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REVIEW

Psoriasis treatment: Unconventional and non-standard modalities in the era of biologics

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Abstract

Psoriasis is a potentially debilitating inflammatory dermatosis affecting 0.2%-4.8% of the population worldwide causing a significant occupational, personal or psychosocial morbidity to these patients for life. The basic aim of psoriasis therapy is to control the disease to maximum possible extent and improve the patient's quality of life. Management of triggers for flare-ups, lifestyle modifications, and dietary supplements are often recommended. Intermittent or rotational therapy with frequent alterations in treatment options is usually needed to reduce toxicity of anti-psoriatic drugs in the absence of safer alternatives. Currently, several biological agents categorized as either T-cell targeted (*e.g.*, Alefacept, Efalizumab) or cytokine modulating (*e.g.*, Adalimumab, Infliximab, Etanercept) are available for treating severe psoriasis. However, their high cost is often precluding for most patients. The usefulness of systemic (methotrexate, cyclosporine, acitretin or several other therapeutic agents) or topical (tar, anthralin, corticosteroids or calcipotriol ointments, phototherapy with or without psoralens) therapies has been well established for the management of psoriasis. The literature is also replete with benefits of less used non-standard and unconventional treatment modalities (hydroxycarbamide, azathioprine, leflunomide, mycophenolate mofetil, isotretinoin, fumarates, topical calcineurin inhibitors, peroxisome proliferator-activated receptors agonists, statins, sulfasalazine, pentoxifylline, colchicine, grenz ray therapy, excimer laser, climatotherapy and balneophototherapy, peritoneal dialysis, tonsillectomy, ichthyotherapy, *etc*.). These can be used alternatively to treat psoriasis patients who have mild/minimal lesions, are intolerant to conventional drugs, have developed side effects or achieved recommended cumulative dose, where comorbidities pose unusual therapeutic challenges, or may be as intermittent, rotational or combination treatment alternatives.

Key words: Acetretin; Azathioprine; Balneophototherapy; Calcineurin inhibitors; Calcipotriol; Calcium dobesilate; Climatotherapy; Colchicine; Cyclosporine; Dapsone; Excimer laser; Fumarates; Grenz ray therapy; Hydroxycarbamide; Ichthyotherapy; Isotretinoin; Leflunamide; Methotrexate; Mycophenolate mofetil; Pentoxifylline; Peritoneal dialysis; Phototherpy; Plaque psoriasis; Peroxisome proliferator-activated receptors agonists; Statins; Sulfasalazine; Tonsillectomy

Core tip: The clinicians must be aware of all available antipsoriasis therapies in view of variable therapeutic outcome(s) that may test one's ingenuity in managing some "difficult to treat" psoriasis patients. The non-standard and off-label therapies will remain an important alternative to more widely used measures in rotational/intermittent treatment(s) or until a therapy that is affordable, safe, effective, and more importantly, remittiv becomes available.

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Table 1 Therapeutic options for psoriasis

Topical agents	Systemic agents	Phototherapy
Emollients	Methorexate	Natural
Tar and anthralin	Retinoids	Dead Sea Therapy
Dithranol	Cyclosporine A	and PUVA-Sol
Corticosteroids	Hydroxyurea	Artificial
Vitamin D analogs	Tacrolimus	PUVA, Bath PUVA,
Tazarotene	Mycophenolate mofetil	UVB and NB-UVB
Salicylic acid	Sulfasalazine	Newer
Tacrolimus/	6-thioguanine	Excimer laser, NB-
pimecrolimus	Calcitriol	UVB light enhanced
5-fluorouracil	Colchicine	Photodynamic
Ascomycin derivatives	Dapsone	therapy
	Azathioprine	
	Fumaric acid esters	
	Biologics: Etanercept,	
	Alefacept, Infliximab,	
	Efalizumab,	
	Adalimumab	

UV: Ultraviolet light; PUVA: Psoaralene ultraviolet A; Sol: Solar; NB-UVB: Narrow band UV.

INTRODUCTION

Psoriasis is a potentially debilitating inflammatory dermatosis affecting 0.2%-4.8% of the population worldwide and with an estimated prevalence of 2.2% to 2.63% in the United States with approximately 150000 newly diagnosed cases per year[1]. All its clinical forms may eventually evolve into chronic plaque psoriasis characterized clinically by well demarcated, erythematous, scaly plaques. Guttate psoriasis is often self limiting, lasting for 12 to 16 wk, without treatment. However, 1/3rd-2/3rd of these patients may later develop chronic plaque psoriasis. Spontaneous remissions in chronic plaque psoriasis, lasting for variable periods of 1 year to several decades, may occur in up to 50% patients. Erythrodermic and generalized pustular psoriasis tend to be severe and persistent. There is no evidence that the disease is anyway different in either gender. There is no known prevention for psoriasis and in most cases, it remains a life long disease manifesting at unpredictable intervals with weekly, monthly or occasional recurrences. Although not life threatening, psoriasis can significantly impair quality of life with as many as 79% of patients with severe disease reporting a negative impact on their lives, and nearly 5% of them had contemplated suicide in a survey by National Psoriasis Foundation[2].

A plethora of anti-psoriatic treatments, both topical and systemic, is available for the management of psoriasis (Table 1). During the past four decades or so systemic methotrexate has been used effectively to treat all forms of psoriasis, including erythrodermic pustular and chronic plaque psoriasis. Despite a major concern for hepatotoxicity associated with its long-term use, it is even indicated for long-term management of severe forms of psoriasis. Currently, several biological agents are being used or evaluated for treating severe psoriasis. The Food and Drug Administration (FDA) approved ones are broadly categorized as either T-cell targeted (*e.g.*, Alefacept, Efalizumab) or cytokine modulating (*e.g.*, Adalimumab, Infliximab, Etanercept). Except for being prohibitory expensive, these apparently have an advantage over current systemic therapies, as systemic adverse effects do not mar their efficacy.

The voluminous literature on treatment of psoriasis is itself indicative of limitations of any therapy. It is often confusing while selecting a treatment regimen as most treatment schedules are aimed to decrease disease severity and extent that it no longer interferes with occupation, personal or psychosocial well-being of the patient. However, the patient's own assessment for their current therapy may remain unsatisfactory. For instance, in two separate surveys 40%-42% of patients felt frustrated with the ineffectiveness of their treatments while 32% reported that treatment was not aggressive enough[2,3]. As psoriasis is a chronic life long disease, safety of a treatment during long-term use too is of major concern. To date there is no absolutely safe, simple and inexpensive treatment for psoriasis and the selection of various strategies has to be individualized. The basic aim of psoriasis therapy is to control the disease to maximum possible extent and improve the patient's quality of life. Although reduction of psoriasis area severity index (PASI) score to 50% is currently considered adequate, there is no clear association among illness impact, subjective well-being, and the disease severity[4]. The patients may also assess their psoriasis as more severe than physicians do necessitating the need for more patient centric therapies[5]. Intermittent or rotational therapy with frequent alterations in treatment options is employed to reduce toxicity of anti-psoriatic drugs while search for safer alternatives continues. This paper focuses and reviews the less used and unconventional treatment modalities which can be useful alternatives to treat psoriasis patients who have mild/minimal lesions, are intolerant to

conventional drugs, have developed side effects or achieved their recommended cumulative dose, where comorbidities pose unusual challenges, or may be as intermittent, rotational or combination treatment alternatives. As management of triggers for flare-ups, lifestyle modifications, and dietary supplements are recommended frequently, it will be prudent to briefly review them alongwith few first line therapies.

MANAGING TRIGGERS

Despite the knowledge accumulated during past few decades that psoriasis is an immune mediated, regeneration-like reaction of the skin in genetically predisposed individuals wherein various cells including keratinocytes, antigen presenting cells, and T-cells play a dominant role at different stages, the exogenous factors which trigger psoriasis or induce flare-ups are poorly understood. A variety of environmental factors such as physical trauma (scratching, insect bites, surgery, sunburn) causing damage to keratinocytes (Koebner's phenomenon), drugs (antimalarial, clopidogrel, beta blockers, angiotensin-converting enzyme inhibitors, lithium, gemfibrozyl, imiquimod, interferon (IFN)-α, IFN-γ, withdrawal of corticosteroids or cyclosporin), infections (bacterial, viral, and yeast), or metabolic disorders such as hypocalcemia (primary or secondary) are implicated triggers for exacerbations[6]. Exacerbation and persistence of psoriasis has been attributed to increased hyper-reactivity to superantigens that are usually viral or bacterial proteins[7]. Bacterial (*Staphylococcus aureus*, *Streptococcus* sp.) endotoxins act as superantigens and activate T-cells, macrophages, Langerhans cells and keratinocyte. Superantigens bind to class II major histocompatibility complex (MHC) molecules and Vβ segments of the T cell receptor resulting in its activation and cytokine release. Balci *et al*[8] found a high prevalence of colonization of skin lesions and nares of psoriasis patients by toxigenic strains of *Staphylococcus aureus* as compared to healthy controls. They also observed a significant relationship between PASI scores and toxin production and suggested association between psoriasis and non-classical superantigens such as *mecA*, *etb* and *see*. Although they did not elucidate on therapeutic implications of their findings, antimicrobial therapy may have some role in psoriasis treatment. Other suggested association between *Candida albicans*, *Borrelia burgdorferi*, and *Pityrosporum ovale* remains unsubstantiated[9-11]. HIV-associated psoriasis usually develop in non-terminal stages of AIDS that is frequently severe, recalcitrant to therapy and has associated arthritis six times more often[12]. Although zidovudine has not been found effective for psoriasis in HIV-negative patients, it reportedly improves HIV-associated psoriasis[13,14]. However, exacerbations in HIV-associated psoriasis were treated more effectively with triple antiretroviral therapy (stavudine 30 mg, lamivudine 150 mg, nevirapine 200 mg; all twice daily)[15]. The role of human papillomavirus type 5, demonstrated in scrapping of lesional skin in nearly 90% of a large series of psoriasis patients, in the etiology of the disease remains to be determined[16].

The association of psoriasis, pustular psoriasis in particular, with hypocalcemia, mostly from hypoparathyroidism (both idiopathic and familial), that resolved after treatment with calcium has been described by several workers[17-20]. Similarly, experimental and clinical demonstration of association between vitamin D deficiency and psoriasis has been further supported by the effectiveness of vitamin D analog (calcitriol) in the treatment of psoriasis[20].

MANAGING LIFESTYLE

Factors such as obesity, smoking and alcohol consumption, diet, and stressful life events have been suggested to affect the course of psoriasis. Although their exact role in the etiology of psoriasis remains unclear, being modifiable they may be important adjunct to the therapeutic management of psoriasis. Psoriasis patients have been observed to present more frequently with obesity than the general population and severe psoriasis, *i.e.*, PASI > 10 and > 20% body surface area involvement[21-23]. Duarte *et al*[21] considered obesity a risk factor for severe psoriasis by observing a strong correlation between PASI > 10 and all obesity parameters; waist circumference, waist hip ratio, and body mass index (BMI). Setty *et al*[22] examined data linking weight gain and incident psoriasis in 78626 women and observed that the relative risk of psoriasis increased with the rise in BMI during the study period of 14 years. The authors attribute this to the production of inflammatory cytokines by adipositis as a possible explanation. There are reports of improved psoriasis in patients who lost weight and after gastric bypass surgery[24-26]. Nevertheless, obesity does not appear to play a role in the new onset of psoriasis or affect the efficacy of adalimumab in the treatment of psoriasis[27,28]. However, prospective data is lacking specifically to evaluate the role of weight loss in psoriasis.

Smoking and alcohol consumption

Recent studies suggest that cigarette smoking increases oxidative damage, promotes inflammatory changes, and enhances expression of genes associated with psoriasis[29]. Several studies across countries have linked current and past smoking habits to the increased severity or new onset psoriasis[30-36]. Smoking > 20 cigarettes daily has been associated with more than two fold increased risk of severe psoriasis, whereas the association between smoking and psoriasis seems to be stronger in women[35,36]. Smoking can worsen severity of psoriasis and makes patients less responsive to therapy[33,35,37]. While non-smokers experience more frequent remissions than smokers, cessation of smoking leads to decreased severity and the excess risk of psoriasis also declines[33,36,38].

There is extensive published literature on excessive alcohol consumption among psoriasis patients in a recent systematic review[39]. Alcohol consumption appears to trigger, exacerbate and influence the severity and the progression of psoriasis and psoriatic arthritis[30,40-42]. The amount consumed and the type of alcohol seems to trigger development and/or exacerbation of plaque psoriasis. Qureshi *et al*[41] in a recent prospective study followed 82869 women for 14 years and showed that consumption of more then 2.3 alcoholic beverages weekly was an important risk factor for new onset psoriasis. They also deduced that consuming non-light beer is an independent risk factor for developing psoriasis in females. Similarly, alcohol consumption at levels higher then 100 g/d appears to be a risk factor for the development and exacerbation of psoriasis in males[40,43]. The exact pathomechanisms by which alcohol triggers or exacerbates psoriasis remain poorly understood. Immune dysfunction/immunosuppression and increased susceptibility for infections, excessive production of inflammatory cytokines, and epidermal hyperproliferation by cycle activators such as cyclin D1 and keratinocyte growth factor have been implicated[44,45]. Not the least, alcohol abuse in psoriasis patients too is associated with decreased response to treatment and has implications for interaction with antipsoriatic medication[43,46,47].

