Symposium - Psoriasis

Psoriasis: What is new in nonbiologic systemic therapy in the era of biologics?

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ABSTRACT

Psoriasis is a common debilitating disease significantly affecting the quality of life of the patients. Majority of the psoriasis patients have mild disease which can be managed by topical therapies. Around 30% of the psoriasis patients require systemic therapy during the course of their disease. There is a vast array of drugs for the treatment. Methotrexate, cyclosporine and retinoids are the most commonly used conventional systemic drugs. Newer studies provide insight into their more effective and safer use and as combination therapy with biologics. In recent times, many new drugs with novel mechanisms of action other than biologics have been tried in psoriasis. In this article, we have reviewed the current developments and new found role of the conventional drugs as well as the newer nonbiologic systemic drugs in the treatment of psoriasis.

Key words: Psoriasis, systemic therapy, new treatments, nonbiologics

INTRODUCTION

Psoriasis is a chronic, inflammatory, multisystem disease which chiefly affects the skin and joints. It is a common disorder affecting approximately 2–3% of the world population.[1] Exact etiopathogenesis of the disease has not been clearly understood despite immense research in this field. However, the common consensus among the researchers is that it is predominantly a T cell mediated disorder occurring in genetically susceptible individuals, influenced by environmental factors.[1]

Parallel to the fresh insight into the etiopathogenesis, there has been a vast expansion in the treatment armamentarium for psoriasis. Various modalities of treatment comprise of topical or systemic medications, photo (chemo) therapy, and an array of biologic agents. Systemic therapies are generally used in patients with severe plaque type disease (>10% body surface area [BSA] or > 10 psoriasis area and severity index [PASI]), generalized pustular psoriasis, psoriatic erythroderma, severe psoriatic arthritis (PsA) and in those who are refractory to topical therapy and phototherapy. Patients with limited disease but having significant physical or psychosocial disability can also be considered for systemic therapy. It is estimated that about 30% of the patients have moderate to severe disease necessitating systemic therapy.[2] Many patients with psoriasis are not satisfied with the treatment results, feel that they are undertreated and desire a more complete control of the disease.[3] Hence, the quest for effective and adequate systemic therapy for psoriasis continues.

In recent years, there has been an increasing trend for use of biologic agents in the treatment of psoriasis. Biologics constitute targeted molecules specifically meant to modulate the chronic inflammation in psoriasis. Five biologic agents including infliximab, etanercept, adalimumab, alefacept and efalizumab have been approved by the Food and Drug Administration (FDA) for use in psoriasis. Efalizumab has been withdrawn from the US market w.e.f 8th June 2009 following reports of four cases of progressive multifocal leucoencephalopathy (PML) (three of whom died) in patients on long-term therapy with this drug. Many new biologics are in various phases of clinical trials. But these drugs have their own limitations like

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high cost, potential serious side effects, indicated in selected individuals, and more importantly, lack of long-term safety data.

Conventional systemic therapy and newer analogues continue to find use in majority of psoriasis patients because of the ease of administration, low cost and vast experience in their use. In this article, we will be reviewing various new developments in the use of conventional systemic therapies (excluding photochemotherapy) as well as the newer nonbiologic systemic drugs for the management of psoriasis.

METHOTREXATE

Methotrexate (MTX) is a gold standard systemic drug even today.[4] Despite the insurgence of various biologic therapies, MTX still is the main stay of treatment either as monotherapy or in combination with other drugs. Traditionally, it was widely believed that its antiproliferative action (folate metabolism antagonism) is primarily helpful in psoriasis. However, results of recent *in vitro* studies suggest that MTX causes inhibition of 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase leading to accumulation of AICAR, which in turn causes increased tissue concentration of adenosine. Primarily, this increased tissue concentration of adenosine accounts for its anti-inflammatory properties leading to symptom alleviation in psoriasis.[5]

Although there are no established maximum or minimum dosages of MTX, weekly dosages usually range from 7.5 to 25 mg given orally or parenterally.[6] Most of the studies reported in literature have used MTX starting at lower doses (7.5 mg/week) and gradually escalating the dose according to the response.[7]

However, at some centers, it has been used at higher doses (0.4–0.5 mg/kg once weekly) to start, with excellent clinical efficacy and good safety profile.[8] Though there are no randomized studies comparing the two dosage schedules, starting with higher dose leads to faster control of the disease activity and shorter duration of therapy which may result in lesser cumulative dose of MTX. It is important to minimize the total cumulative dose of MTX while maintaining disease control and medication tolerance.

