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Systemic Therapeutics in Psoriasis: An Overview

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Abstract

Psoriasis is a common, chronic, inflammatory, multisystem disorder with predominantly skin and joint manifestations affecting approximately 2% of the population. Psoriasis typically follows a relapsing and remitting course. It can occur at any age, although is uncommon in children (0.71%) but the majority of cases occur before 35 years. Psoriasis is associated with significant comorbidities and affects patient's quality of life. Owing to visibility of psoriatic lesions, patients with severe psoriasis are especially vulnerable to social stigmatization. Furthermore, the severity of disease is directly related with lower ratings of self-esteem and a fear of social isolation. Treatment should be tailored to meet individual patient's needs.The impact of psoriasis on a patient's well-being varies greatly and is irrespective of the extent of the disease. Therefore, management should be individualized to optimize response, and should involve both non-pharmacological and pharmacological treatment. Systemic treatment is indicated in the moderate to severe form of psoriasis which in uncontrolled by topical medication and or phototherapy. Commonly used traditional systemic agents include methotrexate, ciclosoporin and acitretin. Introduction of biological agents provide a newer and safer approach of treatment. Some second tier agents may be used for treatment as per need which includes sulfasalazine, hydroxyurea, etc. Ultimately a successful management depends on clinician understanding of the various treatment options, individuality (Prakriti or psychosomatic constitution) as well as recognition of associated co-morbidities.

Key-Words: Psoriasis, systemic therapeutics, traditional agents, biologics, methotrexate

Introduction

Psoriasis is most commonly manifests on the skin of the elbows, knees, scalp, lumbosacral areas, intergluteal clefts and glans penis.Upto30% of patients, also have joints involvement. Both, sciences, Ayurveda and modern medical science accepted that diet, activities, environmental, genetic, immunological and psychological factors play key role in the etio-pathogenesis of dermatological disorders including psoriasis [1].

Psoriasis is considered a single disease entity with several morphologic variants, and a full range of severity and expression based on Heredity (certain HLA types and psoriasis susceptibility genes), environmental factors (such as trauma and climate), co-morbidities (particularly infections and emotional stress), concomitant medications and immune status of the host. To minimize the toxicity of any therapy, proper patient selection and appropriate monitoring is crucial. The administration of any systemic therapy must be individualized.

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Every patient needs to be carefully evaluated with reference to disease severity, quality of life and general medical and psychological status. Successful management of psoriasis patients depends on clinician's understanding of the various treatment options as well as their recognition of associated adverse reactions.

Assessment of disease severity and impact is fundamental to delivering high quality health care and measuring treatment outcomes. Several tools or instruments have been described to assess disease severity and treatment outcome in recent years, such as PASI (psoriasis area and severity index) score, Dermatology Life Quality Index, Physician's Global Assessment, Psoriasis Disability Index, Psoriasis Life Stress Inventory, etc. [2-6].

A clinician should have to assess the impact of disease on physical, psychological and social wellbeing and associated co-morbidities. In non-specialist clinical setting the patient should be refer to dermatologist if there is uncertainty of diagnosis, severe or extensive psoriasis, topical therapy fails to control the disease, nail disease has a major functional or cosmetic impact and psoriasis is having a major impact on a person's

physical, psychological or social wellbeing. When assessing the disease severity in any healthcare setting, there should be proper recording of the body surface area affected, any involvement of nails, high-impact and difficult-to-treat sites (for example, the face, scalp, palms, soles, flexures and genitals), systemic upset such as fever and malaise, etc. and in specialist settings, use a validated tool to assess severity of psoriasis, for example the Psoriasis Area and Severity Index (PASI) [7].

A recent survey found that psoriasis was more likely to be diagnosed by a dermatologist than by a primary care physician. 85 % percent patients with mild psoriasis were diagnosed during an initial visit by the dermatologist when compared with 55% initially seen by a primary care physician. 78% and 60% of patients with moderate to severe psoriasis were diagnosed by dermatologists and primary care physicians, respectively [8].

The severity of the psoriasis is directly co-related to poor quality of life. A population-based survey looking at the association between quality of life and extent of disease showed that nearly 60% of patients with psoriasis report that the disease affects their everyday life and 26% report a change or discontinuation of daily activities [9].

