RAULOCYTE–MACROPHAGE AND GRANULOCYTE COLONY-STIMULATING FACTORS (GM-CSF AND G-CSF)

GRANULOCYTE–MACROPHAGE AND GRANULOCYTE COLONY-STIMULATING FACTORS (GM-CSF & G-CSF)
Properties
These glycoproteins regulate the survival, proliferation, differentiation and functional activation of hematopoietic cells
Uses
• Treatment of neutropenia in settings of myelosuppressive chemotherapy and hematopoietic stem cell transplantation • Other forms of neutropenia (e.g. AIDS-related, in WHIM syndrome, associated with dyskeratosis congenita) • Mobilization of peripheral blood progenitor cells • In dermatology, both have been studied as promoters of wound healing, and GM-CSF has been investigated as a component of melanoma vaccine therapy
Side effects
GM-CSF
• ***Systemic:*** fever, myalgias, bone pain; occasionally flares of autoimmune disease • ***Cutaneous:*** morbilliform eruption (within 24–48 hours of administration; mixed infiltrate with granulocytes/macrophages); pustular or urticarial injection site reactions (Fig. 128.3); Sweet syndrome, small vessel vasculitis, urticarial plaques with tense bullae, epidermolysis bullosa acquisita
G-CSF
• ***Systemic:*** bone pain (transient, mild "dull ache"; 20% of recipients); occasionally, elevated serum uric acid, LDH or alkaline phosphatase • ***Cutaneous:*** Sweet syndrome (within 1–2 weeks of administration); injection site reactions, pyoderma gangrenosum, small vessel vasculitis, folliculitis; histologically, the infiltrate is composed of neutrophils, eosinophils and large histiocytes with cytologic atypia and many mitotic figures
Interactions
Additive effects with other drugs that cause neutrophilia, e.g. corticosteroids, lithium
Pregnancy and lactation
Category C; unknown if excreted in breast milk

Table 128.4 Granulocyte–macrophage and granulocyte colony stimulating factors (GM-CSF & G-CSF). LDH, lactate dehydrogenase; WHIM, warts, hypogammaglobulinemia, infections, and myelokathexis.

he indcations and side effects of granulocyte–macrophage and granulocyte colony-stimulating factors (GM-CSF and G-CSF) are outlined in Table 128.4.

TARGETED IMMUNE MODULATORS

Key features

- Tumor necrosis factor (TNF) inhibitors such as etanercept, adalimumab, and infliximab can be effective treatments for psoriasis, psoriatic arthritis, hidradenitis suppurativa, and other dermatoses in which TNF signaling has a pathogenic role
- Interleukin (IL)-12 and IL-23 signaling is important for the Th17 immune response; ustekinumab binds to the p40 receptor subunit shared by these cytokines and is approved for the treatment of psoriasis and psoriatic arthritis
- The IL-17 inhibitors secukinumab, ixekizumab, and brodalumab are approved for the treatment of psoriasis and (for secukinumab) psoriatic arthritis
- Dupilumab blocks IL-4 and IL-13 signaling and is approved for the treatment of atopic dermatitis
- The IL-1 antagonists anakinra, canakinumab, and rilonacept are used to treat several autoinflammatory diseases, including cryopyrin-associated periodic syndromes and deficiency of the IL-1 receptor antagonist (DIRA)
- Rituximab, an agent that blocks CD20 on B cells, is approved for the treatment of B-cell lymphoma, granulomatosis with polyangiitis, and microscopic polyangiitis; it is also useful in other B-cell-mediated skin diseases such as pemphigus vulgaris
- Omalizumab binds to the IgE receptor on mast cells and is approved for the treatment of chronic urticaria
- Janus kinase (JAK) inhibitors such as tofacitinib and ruxolitinib have efficacy in the treatment of dermatologic conditions including psoriasis and alopecia areata

Introduction

Advances in molecular technology have enabled the development of drugs that target specific proteins involved in disease pathogenesis. This has resulted in effective therapies for a variety of immune-mediated skin disorders, including psoriasis, atopic dermatitis, hidradenitis suppurativa, pemphigus vulgaris, urticaria, and cutaneous B-cell lymphomas as well as the cutaneous manifestations of systemic conditions such as Crohn disease, sarcoidosis, and vasculitis. These drugs, which are referred to as "biologic" agents, work via mechanisms that include altering T-cell activation and differentiation into Th1, Th2, or Th17 cells; blocking cytokines, their receptors, or their intracellular signaling mechanisms; and eliminating pathogenic B cells.

Tumor Necrosis Factor Inhibitors

The FDA has approved multiple tumor necrosis factor (TNF; previously known as TNF-α) inhibitors: etanercept (Enbrel®), etanercept-szzs (Erelzi™), infliximab (Remicade®), infliximab-dyyb (Inflectra®), adalimumab (Humira®), adalimumab-atto (Amjevita®), golimumab

(Simponi®), and certolizumab pegol (Cimzia®). A review of their mechanisms of action, major side effects, and contraindications is followed by a discussion of issues that relate specifically to individual drugs.

