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Textbook of PSORIASIS

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2nd Edition

JAYPEE

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CHAPTER

11

Biologics in Psoriasis

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INTRODUCTION

Psoriasis is a chronic, immune-mediated dermatosis that not only affects the skin, nails, and joints but also subjects the patient to chronic inflammation. The proinflammatory cytokines that are involved in the pathogenesis of psoriasis such as tumor necrosis factor-α (TNF-α), interleukin-17 (IL-17), and IL-23 can synergistically induce other disease processes. This predisposes the patients with psoriasis to other comorbidities such as:

- Autoimmune disorders (psoriasis patients are likely to have association with at least 1 other autoimmune disorder)
- Diabetes mellitus (fourfold increase)
- Myocardial infarction (threefold increase)
- Hypertension (twofold increase)
- Metabolic syndrome (twofold to threefold increase)
- Uveitis (~twofold increase)

This risk profile is directly proportional to the duration of disease and its severity.[1-5] The life expectancy in psoriatic patients is shortened by 3–4 years compared to healthy controls.[6] Hence, we need to treat psoriasis as a systemic disease rather than a cutaneous disorder. The better understanding of the immunopathogenesis of psoriasis led to the development of biologics, which selectively target these cytokines and might have a protective effect not only on psoriasis but also on the other systemic co-morbidities as well.[7-11] Conventional therapies in psoriasis are summarized in Table 11.1. The advantages and disadvantages of using biologics are given in Table 11.2.

TERMINOLOGIES

Biologics

These are the novel, pharmacologically active, large complex molecules developed via recombinant DNA technology. Their active components are derived from biological sources produced by living organisms such as microorganisms, plants, animals, or humans. These include recombinant proteins, cells, tissues, gene therapy, vaccines, and components of

TABLE 11.1: The conventional therapies for psoriasis

Conventional therapy	Dose	Major ADR	Response	Pregnancy category
Cyclosporine	2.5–5 mg/kg/day	• Hypertension • Renal failure • Gingival hyperplasia • Hypertrichosis • Increased risk of non-melanoma skin cancers • Bone marrow suppression • Electrolyte imbalance	• Initial response by—4 weeks • PASI 75 by 4–12 weeks in 50–70% of patients	"C"
Methotrexate[12]	7.5–15 mg/week	• Hepatotoxicity • GI disturbances • Infections (TB) • Bone marrow suppression • Alopecia • Teratogenic (category X)	• Initial response: 4–6 weeks • PASI 75: 12–16 weeks	"X"
Acitretin	25–50 mg/day	• Hepatotoxicity • Dyslipidemia • Mucocutaneous • Cheilitis/Xerosis • Xerophthalmia • Skeletal ADR • Hair loss • Teratogenic (category X)	• Initial response: 4–6 weeks • PASI 75 typically achieved by 12–16 weeks in only 34–52% of patients	"X"
PUVA	• 8 MOP—0.6–0.8 mg/kg • 5 MOP—1.2 mg/kg (0.5 J/cm^2 increment every visit till mild erythema occurs)[13]	• Sunburn • Photoaging • Increased risk of cataract • PUVA lentigines • Nonmelanoma skin cancers	~25–30 sessions (2–3 times/week), or within 9–15 weeks[14-16]	"C"
Apremilast	Start with starter pack to reach a maximum of 30 mg BD	• GI disturbances • URI • Headache • Weight loss • Depression	PASI 75 is seen only in *41%* of patients by 16 weeks	"C"

ADR, adverse drug reaction; GI, gastrointestinal; URI, upper respiratory infection.

blood. Due to recent advancements in the understanding of disease pathogenesis, these target molecules were developed that alleviate the disease by inhibiting or imitating the proteins that naturally occur in the body. Biologics have been a part of the therapeutic

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TABLE 11.2: Need for biologics in dermatology: Its pros and cons in comparison to conventional therapy

Therapeutic agents	Advantages	Disadvantages
Conventional therapy	• Easily available • Long-term research and safety data available compared to biologics • Cost-effective	• Requires frequent dose • Frequent laboratory monitoring • Frequent follow ups • *Multimodal/nonspecific action*: Greater adverse effects • Long-term therapy can lead to organ toxicity such as liver failure and renal failure • *Significant drug interactions*: Difficult to administer in patients with polypharmacy • Most of the drugs are category C or X. Difficult to be used in female patients in reproductive age group
Biologic	• *Targeted action:* ○ Lower incidence of adverse effects ○ Faster action ○ Better efficacy (70% biologic vs. 40% conventional therapy)[17] ○ Longer remission ○ Less frequent monitoring/follow-ups • Lack of CYP metabolism in liver, hence, minimal drug interactions • Better safety profile in patients with multiple co-morbidities, e.g., liver, kidney diseases, diabetes, hypertension • *Convenient dosing*: Easy administration/self-administration • Can be administered with conventional therapy as well	• High cost • Can develop anti-drug antibodies over time (loss of efficacy) • Increased risk of acquiring infections • Lack of oral formulation

CYP, cytochrome P450.

armamentarium of psoriasis for the past 20 years.[18-20] They are original (reference product), i.e., 1st derived and patented, hence expensive.

Examples are Humira (adalimumab), Remicade(infliximab), and Etanercept (Enbrel).

Biosimilars

The WHO defines a biosimilar as a biotherapeutic agent that is similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product.[21] Every step in the manufacturing process

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such as the selection of host cell lines, protein sequencing, and post-translational modifications is crucial and even minor changes in these processes may alter the structural configuration of a biosimilar. Hence, biosimilars are similar but not exactly identical copies of a biologic (can have minor structural variations).[22]

Examples are etanercept (Etacept from Cipla) and infliximab (Infimab from Ranbaxy).

Biogenerics

These are exact copies of the small-molecule drugs with low-molecular weight having the same mechanism of action, efficacy, and safety profile as the parent drug. These are simple and small molecules that are mostly nonimmunogenic; hence, their development is fast and cost-effective. As these are exact copies, they do not require extensive clinical trials for approval instead small clinical trials in healthy volunteers are sufficient.

Biobetters

These are superior to the original drugs with molecular modification. These have better pharmacokinetic and pharmacodynamic profile. Cost of these drugs is higher than the original molecule.

■ RESPONSE TO DRUG

Super Responders

These are patients who exhibit a rapid and sustained clinical response that exceeds the typical average response observed in most patients. They often achieve complete or near-complete remission, shorter in a timeframe or shorter than the stipulated duration of treatment.

Nonresponders

These are of two types—primary and secondary.

Primary Nonresponders

This refers to patients who lack of sufficient response to the therapy during the induction phase (first 12–16 weeks). This is caused due to the pharmacodynamic failure of the drug (the drug fails to target or sufficiently control the inflammatory process). In such cases, either switching or swapping the drug is advised.

