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Cutaneous and systemic psoriasis: classification criteria and personalized treatment

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Abstract

Psoriasis is a chronic, multisystem, inflammatory disease. The typical clinical cutaneous manifestation of psoriasis is scaly erythema or plaque, limited or widely distributed. However, psoriasis is far beyond the skin involvement and provides many challenges, including associated comorbidities. In this review, we classify psoriasis as cutaneous and systemic psoriasis, according to the clinical diversity and associated comorbid diseases, and recommend classification criteria for psoriasis. The key objective of this novel classification is to raise awareness of the complexity of this multifaceted disease and help to better understand and manage this complex disease comprehensively.

Keywords: Psoriasis, cutaneous psoriasis, systemic psoriasis, classification criteria, therapy

Introduction

Psoriasis is a chronic, multisystem, inflammatory disease[1-4] mediated by T cells and dendritic cells. Interleukin 23 (IL-23), IL-17 and tumor necrosis factor TNFα play critical roles in the initiation and maintenance of psoriasis[3,5]. Approximately 36% patients have a family history of psoriasis, and multiple genetic susceptibility loci have been identified[6,7]. A variety of non-specific triggers can provoke psoriasis, including local factors (skin damage, scratching), systemic factors (infections, especially streptococcus and HIV), psychological stress and medications (lithium agents, β-blockers, interferon, non-steroidal anti-inflammatory agents and antimalarial drugs) etc[3-5,8]. Psoriasis is not contagious.

The incidence of psoriasis varies greatly around the world and is related to factors such as race, geographic locations and environment. The prevalence rates of psoriasis are around 1% to 3% in Europe and the United States[9].

The typical clinical cutaneous manifestation of psoriasis is scaly erythema or plaque, limited or widely distributed. Approximately 20-30% of patients with psoriasis also have psoriatic arthritis. Moderate-to-severe psoriasis patients have an increased risk of metabolic syndrome and atherosclerotic cardiovascular disease[10-12]. The current treatment measures are effective and can achieve long-term remission, but they have not yet reached the goal of radical cure. Diagnosis is usually made on clinical findings; skin biopsy is rarely used to diagnose psoriasis[4]. However, major issues on diagnosis and therapy for psoriasis remain unresolved, including the relevance of cutaneous versus systemic comorbidities. Especially, biologics for psoriasis not only cured the cutaneous lesions, but also improved systemic comorbidities[13]. Therefore, it is

more and more urgent to define psoriasis as cutaneous or systemic manifestations. Here, we summarize a new way to classify and diagnose psoriasis.

TYPE OF PSORIASIS

Psoriasis vulgaris is the most common form (affecting approximately 85 to 90% of patients) and usually persists for all life[5,8]. Although there are predilection sites such as the elbows, knees, and the sacral region, lesions may cover the entirety of the skin. Furthermore, psoriasis is associated with a high degree of comorbidities and patients are at an increased risk of developing other chronic and serious health diseases, including arthritis, metabolism disease, diabetes, cardiovascular diseases, hypertension, depression or anxiety, liver disease, Crohn's disease, and lymphoma or other cancers[3,4,8]. Therefore, we recommend psoriasis to be classified as cutaneous psoriasis and systemic psoriasis to fully meet the needs of patients on systemic treatment.

CUTANEOUS PSORIASIS

Plaque psoriasis

Erythematous, scaly, sharply demarcated plaques in different sizes and shapes are hallmarks of psoriasis[3]. Variants of plaque psoriasis include thick versus thin plaque disease[14], and small versus large plaque disease[15]. The initial lesions are red papules or maculopapulars, which gradually expand into a clear red patch and take a variety of forms (such as coins, geographica, oyster shells, etc.), covered with a thick lamellar layer of silvery white scales. When scraping the

silver-white scales on the top layer, the layered characteristics of the scales can be observed, just like scraping wax droplets (candle wax phenomenon). When scraping silvery white scales, a light red translucent film (film phenomenon) is seen. When the film is peeled off, multiple spotted bleeding (Auspitz's sign) can be seen[5]. The candle wax phenomenon, film phenomenon and spot bleeding phenomenon have special diagnostic value for psoriasis. These lesions are typically located on the scalp, extensor surfaces of the extremities, buttocks and trunk but can occur anywhere on the body. The scalp cutaneous lesions are thick and scaly, often beyond the hairline, and the hair is bunched (bundled hair)[4]. Symptoms regularly reported by patients include pain, itch and bleeding in different degrees[16].

