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Case Report

Advances in Treatment Options for Psoriasis

Abstract

Psoriasis is a skin disease that is evidenced primarily by plaques which can be seen throughout the body. Genetic predisposition that combines with an environmental trigger of the immune system is believed to be the root cause of psoriasis. This leads to signaling factors which coordinate the progression of inflammation and psoriatic plaques. Psoriatic patients commonly use topical agents, phototherapy, and systemic agents; however, biological therapies have become increasingly popular. This is primarily due to recent advances in the study of psoriasis which have shown that monoclonal antibodies and dimeric fusion proteins inhibit key signaling molecules within the inflammatory cascade such as TNFα, IL-12 and IL-23. This article reviews the advances made to understand the role of TNFα in the progression of psoriasis, discusses treatment options such as topical agents, phototherapy and systemic agents, and then compares a variety of monoclonal antibodies and dimeric fusion proteins as biological therapies.

Introduction

Psoriasis is a complex autoimmune disorder that affects ~2-3% of the human population [1]. Psoriasis has four major types: plaque, guttate, inverse, and pustular. Plaque psoriasis is the most prevalent and patients with plaque psoriasis suffer from red, itchy, scaly patches which can spread throughout the body [2]. Guttate psoriasis, occurring mostly in children, is seen as small pink-dots in the outer limbs [4]. Inverse psoriasis, commonly observed in overweight people, is evidenced by red lesion in the armpits and private regions [5]. Pustular psoriasis is accompanied by pustules (bumps filled with pus) that lead to fevers, nausea, and muscle weakness [6]. While psoriasis has many different sub-types, it is primarily due to epidermal hyper proliferation and inflammation. Although psoriasis is a recurring condition, it is not a fatal disease.

As a skin disease, psoriasis is mainly due to genetic predisposition and an environmental trigger. Within the genetic component, T cells and the major histocompatibility complex (MHC) play key roles in the progression of psoriatic inflammation [7]. Additionally, mutations within PSORS1 to PSORS9, IL12B of chromosome 5q and IL23R of chromosome 1p play critical roles within the inflammatory cascade [7,10]. Specifically, psoriatic patients have HLSA-Cw6 which codes for MHC class I protein and CDSM variant 5, which leads to corneodesmosin being up-regulated within the epidermis of psoriatic patients [8]. From a genetic side, IL12B and IL23R are involved in the expression of their corresponding receptors, which together play critical roles in T cell differentiation and the inflammatory cascade with key molecules such as necrosis factor-α and nuclear factor kB [9,10]. Additionally, patients suffering from guttate psoriasis have IL36Rn mutations.

Although genetic mutations are critical in engendering psoriasis, environmental triggers are often needed to induce an inflammatory response. Within an adaptive immune response, an antigen enters the body and prompts antigen-presenting skin cells (APSCs) to penetrate the lymphatic system, activate T cells, and engender the secretion of cytokines which induce the inflammatory cascade and psoriatic skin plaques [11,12]. However, in the innate immune system there are more identifiable mediators. For instance, toll-like receptors (TLRs) which are type 1 membrane glycoproteins that recognize pathogen associated molecular patterns (PAMPs), are important in the inflammatory cascade [13]. Within this cascade the keratinocyte barrier can be disturbed, NK lymphocytes can be activated, and natural killer receptors can be expressed. Interferon gamma (IFNγ), released by NK lymphocytes, and TNFα, released by keratinocytes, work together to create inflammation, which is a physical characteristic of plaque psoriasis [14,15]. Another prevalent characteristic of plaque psoriasis is epidermal hyperplasia. Within this condition, keratinocytes proliferate and within the focal regions Type 1 effectors accumulate and induce cytokines such as IL-12, IL-23, IFNγ, and TNFα [16,17]. Specifically, IL-12 and IL-23 are related to T cell differentiation and activation of T helper 1 cells phenotypes.

Signaling molecules and role of TNFα

Additional cytokines play critical roles in adhesion, sub-type specific influx, trafficking and compartmentalization of leukocytes [18]. These include TARC and MDC, which preferentially recruit skin-homing memory T cells via the stimulation of integrin-ICAM-1 adhesive interactions [19]. T cells and Langerhans skin cells also express chemokine receptor GPR-1 (CCR10) for the ligand CTACK (CCL27), which significantly contributes to epidermal localization. Keratinocytes can also induce MIP-3α, which is another pro-inflammatory cytokine [20]. In addition, the epidermis accumulates neutrophils (Munro's microabscesses), which are extremely prevalent in psoriasis [21]. Within the psoriatic scales, there is high content of IL-8 and GRO-α, which are neutrophil-attracting chemokines [21]. IL-8 down regulates IL-10 receptor such that there is a loss of immune-regulation within psoriatic lesions.

