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Review Article

Biologics in dermatology

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ABSTRACT

The role of biologicals in dermatology has seen an exponential growth in the last few years. Biologicals such as TNF-alpha inhibitors have now lost their novelty and are routinely used all over the world. As the pathogenesis of various diseases is now being understood better, we have been able to create more targeted biological therapies for a number of dermatological conditions. We attempt to compile an update on the newer biologicals in use today, and briefly touch upon the older ones as well. We conducted an extensive literature search and have covered TNF-alpha inhibitors, molecules against T cell receptors, Janus Kinase inhibitors, interleukin based molecules, fusion proteins, and some newer biologicals as well. Their mechanisms of action, indications and dosage have been covered in our review.

Keywords: Biologicals, Monoclonal antibodies, Targeted therapy

INTRODUCTION

The role of biologicals in dermatology has seen an exponential growth in the last few years. Biologicals such as TNF-alpha inhibitors have now lost their novelty and are routinely used all over the world. We attempt to compile an update on the newer biologicals in use today, and briefly touch upon the older ones as well.

The various biologicals used in dermatology may be classified as Anti TNF-alpha agents, molecules against specific T cell receptors, Interleukin based molecules, JAK inhibitors, fusion proteins and other miscellaneous types. Each of these will be discussed further.

ANTI-TNF- ALPHA AGENTS

TNF has a vital role in various chronic inflammatory diseases like psoriasis and psoriatic arthritis.[1]

The various TNF-alpha inhibitors are summarized in Table 1.

Table 1: TNF- alpha inhibitors.

Infliximab
Adalimumab
Etanercept (fusion protein)
Golimumab
Certolizumab

Infliximab

It is a chimeric human-mouse monoclonal antibody against TNFα fused to the human IgG1 constant region. By binding to both the solute as well as the transmembrane forms of TNFα, it causes complement mediated destruction of cells producing TNFα. Thus, it

helps reduce cutaneous inflammation and causes apoptosis of lesional keratinocytes.[1]

Indications: Psoriasis vulgaris, psoriatic arthropathy, pustular psoriasis, sarcoidosis, Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, hidradenitis suppurativa, subcorneal pustular dermatosis, pyoderma gangrenosum, toxic epidermal necrolysis, Behçet's syndrome, and SAPHO syndrome.[2]

Dose: 3-10 mg/kg (as IV infusion, given over several hours at weeks 0, 2 and 6 and every 8 weeks thereafter).[3]

Adalimumab

Adalimumab is a highly specific TNF-α inhibitor. It was the first fully human monoclonal anti-TNF-α antibody. It is a human IgG1 monoclonal antibody against both soluble and transmembrane TNFα. It has also been found to increase the number of epidermal Langerhans cells in psoriatic plaques.[4]

Indications: Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, moderate-to-severe chronic psoriasis, and juvenile idiopathic arthritis.[4]

Dose: 80 mg subcutaneously initially, followed by 40 mg every other week (EOW), starting a minimum of 1 week after the first dose.[3]

Etanercept

It is a human dimeric fusion protein of two identical TNFα type II (p75) receptor peptides, which are fused to the Fc portion of the human IgG1. It binds both TNFα and TNFβ in circulation.[1]

Indications: FDA approved for the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthropathy, and plaque psoriasis (moderate-to-severe). It is also effective in scleroderma, recurrent aphthous ulcers, and patients of immunodeficiency, presenting with scarring alopecia, arthritis, diarrhea, and recurrent infections.[5]

Dose: In psoriasis, a starting dose of 50 mg. twice weekly is given for 3 months, followed by 50 mg once weekly. For psoriatic arthritis, the dose is just 50 mg SC weekly. For pediatric psoriasis a dose of 0.8 mg/kg, up to 50 mg weekly has been used, and is considered safe and effective.[3]

Golimumab

Golimumab is a human monoclonal antibody to TNF-α.[3]

Indications: Rheumatoid arthritis, psoriatic arthritis.[3]

Dose: The major advantage of Golimumab is the one monthly dosing schedule. It is administered in the dose of 50 mg subcutaneously.[3]

Certolizumab

Certolizumab is a PEGylated Fab fragment of humanized monoclonal TNF-α antibody. Certolizumab differs from other TNF inhibitors in not having the Fc portion of the antibody and the PEGylation of the fab fragment. Thus it is less immunogenic and has a longer half life.[3]

Indications: Rheumatoid arthritis, Crohn's disease, moderate to severe chronic plaque psoriasis and psoriatic arthritis.[3]

Dose: It is administered subcutaneously in a dose of 400 mg, which is repeated 2 and 4 weeks after the first dose and subsequently a maintenance dose of 400 mg every 4 weeks.[3]

MOLECULES AGAINST SPECIFIC T CELL RECEPTORS

The molecules acting against specific CD receptors on T cells have been summarized in Table 2.