Intramuscular administration is helpful when there is gastrointestinal intolerance to oral dosing or if there are concerns regarding patient compliance. Subcutaneous injection is equally effective and can be self-administered at home. Braun *et al.*[9] found that injectable MTX has higher efficacy and equal tolerability compared to oral route in rheumatoid arthritis patients. Similar study needs to be done in psoriasis patients also. There is a controversy regarding the utility of giving a test dose of MTX. American Academy of Dermatologists recommends a test dose in patients with decreased calculated glomerular filtration rate and those at risk of hematologic toxicity with MTX.[6] Repeat laboratory tests for hematologic effects should be done at approximately 7 days.

Utility of folic acid (FA) supplementation is also debatable. Its use is advocated to limit the toxicity of MTX on liver, blood cells and gastrointestinal tract but there is a concern that it might reduce the efficacy of MTX. Two recent studies by Salim *et al.*[10] and Chladek *et al.*[11] have reported significant reduction in the efficacy of MTX with FA supplementation. Prey *et al.*[12] conducted a systematic review to find out the effect of FA and folinic acid supplementation on MTX associated toxicity and efficacy in inflammatory diseases. They concluded that the FA supplementation is an effective measure to reduce the hepatic adverse effects. Gastrointestinal side effects were also lesser in those who received FA but the difference from the control group was not statistically significant. Effect on the hematologic side effects could not be assessed due to the low incidence of these events. Also, the effect of FA supplementation on the effectiveness of MTX could not be analyzed as markers of activity used in each study were different.

In recent comparative efficacy studies, MTX was found to have slightly lower efficacy compared to cyclosporine A (CSA).[13,14] The drug has also been reported to be safe and effective in childhood psoriasis.[15] Recently, the efficacy of MTX has been compared with biologics in the treatment of psoriasis[7] In a double-blind, placebo-controlled study of MTX versus adalimumab, 250 patients were randomized into three subgroups receiving MTX or adalimumab or placebo. MTX was given in doses of 7.5 mg weekly, increased as needed to 25 mg per week. At week 16, PASI 75 was achieved by 19% in the placebo arm, 36% in the MTX group, and 80% in the adalimumab group. In addition, MTX has been used as a combination therapy with many biologic agents approved by

FDA. The combination therapy increases the efficacy and decreases the dose of individual drug, thereby decreasing the side effects. Specific advantage of combining tumor necrosis factor inhibitors (infliximab) with MTX has been the suppression of neutralizing auto-antibodies formation.[16,17] The drug has been combined with etanercept, when the efficacy of etanercept monotherapy is insufficient.[18] Alefacept has been used with MTX for PsA patients mostly with good results.[19]

Recent reports suggest that the interplay of several factors leads to an increased risk of cardiovascular disease in psoriasis patients and is a leading cause of mortality in this group of patients.[20] Long-term MTX therapy promotes hyperhomocysteinemia and therefore may potentially aggravate the cardiovascular diseases.[21] But a recent study found MTX to have cardio protective effects and it is speculated that probably inflammation, which has a central role in atherogenesis, plaque instability, and thrombosis, is inhibited by MTX.[22] The study also concluded that low to moderate cumulative dose of MTX was more beneficial than the higher dose and concomitant use of FA had an added advantage in the prevention of cardiovascular disease.