Diet and dietary supplements

Diet rich in gluten, polyunsaturated fatty acids, and alcohol has been implicated in the severity of psoriasis in a significant number of patients[48]. An increased incidence of psoriasis in patients with celiac disease has been suggested[49-51]. A gluten-free diet is also suggested to improve psoriasis severity in celiac disease and even in patients with no celiac disease but with immunoglobulin A and/or immunoglobulin G (IgG) antigliadin antibodies[50,51]. However, the link between psoriasis and gluten-intolerance remains poorly understood due to inconsistent data. Nonetheless, all psoriasis patients with celiac disease or gluten-intolerance should have a gluten-free diet for overall wellbeing. Polyunsaturated fatty acids, through overproduction of arachidonic acid derived eicosanoids, influence several inflammatory disorders including psoriasis. The outcome from studies on effect of diet rich in omega-3 polyunsaturated fatty acids remains inconsistent. However, intake of fish rich in omega-3 and vegetarian diets may benefit psoriasis patients, as there is decreased intake of arachidonic acid and consequent reduction in inflammatory eicosanoid formation. Omega-3 fatty acids, especially eicosapentaenoic acid and docosahexanoic acid, compete with arachidonic acid as substrates for cycloxygenase and lipoxygenase, which thereby reduces downstream proinflammatory cytokines in psoriasis plaques. Most studies performed to evaluate their efficacy or fish oil rich in omega-3 fatty acids as dietary supplements in psoriasis report improvement in mean PASI scores[52-57]. However, there is no agreement concerning the dose of oral supplementation to be effective and the outcomes of randomized controlled trials are less effective[55,56]. Parenteral infusions of omega-3 fatty acids has been reported beneficial in patients with acute psoriasis[57]. Systemetic reviews also advocates omega-3 fatty as adjuvant treatment of chronic plaque psoriasis in evidence-based clinical guidelines[58,59]

Although caffeine consumption has been observed to decrease the therapeutic benefit of methotrexate in rheumatoid arthritis[60], it does not appear to effect psoriasis or inhibit anti-inflammatory effect or therapeutic benefits of methotrexate in patients with psoriasis or psoriatic arthritis[61]. Low calorie diet in a study showed a significant improvement after 4 wk as compared to controls and oral vitamin D supplementation can be recommended in psoriasis patients who are not on topical treatment with vitamin D analogues. The reported beneficial role of probiotics in psoriasis needs evaluation[62,63]. Similarly, curcumin [1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione], has been shown to resolve psoriasis by lowering phosphorylase kinase levels in psoriatic epidermis and decreasing Ki-67 cells, which are capable of division[64-66]. Psoriasis patients treated with topical steroid plus oral curcumin 2 g/d achieved best PASI 50, PASI 75, PASI 90 and PASI 100 than patients treated with topical steroids plus placebo in a recent controlled trial and perhaps best used as an adjuvant to other therpies[65]. This phytochemical is one of the curcuminoid extracted from turmeric (curcuma longa), others being demethoxy-curcumin and bisdemethoxycurcumin. It exerts anti-inflammatory activity by inhibition of cyclooxygenase, 5-lipoxygenase and glutathione S-transferase and a number of other molecules but lacks clinical data to support its recommendation as a part of psoriasis treatment. In general, there is no sufficient scientific evidence that any special psoriasis diet is beneficial and the influence of diet on the course of psoriasis remains controversial. Nevertheless, avoiding foods suspected of causing inflammation or flare-ups, and eating low energy diet, will reduce risk for psoriasis comorbidities including obesity, diabetes, and cardiovascular diseases.

Infections and antimicrobial agents

Streptococcal infection and onset of guttate psoriasis and exacerbation of chronic plaque psoriasis have been repeatedly linked so much so that some workers routinely treat exacerbations with antimicrobial agents[67-71]. Saxena *et al*[72] noted significant improvement in PASI score in 30 patients with chronic plaque psoriasis at 12 wk and excellent improvement at 2 years from treatment with intramuscular benzathine penicillin (1.2 million units) fortnightly for 24 wk initially and then given once a week for a 2-year study period. Later, in a single blind randomized case-control study they used oral azithromycin for 48 wk as a single 500 mg/d for 4 d with a gap of 10 d (total 24 such courses) and achieved PASI 75 in 80% patients in the treatment group[73]. No

significant change was noted in control group. However, 20% of treated patients experienced recurrence at the end of one-year study period. Polat *et al*[74] used erythromycin 1000 mg/d and topical corticosteroids in 36 psoriasis patients and only topical corticosteroids in 24 controls for 4 wk. They noted statistically significant difference between the mean PASI of the two groups at the end of the treatment. The treatment used for the study group was also more effective against pruritus. However, these effects were attributed to inhibition of the production of many proinflammatory cytokines, including interleukin-6 (IL-6), IL-8 and TNF-α, perhaps by suppressing NF-κB or activator protein-1, and reduced neutrophil activity by macrolides rather than to their antibacterial properties. It has therefore been suggested that macrolides might be candidates for adjunctive treatment of psoriasis[74,75]. It is always prudent to treat appropriately any suspected coinfection to reduce overall morbidity, although, intervention by antibiotics is not considered of significant benefit by some researchers[76,77].

ANTIMETABOLITES AND OTHER IMMUNOSUPPRESSIVES

The drugs like methotrexate and cyclosporine with their proven efficacy in psoriasis remain well-established thearpies of first choice for moderate to severe psoriasis. Methotrexate (0.2-0.4 mg/kg, 7.5 mg to maximum of 30 mg/wk), alone or in combination with other drugs, is highly effective for the treatment of all forms of psoriasis. Its efficacy almost equals that of cyclosporine A or fumarates but is superior to that of hydroxycarbamide or mycophenolate mofetil (MMF)[78-83]. The efficacy and safety of combination of methotrexate and biologic therapy using adalimumab, etanercept, infliximab, or briakinumab too has been demonstrated in several uncontrolled studies and case series involving patients with psoriatic arthritis as well, and even in patients without previous methotrexate therapy[84-93]. However, methotrexate induced hepatotoxicity ranging from an asymptomatic transaminasemia to hepatic fibrosis and cirrhosis remains the most important concern in addition to vast potential for drug interactions (Tables 2 and 3). Therapeutic guidelines and recommendations have been available from time to time for monitoring methotrexate induced hepatotoxicity (Tables 4 and 5)[94-96]. Unfortunately, the potential efficacy of a topical methotrexate preparation in palmoplantar or plaque psoriasis remains unexploited[97-99]. Drugs like hydroxycarbamide, azathioprine, leflunamide, 5-fluorouracil, paclitaxel, and MMF too have been used infrequently in spite of limited therapeutic benefit *vs* methotrexate.

Hydroxycarbamide

Hydroxycarbamide (hydroxyurea), an antimetabolite, inhibits DNA synthesis by interfering with catalytic activity of the enzyme ribonucleoside diphosphatase reductase during the S-phase of the cell cycle. It was reported to be effective in refractory psoriasis for the first time by Yarbo in 1969. Since then many reports have shown favorable but variable results[100-108]. However, it is probably difficult to evaluate efficacy of hydroxycarbamide from these studies as various workers have used different doses for varying periods of time and evaluated their patients by different criteria. For instance, Layton *et al*[102] in their study of 86 patient with extensive chronic plaque psoriasis treated with hydroxycarbamide (0.5-1.5 g/d given for 3-96 mo), observed satisfactory remission in 61% patients while other 39% patients had inadequate response or significant relapse during treatment. While Sharma *et al*[101] obtained 76% reduction in the mean PASI score with hydroxyurea (1-1.5 g/d) given for 12 wk. Moschella *et al*[103] administered intermittent courses of hydroxycarbamide over a period of 18 mo to treat 60 patients with severe or incapacitating psoriasis and noted good to excellent response in 63% patients in first 6 wk and in 50% patients in 18 mo respectively. Boyd *et al*[104] in their review summarized therapeutic experience with hydroxycarbamide as excellent in 18%-38% and poor in 15%-20% patients. Weekly doses of hydroxylcarbamide too have been tried with variable success[109]. Hydroxycarbamide, 3.0 or 4.5 gm administered in weekly doses, was found effective in small number of patients and devoid of serious side effects as compared to its reported safety profile of daily therapy in a comparative study[81]. Eight (53%) patients did not show adequate response (< 25% reduction in PASI) at the end of 4 wk and 8 (53%) patients had mild to moderate improvement (25%-75% reduction in PASI) at 8 wk of treatment. However, at the end of 12-wk study period only 2 (13%) patients achieved marked improvement (> 75% reduction in PASI), 11 (73%) patients had mild to moderate improvement (25%-75% reduction in PASI) and 2 (13%) patients did not respond at all. The mean percentage reduction in PASI score was 48.47% ± 26.53% at the end of 12 wk. However, methotrexate (15-20 mg/wk) was faster in clearing the lesions and associated with higher adverse effects than hydroxycarbamide. Cutaneous or nail pigmentation, diffuse reversible alopecia, gastrointestinal symptoms, hematological and liver function abnormalities are usual side effects reported in 33% and 43% patients while hematologic side effects comprised 21% and 35% after prolonged hydroxycarbamide therapy in two separate studies[102,103]. Kumar *et al*[110] reported side effects in their 65.5% patients, pigmentation of nails, skin or mucosa being the commonest one seen in 58.6% patients. Sharma *et al*[101] also observed post-inflammatory lesional and nail hyperpigmentation in all their 34 patients apart from hematological adverse effects and skin infections in 23.53% patients. More uncommon and severe adverse reactions necessitating discontinuation of therapy include "flu-like" syndrome, cutaneous

Table 2 Adverse effects of methotrexate therapy

System involved	Adverse effects
General	Fatigue, headaches, chills and fever, dizziness
Skin	Pruritus, pain and burning, urticaria, mild reversible alopecia, ecchymosis, acute ulcerations of psoriatic lesions, reactivation of phototoxic responses
Blood	Bone marrow depression, leukopenia leading to decreased resistance to infection, anemia, thrombocytopenia, bleeding, and megaloblastic anemia, Pancytopenia
Gastrointestinal system	Nausea and anorexia, diarrhea, vomiting, ulcerative stomatitis, pharyngitis, enteritis
Urinary system	Azotemia, microscopic hematuria, cystitis, nephropathy
Respiratory system	Acute pneumonitis, pulmonary fibrosis
Nervous system	Headaches, dizziness, drowsiness, blurred vision, acute depression
Reproductive system	Teratogenesis, defective oogenesis, menstrual dysfunction, reversible oligospermia, defective spermatogenesis
Uncommon side effects	Anaphylaxis, acral erythema, epidermal necrosis, vasculitis, osteopathy, lymphoma

Table 3 Methotrexate drug interactions of significance

Interacting drug	Mechanism/comments
Drugs that increase methotrexate drug levels and toxicity	
Salicylates	Decrease renal excretion, displacement from plasma proteins
NSAIDs	Decrease renal excretion, displacement from plasma proteins
Sulfonamides	Decrease renal excretion, displacement from plasma proteins
Dipyridamole	Increased intracellular accumulation of methotrexate
Probenecid	Increased intracellular accumulation of methotrexate, decreased renal tubular function
Chloramphenicol	Displacement from plasma proteins
Phenothiazines	Displacement from plasma proteins
Phenytoin	Displacement from plasma proteins
Tetracyclines	Displacement from plasma proteins
Drugs that simultaneously inhibit folate metabolic pathway-increase hematologic toxicity	
Trimethoprim	Inhibition of dihyrofolate reductase
Sulfonamides	Inhibition of dihydropteroate synthetase
Dapsone	Inhibition of dihydropteroate synthetase
Drugs that may synergistically increase hepatotoxicity-common target organ	
Systemic retinoids	Common target organ for toxicity-liver
Alcohol	Common target organ for toxicity-liver

NSAID: Nonsteroidal anti-inflammatory drug.

Table 4 Guidelines for monitoring psoriasis patients receiving methotrexate by utilizing PIIINP levels

Indications for considering withdrawal of methotrexate	Elevation of PIIINP above 10.0 μg/L in at least 3 samples in one 12-mo period
Indications for considering liver biopsy	Elevation of pretreatment PIIINP above 8.0 μg/L Elevation of PIIINP above 8.0 μg/L in 2 consecutive samples Elevation of PIIINP above the normal range (1.7-4.2 μg/L) in at least 3 samples over a 12 mo period
Remarks: Serum for PIIINP measurement should be collected prior to starting methotrexate and should subsequently be measured every 2-3 mo during continued treatment	

Table 5 Grading of Liver biopsy as per Roenigk scale and recommendations for further methotrexate therapy

Biopsy grade	Liver histopathologic findings	Recommendation
I	Normal; fatty infiltration, nuclear Variability and portal inflammation- mild	May continue methotrexate
II	Fatty infiltration, nuclear variability, portal tract expansion, inflammation and necrosis- moderate to severe	
IIIA	Fibrosis-mild	May use methotrexate with caution and repeat biopsy at 6 mo
IIIB	Fibrosis-moderate to severe	Should not be given except in exceptional circumstances
IV	Cirrhosis	

vasculitis, leukopenia, thrombocytopenia, and fixed drug eruption[103,104]. Side effects like lesional erythema and tenderness, lesional and nail hyperpigmentation, arthralgia, dryness of mouth, periorbital swelling and diarrhea 3 d after the weekly dose of hydroxycarbamide not warranting discontinuation of treatment were

observed by Ranjan *et al*[81]. This low incidence of side effects and particularly absence of serious ones like hematologic toxicity was attributed to less number of doses used for short period of 1 to 2 d in a week. It is also observed that some variants of psoriasis may respond better to hydroxycarbamide than others. A good clearance in pustular psoriasis patients treated with 1-2 g/d hydroxycarbamide has been observed in 45%-63% of psoriasis patients treated[105,107]. The response is slow in erythrodermic or guttate psoriasis and palmoplantar pustulosis[103,105,107,108]. Hydroxycarbamide and infliximab combination was more effective in treating a case of recalcitrant psoriasis who had failed therapy with acitretin, bath Psoralen ultraviolet-A (PUVA), narrow band ultraviolet B (UVB), topical tar ointment, diathranol, vitamin D analogs and steroids[111]. However, its use in combination with other psoriasis treatment remains understudied. Despite slow response, hydroxycarbamide appears a reasonable alternative to methotrexate in patients who either develop gastrointestinal or hepatotoxic side effects due to methotrexate, or have achieved its recommended cumulative dose.