Nail involvement (fingernail or toenail) is mostly manifested as "thimble-shaped" pitting, leukonychia, lunular red spots and nail plate crumbling. Other nail bed lesions reported in psoriasis include onycholysis, subungual hyperkeratosis and splinter haemorrhages[17-19]. Nail psoriasis occurs in approximately 50% of patients with psoriasis at the time of diagnosis with a lifetime incidence of 80–90%[4,20].

Guttate psoriasis

Guttate psoriasis tends to be common in in children and young adults. There is usually a history of a sore throat associated with group B streptococcal infection before onset. The sudden onset can spread throughout the body within a few days. The lesions are 0.3 to 0.5 cm in size, with papules and maculopapular eruptions[3]. The skin is flushed, covered with a few scales, and the degree of itching varies. A third of children with guttate psoriasis go on to develop chronic plaque psoriasis in later life[21-23].

Pustular psoriasis

Pustular psoriasis is characterized by white coalescing pustules, which can either take the form of generalized or localized distribution. The localized pustular psoriasis can further be divided into palmoplantar pustulosis (pustular psoriasis of the palms and soles) and continuous acrodermatitis.

Generalized pustular psoriasis

Generalized pustular psoriasis is often acute onset, on the basis of psoriatic cutaneous lesions or normal skin. Superficial aseptic small pustules appear rapidly, with size ranging from needle tip to millet, light yellow or yellow-white, often densely distributed, and can be fused into flaky pus lakes[3]. Cutaneous lesions can develop quickly to the whole body, accompanied by swelling and pain[24]. Often accompanied by systemic symptoms, such as chills and high fever, showing a remittent fever type. The patient may have a grooved tongue, and the nails and toenails may be thick and turbid. Generally, the pustules dry and crust after 1 to 2 weeks, and the condition is naturally relieved, but it can be repeated periodically[21]. It may also be precipitated by withdrawal of systemic corticosteroids or infection and represents unstable disease. The patient can also die due to secondary infection and systemic failure.

Palmoplantar pustulosis

Cutaneous lesions are confined to the palms and soles of the feet, symmetrically distributed, lesions in palms are more likely to occur in the middle and inner part and can be extended to the back of the hands and fingers[3]. The cutaneous lesions are batches small pustules that occur on the basis of erythema. After 1 to 2 weeks, the pustules rupture, crust, and desquamate. Nails are

often affected, with pitting, lateral grooves, longitudinal crests, nail turbidity, nail stripping and empyema[21].

Acrodermatitis continua of Hallopeau

This is a rare type of localized form of pustular psoriasis. Clinically, tender sterile pustular eruptions are present on one or more digits. Psoriatic lesions can be seen on the fingertips, sometimes on the toes[21]. Scales and crusts can be seen after the pustules, pustules may also be present on the nail bed (under the nail plate), and the nail plate may come off.

Erythrodermic psoriasis

It is manifested as diffuse flushing, infiltration and swelling of 90% or more of the body with a large number of bran-like scales, during which there may be flaky normal skin (skin island). This variant consists of complete or almost complete involvement of the skin and is characterized by gradual coalescence of red plaques, accompanied by systemic symptoms such as fever, superficial lymphadenopathy and other systemic symptoms. The course of disease is long and easy to relapse[3,21].

Inverse psoriasis

Inverse psoriasis is also called intertriginous or flexural psoriasis. The lesions present in the folds or rubbing areas, including the hip groove, armpit, groin, under the breast, retro-auricular regions and glans. The cutaneous lesions are dark red smooth and shiny plaques that extend to the junction of the skin folds, similar to intertrigo, and the surface of the cutaneous lesion is moist[25]. Inverse psoriasis is usually devoid of scales.

Stages and severity of cutaneous psoriasis

According to the development of the disease, cutaneous psoriasis can be divided into three main stages: progressive, stationary and regressive.

Progressive stage: new cutaneous lesions continue to appear, infiltrated inflammation obviously with blush around. Injuries such as acupuncture, scratching and surgery can lead to damaged parts develop typical psoriatic cutaneous lesions, called isomorphism or Köbner phenomenon or isomorphic response.

Stationary stage: cutaneous lesions are stable, no new cutaneous lesions appear, with light inflammation and more scales;

Regressive stage: the cutaneous lesions shrink or flatten, the inflammation basically subsides with hypopigmentation or pigmentation.