Non-alcoholic steatohepatitis (NASH) has been reported more commonly in psoriasis patients.[23] This group of patients are at a higher risk of development of cirrhosis if treated with MTX. Updated guidelines on liver biopsy to assess MTX induced toxicity recommend that psoriasis patients should be divided into two groups based on the presence of risk factors for liver injury.[6] Low risk psoriasis patients need not undergo baseline biopsy and liver function tests should be done at regular intervals. Liver biopsy is done at a cumulative dose of 3.5–4 g or earlier if there are more than five persistent elevations in five of nine aspartate aminotransferase (AST) levels over a 12-month period or if there is a decline in serum albumin below the normal range with normal nutritional status in the setting of well-controlled disease.[6] In the high risk patients, baseline liver biopsy is done after giving MTX for 2–6 months and repeat biopsy is done after every 1–1.5 g of cumulative dose.[6]

There is a continued search for laboratory tests which could replace liver biopsy for detection of liver fibrosis. Two recent studies have found estimation of pro-collagen 3 N-terminal peptide (PIIINP) as a useful marker of liver damage and that liver biopsies could be entirely avoided if PIIINP levels remained stable.[24,25] PIIINP assay has a limitation that it is not organ specific and measures ongoing fibrogenesis only. There are various other direct and indirect markers of ongoing liver fibrosis, which have been investigated and found to have 90% sensitivity in chronic liver disease patients.[26] Different markers have been combined to calculate indices which have been applied for the detection of liver fibrosis with varying degrees of success.[27,28] Indirect markers of liver fibrosis include α2-macroglobulin, α2-globulin, γ-globulin, apolipoprotein A1, γ-glutamyltransferase and total bilirubin.[29] Direct markers of fibrosis in addition to PIIINP, include procollagen I, type IV collagen, laminin, hyaluronic acid (HA), tissue metalloproteinases and their inhibitors.[29] These markers need to be tested in large number of psoriasis patients to find their utility in the detection of MTX-induced liver fibrosis.

Recent (2009) American Academy of Dermatologists recommendations have modified the list of absolute and relative contraindications to be observed when prescribing MTX.[6] Besides pregnancy and lactation, alcoholic liver disease or other chronic liver disease, immunodeficiency syndromes, bone-marrow hypoplasia (leukopenia, thrombocytopenia, or significant anemia) and hypersensitivity to MTX are now considered as absolute contraindications for MTX. While relative contraindications include abnormalities in renal and liver functions, active infection, obesity, diabetes mellitus, concomitant use of hepatotoxic drugs, recent vaccination with a live vaccine, and unreliable patient. Recommendations in relation to pretreatment testing and tests for monitoring during MTX therapy continue to be the same.

Comparing MTX *vis a vis* biologics, it has main advantages of low cost, oral administration, established safety data and proven efficacy over more than last five decades.

CALCINEURIN INHIBITORS: CYCLOSPORINE, TACROLIMUS, PIMECROLIMUS, VOCLOSPORINE

CSA has the highest efficacy among all the nonbiologic systemic therapies. It is called the crisis drug as it is effective in cases resistant to other modalities and brings rapid control even in very severe cases. CSA is given in doses of 2.5–5 mg/kg/day. Many studies have shown that CSA, when used for 12–16 weeks, leads to

a significant improvement in psoriasis in up to 80–90% of patients.[30-32] This drug has been found to be useful in the management of childhood psoriasis also.[33,34] A recent review of its use in children has suggested that the side effect profile is similar to that of adults.[35]

Main problems with CSA are drug-induced hypertension, renal side effects, increased incidence of malignancy and rebound flare after stopping the drug. Long-term therapy results in permanent renal scarring and loss of function. Patients who are treated with CSA for more than 2 years continuously have especially high risk of developing irreversible renal damage. To avoid this dreaded complication, CSA should be given in intermittent courses of maximum 12 weeks duration.[36-38] Another concern with CSA is the increased incidence of cutaneous squamous cell carcinomas (SCC) especially in patients who have previously received PUVA (psoralen + UV A) therapy. In a large (5-year follow up) cohort study evaluating more than 1200 subjects on long-term CSA, there was a sixfold increased risk of nonmelanoma skin cancers, especially SCC, in patients who had received additional PUVA therapy, whereas the incidence of internal malignancy was not found to be high as compared to the general population.[39]

After an initial observation of the improvement of psoriasis in one heart and three liver transplant recipients on tacrolimus, the drug was tested in severe recalcitrant psoriasis patients with good response.[40] Subsequently, a double-blind, placebo-controlled study conducted by European FK 506 multicenter psoriasis study group reported 83% PASI reduction in 27 psoriasis patients at the end of 9 weeks.[41]

