Review Article

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Biologics in Dermatology: A Brief Review

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Abstract
With the advent of biologic therapy, the treatment of various systemic and cutaneous diseases, especially autoimmune diseases, has been revolutionized. Most of the treatment modalities available prior to biologics aimed at producing clinical improvement of the disease without targeting the actual causative factors. Biologics are protein molecules produced by recombinant DNA technology, which target the specific sites in the immune-pathogenesis pathway of the diseases. Because of the specific action on immune system, biologics are presumed to have lesser side effect profile compared to the traditional immune-suppressants. However, the use of biologics is still limited because of unknown long-term safety profile and various aspects of the biologics need to be thoroughly evaluated by conducting large scale studies worldwide. In this review we give a brief description of various biologic agents that are known till date.
Keywords: Biologics; proteins; autoimmune diseases.

INTRODUCTION

The US Food and Drug Administration (USFDA) considers the following as biologics: any therapeutic serum, toxin, antitoxin, vaccine, virus, blood, blood component or derivative, allergenic product, analogous product, or derivatives applicable to the prevention, treatment, or cure of injuries or disease of man[1]. However, generally, biologics refer to protein molecules therapeutically used in various diseases so as to target specific points in the inflammatory cascade of these disorders [2]. Hope for an improved tolerability, convenience in usage and lasting remissions, combined with increased knowledge of immune-pathogenesis of various cutaneous diseases has led to the introduction of biologics as alternative immune-modulating agents in the field of dermatology.

CLASSIFICATION

Biologics are generally divided into three major groups [3]:

a) Monoclonal antibodies
b) Fusion antibody proteins
c) Recombinant human cytokines and growth factors

The main groups and the principal agents in each group are summarised in Box 1 and described below.

A) MONOCLONAL ANTIBODIES

Monoclonal antibodies target specific cell-surface receptors. In the early days of biologic therapy, purely murine monoclonal antibodies were used. However, due to the development of antimurine antibodies, which blocked their action, these could be given only for very short periods. The monoclonal antibodies used now have different amounts of murine sequences in the variable region. They may be categorised into three classes:

(a) chimeric antibodies comprising of 30% murine genes fused with human antibodies
(b) humanised antibodies, which have 10% murine sequences, and
(c) human antibodies, which are solely derived from human immunoglobulin genes 4.

Principal monoclonal antibodies with therapeutic relevance in Dermatology

The principal monoclonal antibodies known till date are enumerated in Box 1 and described briefly below.

1. Infliximab

Infliximab (trade name Remicade) is a human-mouse monoclonal antibody that binds to and inhibits the activity of TNF-α, and also causes lysis of TNF-α producing cells[5].

Important uses of Infliximab

Psoriasis: Infliximab is approved for the treatment of psoriatic arthritis and plaque psoriasis by FDA[6, 7]. Infliximab may also be of value in recalcitrant or unstable disease and in generalised pustular psoriasis. It is given as an IV (intravenous) infusion in doses of 5 or 10 mg/kg, over a period of 2 hours at weeks 0, 2, 6 and may be followed by repeat single infusions at 8-12 week intervals [8]. In various controlled trials, improvement at 10 weeks has been noted in 87% of patients [7, 9].

Atopic dermatitis: Infliximab has also been evaluated in a study of atopic dermatitis [10]. At 2 weeks, there was significant

improvement in all patients. At 10, 14, and 30 weeks, variable response was seen.

Box 1: Classification of biologics

Monoclonal antibodies

- Anti-TNFα: Infliximab, Adalimumab, Certolizumab, Golimumab
- Anti-LFA1: Efalizumab
- Anti-CD20: Rituximab
- Anti-IL-12 and anti-IL-23 monoclonal antibody: Ustekinumab
- Anti-CD2 antibody: Siplizumab
- Anti-CD4 antibody: Orthoclone (OKTcdr4a)
- Anti-CD25 antibodies: Basiliximab, Daclizumab
- Anti-CD80r: Galiximab (IDEC 114)
- Anti-IgE: Omalizumab

Fusion antibody proteins

- Etanercept
- Alefacept
- Abatacept
- Onercept
- Denileukin Diftitox

Recombinant human cytokines and growth factors

a) Interferons

- Interferon α (IFNα)
- Interferon γ (IFNγ)
- Interleukin 1 Receptor antagonist (IL1Ra)
- Interleukin 2 (IL-2)
- Interleukin 4 (rhIL-4)
- Interleukin 10 (rhIL-10)
- Interleukin 11 (rhIL-11)

b) Granulocyte macrophage colony stimulating factor (GM-CSF)

c) Platelet derived growth factor (PDGF)

Hidradenitis suppurativa: Long-term efficacy has also been evaluated in hidradenitis suppurativa. In one study, some patients had no evidence of recurrence after 2 years, while others relapsed within a mean of 8.5 months[11].