Secondary Nonresponders

These are patients who initially exhibit a good response to the therapy but eventually lose efficacy over time. This is caused primarily due to the development of anti-drug antibodies (ADAs) (immunogenicity) to the biologic.

Partial Responders

These patients respond suboptimally to the therapy. For example, they might reach PASI 50 but do not progress further to reach PASI 75 or PASI 90.

Biologic Holiday

This refers to a planned, temporary interruption of biologic therapy. These are often implemented during planning of pregnancy, major surgery, active infections, etc.

PASI 50

This refers to a 50% reduction of from the baseline PASI score.

PASI 75

This refers to a 75% reduction of from the baseline PASI score.

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NOMENCLATURE

The nomenclature of a "biologic" follows a structured format comprising the following components as given below (Fig. 11.1 and Table 11.3).

- *Prefix*: This is a unique variable in drug's name that has no therapeutic or chemical meaning. It is generally 2–5 letters long. It helps to distinguish between two biologicals that have same source and target. For example, *ada*—lim-u-mab and *Gol*—lim-u-mab.
- *Substem A*: This signifies the target of the biologic, e.g., -ta- for tumor.
- *Substem B*: This denotes the source of the biologic, e.g., human or chimeric.

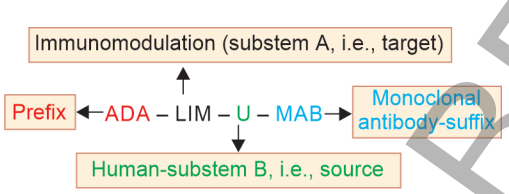

Fig. 11.1: Components in the name of a biologic

- *Suffix*: This denotes the pharmacologic class of the drug, e.g., -mab- for monoclonal antibody, -cept- for receptor.

CLASSIFICATION

Biologics can be classified based on:

- *Structure of the molecule*:
  - Monoclonal antibodies (Table 11.4)
  - Fusion proteins
  - Recombinant human cytokines
- The mechanism of action of the molecule
- Disease targeted

Structure of Monoclonal Antibody (as Shown in Fig. 11.2)

These are Y-shaped protein molecule four polypeptide chains—two light chains and two heavy chains connected via disulfide bonds.

- *Variable region*: This is formed by the upper portion of the antibody which comprising the portions of heavy (VH)

TABLE 11.3: The component used in the nomenclature of biologic[22,23]

-Prefix-	-Sub-stem A-	Target	Sub-stem B	Source/ Origin	-Suffix-	
A variable or unique constant of letters*	-anibi-	Angiogenesis	-a-	Rat	-mab	Immunoglobulin variable domain
	-b(a)- -ba(c)-	Bacterial	-e-	Hamster	-cept	Receptor
	-f(u)- -fung-	Fungal	-i-	Primate	-nib	Tyrosine kinase inhibitor
	-k(i)- -ki(n)-	Interleukin	-o-	Mouse		
	-l(i)- -li(m)-	Immunomodulating	-u-	Human		
	-n(e)- -ne(u)(r)-	Nervous system	-xi-	Chimeric		
	-tox(a)-	Toxin	-zu-	Humanized		
	-t(u)-	Tumor				
	-v(i)-	Viral				

*The word "Peg-" can be used if it is pegylated.

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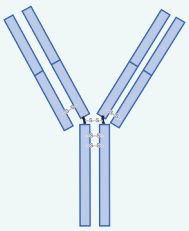
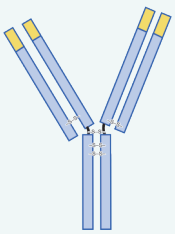
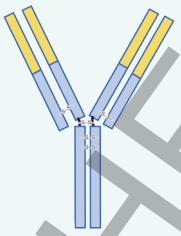
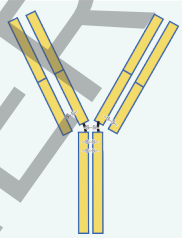
TABLE 11.4: The types of monoclonal antibodies

Type	Human	Humanized	Chimeric	Murine
Structure				
Origin/Source	100% human source	90% human + 10% nonhuman, e.g., mouse	Human constant region + other species variable region (commonly used—mouse)	0% human
Suffix	-u-mab-	-zu-mab-	-xi-mab-	-O-mab-
Examples	• Adalimumab • Golimumab • Secukinumab • Ustekinumab	• Omalizumab • Risankizumab • Ixekizumab • Certolizumab (pegylated humanized monoclonal antibody—the structure and advantages of pegylation are given in Figure 11.3)	Infliximab	• Tositumomab • Muromonab
Potential for immunogenicity	**Lowest** → **Highest**			

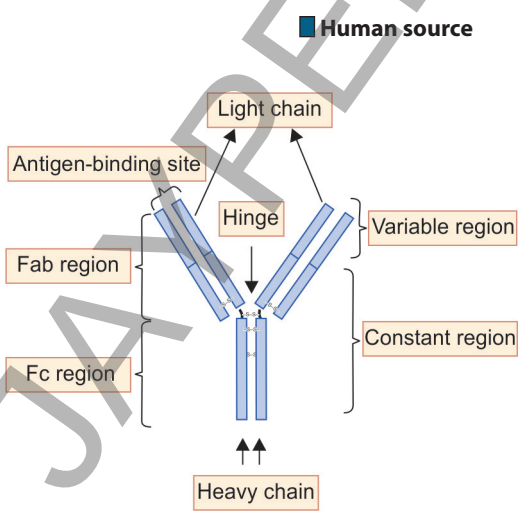


Fig. 11.2: The structure of monoclonal antibody

and light chains (VL) responsible for antigen recognition and binding and specificity of the molecule.

- *Constant region*: This forms the lower part of the antibody comprising constant heavy chains (CH) and constant light chains (CL).
- *Fab (fragment antigen-binding) region*: This binds to the target antigen.
- *Fc (fragment crystallizable) region*: It interacts with immune cells and receptors to trigger a response.
- *Hinge*: The area connecting the Fab and Fc region via disulfide bonds

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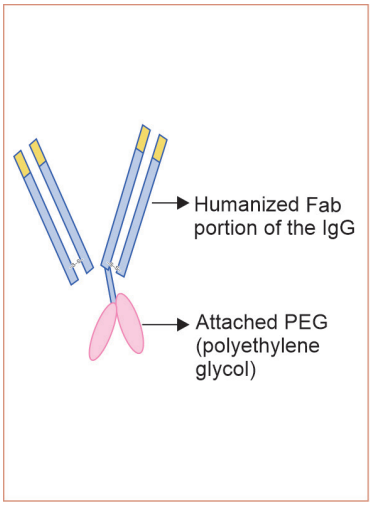

Advantages of pegylation in certolizumab:
Better pharmacokinetic profile:
- Larger molecular size (hydrodynamic size) leads to:
  - ↓ Renal clearance
  - ↓ Proteolytic degradation
- Prolonged T1/2
- Extended dosing interval—better compliance