The severity of cutaneous psoriasis can be helpful in guiding management and is classified as mild, moderate and severe psoriasis (Table1).

Table 1. Severity of cutaneous psoriasis

Mild	Moderate	Severe
BSA<3%	3%≤BSA<10%	BSA≥10%
PASI<3	3≤PASI<10	PASI≥10
IGA=1	IGA=2	IGA=3/4

SYSTEMIC PSORIASIS

In addition to psoriatic cutaneous lesions, other systemic diseases can occur previously, simultaneously or sequentially. More and more data suggest that psoriasis is more than "skin deep" and has important systemic manifestations that are shared with other chronic inflammatory diseases[8]. After the treatment of psoriatic lesions improves, the associated systemic symptoms generally improve[26]. Therefore, psoriasis is a systemic inflammatory disease that affects multiple systems [1-4]. A diverse team of clinicians with a range of expertise should be referred to diagnose and treat systemic psoriasis.

Psoriatic arthritis

Nearly 30% of psoriasis patients progress to psoriatic arthritis [27]. In addition to cutaneous lesions, psoriatic arthritis can occur in any joint, including the large joints of the elbow and knee, the small joints of the fingers and toes, the spine and the sacroiliac joints[28]. It can be manifested as joint swelling and pain—either oligoarticular or polyarticular, limited mobility, and joint deformity in severe cases, which is progressive, but rheumatoid factor is often negative[3,29]. X-ray showed cartilage disappeared, osteoporosis, joint cavity stenosis with

varying degrees of joint erosion and soft tissue swelling. Up to 90% of patients with psoriatic arthritis show nail involvement[17,30].

The subtypes of psoriatic arthritis includes distal subtype (damage to the proximal and distal interphalangeal joints of the hands and feet), oligoarthritis (inflammation that involves four or fewer joints), polyarthritis (affects five or more joints), arthritis mutilans (resorption and shortening of finger bones), axial/ankylosing spondylitis, enthesitis and dactylitis[31].

Psoriatic metabolic syndrome

Moderate to severe psoriasis is associated with the metabolic syndrome, which includes obesity, hypertension, hyperlipidemia and diabetes mellitus[10-13].

Psoriatic diabetes

Diabetes is diagnosed in addition to psoriatic lesions, or (1) a random blood glucose ≥ 11.1 mmol/L (200 mg/dl) or plus (2)a fasting plasma glucose level ≥ 7.0 mmol/L (126 mg/dl) or (3) a plasma glucose level of 2 hours post glucose-load ≥ 11.1 mmol/L (200 mg/dl)[9,32].

Psoriatic cardiovascular disease

Psoriasis is an independent risk factor for cardiovascular diseases, including hypertension[26], hyperlipidemia, major adverse cardiovascular events and myocardial infarction[29,33-36].

Psoriatic nephropathy

Kidney damage occurs in those diagnosed with immune-related nephropathy[29,37-39]. Psoriasis is considered to be an independent element of chronic kidney disease and end-stage renal disease.

Psoriatic bowel disease

Patients diagnosed as inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colon disease, share similarities in genetic susceptibilities and immune-mediated inflammation with cutaneous psoriasis[40-43]. There are significant bidirectional associations between psoriasis and IBD[42].

Psoriatic brain diseases

Psoriasis has an extensive emotional and psychosocial effect on patients. Psoriasis patients are accompanied by depression/mania, multiple sclerosis or other mental symptoms, and may also have a significantly decreased quality of life and psychological burden including anxiety, depression, and suicidal thoughts and behavior[44-46].

Psoriatic pulmonary disease

Interstitial lung disease or chronic obstructive pulmonary disease (COPD) in patients with psoriasis[47-49].

Psoriatic liver disease

Psoriasis is more common accompanied by nonalcoholic fatty liver disease[50], liver fibrosis[51] or abnormal liver function.

Psoriatic uveitis

Uveitis is a known ophthalmologic manifestation of inflammation of iris, ciliary body and choroidal tissues. It is characterized by redness of the conjunctiva, eye pain, blurred vision and flying mosquitoes. Significantly increased risk of both prevalent and incident uveitis were observed among patients with psoriasis[52].

Psoriatic lupus erythematosus

It is rare for patients with psoriasis to have lupus erythematosus at the same time[13]**.** Serologically positive lupus erythematosus patients associated with psoriasis or induced by psoriasis treatment drugs.

