Coal Tar to Biologic: Search for Ideal Therapy for Psoriasis Continues…

Psoriasis is a chronic immune-mediated disorder that affects 2%–3% of global population. The most prevalent presentation is chronic plaque-type psoriasis. Associated comorbidities are cardiac, rheumatologic, ophthalmic, and psychiatric symptoms.[1] Psoriasis tends to remain active throughout a patient's lifetime, meaning that it often requires lifelong treatment.[2]

The available treatment modalities and their indications are depicted in Figure 1. It is also obvious that not all treatment options work for every patient.

The use of tar products for the treatment of localized psoriasis has decreased over time. Now, it is used mainly for scalp psoriasis as shampoo and in plantar psoriasis. Often poorly tolerated by patients because of cosmetic issues, including staining of clothes and tar odor; other potential adverse events include irritant contact dermatitis, folliculitis, and photosensitivity. Coal tar is carcinogenic in animals, but in humans, there are no convincing data proving carcinogenicity.

When psoriasis is extensive or refractory to topical therapy and phototherapy, conventional systemic psoriasis therapies such as methotrexate (MTX), cyclosporine A (CsA), and acitretin are used.[3] To identify patients who may benefit from systemic treatments, the "rule of tens" (body surface area (BSA) affected >10%, Psoriasis Area and Severity Index >10, or a Dermatology Life Quality Index >10) has been proposed.[4] Exception to this rule is severe psoriasis of the palms and soles or severe scalp psoriasis though affects <5% of the BSA; the significant negative effect on the quality of life of the patient makes a systemic approach to treatment appropriate for such conditions.

Methotrexate

It is the most commonly prescribed traditional systemic therapy worldwide for psoriasis. It is dramatically effective in even the most severe cases of psoriasis. MTX has been shown to exhibit different responses based on the genetic expressions and variations of the genes SLC19A, SHMT, ABCB1, ATIC, and MTHFR. Hence, pharmacogenetic testing can be used as a means to individualize a patient's medical regimen to prevent future adverse drug events. MTX has been used in combination with all of the approved biologic agents for psoriasis. The greatest experience is with tumor necrosis factor (TNF) inhibitors. It is not known whether the use of MTX and biologics causes additive immunosuppression as this combination has primarily been studied in patients without psoriasis, and the differing baseline risks associated with these diseases make this distinction uncertain. Treatment with MTX/anti-TNF agents reduces both inflammatory burden and the risk of cardiovascular disease.

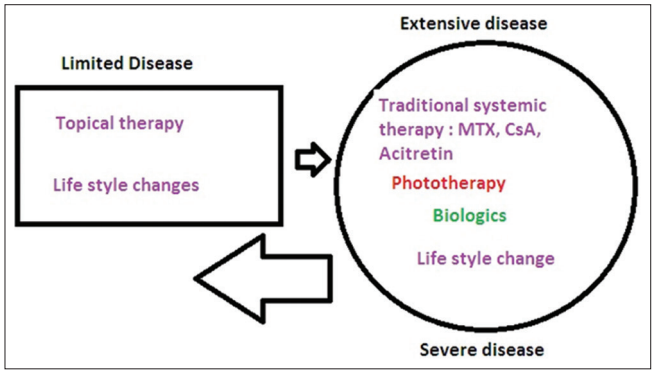

Figure 1: Therapeutics available for the treatment of psoriasis

Cyclosporine A

It is most effective treatments available for psoriasis. If used for longer term (3–5 years), patients will develop some degree of glomerulosclerosis. Guidelines in the USA limit its use to 1 year, whereas in the UK, it is allowed for 2 years. In severe flares of psoriasis, CsA frequently induces a rapid remission. Withdrawal/tapering of CsA has to be meticulous.

Acitretin

Acitretin is least effective as monotherapy. It is often used in conjunction with ultraviolet B (UVB) or psoralen plus UVA phototherapy. Acitretin is particularly effective in patients with palmoplantar psoriasis. Acitretin is not immunosuppressive, hence can be used in combination with biologic therapies. Acitretin's major side effect is teratogenicity; hence, its use is limited to male and female patients of nonchildbearing potential.

Phototherapy

A standard protocol is recommended for the use of phototherapy in the management of psoriasis. Basic phototherapy education such as the use of goggles in all patients and the use of genital shields in male patients is very important. The dosage of UVB may be administered according to the Fitzpatrick skin type or the minimal erythema dose, with subsequent dosages adjusted accordingly. The response is observed at 8–10 treatments. Single course consists of 15–20 treatments and then maintenance therapy may prolong remission. Topical targeted phototherapy (excimer laser/lamp) is indicated for adult and pediatric patients with mild, moderate, or severe psoriasis with <10% BSA involvement.