Traditional, pharmaco-therapeutics includes emollients, topical corticosteroids, phototherapy, and systemic medications [10]. Topical medication is often used as first line treatment for mild to moderate psoriasis. Phototherapy is reserved for widespread disease, or when the psoriasis is unresponsive to topical treatment. Systemic therapies are reserved for moderate to severe disease. Therapies for psoriasis are not curative but provide symptomatic management [11]. The economic burden, along with the clinically relevant reductions in quality of life experienced by many patients with psoriasis, underscores the need for prompt, effective, and sustained disease management [12].

Systemic Therapeutics in Psoriasis

The therapeutic approach must be individualized based on the spread of the disease, anatomical location, impact on quality of life, possible co-existence of psoriatic arthritis or other co-morbidities as well as the patient's compliance with the treatment.Treatment with systemic agents is typically reserved for severe, refractory, widespread or incapacitating disease, pustular or erythrodermic forms, and psoriatic arthropathy. The 3 most commonly used traditional systemic agents for psoriasis are methotrexate, Ciclosporin and Acitretin. Close clinical and laboratory monitoring for associated toxicity is mandatory for all 3 agents. Methotrexate and ciclosporin are immunosuppressant drugs. Patients undergoing systemic treatment are required to have regular blood and liver function tests due to the toxicity of the medication [13].

Novel systemic treatments for psoriasis include a rapidly expanding range of biological therapies. These are proteins (usually antibodies) with highly specific actions. Severe forms of psoriasis such as erythrodermic and generalized pustular psoriasis can be life-threatening and may require urgent treatment in hospital [14]. The biological agents used as third line therapy which includes adalimumab, etanercept, infliximab and ustekinumab. These should be prescribed by specialist dermatologists in secondary or tertiary care settings.

The need for safe and effective therapies together with an increased understanding of the pathogenesis of psoriasis had led to development of targeted biologic therapies. Rather than general suppression of immune system via drugs such as methotrexate or ciclosporin biologic target the specific alterations responsible for the pathogenesis of psoriatic lesions. These agents, therefore, offer a promising alternative for patients with moderate to severe disease.

In recent years, biologics have changed the treatment of psoriasis, giving us additional therapeutic options that are potentially less toxic to the liver, kidneys, and bone marrow and are not teratogenic. Nevertheless, traditional systemic therapies continue to play an important role in the treatment of psoriasis with their oral route of administration and their low cost (when compared with biologics) making them an important treatment option in the appropriate patient. Methotrexate is the most commonly prescribed traditional systemic therapy worldwide for psoriasis. Methotrexate can be dramatically effective even in the most severe cases of psoriasis. It has been used in combination with all of the approved biologic agents for psoriasis.

In addition to traditional systemic agents and biologics some other drugs, not specifically licensed for psoriasis, have been found effective. These include the antimetabolite tioguanine, the cytotoxic agent hydroxyurea, sulfasalazine, the immuneosuppresant mycophenolate mofetil, azathioprine and tacrolimus. These have all been used effectively to treat psoriasis when other treatments have failed.

Methotrexate

Methotrexate is an antimetabolite agent that has been used for many years in psoriasis treatment and remains one of the most effective therapies. Methotrexate has been used for psoriasis since the 1950s and remains the most widely prescribed drug for severe psoriasis

worldwide. Methotrexate is a folic acid antagonist that interferes with purine synthesis and thus inhibits DNA synthesis and cell replication. In addition to the anti-mitotic effect, it also has a specific activity of T cell suppression and, in low dose; methotrexate has anti-inflammatory and anti-proliferative effects.By inhibiting the DNA synthesis it directly inhibits epidermal cell proliferation and thus, slows down cell turnover rate [15-17].

Oral therapy is given once weekly, occasionally fortnightly. Daily regimens are dangerous and have been abandoned. For a 70 kg adult, an initial test dose of 5–10 mg is given to avoid early toxicity. Maintenance doses should be achieved by gradual increases of 2.5–5 mg/week, and usually range between 7.5 to 30 mg/week. Methotrexate may be given as a single weekly oral dose, or divided into three doses per day. Parenteral therapy is equally safe, similar doses being given intramuscularly, subcutaneously or intravenously every 7–14 days. The subcutaneous route is becoming popular with the advent of this form of administration as the norm for patients on biologic therapies. In the elderly, the effective dosage of methotrexate is below the above range, and toxicity may be more readily encountered with higher dosage, probably owing to reduced renal clearance. Patients over 80 years of age have been adequately treated with as little methotrexate as 2.5 mg/week [18].