TNFα is a pleiotropic pro-inflammatory cytokine that is markedly up-regulated in psoriatic patients. It is produced by activated

macrophages, natural killer (NK) cells, $CD4^+$ and $CD8^+$ T cells in response to stimulation by antigens, pathogens, immune complexes, pro-inflammatory cytokines and TNFα itself by auto-feedback loop [22]. TNFα is a transmembrane homo-trimeric protein, with each monomer being ~26kDa in molecular weight [23]. Upon proteolytic cleavage by TACE/ADAM17, a soluble trimer of TNFα of ~51kDa is released as an inflammatory cytokine [23]. The soluble version of TNFα binds to TNF receptor 1 (TNFR1; p55 CD120a) and TNF receptor 2 (TNFR2; p75; CD120b) [24]. Both TNF receptors 1 and 2 are part of a family of membrane and soluble proteins that are involved in cell differentiation, survival, apoptosis, production of cytokines and chemokines and the inflammatory response [25]. Specifically, TNFR1 is the primary receptor of TNFα activity, while TNFR2 is involved in the activation of T cells, regulation of lymphocytes, and synergization with TNFR1 [25].

In addition, TNFα, which stimulates the production of chemokines, is a chemo-attractant protein that mediates the stimulation and activation of lymphocytes [26]. TNFα up-regulates adhesion molecules and then facilitates lymphocytes to the skin. It also increases the vascular endothelial growth factor, which increases capillary permeability in angiogenesis [26]. This increase in capillary density, recruitment of immune cells to the epidermis, and accumulation of keratinocytes and other mediators within the inflammatory cascade, all lead to erythema and psoriatic plaques [26]. Additionally, TNFα induces macrophages to produce cytokines IL-6 and IL-1 [28]. TNFα also increases expression of adhesion molecules [24].

Also, the TNF receptors, upon binding to TNFα, undergo conformational changes in which SODD (silencer of death domains) is released from the intracellular domain [24]. This allows for the TRADD (TNFα receptor 1 associated death domain protein) to bind to the death domain and allow for activation of NF-kB, which is a transcription factor that plays a critical role in inflammation, activation of MAPK pathways, and induction of death signaling [24]. Hence, targeting cytokines, chemokines, TNF-α, and interleukins are effective therapeutic goals in treating plaque psoriasis.

Treatment options

Currently there are a wide range of therapies available to combat plaque psoriasis. These include topical treatments, phototherapy, tonsillectomy, systemic therapies and biologics. Topical treatments and systemic therapies are being prescribed as the first line treatment options whereas phototherapy is no longer in use because of significant side effects. Recently, advances have been made to understand the molecular basis of psoriasis which led to the development of new class of biologics as treatment options.

Topical treatment

The most common medication is topical treatment, a medication that is applied directly to skin plaques. These include corticosteroids, anthracene derivatives, vitamin D3 derivatives, and retinoids. These topical agents work by normalizing excessive cell proliferation, reducing inflammation, and hindering swelling to prevent psoriatic plaques [27]. Some of the topical steroids are derived from the corticosteroid hormones that are produced by the human adrenal glands. Other topical agents incorporate salicylic acid, which is a keratolytic (peeling agent), to directly remove the scales of psoriatic plaques [28]. Dovonex (calcipotriene) uses synthetic vitamin D3 to hinder cell growth and to remove lesions. Taclonex (calcipotriene and betamethasone dipropionate) slows epidermal cell growth and reduces inflammation [29]. Tazorec (tazarotene) is a vitamin A derivative, vectical (calcitriol) is a natural form of Vitamin D3, and zithranol-RR (antralin) uses synthetic chrysarobin [29]. Although topical agents are the first-line of defense for mild to moderate psoriasis, other treatment options also exist.