Newer calcineurin inhibitors including pimecrolimus and voclosporine, with higher efficacy and better side effect profile are increasingly being tried in psoriasis. Oral pimecrolimus was initially used by Rappersberger *et al.*[42] with high clinical efficacy and good tolerability. Subsequently, in a large, double-blind, dose-finding study, pimecrolimus given in doses of 20 and 30 mg twice daily in psoriasis patients, caused a mean percentage reduction in PASI by 51.3% and 54% respectively at week 7 from the baseline.[43] The drug was well tolerated and there were no clinically relevant abnormalities in the laboratory parameters.

Voclosporine is a novel calcineurin inhibitor having higher affinity for calcineurin and faster clearance of its metabolites from the body, as compared to CSA. The drug has been found to be effective in psoriasis in phase II and III studies.[44,45] In phase II studies, PASI 75 response was achieved in 67% of cases receiving 1.5 mg/kg/day of voclosporine without much change in blood pressure or concentrations of lipids or triglycerides. In phase III dose-finding study, 451 plaque psoriasis patients received either voclosporine or placebo. At the end of 12 weeks, PASI 75 response was achieved in the voclosporine 0.2, 0.3, and 0.4 mg/kg groups by 16, 25, and 47% of patients, respectively, and in the placebo group by 4% of patients. Voclosporine with high efficacy comparable to CSA and better safety profile is a promising future therapy for psoriasis.

RETINOIDS: ACITRETIN, ISOTRETINOIN, TAZAROTENE, BEXAROTENE

Retinoids are vitamin A derivatives, which modulate epidermal proliferation and differentiation, have immunomodulatory as well as anti-inflammatory properties. Acitretin, the active metabolite of etretinate, is the most commonly used oral retinoid for psoriasis. It is less effective compared to MTX and CSA as monotherapy and requires 3–6 months to achieve maximal response. It has been used in different doses in clinical trials and the results are largely dose dependent.[46]

Acitretin as monotherapy is particularly considered to be effective in exfoliative erythrodermic psoriasis and pustular psoriasis.[47] It has been extensively used in combination with ultraviolet B (UVB) or PUVA therapy for chronic plaque type psoriasis with enhanced efficacy, reduced treatment frequency, duration, and cumulative UV doses, resulting in a more effective, convenient, and safer treatment.[48]

Important advantages with this drug are chemoprevention against malignancy and that it is not immunosuppressive. Therefore, it is the drug of choice in human immunodeficiency virus (HIV) positive patients with psoriasis and is also used as combination therapy with biologics.[49]

Acitretin has significant adverse effects like teratogenic potential, hyperlipidemia, mucocutaneous side effects, diffuse idiopathic hyperostosis, liver toxicity, and pseudotumor cerebri-like symptoms. Women of childbearing age should use adequate contraception

for at least 3 years after discontinuing the use of acitretin. Isotretinoin is an option in women of child bearing age as its elimination half life is short and adequate contraception should be maintained for at least 1 month after stopping the drug.

Newer generation retinoids (tazarotene) are increasingly being used for psoriasis because of their better pharmacokinetic properties and selectivity for the beta and gamma subtypes of retinoic acid receptors (RARs), resulting in targeted action on psoriatic keratinocytes, thereby minimizing the risk of adverse effects. The wash out period of tazarotene is short due to shorter half-life of 7–12 hours of its active metabolite, tazarotenic acid. Therefore, the contraception may only be necessary for a few days after the last dose. Tazarotene has been found to be an effective, safer and better tolerated oral retinoid for psoriasis patients in phase III studies.[50] Unlike other retinoids, it does not significantly increase the prevalence of hypertriglyceridemia, hypercholesterolemia, abnormal liver function test results, desquamation, eye dryness, or alopecia. This drug has been safely used for up to 52 weeks.[50]

Bexarotene is a synthetic retinoid X receptor (RXR)-selective retinoid. In phase II multicentric study, >50% improvement in modified PASI, plaque elevation, and physician's global assessment was seen in 22, 52, and 36% of patients, respectively.[51]

Retinoids have several advantages over conventional systemic drugs like they are not immunosuppressive, there is no limitation of cumulative dose, and they cause no significant hepatic or renal toxicity. Therefore, these are good candidates for combination and maintenance therapy both with conventional systemic anti-psoriatic drugs as well as with the biologic agents.