Azathioprine and 6-thioguanine

Azathioprine, an analogue of physiologic purines (adenine, hypoxanthine, guanine), is approved for use in rheumatoid arthritis and renal transplant recipients for its immunosuppressive activity. It is also used in dermatology for the treatment of blistering disorders, parthenium dermatitis, atopic dermatitis or other inflammatory dermatoses. It is rapidly absorbed after oral ingestion and nearly 30% is protein bound. After absorption, azathioprine is converted *in vivo* to 6-mercaptopurine and then its active metabolite, the nucleotide thioinosinic acid. Its maximum effect is on rapidly dividing cells and it may block the active enzyme and antigenic sites due to its alkylating effect on sulfhydril amino groups. It inhibits mitosis, B-cell proliferation, suppresses T lymphocyte function, and antibody formation. It requires at least 6-8 wk for its onset of action. The recommended dose of azathioprine is 100-150 mg/d (1.5-3 mg/kg per day). Sufficient perspective data from randomized trials is lacking but reports have shown its efficacy in severe psoriasis. DuVivier *et al*[112] observed 75%-100% clearance of psoriasis in 13 psoriasis patients among 19 of 29 patients who had benefited from treatment with azathioprine. It was found effective in another 5 of 10 treatment-resistant psoriasis patients with $\geqslant$ 25% improvement[113]. Hacker *et al*[114] used azathioprine in a psoriasis patient who had failed conventional psoriasis therapy (methotrexate, etretinate, corticosteroids) because of inadequate response or adverse effects. Azathioprine was as effective as other drugs in the treatment of psoriatic arthritis as well in a long-term study[115]. Remissions for > 5 years have been reported in 10 psoriasis patients following treatment with azathioprine pulse therapy in a recent study[116]. The researcher used azathioprine "intermittent high dose" (500 mg on 3 consecutive days) repeated every month along with "continuous low dose" (100 mg daily) during the intervening period comprising "one azathioprine pulse" of treatment. The patients were treated in Phase-1 until clearance that occurred after 1-5 pulses (average 3.7 pulses). The responders were shifted to Phase-2 and received same pulse dosing for another 9 mo followed by Phase-3 of "continuous low dose therapy" for one year. The patients were followed up without any treatment (Phase-4). Additionally, patients were treated with oral methotrexate (15 mg weekly), topical tar ointment before starting azathioprine pulse therapy for faster clearance. However, gastrointestinal intolerance, and bone marrow and liver toxicity at high dose remain a major concern. Azathioprine has been used effectively to treat patients with concurrent psoriasis and bullous pemphigoid and seems to be a good choice for such patients during corticosteroid weaning[117-119].

The major adverse effects of azathioprine include myelosuppression (anemia, leukopenia, thrombocytopenia, pancytopenia) that is more common among population having inherited deficiency of thiopurine S-methyltransferase (TPMT) activity. Liver toxicity (elevation of bilirubin, transaminases and alkaline phosphatase), and gastrointestinal side effects (nausea, vomiting, diarrhoea, oral ucers, esophagitis, steatorrheoa) are less common in recommended dosed. Nevertheless, patients should be monitored weekly for 1 mo, then every 2 weekly for 2 mo, and monthly or more frequently for hematologic or hepatic toxicity when dose alteration or other therapy changes are made/planned. Measurement of thiopurine methyltransferase levels can be used for guiding dosing pattern[120].

Six-thioguanine is the active form of azathioprine that works by inhibition of purine synthesis. It seems suitable alternative therapy for patients of who are failures or excluded for methotrexate, retinoids, or PUVA therapy. It is as effective or perhaps more effective in treating psoriasis than its parent drug. Zackheim *et al*[121] treated 48 patients having extensive plaque psoriasis with 6-thioguanine. They observed > 75% improvement as an initial response in 79%, > 50% improvement in 8% (including two patients with palmoplantar pustular psoriasis) while 13% had < 50% improvement. Almost 50% improvement continued in 65% patients during follow-up of 21 years (median 13 mo). The therapy was more effective, and better tolerated than methotrexate in majority of the patients who had changed from methotrexate due to inadequate response or side effects. Zackheim *et al*[122] made similar observations in their retrospective study of 81 patients with plaque psoriasis and five of palmoplantar pustular psorasis. A pulse-dosing schedule of 2 or 3 times per week showed marked improvement in 10 (71%) of 14 patients studied and maintenance dose varied from 120 mg twice a week to 160 mg 3 times a week[123]. Pulse dosing schedule

of 6-thioguanine is recommended to minimize its more serious adverse effects like myelosuppression, pancytopenia, and acute hepatitis but requires regular clinical and laboratory follow up[124]. Nausea, headache and fatigue occur less frequently.

Leflunomide

Leflunomide is an immunosuppressive disease-modifying antirheumatic drug. It is a prodrug and 70% of the drug administered converts into its active metabolite teriflunomide that inhibits mitochondrial enzyme dihydro orotate dehydrogenase (an enzyme involved in de novo pyrimidine synthesis). It is primarily indicated for treating rheumatoid arthritis and is found beneficial for the treatment of psoriasis with concurrent psoriatic arthritis. Kaltwasser *et al*[124] in a double blind, randomized placebo controlled study comprising 182 patients with psoriasis and psoriatic arthritis achieved a PASI 75 response at 24 wk in 17% patients in leflunomide group. While only 8% patients in placebo group had similar response. Similarly, psoriatic arthritis responded in 59% patients in leflunomide and systemic corticosteroids group *vs* 30% patients in placebo group.

Gastrointestinal irritation, elevated liver enzymes, leukopenia, drug eruption, headache, increased risk of infections, anaphylaxis, angiooedema, anaemia, agranulocytosis, eosinophilia, leucopenia, pancytopenia, vasculitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, oral ulcers, cutaneous lupus erythematosus, severe infection, interstitial lung disease, cirrhosis and liver failure, and teratogenicity are usual adverse effects[125]. Adequate contraception is recommended during leflunomide and additionally for 3 mo in males and 2 years in females after stopping the drug. Although combination of methotrexate and leflunamide is apparently more effective than either drug used alone (in rheumatoid arthritis), care should also be taken for concomitant use of methotrexate as combination may lead to severe or fatal hepatotoxicity[126]. Similarly, concurrent vaccination with live vaccines (like haemophilus influenzae type b vaccine and yellow fever vaccines) should be avoided due to the potential of severe infection because of immunosuppression from leflunamide.

Fluorouracil

Fluorouracil (5FU), an antimetabolite, acts principally by inhibiting thymidylate synthase leading to inhibition of pyrimidine thymidine synthesis. This anucleoside is important for deoxyribonucleic acid (DNA) replication. Thymidylate synthase catalyses methylation of deoxyuridine monophosphate to form thymidine monophosphate that is inhibited by 5FU therapy leading to cell death of rapidly dividing tumor cells and decreases epidermal proliferation[127]. Systemic fluorouracil is used for breast, anal, colorectal esophageal, pancreatic, gastric, and head and neck cancers. It is available as a solution, cream or a sustained-release preparation in various concentrations (0.5%, 1%, and 5%) for topical/intralesional use in actinic keratoses and Bowen's disease.

Due to its inhibitory effect on epidermal cell proliferation 5FU has been used topically, intralesionally or orally for treating plaque psoriasis[128-134]. As early as 1972, Tsuji *et al*[128] treated 13 patients with psoriasis using topical fluorouracil 5% ointment under occlusion. The treated lesions became necrotic followed by re-epithelization after stopping the ointment and complete clearance. Pearlman *et al*[129,130] used intralesional 1 mL fluorouracil (50 mg/mL) for 1-3 injections at 1- to 2-wk intervals (average 2 injections/patient) in 11 patients with psoriasis. The lesions improved in 2 wk and cleared completely in 4 wk. Subsequently, long remissions were observed in both the studies without significant systemic toxicity. Combining it with epinephrine for intralesional treatment showed improved response requiring single-dose treatment in 53 patients[132,133]. The combination was superior in improvement of psoriatic plaques than pulsed dye laser or betamethasone in a comparative study[133]. In a recent open-randomized-controlled study, 40 patients were treated with intralesional 5FU (0.1 mL/cm^2) weekly for three injections[134]. Total or near total clearance of lesions occurred in 35 patients at 12 wk. It was also effective for treating acrodermatitis continua of Hallopeau[135]. Gastrointestinal upsets, persistent hiccups, mucositis, headache, myelosuppression, photosensitivity, cardio toxicity, and mood alterations are common adverse effects of oral 5FU while pain, necrosis, and hyperpigmentation occurs from intralesional therapy.

Paclitaxel

Paclitaxel, a complex diterpene, is synthetic or derived from the bark of the Pacific yew tree (Taxus baccata). This chemotherapeutic agent demonstrates substantial anti-tumor effect in carcinoma of the breast, ovary, and lung, head and neck, bladder, testes, esophagus and endometrium. It has modest effect in Kaposi's sarcoma, lymphoma and carcinoma of the stomach and cervix. It has shown antiproliferative, antiangiogenic, and anti-inflammatory properties prompting a phase Ⅱ pilot study for its efficacy in 12 patients with severe psoriasis[136]. A dose-dependent decrease in PASI scores varying from 15% to 80% in different patients was observed. Higher dose (75 mg/m^2 every 4 wk for 6 doses) produced more significant results than lower dose at more frequent intervals; 37.5 mg/m^2 every 2 wk for 3 doses and 50 mg/m^2 for additional 6 doses. No patient had myelosuppression (usual with doses > 100 mg/m^2 every 3 wk), but hypersensitivity reactions occurred in two patients and another patient had flare up of Crh-on's disease. A new oral formulation, nanoemulsion of paclitaxel, has increased bioavailability in experimental animal models but needs evaluation for its clinical efficacy and safety among psoriasis patients[137].

MMF

MMF is an immunosuppressive drug used extensively in organ transplant recipients to prevent graft rejection prior to its usage for treating autoimmune blistering dermatoses (bullous pemphigoid, pemphigus vulgaris). It metabolizes to mycophenolic acid that inhibits de novo purine synthesis in B and T cells by inhibition of inosine monophosphate dehydrogenase enzyme for selective lymphocyte immunosuppressive effect. Haufs *et al*[138] reported first use of MMF for psoriasis leading to several case reports and uncontrolled studies demonstrating variable and beneficial effect of MMF for treating psoriasis[139-145]. Subsequent studies found MMF less effective as compared to methotrexate or cyclosporine but reported less nausea than methotrexate and renal toxicity than cyclosporine[82,146]. Beissert *et al*[146] observed a superior efficacy of cyclosporine as compared to that of MMF in a prospective, multicenter, randomized trial to treat chronic plaque-type psoriasis. However, there was no difference in time to relapse, side effects, and psoriasis disability index. As monotherapy, its overall PASI 75 achievement rate is less than 20% and PASI 50 is nearly 50%[144-146]. MMF also appears a reasonable alternative for patients with cyclosporine induced nephrotoxicity. Although PASI score increased in each patient treated with MMF after a 2-4 wk washout period of cyclosporine, the cyclosporine induced deranged renal function was significantly improved in a study evaluating switching from cyclosporine to MMF[147]. Regression of erythema, induration and scaling of psoriasis plaques has been reported from topical MMF but further evaluation is needed[148].

MMF has been also used successfully with cyclosporine minimizing toxicity of both drugs. Ameen *et al*[149] reported moderate to good improvement with cyclosporin (2.5 mg/kg per day) and MMF (3 g/d) in 3-11 mo among 78% patients with severe recalcitrant psoriasis. It also appear good choice in psoriasis patients having concurrent immunobullous disorders or HIV infection[150,151].

Severe gastrointestinal side effects (nausea, diarrhoea) and reversible hematologic toxicity are common. Hematologic malignancies, progressive multifocal leukoencephalopathy and serious infections have been reported in transplant recipients receiving MMF but are uncommon in psoriasis patients treated with MMF[152,153]. Nevertheless, all patients under treatment with MMF will routinely require evaluation for therapy-related complications by complete blood counts, hepatorenal function tests, and electrolyte estimation, and serious infections or neoplasia as per guidelines[142]. Despite unavailability of high-quality clinical trials, MMF in recommended doses of 1-1.5 g twice daily (maximum dose 3 g/d) appears a good alternative for the treatment of psoriasis in patients who are unable to take other drugs due to contraindication or toxicity or for maintaining disease control achieved from other therapies.