Reduced immunogenicity:
- PEGylation provides steric shielding of antigenic epitopes, thereby reducing immune recognition but this effect is not absolute. It does form ADA but comparatively at a lower rate than other TNF-α inhibitors

Better safety profile in pregnancy/lactation:
- Placental transfer of the immunoglobulin occurs via neonatal Fc receptor (FcRn)
- Certolizumab lacks Fc region. Therefore, it does not bind FcRn. Hence, minimal active placental transfer
- Preferred drug of choice in pregnancy
- It does not get transferred in breast milk. Hence, has a better safety profile in lactation compared to other biologicals

Fig. 11.3: The structure of certolizumab and the advantages of pegylation

Classification of Monoclonal Antibodies Based on Molecular Structure (Table 11.4)

- *Fully human*: These are derived fully from the human source with least immunological adverse effects, e.g., adalimumab.
- *Humanized*: These are derived predominantly from the human source (~90%) with a part of it derived from non-human source, e.g., omalizumab, ixekizumab, and risankizumab.
- *Chimeric*: In this, the variable portion of the immunoglobulin structure is formed from nonhuman source, whereas the constant portion is formed from human source, e.g., infliximab.
- *Murine*: This is derived from completely nonhuman source. It has highest immunogenic ADR, e.g., tositumomab.

■ FUSION PROTEINS (TABLE 11.5)

Fusion proteins are bioengineered chimeric proteins created by linking functional domains of two or more distinct proteins to create a molecule which has combined properties of both. These newly formed proteins have enhanced functionality, better solubility, greater stability, or targeted drug delivery making it a superior to its parent molecule. Biologicals used in management of psoriasis which belong to this group are receptor fusion proteins and have suffix *-cept, e.g., abatacept and e*tanercept

Etanercept is a dimeric protein formed by the fusion of extracellular domain of TNFR (tumor necrosis factor receptor) and the Fc portion of the monoclonal antibody as shown in Figures 11.4A to C.

■ RECOMBINANT HUMAN CYTOKINES

Here, the cytokines are produced through recombinant DNA technology to be used in various inflammatory disorders, e.g., anakinra (IL-1 receptor antagonist).

■ PATHOGENESIS OF PSORIASIS AND MECHANISM OF ACTION OF BIOLOGICALS[36-38]

The pathogenesis of psoriasis is initiated by a triggering event such as trauma, infection, or

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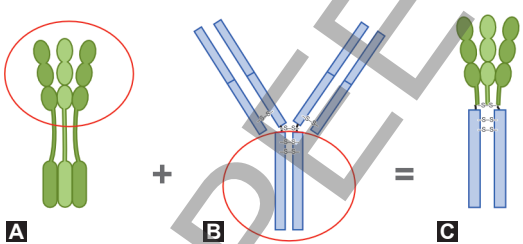
TABLE 11.5: Biologicals commonly used in psoriasis

Classification of drugs	Drugs	Source/Origin	FDA approval
TNF inhibitors	Etanercept	Fully human dimeric fusion protein formed by linking the Fc portion of IgG extracellular domain of TNFR(p75)	2004[24]
	Infliximab	Chimeric (mouse 25% and human 75%) IgG1 monoclonal antibody	2006[25]
	Adalimumab	Fully human recombinant IgG1 monoclonal antibody	2008[26]
	Certolizumab	PEGylated Fab fragment of humanized monoclonal TNF-α antibody	2018[27]
	Golimumab	Fully human recombinant IgG1 monoclonal antibody	2009 (PsA)[28]
IL-12/23 inhibitors	Ustekinumab	Fully human IgG1κ monoclonal antibody	2009[29]
IL-17A inhibitors	Secukinumab	IL-17A fully human IgG1κ monoclonal antibody	2015[30]
	Ixekizumab	IL-17A humanized IgG4 monoclonal antibody	2016[31]
IL-17RA inhibitor	Brodalumab	Fully human IgG2κ monoclonal antibody	2017[32]
IL-23 inhibitors	Guselkumab	Fully human IgG1λ monoclonal antibody	2017[33]
	Tildrakizumab	Humanized mouse IgG1k monoclonal antibody	2018[34]
	Risankizumab	Humanized IgGκ monoclonal antibody	2019[35]

FDA, Food and Drug Administration; IL, interleukin; TNF, tumor necrosis factor.



Figs. 11.4A to C: The structure of fusion protein—etanercept (C) formed by the fusion of the extracellular portion of the tumor necrosis factor receptor (A) with the Fc portion of the monoclonal antibody (B)

drugs occurring in a genetically susceptible patient. This causes the stressed keratinocytes to release DNA (self-DNA) fragments that combine with cathelicidin LL37 (a potent anti-microbial peptide released in response to stressed keratinocytes) to form a LL37-DNA complex initiating an autoimmune process. This stimulates the recruitment of plasmacytoid dendritic cells (pDCs) in the dermis that usually reside in the blood and peripheral lymphoid organs. The pDC binds with the LL37-DNA complex via Toll-like receptors and stimulates production of IFN-α which recruits and activates myeloid dendritic cells. These myeloid dendritic cells (APC) migrate to the regional lymph node and present the antigen to the naïve T cells directing it to differentiate into Th1, Th17, and Th22 via production of specific cytokines (as shown in Figure 11.5 and Table 11.6). These cells migrate via blood vessels and lymphatics to the psoriatic dermis attracted by the keratinocyte-derived chemokines CCL20, CXCL9-11, CCL17, and CCL27 resulting in a chronic inflammation.

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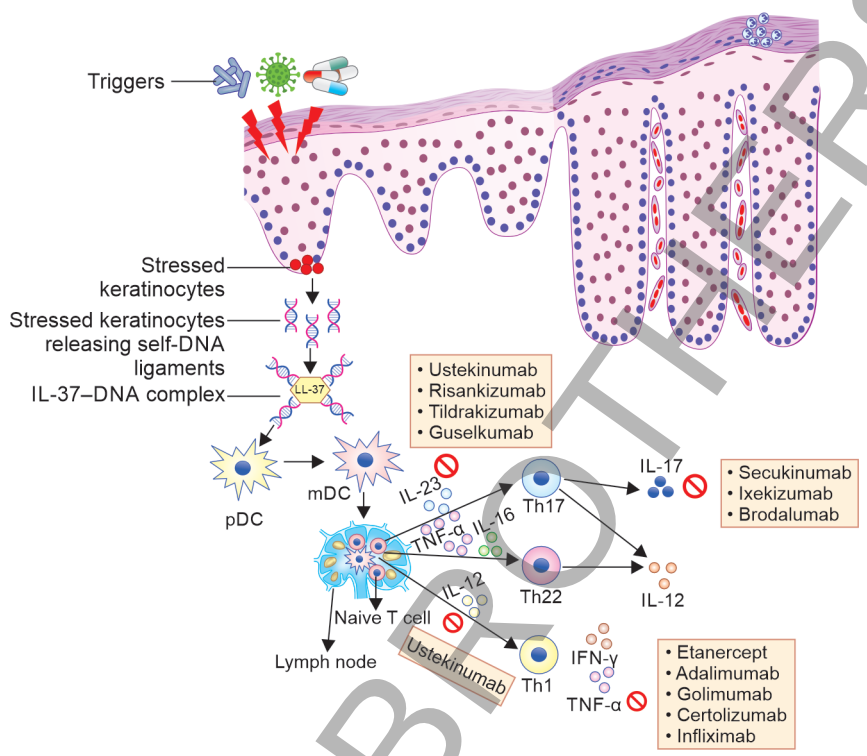