2. Adalimumab

Adalimumab (Humira®) is a human IgG1 monoclonal antibody directed against TNF-α. Adalimumab is given in a dose of 40 mg subcutaneously (SC) every other week as self-injection [5, 12].

Important uses of Adalimumab

Psoriasis: Adalimumab rapidly reverses the decrease in epidermal Langerhans cell density in psoriatic plaques [13]. In a trial, patients with psoriatic arthritis received adalimumab every other week for 24 week[14]. It was well-tolerated and helped improve joint and skin manifestations significantly.

Hidradenitis suppurativa: An increasing number of reports in refractory hidradenitis supprativa have shown successful control with adalimumab [15, 16, 17].

3. Basiliximab

Successful treatment for severe psoriasis and generalised pustular psoriasis has been reported with basiliximab, an interleukin-2 receptor (IL-2R; CD25) chimeric monoclonal antibody [18, 19].

4. Daclizumab

Daclizumab is a humanised monoclonal antibody thatbinds to the CD25 subunit of the IL-2 receptor onT-cells, thus blocking T-cell proliferation. It has been tried in recalcitrant psoriasis and HIV-associated psoriatic erythroderma with a mean reduction in PASI of 30% [20, 21 22].

5. Siplizumab

Siplizumab (Medi-507) is a humanisedmonoclonal antibody directed against CD2. It is designed to block stimulationby inhibiting the CD2–LFA-3 interaction. In earlyphase studies in psoriasis, significant response to therapy has been noted[23].

6. Efalizumab

Efalizumab is a recombinant humanised monoclonal IgG1 antibody that binds to CD11a, a subunit of leukocyte function-associated antigen 1 (LFA-1) [24]. It destabilises and decreases the trafficking of T-cells into dermal and epidermal tissues.

Important uses of Efalizumab

Psoriasis: Efalizumab was approved by the US FDA in October 2003 for the treatment of psoriasis[5]. It is currently the only biologic agent approved for continuous administration to adult patients[24]. The licensed dose of efalizumab is 1 mg/kg weekly as a subcutaneous self- administered injection for 12 weeks, following a first conditioning dose of 0.7 mg/kg [24].

Lichen planus: There is one case report of 3 months duration of treatment with efalizumab for lichen planus with resolution of skin lesions and pruritis [25].

7. Rituximab

Rituximab is a monoclonal humanised antibody directed again in the B cell-specific antigen CD20.

Important uses of Rituximab

Lymphoma: It has been used in patients with CD20-positive

non-Hodgkin's lymphoma in a dosage of 375 mg/m^2 for four infusions[26].

SLE: In systemic lupus, dose escalation studies revealed no differences with respect to clinical outcome in patients who received either a single infusion of 100 mg/m^2, a single infusion of 375 mg/m^2, or four weekly infusions of 375 mg/m^2[27].

Blistering diseases: For patients with blistering diseases, most patients receive the lymphoma dosage schedule. However, serious side effects were considerably higher.

There are reports of refractory pemphigus patients who received infusions of rituximab and had rapid resolution of lesions and a long lasting clinical remission [28, 29, 30].

8. Galiximab

Galiximab a humanised monoclonal antibody directedagainst CD80 and blocks its interaction with CD28 on the T cell, for T-cell stimulation [31]. Clinicaldata for this drug are just beginning to emerge with 40% of patients achieving at least 50% reduction in PASI after receiving4 biweekly doses in a trial[32, 33].

9. Ustekinumab

It is a fully human monoclonal antibody targeting IL-12 and IL-23, presently undergoing clinical trials for psoriasis and psoriatic arthropathy[2, 34]. In placebo-controlled studies, (PHOENIX 1) and (PHOENIX 2) have shown that ustekinumab could control plaque psoriasis with only four injections a year resulting in greater ease of use and more sustained relief[35, 36].