RETINOIDS AND RETINOID ACID METABOLISM BLOCKING AGENTS

Retinoids are synthetic and natural compounds that have biologic activity like that of vitamin A. Tretinoin and isotretinoin are the first generation retinoids while etretinate and acitretin are the second generation retinoids which are aromatic retinoids and supposed to be more effective in psoriasis and other keratinization disorders than first generation retinoids. Bexarotene and alitretinoin belong to third generation. The systemic retinoids, alone or in combination with other systemic (methotrexate, cyclosporine, hydroxyurea, PUVA) or topical agents (calcipotriene, coal tar ointment, steroids), or in rotational and sequential therapy constitute an important form of therapy in severe and resistant psoriasis. Retinoids are effective even as monotherapy particularly in exfoliative erythrodermic psoriasis and pustular psoriasis[154]. However, clinical data suggest that retinoid monotherapy may be less effective than other systemic agents in short term treatment of chronic plaque and guttate psoriasis. The advantage lies in their being not associated with immunosuppression or limitation of cumulative dose, and having no significant hepatic or renal toxicity. Therefore, they can be used alone or in combination with conventional therapies for psoriasis or biologic agents for treatment and maintenance therapy as well as in HIV affected patients with psoriasis. The exact mechanism of action of retinoids in psoriasis is not understood comprehensively. There are two families of retinoid receptors, a retinoic acid receptor (RAR) family and retinoid X receptor (RXR) family, each having three isoforms: α, β and γ. They perhaps exert their therapeutic effect by modulating three major pathogenic features of psoriasis, abnormal keratinocyte differentiation, keratinocyte hyperproliferation and tissue infiltration by inflammatory cells thus decreasing scaling, erythema and thickness of the plaques. They induce hypergranulosis and decrease number of tonofilaments and desmosomes, and widening of intracellular space causing a keratolytic effect. They inhibit neutrophil migration, alter cytokine production by T lymphocyte, interfere with keratinocyte responsiveness to cytokines or abolish resistance of keratinocytes to apoptosis[155]. However, isotretinoin has no clearly identified affinity for any retinoid acid receptor. Acitretin, an active metabolite of etretinate, is the most frequently used oral retinoid to treat psoriasis despite its lower efficacy as monotherapy *vs* methotrexate or cyclosporine. Its combination with UVB (reUVB) or PUVA (rePUVA) increases the responses of both modalities reducing the number and duration of therapy sessions needed to achieve clearance and decrease the cumulative adverse effects of ultraviolet (UV) radiation[156]. It can also be combined with other systemic agents like methotrexate, cyclosporine and hydroxyurea, biological therapies or with topical agents like calcipotriene and steroids in rotational and sequential therapy[157]. The efficacy of retinoids in

combination with biological therapies has been reported in several uncontrolled studies and case reports[158-167]. Ontheotherhand, other retinoids remain under evaluated for treating psoriasis.

Isotretinoin

Isotretinoin up to 2 mg/kg per day has been used in treating psoriasis[168]. Isotretinoin was first used in the treatment of psoriasis in 1973. Hotard *et al*[169] analyzed the medication prescribed to patients with a primary and only diagnosis of psoriasis spanning a period of 5 years. Out of 8.5 million visits, only 39% of the patients receiving systemic treatments were women. With respect to retinoids, it was observed that women received less etretinate (35% women among 100 patients on etretinate) than men but more isotretinoin (100% women) than men were, as all 9 patients who received isotretinoin were young females. Isotretinoin is considered more effective in pustular psoriasis than in chronic plaque psoriasis[170-173]. Moy *et al*[171] successfully treated 10 of 11 patients with pustular psoriasis using isotretinoin. Pustulation ceased after 3 to 5 d of treatment with daily dose of 1.5-2 mg/kg per day but recurrences were frequent on reduction of the dose. The pustulation subsided when the dose was increased again or most patients required additional agents to control their disease. Similarly, Al-Shobaili *et al*[174] found excellent outcome in a 16-year-old girl treated with isotretinoin for pustular psoriasis. Isotretinoin can be administered safely in patients who have developed adverse effects to etretinate. Marhold *et al*[175] reported a case of 29 years old female patient suffering from severe pustular psoriasis and had increased liver enzymes while on etretinate. Liver biopsy revealed changes of drug induced hepatitis. After normalization of the liver parameters following withdrawal of etretinate, isotretinoin was administered during a severe relapse. Contrarily, isotretinoin was well tolerated and resulted in a good therapeutic response. Vahlquist *et al*[176] also used isotretinoin in a patient of pustular psoriasis of palms and soles, who developed hepatitis after treatment with etretinate. However, they found it only marginally effective. Patients with plaque psoriasis can be treated with isotretinoin in a dose up to 1.5-2 mg/kg per day. Increasing small doses of isotretinoin are recommended initially while treating erythrodermic psoriasis in order not to provoke the disease[177,178]. Etretinate and acitretin has been shown to control chronic plaque psoriasis more effectively than isotretinoin when used as a single agent. Moy *et al*[171] compared isotretinoin with etretinate in chronic plaque psoriasis. Ten patients who had psoriasis affecting 20%-50% of their body surface area were treated with isotretinoin 1.5 mg/kg per day for at least 8 wk, and other 19 patients who had psoriasis affecting 40%-90% of their body surface area were treated with etretinate 0.75 mg/kg per day for the same period. Eighteen out of 19 patients treated with etretinate had either a complete or a moderate response, while only 4 of 10 patients treated with isotretinoin were moderate or complete responders. It showed a significant difference in efficacy in favour of etretinate. However, isotretinoin has shown equal efficacy to other retinoids when combined with psoralen photochemotherapy[179,180]. Combination of isotretinoin with PUVAsol was clinically more effective in clearing lesions of chronic plaque psoriasis and improved quality of life than PUVAsol alone in a recent study[180]. The mean percentage reduction in PASI score at the end of 12 wk was 51.92 ± 23.83 and 3 (27.27%) patients achieved marked to complete remission in a recent study comparing it with methotrexate[181]. Isotretinoin appeared less effective than methotrexate and only 4 (36.36%) patients had either mild improvement or were non responder in the first 8 wk.

Adverse effects of retinoids

Diffuse interstitial skeleton hyperostosis, premature epiphyseal closure, pseudotumour cerebri, severe headache and hepatotoxicity are potential important adverse effects. Musculoskeletal (arthralgia, myalgia, fatigue, muscle weakness, tendonitis), neuropsychiatric (mild depression, headache) and gastrointestinal (nausea, vomiting, abdominal pain) abnormalities may also occur. The retinoid tretogenecity remains the major concern and limitation for their use. When taken in the first trimester, they cause severe embryonic abnormalities in up to 50% and spontaneous abortion in up to one third of pregnancies. Malformations occur even with short periods of use, therefore no systemic dose of retinoids is considered safe during pregnancy. The most frequently described congenital malformation from isotretinoin is "the isotretinoin dysmorphic syndrome". It includes facial malformations (rudimentary external ears, absent or imperforate auditory canals, triangular microcephalic skull with large occiput and narrowing of the frontal bone, cleft palate, microphthalmia, depressed mid face), central nervous system anomalies (hydrocephalus, cranial nerve dysfunction), and cardiac malformations (over riding aorta, interrupted or hypoplastic aortic arch, atrioventricular septal defects, abnormal origin of the subclavian arteries). Limb reduction defects and thymic aplasia too have been described[182]. Hersh *et al*[183] reported that 10% of live birth records examined showed malformations of pregnancies occurring within 30 d after isotretinoin discontinuation. However, women who conceive one cycle after discontinuing isotretinoin are advised that their teratogenic risk is not higher than baseline[184]. The risk of retinoid embryopathy in fetuses fathered by men taking isotretinoin is minimal, if any.

Retinoids also adversely affect the skin (xerosis, palmoplantar and digital desquamation, retinoid dermatitis, photosensitivity, pyogenic granuloma, staphylococcus infections), the hair and nails (telogen effluvium, abnormal hair texture, dryness, fragility,

paronychia, onycholysis), the eye (dry eyes with visual blurring, blephrocunjunctivitis, photophobia), and mucous membranes (chelitis, dry mouth, sore mouth and tongue, nasal mucosa dryness, epistaxis). The majority of case control and other epidemiological studies have shown no association between mood change, depression, psychosis and suicide ideation, and isotretinoin use. Nevertheless, individual idiosyncratic psychological adverse response to the drug cannot be excluded[185]. Similarly, the current evidence is insufficient to establish a causal association between isotretinoin and inflammatory bowel disease[186].

New generation retinoids

Because of high selectivity for the β and γ subtypes of RARs the new generation retinoids have targeted action on psoriatic keratinocytes with minimum risk of adverse effects. They have better pharmacokinetics, and half-life of active metabolite of tazarotene (tazarotenic acid) is only 7-12 h. This imparts the advantage of contraception just being necessary for a few days after the last dose. The efficacy, safety and tolerability of tazarotene for psoriasis patients have been reported in phase Ⅲ trials[187]. It has been used safely for up to 52 wk without any significant increase in retinoid toxicities like hypertriglyceridemia, hypercholesterolemia, altered liver function tests, alopecia or conjunctival dryness. Several studies have also examined the safety and tolerability of topical tazarotene (0.1% and 0.05% gels), alone or in combination with topical corticosteroids (clobetasole, mometasone, flucinonide), calcipotriene or phototherapy for treating psoriasis[188-193]. Tazarotene 0.1% is generally more effective than the 0.05% cream. Tazarotene gel is non-sensitizer, non-phototoxic or non-photosensitizing, and treatment-related adverse effects like mild-to-moderate local skin irritation occur mainly from tazarotene 0.1% but systemic adverse effects do not occur.

Bexarotene, a synthetic RXR-selective retinoid, is an available treatment for cutaneous T-cell lymphoma. Antipsoriatic effect of oral bexarotene in doses up to 3.0 mg/kg per day during 12 wk of treatment has been evaluated on proliferation, differentiation, and inflammation parameters[194,195]. Smit *et al*[194] observed > 50% improvement in modified PASI, plaque elevation, and physician's global assessment in 22%, 52%, and 36% of patients, respectively, in a phase Ⅱ multicentric trial. No serious treatment related adverse events occurred. However, studies for the optimal dose and its potential as a new therapeutic modality are warranted. Similarly, therapeutic potential of topical bexarotene gel 1% in psoriasis needs further evaluation[196]. Oral Alitretinoin (9-cis-retinoic acid) 30 mg/d, alone or in combination with etanercept is another promising therapy for recalcitrant palmoplantar pustulosis or hyperkeratotic palmoplantar psoriasis but warrants confirmation of its efficacy and safety by controlled studies[197,198].

Contraindications, drug interactions and monitoring guidelines

Absolute contraindications for the use of retinoids are pregnancy or woman who is likely to become pregnant, non-compliance with contraception, nursing mothers, or individuals with known hypersensitivity. Relative contraindications include leukopenia, moderate to severe cholesterol or triglyceride elevation, and significant hepatic or renal dysfunction. Monitoring of concomitant medications that may interact with retinoids is required (Table 6). Pregnancy test in women of childbearing age, complete blood count, liver and renal function tests, complete lipid profile and urinalysis if indicated should be performed at baseline and repeated monthly for the first 3-6 mo, and then every 3 monthly. X-ray of wrist, ankle or thoracic spine at baseline and periodically are needed if retinoids are required for a long duration. Ophthalmologic examination is done as and when required.

According to iPLEGE program, the patient is advised to have a negative pregnancy test before isotretinoin use, every month during treatment, at the end of treatment and 1 mo after stopping treatment. The women must use two form of contraception for at least 1 mo prior to initiation of isotretinoin, during and one month after discontinuing therapy. Women of childbearing potential must access the iPLEDGE system at the time of first prescription and then at each subsequent prescription.

Retinoid acid metabolism blocking agents

Retinoid acid metabolism blocking agents, liarazole and talarozole, are retinoid mimetic drugs that act by blocking cytochrome P-450 dependent 4-hydroxylation of all-trans-retinoic acid. They modulate intracellular levels of endogenous retinoids and in turn normalize aberrant epithelial growth and differentiation. As the plasma all-trans-retinoic acid levels do not increase beyond physiologic levels, the retinoid-associated adverse effects are less frequent despite their efficacy similar to that of retinoids. Talarozole is a more selective inhibitor of the enzyme retinoic acid 4-hydroxylase and is effective in lower doses causing less side effects. Due to their rapid metabolism and clearance unlike synthetic retinoids, these drugs are safer for women and children. Liarazole was found effective for both palmoplantar pustular psoriasis and chronic plaque psoriasis in double-blind, randomized, placebo-controlled trials[199,200]. In a small pilot study, a noticeable improvement was observed in 4 of 7 patients with palmplantar pustular psoriasis treated with liarazole (75 mg, twice daily) as compared to 1 in 8 patients receiving placebo[199]. The lowest effective dose was 75 mg twice daily in a dose ranging, randomized, placebo controlled trial. A marked improvement occurred in 18% in liarozole 50 mg, 11% in 75 mg, 38% in 150 mg and 6% subjects in placebo group subjects, respectively[200]. Verfaille *et al*[201] treated 19 patients of psoriasis with talarozole (1 mg) for 8 wk and observed significant reduction in PASI. No formal

Table 6 Drugs interacting with retinoids

Interacting drug	Mechanism/comments
Drugs that may increase retinoids levels and/or toxicity	
Vitamin A	Induces hypervitaminosis A like toxicities
Tetracycline, doxycycline and minocycline	Increase pseudotumour cerebri risk
Macrolides, Azoles, *etc.*	Other CYP 3A4 inhibitors increase its level
Drugs that may reduce retinoids level	
Rifampicin, rifabutin	Induction of CYP 3A4
Anticonvulsants-phenytoin, Phenobarbital, carbamazepine	Induction of CYP 3A4
Drugs that may synergistically increase hepatotoxicity	
Methotrexate	Common target organ for toxicity-liver
Alcohol	Common target organ for toxicity-liver
Drugs whose levels are changed by retinoids	
Cyclosporine A	Cyclosporine A levels are increased *via* competition for CYP 3A4

announcement has been made for the results of phase II clinical trial for of its oral formulation, and phase I clinical trial for topical formulation[202].

FUMARIC ACID ESTERS

Althoguh fumaric acid was found effective in systemic treatment of psoriasis as early as 1959, the drug is licensed only in Germany and Netherlands for short-term (< 6 mo) use in patients with severe psoriasis when topical therapy is not indicated[203]. However, successful completion of a phase 3 study for use of its improved formulation in psoriasis has greatly renewed worldwide interest for this drug. The commercial preparations Fumaderm® initial and Fumaderm® have mixture of dimethylfumarate and three salts of ethyl hydrogen fumarate. (Fumaderm® initial contains dimethylfumarate 30 mg per tablet; Fumaderm® has dimethylfumarate 120 mg per tab).