Phototherapy

Another common type of treatment for psoriasis is phototherapy, which is a method that has been in place since 1976. Phototherapy is more commonly known as Ultra-violet therapy and it is used to treat moderate to severe plaque psoriasis. The methodology relies on using UV-C (100-290nm), UV-B (290-320nm), and UV-A (320-400nm) light that lead to keratinocyte apoptosis and hence reduce the development of plaques within the affected individuals [30]. However, this therapy has many limits because the exact mechanism is yet to be understood and repeated UV exposure is known to lead to skin cancer [30].

Tonsillectomy

Streptococcal infection has been connected to the onset of plaque psoriasis within a subset of patients. A critical component within this triggering mechanism could be the infection activating T cells to epitopes of keratin within the skin [31]. Since, palatine tonsils are an immunological organ that may create auto-reactive T cells to epitopes within the skin, tonsillectomy has recently gained traction as a valuable treatment option for psoriatic patients [31].

Systemic therapies

Systemic therapies are treatment options that affect systems involving the entire body. One well known type of systemic drug is methotrexate, which was found to be an effective treatment for psoriasis since 1950s and was approved by the FDA in the 1970s [32]. Psoriatic patients can take methotrexate orally in either as a pill or liquid form once a week [32]. On the molecular level, methotrexate is a class of medications known as antimetabolites that inhibit enzymes within purine metabolism, inhibit T cell activation, and suppress intercellular adhesion molecule expression by T cells [33]. Since psoriasis has a large inflammatory component that is mediated by activated T cells and adhesion molecules, methotrexate works well as a systemic agent to target molecules within the inflammatory cascade to prevent the progression of psoriasis.

Other forms of systemic therapies, such as cyclosporine and acitretin (Soriatane), work well against plaque psoriasis but also carry significant side effects. Specifically, cyclosporine daily, is an oral drug that combats psoriasis by suppressing the growth of immune and skin cells [34]. Hence, long-term use of cyclosporine compromises the immune system and has side effects such as impaired kidneys and high blood pressure [35]. Acitretin, which is developed from vitamin A, is a daily oral drug that works well with phototherapy to combat psoriasis [36]. Specifically, acitretin affects the growth and shedding

process of skins cells; however, it has numerous side effects such as hair loss, depression, and birth defects [37].

Biologics

Recently many biological drugs have been developed to treat several autoimmune diseases including psoriasis. Biological drugs are mainly recombinant and/or purified therapeutic proteins that are derived either from living cells cultured in laboratory settings or purified from living sources [38]. These drugs are given by injection or intravenous (IV) infusion [38]. While biological drugs purified from living sources such as human plasma, have been successfully used to treat human diseases for the past several decades, modern molecular biologic and biochemical techniques have greatly accelerated the production of effective biological drugs using recombinant methods [38]. Unlike systemic drugs which are known to impact the entire immune system non-specifically, biological drugs have the potential to work more effectively and specifically [38]. These biological drugs have the ability to target specific molecules within the immune system [38]. The most prevalent biological drugs developed to treat psoriasis target specifically either TNFα or interleukins 12 and 23 [38]. Since these molecules play specific roles during the development of plaque psoriasis, targeting them with biological molecules has been very effective. Currently available biological therapies to treat psoriasis are monoclonal antibodies targeting either TNFα or interleukins 12 and 23, and an IgG1 fusion protein targeting TNFα.

Monoclonal antibodies and fusion proteins as specific biological therapies for psoriasis

Monoclonal antibodies (MAbs) are mono-specific antibodies that are made by the same immune cells, in contrast to the polyclonal antibodies that are made by different immune cells [39]. MAbs are particularly useful in that they bind to a particular epitope and hence are specific for molecules [39]. MAbs were previously made by hybridoma cells in which mice were immunized by a particular antigen and then myeloma cells were fused with the spleen cells from the mice to produce a cell line that would constitutively produce antibodies [39]. However, since MAbs were made from mice and not humans, there existed notable structural differences [40]. Hence, another approach was used by adopting recombinant DNA method to produce chimeric antibodies in that they are part mouse and part human.

In contrast, dimeric IgG fusion proteins consists of polypeptides that each have non-immunoglobin polypeptide domains and a dimerizing IgG Fc domain along with a polypeptide linker [41]. Dimeric IgG fusion proteins are particularly important in increasing the serum half-life of polypeptide chains and hence are very useful in treating the inflammatory cascade for plaque psoriasis [41].