Table 2: Molecules against specific T cell receptors.

Anti CD 2	Siplizumab
Anti CD 4	Orthoclone
Anti CD 20	Rituximab
Anti CD 25	Basiliximab
	Daclizumab
Anti CD 80r	Galiximab

Siplizumab: (Medi-507)

CD2 is a receptor expressed on CD4+ and CD8+ memory T cells, and NK cells as well. Siplizumab is a humanized IgG1 monoclonal directed against CD2. Thus by blocking CD2, it prevents the proliferation and activation of memory T cells, which subsequently results in a decreased activity of the psoriatic process.[6]

Indications: Chronic plaque psoriasis.[6]

Dose: 0.1-0.7mg weekly for 12 weeks.[7]

Orthoclone

It is a humanized antihuman CD4 IgG4 monoclonal antibody. It prevents the recognition of the MHC-bound antigen by an appropriate T-cell receptor, thereby preventing T cell activation.[8]

Indications: Moderate- to-severe psoriasis.[8]

Rituximab

Rituximab is a chimeric monoclonal antibody targeted against CD20. It acts by destruction of autoreactive B cells, and it's effect last from six to nine months.[9]

Indications: Pemphigus, B-cell lymphoma, lymphoproliferative disorders, and inflammatory conditions that are refractory to conventional treatment, such as rheumatoid arthritis, refractory idiopathic thrombocytopenic purpura, thrombotic thrombo-cytopenic purpura, severe interstitial lung disease associated with connective tissue disease, and some vasculitides.[9]

Dose: It may be administered according to any of the following protocols:

Lymphoma protocol- 375 mg/m^2 body surface area weekly for four weeks. This is the most commonly followed protocol.[10]

Rheumatoid arthritis protocol- Two doses of rituximab 1g, given 15 days apart.[9]

Basiliximab

Basiliximab is a chimeric monoclonal antibody that targets the IL- 2Rα receptor (also known as the CD25 antigen) of T cells.[11]

Indications: Severe recalcitrant psoriasis and palmoplantar pustular psoriasis[11]

Dose: Two doses of 20 mg Basiliximab given Intravenously, 4 days apart.[11]

Daclizumab

Daclizumab is a humanized monoclonal anti CD 25 (α-subunit) antibody.[12]

Indications: Chronic plaque Psoriasis, recalcitrant psoriasis and HIV-associated psoriatic erythroderma.[12]

It has been withdrawn from markets in 2018 due to the high risk of encephalitis and meningoencephalitis.

Galiximab

It is an anti-CD80 monoclonal antibody with a human IgG1 constant region. The CD80 receptor is involved in T cell activation and is found on antigen presenting cells and certain activated T cells. Blockade of this receptor by Galiximab causes a decrease in lesional T cells, thus resulting in an improvement in the psoriatic plaques. [13]

Indications: Moderate to severe chronic plaque psoriasis.[13]

INTERLEUKIN BASED MOLECULES

The various molecules associated with interleukins, acting as either agonists or antagonists have been summarized in Table 3.

Table 3: Interleukin based molecules.

IL-1Ra	Anakinra
Il-2	Antitumour Th1 cytokine
IL-4	Th2 cytokine
Anti IL4a	Dupilumab
Anti-IL-5	Mepolizumab
Anti-IL-8	ABX-IL8
IL-10	Tenovil
IL-11	Oprelvekin
Anti- IL-12 and 23	Ustekinumab Briakinumab
Anti IL-13	Tralokinumab Lebrikizumab
Anti IL-17	Secukinumab Brodalumab Ixekizumab Bimekizumab
Anti IL-23	Guselkumab Risankizumab Tildrakizumab
Anti IL-31rA	Nemolizumab

Anakinra: (IL1Ra)

Anakinra is a recombinant IL-1Ra. It differs from endogenous IL-1Ra by an additional methionine residue at the amino terminus, and as it is a non-glycosylated form of human IL-1Ra. It blocks the functions of Interleukin-1 such as inflammation, and thus acts as a biological immunomodulator.[14]