10. Certolizumab pegol

Certolizumab is the recombinant antibody Fab' fragment of a humanised TNF inhibitor monoclonal antibody. A study in chronic plaque psoriasis showed that certolizumab pegol, given subcutaneously every two weeks, over a period of 12 weeks shows significant improvement [37].

11. Golimumab

Golimumab, a fully human monoclonal antibody is at present undergoing Phase III clinical trials in psoriatic arthropathy [38].

12. Orthoclone or OkT4a

It is a humanised antihuman CD4 IgG4 monoclonal antibody preventing the recognition of the MHC-bound antigen by an appropriate T-cell receptor, hence T cells do not get activated [39]. Several studies have found orthoclone to be effective in moderate to severe psoriasis [40, 41].

13. ABX-IL8

ABX-IL8 is a fully human monoclonalantibody designed to bind free IL-8, a key chemokine in psoriasis and deactivate it in theskin[42, 43]. In early trials, the drug has demonstrated good clinical responsein psoriasis [44, 45].

14. Omalizumab

Omalizumab is a recombinant, humanised, monoclonal antibody against immunoglobulin IgE. This agent acts as a neutralising antibody by binding IgE at the same site on IgE as its high-affinity receptor, FcεR$_1$, thus inhibiting the biological effects before the generation of allergic symptoms [46]. There are reports of the efficacy of omalizumab in chronic urticaria [47], cold urticaria [48] and atopic dermatitis [49].

15. Mepolizumab

Mepolizumab is a humanised monoclonal IgG antibody to the IL-5 molecule, which is essential for eosinophil growth and differentiation. Two weekly infusions showed significant clinical improvement in atopic dermatitisand clinical trials are underway for hyper-eosinophillic disorders [50, 51].

16. SMART Anti–IFN-γ

SMART anti–IFN- γ,a humanised monoclonal antibody, binds and inactivates IFN- γ, an important Th1 cytokinein psoriasis. Early phase studies are being performed at this time [52].

B) FUSION ANTIBODY PROTEINS

Fusion proteins, also known as chimeric proteins, are proteins which are created by the fusion of the receptor domain of a human protein with the constant region of human IgG. The resultant fusion protein binds specifically to a ligand or co-receptor [53]. The most commonly used fusion proteins in dermatology are briefly described below and enumerated in Box 1.

1. Alefacept

Alefacept is a bivalent recombinant fusion protein composed of the first extracellular domain lymphocyte function antigen 3 (LFA-3), fused to the hinge domain of human IgG1. The LFA-3 portion of alefacept binds to CD2 receptors on T-cells, thereby blocking their natural interaction with LFA-3 on antigen presenting cells (APCs). The IgG1 portion of alefacept binds to FcγR receptor on natural killer cells to induce T-cell apoptosis [54].

Important uses of Alefacept

Psoriasis: The US FDA approved alefacept in January 2003 for treatment in adult patients with moderate to severe chronic plaque psoriasis. It is given by intramuscular or intravenous route with a dose of 10-15 mg IM weekly or 7.5 mg IV weekly

and a 12 week course is recommended [5, 54]. Two 12-week courses showed a75% or greater reduction in the PASI [55].

Alopecia areata: Case reports have shown that alefacept may be effective in the treatmentof AA[56, 57].

Pyoderma gangrenosum: Alefacept has been used for pyoderma gangrenosum and improvement was shown in 25% of these patients [58].

Other Indications

Some of the off-label conditions where alefacept has been used with success are graft-versus-host disease (GVHD), lichen planus, alopecia areata, atopic dermatitis, mycosis fungoides,alopecia universalis, erosive lichen planus,Hailey-Hailey diseaseand hand dermatitis [58, 59, 60, 61, 62, 63].

2. Denileukin diftitox

Denileukin diftitox is a novel recombinant fusion protein consisting of fragments of diphtheria toxin linked to human interleukin-2 and works by targeting the high-affinity interleukin-2 receptors. It was tried in patients with recalcitrant psoriasis and the rate of improvement for treated patients was found to be significant [64].

3. Abatacept (Ctla4ig)

It is a fusion protein composed of the extracellular domain of CTLA4 and the Fc region of IgG4. It interferes with T-cell activation by competitively binding the B7.1 and B7.2 molecules on the surface of APC [65]. In a study, patients with stable psoriasis vulgaris showed good improvement with IV infusion of abatacept [33]. A second generation CTLA4Ig, Belatacept, is currently under Phase II clinical trial for allograft diseases [66].

