The Risk/Benefit Profile of Biological Therapy in Dermatological Diseases

Essay

Submitted for Partial Fulfillment of Master Degree in

Dermatology & Venereology

Presented by

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(M.B., B.CH.)

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Introduction

Biological therapeutic agents are partially or fully humanized proteins that target different pathways of the immune response ***(Grubeck et al., 2002).***
The biological therapy began with the discovery of immunization more than 200 years ago. About a century later, biological therapy was used to treat cancer patients ***(Girolomoni et al., 2002).***

In the mid-1980s, encouraging results were seen in the use of interferon to treat a rare blood disorder called hairy-cell leukemia, as well as chronic myelogenous leukemia, AIDS-related Kaposi's sarcoma, and genital warts ***(Bickels et al., 2002).*** More recently, it was proved that the human immune system could be directed to discriminate between healthy cells and cancerous ones ***(Wallack et al., 2006).***

The long-term nature of chronic dermatological diseases creates psychological and financial burden that impacts the patients' quality of life. Biologics are the newest therapeutic agents used in a variety of dermatological diseases. These agents act relatively quickly and effectively, but, used to treat patients for long periods of time, so there is a need to review the safety and efficacy of these agents ***(Soccio et al., 2009).***

Most biological agents can be placed in one of three groups depending on their mechanism of action: **cytokine blockade**: Interleukin (IL)-1 receptor antagonist, IL-18 binding protein, soluble tumor necrosis factor (TNF) receptor, antibodies to TNF-α, IL-6, IL-15 and IL-17 and BLYS (B lymphocyte stimulator); **cell depletion:** antibodies to cluster of differentiation (CD) 20 on B cells; **regulatory cell surface receptor blockade:** abatacept (cuentaneous T lymphocytic antigen (CTLA)-4 fusion protein), efalizumab (anti-CD11a antibody), alefacept (LFA-3 fusion protein) ***(Borjon et al., 2006).***

Etanercept (a dimeric fusion protein comprising the extracellular ligand-binding portion of the human p75 TNF receptor and the fragment crystallization (Fc) portion of human IgG1), **adalimumab** (a fully human monoclonal immunoglobulin G1 (IG1) antibody), **alefacept** (a recombinant fully human leukocyte function-associated antigen (LFA-3-IgG1), **efalizumab** (is a recombinant humanized monoclonal antibody against the alpha subunit (CD11a) of LFA-1) **, infliximab** (a monoclonal antibody that consists of a murine fragment antigen binding (Fab) portion specific for human TNF-alpha and the constant region (Fc) of human IgG1), **rituximab** (monoclonal humanized antibody directed in the B cell-specific antigen CD20), and intravenous immunoglobulin (IVIG) are biological drugs that have been evaluated in patients with psoriasis and psoriatic arthritis ***(Graves et al., 2007).***

These drugs have been also evaluated for other dermatologic diseases including: pyoderma gangrenosum, pemphigus, vasculitis, hidradenitis suppurativa, lichen planus, atopic dermatitis, alopecia areata, cutaneous sarcoidosis, behçet's disease, wegener's granulomatosis, pityriasis rubra pilaris, dermatomyositis, connective tissue diseases, non-Hodgkin's lymphoma, mucinosis and urticaria ***(Gordon et al., 2006).***

The British Association of Dermatology has recently published detailed guidelines covering the criteria of choice of biological drugs, according to these guidelines; efalizumab is preferred for patients with a high risk of latent tuberculosis or evidence of demyelinating diseases. Infliximab is recommended when rapid disease control is required, and etanercept is to be chosen for the treatment of stable psoriasis, patients with moderate-to-severe psoriasis in adults who failed to respond to, had a contraindication to, or were intolerant of other systemic therapy including cyclosporin A, methotrexate, or PUVA, respond to these therapies. The drug has been shown effective also in the treatment of erythrodermic and pustular psoriasis ***(Pastore et al., 2008).***

The use of tumor necrosis factor-alpha (TNF-alpha) inhibitors in the management of chronic inflammatory conditions is increasing in dermatology, but it was associated with skin reactions as leukocytoclastic vasculitis, urticaria, eczema and a pustular eruption involving the palms and soles. The mechanism for these eruptions is not known, but it has been postulated that TNF-alpha and interferon cross regulation play an important role in their pathogenesis ***(Kristjansson et al., 2008).***