FUMARIC ACID ESTERS

Fumaric acid esters (FAE) are a mixture of dimethylfumarate (DMF) and monoethylfumarate salts commonly used in Northern Europe, particularly in Germany and the Netherlands, as the first line systemic treatment for chronic plaque psoriasis, with proven efficacy and low toxicity. It is given in doses of 120–720 mg (DMF) daily.

The mechanism of action of the drug is only partially understood. Lehmann *et al.*[52] in an *in vitro* assay found that DMF and diethylfumarate are the active compounds and FAE mediates its immunomodulatory activity by the induction of the anti-inflammatory stress protein, heme oxygenase 1.

Balasubramaniam *et al.*[53] from United Kingdom reported good efficacy and safety of FAE, both as monotherapy and in combination therapy with CSA, acitretin, hydroxyurea and MTX. In another nonrandomized prospective cohort study, 80 patients with severe, recalcitrant, chronic plaque psoriasis received FAEs.[54] Of the total patients, 59% were on other concomitant oral anti-psoriatic agent. At 3 months, PASI 90 was achieved in 4%, PASI 75 in 8% and PASI 50 in 20% of cases. Side effects were reported by 74% of patients, resulting in cessation of FAE in 36% of cases. Most common side effects were diarrhea, abdominal pain and flushing, whereas lymphopenia occurred in 33% of patients.

Reich *et al.*[55] analyzed the data of 984 patients who were treated with FAE for at least 24 months (mean duration 44 months). There was marked improvement in 67% after 6 months, 78% after 24 months, and 82% of patients after 36 months of therapy. Changes of laboratory parameters were usually insignificant.

Recent studies suggest that FAEs are effective as monotherapy and can be used in combination with other oral anti-psoriatic agents. Subjective side effects are mainly gastrointestinal and flushing. The drug does not affect the liver and renal functions significantly but lymphopenia is a common adverse effect which needs close monitoring.

HYDROXYUREA

Hydroxyurea is an antimetabolite which works by inhibiting DNA replication. Its efficacy in psoriasis is known for 30 years.[56] The drug has not been extensively used in psoriasis. There is a renewed interest in its use from India. Kumar *et al.*[57] treated 31 patients of chronic plaque type disease with 1–1.5 g daily doses of hydroxyurea. Over half of the patients showed more than 70% reduction in PASI score. Sharma *et al.*[58] used it in 34 psoriasis patients with similar results. Their three patients developed leukopenia requiring discontinuation of the drug.

In a recent comparative study of MTX and hydroxyurea, there was 77% and 49% reduction in the mean PASI

score, respectively, at 12 weeks.[59] Gach *et al.*[60] used hydroxyurea in combination with infliximab to treat a recalcitrant case of psoriasis.

Major adverse effect of hydroxyurea is bone marrow toxicity, whereas liver and renal toxicity are rare. It provides a useful cheap alternative for systemic treatment of psoriasis.

MYCOPHENOLATE MOFETIL

Mycophenolate mofetil (MMF) is a prodrug of mycophenolic acid. It is a lymphocyte selective immunosuppressive agent which acts by non-competitive inhibition of *de novo* purine synthesis due to inhibition of inosine monophosphate dehydrogenase enzyme. MMF was first used for psoriasis in 1998.[61] Subsequently, there are many reports suggesting the efficacy of MMF in psoriasis.[62,63]

Beissert *et al.*[64] carried out a prospective, multicenter, randomized trial comparing the efficacy of MMF with that of CSA for the treatment of chronic plaque-type psoriasis. After 12 weeks, CSA demonstrated a significantly superior efficacy compared to MMF but there was no difference in time to disease relapse, side effects, and psoriasis disability index.