The advances made in producing MAbs and dimeric IgG fusion proteins shown that biological therapies are effective options for treating plaque psoriasis [42]. The anti-TNF MAbs binds to TNFα and the anti-IL12 and IL23 MAb binds to the p40 shared domain of IL-12 and IL23 [42]. Upon binding, these biological therapies can control the progression of plaque psoriasis by inhibiting specific signaling molecules within the inflammatory cascade. These biological therapies include Enbrel, Humira, Remicade, Simponi, and Cimzia. Additionally, there are several more in the advanced phase of clinical trials.

Amgen is marketing Enbrel (etanercept), which was approved by USFDA to treat moderate to severe psoriasis [43]. Enbrel is an IgG fusion protein in which the Fc region of human IgG1 is fused to two domains of TNFα receptor 2 (p75) [43]. The TNFα receptor 2 domain allows Enbrel to bind to TNFα, the F_c region IgG1 part of Enbrel allows for it to bind to B cells, and the mast cell F_c receptors allow for reduced stimulation [43]. Enbrel has a molecular weight of ~110kDa and binds to TNFα with 11pM affinity [44]. Psoriatic patients are treated with Enbrel with monthly injections [44]. Additionally, since Enbrel is a fusion protein it has an extended serum half-life within the blood stream and has long lasting biological effects [44].

Humira (adalimumab) is a fully human anti-TNFα MAb based therapeutic drug developed by Abbott Laboratories and has been approved by USFDA to treat plaque psoriasis [45]. Humira's molecular weight is ~148kDa and it contains human IgG1 kappa chain framework. Humira binds specifically to the soluble and transmembrane bound TNFα [45]. Hence Humira effectively inhibits TNFα function by steric interaction. Humira has 14 days of *in vivo* half-life within the serum and binds to soluble TNFα with ~127pM affinity [46]. Psoriatic patients take ~160 mg loading dose, 80mg second dose after two weeks, and 40mg dose every two weeks thereafter as injections directly under the skin [47]. Humira is another effective biological treatment for psoriatic patients as it inhibits both the soluble and transmembrane form of TNFα, which is a key component in the inflammatory cascade found within psoriatic plaques.

Remicade (infliximab) is a mouse-human chimeric anti-TNFα MAb based drug marketed by Janssen Biotech to treat psoriasis and psoriatic arthritis [48]. It is a ~149kDa protein that has IgG1 kappa chain that binds specifically to soluble TNFα and transmembrane TNFα to inhibit the pro-inflammatory functions of TNFα [48]. Remicade binds to TNFα with ~44pM affinity [49]. In addition, Remicade has an *in vivo* half-life of roughly 8.5 days [49]. Psoriatic patients take Remicade through IV; with 4 mg/kg patient at initial weeks and then 2 to 6 mg/kg every 8 weeks thereafter [49]. Remicade is also an effective biological treatment for psoriatic patients due to its ability to specifically inhibit TNFα, which is a pro-inflammatory cytokine found up-regulated within psoriatic patients.

Simponi (golimumab) is a fully human IgG1 kappa MAb, produced by Janseen Biotech that also binds to soluble TNFα as well as the transmembrane bound TNFα to inhibit the pro-inflammatory functions of TNFα [50]. Simponi has a molecular weight of ~147kDa, in vivo half-life of 14 days, and binds to soluble TNFα with 18pM. Psoriatic patients take Simponi once a month in 50 mg dose as injections directly under the skin [51]. Simponi binds directly to TNFα and inhibits its pro-inflammatory functions [51].

Cimzia (certolizumab pegol) PEG is a human IgG1 kappa chain Fab' fragment conjugated to PEG and has an approximate molecular weight of ~95 kDa [52]. It is also a biological drug that binds to both soluble and transmembrane TNFα. Cimzia blocks the pro-inflammatory functions of TNFα. It has ~14 days of *in vivo* human

serum half-life and it binds to soluble TNFα with ~90pM affinity [52]. Psoriatic patients take 400 mg of Cimzia via injection at week 0, 2, and 4, and then 200 mg every other week thereafter [52].

