REVIEW ARTICLE

TNF blockers for Psoriasis in 2020: Concise review

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ABSTRACT

As of today, four Tumor Necrosis Factor (TNF) blockers are approved by FDA for the treatment of psoriasis and psoriatic arthritis. Although, they act by blocking the effect of TNF. But, they differ from each other, in both their pharmacokinetic and pharmacodynamic properties. They also differ in the target epitopes on the TNF molecules, which actually make them totally different drugs. These agents have been in use for almost two decades, and their long term efficacy and survival in real life patients have also been studied extensively. In this brief review, I have discussed the mechanism of action, dosage, indications, adverse effects, monitoring and complications associated with each one of them, highlighting the similarities and important differences between them.

INTRODUCTION

TNF alpha cytokine is an important mediator in the pathogenesis of inflammatory disorders and psoriasis. TNF alpha blockers are antibodies and fusion proteins that block the TNF monokine, and are successful in controlling many inflammatory diseases including psoriasis. This group of agents has been widely used in the therapy of immune mediated inflammatory diseases for almost two decades. Their success paved the way for a new era in therapy of psoriasis and psoriatic arthritis.

Differences and similarities

In dermatology, four TNF blockers were approved in the treatment of psoriasis and psoriatic arthritis.[1-4] They share in common their ultimate effect which is to nullify TNF. However; may differ in both their pharmacokinetics and pharmacodynamics. Nevertheless; they also differ in the target epitopes on the TNF molecules which make them in reality totally different drugs.[5]

Drug	Molecule	FDA approval For PSO	Half life in days	Mean Cord blood level in µg/ml	PASI 75 at 12/16 weeks	ACR 20 at 24 weeks	Average Survival % after 4 years (efficacy)
Etanercept	Two soluble p75 TNFR (sTNFR2) molecules fused to the Fc fragment of human IgG1.	2004	3	0.1	54 (50 mg twice weekly)	50	51
Infliximab	Mouse/human chimeric mAb IgG1	2006	10.5	4.9	81	54	49
Adalimumab	human monoclonal antibody IgG1 mAb	2008	14	1.1	71	57	62
Certolizumab	Humanized PEGylated Fab' IgG fragment of mAb	2018	14	no quantifiable levels (<0.032 µg/mL)	74	59	Not yet available

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Points of strength

These drugs have been used for almost two decades; many RCTs were done for different indications, age groups, and phenotypes. The long term efficacy and survival of each drug in real life patients were also studied extensively. Moreover; the short term and the long term adverse effects are well known, that give TNF blockers a unique point of strength over the newest biologics.

TNF blockers were considered by GRAPPA as first lines biologics in all forms of psoriatic arthritis; peripheral, axial, dactylitis and enthesitis in patients not responding to disease-modifying ant rheumatic drug (DMARDs disease-modifying anti rheumatic drug (DMARD).[6-8]

An added value to TNF blockers is the wide range of approvals (FDA and EMA) across immune-mediated inflammatory disorders in different age groups and situations.[1-3] Psoriasis is associated with increased incidence of many auto-inflammatory and autoimmune diseases such as inflammatory bowel diseases, hidradenitis suppurativa, psoriatic arthritis and uveitis, which all can be managed using the same drug if occurring concurrently.

TNF blockers are approved for a spectrum of inflammatory diseases in children of age group from 4 to 17 years and add an extra-advantage for these agents. Moreover; there is a growing evidence that TNF blockers may improve and prevent psoriasis comorbidities such as cardiovascular disease and metabolic syndrome.[9,10] Physicians and patients are both familiar with nonstandard dosage regimens of TNF-α blockers, including dose escalation and treatment withdrawal and re-induction.

Contraindications

All the biologics may induce antibodies that may cause immune reaction against the drug or other ingredients. Hypersensitivity to the individual drug or any of its components is a contraindication for further use. It is also contraindicated to use TNF blockers in cases of current acute and chronic infections especially TB infection; personal history of multiple sclerosis, congestive heart failure NYHA grade III/IV, and recently diagnosed patients with malignancies. (i.e. within 5 years).[1-4]

Monitoring

It has been widely recommended to test patients before start of TNF blockers for the presence of TB infection and both Hepatitis B and C. The test may be repeated annually or whenever a current infection is suspected.

a. CXR and TB test: Pretreatment test for latent TB (PPD, T-Spot, or Quantiferon Gold)
b. Serological tests for hepatitis B and C (HbSAg and hepatitis C antibody tests)

Adverse effects

All TNF blockers have black box warning for the possibility of increasing both infections and malignancy. Other reported side effects are hypersensitivity (especially Infliximab), autoimmunity and paradoxical reactions.