This drug has been safely administered in HIV patients with psoriasis.[65] MMF is a good choice in psoriasis patients concurrently suffering from immunobullous disorders.[66]

RETINOIC ACID METABOLISM BLOCKING AGENTS: LIAROZOLE, TALAROZOLE (RAMBAZOLE)

The novel systemic all-trans retinoic acid metabolism blocking agents (RAMBA) act by blocking cytochrome P-450 dependent 4-hydroxylation of all-*trans*-retinoic acid (ATRA), modulating the intracellular levels of endogenous retinoids, leading to normalization of aberrant epithelial growth and differentiation. The plasma ATRA levels do not rise beyond physiologic levels.

RAMBA are retinoid mimetic drugs with a side effect profile similar to that of retinoids but of lower incidence. These drugs can be given more readily to women and children than retinoids as there is rapid clearance of the RAMBA unlike the available synthetic retinoids which may stay in the body for a long time. Liarazole was found to be effective for both chronic plaque psoriasis as well as the palmoplantar pustular psoriasis in double-blind, randomized, placebo-controlled trials.[67,68]

Subsequently, talarozole has been used for psoriasis patients as this drug is a more selective inhibitor of the enzyme retinoic acid 4-hydroxylase, necessitating reduced dose and hence fewer side effects. Verfaille *et al.*[69] treated 19 patients of psoriasis with 1 mg talarozole, resulting in significant reduction in PASI in 8 weeks. Talarozole is in the phase II clinical trial stage.[70]

LEFLUNOMIDE

Leflunomide acts by inhibiting *de novo* pyrimidine synthesis. It is a disease-modifying antirheumatic drug which can be particularly beneficial for psoriasis patients with concurrent PsA. In a double blind, randomized, placebo-controlled trial of 182 patients of psoriasis and PsA, a PASI 75 response was achieved in 17% among leflunomide group versus 8% in the placebo group at 24 weeks.[71] PsA responded in 59% in leflunomide group versus 30% in placebo group. Patients were allowed concurrent use of low-dose systemic corticosteroids for the treatment of their PsA.

Adverse effects caused by leflunomide are gastrointestinal irritation, elevated liver enzymes, leukopenia, drug eruption, headache, increased risk of infections, and teratogenicity.[72] Adequate contraception should be maintained during therapy with leflunomide and additionally for 3 months in males and 2 years in females after stopping the drug.

RAPAMYCIN INHIBITORS: SIROLIMUS AND EVEROLIMUS

Sirolimus is similar in structure to CSA and tacrolimus but it is not a calcineurin inhibitor. Sirolimus binds to FK506 binding protein12 (FKBP12) and interrupts the cell cycle progression from G1 to the S phase, leading to the suppression of T-lymphocyte activation and proliferation.[73]

In a large multicenter study of 150 patients with severe chronic plaque psoriasis, oral sirolimus, CSA, and a combination of the two were assessed.[74] Comparable results were obtained in patients treated with CSA alone (5.0 mg/kg/day) and in those treated with subtherapeutic CSA (1.25 mg/kg/day) combined

with sirolimus (3.0 mg/m^2). Sirolimus monotherapy was found to be ineffective. Sirolimus and CSA can be used as combination therapy limiting their cumulative toxicity. Sirolimus causes less nephrotoxicity, neurotoxicity, and hypertension compared to CSA or tacrolimus.

Everolimus is a semisynthetic, immunosuppressive and antiproliferative macrolide derived from sirolimus, with better pharmacokinetic properties. It has successfully been used in combination with subtherapeutic doses of CSA to treat a woman with severe psoriasis refractory to traditional therapies.[75]

THIAZOLIDINEDIONES

Thiazolidinediones (TZD) are used as insulin sensitizers in type 2 diabetes mellitus. These drugs lower insulin resistance in peripheral tissues and reduce hepatic glucose output by binding to peroxisome proliferator-activated receptors (PPAR) gamma. Shafiq *et al.*[76] undertook a double-blind, randomized, placebo-controlled study to test the efficacy of pioglitazone as monotherapy in psoriasis patients. Seventy patients with moderate to severe psoriasis received either pioglitazone 15 mg or pioglitazone 30 mg or placebo for 10 weeks. The percentage reduction in mean PASI scores was 21.6, 41.1 and 47.5% in the placebo, pioglitazone 15 mg, and 30 mg groups, respectively. There were no serious adverse events noted except for a fall in hemoglobin in one patient and elevation of liver enzymes in two patients.