The esters are used as fumaric acid itself is poorly absorbed after oral intake. They have almost complete absorption in the small intestines. The dimethylfumarate is rapidly hydrolyzed to more active metabolite monomethylfumarate by esterases. Dimethylfumarate and its metabolite monomethylfumarate are the principal active ingredients. Its interaction with intra- and extracellular thiols (glutathione) is considered the primary mechanism of action[204]. This inhibits NF-κB-mediated transcription of intracellular mediators (TNF-α or IL-8) and adhesion molecules (E-selectin, ICAM-1, VCAM-1). Other work suggests their therapeutic benefit by shift of the Th1-cytokines pattern towards Th2-type cytokine pattern associated with reduction in peripheral lymphocytes (primary T cells) inhibiting proliferation of epidermal keratinocytes in psoriasis patients[203,204]. Fumarates at higher concentrations inhibit induction of apoptosis and maturation of dendritic cells, which have an important role in immunologic reaction, and development and maintenance of an inflammatory response. These effects have been also demonstrated to be mediated by interference of the intracellular redox system.

Clinical studies from 1990s have reported a substantial reduction in PASI score following treatment with fumaric acid. Its efficacy and safety have been reported frequently and reviewed comprehensively[205-215]. Altmeyer *et al*[208,209] in two separate studies noted nearly 50% reduction in PASI in 50 patients with severe psoriasis and 80% in 83 patients respectively after 16 wk of treatment with Fumaderm®. Mrowietz *et al*[210] also reported 80% reduction in PASI after a 16-wk open-label multicenter study. The efficacy of fumarates is also confirmed in recent years. Litjens *et al*[211] reported nearly 53% reduction in PASI in 20 psoriasis patients while substantial improvement or clearance was observed by Carboni *et al*[212] in 71% of 40 psoriasis patients after 12-wk treatment with fumarates. Twenty percent patients achieved a statistically significant reduction in PASI from 13.9 ± 9.0 to 11.3 ± 9.2 in a single center study from United Kingdom[213]. The efficacy of fumaric acid ester in treating mild psoriasis too has been documented in a recent Italian study[214]. Reich *et al*[215] retrospectively analyzed the data of 984 patients with psoriasis for the long-term safety and efficacy of fumaric acid ester. Either the patients were on 24 mo of continuous treatment or at least 36 mo of intermittent treatment (mean duration 44 mo). Overall, 31%, 67%, 76%, 78% and 82% of the patients showed a substantial improvement or were clear of symptoms after 3, 6, 12, 24 and 36 mo, respectively, without significant laboratory abnormality or serious adverse effects. Although the efficacy of fumarates has been also demonstrated in psoriatic arthritis, nail psoriasis, and palmoplantar pustulosis, they are not recommended to treat psoriatic arthritis currently for lack of significant activity in arthritis, dactylitis, and enthesitis[216-219].

The therapy is usually initiated with low dose and escalated weekly until clinical response (usually observed in 4-6 wk) or a maximum dose of 1.2 g/d is achieved. Treatment with fumaric acid esters can be maintained for up to 2 years. Short-term intermittent therapy until major improvement followed by drug withdrawal is another mode of therapy. Although no rebound phenomenon or pustular exacerbation occurs, gradual tapering to minimal threshold dose is recommended to prevent relapse in patients with high disease activity.

The comparative efficacy of fumaric acid esters *vs* other systemic therapies remains understudied and so is that of their combination with other systemic therapies. Methotrexate and fumarates were equally effective without significant adverse events in the treatment of patients with psoriasis in a small, short-term study. Fallah Arani *et al*[83] in a first ever randomized controlled trial treated 60 patients with moderate to severe psoriasis vulgaris either with methotrexate (30 patients; 15 mg/Wk) or fumarates (30 patients; 30 mg, followed by 120 mg) for 16 wk. They reported 50% reduction in PASI at 12 wk of 42% and 60% patients in fumaric

acid esters and methotrexate group, respectively. PASI 75% was observed in 19% of fumaric acid esters and 24% of methotrexate group, respectively. Two patients in fumaric acid esters and 4 in methotrexate group dropped out due to adverse effects. Gollnick *et al*[220] found combination of oral fumaric acid esters and topical calcipotriol significantly more effective and faster acting than monotherapy with slight fumaric acid esters-sparing effect imparting a superior benefit/risk ratio. Combination produced higher and early mean reduction in PASI (76% *vs* 52%) and PASI 50 in 3 wk *vs* 9 wk. Fumarates can be combined with UVA or UVB during initial 3 wk of therapy[203]. There are reports of successful use in combination with methotrexate, acitretin, hydroxyurea or ciclosporin but combining retinoids have no additional benefit[221]. However, their combination with other systemic therapies is not recommended currently.

The fumaric acid esters are safe in inducing remission in a reasonable time and retain it through extended periods. Gastrointestinal complaints (nausea, abdominal cramps, or diarrhea) occur in up to 60% of patients in first few weeks of therapy. These symptoms can be reduced by dose reduction, taking the drug with milk, or addition of aluminium hydroxide, metoclopramide, ranitidine or pentoxifylline[222,223]. Flushing is seen in 30%-50% as feeling of warmth, facial flushing, and headache lasting for minutes to hours, and may be severe. It can be ameliorated with administration of acetylsalicylic acid. Leukocytopenia, lymphopenia, and eosinophilia can occur. The development of progressive multifocal leukoencephalopathy in two patients treated with Fumaderm® has been attributed to therapy associated prolonged severe lymphopenia[224,225]. Leukopenia below 3000/μL and lymphopenia below 500/μL, thus, need drug withdrawal or reduced doses. Eosinophilia is transient, seen in 4-10 wk of therapy, and improves after the drug withdrawal/reduction[226]. Occasional renal toxicity is observed and proteinuria when occurs will disappear following drug cessation or dose reduction[227,228]. Isolated elevation of serum bilirubin, hepatic enzymes, serum creatinine or potassium, and dyslipidemia may occur but increased susceptibility for infections or development of malignancies is not observed. Progressive multifocal leukoencephalopathy is a potentially severe toxicity. Discontinuation of therapy from adverse effects may be needed in 30%-40% cases.

CALCINEURIN INHIBITORS

Calcineurin or protein phosphatase 3, a calcium-dependent serine-threonine phosphatase, activates the T cells of the immune system and can be blocked by drugs called calcineurin inhibitors that include cyclosporine, tacrolimus, pimecrolimus and voclosporine. Both cyclosporine and tacrolimus are chemically distinct molecules. They bind to the intracellular immunophilins cyclophilin and FKBP-12 respectively. Both inhibit the phosphatase action of calcineurin required for the movement of nuclear factors in activated T cells to the chromosomes where subsequent cytokine synthesis occurs. They prevent IL-2 production in T cells and decreased secretion of IL-2 prevents proliferation of the inflammatory response *via* B cells and T cells. This attenuated inflammatory response greatly reduces the overall function of the immune system producing clinical response. Cyclosporine (cyclosporine A), a neutral cyclic undecapeptide, is derived from fungus *Tolypocladium inflatum gams*. It has been approved in the United States for 1-year and in Europe for 2-year of continuous therapy. Cyclosporine (2.5 to 5 mg/kg per day) has efficacy comparable to that of biologics in rapid control of severe, widespread, intensely inflammatory and erythrodermic psoriasis, cases resistant to other treatments, and nail psoriasis. Several studies have noted that 80%-90% of patients improve significantly after 12-16 wk of cyclosporine therapy[229,230]. The drug is also useful in treating childhood psoriasis with results and adverse effect profile similar to that is seen in adults[231-233]. However, early rebound flare up of psoriasis occurs after stopping the drug. Headache, tremors, and paresthesia/hyperesthesia are common adverse effects with short-term therapy. An irreversible nephrotoxicity and/or hypertension following long-term therapy especially in patients treated continuously with cyclosporine for > 2 years is of serious concern. Another major concern is almost six fold increased incidence of non-melanoma skin cancers like squamous cell carcinomas with long-term low-dose cyclosporine therapy especially when it is used in combination with PUVA (psoralen + UVA) therapy[234].

Voclosporine

This relatively new member of calcineurin inhibitors has higher affinity for calcineurin, faster clearance of metabolites from the body, high efficacy and a better safety profile as compared to cyclosporine. Nearly 67% patients receiving 1.5 mg/kg per day of voclosporine achieved PASI 75 in phase Ⅱ trial[234]. Similarly, 16%, 25% and 47% patients achieved PASI 75 response at 12 wk after voclosporine 0.2, 0.3, and 0.4 mg/kg, respectively, in a phase Ⅲ dose-finding placebo-controlled study comprising 451 patients with chronic plaque psoriasis as compared to 4% patients in the placebo group[235]. No significant adverse events or alterations in blood pressure, lipids or triglycerides were observed.

Topical calcineurin inhibitors

After noticing incidental improvement of psoriasis following systemic tacrolimus to prevent rejection in one heart and three liver transplant recipients, the researchers reported good response to the drug in other three patients with severe, recalcitrant and treatment resistant psoriasis[236]. Subsequently, European FK 506 multicenter psoriasis study group in a double-blind, placebo-controlled study comprising 50 patients with

severe recalcitrant plaque-type psoriasis randomized to receive treatment with either oral tacrolimus (FK 506) (*n* = 27) or placebo (*n* = 23) reported 83% PASI reduction in 27 psoriasis patients at the end of 9 wk[237]. Similarly, Rappersberger *et al*[238] used oral pimecrolimus with high clinical efficacy and good tolerability. The drug was well tolerated without clinically relevant laboratory abnormalities in a large, double-blind, dose-finding study[239]. Oral pimecrolimus, given as 20 and 30 mg twice daily in psoriasis patients, demonstrated a mean percentage reduction in PASI by 51.3% and 54%, respectively, at week 7 from the baseline. However, availability of topical formulations of tacrolimus and pimecrolimus (approved for atopic dermatitis) renewed interest for their use in the treatment of psoriasis as an alternative to topical corticosteroids. Mrowietz *et al*[240] used pimecrolimus (0.3% or 1%) to treat 10 patients with chronic plaque psoriasis in double-blind randomized-controlled study. Total scores decreased by 92% for clobetasol, by 82% for pimecrolimus (0.1%), by 63% for pimecrolimus (0.3%), and by 18% for control. They are most effective in recalcitrant psoriasis affecting the face, genitals, and intertriginous areas[241-245]. Tacrolimus (0.1%) ointment completely cleared psoriasis of face, intertriginous skin or both in 81% of 21 patients at end of study period of 57 d[242]. It also demonstrated complete clearing (24.8% *vs* 5.8%) in another randomized-controlled study at day 8, and 65.2% *vs* 31.5% at 8 wk in 80% of 167 patients with facial and intertriginous psoriasis[243]. Other researchers also made similar observations for efficacy and safety of topical tacrolimus with nearly 80% of patients having complete clearance of psoriasis on the face, genitalia, intertriginous areas, and corporal plaques[244]. Tacrolimus ointment improved plaque psorisis in a microplaque assay[246]. It has been also used with equal efficacy and safety in pediatric patients. Brune *et al*[247] evaluated tacrolimus 0.1% ointment in a single-centre open-label trial by treating 11 children aged between 6 and 15 years having psoriasis of face, folds or both. All patients had clearance or achieved excellent response within first 30 d itself. However, it is less effective for hyperkeratotic plaques involving back, trunk, elbows, and knees, perhaps from poor penetration[248]. Combining tacrolimus (0.1%) with salicylic acid (6%), or calcipotriene (0.005%) improves outcome in such cases[249,250]. Using tacrolimus or pimecrolimus under occlusion is also associated with improved efficacy in treatment of psoriasis[251]. Changing formulations for tacrolimus or pimecrolimus to improve its penetration and cutaneous bioavailability is another promising area for research. Topical liposomal tacrolimus was found nine times more effective than tacrolimus ointment in experimental studies[252]. Polymeric micelles- methoxy-polyethylene glycol-dihexyl substituted polylactide (MPEG-dihexPLA), a biodegradable and biocompatible diblock copolymer, as a nanocarrier was highly efficient for selective cutaneous delivery of tacrolimus experimentally[253].

Burning sensation and/or pruritus, usually in first few days of application of tacrolimus or pimecrolimus, is considered secondary to release of neuropeptides such as substance P[254]. Although United States FDA has issued "black-box" warning considering the risk for lymphoma and skin cancer, there is no convincing data for enhanced risk for the development of either cutaneous or systemic malignancy after topical use in large number of patients with atopic dermatitis for up to 4 years[255,256].