Cutaneous sarcoidosis is known as one of the great imitators in dermatology. Corticosteroids are the mainstay of treatment for sarcoidosis, alternative drugs, such as anti-TNF-α may be required in chronic resistant sarcoidosis or in conditions where systemic corticosteroids are contraindicated. Efficacy of these drugs in patients with sarcoidosis, depends on patients' convenience, access to treatment, and patients' preferences. Also efficacy depends on their tolerance to their side effects which include injection site reactions, infusion reactions and rarely optic neuritis, exacerbations of multiple sclerosis, aplastic anemia, interstitial lung disease, lupus like syndromes, hepatotoxicity, serious respiratory and skin infections ***(Rubio et al., 2008).***

Intralesional therapy modalities generally lack the severe side effects of systemic therapies and can be desirable alternatives to surgery, systemic therapy, or radiotherapy. Intralesional IL-2 is effective in the treatment of malignant tumours, as melanoma metastases, and can be used in squamous cell carcinoma, metastatic eccrine poroma, malignant haemangioendothelioma and carcinoma erysipeloides ***(Radny et al., 2003).***

Interferon-α 2b (IFNα 2b) had proved to have some consistent anti tumor activity in locally advanced and metastatic diseases as melanoma and cutaneous lymphoma but it was associated with significant toxicity resulted in limitation of their widespread acceptance, this finding did not change the world-

wide debate on whether the clinical benefit of (IFNα2b) could be offset by its toxicity ***(Agarwala et al., 2002)***.

Toxic side effects, uncertainties about its efficacy, its relative economic burden, and burdensome treatment duration and monitoring, have led many physicians to question the risk/benefit ratio of it as adjuvant therapy in melanoma patients at high risk of recurrence ***(Sileni et al., 2006).***

In discussing long-term safety of biological therapy, there are multiple rare side effects that together create a long list of adverse events that may overemphasize the true risks seen in clinical practice. It is important to assess the true risks with the benefits of these biologics in treating patients with these drugs as the majority of patients can expect long-term benefits and good outcomes ***(Lima et al., 2009).***

Aim of the essay

Searching for new advanced studies in biological therapy, concerning its therapeutic role in different skin diseases including inflammatory diseases and malignancies, and its risk/benefit on the patient's health.

The essay will include:

- Introduction and Aim of the essay
- Review of Literature
- English Summary
- References
- Arabic Summary

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(نرفع درجات من نشاء وفوق كل ذي علم عليم)

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- **B cells:** B-lymphocytes.
- **BCG:** bacillus calmette–guérin.
- **BADBIR:** British Association of Dermatologists Biologic Interventions Register.
- **BSA:** body surface area.
- **BSR:** British Society for Rheumatology.
- **CBC:** complete blood count.
- **CD cells**: cluster of differentiation cells.
- **Ch**: constant domain of the heavy chain of human immunoglobulin.
- **CTLA-4:** cytotoxic T lymphocyte-associated antigen 4.
- **DNA:** deoxyribonucleic acid.
- **DLQI:** dermatology life quality index.
- **FasL**: Fas ligand.
- **FDA:** food and drug administration.
- **HIV:** human immunodeficiency virus.

- **HLA:** human leukocyte antigen.
- **HPV:** human papillomavirus.
- **IFNAR:** interferon alpha-receptor.
- **IFNGR:** interferon gamma-receptor.
- **IFNs:** Interferons.
- **IgA:** immunoglobulin A.
- **IGE:** immunoglobulin E.
- **IgG:** immunoglobulin G.
- **IL:** interleukin.
- **IL-1RA:** interleukin-1 receptor antagonist.
- **IM:** intramuscular.
- **INF:** interferon.
- **IV:** intravenous.
- **IVIG**: intravenous immunoglobulins.
- **mAbs:** monoclonal antibodies.
- **MHC:** major histocompatibility complex.
- **MMP:** metalloproteinases.
- **NYHA:** New York Heart Association.
- **PASI:** psoriasis area-and-severity index.