AMP, antimicrobial peptide; IFN-α, interferon-α; IL, interleukin; TNF-α, tumor necrosis factor-α.

Fig. 11.5: The pathogenesis of psoriasis along with the target of action of various biologics. The trigger causes the keratinocytes to release self-DNA and RNA that binds with the AMP cathelicidin (LL-37) to form a LL-37-DNA complex that stimulates plasmacytoid dendritic cells (pDC) which in turn produces IFN-α to recruit and activate myeloid dendritic cells. These myeloid dendritic cells (APC) along with the antigen reach the lymph node and present it to Naïve T-cells and release various proinflammatory cytokines such as IL-23, TNF-α, IL-16, and IL-12 which stimulate the naïve T-cells to differentiate into Th17, Th-22, and Th-1 cells that initiate and maintain the inflammatory cascade

INDICATIONS OF BIOLOGICS IN PSORIASIS[39]

- Patients having *moderate-to-severe psoriasis* defined by the following criteria:
  - PASI of ≥10%
  - BSA involvement of ≥10%
  - Dermatology life quality index (DLQI) of ≥10

  } *"Rule of 10"*

  Note: Sometimes certain special clinical situations might change the "mild psoriasis" to "moderate–severe psoriasis". For example, involvement of visible areas or severe nail involvement
- *Disease causing functional disability* or affecting day-to-day activities like severe palmoplantar psoriasis
- *Lack of efficacy: Severe disease persisting for ≥6 months with unsatisfactory clinical response* to common conventional therapeutic agents such as methotrexate, cyclosporine, acitretin, phototherapy (NBUVB/PUVA), and only short-term remission post cessation of therapy.

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TABLE 11.6: Pathomechanism of proinflammatory cytokines in psoriasis and therapeutic targets of biologics in psoriasis

Cytokine	Source	Role in psoriasis	Inhibitors
TNF-α	• Activated keratinocytes • Macrophages • Dermal fibroblasts • Langerhans cells • NK cells • Mast cells • Neurons • Smooth muscle cells	• The principal role of TNF is the regulation of immune cells, inflammation, cell proliferation, differentiation, apoptotic cell death, tumorigenesis, and viral replication in various types of cells • TNF cytokine signaling occurs through three major pathways ○ NF-kB pathway ○ MAPK pathway ○ DISC (death inducing signaling complex) via death domain • TNF-α causes keratinocyte hyperproliferation by producing proinflammatory cytokines such as IL-1, IL-6, and IL-8 that initiates and maintains inflammatory cascade • Promotes differentiation of T-cells to Th17 and Th22 cells to produce IL-17 (potent proinflammatory cytokine) • Accelerates production of adhesion molecules like ICAM-1, VCAM-1, E-selectin from endothelial cells • Causes induction of apoptosis	• *Etanercept* • *Adalimumab* • *Golimumab* • *Infliximab* • *Certolizumab*
IL-12	• Monocytes • PMNL • Dendritic cells	• It is a T cell stimulator factor that media • tes the conversion of naïve T cells to Th1 cells and activates it • It stimulates production of IFN-γ and TNF-α from the T cells	*Ustekinumab (IL-12/23)*
IL-17	• T-cells • NK cells • Neutrophils and eosinophils	It promotes production of proinflammatory cytokines such as IL-6, IL-1, TNF-, IL-β that promotes keratinocyte proliferation and neutrophil chemotaxis (Munro's microabscess)	• *Secukinumab* • *Ixekizumab* • *Brodalumab*
IL-22	• T-cells • Dendritic cells	Promotes keratinocyte proliferation and hinders its differentiation	
IL-23	• T-cells • Dendritic cells • Macrophages • B-cells • Endothelial cells	• It directs naive T-cells to differentiate into Th17 cells which produces proinflammatory cytokines such as IL-17 and IL-22 and IFN-γ • It binds to its IL-23 receptor and activates JAK-STAT pathway triggering inflammation	• *Ustekinumab (IL-12/23)* • *Risankizumab* • *Tildrakizumab* • *Guselkumab*
IFN-γ	• NK cells • T-helper cells • Cytotoxic T cells	Initiates, drives, and maintains inflammation making psoriasis a chronic inflammatory disease	

IL, interleukin; IFN, interferon; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor kappa B; TNF-α, tumor necrosis factor-α.

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"Unsatisfactory clinical response" or "therapeutic failure" is defined as <50% improvement from the baseline PASI or BSA or <5-point improvement in DLQI even after 3 months of treatment with adequate dose of conventional therapy as already discussed in Table 11.1.

- *Adverse drug reactions to common conventional therapy*
- *Presence of concomitant co-morbidities like PsA*
- *Absence of contraindications* to biologic therapy

TUMOR NECROSIS FACTOR-α INHIBITORS (TABLE 11.7)

Introduction

Tumor necrosis factor-α is a homotrimeric protein and an important proinflammatory cytokine involved in the pathogenesis of psoriasis and various autoimmune disorders such as rheumatoid arthritis, inflammatory bowel disease (IBD), etc.

- *Source*: Activated keratinocytes, macrophages, dermal fibroblasts, Langerhans cells, NK cells, mast cells, neurons, and smooth muscle cells

Types of Tumor Necrosis Factor-α[40,41]

- *Transmembrane (TmTNF) form*: This form is bound to the plasma membrane that is cleaved by TACE (TNF-α-converting enzyme) to the soluble form. Tm-TNF-α primarily binds to TNFR2 and promotes cell survival, proliferation, and regeneration.
- *Soluble form* (s-TNF-α)*:* This is the free form. It primarily binds to TNFR1 and regulates inflammation and apoptosis.

Receptors[40,41]

- *TNFR1(p55)*: This is expressed ubiquitously in most of the tissues and mediates inflammatory responses and apoptosis.
- *TNFR2(p75)*: This is mainly expressed on immune cells like T-regulatory cells and mediates cell survival, regeneration, and inflammation. There is downregulation of TNFR2 response in most of the autoimmune diseases.