Before treatment, renal, hepatic and marrow function must be shown to be normal. If renal function is impaired, a reduced dosage of methotrexate may be given with extreme care and regular monitoring. Liver function tests and blood urea or creatinine levels should be checked every 3–4 months during maintenance therapy. Numerous toxic effects of methotrexate therapy have recognized. In a long-term study, 73% of patients had side effects, most frequently abnormal liver-function tests, nausea and upper gastro-intestinal symptoms [19-20].

Clinical response is usually evident in 7–14 days, but maximal response may take 4–8 weeks. In addition to the drugs reviewed, furosemide (frusemide) has induced severe toxicity in one patient and a profound fatal leukopenia in another, probably by interfering with tubular secretion of the drug. Diuretic therapy should be avoided if possible, and used only with great caution if cardiac failure threatens. In the treatment of erythrodermic or pustular psoriasis where gross oedema, especially of the legs, is common, the temptation to use diuretics, especially furosemide (frusemide) should be resisted. As the psoriatic inflammation is controlled, a spontaneous diuresis will follow [21].

Folic acid supplementation increases tolerability and reduces the risk of pancytopenia, nausea, macrocytic anemia, liver enzyme elevations without altering efficacy and reduces the chances of bone marrow suppression [22].It is now established beyond all doubt that methotrexate is hepatotoxic, causing fibrosis and cirrhosis, the incidence of which has varied in different series [23-24].

Anagen alopecia, cutaneous erosions, ulceration and bleeding are rare with weekly dose regimens. Other uncommon side effects include epidermal necrosis, candidiasis, folliculitis, ataxia, kerato-conjunctivitis, depression and other psychotic symptoms, reactivation of tuberculosis and other pulmonary illnesses. Gastrointestinal bleeding has been reported. Fatal complications of therapy include rapidly progressive renal failure and septicemia, as well as the con-sequences of irreversible marrow or hepatic failure. Death has followed a single intravenous injection in a patient with severe renal failure [25-26].

Despite these limitations, methotrexate has a secure place in the treatment of severe psoriasis which is resistant to conventional topical therapy and photo-chemotherapy. It is particularly valuable in the chronic erythrodermic and generalized pustular forms, where it may be life-saving, and for weaning such patients off systemic steroids [27].

Methotrexate has been combined successfully with various other therapies such as UVB phototherapy, PUVA and etretinate, in the hope of reducing dosage and therefore toxicity of each modality, while maintaining efficacy. Methotrexate and acitretin should only be used with caution because of the risk of hepatitis. Combining methotrexate with ciclosporin appears to be effective in patients with poorly tolerated or ineffective monotherapy. Colchicine and methotrexate together have been used in generalized pustular psoriasis, and methotrexate can be used to maintain clearance induced by PUVA or a dithranol regimen [28-30].

Ciclosporin

Ciclosporin is a cyclic polypeptide (undecapeptide) consisting of eleven amino acids. It is derived from the fungus Tolypocladium inflatum Gams. It is first described in 1976 [31]. It suppresses the activation of the calcium dependent phosphatase calcineurin, inhibiting lymphokine secretion (e.g.,IL-2, IFN- γ, GM-CSF, IL-3, IL-4, TNF-α and IL-17) which leads to diminished activation of T lymphocytes. Ciclosporin also inhibits antigen presenting cells [32-34].

Ciclosporin binds to the intracellular immunophilin, cyclophilin to form a complex, which further binds to and inhibits the enzymatic activity of calcineurin

phosphatase, a serine-threonine phosphatase that depends on calcium and calmodulin for its activity, consequently, calcineurin cannot dephosphorylate an important transcription factor, the cytoplasmic component of nuclear factor of activated T cells (NF-ATc). Transport of NF-ATc to the cell nucleus, and binding of NF-ATc to the promoter region of the IL-2 gene nuclear component of NF-AT (NF-ATn), is therefore blocked and T cells can no longer produce IL-2, a cytokine required for complete activation of the T-cell pathway, granulocyte-macrophage colony-stimulating factor, and interferon-γ production [35-37].
The consequences of ciclosporin action include [38].

