adalimumab has been studied as monotherapy and in combination with methotrexate and other DMARDS. It has also been studied in patients who have failed at least one previous DMARD, remained on stable doses of current DMARD therapy, or are DMARD-naíve. In all populations, adalimumab is superior to placebo in controlling the signs and symptoms of RA.
* Etanercept, infliximab, and adalimumab have been shown to slow or inhibit the radiographic progression of joint destruction in rheumatoid arthritis.
* ***Psoriatic Arthritis***
* All three of these anti-TNF agents are approved by the FDA for the treatment of psoriatic arthritis. Each has demonstrated efficacy as monotherapy in randomized, placebo-controlled studies.
* Anti-TNF drugs are now the most known effective drugs for treatment of PsA 🗹.
* Radiological progression decreases significantly with Anti-TNF drugs, but the characteristic PsA radiological picture (pencil-in-cup or diffuse osteolysis) do not change due to the more fixed nature of these changes 🗹.
* In case of failure or lost efficacy of one anti-TNFα drug in treatment of PsA, switch to other anti-TNFα drugs may be beneficial 🗹.
* ***Ankylosing Spondylitis 🗹***
* TNF-α appears to play a key role in promoting inflammation in AS.
* The proved anti TNF-α for AS are:
* They are proved to produce sustained response in primary outcomes (morning stiffness, nocturnal pain, patient's global assessment and finctional index) and secondary outcomes (spinal and chest range of movement, enthesitis and acute phase reactants).
* MRI shows 86 % reduction in acute inflammatory lesions over 24 weeks of treatment.
* For patients with AS and concomitant IBD, monoclocal antibody to TNF is preferred (infliximab or adalimumab).
* ***Other Spondyloarthropathies***
* Small, open label studies suggest that etanercept and infliximab have efficacy in the treatment of undifferentiated spondyloarthropathy and reactive arthritis and the axial and peripheral arthritis associated with inflammatory bowel disease. However, none of the anti-TNF agents have been rigorously studied in prospective, double-blinded placebo controlled studies for these diseases.
* ***Juvenile Idiopathic Arthritis***
* Etanercept is the only anti-TNF agent to be approved by the FDA for the treatment of juvenile idiopathic arthritis. It has been rigorously studied in both short- and long-term clinical trials and has been found to be efficacious when used as monotherapy or as an addition to treatment with methotrexate.
* Infliximab, but not etanercept, can be used in JIA associated uveitis 🗹.
* Anti TNF are proved to be very effective in poJIA, including those cases resistant to MTX 🗹.
* They are also effective in eJIA, but less effective in sJIA 🗹.
* Side effects 🗹:
	+ ***Mild:***
		- * Injection-site inflammation: for etanercept and adalimumab.
			* Injection related allergy: for infliximab. To decrease allergic reaction, premedication with paracetamol, or steroid may be needed.
			* Mild infection (upper respiratory).
			* Headache.
	+ ***Severe:***
		- * Neurologic (demyelinating) complications.
			* Psychological upset.
			* Severe infections (specially related to varicella).
			* Cutaneous vasculitis.
			* Pancytopenia.
			* Development of other autoimmune diseases.
			* No cases of malignancy is recorded in children.
* ***Adult Still Disease***
* A small open-label study suggests that etanercept may reduce the signs and symptoms of adult Still disease.
* ***Wegener Granulomatosis***
* A large randomized study of etanercept added to standard therapy for Wegener granulomatosis demonstrated **NO** additional efficacy in maintaining remission.
* **Dosing**
* Etanercept: Given either as a single, 50-mg injection once weekly or as a 25-mg subcutaneous injection twice weekly. Must be refrigerated and reconstituted in sterile solution before being administered.
* Infliximab: Infusion is given in a doctor's office or infusion center and takes approximately 2–3 hours to complete. Administered as an intravenous infusion beginning with a loading dose of 3 mg/kg at 0, 2, and 6 weeks. Dosing is usually maintained at 3 mg/kg every 8 weeks. Flexibility in dosing allows for the dose to be increased up to 10 mg/kg and/or the interval decreased to as little as every 4 weeks, depending on response to therapy.
* Adalimumab: Given as a single, 40-mg subcutaneous injection once every other week. Medication comes preloaded in a syringe, does not need to be reconstituted, and should be refrigerated before use. Dosing flexibility allows the medication to be given as often as 40 mg every week as clinical conditions warrant.
* **Initiating Therapy**