Recently, pioglitazone and acitretin have been used in combination with higher efficacy compared to control group receiving acitretin alone.[77] Bongartz *et al.*[78] used pioglitazone in 10 patients of PsA with a good response. Troglitazone efficacy in psoriasis has also been reported.[79,80] A recent study demonstrated that rosiglitazone is not more effective than placebo.[81]

In the recent times, there has been growing literature on the association between psoriasis and metabolic dysfunction, including insulin resistance, obesity, dyslipidemia, and cardiovascular diseases. TZD would help psoriasis patients additionally in fighting against these metabolic dysfunctions as they are insulin sensitizers and possess an array of beneficial effects including normalizing blood pressure, increasing high-density lipoprotein, and improving fibrinolysis.[82]

AZATHIOPRINE

Azathioprine is an immunosuppressant used in the treatment of blistering disorders, atopic dermatitis and various inflammatory dermatoses. There are no randomized trials but few open label studies suggest its efficacy in psoriasis.[83,84]

There are some recent reports to suggest that this drug could be a good choice in psoriasis patients with concurrent bullous pemphigoid.[85,86]

Azathioprine acts slowly requiring at least 6–8 weeks for the onset of action. Important adverse effects include myelosuppression, liver toxicity and gastrointestinal side effects. Thiopurine methyltransferase (TPMT) levels should be measured to guide dosing.[87]

PACLITAXEL

Paclitaxel is a chemotherapeutic agent having antiproliferative, antiangiogenic, and anti-inflammatory properties. In a phase II pilot study involving 12 severe psoriasis patients, there was a dose-dependent response with decrease in PASI scores varying from 15% to 80% in different patients.[88] Two patients had hypersensitivity reactions, whereas none developed myelosuppression.

Nanoemulsion formulation of paclitaxel enhanced the peroral bioavailability of the drug in rats.[89] However, these newer formulations need evaluation in psoriasis patients to establish their efficacy as well as the safety.

NEOVASTAT (AE-941)

Neovastat is extracted from shark cartilage by homogenization and ultrafiltration. It is vascular endothelial growth factor (VEGF) antagonist and has been shown to have anti-angiogenic and anti-inflammatory properties in an *in vitro* assay.[90]

Sauder *et al.*,[91] in a randomized phase I/II dose-comparison clinical trial involving 49 psoriasis patients, showed that patients receiving 60, 120, or 240 ml/day of neovastat showed statistically significant decrease in PASI score in 30.8, 41.7 and 50% of the patients, respectively. Nonserious drug-related adverse events affected the gastrointestinal system in 12 of 49 patients (primarily nausea, diarrhea, vomiting, flatulence, and constipation) and the skin and appendages in 4 of 49 patients (primarily acne and rash).

The antiangiogenic agent neovastat is a new therapeutic approach in the management of psoriasis but more extensive studies need to be done before the drug is approved for the treatment of psoriasis.

INVESTIGATIONAL THERAPIES

Immunotherapy

Most of the treatment modalities provide symptomatic relief and do not lead to permanent cure or long-term remission. Immunotherapy is under evaluation so as to produce immunomodulation and long-term remission. Immunotherapy probably works by inducing a transient Th1 response with compensatory Th2 response. After preliminary investigations, two intradermal injections of heat-killed suspension of *Mycobacterium vaccae* (*M. vaccae*) were given at 3 weeks interval to chronic plaque psoriasis patients.[92] Improvement in PASI score was seen in 19 of 21 patients and the improvement persisted for 6 months. A subsequent study supported its efficacy.[93]

Balagon *et al.*[94] tested psoriasis vaccine (PVAC) which is a more potent derivative of *M. vaccae*. It contains heat-killed, delipidated, deglycolipidated *M. vaccae*. In an open trial, 65% patients showed more than 50% reduction in the PASI score at 12 weeks after the injections. In two subsequent studies investigating PVAC in psoriasis and PsA patients, it was found to be ineffective.[95,96]

Mw (*Mycobacterium w*) vaccine has been tried in psoriasis patients in small studies. Rath *et al.*[97] conducted a pilot study in which 24 patients received two injections of Mw vaccine at 3 weeks interval. In 4 months, 16.6% had marked improvement (>50% reduction), 62.5% had moderate improvement (25–50% reduction), and 16.6% showed no change (<25% reduction).