Mechanism of Action of Tumor Necrosis Factor-α[42,43]

The transmembrane TNF (TmTNF) is cleaved by the TACE (TNF-α-converting enzyme) to soluble TNF-α. Though both of these forms bind to TNFR1 and TNFR2. Soluble form of TNF-α predominantly binds to the TNFR1 which activates the TRADD (death domain) and initiates inflammation and apoptosis via NF-kB, MAPK, Caspase-8, and MLKL. The transmembrane TNF-α predominantly binds with TNFR2 and activates TRAF-2 pathway and initiates AKT, NF-kB, and MAPK and predominantly engages in cell growth, proliferation, and regenerations effects. The mechanism of action of TNF-α is given in Figure 11.7.

The TNF-α inhibitors commonly used in psoriasis include:

- Etanercept
- Adalimumab
- Infliximab
- Certolizumab
- Golimumab

Contraindications of TNF-α Inhibitors

- Known *hypersensitivity reaction* to the drug (in case of allergy to *murine proteins*, AVOID infliximab)

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TABLE 11.7: TNF-α inhibitors in a nutshell

	Adalimumab (Humira)[54-56]	Infliximab (Remicade injection)	Certolizumab (Cimzia)	Golimumab (Simponi)	Etanercept (Enbrel)
Structure	Purely human IgG1 monoclonal Antibody	Chimeric monoclonal IgG1κ antibody with human (75%) and mouse (25%) components	Certolizumab is a PEGylated monoclonal antibody formed by the fusion of humanized Fab and 2 PEG units fused together	Fully human monoclonal IgG1κ antibody	Fully human dimeric fusion protein (p75 of TNF receptor is linked to Fc portion of IgG1)
Mechanism of action	It binds to both soluble and transmembrane TNF-α and neutralizes them	It binds to both soluble and transmembrane TNF-α and neutralizes them	It binds to both soluble and transmembrane TNF-α and neutralizes them	It binds to both soluble and transmembrane TNF-α and neutralizes them	Acts as a soluble TNF receptor fusion protein that binds TNF-α and lymphotoxin-α (TNF-β)
Indications					
FDA approved[57]	• Moderate-to-severe chronic plaque psoriasis • Psoriatic arthritis • Rheumatoid arthritis • Ankylosing spondylitis • Juvenile idiopathic arthritis • Ulcerative colitis • Crohn's disease	• Moderate-to-severe chronic plaque psoriasis • Psoriatic arthritis • Rheumatoid arthritis • Ankylosing spondylitis • Ulcerative colitis • Crohn's disease	• Moderate-to-severe psoriasis • Psoriatic arthritis • Rheumatoid arthritis • Ankylosing spondylitis • Crohn's disease	• Psoriatic arthritis • Rheumatoid arthritis • Ankylosing spondylitis • Ulcerative colitis • Juvenile idiopathic arthritis	• Moderate-to-severe psoriasis • Psoriatic arthritis • Rheumatoid arthritis • Ankylosing spondylitis • Juvenile idiopathic arthritis

Continued

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Continued

	Adalimumab (Humira)[54-56]	Infliximab (Remicade injection)	Certolizumab (Cimzia)	Golimumab (Simponi)	Etanercept (Enbrel)
Off label indications[58-64]	• Pyoderma gangrenosum • Behçet's disease • Pemphigus vulgaris • Sarcoidosis • Wegner's granulomatosis • Multicentric reticulohistiocytosis • Alopecia areata	• Uveitis • Behçet's disease • Hidradenitis suppurativa • Sjögren's syndrome • Sarcoidosis • Juvenile arthritis • Vasculitis • SLE	• Uveitis • Behçet's disease • Hidradenitis suppurativa • Sjögren's syndrome • Sarcoidosis • Juvenile idiopathic arthritis	• Nonradiographic axial spondyloarthritis • Behçet's disease • Hidradenitis suppurativa	• Behçet's disease • Hidradenitis suppurativa • Pyoderma gangrenosum • SAPHO syndrome • Juvenile idiopathic arthritis • Sjögren's syndrome
Pharmacokinetics					
Peak	1–2 weeks	By the end of infusion[65]	54–171 hours[66]	2–6 days[67]	48–60 hours[68]
Half life	~14 days	~9.5 days[69]	14 days[70]	~2 weeks[71]	4.8 days[68]
Bioavailability	64% post a single injection	100% after IV infusion	76–88% (~80%)[70]	51–53%[71]	58%[68]
Formulation	Adalimumab is available as prefilled syringe or Pen at a dose of: • 80 mg/0.8 mL (loading dose) • 40 mg/0.8 mL • 40 mg/0.4 mL • Pediatric—20 mg/0.4 mL (The method of administration of prefilled syringe is given in Figure 11.6)	Infliximab is available as 100 mg lyophilized powder which is to be reconstituted in 10 mL of sterile water and injected in 250 mL of 0.9% saline	Certolizumab is available as lyophilized powder that can be reconstituted with sterile water (1 mL of water per 200 mg vial) or Prefilled syringe: 200 mg/mL[72]	Golimumab is available in 50 mg/0.5 mL or 100 mg/mL in single-dose prefilled syringes or autoinjectors	25 mg lyophilized powder to be reconstituted in 1 mL of sterile water and 50 mg prefilled syringes

Continued

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Continued

	Adalimumab (Humira)[54-56]	Infliximab (Remicade injection)	Certolizumab (Cimzia)	Golimumab (Simponi)	Etanercept (Enbrel)
Route of administration	Subcutaneously	IV	Subcutaneous	Subcutaneous	Subcutaneous
Dose	It is administered at an initial dose of 80 mg SC followed by 40 mg after 1 week, and thereafter 40 mg every other week	It is administered in the dose of 3, 5, or 10 mg/kg, diluted in 250 mL of normal saline, by intravenous infusion over 2 hours, repeated at 2 and 6 weeks (the induction phase) Maintenance: 8 weeks (the maintenance phase)	400 mg (2 injection 200 mg each) at 0, 2, and 4 weeks followed by a maintenance of 400 mg every 4 weeks	The recommended dose is 50 mg subcutaneously once monthly.	It is started as 50 mg twice a week for 3 months followed by a maintenance dose of 50 mg/week
Storage[73]	2–8°C	2–8°C	2–8°C	2–8°C	2–8°C
ADR—given in Table 11.8					
Special situations					
Pregnancy category[74]	"B" Adalimumab, an IgG1 antibody *can cross the placenta* (maximum in 3rd trimester). It should be given only in *recalcitrant cases* after analyzing *the risk–benefit ratio*	"B"	*"B"—safest biologic*	"B"	"B"

Continued

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Continued

	Adalimumab (Humira)[54-56]	Infliximab (Remicade injection)	Certolizumab (Cimzia)	Golimumab (Simponi)	Etanercept (Enbrel)
Lactation[74]	• *Minimal amount* of adalimumab is secreted in breast milk • Due to large molecular size of adalimumab, it most likely gets destroyed and is not absorbed in the infant's GIT. However, there is paucity of clinical data. Hence, *usage with caution* is advised	May be used with caution	Probably safe	Probably safe	May be used with caution
Liver failure	No dose adjustment required	Caution advised	No dose adjustment required	No dose adjustment required	No dose adjustment required
Renal failure	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required	No dose adjustment required
Geriatric patients	No dose adjustment required	No dose adjustment required. But chances of adverse effects especially infections are greater compared to young adults[75]	No dose adjustment required	No dose adjustment required	No dose adjustment required

ADR, adverse drug reaction; GIT, gastrointestinal tract; TNF-α, tumor necrosis factor-α.