Indications: Rheumatoid arthritis, Schnitzler's syndrome, and psoriatic arthropathy.[14]

Dose: 100 mg as a subcutaneous injection, once daily. It may be combined with methotrexate therapy as in rheumatoid arthritis, or with thalidomide in Schnitzler's syndrome.[14]

IL-2

Interleukin-2 is an antitumour cytokine produced endogenously by Th1 cells activated by antigen presenting cells (APC). It activates T cell growth and differentiation, as well as activates NK cells.[14]

Indications: Cutaneous T cell lymphoma (CTCL) and metastatic melanoma.[14]

Dose: High IV doses of 600,000-720,000 IU/kg have been used in melanoma, with a 15-20% response.[14]

IL-4

Interleukin-4 is a cytokine produced by NK cells, mast cells and basophils, that induces selective Th2 differentiation of CD4+ T cells.[14]

Indications: Psoriasis.[14]

Dose: 0.5 to 5 mg/kg is given by subcutaneous injection thrice a week.[14]

Dupilumab (Dupixent)

Dupilumab is a monoclonal antibody that blocks the interleukin 4 (IL-4) receptor α. Since the IL-4α subunit is shared by IL-4 and IL-13, this results in a IL-4/13 antagonism, resulting in a reduced Th2 response.[15]

Indications: Moderate-to-severe atopic dermatitis, asthma.[15]

Dose: Initial dose of 600 mg (two 300 mg subcutaneous injections in different sites), followed by 300 mg every other week.[15]

Mepolizumab

Mepolizumab is a Humanised monoclonal IgG antibody to IL-5. IL-5 plays a key role in eosinophil growth and differentiation.[16]

Indications: Atopic dermatitis and hypereosinophilic disorders.[16]

Dose: Two weekly intravenous infusions are administered.[16]

ABX-IL8

It is a fully human monoclonal antibody that targets free Interleukin-8 and deactivates it in the skin.[17]

Indications: It has shown promising results in psoriasis.[17]

Dosage: It is administered intravenously by 4 to 5 intravenous infusions.[17]

Tenovil or interleukin 10 or rhIL-10

IL-10 is an anti-inflammatory cytokine produced by Th2 cells, keratinocytes, mast cells, macrophages, and some B cells. It acts on antigen presenting cells such as monocytes, macrophages, and dendritic cells, and induces a reduction in various proinflammatory Th1 cytokines, while stimulating B cells and inducing Th2 cell activation.[14]

Indications: It was found to be reduced in psoriatic plaques, and has proven to be very efficacious in inducing long term remissions in psoriasis.[14]

Dose: Recombinant human IL-10 (Tenovil) can be given in subcutaneous injections at doses of 4 mg/kg, three times a week.[14]

Oprelvekin or interleukin 11 or rhIL-11

IL-11 is anti-inflammatory cytokine that causes a reduction in Type 1 cytokines and it's interaction with T cells causes differentiation along the Th1 lineage.[14]

Indications: Chemotherapy-induced thrombocytopenia, psoriasis.[14]

Dose: 2.5 or 5 mg/ kg, by subcutaneous injection for psoriasis.[14]

Ustekinumab

It is a fully human IgG1 kappa (κ) monoclonal antibody targeting IL-12 and IL-23. Ustekinumab binds to the p40 subunit shared by interleukin (IL)-12 and 23, and blocks their binding with their receptor. This stops key cytokine production and signalling integral to inflammatory diseases.[3]

Indications: Psoriasis, psoriatic arthropathy and Crohn disease. It was earlier also used in multiple sclerosis (MS), but was discontinued subsequently due to the lack of efficacy. [3]

Dose: 45 mg or 9 0mg subcutaneously at weeks 0 and 4 and then every 12 weeks.[3]

Briakinumab

Briakinumab is a fully human IgG1 monoclonal antibody, which is another IL-12/23p40 antagonist. It was being developed for the treatment of inflammatory bowel disease, rheumatoid arthritis and psoriasis, but its biological license application was withdrawn in 2011.[18]

Tralokinumab

Interleukin-13 is a Type 2 cytokine, produced by Th2 cells, and is known to be associated with asthma and atopic dermatitis.[19] Tralokinumab is an anti-interleukin-13 human monoclonal antibody.[19]

Indications: Severe, uncontrolled asthma and Atopic dermatitis.[19]