Mechanism of action

Infliximab, adalimumab, golimumab, and certolizumab pegol are monoclonal antibodies, while etanercept is a dimeric fusion protein composed of the extracellular portions of two p75 TNF receptors linked to the Fc portion of IgG1 (Fig. 128.4). Although all four monoclonal antibodies target human TNF, infliximab is chimeric (human–mouse) IgG1, adalimumab and golimumab are human recombinant IgG1, and certolizumab pegol is a humanized pegylated Fab fragment (see Table 128.5).

All of the TNF inhibitors can bind to soluble TNF and block its ability to activate TNF receptors (see Fig. 128.4). By interacting with membrane-bound TNF, the IgG1 monoclonal antibodies can also activate complement-dependent cytotoxicity and induce cellular apoptosis[12]. This capacity to destroy TNF-producing cells may explain the greater efficacy of these monoclonal antibodies compared to etanercept in the treatment of granulomatous conditions as well as the potentially higher risk of infections associated with their use. In addition to the anti-inflammatory effects of TNF inhibitors, blocking TNF signaling may have an impact on the neuroendocrine system[13].

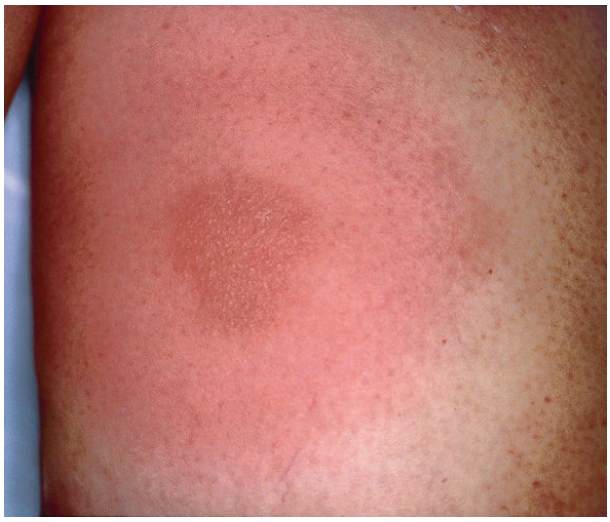


Fig. 128.3 Erythematous edematous plaque at the site of GM-CSF injection.

Contraindications

Each TNF inhibitor is contraindicated in patients with known hypersensitivity to that particular medication, and infliximab is contraindicated in those with an allergy to murine proteins. These agents should be avoided in patients with a significant active infection, malignancy, congestive heart failure (especially if unstable), or multiple sclerosis[14,15].

Major side effects (Table 128.6)

Infections

Disseminated and/or opportunistic infections such as histoplasmosis, coccidioidomycosis, listeriosis, and *Pneumocystis jiroveci* pneumonia may occur in patients treated with TNF inhibitors[16]. An increased risk of symptomatic mycobacterial infections (Fig. 128.5), including reactivation of latent tuberculosis, has also been observed in patients treated with these agents. However, most of the studies evaluating the risk of infection associated with the use of TNF inhibitors have been in patients with rheumatoid arthritis or inflammatory bowel disease, who often concomitantly receive additional immunosuppressive agents. A meta-analysis of 20 randomized controlled trials (total n=6810) of TNF inhibitor therapy for psoriasis or psoriatic arthritis over periods of 12–30 weeks found no association between the use of these agents and the risk of infection (overall or serious) when adjusted for different follow-up times in treatment and control groups[17].

Recommended monitoring for dermatologic patients receiving TNF inhibitors is outlined in Table 128.7. A purified protein derivative (PPD) skin test, IFN-γ release assay (e.g. QuantiFERON® TB Gold, T-SPOT®.TB), and/or chest X-ray (e.g. if immunosuppression or history of tuberculosis) is required at baseline and (typically) repeated annually during therapy. Patients with untreated latent tuberculosis should receive antituberculous therapy prior to treatment with a TNF inhibitor. Reactivation of hepatitis B virus has also been observed in patients who are chronic hepatitis B carriers (i.e. hepatitis B surface antigen positive) while receiving a TNF inhibitor, so patients should be evaluated for hepatitis B virus infection prior to therapy (Table 128.8). TNF inhibitors do not generally appear to have an adverse effect on viral load or hepatitis activity in psoriasis patients with chronic hepatitis C virus infection[18].

Risk of malignancy

The potential of TNF inhibitors to increase the risk of malignancy is controversial and may be dependent upon the disease that is being treated. TNF inhibitor therapy in patients with rheumatoid arthritis has been associated with an approximately threefold increase in the risk of lymphoma and malignancy in general[19,20], but this patient group is known to have a heightened susceptibility to lymphoma and often