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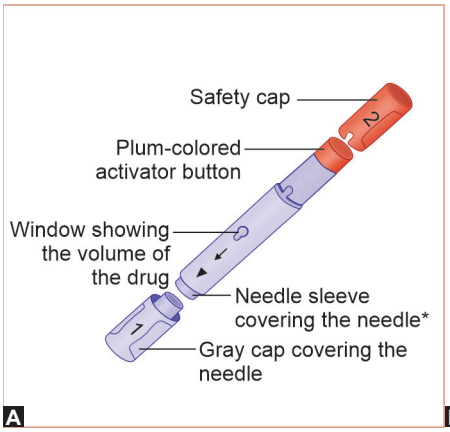

Steps for adalimumab injection:

1. Prepare the skin with alcohol swap and allow it to dry
2. Remove the gray cap (number 1 marked on it)*
3. Remove the plum cap (number 2 marked on it)+
4. Visualize the volume window
5. Hold the injection site between the index finger and thumb
6. Push the plum button after the gray end is in contact with the skin
7. Hear the click
8. Notice the window becoming yellow as it gets filled with the drug
9. Count 10 (wait for 10 seconds for the entire drug to be delivered → yellow color to empty and the fluid in the window has stopped moving)
10. Remove the pen (the needle sleeve would have covered the needle).
11. Dispose the pen in the special container provided

B

**Gray cap secures the needle*
+Plum cap secures the trigger

Figs. 11.6A and B: (A) The self-injectable pen of adalimumab and (B) the steps involved in the injection (B)[76]

TABLE 11.8: Adverse effects of TNF-α inhibitors

Infections	• *Common infections*: LRTI and URTI • Tuberculosis (active TB/reactivation of LTBI) • *Opportunistic infections*: Histoplasmosis, cryptococcosis, coccidioidomycosis, pneumocystis, *Pneumocystis jirovecii* pneumonia, aspergillosis, invasive fungal infections • HIV • Hepatitis B and C infection
Injection site reactions	Pain, pruritus, erythema, edema, and urticaria
Hypersensitivity reaction	• Urticaria • Drug rash • Rarely anaphylaxis/angioedema
Paradoxical psoriasis	Exacerbation of psoriasis in an already responsive patient
Drug-induced lupus	• They lack classical signs of lupus • Predominantly presents with fever, joint pain, and serositis
Exacerbation of demyelinating disorders	• Multiple sclerosis • Transverse myelitis • Optic neuritis • Guillain–Barré syndrome • Progressive multifocal leukoencephalopathy
MACE (major adverse cardiac events)	• New onset/worsening of cardiac failure • Arrythmias • MI

Continued

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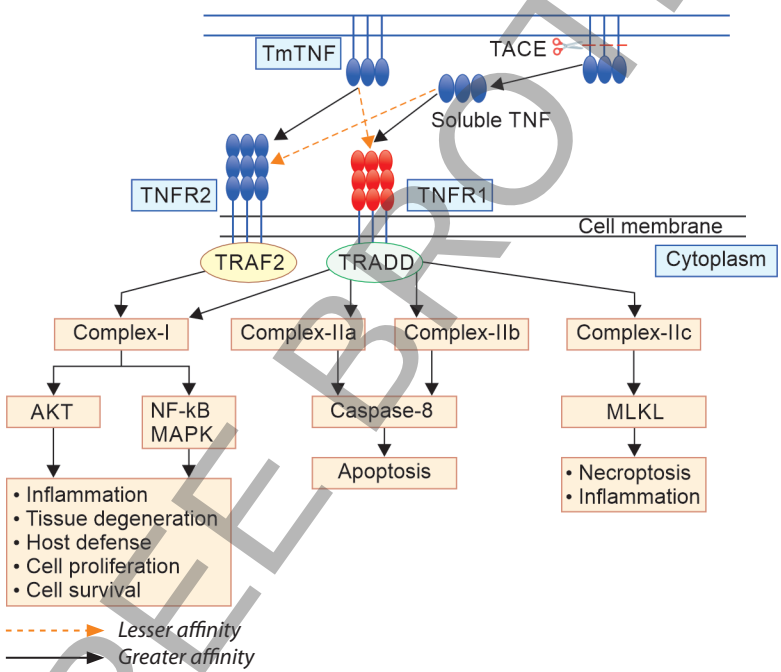
Continued

Increased risk of malignancy	• Nonmelanoma skin cancers • Melanoma • Lymphoma
Hematological adverse effects	• Neutropenia • Thrombocytopenia • Pancytopenia
Infusion reaction	Common with infliximab

LRTI, lower respiratory tract infection; LTBI, latent tuberculosis infection; MI, myocardial infarction; URTI, upper respiratory tract infection.



TmTNF, transmembrane TNF; TRADD, TNF receptor 1-associated death domain; NF-kB, nuclear factor-kappa B; TNFR: TNF-α receptor; TACE, TNF-α-converting enzyme; MAPK, mitogen activated protein kinases; MLKL, mixed lineage kinase domain like protein (necrosome).

Fig. 11.7: The mechanism of action of TNF-α

- *Active infections*
- *Tuberculosis*
- *Hepatitis-B*
- Concomitant administration with *anakinra*
- *Demyelinating disorders*, e.g., multiple sclerosis
- *Malignancies*
- *Congestive heart failure*
- Concomitant administration *with live vaccines* (Box 11.1)[44]

But if the vaccine is mandatory/planning to newly start a biologic:[44]

- It is recommended to complete all the live vaccines before starting biologic therapy.

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- Wait for at least 2–4 weeks to allow sufficient multiplication of viral particles and the development of adequate immunity in the body. The reason for this is that patients on biologics may not mount an adequate immune response to the vaccine.
- *Already on biologic*: *Stop the biologic for 2–3 half lives* before the administration of vaccine and then delay the subsequent dose by 2–4 weeks.