TB

TNF is the main cytokine for granuloma formation in TB infection. Eventually, it is expected that TNF blocker therapy increases the risk or TB reactivation. A Brazilian population-based study of TNF blockers use in inflammatory disorders including psoriatic arthritis showed that therapy was associated with an 18 folds increased in TB incidence. However; Etanercept showed much

lower incidence of TB reactivation compared to Adalimumab and certolizumab.[11] TNF blockers induced reactivation of TB was also reported in Qatari patients, and this occurred mainly in the first few months of therapy.[12]

Hepatitis

TNF-alpha inhibitors are generally avoided in patients with HBV infection due to concerns as well as actual incidences for viral reactivation. In contrast, TNF-alpha inhibitor therapy is one of the preferred biologic therapies for patients with HCV infection, provided consultation with a hepatologist and close monitoring are feasible. Many articles reported the reactivation of HBV infection in HBsAg-positive patients using TNF blockers therapy for psoriasis and psoriatic arthritis.[13] In one series of seven psoriatic patients with HBsAg+ and undetectable vral DNA were followed after therapy of Etanercept or Adalimumab for 29 months without antiviral prophylaxis. Three out of seven developed HBV reactivation.[14]

It is advisable to give HBsAg+ patients with antiviral prophylaxis before starting therapy and to continue for at least 6-12 months after immune suppressant discontinuation.[15]

Etanercept, when used in a small randomized trial as adjuvant therapy in HCV positive patients. Patients were either given Etanercept with interferon or ribavirin. HCV RNA clearance was achieved more with patients receiving Etanercept than patients taking interferon or ribavirin monotherapy or placebo.[16]

HIV test

In many instances it is not mandatory to perform screening test for HIV infection; and it depends upon the physician's judgment, patient's history and risk factors.

Vaccination

Psoriasis patients on TNF blocker therapy may only receive live attenuated vaccines before start of treatment or after therapy interruption. The duration between vaccination and start/restart in up to expert opinion, also the period of interruption of therapy whether it is 4 weeks or 2-3 half lives of the drug is controversial. Recombinant Inactivated or ''dead'' vaccines may be given during TNF therapy. However; it is questionable whether therapy may decrease the desired proactive effects of vaccines. A severely hampered antibody response to HBV vaccination was noted in patients with AS treated with TNF-blocking agents.[17]

Malignancy

TNF is one of the factors that the body relies upon in its resistance against malignant tumors. So it is expected that TNF blockers may interfere with the proper defense against cancer. However; after two decades of their use, they have proved to be less hazardous than expected. In a nationwide registry in Denmark; administration and the timing of start of therapy by TNF blockers were not associated with the development of new cancer or recurrence of previous cancer.[18]

In USA, when used as monotherapy, TNF blockers were not associated with an increased risk of any solid or lympho-reticular tumour. However, both melanoma and non-melanoma skin cancers as well as recurrence of previous malignancy should be looked for in susceptible population during treatment with TNF blockers.[19,20]

Use in Pregnancy and lactation

Psoriasis and psoriatic arthritis are chronic inflammatory diseases, should be considered as a independent risk of possible adverse pregnancy outcomes. TNF blockers are relatively safe dur-

ing pregnancy and lactation. TNF alpha inhibitors are safe in men attempting or seeking for conception with their partners.

Because of drug delivery to the fetus, neonates and infants should be considered immune-suppressed for at least 3 month (depending on the TNF inhibitor) postpartum in mothers who have been on TNF-inhibitors. There is a greater theoretical risk with use during the third trimester of pregnancy owing to trans-placental transfer of TNF blockers, with the exception of certolizumab which showed minimal or no placental transfer.

In the latest version of the British Association of Dermatologists guidelines for biologic therapy for psoriasis it is strongly recommended to consider using certolizumab as a first-line choice when starting biologic therapy in women planning conception.[21] Adalimumab has been FDA approved for use during pregnancy up till week 20 of gestation.[22]

In population based study in three Scandinavian countries; TNF blocker (except for Certolizumab) were associated with increased risk for preterm birth, small for date babies and caesarean section procedure. In the same population, another study showed that infants born to psoriatic mothers exposed to TNF blockers during pregnancy had increased incidence rate ratios of hospital admissions for infections and antibiotic prescriptions in their first two years of life.[23,24]

TNF blockers in general are considered compatible with breastfeeding. A decision to continue or discontinue breastfeeding during therapy is a decision that critically balances the mother's benefits from therapy and the infant's risks and needs if breastfeeding is continued.[21] In the end, risks associated with TNF blockers therapy should be weighed against the yet uncertain risk of adverse outcomes on pregnancy outcomes and infants born to women with moderate to severe psoriasis.

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