THIAZOLIDINEDIONES AND STATINS

Thiazolidinediones, pioglitazone, troglitazone, and rosiglitazone, are used for the treatment of non-insulin-dependent diabetes mellitus. They lower insulin resistance in peripheral adipose and muscle tissues, and decrease hepatic gluconeogenesis by binding to peroxisome proliferator-activated receptors (PPAR) γ. They also have cardiovascular benefits because of their property of lowering blood pressure, improving endothelial cell function/fibrinolysis, and increasing high-density lipoprotein. Increased expression of PPAR β/δ has been observed in activated T cells in human psoriatic lesions while experimental studies have shown that activation of PPAR β/δ in the epidermis could sustain a psoriasiform inflammation with keratinocyte hyperproliferation, accumulation of dendritic cells and endothelial activation[257,258]. Experimentally, topical PPAR β/δ antagonists effectively reversed PPAR β/δ activation triggered psoriasis-like changes[259]. The PPARγ agonists said to act *via* modulating anti-inflammatory actions by decreasing inflammatory cytokines like IL-2, TNF-α and IFN-γ, and down regulating the expression of adhesion molecules like VCAM-1[260]. They also inhibit the production of IL-17 by $CD4^+$ cells, and neoangiogenesis/angiogenesis both *in vitro* and *in vivo*[261,262]. Shafiq *et al*[263] in a double-blind randomized placebo-controlled clinical trial evaluated pioglitazone monotherapy in 70 patients with moderate to severe psoriasis. Three groups of patients received placebo, pioglitazone 15 or 30 mg/d, respectively for 10 wk. Psoriasis cleared or almost cleared in 40% of treated patients compared to 12.5% of patients in placebo group at end of the study period. The results were better with higher dose of pioglitazone and mean percentage reduction in mean PASI score was 21.6%, 41.1% and 47.5% in the pioglitazone 15 mg, 30 mg, and placebo groups, respectively. Adverse events like decreased hemoglobin in one patient and elevation of liver enzymes in two patients did not warrant withdrawal from study. In another open-label study, Bongartz *et al*[264] reported statistically significant reduction with pioglitazone 60 mg/d and non-steroidal anti-inflammatory drugs in average number of painful and/or swollen joints and a 38% reduction of PASI score in 10 patients after 12 wk of treatment. A 3-mo treatment period appears appropriate for any significant clinical response as most improvement occurred between 6 and 12 wk. The pioglitazone in combination with methotrexate or

acetretin seems more effective in improving plaque psoriasis in two recent studies than control groups receiving methotrexate or acetretin alone. Lajevardi *et al*[265] in a randomized controlled, assessor-blinded study compared the efficacy of methotrexate and combination of methotrexate and pioglitazone in 22 patients in each group. The PASI 75 was achieved in 63.6% with combination treatment as compared to 9.1% with methotrexate alone at end of 16 wk study period. Mean percentage reduction was 70.3% *vs* 60.2% in combination *vs* methotrexate alone group. Mittal *et al*[266] reported mean percentage reduction in PASI score of 64.2% in acetretin plus pioglitazone group as compared to 52.7% in acetretin plus placebo group after 12-wk study period. Its combination with other systemic therapy remains unevaluated. Troglitazone also normalized histological changes of psoriasis and reduced hyperplasia in experimental murine and human skin models. A substantial efficacy of troglitazone in psoriasis too has been reported in similar studies[267,268]. However, rosiglitazone was no more effective than placebo in a recent study[269]. Moreover, the drug has been withdrawn because of idiosyncratic hepatotoxicity.

Thiazolidinediones, due to their effect on lipid and glucose metabolism, appear to be therapy of choice for psoriasis associated with metabolic comorbidities like insulin resistance, obesity, dyslipidemia, or cardiovascular diseases. Pioglitazone 150 mg/d also led to complete remission of psoriasis in a 65-year-old man with non-alcoholic steatohepatitis and diabetes who had not responded to treatment with ursodeoxycholic acid[270]. However, topical formulations of these agents need further evaluation as no change was observed in PASI scores in a study comprising 8 patients with plaque psoriasis treated with topical 0.5% rosiglitazone[271]. Apparently, thiazolidinediones make useful therapeutic options for psoriasis and pioglitazone remains the most studied drug among its peers. Although more evaluation is needed for pioglitazone, alone or its combination with methotrexate, acetretin or other antipsoriatic drugs, it appears a relatively safe, convenient, and effective therapeutic option for psoriasis.

Statins

Statins include atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. They were developed originally to treat lipid disorders in patients with hypercholesterolemia. They have significant immuno-modulating properties and studies have shown that they modify Th1/Th2 response to Th1 response, inhibit MHC-Ⅱ induction, cytokine release, inhibit mast cells degranulation, and induce apoptosis. CCL20/CCR6 interaction also plays an important role in the pathogenesis of psoriasis. Kim *et al*[272] investigated an inhibitory effect of statins on CCL20/CCR6 interaction and could demonstrate that IL-1β, TNF-α, and IL-17A significantly increased CCL20 production from HaCaT cells. Fluvastatin and simvastatin, but not pravastatin seemed to reduce this effect. Statins have shown to reduce inflammatory markers and when added to standard psoriasis therapy may improve disease severity. Statins show a hierarchy in their anti-inflammatory activity (cerivastatin > atorvastatin > simvastatin > pravastatin > lovastatin > fluvastatin)[273]. However, studies on their potential role in preventing psoriasis have yielded conflicting results. A decreased progression of psoriasis is shown to be associated with statin intake in several studies[274-279]. Contrarily, statins have been implicated for deterioration of skin lesions as well[280-283]. Shirinsky *et al*[279] in an 8-wk pilot study for the efficacy of simvastatin (40 mg/d) observed beneficial effects in seven patients with plaque psoriasis. Brauchli *et al*[275] observed no link between long-term use of statins and the decreased risk of psoriasis diagnosis in a case-control retrospective analysis of 36702 cases of psoriasis identified between 1994 and 2005 from United Kingdom based General Practice Research Database. However, they observed a reduced psoriasis risk for short-term statin users. Whereas, another retrospective cohort study assessed the relationship between adherence with statins and the risk of psoriasis among 205820 health plan enrollees in Israel (mean age 55 years; 54.1% female) and found that high and long-term adherence with statins is not associated with a meaningful reduction in the risk of psoriasis[280]. Another aspect of statins use is their combination with other antipsoriasis therapy. It showed a trend toward greater improvements in psoriasis severity in a study comprising 232 patients using topical corticosteroids, topical vitamin D, and some anti-ischemic treatments[274]. The patients on statins (n = 66) had more severe disease (BSA of 13.26%) before starting new psoriasis medication as compared with 12.25% for the patients in nonstatin (n = 166) group. Interestingly, the trend reversed after initiating medication, with a BSA of 5.21% *vs* 7.43% for the statin *vs* nonstatin users. There was overall 64% reduction in psoriasis severity in statin group as compared with 45% reduction in the nonstatin group. Although the difference was not statistical significance, trend for those treated with statins was toward greater improvement. Combined treatment with simvastatin and topical betamethasone also provided better clinical outcome in a double-blind study comprising 30 subjects with plaque-type psoriasis randomized to two groups[278]. Oral simvastatin (40 mg/d) combined with topical betamethasone (50% in pet) ointment in first group, whereas the second group received topical betamethasone (50% in pet) ointment and oral placebo. PASI score decreased significantly in both groups after study period of 8 wk. However, the reduction in PASI score was more expressed in simvastatin group patients. The potential efficacy of adding topical simvastatin to topical calcipotriol in plaque psoriasis also needs confirmatation[284]. Effects of combined treatment with atorvastatin (40 mg/d) *vs* placebo and keratolytics and/or corticosteroids were studied by Faghihi *et al*[276] in a prospective, randomized, double-blind, placebo-

controlled study. Oral atorvastatin was not associated with therapeutic benefit in patients with PASI scores < 12 points prior to addition of statin and the differences in mean PASI score were not statistically significant in two groups. Statins associated adverse effects like myopathy, proteinuria, elevated transaminases, or haemorrhagic stroke were not noted by these studies. Simvastatin presents the highest risk of toxicity *via* mechanism of CYP3A4 inhibition. It is not uncommon to find statins triggering/aggravating psoriasis. Cozzani *et al*[281] reported worsening of psoriasis in a patient 3 mo after atorvastatin and considerable improvement after discontinuation of atorvastatin. There is also report of exacerbation of psoriasis following pravastatin use[282]. Despite reduction in all-cause mortality among people without evidence of cardiovascular disease treated with statins, the major concern from wide use of statins in psoriasis is possible drug interactions between concomitant antipsoriatic or other therapies (methotrexate, cyclosporine, fibrates, macrolides, warfarin, digoxin, and azole antifungals)[285,286]. Potential interaction between fluvastatin and cyclosporine, primarily metabolized by CYP2C9 and not CYP3A4, is low[286].

It is perhaps too early to recommend use of statins in psoriasis as stand alone therapy as sufficient perspective data is lacking. The misinterpretation of available data is also possible as patients using statin are likely to change towards a healthier lifestyle as has been suggested by Brauchli *et al*[275]. Nonetheless, statins seems reasonable adjuncts to psoriasis therapy in view of the fact that psoriasis patients have a significant risk for metabolic disturbances and cardiovascular diseases.

ANTI-INFLAMMATORY AND OTHER DISEASE MODIFYING DRUGS

The utility of anti-inflammatory drugs as monotherapy is limited. While some of these agents like sulfasalazine have well identified advantage especially in psoriatic arthritis, others may perhaps have just more than a placebo effect. Nevertheless, their significance is perhaps in "add-on" therapy to ameliorate accompanying symptoms of inflammation and being sick.

Sulfasalazine

Sulfasalazine, a sulfa drug, is a derivative of mesalazine formed by combining sulfapyridine and salicylate with an azo bond. Sulfasalazine is primarily used for the treatment of inflammatory bowl disease including Crohn's disease and ulcerative colitis. It is also indicated for the treatment of rheumatoid arthritis or other inflammatory arthritis such as psoriatic arthritis. The recommended dose is 500 mg three times daily and increased as needed/tolerated. Sulfasalazine metabolizes to sulfapyridine that is responsible for some of the anti-arthritic effects and side effects of sulfasalazine from high serum concentrations of sulfapyridine and poor acetylation of the drug. Its other metabolite, 5-aminosalicylic acid (5-ASA), is considered responsible for its major therapeutic effect. However, its exact mechanism of action is not understood well but its anti-inflammatory effect is attributed to inhibition of dihydrofolate reductase and folate absorption. Sulfasalazine has been found effective in the treatment of psoriasis, spondyloarthropathy and psoriatic arthritis[287-299]. In a double-blind, randomized, controlled trial of sulfasalazine, intolerable adverse effects warranted discontinuation of treatment in 8 of 25 patients while other 7 of 17 patients, who continued treatment, showed 60%-89% improvement in their psoriasis[288]. In a small study, 3 of 8 patients in sulfasalazine group had moderate (50% to 70%) improvement of PASI score as compared 70% (very good response) improvement in PASI score in 6 of 7 patients in methotrexate group[293]. Significant improvement was observed in morning stiffness, number of painful joints, articular index, clinical score, and pain score, with the favourable response more pronounced in the polyarticular group and response became visible as early as 4 wk[289,297]. In a large double blind, placebo-controlled study 58% of 221 patients with moderate to severe psoriasis improved with sulfasalazine (2 g/d) over 36 wk and showed improvement in their psoriatic arthritis compared with 45% in the placebo group[290]. Rahman *et al*[295] treated 36 patients with sulfasalazine (3 g/d). One or more side effects warranted discontinuation of drug in 14 of 16 patients within 3 mo. A 50% reduction in actively inflamed joint count was noted in 7/20 patients at 6 mo and 11/15 patients at 12 mo as compared to 7/19 patients in the control group at 6 mo and 10/20 patients at 12 mo. Combe *et al*[299] also noted significant improvement in their study of 120 patients. Overall, the benefit remains marginal with no halt in radiographic progression in psoriatic arthritis and significant number of patients experience adverse effects. The axial disease also does not appear to improve significantly[294]. Comparatively, cyclosporine was more effective than sulfasalzine in the treatment of psoriatic arthritis in an open trial[298].

Although adverse effects are not serious, may occur in about 60% of patients requiring withdrawal from study in 15% patients[295]. Gastrointestinal intolerance (nausea, heartburn, vomiting, and diarrhea), malaise, headache, arthralgia, drug fever, and reversible oligospermia are common while leukopenia and agranulocytosis, and haemolytic anemia in G6PD deficient individuals are more serious adverse effects[296]. Skin eruptions can also occur and caused 4 of 23 patients receiving drug to drop out in a trial[288]. As the effect of sulfasalazine remains variable, its usage must be weighed against risk *vs* benefit of the drug. It must not be combined with methotrexate due to enhanced hepatorenal toxicity.

Colchicine

Colchicine, an alkaloid extracted from the plant

Colchicum species (*C. autumale*), has anti-inflammatory response by interfering neutrophil chemotaxis and inhibition of cell-mediated immune responses. It is mostly used to treat acute gout in a dose of 0.6 to 1.2 mg once or twice daily while its efficacy in psoriasis varies from being effective to having no effect on skin lesions. Wahba *et al*[300] observed significant clearing of skin lesions in 11 of 22 patients treated with colchicine (0.02 mg/kg per day) with symptomatic improvement observed in four patients with arthralgias. No significant difference was reported in 25 patients treated with colchicine (0.6-1.8 mg/d) or placebo at 23 wk in a subsequent placebo controlled study while colchicine was also associated with more adverse effects necessitating withdrawal from study in three patients[301]. Seideman *et al*[302] in a double blind, placebo controlled, and cross over study found significant improvement in joint pain and swelling, and grip strength in 10 of 12 patients after 16 wk treatment with colchicine (1.5 mg/d). Complete remission of pustular psoriasis occurred in 3 of 4 patients after colchicine treatment[303]. Palmoplantar pustulosis too has been treated successfully with some exceptions[304-306]. However, the potential efficacy of topical colchicine needs further evaluation[307]. Colchicine associated gastrointestinal adverse effects at doses above 2-3 mg/d are the major concern and may occur in 80% of patients and can be an indicator of maximum therapeutic dose. Myopathy and neuropathy may occur in long-term therapy while pancytopenia and renal failure results from overdose of the drug. Colchicine may be more useful in psoriatic arthritis, pustular psoriasis and palmoplantar psoriasis in a subset of patients, but more perspective data will be required to establish the role of colchicine in the management of psoriasis.