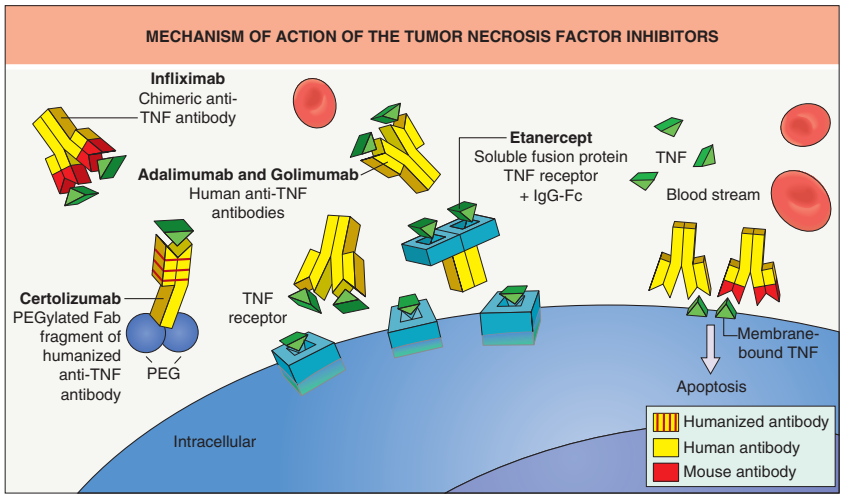


Fig. 128.4 Mechanism of action of the tumor necrosis factor (TNF) inhibitors.

NOMENCLATURE FOR MONOCLONAL ANTIBODIES AND FUSION PROTEINS						
Prefix	**Sub-stem A: *target* system [previous nomenclature system]**		**Sub-stem B: *source* system**		**Suffix**	
Variable "Peg-" can be used if pegylated (or can add pegol as a second word)	-anibi-	Angiogenesis	-a-	Rat	-mab	Immunoglobulin variable domain
	-b(a)- [-ba(c)-]	Bacterial	-e-	Hamster		
	-f(u)- [-fung-]	Fungal	-i-	Primate	-cept	Receptor (takes the place of a variable domain)
	-k(i)- [-ki(n)-]	Interleukin	-o-	Mouse		
	-l(i)- [-li(m)-]	Immunomodulating	-u-	Human	-nib	Tyrosine kinase inhibitor
	-n(e)- [-ne(u)(r)-]	Nervous system	-xi-	Chimeric†		
	-tox(a)-	Toxin*	-zu-	Humanized‡		
	-t(u)-	Tumor				
	-v(i)-	Viral				

*If conjugated to (rather than directed at) a toxin, the suffix -tox can be used in a second word.
†Contains contiguous *foreign*-derived amino acids comprising the *entire variable* region (both heavy and light chains), linked to a constant region of human origin.
‡Has segments of foreign-derived amino acids *interspersed* with human-derived amino acids in the *variable* region, linked to a constant region of human origin.

Table 128.5 Nomenclature for monoclonal antibodies and fusion proteins. For example, ada-lim-u-mab, inf-li-xi-mab and certo-li-zu-mab pegol are immunomodulating immunoglobulins that are human, chimeric and humanized, respectively.

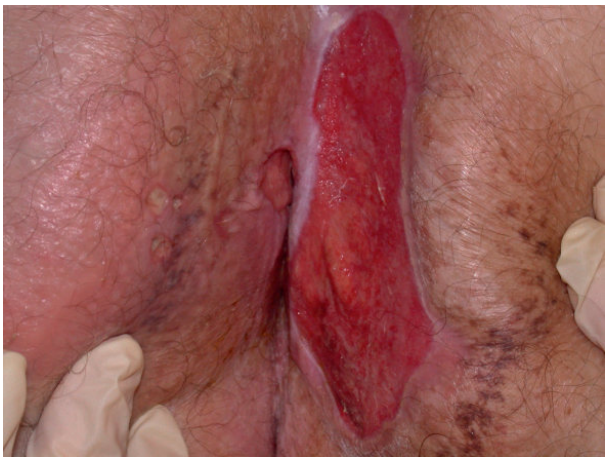


Fig. 128.5 Atypical mycobacterial infection complicating adalimumab therapy. This patient was being treated for Crohn

receives additional immunosuppressive agents. Most studies have not demonstrated an increase in the risk of other internal malignancies in patients treated with TNF inhibitors[21]. However, in one study there appeared to be an increased risk of solid malignancies associated with etanercept therapy for granulomatosis with polyangiitis[22]. In addition, non-melanoma skin cancers and melanoma may be more frequent in patients with rheumatoid arthritis who are treated with TNF inhibitors than those who do not receive these agents[23]. A meta-analysis of 20 randomized controlled trials (total n=6810) of TNF inhibitor therapy for psoriasis or psoriatic arthritis over periods of 12–30 weeks found no significant association between the use of these agents and the development of malignancy[24].

Adolescents and young adults with inflammatory bowel disease who receive infliximab and concomitant azathioprine or 6-mercaptopurine appear to have an increased risk of a rare, aggressive hepatosplenic T-cell lymphoma. In an analysis of 48 malignancies in children and adolescents treated with TNF inhibitors that were reported to the FDA[25], it was noted that half were lymphomas, almost two-thirds were in patients taking infliximab, and 88% of the patients were concomitantly receiving another immunosuppressive agent. Although the incidence of malignancy was higher than the background rate in the general pediatric population, the potential role of other medications as well as the underlying disorders, primarily inflammatory bowel disease and juvenile idiopathic arthritis (JIA), precluded establishing a causal relationship with TNF inhibitor therapy.