Dosing: Administered as subcutaneous injections of 300 mg every two to four weeks.[19]

Lebrikizumab

Lebrikizumab is an anti-IL-13 monoclonal antibody. IL-13 is an important mediator of type 2 inflammation, and plays a major pathogenic role in atopic dermatitis.[20]

Indications: Moderate to severe atopic dermatitis in adults, (supplementary to topical corticosteroid treatment), moderate to severe asthma.[20]

Dose: 125 mg as subcutaneous injections, every 4 weeks.[20]

Anti IL-17

T helper cells were originally divided into Th1 and Th2. Th17, a new group, playing a major role in protection from endogenous and exogenous antigens was discovered in 2005.

Interleukin-17 is the main Th17 cytokine playing a vital role in the pathogenesis of psoriasis. Three agents that block IL-17, are used for the treatment of psoriasis: secukinumab, brodalumab and ixekizumab.[21]

Secukinumab

Secukinumab is a fully humanized, monoclonal anti-IL-17A antibody.[21]

Indications: Moderate to severe plaque psoriasis, Active psoriatic arthritis and Ankylosing spondylitis. [21]

Dose: Two subcutaneous injections of 150 mg (totally 300 mg) at weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks.[22]

Brodalumab

Brodalumab is a human, anti-IL17RA monoclonal antibody, which acts by blocking the activity of IL17RA, 17A/F and 17E.[21]

Indications: Psoriasis, psoriatic arthritis.[21]

Dose: Administer 210 mg of Brodalumab by subcutaneous injection at weeks 0, 1, and 2 followed by 210 mg every 2 weeks.[23]

Ixekizumab

Ixekizumab is a humanized IgG4 monoclonal antibody that acts by neutralizing IL-17.[21]

Indications: Moderate to severe plaque psoriasis, Psoriatic arthritis.[21]

Dose: In moderate or severe plaque psoriasis, a starting dose of 160 mg subcutaneously is used, followed by 80 mg subcutaneously every 2 weeks for the following 12 weeks. After that, one dose of 80 mg per month is administered.

In psoriatic arthritis, a first dose of 160 mg followed by once monthly doses of 80 mg are used.[24]

Other agents acting on the IL-17—Th17 pathway

Anti-IL-17 antibodies are currently being investigated, such as bimekizumab, ALX-0761, CJM112, CNTO 6785, LY3074828, and SCH-900117.[21]

MSB0010841 is an anti IL-17 nanoantibody which is also under study for the treatment of psoriasis.[21]

Dual anti IL-17/TNF-α inhibitors (e.g. ABT-122, COVA322) are now in early clinical trials. Fynomers are small proteins that bind to two different antibodies, allowing the creation of such bi-specific, fully human anti-TNF and anti-IL-17A antibodies (FynomAb® COVA322).[21]

Guselkumab

Guselkumab is a humananized monoclonal antibody that binds to the p19 subunit of IL-23. IL-23 plays a pivotal role in the development of Psoriasis.[25]

IL-23p19 and IL-12/23p40 messenger RNA (mRNA) are upregulated in psoriatic lesions, and the levels have been shown to reduce with directed treatment.[25]

Indications: Moderate-to-severe psoriasis.[25]

Dose: 100 mg via subcutaneous injection at week 0, week 4, and every 8 weeks thereafter.[25]

Risankizumab

Interleukin-23 is an important cytokine in the pathogenesis of psoriatic inflammation. Risankizumab is a humanised IgG1 monoclonal antibody targeting the p19 subunit of IL-23.[26]

Indications: Psoriasis, psoriatic arthritis (PSA), ulcerative colitis and Crohn's disease.[26]

Tildrakizumab

Il-23 is a key cytokine in the pathogenesis of Psoriasis. Tildrakizumab is a humanized monoclonal antibody selectively targeting the p19 subunit of IL-23.[27]

Indications: Moderate to severe plaque psoriasis.[27]

Dose: 100 mg subcutaneously at weeks 0, 4, and every twelve weeks thereafter.[28]

Nemolizumab

Nemolizumab is an anti-IL-31 receptor A monoclonal antibody. It has been shown to alleviate improved pruritus, dermatitis, and sleep in adults with atopic dermatitis.[29]

Indications: Moderate-to-severe atopic dermatitis.[29]

Dose: Given as subcutaneous injections, 0.1 to 3 mg/kg, 4-8 weeks apart.[29]

JAK INHIBITORS

Janus kinase (JAK) inhibitors (Table 4) reduce T- cell mediated inflammatory responses. Recent studies have shown that JAK inhibitors (JAKis) are effective in the treatment of many autoimmune diseases. e.g. alopecia areata.[30]

Table 4: JAK inhibitors.