Dapsone

Therapeutic efficacy of this well-known antileprosy drug was first reported in a patient of generalized pustular psoriasis who was managed on a regimen of long-term systemic triamcinolone and dapsone[308]. Subsequently, several reports of its successful use in the treatment of childhood pustular psoriasis appeared[309-311]. An excellent response from dapsone was noted in 19 of 26 children while other five children had moderate response when treated with dapsone[310]. The response improved further when dapsone was combined with triptolide (the active ingredient in a Chinese herb) and erythromycin. Dapsone (100 mg/d) was also effective in treating inverse psoriasis involving genital skin fold[312]. The usual dose for pustular psoriasis in children is 1 mg/kg per day or 50-300 mg/d in adults and decreased to a low maintenance dose after effective control. The mechanism of its action in psoriasis has been postulated to be due to its anti-inflammatory effects by virtue of interference with neutrophil chemotaxis, blockage of prostaglandin- and leukotriene-mediated inflammation, and inhibition of myeloperoxidase in neutrophils and eosinophils, preventing tissue injury from oxygen radicals. Woolly headedness, anemia, dose-related methemoglobinemia, hemolysis in glucose-6-phosphate dehydrogenase (G6PD) deficient patients, agranulocytosis, hepatitis, dapsone hypersensitivity syndrome, peripheral neuropathy are some of its potential adverse effects requiring periodic evaluation. The utility of dapsone appears exciting but few well-controlled clinical studies are highly desirable to evaluate efficacy of this very versatile low-cost treatment in psoriasis.

Pentoxifyline

Pentoxifylline, a methylxanthine derivative, is a non-selective inhibitor that moderates the intracellular levels of cyclic adenosine monophosphate (cAMP) and cyclic guanisine monophosphate by decreasing their hydrolysis and augments cyclic nucleotide-dependant signal transduction leading to variable effects on inflammation[313,314]. It reduces blood viscosity, inhibits aggregation of platelets, erythrocytes and leukocytes, inhibits thrombus formation and improves microcirculation and tissue perfusion because of hemorheologic actions[315]. It also suppresses *TNFα* gene transcription, expression of TNF mRNA and secretion of TNF protein in macrophages and monocytes. The anti-TNF effect and antiproliferative effect of pentoxifylline is speculated to be responsible for its efficacy in psoriasis[293,316]. Magela Magalhães *et al*[317] in a randomized, placebo-controlled trial treated 61 patients with active psoriasis with pentoxifylline 400 mg/d or placebo. Clinicopathologic evaluation 8 wk after treatment showed no statistically significant differences from pre-treatment features between the two groups. el-Mofty *et al*[293] in a randomized controlled trial studied efficacy of sulfasalazine and pentoxifylline. They divided 32 patients in four groups treated either with sulfasalazine (group A), pentoxifylline (group B), both drugs (group C), or methotrexate (group D), respectively. Combination of sulfasalazine and pentoxifylline produced a better response than either drug used alone but methotrexate was superior in clearing the psoriasis at weeks 0, 2, 4, 6 and 8 of follow up. Its combination with fumaric acid esters is also said to reduce the severity and incidence of fumaric acid esters associated flushing and gastrointestinal side effects[224]. Similarly, use of pentoxifylline with cyclosporine might reduce later's nephrotoxicity[318]. Overall, its usefulness as monotherapy appears limited as compared to its combination with other antipsoriatic therapy. It is perhaps better to use it as only "add-on" therapy in the treatment of psoriasis[319].

PHOTOTHERAPY RELATED PROCEDURES

Phototherapy using UV light from sun or artificial source is a well-established treatment option in psoriasis of moderate severity, palmoplantar psoriasis, guttate and small plaque variety. UV light of both, broadband (BB) UV-B (290-320 nm) and narrowband (NB) UV-B (311-313 nm), and UV-A (320-400 nm) wavelength is predominantly used in psoriasis therapy. Comparatively, NBUV-B phototherapy is superior to BBUV-B in efficacy

and remission periods but is equal or less effective than PUVA therapy[320-325]. PUVA is useful in thick plaque psoriasis, palmoplantar psoriasis (particularly with topical psoralene), and for UVB phototherapy non-responders. However, UV-B phototherapy has added advantage of ease of administration and no psoralene toxicity (gastrointestinal intolerance, hepatotoxicity, phototoxicity, photodamage, premature aging, cataract, risk of skin cancers). Combination of PUVA or UV-B phototherapy has been used along with various topical (corticosteroids, calcipotriene, anthralin, tazarotene) or systemic treatments (methotrexate, retinoids) for enhanced therapeutic effect even at lower than recommended doses[326-329]. A combination of PUVA and UV-B has cleared psoriasis more effectively with an average of 11.3 treatments at doses much lower than needed for monotherapy[330]. The overall objective is to maintain minimum perceptible erythema for optimal dosing until 20-25 treatments, total or near total remission, or no further improvement is noticeable. The treatment is continued with reduced frequency to maintenance therapy once the remission is achieved. Nevertheless, the limitation is its contraindication in patients with erythrodermic or photo aggravated psoriasis, photosensitive disorders (systemic lupus erythematosus), personal or family history of melanoma or other skin cancers, and severe actinic damage. Eye protection is essential during UV phototherapy and ingestion of psoralene is contraindicated in children aged < 12 years.

Photodynamic therpay

Photodynamic therapy or photochemotherapy using topical aminolevulinic acid has been tried in psoriasis with inadequate clinical response in a randomized study comprising 29 patients[331]. Results have been discouraging in a recent randomized double-blind trial of this modality in 12 patients with psoriasis[332]. The therapy is frequently associated with severe pain and burning during and after treatment warranting its discontinuation. Topical hypericin, methylene blue, and systemic ALA and verteporfin are perhaps better tolerated photosensitizers for photodynamic therapy[333]. Like photodynamic therapy, photopheresis and extra-corporeal photochemotherapy are ineffective for skin lesions or psoriatic arthritis[334,335] and not prefered.

Grenz ray therapy

Grenz rays are essentially short-wavelength X rays with a wavelength of 0.07 to 0.4 nm, which is also in the range of long-wavelength ultraviolet radiation. They are produced at low kilovoltages with very limited penetration ability; up to the first half millimeter of the skin. Grenz ray therapy has been used effectively in many inflammatory dermatoses (eczemas, lichen planus, acne, Hailey- Hailey disease, mycosis fungoides) perhaps for their anti inflammatory effect and ability to decrease Langerhans cells in the epidermis[336]. Many researchers have reported good response from grenz rays (4 Gy weekly for 6 wk) therapy in psoriasis as well. Grenz rays therapy was effective in 14 of 16 patients with scalp psoriasis in a double-blind bilateral trial leading to complete clearing of scalp lesions treated with grenz rays for 6 wk and the remission lasted for 3 mo in 9 of these patients[337]. Grenz rays combined with topical corticosteroids cleared scalp psoriasis faster than topical corticosteroids alone in 17 patients with symmetrical scalp psoriasis lesions in a double-blind study[338]. The remission also lasted longer with combination therapy than when grenz rays were used alone. Lindelöf *et al*[339] compared grenz ray therapy alone with combination of grenz rays and topical betamethasone dipropionate in 40 patients with scalp psoriasis randomized into two groups. One group received 4 Gy of Grenz rays administered on six occasions at intervals of 1 wk and the other group was given the same Grenz ray treatment plus topical corticosteroid. The patients were assessed before and after Grenz ray therapy. Psoriasis cleared significantly in 16 out of 19 (84%) of the patients in the Grenz ray group, and I3 out of I8 (72%) of the patients in the combination group but the remission did not differ significantly between the two groups at end of follow-up of 6 mo. Remissions were longer with combination of grenz rays and selenium sulphide shampoo in combination as compared to placebo shampoo and Grenz rays[340]. Grenz ray therapy was also effective in a limited manner and appears to be a useful adjunct to other therapies for palmoplantar psoriasis and nail psoriasis particularly for nails with normal thickness[341,342]. The grenz ray therapy (4 Gy weekly for 6 wk) showed moderated but significant improvement of palmoplantar pustulosis in 15 patients in a randomized placebo controlled bilateral study[341]. The efficacy of grenz ray therapy was assessed in 22 patients with nail psoriasis in a randomized, bilateral controlled study[342]. One hand was allocated to treatment group receiving 5 Gy of grenz rays at weekly interval on 10 occasions. The placebo group received simulated therapy. The patients receiving active treatment showed moderate but significant improvement when psoriatic nails of normal thickness as compared to the control group. Overall, current evidence on its efficacy for psoriasis remains limited and development of non-melanoma skin cancers is a concern in the long term in addition to reported adverse effects of erythema and pigmentation[336,343].

Excimer laser

The monochromatic excimer laser used 308 nm xenon chloride light source and can deliver supra-erythemogenic doses up to 6 MED (2-6 MEDs) focally to the individual skin lesion for targeted phototherapy to minimize radiation and number of treatments. Initially used as three times weekly with an average of 10-12 treatments needed normally for improvement[344]. Asawanonda *et al*[345] reported at least 75% clearing of psoriasis in 72% of 124 patients after an average 6.2 treatments with excimer laser delivered twice

weekly. Higher response was noted with excimer laser in comparison with pulse-dye laser in a recent comparative study; few patients also responded better with the pulse-dye laser[346]. Patients in both the groups had remissions lasting more than 3 mo to 1 year. Blistering, burning and pain, and postinflammatory hyperpigmentation are potential side effects of excimer laser.

Climatotherapy and balneophototherapy

Exposure to sunlight is well known to improve psoriasis in majority. Daily bathing in Dead Sea water followed by exposure to sunlight perhaps remains the most studied mode of climatotherapy. The efficacy of Dead Sea climatotherapy has been attributed to the, high mineral contents, climatic conditions, and its location at about 400 m below sea level. Exposure to UV light through a mineral haze surrounding the beaches for 15 min daily to begin with is increased gradually depending on skin type to a maximum of 3 h/d for 3-4 wk. A 2 wk therapy is also considered optimal by some workers[347]. The therapy has been found effective in psoriasis decreasing PASI scores by 75% or more with long remissions[348-350]. Harari *et al*[351] observed 95.5% improvement of pre-treatment mean PASI score that decreased from 31.7 to 1.42 in 64 patients after 4-wk Dead Sea climatotherapy. All patients achieved PASI 50 and 75.9% of them reached PASI 75 during the same period. The median time of remission was 23 wk after a median duration of 33.6 wk. However, no long-term changes in psoriasis severity and quality of life were observed following Dead Sea climatotherapy in an earlier study[352]. Nevertheless, improvement is considered comparable to that from NB-UVB or PUVA therapy and other treatment modalities[351,353]. It was effective in psoriatic arthritis and has been used safely in pediatric patients[354-357]. Although considered expensive and time consuming, Shani *et al*[350] found it cost-effective considering the cost involved in travel, hotel accommodations, medical and laboratory charges, loss of productive days, adverse effects, and time taken for recovery of inpatient treatment. It has been combined safely and effectively with acitretin for psoriasis therapy[355].

Balneophototherapy involves salt-water baths and artificial ultraviolet radiation as an alternative to climatotherapy at the Dead Sea. Although high clearance rates have been reported with balneophototherapy[358,359], combination of Dead Sea bathing and sun exposure was more effective with 83% improvement as compared to 73% improvement with sun exposure alone and 28% improvement in psoriatics who only soaked in Dead Sea salts[360]. Climatotherapy is considered safe and adverse effects of this non-drug therapy such as sunburn, pruritus, folliculitis, solar elasotsis, solar lentigens, poikiloderma and wrinkles may occur[349,350,361]. Photodamage, malignant melanoma and non-melanoma skin cancer are other potential risks associated with long-term therapy.

Phototherapy for treating psoriasis, as standalone therapy or in combination with other modalities, remains as good an option as it was before therapies that were more effective became available. NBUV-B phototherapy is preferred being simpler and cheaper than all these procedures, virtually safer and free of adverse effects associated with psoralene ingestion.

PHYSICAL MODALITIES

Because of inherent complications, these physical treatment modalities should not be preferred to other therapeutic modalities or biologicals even in resistant debilitating disease.

Dialysis and related procedures

A report on incidental clearance of psoriasis lesions following haemodialysis in 1976 lead several small studies reporting a variable response[362-367]. Twardowski[363] also performed hemodyliasis for psoriasis in a non-uremic patient. A review of these reports reveals that peritoneal dialysis was more effective than hemodialysis. With 3-4 continuous ambulatory peritoneal dialyses per day, the psoriasis cleared completely in the two patients with renal failure and improved in the other two patients with normal renal function[368]. However, continuous treatment is perhaps required to prevent relapse. In a randomized double-blind crossover study treatment with sham and real peritoneal dialysis was performed in severe chronic plaque psoriasis unresponsive to conventional therapies including methotrexate[369]. Two patients cleared completely, two patients had more than 75% clearance and one patient had no significant response in peritoneal dialysis group while none of the 5 patients in the control group had any response. Sobh *et al*[370] treated 40 patients with severe psoriasis after their random grouping for haemodialysis (group-1), peritoneal dialysis (group-2), and treatment with modified Goeckerman (group-3). Ten dialysis sessions showed better response in peritoneal than haemodialysis, and both were better than Goeckerman treatment. There were no significant changes in plasma, or tissue zinc and copper levels while there was a significant decrease in IgG deposits after treatment in the three groups. Contrarily, Nissenson *et al*[371] in a randomized controlled trial of haemodialysis in seven patients with severe psoriasis observed no significant objective improvement. They performed a 24 h course of haemodialysis in three patients once daily for 4 d and repeat haemodialysis after 4 wk. Sham dialysis was performed in similar manner in four patients. In another study, 4/8 (50%) patients in haemodialysis group and 6/10 (60%) patients in peritoneal dialysis group, respectively, improved at the end of six months[372]. The benefit was temporary and one patient developed exfoliative dermatitis 11 d after haemodialysis. Three patients of Llewellyn *et al*[373] neither tolerated nor benefited from peritoneal dialysis. The exact mechanism of action of this procedure is poorly understood and is postulated to be from decreased IgG, increased fibronectin level, and postulated removal (from bloodstream) of growth-

promoting substances, psoriasis-related factors, activated polymorphonuclear leukocytes, interference with neutrophil migration[371,372].