Autoimmunity

Treatment with TNF inhibitors is associated with an increased likelihood of developing antinuclear and anti-dsDNA antibodies. Signs and symptoms of cutaneous and systemic lupus erythematosus (SLE) occasionally arise in patients receiving TNF inhibitors, but in general these manifestations resolve upon cessation of treatment[26–28]. Conversely, several small case series have reported marked improvement of subacute cutaneous lupus erythematosus by etanercept[29,30] (Fig. 128.6). It is not necessary to evaluate patients for autoantibodies before or during therapy with TNF inhibitors. However, the development of antinuclear antibodies may be linked to loss of TNF inhibitor efficacy[31].

Demyelinating diseases

Although etanercept was originally utilized as a therapy for multiple sclerosis, new onset or exacerbation of multiple sclerosis or other demyelinating diseases represents is a potential complication of TNF inhibitor treatment[14]. In some patients, the symptoms of multiple sclerosis have abated despite continued therapy. It seems reasonable to avoid using TNF inhibitors in patients with a history of multiple sclerosis or other demyelinating diseases.

Congestive heart failure

There have been reports of congestive heart failure worsening or developing in patients receiving TNF inhibitors. As a result, it is recommended that therapy with TNF inhibitors be avoided in patients with unstable cardiac disease.

Cutaneous reactions

A variety of adverse skin reactions to TNF inhibitors have been described (Table 128.9). There are reports of new-onset psoriasis in patients with no previous history of psoriasis, often manifesting as palmoplantar pustulosis (Fig. 128.7)[32]. The exact mechanism for this reaction is not known, and it is possible that some patients with presumed rheumatoid arthritis actually had psoriatic arthritis. Cutaneous small vessel vasculitis and interstitial granulomatous dermatitis (IGD) can also develop in patients undergoing TNF inhibitor therapy[33], but a subset of these patients have rheumatoid arthritis, which itself can be associated with vasculitis and IGD[34]. Additional cutaneous reactions that have been described in patients receiving TNF inhibitors include eczematous eruptions, lichenoid dermatitis, and other granulomatous conditions[35].

Vaccination

Live vaccines are contraindicated in patients receiving TNF inhibitors (Table 128.10). The effectiveness of vaccines in patients receiving these

FDA WARNINGS AND PRECAUTIONS FOR TARGETED IMMUNE MODULATORS WITH DERMATOLOGIC INDICATIONS
TNF inhibitors: adalimumab, certolizumab, etanercept, golimumab, infliximab
• Increased risk of serious infections, including tuberculosis, bacterial sepsis, systemic fungal infections (e.g. histoplasmosis), and infections due to opportunistic pathogens • Risk of hepatitis B virus reactivation • Malignancies (especially lymphomas) have been reported in patients receiving these agents, including children and adolescents - For *infliximab*, lymphomas are seen more often than in the general population and fatal hepatosplenic T-cell lymphomas have developed in patients with inflammatory bowel disease who were also receiving azathioprine or 6-mercaptopurine - An increased risk of non-melanoma skin cancer and melanoma has been observed in patients with rheumatoid arthritis treated with TNF inhibitors • Congestive heart failure (exacerbation or new onset) has been observed • Demyelinating disease (exacerbation or new onset) has been observed • Anaphylaxis or severe allergic reactions can occur, including serum sickness-like reactions to *infliximab* • Other potential adverse events include autoimmune hepatitis, cytopenias, and a lupus-like syndrome; see Table 128.9 for additional cutaneous side effects
Ustekinumab
• Serious infections have been observed; may increase the risk of infection and reactivation of latent infections - Patients genetically deficient in IL-12/IL-23 have an increased risk of severe infections with mycobacteria and *Salmonella* - BCG vaccination should not be given in the year prior to initiation or the year following completion of ustekinumab therapy • Could potentially increase the risk of malignancies • Hypersensitivity reactions (e.g. angioedema, anaphylaxis) can occur • Reversible posterior leukoencephalopathy syndrome has been reported
IL-17 inhibitors: ixekizumab, secukinumab, brodalumab
• Serious infections have been observed; may increase the risk of infection and reactivation of latent infections - Patients genetically deficient in IL-17 are prone to chronic mucocutaneous candidiasis • New onset and exacerbation of inflammatory bowel disease have occurred • Hypersensitivity reactions (e.g. angioedema, anaphylaxis) can develop • For *brodalumab*: suicidal ideation and behavior, including complete suicides, have occurred
Dupilumab
• Hypersensitivity reactions can occur • Conjunctivitis and keratitis may develop
IL-1 inhibitors: anakinra, canakinumab, rilonacept
• Increased risk of serious infections • Coadministration with TNF inhibitors is not recommended • Hypersensitivity reactions (e.g. angioedema, anaphylaxis) can develop
Rituximab
• Severe infusion reactions can occur - 80% of fatal reactions occur with the first infusion • Tumor lysis syndrome can develop in lymphoma patients, especially those with a high tumor burden, and lead to acute renal failure • Progressive multifocal leukoencephalopathy has been reported • Serious infections (bacterial, fungal, or viral) up to 1 year after completing therapy and reactivation of viral infections may occur, especially hepatitis B virus reactivation with fulminant hepatitis • Cardiac arrhythmias and angina can occur and may be life-threatening. • Bowel obstruction and perforation have been described • Stevens–Johnson syndrome/toxic epidermal necrolysis and onset of paraneoplastic pemphigus have been described
Omalizumab
• Administer only in a healthcare setting prepared to manage anaphylaxis, which can be life-threatening, and observe patients for an appropriate period after administration • Patients can develop serum sickness-like reactions with fever, arthralgias, and an urticarial eruption • Malignancies have been observed in clinical studies of asthma patients, although a recent meta-analysis did not find an increased risk of malignancy • Do not abruptly discontinue corticosteroids upon initiation of omalizumab therapy