BOX 11.1: The common live vaccines

- Bacillus Calmette–Guérin (BCG)
- Cholera
- Varicella
- Herpes zoster (shingles)
- Influenza (including H1N1)
- Adenovirus
- MMR
- Rotavirus
- Polio (oral polio vaccine)
- Typhoid (*oral form)*
- Yellow fever

MMR, measles, mumps, and rubella.

Laboratory Monitoring of TNF-α Inhibitors

Preinitiation of therapy (baseline):

- Complete blood count (CBC) (to rule out anemia, neutropenia, and pancytopenia)
- Erythrocyte sedimentation rate (ESR)/ C-reactive protein (CRP)
- Liver function test (LFT)
- Tuberculin skin test (Table 11.9), IGRA, chest X-ray (to rule out active/latent tuberculosis) (LTBI—the monitoring of tuberculosis in patients on TNF-α inhibitors is given in Flowchart 11.1)
- HIV
- Hepatitis B surface antigen (HbsAg) (Table 11.10 shows the interpretation of test results of hepatitis B)
- Anti-HbsAg antibodies
- Anti-HbC
- Anti-HCV antibodies

TABLE 11.9: Tuberculin skin test/Mantoux test interpretation[48,49]

Risk factors	Positive reaction
• Close/recent contact with TB • Past history of TB (fibrotic changes in chest X-ray) • *Immunosuppression*: ○ HIV infection ○ Organ transplant patients ○ On immunosuppressant drugs	*TST ≥ 5 mm*
• Recent travel to endemic countries (<5 years) • Injectable drug abusers • Healthcare workers • People living in crowded areas like shelters, prisons, etc. • Patients with co-morbidities like diabetes, malignancy, etc. • Children <4 years of age	*TST ≥ 10 mm*
Healthy people with no risk factors	*TST ≥ 15 mm**

*Reactions >15 mm are unlikely to be due to previous BCG vaccination or exposure to environmental mycobacteria.
TST, tuberculin skin test.

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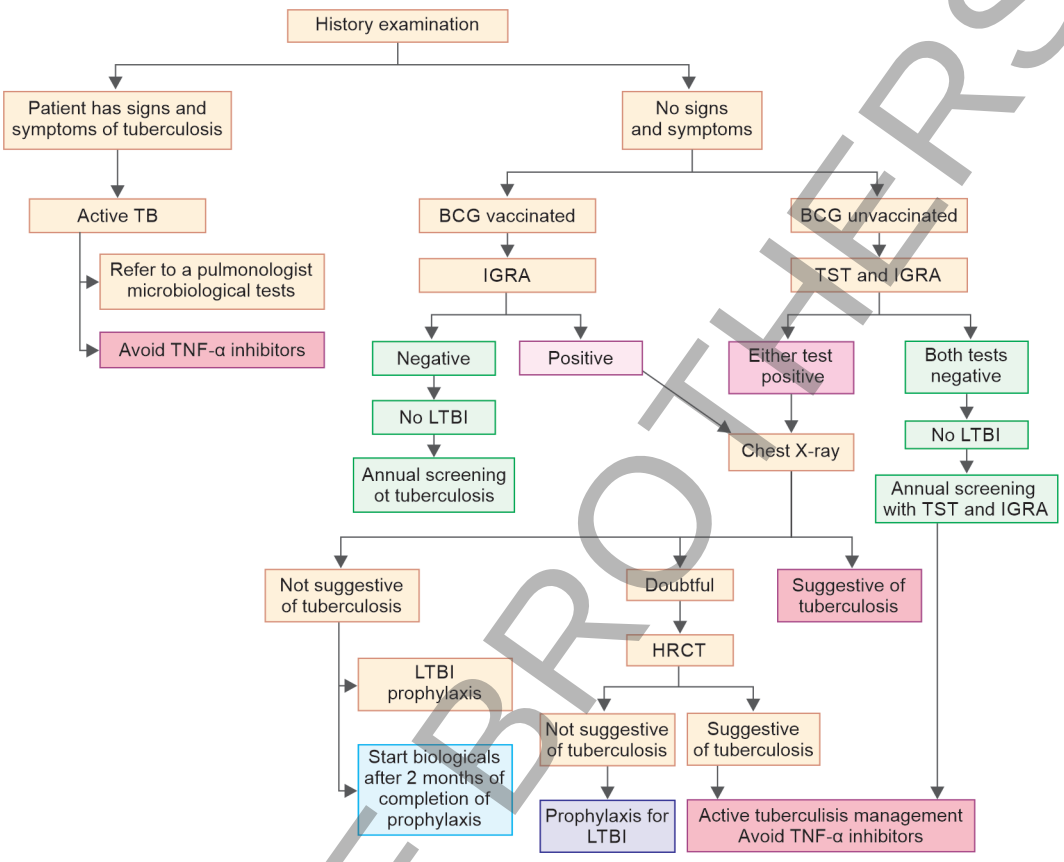

BCG, bacillus Calmette–Guérin; HRCT, high-resolution computed tomography; IGRA, interferon-gamma release assay; LTBI, latent tuberculosis infection; TNF-α, tumor necrosis factor-α; TST, tuberculin skin test.

Flowchart 11.1: Algorithm for screening and management of tuberculosis prior starting TNF-α inhibitors[45-47]

TABLE 11.10: The interpretation of test results of hepatitis B[51-53]

	HBsAg	Anti-HBsAb	Anti-HBcAb	IgM anti-HBcAb	Comments
Susceptible	–	–	–		Negative
Immune/natural infection	–	+	+		Can reactivate with immunosuppressive therapy (measure HBV DNA)
Immune/hepatitis B vaccine	–	+	–		
Acutely infected	+	–	+	+	Measure HBV DNA Treat with anti-viral agents—tenofovir, entecavir, telbivudine
Chronically infected	+	–	+	–	Management of hepatitis B
Resolved infection	–	–	+		Can reactivate with immunosuppressive therapy, measure HBV DNA

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- ECG/ECHO (TNF-α inhibitors are prone to cause MACE)
- Urinalysis
- Pregnancy test (though of the drugs belong to category B there are paucity of safety research data and can cross the placenta by 3rd trimester except certolizumab)
- Skin and lymph node examination to rule out malignancy

Laboratory monitoring during therapy:

- *CBC, LFT*—at *4 weeks, 12 weeks then every 3–6 months* (for infliximab, repeat these investigations at 2 weeks, 6 weeks, and before each infusion)
- Rule out serious infections like *tuberculosis, HIV, hepatitis B, and hepatitis C—annually*
- *ECG/ECHO* (to rule out *MACE* related to TNF-α inhibitors)—*annually*

Evaluation for Tuberculosis before Starting Biologics

- Thorough history and examination should be done in all the patients. If the patient has signs and symptoms *of active tuberculosis*, appropriate management for active tuberculosis should be initiated, and *TNF-α inhibitors should be deferred.*
- If there are no signs and symptoms of tuberculosis, do *TST* (tuberculin skin test, the interpretation of tuberculin skin test is given in Table 11.9) *and IGRA. If both are negative, then biologicals can be started.*
- *If either of these tests (TST or IGRA) turn out to be positive,* perform a chest X-ray. If it is suggestive of tuberculosis then undertake active management of tuberculosis and if it is not suggestive of tuberculosis, then *provide prophylaxis for LTBI* (as given in Table 11.11) and *start biologicals only after 2 months of prophylactic therapy.*
- The algorithm for evaluation of patients before starting biologic therapy is given in Flowchart 11.1.