1. Depletion of lymphocytes and macrophages in the epidermis and dermis.
2. Down-regulation of cellular adhesion molecule expression in the dermal capillary endothelium.
3. Restricted activation of antigen-presenting cells, natural killer cells and T cells.
4. Inhibition of keratinocyte hyperproliferation
5. Restricted release of histamine from mast cells.

Ciclosporin is a lipophilic molecule having somewhat poor bio-availability from conventional orally administered formulation; therefore, a micro-emulsion preparation has developed with greater hydrophilicity and higher bioavailability [39-40].
Ciclosporin is highly lipophilic, but is active orally and metabolized in the liver by the cytochrome P-450 system. Other major exclusion criteria include renal dysfunction, uncontrolled hypertension, past or present malignancy, history of epilepsy, acute infections, other immunosuppressive therapy, con-comitant therapy with nephrotoxins, previous serious side effects from ciclosporin and known hypersensitivity. Minor exclusion criteria include abnormal liver function, previous therapy that may predispose to skin malignancy, malabsorption, drug or alcohol abuse, and concomitant treatment with drugs that affect the metabolism of ciclosporin. NSAIDs are often used by patients with psoriatic arthropathy, and may enhance the nephrotoxicity of ciclosporin [41].
An initial daily oral regimen of 2.5 mg/kg/day equally divided in two doses has been recommended. Improvement may be seen within days, but if this does not occur within 2 weeks, the dosage may be increased gradually to a maximum of 5 mg/kg/day [42].
A systematic review of therapies for severe psoriasis concluded that ciclosporin is a well-tested treatment for severe psoriasis and in the short term is probably more effective than other forms of systemic therapy. Ideally, ciclosporin should be used for short courses of 3–4 months (maximum duration). Only in some exceptional circumstances the ciclosporin should be used as continuous therapy for periods exceeding 3-4 months [43-45].
The most important side effects associated with ciclosporin are dose related hypertension and nephrotoxicity. The blood pressure may rise sharply within weeks of starting treatment, and plasma creatinine levels may increase or glomerular filtration rates decrease within the same period [46]. Ciclosporin is a widely used alternative of methotrexate, providing rapid and reliable improvement in 80% to 90% of the patients [47].
Several further comparative studies have demonstrated a good response to treatment with PASI 75 achieved in approximately 50%–70% [48-50]. Current guidelines typically recommend short course therapy for up to 12 weeks where possible [51].

Retinods

Vitamin A has long been recognized to have profound effects on epithelial differentiation. Its deficiency leads to cutaneous hyperkeratosis and squamous metaplasia of mucous membranes which stimulates the development of synthetic derivatives. Term ‘retinoid’ has been given to a family of natural and synthetic analogues of vitamin A [52-53].
The oral retinoids have been used to treat psoriasis since the early 1980s. Etretinate was the first retinoid introduced for the treatment of severe psoriasis and replaced in 1988 by acitretin, the active metabolite of etretinate. Common retinoid used in the treatment of psoriasis is acitretin. Unlike the methotrexate and ciclosporin it is not an immunosuppresant and has no formal restrictions on duration of therapy.
In the epidermis, acitretin reduces the proliferative activity and favors the differentiation of epidermal keratinocytes. Acitretin inhibits the induction of Th17 cells and promotes the differentiation of T-regulatory cells [54]. The most common side effects include hyperlipidemia and elevated liver enzymes. [55].
Treatment should be initiated and maintained at or below 0.5-1mg/kg/day or 25-50mg/day depending on therapeutic response and side effects to limit short term and long term toxicities for a usual duration of 6 to 12 weeks or 6 to 9 months. It is administered once or twice a day with meals [56]. The most common adverse effects include mucocutaneous ailments (like xerosis, cheilitis, skin fragility, and epistaxis) and minor reversible alterations in liver enzymes and lipids, which rarely necessitate cessation of therapy [57]. The most feared complications are teratogenicity and effects on bone. Acitretin response is relatively slow and a period of 3 to 6 month required to achieve a optimal response. For these reasons, the combination of

retinoids and UV light therapy may be considered where feasible and appropriate.

Although the half-life of acitretin is 49 hours, acitretin may transform either spontaneously, or as a result of alcohol ingestion, into etretinate, which has a half-life of 168 days. Based on this long half-life, it can take up-to 3 years for etretinate to be eliminated from the body. For these reasons, acitretin is contraindicated in womens, plan to become pregnant or those fail to use adequate contraception for 3 years after discontinuing acitretin [58].