Table 128.6 US Food and Drug Administration (FDA) warnings and precautions for targeted immune modulators with dermatologic indications. Live vaccines (see Table 128.10) should not be given to patients receiving these medications. BCG, bacillus Calmette–Guérin; IL, interleukin; LE, lupus erythematosus; TNF, tumor necrosis factor.

agents is unknown, but an immune response to influenza and pneumococcal vaccines has been documented[36]. It is recommended that patients (especially children) be brought up-to-date with all immunizations prior to initiating treatment with TNF inhibitors.

Etanercept

Introduction

Etanercept (Enbrel®) and etanercept-szzs (Erelzi™) are fusion proteins consisting of the extracellular domain of the TNF receptor fused with the Fc portion of human IgG1[37].

Indications

Etanercept has been approved for the treatment of moderate to severe plaque-type psoriasis in adults since 2004 and in children ages 4–17 years since 2016. Depending on the regimen (see below), ~30–60% of patients achieve a 75% improvement in their Psoriasis Area and Severity Index (PASI) score; significant decreases in fatigue and depression have also been described[38,39]. Other approved indications for etanercept include rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis in adults as well as JIA in children ≥2 years of age.

Etanercept has been used to treat a variety of other mucocutaneous disorders, including dermatomyositis, cutaneous lupus erythematosus, lichen planus, autoimmune bullous diseases (especially mucous membrane [cicatricial] pemphigoid), neutrophilic dermatoses (including pyoderma gangrenosum), hidradenitis suppurativa, multicentric reticulohistiocytosis, relapsing polychondritis, toxic epidermal necrolysis, and GVHD[29,40,41]. Although successful treatment of sarcoidosis has been described in case reports and small series, etanercept therapy

RECOMMENDED EVALUATION FOR PATIENTS RECEIVING TARGETED IMMUNE MODULATORS FOR DERMATOLOGIC DISORDERS

Baseline history and physical examination

- Complete medical history, including prior/current medications, vaccinations*, and allergies
- Complete physical examination
- Pay particular attention to history, risk, symptoms, and signs of:
  - Tuberculosis and other chronic as well as acute infections
  - Malignancy
  - Neurologic disorders
  - For *TNF inhibitors*: congestive heart failure
  - For *ustekinumab*: atherosclerosis
  - For *rituximab*: arrhythmias
  - For *brodalumab*: depression, suicidal ideation/behavior
  - For *IL-17 inhibitors*: inflammatory bowel disease
  - For *rituximab* and *tofacitinib*: risk factors for intestinal perforation (e.g. diverticulitis)

Laboratory testing

Prior to treatment	*During treatment*
• PPD**/interferon-γ release assay† and/or (e.g. if immunosuppression or history of tuberculosis) chest X-ray • CBC and CMP • Hepatitis B and C virus serologic profiles • Consider HIV testing • For *tofacitinib/other JAK inhibitors*: also lipid profile	• Annual PPD**/interferon-γ release assay† and/or chest X-ray • CBC and CMP every 3–12 months, or as noted below or clinically indicated - For *anakinra*: CBC monthly for 3 months and then every three months - For *tofacitinib/other JAK inhibitors*: CBC, CMP, and lipid profile within 1–2 months and then every 3 months

*Recommended vaccines should be administered prior to initiation of therapy, with live vaccines (see Table 128.10) given at least 2–4 weeks prior to starting the medication; the bacillus Calmette–Guérin (BCG) vaccine should not be given in the year prior to beginning or the year after completing ustekinumab therapy.
**≥5 mm of induration should be considered as positive.
†e.g. QuantiFERON® TB Gold or T-SPOT®.TB.

Table 128.7 Recommended evaluation for patients receiving targeted immune modulators for dermatologic disorders. CBC, complete blood count with differential, CMP, comprehensive metabolic panel (includes liver function tests); IL, interleukin; JAK, Janus kinase; PPD, purified protein derivative skin test; TNF, tumor necrosis factor.