While some psoriasis patients with renal disease may benefit from dialysis, the severe psoriasis itself independently predicts chronic kidney disease[374]. Haemodialysis may also cause relapse, worsening of pre existing psoriasis or trigger *de novo* psoriasis during chronic hemodialysis for renal disease. New-onset psoriasis may occur during both haemodialysis and peritoneal dialysis and factors implicated include dialysis-induced growth factor, cytokines, and chemokines in psoriasis development[375-377].

The outcome of hemofiltration, leukopheresis, cardiopulmonary bypass, and exchange with fresh frozen plasma in psoriasis treatment has been variable[378-381]. Plasma exchange gave no or only partial remissions but no controlled studies are available[382,383]. However, a controlled study noted no beneficial effect from sham and true plasma pheresis and leucopheresis[384]. Forced osmotic diuresis simply does not work[385]. Among all, peritoneal dialysis may favourably influence psoriasis outcome but never preferred unless it is required for its well-defined indications.

Tonsillectomy

Exacerbation, persistence or new onset of chronic plaques psoriasis within a subset of psoriatics is often attributed to hyper-reactivity to super-antigens, usually viral or bacterial proteins. Streptococcal infection has been the most implicated trigger in such instances. It has been suggested that some auto-reactive T cells primed against streptococcal proteins may cross react with keratinocytes (molecular mimicry) causing exacerbation of psoriasis. Molecular studies have suggested that auto-reactive T cells from tonsils can enter the circulation with homing to the skin triggering exacerbations/persistence of psoriasis. Tonsillectomy perhaps offer a valuable treatment option for such patients However, most reports in the literature on tonsillectomy comprise small case series or case reports pertaining to Japanese patients with acute guttate psoriasis, chronic plaque psoriasis or palmoplantar pustulosis. A complete clearance of guttate psoriasis and proteinuria was reported 2 and 6 mo after tonsillectomy in two patients, respectively[386]. Similarly, complete clearance of recurrent guttate psoriasis with remissions lasting for 16 mo was observed in two patients 1-2 mo after tonsillectomy[387]. Hone *et al*[388] reported complete clearance in 5 (83%) patients in a retrospective study comprising six patients with guttate psoriasis. However, the effect of tonsillectomy in guttate psoriasis remains poorly studied despite strong suggestion for its association with streptococcal pharyngitis. The clinical improvement in plaque psoriasis and reduction of circulating streptococcal and keratin peptide-reactive IFN-γ-positive CD8-positive skin-homing T cells is closely related[389]. However, the benefit of tonsillectomy in chronic plaque psoriasis remains ambiguous at best. In a questionnaire based retrospective study of 74 Danish patients with plaque psoriasis, 32% patients each reported complete or significant clearance of recalcitrant psoriasis vulgaris while 39% patients had some improvement[390]. Worsening of disease was reported by 7% and 22% experienced no improvement. There was also no statistical difference in the benefit of tonsillectomy for patients who reported flare up of their skin disease and who reported no effect from tonsillitis. Hone *et al*[388] reported complete or partial clearance of psoriasis plaques after tonsillectomy in 29% patients each, respectively; three of seven (42%) patients did not benefit at all. Recently, Thorleifsdottir *et al*[389] noted a significant reduction in PASI score ranging from 30%-90% in 86% of 29 patients *vs* 0% in controls in a randomized clinical trial of tonsillectomy in chronic plaque psoriasis. Nearly, 60% patients achieved PASI 50 and the improvement was apparent 2 mo after tonsillectomy that lasted for over 2 years. Rachakonda *et al*[391] also made similar observations in a recent systematic review of 20 publications of last 53 years comprising 545 patients with psoriasis who were evaluated for or underwent tonsillectomy.

The therapeutic efficacy of tonsillectomy was also analysed in 12 patients among 385 patients with generalize pustular psoriasis in a 1999 report by Ozawa *et al*[392]. The disease decreased in approximately 50% but only 2 (16.7%) patients showed clear-cut benefit. The exacerbation of palmoplantar pustulosis too has been imputed to acute tonsillitis pioneering its treatment with tonsillectomy[393-399]. Subjective marked or complete remission after tonsillectomy was reported by 89% of respondents to a questionnaire who had been treated for palmoplantar pustulosis by tonsillectomy[400]. Thirteen of 15 patients with palmoplantar pustulosis in another study reported effective to complete response 3 mo after tonsillectomy, no or partial response was also observed in one patient each[401]. Takahara *et al*[394,399] in two separate studies noted subjective improvement after tonsillectomy in 87% and 94% patients with palmoplantar pustulosis, respectively. Wu *et al*[400] have recently reviewed available evidence for the benefit of tonsillectomy in treatment of psoriasis. Overall, tonsillectomy may be useful for a subset of these patients in view of high rates of reported response to the procedure. However, additional well-designed studies including patients of diverse ethnicities will be needed for any recommendations. Moreover, the benefit must outweigh the risk associated with the procedure as disease remission after tonsillectomy was only for over two years or so in the reviewed reports. Long-term antimicrobial therapy will perhaps be more useful in such cases unless tonsillectomy is required due to its well-established indications[401].

Ichthyotherapy

Ichthyotherapy (Ichthys-Fish, Greek) means treatment

for skin by using fish *Garra rufa*, commonly known as "nibble fish" or "doctor fish of Kangal", which is a natural inhabitant of river basins in Central Eurasia. It is widely used in beauty and foot spas, and for the treatment of wounds or skin disorders like psoriasis and dermatitis that has made Kangal (Turkey) a popular health resort[402]. The treatment involves lying in the ponds/spas and let the fish nibble on the scales and loose skin on the affected areas. Although the utility of Garra rufa in the treatment of psoriasis was identified as early as 1989 by Turkish researchers[403,404], no controlled studies have been carried out for its efficacy. The two recent short-term, uncontrolled studies report beneficial effects of ichthyotherapy in psoriasis. Ozçelik *et al*[405] followed up 14 of 87 patients with chronic plaque psoriasis having prolonged immersion (mean 7.4 ± 1.1 h/d, mean 11.5 ± 6.6 d) in warm spring spas of Kangal containing *Garra rufa*. They reported complete clearance at 21 d in 8 (57.14%) and partial clearance in 6 (42.85%) patients, respectively. Two patients with erythrodermic or pustular psoriasis could not use this mode of therapy due to pain. Thirty-five of 87 patients experienced significantly longer remissions as compared to patients treated with topical corticosteroids alone. The overall beneficial effect was attributed to de-scaling of skin lesions by the fish, high selenium content and jacuzzi effect in spa water, natural sunlight, and reverse Koebner's phenomenon. Grassberger *et al*[406] used ichthyotherapy in a controlled medical setting to eliminate potential risk of infections associated with this mode of therapy. They evaluated its efficacy in 67 Austrian patients with moderate to severe chronic psoriasis who had undergone fish spa therapy for 2 h/d for three weeks in a tub containing garra rufa combined with short-term UV-A exposure and emollient application after each session. The tub and the fish were used exclusively for one individual patient. The bath water temperature was maintained at 36 ℃-37 ℃, filtered and disinfected constantly, and changed every 3-4 times a day. Overall, there was 71.7% reduction in PASI score and 87.5% patients reported a more favourable response *vs* other therapies. PASI ⩾ 75 and PASI ⩾ 50 were noted in 31 (46.3%) and 61 (91%) patients, respectively. Mean remission period was 8.58 mo and 65% patients reported decreased severity of relapse. They attributed beneficial effects to the relaxing effect of baths, decreased stress and psychological wellbeing contrary to the earlier belief.

Although no significant side effects were noted in these studies, pain, bleeding from nibbled skin lesions or transmission of viral and bacterial infections remains a potential risk[406,407]. The main concern about the use of fish spas involves the transmission of infectious agents such as *Mycobacterium marinum, M. fortuitum and M. chelonae, Aeromonas spp. (*Aeromonas folliculitis*), Streptococococcus spp*., *Salmonellae* (soft tissue infections, pustular dermatitis), *Vibrio cholerae*, *V. vulinficus*, or *Klebsiella spp* (wound infections) particularly among patients with diabetes, a common psoriasis co-morbidity, causing significant morbidity.

COMMENTS

The usefulness of various therapies, systemic (methotrexate, cyclosporine, acitretin or various biological therapeutic agents) or topical (tar, anthralin, corticosteroids or vitamin D analog ointments, phototherapy with or without psoralens) has been well established. The utility of vitamin D analogs (calcipotriol, calcitriol, tacalcitol, maxacalcitol, becocalcidiol) in psoriasis needs a mention here since these are important in sequential therapy as monotherapy or in combination with topical corticosteroids (halobetasol, clobetasol, betamethasone dipropionate) for added benefit and steroid-sparing effect. Over the years several clinical studies across the regions have demonstrated efficacy and safety of topical calcipotriene without tachyphylaxis or skin atrophy observed with topical corticosteroids[408-412]. Calcitriol is as effective as betamethsone propionate or short-contact dithranol therapy, and significantly more effective than calcipotriene for the treatment of facial, hairline, and flexural psoriasis with better tolerability. While several studies have demonstrated efficacy of tacalcitol in the treatment of mild to moderate plaque psoriasis, nail psoriasis and scalp psoriasis, maxacalcitol (25 μg/g) is considered more effective than once-daily calcipotriol[413-418]. However, noncompliance for vitamin D analogs reported in 12%-20% patients is due to lesional and perilesional irritation with accompanying perilesional erythema, stinging, itching, and/or burning following topical application[419-423]. Hypercalcemia, hypercalciuria and parathyroid hormone suppression are rare but potential systemic adverse effects and occur because of using more than recommended dose of 100 g/wk or in the presence of impaired calcium metabolism or underlying renal disease[424-428]. Relatively high cost of therapy is another reason for noncompliance.

Emollients, especially petrolatum-containing products, remain a main stay of any treatment. They retain moisture in the stratum corneum and increase local penetration of topical medications. Petrolatum ointment has an antipsoriatic effect while combination with salicylic acid (3%-6%) will have descaling effect on psoriasis plaques and enhance penetration of corticosteroid. Ichthyol pale (4% sodium shale oil sulfonate), a substitute for coal tar with conventional moisturizing properties, also offers anti inflammatory, antipruritic and antimicrobial actions because of high sulphur content[429,430]. All these can be used alternating with gradual withdrawal of topical steroids for the maintenance stage. Anecdotal efficacy of topical aminophylline 4% ointment could not be substantiated[431,432]. Changing topical formulations for improved drug delivery and cutaneous bioavailability appears another area for for future researchers.

Apremilast is recently FDA approved oral therapy of active psoriatic arthritis in adult patients. It was found superior over placebo in phase 3 randomised, placebo-controlled trial (PALACE 1-4 study) comprising patients with active psoriatic arthritis[433]. Overall, it was also

equally effective as monotherapy as in combination with existing DMARDs. There was also improvement in the PASI 50 (51% *vs* 19%) and PASI 75 (21% *vs* 5%) compared with placebo. Headache, nausea, and diarrhea were the only significant adverse effects reported. Apremilast 30 mg twice daily was also effective in chronic plaque psoriasis in a phaes 3 multicenter, randomized, placebo-controlled trial (ESTEEM 1 study)[434]. Its exact mechanism of action needs elucidation but said to regulate inflammatory mediators by inhibition of phosphosphodiesterase 4 enzyme in immune cells leading to increase in intracellular cAMP levels.

Peptide-T, tyrosine kinase inhibitors (Erlotinib), p38 mitogen activated protein kinase inhibitors, protein kinase-C inhibitors, nerve growth factor receptor blocker, rapamycin inhibitors (sirolimus, everolimus) constitute experimental therapies[435-441]. Alternative approaches (acupuncture, ayurvedic medicine, traditional Chinese medicine, homeopathic medicine, naturopathic medicine, *etc*.), and immunotherapy (heat-killed delipidated, deglycolipidated *Mycobacterium vaccae*, *Mycobacterium w* or anti-leishmania vaccines) forms other interesting area of research despite variable results[442-445].

It is also interesting to note the evolution of psoriasis and its therapeutic modalities. The concept of keratinocyte dysfunction led to treatment with phototherapy, methotrexate, and retinoids before 1980s, whereas, cyclosporine was introduced after it was considered an immunologic disease during 1980s. Alefacept, efalizumab, and TNF-α blockers were developed during 1990-2005 as psoriasis evolved as a disease of altered cytokine profile (IL-12/Th1-mediated). In recent years, ustekinumab and secukinumab have been developed in view of IL-23/Th17-mediated cytokine profile in psoriasis. Normalization of angiogenesis, an important pathologic component of psoriasis lesions, appears emerging concept for novel antiangiogenic agents for more targeted therapy; may be in combination or as an alternative to conventional therapies. Calcium dobesilate inhibits VEGF and interferes with fibroblast growth factor-induced neoangiogenesis; the efficacy of topical 5% cream in limited plaque psoriasis appears promising[446-448]. Neovastat, also a VEGF antagonist with anti-angiogenic and anti-inflammatory properties, has shown statistically significant reduction in PASI score in randomized phase Ⅰ/Ⅱ dose-comparison clinical trials comprising 29 patients with psoriasis[449]. More well designed studies are required before these drugs are approved for the treatment of psoriasis. Finally yet importantly, the clinicians must be apprised of all available antipsoriasis therapies in view of variable therapeutic outcome(s) that may test one's ingenuity in managing some of the "difficult to treat" patients. It seems that nonstandard and off-label therapies will remain an important alternative in rotational/intermittent treatment(s) or to more widely used and evidence based treatments until a therapy that is affordable, safe, effective, and more importantly, remittiv becomes available.

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