The most common laboratory abnormality seen in patients treated with acitretin is hyperlipidemia, withas many as 25% to 50% of patients experiencing increase in serum triglycerides. Therefore, lifestyle modification to prevent/reduce hyperlipidemia should be encouraged in patients with psoriasis, treated with oral retinoids [59].

Despite the high incidence of nuisance side effects, acitretin has been a valuable addition to the anti-psoriatic weaponry, especially in generalized pustular psoriasis. The drug should not be used in children except in compelling circumstances and in young women unless essential. Active liver disease and pre-existing hyperlipidemia are contraindications to treatment.

Biologics

A new class of drugs that has shown notable promise for the management of psoriasis has been designated as the biologics.The biologics act at the cellular level to target specific processes that are involved in the genesis of a particular disease. Because their mechanism of action is specific, they tend not to have the widespread side effects that are associated with more globally acting agents such as corticosteroids. There are three principle forms of biologics are available which are monoclonal antibodies, fusion proteins, and recombinant cytokines or growth factors [60].

In general biologics are highly effective, including the patients in whom standard systemic agents are either ineffective or contraindicated. However, the recent withdrawal of one agent, efalizumab, on safety grounds, coupled with their high cost illustrates the need for careful patient selection. Biologics provide selective, immunologically directed intervention at key steps in the pathogenesis of the disease which include inhibition of the initial cytokine release & langerhans cell migration, targeting activated T cells, preventing further T-cell activation and eliminating pathologic T cells, blocking the interactions that lead to T-cell activation or migration into tissue, altering the balance of T-cell types and inhibition of pro-inflammatory cytokines, such as tumor necrosis factor [61]. At present, there are five biological agents licensed for the treatment of psoriasis vulgaris which are as follows [62].

1. Infliximab, a chimeric human-immune antibody to TNF-α.
2. Adalimumab, a fully human recombinant antibody to TNF-α.
3. Ustekinumab, a fully human recombinant antibody to the p40 component of IL-12/IL-23.
4. Etanercept, a fully human soluble p75 TNF-α receptor fusion protein.
5. Alefacept, a fusion protein of lymphocyte function which is associated with antigen-3 and IgG that inhibits T-cell activation. It is not licensed in the UK.

Infliximab is administered by intravenous infusion while the others are administered by subcutaneous injection [63].

Systemic corticosteroids

The glucocorticoids (steroids) have shown themselves to be double edged weapon. The flourinated forms such as triamcinolone and betamethasone have more effect on psoriasis than prednisolone [64-65].

Systemic steroids should not be used in the routine care of psoriasis. They should be used in the management of persistent or uncontrollable erythroderma that is causing metabolic complications and in fulminating generalized pustular psoriasis of the von Zumbusch type if other drugs are contraindicated or ineffective [66]. Psoriasis may remain labile and treatment resistant for many months after the withdrawal of systemic corticosteroids [67].

Steroids exert anti-inflammatory and immunosuppressive effects by modulating the genes involved in inflammatory pathways, including inhibition of cytokine production and reduction of such mediators of inflammation like prostaglandins and leucotrienes, inhibition of T-cell proliferation and T-cell dependent immunity and suppression of fibroblast and endothelial cell functions. Corticosteroids also have anti-proliferative effects, by delaying the onset of DNA synthesis and decreasing the mitotic rate [68-69].

Conclusion

Management strategy requires current, comprehensive knowledge of available therapies including the mechanism of action, clinical action spectrum, potential toxicity, and appropriate monitoring. Management also requires appropriate & regular education and support of the patient and the family. Systemic treatments including biologics opened new pathways for the treatment of psoriasis. Among the traditional systemic agents, methotrexate remains an

excellent and cost effective treatment. Patients experiencing failure and toxicity with the traditional systemic agents should offers more potent treatment options like biologics having targeted approach for treatment and second tier agents like tacrolimus, sulfasalazine, hydroxyurea, etc. Despite the several limitations, the traditional systemic agents especially methotrexate continues to serve as an important option for the treatment of psoriasis. Combination, rotational and sequential therapy may provide better options to improve overall efficacy. With advances in biotechnology, the future researches may provide more effective and safer therapeutic options for psoriasis which target the specific molecular mechanism involved in the pathogenesis.

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