Key Points

- Latent tuberculosis infection (LTBI)—The WHO defines LTBI as a state of persistent immune response to stimulation by

TABLE 11.11: CDC recommendation for prophylaxis latent tuberculosis infection (LTBI).[50]

Drugs	Duration (months)	Interval	Rating* (Evidence)†	
			HIV-	HIV*
Isoniazid	9	Daily	A (II)	A (II)
		Twice weekly	B (II)	B (II)
Isoniazid	6	Daily	B (I)	C (I)
		Twice weekly	B (II)	C (I)
Rifampin-pyrazinamide	2	Daily	B (II)	A (I)
	2–3	Twice weekly	C (II)	C (I)
Rifampin	4	Daily	B (II)	B (III)

*A—preferred; B—acceptable alternative; C—offer when A and B cannot be given.

†I—randomized clinical trial data; II—data from clinical trials that are not randomized or were conducted in other populations; III—expert opinion.

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M. tuberculosis antigens without evidence of clinically manifested active TB.
- Chest X-ray will more or less be *negative* in *LTBI* patients as the bacilli are not active to produce granulomas.
- If the patient is already on immunosuppressants, Mantoux test (TST) will not be valid hence go for IGRA to diagnose LTBI.
- *If the patient is on LTBI prophylaxis*: TNF-α can be started only after 2 months of completion of the prophylactic therapy.
- If the patient has a previous history of tuberculosis and has not completed the full course of DOTS → exclude the active tuberculosis (if active, start on ATT and complete full course). Initiate the prophylactic therapy for LTBI, wait for 2 months and then only start TNF-α inhibitors.
- If the patient has fibrotic or calcific lesions on chest X-ray, then further evaluation is required.

The adverse effects of TNF-α inhibitors and its management aspects are discussed in detail in the following section.

Infections

- These are one of the *most common ADR* of TNF-α inhibitors. Infections that might be encountered while on TNF-α inhibitors are given below:
  - *Common infections*:
    - Upper respiratory tract infections (URTI)
    - Lower respiratory tract infections (LRTI)
  - *Serious infections*:
    - Tuberculosis (active TB/reactivation of LTBI)
    - *Opportunistic infections*: Histoplasmosis, cryptococcosis, coccidioidomycosis, *Pneumocystis jirovecii* pneumonia, aspergillosis, and invasive fungal infections
    - HIV
    - Hepatitis B and C infection (risk of viral reaction is higher)
- *Avoid TNF-α inhibitors* in cases of chronic/severe infections and *concomitant TB, HIV, and hepatitis infections.*
- Most of the studies that demonstrate serious infections were predominantly reported in patients with rheumatoid arthritis or IBD who were concomitantly receiving additional immunosuppressants rather than in patients with psoriasis.
- In a review article by Erica D Dommasch et al., analyzing 20 randomized controlled trials involving 6,810 patients treated with TNF-α inhibitors, no significant increase in the risk of serious infections or malignancy was observed with short-term use.
- *Key points in case of infection during therapy:*
  - If the infection requires antibiotic therapy, *temporarily withhold TNF-α inhibitors*
  - If the infection is serious and opportunistic—*stop TNF-α inhibitors*
  - The risk of infection increases significantly in patients receiving:
    - Multiple immunosuppressants
    - Combination biologic therapy
  - The risk of infection is influenced, in part, by the elimination half-life of the biologic agent and the duration of functional immunosuppression following cessation of therapy. The half-lives and duration of immunosuppression post cessation of therapy are given in Table 11.12. The half-life also influences the washout period, recurrence and remission, and dosing schedule.

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TABLE 11.12: Half lives and suration of immunosuppresion post cessation of therapy of various biologics in psoriasis[77,78]

Target	Biologic	Half life	Duration of immunosuppression post cessation of therapy
TNF-α inhibitors	Adalimumab	14 days	3–6 months
	Infliximab	~9.5 days	3–6 months
	Certolizumab	14 days	3–6 months
	Golimumab	~2 weeks	3–6 months
	Etanercept	~4.8 days	1 month
IL-17 inhibitors	Secukinumab	27 days	6–12 months
	Ixekizumab	13 days	3–6 months
	Brodalumab	11 days	6–7 weeks (mean 46 days)*[32]
IL-12/IL-23 inhibitors	Ustekinumab	~21 days (15–32 days)	6–12 months
IL-23 inhibitors	Risankizumab	~28 days	4–5 months[79]
	Tildrakizumab	23.4 days	5–6 months[79]
	Guselkumab	15–18 days	3–4 months[80]

*Following discontinuation of brodalumab, high relapse rates are observed, with relatively rapid loss of clinical response. The reason for this is rapid waning off of immunosuppressive effect is attributed to the reversible and the IL-17 receptor A without depletion or durable suppression of active/pathogenic T-cells. Hence, there is rapid restoration of IL-17 pathway-mediated inflammatory signaling post cessation of drug.

Tuberculosis[81-84]

- TNF-α plays a central role in initiation and maintenance of granuloma formation in tuberculosis (a crucial step in maintaining the containment of infection). Reduced levels of TNF-α can cause inadequate activation of T-lymphocytes and macrophages leading to formation of disorganized granuloma and subsequent increased bacillary proliferation.
- The relative risk of acquiring tuberculosis post TNF-α therapy is increased by 25 times which is highest during the 1st year of anti-TNF-α therapy. This is most likely due to the reactivation of latent tuberculosis. Hence, screening is essential and important prior to initiation of therapy.
- Adalimumab and infliximab are associated with a greater risk of tuberculosis compared to etanercept and certolizumab.[81] Several studies have demonstrated that tuberculosis develops earlier following infliximab therapy compared with etanercept. This difference is attributed to variations in the pharmacologic and structural characteristics of TNF-α inhibitors. Their propensity to cause tuberculosis varies as shown below:
  - *Etanercept*:[85,86]
    - Binds to both s-TNF and tm-TNF at a ratio of 1:1
    - Its affinity for TNFR2 is greater than TNFR1 as this is formed by the fusion of p75 or TNFR2 with the Fc portion of monoclonal antibody.
    - Etanercept has lower affinity to tm-TNF compared to adalimumab and infliximab.

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