Subsequently, this vaccine was tested in 45 patients with mild to moderate plaque-type psoriasis.[98] In this study, results were not encouraging, with less than 40% patients showing mild to moderate improvement.

Another vaccine, psoraxine, which was originally developed to induce resistance against leishmaniasis, is still in experimental stages for psoriasis.[99]

Peptide-T

Peptide-T is a synthetic octapeptide that shares a segment of the envelope glycoprotein (gp 120) of the HIV. Its use in a HIV negative patient of psoriasis with PsA was reported for the first time in 1989.[100] It is speculated that peptide-T acts by inhibition of interferon (IFN)-gamma production and induction of interleukin (IL)-10.[101] Marcusson *et al.*[102] treated nine patients of recalcitrant and long-standing psoriasis with 2 mg peptide-T intravenous daily injections given for 28 days. Eight of them showed less than 50% improvement by day 28 and five patients had more than 50% improvement at 3 months. Limitations with peptides are that they exhibit poor absorption, get easily metabolized and are immunogenic.

Recently, synthetic analogues of natural product, amygdalin, were tested on human keratinocyte cultures and found to have effects similar to that of peptide-T.[103] These synthetic analogues need further exploration in psoriasis patients.

Tyrosine kinase inhibitors

There are individual reports of clinical improvement in psoriasis with tyrosine kinase inhibitors (TKI) when given to cancer patients.[104] SU-011248 is a VEGF receptor-tyrosine kinase inhibitor which has been tried in psoriasis.[105] Further prospective randomized control studies need to be done to prove their efficacy.

p38 Mitogen activated protein kinase inhibitor

Intracellular protein cascades such as mitogen activated protein kinases (MAPK) are involved in cell cycle kinetics. Novel p38 MAPK inhibitor, BMS-582949, is in phase II studies for inflammatory diseases including rheumatoid arthritis, psoriasis and atherosclerosis.[106]

Protein kinase C inhibitors

Protein kinase C (PKC) inhibitors block early T cell activation. AEB071 strongly and selectively inhibits the classical (α, β) and the novel theta (θ)-PKC isoforms. In a recently published study, AEB071 was given orally to 32 patients with severe plaque psoriasis for 2 weeks.[107] There was a dose-dependent response, with PASI 75 achieved in 69% of the treatment group receiving 300 mg twice daily. Larger patient cohorts and longer treatment periods are required to establish its safety and efficacy in psoriasis.

Phosphodiesterases

The phosphodiesterases (PDE) are the enzymes which degrade second messenger molecules cAMP and cGMP. They have broad anti-inflammatory effects and therefore have been tried in psoriasis and atopic

dermatitis. Dose-limiting side effects of PDE are nausea, diarrhea, vomiting and abdominal pain. In a pilot study, oral apremilast, a PDE-4 inhibitor, was given to 19 psoriasis patients. There was improvement in 73% of cases with mild adverse effects.[108] Further studies are warranted.

Nerve growth factor receptor blocker

Recent research supports the role of nerve growth factors (NGFs) and neurogenic inflammation in the pathogenesis of psoriasis.[109] Novel therapeutic agent K252a is a high-affinity NGF receptor blocker. It improved psoriatic plaques in severe combined immunodeficient mouse-human skin model of psoriasis.[110]

CONCLUSION

Treatment of psoriasis is still evolving. MTX, CSA and retinoids are well-established and time-tested drugs. In recent times, there has been vast expansion in the armamentarium of therapeutic agents for psoriasis as we have entered the exciting new era of biologic therapy. Long-term experience with biologics is still limited, both with regard to efficacy and, more importantly, safety. Although preliminary results are encouraging, these drugs are also not curative, need parenteral administration, have significant adverse effects, and additionally, loss of efficacy on long-term therapy as well as disease unresponsiveness have been observed. Therefore, the search for safer, orally administered newer and cheaper drugs is imperative.

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