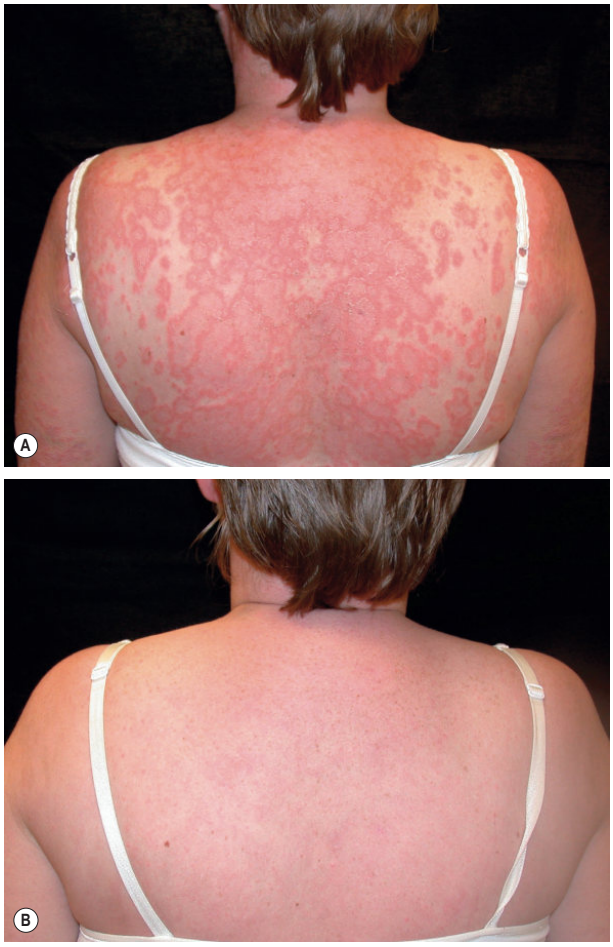


Fig. 128.6 Excellent clinical response to etanercept. Subacute cutaneous lupus erythematosus, before (**A**) and after (**B**) administration of etanercept.

failed to improve systemic manifestations of sarcoidosis in randomized controlled trials[42]. Presumably, all of the disorders for which etanercept is effective are characterized by elevated levels of TNF in the circulation and/or affected tissues.

Dosages

For most of its indications, etanercept was initially approved to be administered subcutaneously at a dose of 25 mg twice weekly in adults. Shortly after its approval for psoriatic arthritis, it was demonstrated that 50 mg weekly gave equivalent results to 25 mg twice weekly. The approved dose for moderate to severe plaque psoriasis is 50 mg twice weekly for the first 3 months, followed by 50 mg weekly. Some physicians choose to initiate therapy at a dose of 50 mg weekly and only escalate the dose if the patient fails to respond after 6 to 12 months. Etanercept is available in 25 and 50 mg prefilled syringes, 50 mg autoinjectors, and 25 mg multiple-use vials. The recommended dose for pediatric psoriasis is 0.8 mg/kg (maximum 50 mg) weekly.

Specific side effects

Side effects shared with other TNF inhibitors are discussed above and summarized in Tables 128.6 and 128.9. Injection site reactions are the most common side effect of etanercept (Fig. 128.8) but in general are mild to moderate and diminish in frequency after the first month of treatment. Erythema, pruritus, pain, and swelling have been described, and "recall" reactions at sites of previous injections have been reported. These reactions do not progress to anaphylaxis.

Interactions

The concomitant use of etanercept and methotrexate is approved for the treatment of rheumatoid arthritis and psoriatic arthritis. Due to the potential for increased immunosuppression, combination of etanercept with other targeted immune modulators should generally be avoided. A study of anakinra plus etanercept for patients with rheumatoid arthritis found no increase in efficacy but a substantial increase in the frequency of infection[43]. Etanercept has been used together with narrowband UVB without an increase in adverse events and with added therapeutic benefit[44,45].

Use in pregnancy

Etanercept is pregnancy category B, with no evidence of harm to the fetus in animal studies. Studies in pregnant women have not been conducted. It has been suggested that etanercept and other TNF inhibitors be avoided after the first trimester[46]. It is not known whether etanercept is secreted in breast milk; however, in general, this drug is not absorbed via an oral route.

Infliximab

Introduction

Infliximab (Remicade®), infliximab-dyyb (Inflectra®), and infliximab-abda (Renflexis®) are chimeric human–mouse monoclonal IgG1 antibodies, and their target is human TNF[47].

INTERPRETATION OF HEPATITIS B AND C SEROLOGIC TEST RESULTS					
Hepatitis B (HBV)					
	HBsAg	*Anti-HBs Ab**	*Anti-HBc Ab**	*IgM Anti-HBc Ab*	*Comments*
Susceptible	–	–	–		
Immune/natural infection	–	+	+		Can reactivate with immunosuppressive therapy^; consider serial measurement of HBV DNA
Immune/Hep B vaccine	–	+	–		
Acutely infected	+	–	+	+	Measure HBV DNA; treat with antiviral agent (e.g. tenofovir, entecavir, telbivudine) prior to immunosuppressive therapy
Chronically infected	+	–	+	–	See Acutely infected
Resolved infection > false-positive anti-HBc Ab, "low level" chronic infection, resolving acute infection	–	–	+		With exception of false-positive anti-HBc Ab, can reactivate with immunosuppressive therapy^; measure HBV DNA
Hepatitis C (HCV)					
	*Anti-HCV Ab***		*HCV RNA*		*Comments*
Current HCV infection	+		detected		Treat with antiviral agents (e.g. sofosbuvir + ledipasvir)
No current HCV infection	+		–		Can reactivate with immunosuppressive therapy^^; consider serial measurement of HCV RNA

*IgG Ab.
**If anti-HCV Ab present, then presumptive HCV infection (current or past that has resolved) and need to test for HCV RNA.
^Includes TNF inhibitors, rituximab, chemotherapy.
^^Includes rituximab, chemotherapy; TNF inhibitors have been used safely.