Biologic Agents

Protein-based drugs derived from living cells are becoming commonplace in dermatology for the treatment of psoriasis.[5,6] Biologic therapies for psoriasis utilize molecules designed to block specific molecular steps important in the pathogenesis of psoriasis and now comprise a number of well-established, licensed, treatment options for patients with severe disease. Eligibility criteria for biologic therapy vary according to various national guidelines. Main criteria being severe disease (rule of tens) where phototherapy and alternative standard systemic therapy are contraindicated or cannot be used due to the development of or risk of developing clinically important treatment-related toxicity; intolerant to standard systemic therapy; unresponsive to standard systemic therapy; significant, coexistent, unrelated comorbidity which precludes the use of systemic agents such as CsA or MTX; and severe, unstable, life-threatening disease. Available biologics for the psoriasis are listed in Table 1. Biologic therapies target the immune system; hence, it is important to use all measures to prevent infection, including vaccinations. Administration of live vaccines must be avoided in patients being treated with biologics under all circumstances. Patients need to be periodically reevaluated for the development of new symptoms including infection and malignancy. They are contraindicated in patients with active and serious infections. If patients develop serious infections (usually defined as an infection that requires antibiotic therapy), while being treated with a biologic agent, it is prudent to hold the biologic until the infection has resolved.

Table 1: Biologics and small molecules for psoriasis

Biologic	Target	Approved for psoriasis
Adalimumab	TNF-α	2008
Apremilast	PDE-4	2014
Etanercept	TNF-α	2004
Infliximab	TNF-α	2006
Secukinumab	IL-17A	2015
Ustekinumab	IL-12/IL-23 p40	2009

TNF-α: Tumor necrosis factor-alpha, PDE-4: Phosphodiesterase 4, IL: Interleukin

Table 2: Characteristics of an ideal drug

Ideal drug/therapeutics for psoriasis therapy
Oral agent
Flexible dosage schedule
Reversible/insignificant side effects
No teratogenicity/mutagenicity
Can be used in any chronic illness, for example, diabetes/ hypertension
Easy laboratory monitoring
No visible telltale signs of disease
Cost effective/economic
PASI 90 achievement
Track record of the drug

PASI: Psoriasis Area and Severity Index

In resource-poor setup, the cost, lack of trained medical people to administer the biologics and endemic nature of tuberculosis in developing countries makes the use of biologics a difficult task. Can there be any ideal drug/ therapy for psoriasis? A question which needs to be answered thoughtfully. Table 2 lists the characteristics of an ideal drug as required by patient and treating dermatologist. Table 3 compares the available therapeutic agents in terms of listed 'ideal drug/therapy' points.

The comparison table gives us a brief idea that we are left with MTX or biologics as near ideal choice of therapy for psoriasis at present. CsA, retinoids, and phototherapy are used in special circumstances. We may have to choose the therapeutic agents based on affordability and availability. In resource-poor setup, MTX alone may be used as long as it remains effectual and well tolerated. Phototherapy alone and MTX followed by narrowband UVB are better options. In affordable scenario, biologics are the best bet.

When no ideal agent is available, to minimize the toxicity of any therapy, proper patient selection and appropriate monitoring are crucial. The decision to administer MTX, CsA, acitretin, or any other traditional therapy must be individualized. Every patient needs to be carefully

Table 3: Comparison of available therapeutic agents as "ideal agent" characteristics

Characteristics	MTX	CsA	Retinoid	Photo	Biologics[5,6]
Oral	+	+	+	−	− (except apremilast)
Flexible dose	+	+	+	+ (needs setup)	To some extent
Side effects	+++	++++	+++	+	+
Teratogenicity/mutagenicity	−/+	−	+++/−	−	−
Laboratory monitoring	+++	++++	+++	−	++
Cost effective	+++++	++	+++	++++	−
PASI 90	15%	−	−	−	+ (79% secukinumab)
Cardioprotective	++	−	−	−	++
Combination/other drug/bio	+++ (biologics)		++ (retinoid-PUVA)	+ (retinoid-PUVA)	++
Track record	+++++	+++	++	++	+

PUVA: Psoralen plus ultraviolet A, PASI: Psoriasis Area and Severity Index, MTX: Methotrexate, CsA: Cyclosporine A

evaluated with reference to disease severity, quality of life, and general medical and psychologic status.

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