Ruxolitinib
Tofacitinib
Baricitinib
Filgotinib
Decernotinib
Upadactinib- selective JAK-1 inhibitor

Ruxolitinib (INCB018424 or INC424)

Ruxolitinib, a selective inhibitor of JAK 1 & 2 and to some extent TYK, is the first agent approved by FDA for the treatment of myelofibrosis. JAK 1 & 2 play a role in the development of myelofibrosis. Ruxolitinib produces it's anti- inflammatory effects by interrupting IL-17 signaling axis.[30]

Indications: Myelofibrosis, Alopecia areata and vitiligo. It is particularly useful in facial vitiligo.[30]

Dose for the treatment of Alopecia Areata:[31]

- Oral: 10-30 mg daily.
- Topical: 0.6% BID.

Dose for the treatment of vitiligo.[30]

Topical: 1.5% Cream BID.

Tofacitinib (CP-690,550)

It was the first developed JAK inhibitor and has been found effective in alopecia areata.[30]

Dose for the treatment of alopecia areata:[32]

- Oral: 5 mg BID
- Topical: 2% BID.

Baricitinib (LY3009104 or INCB028050)

It is a potent selective inhibitor of JAK 1 & 2 along with some degree of inhibition of JAK 3 and other kinases. Only a single case report showing the efficacy in alopecia areata is currently available.[33]

Second generation JAK inhibitors: (decernotinib, peficitinib, filgotinib, fedratinib, momelotinib, and lestaurtinib)

These agents show more specific JAK receptor selectivity, but are still in the developemental stages. Current studies show a similar efficacy in Alopecia areata with the advantage of fewer side effects and toxicity. They have also shown good results in rheumatoid arthritis.[34,35]

Upadactinib

Non- selective JAK inhibitors such as Tofacitinib had significant tolerability issues due to activity against reticulocytes and NK cells as well. Selective JAK1 inhibitors such as Upadactinib (ABT-494) offer the benefit of selective activity against JAK1 dependent cytokines such as IL-6 and IFNγ, while decreasing effects on reticulocytes and NK cells. This offers a much better risk: benefit profile.[36]

Indications: Atopic dermatitis and rheumatoid arthritis.[36]

FUSION PROTEINS

The various fusion proteins in use as biologicals are summarized in Table 5.

Table 5: Fusion proteins.

Alefacept	LFA3 + IgG1, blocks CD2
Denileukin diftitox	IL-2 + Diphtheria toxin
Abatacept	CTLA4 + IgG
Onercept	Soluble p55 TNF binding protein
Etanercept	TNFα + IgG1

Alefacept: (Amevive)

LFA3 is an IgG molecule expressed on antigen presenting cells. It is a ligand for CD2 which is expressed on T cells and NK cells. It acts as a signal for T cell activity and proliferation.

Alefacept is a recombinant fusion protein of LFA3 and IgG1. It blocks the LFA3-CD2 interaction, thus hindering T cell activation.[3]

Indications: Alefacept was the first biologic to receive FDA approval for the treatment of psoriasis in January 2003. It is also used in psoriatic arthropathy, alopecia areata, atopic dermatitis, mycosis fungoides, alopecia universalis, erosive lichen planus, and Hailey-Hailey disease.[3]

Dose: 15 mg IM/7.5 mg IV weekly for 12 weeks followed by a 12-week holiday.[3]

Repeat courses are considered for patients only after a 12-week drug holiday provided that CD4+ T lymphocyte counts are within the normal range.[3]

Denileukin diftitox

Denileukin diftitox or DAB389IL-2 is a recombinant fusion toxin formed by linking of human IL- 2 gene and the active ADP-ribosyltransferase domain of the diphtheria toxin. It binds to the IL-2 receptor, and enters the endoscope by endocytosis. It then cleaves the ADP-ribosyltransferase unit and causes apoptosis of the cell by inhibiting protein translation.[14]

Indication: It is approved by the FDA for the treatment of cutaneous T-cell lymphoma (CTCL) at doses of 9ìg/kg/day or 18ìg/kg/day IV over 15 minutes.[14]