Table 128.8 Interpretation of hepatitis B and C serologic test results. Shading emphasizes need to treat prior to instituting immunosuppressive therapy.
Courtesy, Jean L Bolognia, MD.

Indications
Infliximab is approved for the treatment of adults with chronic severe plaque-type psoriasis. Compared with the other TNF inhibitors, its onset of action tends to be faster and a higher proportion of patients (~75–85%) achieve a 75% reduction in the PASI score[48]. Infliximab is also approved for the treatment of adults with psoriatic arthritis, Crohn disease (including associated fistulas), ulcerative colitis, rheumatoid arthritis and ankylosing spondylitis, as well as children ≥6 years of age with Crohn disease and ulcerative colitis. Infliximab appears to be useful for pyoderma gangrenosum, whether or not it is associated with inflammatory bowel disease[49]. It has been effective as a treatment for sarcoidosis, granulomatous cheilitis, Behçet disease, various vasculitides, pityriasis rubra pilaris, reactive arthritis, subcorneal pustular dermatosis, GVHD, Sjögren syndrome, multicentric reticulohistiocytosis, and hidradenitis suppurativa[50].

Dosages
In patients with plaque psoriasis, the typical infliximab regimen is 5 mg/kg administered by slow intravenous infusion at 0, 2 and 6 weeks, and then every 8 weeks. However, doses ranging from 3 to 10 mg/kg have been utilized, and the frequency of administration as well as the dose can be adjusted when the response is inadequate. For Crohn disease, rheumatoid arthritis, and psoriatic arthritis, it is approved for concomitant administration with methotrexate, azathioprine, or low-dose prednisone. Loss of efficacy over time may be related to the development of neutralizing anti-chimeric antibodies and has been associated with the presence of antinuclear antibodies[51,52]; the concurrent administration of low-dose weekly methotrexate may help to prevent the formation of anti-chimeric antibodies.

Specific side effects
Side effects shared with other TNF inhibitors are discussed above and summarized in Tables 128.6 and 128.9. Infusion-related reactions are the most commonly reported side effect of infliximab, occurring in ~15% of patients. The incidence of severe reactions, in particular anaphylaxis, is ~1%. Associated symptoms include fever, chills, pruritus, urticaria, chest pain, hypotension, hypertension, and shortness of breath. Infusion reaction risk has been linked to the presence of human anti-chimeric antibodies. Risk of reactions may be lessened by a slower infusion rate or concomitant use of methotrexate, azathioprine, or corticosteroids.

Interactions
Infliximab should not be administered together with other targeted immune modulators due to the potential for additive immunosuppression; concomitant use with anakinra or abatacept has been associated with the development of severe infections.

Use in pregnancy
Infliximab is rated pregnancy category B. However, because it crosses the placenta and can lead to an increased risk of infection in the infant, use in pregnancy should be avoided unless the benefits outweigh the risks. It is not known whether infliximab is secreted in breast milk, and its administration to nursing mothers is not recommended.

Adalimumab

Introduction
Adalimumab (Humira®) and adalimumab-atto (Amjevita®) are human recombinant IgG1 monoclonal antibodies with specificity for human TNF[53].

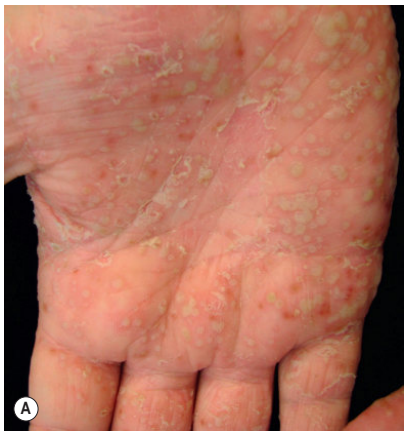
Indications
Adalimumab is approved for the treatment of moderate to severe plaque-type psoriasis in adults, and ~50–80% of patients achieve a 75% improvement in their PASI score[47]. It is also approved for the treatment of moderate to severe hidradenitis suppurativa in adults, with ~40–60% of patients achieving a 50% reduction in the abscess/