* The risk of reactivation of latent tuberculosis should be assessed and should include, at a minimum, a baseline purified protein derivative prior to initiation of therapy. Many physicians obtain a chest radiograph as well.
* The risk of latent histoplasmosis and coccidioidomycosis infection should be considered in patients from endemic regions.
* No baseline or routine laboratory testing is officially recommended.
* Age-appropriate cancer screening, while not officially recommended, may be of benefit prior to initiating therapy.
* Patients are recommended not to receive live vaccinations after initiating or continuing therapy.
* Patients should be monitored for injection site or infusion reactions while receiving therapy.
* Anti-TNF agents should not be used in patients with a history of multiple sclerosis of any other demyelinating disease.
* **Special Precautions**
* TNF antagonists should not be used in patients with a history of latent tuberculosis unless they have completed an adequate course of prophylactic therapy.
* The TNF antagonists are contraindicated in patients with active acute or chronic infections.
* Patients receiving infliximab should have baseline screening for infection, including temperature and symptom assessment, prior to each infusion.
* Patients should be instructed to contact their physician if any symptoms of acute infection develop.
* The anti-TNF agents should not be used in patients with active or suspected malignancies.
* Hypersensitivity to an anti-TNF agent is a contraindication to its use.
* Patients with previous allergies to mouse-derived products should not receive infliximab.
* All anti-TNF agents are pregnancy category B.
* The use of anti-TNF agents in the setting of hepatic disease or renal failure has not been studied.
* Infliximab is specifically contraindicated in patients with moderate or severe congestive heart failure; extreme caution should be exercised for the other anti-TNF agents in this setting.
* **Complications**
* Post-marketing surveillance of these agents has reported hospitalizations and deaths from serious infections, although randomized trials have not demonstrated an increased frequency of serious infections
* Blockade of TNF poses a theoretical risk of increased malignancy. There are post-marketing reports of lymphomas developing in patients treated with either etanercept or infliximab, but it remains to be determined if there is an actual increase in the incidence of malignancy.
* Etanercept and adalimumab are associated with a high degree of mild to moderate injection site reactions, including erythema, pruritus, pain, and/or swelling, reactions which are commonly self-limiting, early in the course of therapy.
* Infliximab is associated with a significant incidence of infusion reactions within 1–2 hours after receiving the therapy, including fever, chills, urticaria, and cardiopulmonary symptoms.
* Infliximab has been linked to a serum-sickness type of syndrome.
* The use of the anti-TNF agents, especially infliximab, can lead to the development of antibodies to the agent. Whether these antibodies influence efficacy or adverse reactions is uncertain.
* Anti-TNF agents can induce antinuclear antibodies and other autoantibodies, and rarely, a lupuslike syndrome.
* Use of anti-TNF agents may worsen symptoms of congestive heart failure.
* Rarely, a demyelinating syndrome has been observed in patients using anti-TNF agents.
* Cytopenias and aplastic anemia have been reported in sporadic cases of patients on anti-TNF agents.
* **Discontinuing Therapy**
* TNF antagonists should be discontinued if active infection, malignancy, or a serious adverse event develops.
* Because of their relatively long half-lives, the immunosuppressive effects of infliximab and adalimumab should be considered when evaluating and treating those patients who have recently discontinued use of the drugs.
* **Summary**
* The TNF antagonists are effective in reducing the signs and symptoms and inhibiting structural joint damage of patients with moderate or severe rheumatoid arthritis. They are of proven efficacy in controlling the signs and symptoms of ankylosing spondylitis and psoriatic arthritis.
* Lack of long-term safety data, need for parenteral administration, and high cost should be considered when tailoring this therapy to specific patients.

**وآخر دعوانا أن الحمد لله رب العالمين**

**د. أحمد رشدي العجمي**

N.B. for all writings of this series, 🗹refers to (Primer on the rheumatic diseases) © refer to (current of rheumatology) and $ refers to (rheumatology secrets). Also ☺ refers to conference talks by some professors.