Abatacept

It is a fusion protein of CTLA4 and the Fc region of IgG4. It inhibits T-cell activation by competitively binding to the B7.1 and B7.2 molecules on the surface of antigen presenting cells.[14]

Indication: Psoriasis vulgaris, rheumatoid arthritis.[14]

A second generation CTLA4Ig, Belatacept, is currently under phase II clinical trial for allograft diseases.[14]

Onercept

Onercept is a recombinant human soluble p55 tumour necrosis factor binding protein.[37]

Indication: Psoriasis and psoriatic arthritis.[37]

It is administered subcutaneously three times a week at a dose of 150 mg, for 12 weeks.[37]

MISCELLANEOUS

A few other biologicals in use today are listed in Table 6.

Table 6: Miscellaneous.

Belimumab	Anti BLyS
Avelumab	Anti PD-L1
Tezepelumab	Anti TSLP
Lanadelumab	Kallikrein Inhibitor
Efalizumab	Anti LFA-1
Omalizumab	Anti IgE
Ligelizumab	Anti IgE
SMART anti-IFN-gamma	Anti IFN-gamma
IFN-apha	
IFN-gamma	
GM-CSF	
PDGF	
IVIG	

Belimumab

It is a fully human IgG1λ recombinant monoclonal antibody directed against BLyS (B lymphocyte stimulator protein). It causes decreased B cell survival and lowers the amount of autoantibodies produced.[38]

Indications: Belimumab is the first FDA approved targeted biological for SLE. Indication includes autoantibody positive patients with active SLE who are already on standard therapy.[38]

Dose: Intravenous infusion - 10 mg/kg of reconstituted drug administered over 1 hour.

Initial 3 doses: interval of 2 weeks.

Next doses: repeated every 4 weeks.[38]

Avelumab

Programmed death ligand-1 (PD-L1) is an immunosuppressive ligand that binds to T cells, and inhibits T-cell activation, proliferation, and cytotoxicity.[39]

Avelumab is an anti-programmed cell death ligand 1 (PD-L1) monoclonal antibody, which can utilize both innate and adaptive immune systems in it's anti- cancer properties.[39]

Indications: Merkel cell carcinoma.[39]

Dose: 10 mg/kg by intravenous injections, every 2 weeks.[39]

Tezepelumab

Tezepelumab (AMG 157/MEDI9929) is a human IgG2 monoclonal antibody against TSLP (Thymic stromal lymphopoietin), thereby blocking it's interaction with the TSLP receptor complex.[40]

Thymic stromal lymphopoietin (TSLP) is a pro-inflammatory cytokine produced by epithelial cells. It is vital for the regulation of type 2 immunity by exerting a regulatory effect on dendritic cells, T and B cells. It also enhances Th2 dependent antigen specific cytokine production.[40]

Indications: Atopic dermatitits, Asthma.[40]

Dose: It is administered subcutaneously every two to four weeks.[40]

Lanadelumab

Lanadelumab (DX-2930) is a fully human monoclonal antibody targeted against plasma kallikrein. Kallikrein is an important regulator of Hereditary Angioedema with C1 esterase deficiency.[41]

Indications: Hereditary angioedema[41]

Dose: The recommended starting dose is 300 mg by subcutaneous injection every 2 weeks. In patients who are stably attack free on treatment, a dose reduction of 300 mg every 4 weeks may be considered, especially in patients with low weight.[42]

Efalizumab

LFA-1 or lymphocyte function associated antigen-1, is a heterodimer of CD11a and CD18. It is one of the β2-integrins, found on T cells, B cells, macrophages and neutrophilc. Efalizumab is a humanised IgG1 monoclonal antibody specific to LFA-1. It thus prevents binding of LFA-1 to ICAM-1 on keratinocytes, thus blocking the movement of T cells into the skin.[43]

Indications: FDA approved for moderate to severe plaque psoriasis in October 2003, although it is not very effective in psoriatic arthropathy. It was used preferentially in palmoplantar psoriasis, psoriasis in overweight patients and in non-responders to TNF inhibitors. It was also used in lichen planus.[43]

It was subsequently withdrawn in 2009 due to a high risk of progressive multifocal leukoencephalopathy.[43]

Dose: Subcutaneous injections with an initial loading dose of 0.7 mg/kg followed by 1.0 mg/kg weekly, to a maximum weekly dose of 200 mg.[43]