CUTANEOUS SIDE EFFECTS OF TARGETED IMMUNE MODULATORS
Injectable agents
• Injection site reactions, e.g. erythema/edema, occasionally small vessel vasculitis; "recall" reactions at previous sites
Tumor necrosis factor inhibitors
• New-onset psoriasis, especially palmoplantar pustulosis • Interstitial granulomatous dermatitis and other granulomatous eruptions • Cutaneous small vessel vasculitis • Eczematous eruptions • Lichenoid dermatitis • Lupus-like syndrome-associated malar rash or discoid lesions • Other types of cutaneous lupus, e.g. SCLE, chilblain lupus
Epidermal growth factor receptor inhibitors
• Papulopustular (acneiform) eruption (see Ch. 36) • Paronychia, ingrown nails, periungual pyogenic granulomas, acral desquamation • Xerosis, fissures, skin fragility • Seborrheic dermatitis, blepharitis • Telangiectasias, hyperpigmentation • Increased severity of radiation dermatitis • Trichomegaly, facial hair growth, frontal alopecia, curly brittle hair
Other kinase inhibitors and blocking antibodies – see Table 21.16
• "Hand–foot reaction" (often eventuating in hyperkeratosis) > intertriginous erythema/erosions (variant of toxic erythema of chemotherapy) • Facial swelling (especially periorbital) and erythema • Exanthematous eruptions (truncal or generalized) • "Erythema marginatum hemorrhagicum", erythema multiforme or SJS-like eruptions, lichenoid dermatitis, small vessel vasculitis (may have an annular configuration), Sweet syndrome, panniculitis • Pruritus, xerosis, fissures, spiny follicular keratoses/keratosis pilaris, acneiform eruptions, seborrheic dermatitis, hyperhidrosis • Rapid development of verrucous papules, actinic keratoses, keratoacanthomas, or squamous cell carcinomas; eruptive melanocytic nevi, melanoma • Photosensitivity, ultraviolet recall dermatitis, inflammation of actinic keratoses • Leukoderma, yellowish discoloration of the skin, hyperpigmentation • Subungual splinter hemorrhages, onycholysis, brittle nails, periungual pyogenic granulomas • Hair de-/repigmentation, alopecia, curly brittle hair, scalp dysesthesia

Table 128.9 Cutaneous side effects of targeted immune modulators. New-onset palmoplantar and inverse psoriasis has also been reported to be by the interleukin-17 inhibitor sekukinimab. Allergic reactions manifesting with urticaria and angioedema can also occur with most agents. SCLE, subacute cutaneous lupus erythematosus; SJS, Stevens–Johnson syndrome.

VACCINES THAT CONTAIN LIVE ATTENUATED VIRUSES OR BACTERIA
Adenovirus
Bacillus Calmette–Guérin (BCG)
Cholera, *oral form in the US*
Herpes zoster (shingles)
Influenza (including H1N1), *intranasal form*
Measles, mumps, and rubella
Rotavirus
Polio, *oral form*
Typhoid, *oral form*
Vaccinia (smallpox vaccine)
Varicella
Yellow fever

Table 128.10 Vaccines that contain live attenuated viruses or bacteria.



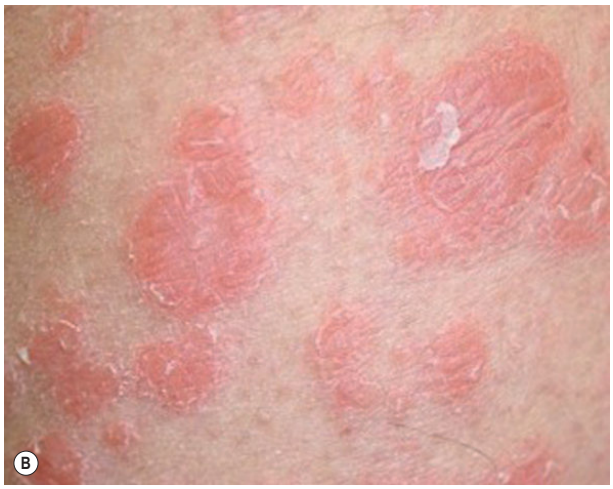


Fig. 128.7 Psoriasiform reactions to tumor necrosis factor inhibitors. A Palmoplantar pustulosis that developed as a complication of infliximab. **B** Eruption of plaque-type psoriasis in a patient receiving infliximab therapy. The patient had received infliximab for GVHD of the gastrointestinal tract.

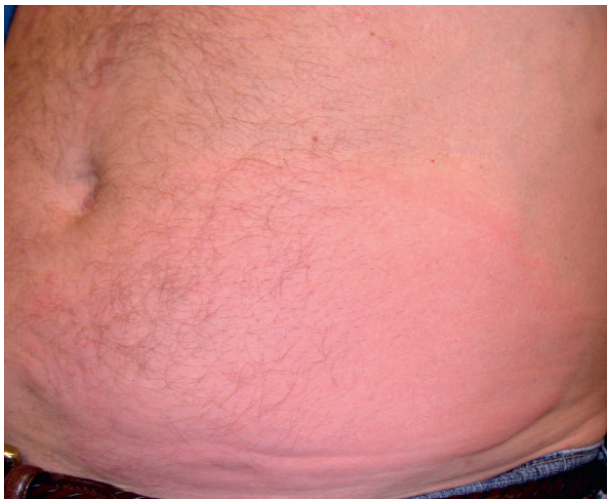


Fig. 128.8 Etanercept injection site reaction. Similar reactions occur with nearly all subcutaneously injected biologic