4. Etanercept

Etanercept is a recombinant fully human dimeric fusion protein comprising of the human TNF-α p75 receptor and the Fc portion of human IgG1 molecule. It functions as a TNF inhibitor, thereby preventing interaction with its cell surface receptors on target cells and blocking its pro-inflammatory effects.

Important uses of Etanercept

Psoriasis: Etanercept (Enbrel®) is FDA approved for use as subcutaneous monotherapy in psoriasis. Several clinical trials have shown that it is effective[67, 68, 69, 70]. The adult dose is 50 mg/week, given subcutaneously for three months [5]. The drug is also indicated for treatment of psoriatic arthritis [71, 72].

Hidradenitis supprivata:There is a study of etanercept in patients with severe hidradenitis with more than 50% score improvement[12].

5. Onercept

Onercept is a recombinant human soluble p55 tumour necrosis factor binding protein under development for the potential treatment of psoriasis and psoriatic arthritis[73].

C) RECOMBINANT HUMAN CYTOKINES AND GROWTH FACTORS

Cytokines are non-immunoglobulin proteins and glycoproteins produced by a wide variety of cells in the human body and released in response to any immune stimulus [74, 75]. Recombinant cytokines or cytokine antagonists have been used as immunomodulators [76]. The principal recombinant cytokines used in dermatology, enumerated in Box 1, are described below.

1. Interferons (IFNs)

IFNs, a family of related proteins, are produced by virus-infected leucocytes. They exhibit anti-proliferative, immune-modulatory and anti-neoplastic functions [77].

· ***Interferon α***

Recombinant IFNα is given as a subcutaneous or intramuscular injection to treat verruca vulgaris [78] , condyloma acuminatum [79], cutaneous T cell lymphoma [80], Kaposi's sarcoma (AIDS related) [81], melanoma [82], basal cell carcinoma [83], squamous cell carcinoma [84], actinic keratosis [85], Behçet's disease [86], hemangiomas [87] and keloids [88].

The injections are usually given thrice weekly and the dose (depending on the condition being treated) varies from low-dose therapy for condyloma acuminatum to high-dose therapy for melanoma [89, 90]. Of late, pegylated IFNα is being used for convenience, because it has a longer half-life and hence can be given once weekly [80].

· ***Interferon-γ***

It is FDA approved for the treatment of chronic granulomatous disease [91] and has also been used in atopic dermatitis [92]and cutaneous T cell lymphoma [90].

2. Interleukin 1 receptor antagonist (IL1Ra, Anakinra)

Anakinra is the non-glycosylated form of human IL-1Ra and acts by blocking the functions of the naturally occurring IL-1[93]. Good results have also been reported in Schnitzler's syndrome[94], familial cold auto-inflammatory syndrome [95] and psoriatic arthropathy[96]. It is given by subcutaneous injection 100 mg once a day.

3. Interleukin 2

Recombinant IL-2 is an antitumour cytokine that has been used in cutaneous T cell lymphoma (CTCL) and metastatic melanoma [97]. When given intravenously in high doses of 600,000-720,000 IU/kg in melanoma, IL-2 has produced a 15-20% overall response, with complete cure in 4-6% [98].

4. Interleukin 4 (rhIL-4)

In a dose-escalation study (0.5 to 5mg/kg given by subcutaneous injection thrice a week), IL-4 has been shown to cause improvement in psoriasis by inducing Th2 differentiation in human $CD4^+$ T cells [99].

5. Interleukin 11 (rhIL-11, Oprelvekin)

It has also shown reasonably good results in the treatment of psoriasis at doses of 2.5 or 5mg/ kg, by subcutaneous injection [100].

6. Granulocyte macrophage colony stimulating factor (GM-CSF)

GM-CSF acts by stimulating stem cells to produce granulocytes, monocytes and macrophages [101]. Recombinant human GM-CSF has been used to promote wound healing in ulcerated skin for example leg ulcers [102, 103], and for the treatment of melanoma [104] and Sezary syndrome [105].

7. Platelet derived growth factor (PDGF)

PDGF is a dimeric glycoprotein which regulates and promotes granulation tissue formation, re-epithelialisation and wound angiogenesis [106]. Recombinant PDGF-BB topical gel (100ìg/g), applied once daily, has been approved by FDA for the treatment of diabetic foot ulcers [107, 108].

8. Recombinant Human IL-10

Recombinant Human IL-10 (Tenovil)can be given in subcutaneousinjections. Early phase clinical trials have shown thatrecombinant human IL-10 three times a week improved psoriasis [109, 110].