Omalizumab

Omalizumab is a humanised monoclonal antibody against immunoglobulin E. It thus causes reduced binding of IgE to it's high affinity receptor FcεR I. Thus IgE mediated sensitization of cells and inflammatory changes decrease.[43]

Indications: It is used in atopic dermatitis, cold urticaria and chronic urticaria.[43]

Dose: Dosing is based on weight and pretreatment serum IgE levels and is administered via subcutaneous injection every 2 to 4 weeks.[3]

Ligelizumab

Ligelizumab is another anti IgE monoclonal antibody currently in phase III trials for the treatment of chronic spontaneous urticaria.[44]

Indications: Chronic spontaneous urticaria.[44]

SMART anti IFN-gamma

It is a humanised monoclonal antibody against IFN-gamma, which is an important Th1 cytokine involved in the pathogenesis of psoriasis.[44]

Indication: Psoriasis.[44]

IFN-alpha

IFNα constitute a group of about 20 proteins that are produced by virus-infected leucocytes. Type I Interferons such as IFNα, IFNβ, IFNε, IFNê, and IFNω are a primary defence against various viral infections. They directly inhibit viral replication, stimulate the adaptive immune response, stimulate Natural Killer cells, promotes the Th1 response and inhibit the Th2 response. This results in antiproliferative and immunomodulatory functions.[43]

Indications: Verruca vulgaris, condyloma acuminatum, cutaneous T cell lymphoma, Kaposi's sarcoma, melanoma, basal cell carcinoma, squamous cell carcinoma, actinic keratosis, mastocytosis, Behçet's disease, hemangiomas and keloids.[43]

Dose: Subcutaneous or Intramuscular injections, given thrice weekly. The dose varies from low to high, depending on the indication. For example, a low dose may suffice for condyloma accuminata, whereas, melanomas require a high dose. [43]

Pegylated IFNα offers the advantage of greater patient compliance due to longer half-life and once weekly dosing.[43]

IFN-gamma

Endogenous IFNγ is an interferon synthesized by activated Th1 CD4 T cells, CD8 T cells, and NK cells, with a stimulatory role for the adaptive immune system, with suppression of Th2 cytokines. It also has an antiviral role and antiproliferative role against some cells.[45] Recombinant IFNγ retains the immunoregulatory, antiviral, and antineoplastic activities of Endogenous IFNγ, and is used to treat a variety of conditions.[45]

Indications: Chronic granulomatous disease, atopic dermatitis and cutaneous T cell lymphoma.[43]

Dosage:

BSA >0.5 m^2: 50 mcg/m^2 SC 3 times/week.
BSA ≤0.5 m^2: 1.5 mcg/kg SC 3 times/week.[45]

GM-CSF

GM-CSF or granulocyte-monocyte colony stimulating factor is a leukocyte growth factor secreted by macrophages, T cells, mast cells, endothelial cells, and fibroblasts. It stimulates stem cells to form granulocytes and monocytes.[14,43]

Indications (dermatological): To promote wound healing in ulcerated skin (e.g., leg ulcers), for the treatment of melanoma and Sezary syndrome.[14]

Dose: It may be administered intravenously or subcutaneously.[14]

PDGF

PDGF is a glycoprotein dimer formed by two A or two B chains. It is synthesized endogenously by platelets, neutrophils, macrophages, and smooth muscle cells. PDGF-BB is very useful in wound healing due to it's role in promoting the formation of granulation tissue, re-epithelialization and wound angiogenesis.[14]

Indications: Diabetic foot ulcers.[43]

Dose: Recombinant PDGF-BB topical gel (100ìg/g), applied once daily.[43]

IVIG

IVIG is a collection of pooled human plasma from 1000 to 15000 donors. It is composed of more than 90% IgG, along with small amounts of IgM and IgA. Out of the IgG fraction, IgG1 constitutes about 70.3%, IgG2 is 24.7%, with small amounts of IgG3 and IgG4.[3]

Dermatological indications: Autoimmune bullous disorders, connective tissue diseases, toxic epidermal necrolysis, vasculitides, urticarias, pyoderma gangrenosum (PG), scleromyxedema, pretibial myxedema, nephrogenic fibrosing dermopathy, Kaposi's sarcoma, mixed connective tissue disease, anticonvulsant syndrome and polymorphous light eruption.[3,46]

Dose: 2 gm/kg/cycle intravenously, every 3-4 weeks. Each 2 gm/kg dose is sufficient to cause a fivefold rise in serum IgG titres.[46]

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