Other than TNFα inhibitors, one more biological drug currently available to treat psoriasis is Stelara (ustekinumab). Stelara is a fully human IgG1k MAb marketed by Janseen Biotech and targets both interleukin-12 and interleukin-23 [53]. Stelara functions as an effective biological therapy for psoriatic patients by binding to the common p40 subunit of interleukin-12 and interleukin-23 [v]. These two cytokines are involved in the activation of T cells and are key mediators in the Th1 and Th17 inflammatory pathways [53]. Psoriatic patients take 45 mg injections of Stelara at weeks 0 and 4, and then every 3 months thereafter [53]. Stelara works by blocking IL-12 and IL-23 from activating T cells, which play a crucial component within the inflammatory cascade of the development of plaque psoriasis; hence, it is an effective treatment option for psoriatic patients.

While the aforementioned biological drugs are effective in treating moderate to severe plaque psoriasis, there are side effects, especially in relation to the monoclonal antibodies and dimeric fusion proteins. For instance, many of the biological drugs suppress the immune system, hence they increase the chances of infections and some forms of cancer [54]. Other side effects include headaches, abdominal pain, and upper-respiratory infections [54].

Currently, there are numerous biological drugs in the research and development pipeline to treat psoriasis. For example, Amgen and AstraZeneca completed phase III trials of Brodalumab to treat moderate to severe arthritis. Brodalumab works by binding to the IL-17 receptor and blocking IL-17 receptor ligands from inducing inflammation [55]. Brodalumab is taken by subcutaneous injection every two weeks at a dosage of either 140mg or 210mg [55]. Brodalumab is one of many other monoclonal antibodies that show promise in treating plaque psoriasis.

Conclusion

While plaque psoriasis is a recurring disease many treatment options exist such as topicals, phototherapy, and systemic agents. Well-known and new biological therapies have shown much potential for significantly curbing the progression of the disease. Since cytokines such as TNFα, IL-12, and Il-23 play significant roles in the progression of the inflammatory cascade, biological drugs have been developed to target these cytokines and hence reduce the development and advancement of plaque psoriasis. Anti-TNFα MAbs such as etanercept, adalimumab, infliximab, and golimumab bind to soluble TNFα and inhibit its role in inflammation. Additionally, ustekinumab targets IL-12 and IL-23, which then delays the activation of T cells, which also play critical roles in inflammation. Hence, current biological therapies and future ones that will target additional cytokines within the inflammatory cascade have the potential to make plaque psoriasis a much more manageable disease.

Expert Commentary

Psoriasis is a chronic autoimmune disease that has many different risk factors including genetic predisposition and environmental triggers. Psoriatic patients often use topical agents such as those that incorporate corticosteroids as a first-line defense to control the epidermal hyper proliferation. Phototherapy is another common option as it induces keratinocyte apoptosis. Additionally, systemic agents are effective in treating psoriasis but have many side effects mainly because they are non-specific and have impacts throughout the body. Recent advances in the study of psoriasis and other autoimmune diseases have shown that mediators within the inflammatory cascade can be specifically inhibited by biological drugs with minimal side effects. Currently, there is a plethora of anti-TNFα mAbs on the market, with many binding within the picomolar range, and effectively inhibiting the progression of inflammation and development of plaque psoriasis. Other biological drugs such as ustekinumab inhibit interleukins that coordinate T cell activation, which are critical mediators of inflammation as well.

Five-year review

Although significant advances have been made in the past 30 years in the study of psoriasis and similar autoimmune diseases, additional research in the next five years will allow for a greater understanding of unresolved mediators within the inflammatory cascade to more comprehensively treat psoriatic patients. Recently much emphasis has been placed on the role of Th1, Th2, and Th17 and their associated cytokines in the initiation and advancement of psoriasis. Current and future experimental studies will be able to better discern the roles of each of these helper T cells lineages in differentiation, cytokine production, and progression of psoriasis.

Key Issues

- Psoriasis currently affects ~2-3% of the human population.
- Psoriasis has many forms such as guttate, inverse, and pustular; however, plaque psoriasis is the most common and it is notable for inflammation.
- Genetic predisoposition within the genes for T cell and major histocompatibility complex is strongly correlated with the onset and progression of plaque psoriasis.
- An environmental trigger is introduced which leads to an adaptive and innate immune response.
- An inflammatory cascade results and manifests into plaque psoriasis.
- Signaling molecules such as TNFα, IL-12, and IL-23 play critical roles within the inflammatory cascade and the manifestation of plaque psoriasis.
- Therapies include topical, UV, systemic agents, and biological drugs.
- Anti-TNFα mAbs have been proven as successful and new biologic drugs such as dimeric fusion proteins to target interleukins show much promise in treating and controlling plaque psoriasis.

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