SIDE EFFECTS OF BIOLOGICS [5, 111, 112, 113]

Some of the adverse effects of biologics are described below:

- Allergic reaction and antibody formation: Mostly seen with TNF-α blockers.
- Mild transient injection site reactions: Comprising of erythema, oedema and bruising, noted with etanercept in 10-20% of cases in the first month of therapy. Antibodies to etanercept may develop in 6% of patients.
- Infusion reaction: Occurs during or within 1-2 hours of treatment and may affect up to 20% of all the patients treated with infliximab, rarely anaphylactic shock may occur.
- Acute flu-like symptoms: Headache, chills, fever, nausea and myalgia may occur within 48 hours after administration of the first two doses of efalizumab and Interferon α.
- Infections: Reactivation of tuberculosis may occur on treatment with anti-TNF-α agents and sepsis secondary to*Listeria monocytogenes* and *Histoplasma capsulatum* have been reported [113].
- Malignancy: Patients previously treated with PUVA represent an at-risk group.
- Demyelinating disease: Worsening of multiple sclerosis and demyelination reported with infliximab.
- Thrombocytopenia: Occurs with efalizumab and warrants discontinuation of therapy.
- Autoimmune haemolytic anemia: Occurs 4-6 months after the start of treatment with efalizumab.
- Congestive cardiac failure: Worsening of congestive cardiac failure with TNF-α blockers is reported to occur.
- Antinuclear antibodies and lupus-like syndrome: May develop during therapy with anti-TNF-α agents, but not associated with symptoms and signs of lupus in the majority.
- Hepatitis: Reported following infliximab therapy, occurring from 2 weeks to more than a year after initiation of treatment. Treatment should be stopped in the event of jaundice and/ or marked elevations (>5 times the upper limit of normal) in liver enzymes.

PATIENT SCREENING FOR BIOLOGIC THERAPY [113, 114]

All patients to be put on biologics should undergo a thorough evaluation including detailed clinical history, physical examination and relevant investigations with particular reference to known toxicity profile of the agent being considered. The investigations generally advised are[113]: full blood count, liver and renal function tests, screening for hepatitis and HIV infection, anti-nuclear antibodies, anti-ds DNA, urine analysis, chest X-ray and Tuberculin skin testing.

For efalizumab, haemogram (including platelet count) is recommended monthly for the first 3 months and then every 3 months. For TNF blockers, it is done at 3 months initially and repeated every 6 months.

Liver and renal function tests, serum electrolytes and urine analysis are done at 3 months initially and then every 6 months.

EXCLUSION CRITERIA/ CONTRAINDICATIONS

There are various contraindications for use of biologics, warranting their exclusion and precautions are to be exercised

because of their immune-modulator properties. The main exclusion criteria are: active tuberculosis, severe congestive heart failure, patients having >200 treatments of PUVA (because of a risk of developing malignancies with anti- TNF agents), history of demyelinating disease or optic neuritis, hepatitis B and C positivity, HIV positivity, premalignant states, active infections and high risk states such as chronic leg ulcers, persistent or recurrent chest infections and indwelling urinary catheter infections, pregnancy and breast-feeding.

ASSESSMENT OF THE RESPONSE TO BIOLOGICS

Many scoring systems for assessing the severity of various dermatological diseases exist. These scoring systems and other indices can be used for assessment of response to the use of biologics. For example, for evaluation of improvement in psoriasis, PASI (psoriasis area and severity index) and DLQI (dermatology life quality index) are recommended at 3 months initially and then every 6 months [113]. Reduction in baseline PASI score of >75% is the standard used by FDA to assess the efficacy of a new psoriasis agent [115]. Similarly in atopic eczemas, improvement is monitored based on the Eczema Area and Severity Index, Pruritus Severity Assessment and DLQI. Reduction of the Eczema Area and Severity Index score by 50% is considered excellent, 30-49% moderate and <29% non-significant.

SUMMARY

To summarise, biologics represent the future of therapeutics, not only in dermatology but also in other fields of medicine. Among the various dermatological disorders where they are used, biologics have been most evaluated in psoriasis [116]. However, the possibility of serious infections and the oncogenic potential combined with the high cost of the drugs limit their routine use at the present stage [117]. Regular re-evaluation of efficacy and safety is essential if these agents are to be used to the maximum benefit of patients[118].

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