Psoriasis with malignancy

Psoriasis has also been associated with a low but elevated risk of malignant tumors of the skin or internal organs[29].

CLASSIFICATION CRITERIA FOR PSORIASIS

At present, there is no uniform standard for the diagnosis of psoriasis. Based on the clinical manifestations of psoriasis, we propose to classify psoriasis as cutaneous psoriasis and systemic psoriasis according to the following classification criteria (Table 2). A family history should be taken to further elucidate the diagnosis. If there is still doubt about the diagnosis, a simple punch biopsy can be performed.

Table 2. Classification criteria for psoriasis from CPRWERG

medical indexes	symptom	weight/score*
Cutaneous psoriasis： **Score 4 or above**		
Silver White Scales	white scales, falling off in layers after scratching, called candle wax phenomenon	1
Film Phenomenon		2
Auspitz's sign		3
Hyperkeratosis & parakeratosis	Thickened cornified layer & cell nuclei present in the cornified layer	1
Highly reduced or absent Granular Layer		1
Acanthosis with elongated rete ridges	Thickening of viable epidermal layers	1
Angiogenesis	Dilated and contorted blood vessels reach into the tips of the dermal papillae	1
Pustulosa psoriasis： score 5 or above		
Cutaneous psoriasis (Prerequisites)	Current or previous history of cutaneous psoriasis or family history of psoriasis	3
Fever	temperature≥ 37.5℃	1
Pustule	On the basis of generalized erythema, multiple aseptic pustules, densely distributed or fused into flakes	2
	Pustules are easy to rupture and form flakes	1
Subcorneal pustulosis	The pathological manifestation is the aggregation of neutrophils to form subcorneal pustulosis, Kogoj's spongy abscess	1
Erythroderma psoriasis： score 5 or above		
Cutaneous psoriasis (Prerequisites)	Current or previous history of cutaneous psoriasis or family history of psoriasis	3
Skin lesion area is over 90%	Diffuse flushing, infiltration and swelling of the skin all over the body, accompanied by a large	2

	number of bran-like scales, with flaky normal skin island	
Fever	temperature ≥ 37.5℃	1
Systemic psoriasis： score 6 or above		
Cutaneous psoriasis (Prerequisites) (3 scores)	Current or previous history of cutaneous psoriasis or family history of psoriasis	3
Psoriatic arthritis[31,53] (≥3 scores)	Finger (toe) nail changes	1
	Rheumatoid factor negative	1
	Finger (toe) arthritis	1
	Joint pain lasting more than 1 month	1
	Imaging showed new bone formation around the joint	1
Psoriatic metabolic syndrome[10] (≥3 scores)	Increased waist circumference (Male>40 inches (102 cm) Female>35 inches (88 cm))	1
	Hyperglycemia: fasting blood glucose: ≥ 6 mmol/l (100 mg/dL), and/or have been diagnosed with diabetes and treated	1
	Hypertension: systolic/diastolic blood pressure ≥130/85mmHg, and/or diagnosed with hypertension and treated	1
	Fasting triglyceride ≥ 150mg/dL	1
	HDL cholesterol male <40, female <50mg/dL	1
Psoriatic diabetes[9] (≥3scores)	HbA1c ≥ 6.5 % (≥ 48 mmol/mol)	3
	random blood glucose≥ 200mg/dl (≥ 11.1 mmol/l)	3
	fasting blood glucose ≥ 126 mg/dl (≥ 7.0 mmol/dl)	3
	two hours postprandial blood glucose （2hPBG） ≥ 200mg/dl (≥ 11.1 mmol/l)	3
Psoriatic cardiovascular disease[29] (≥3scores)	Coronary heart disease	3
	Atherosclerosis	3

	Hyperlipidemia	3
	hypertension	3
	Ischemic heart disease	3
Psoriatic nephropathy (≥3scores)	Urine protein 1 + and above or 0.5g/24h	3
	Hematuria or erythrocyte cast	1
	abnormally increased Urea nitrogen	1
	Abnormally elevated creatinine	3
Psoriatic bowel disease (≥3scores)	Confirmed Crohn's disease	3
	Confirmed ulcerative colitis	3
Psoriatic brain disease (≥3scores)	Depression/mania	3
	Psychiatric symptoms	3
	Multiple sclerosis	3
Psoriatic pulmonary disease[29] (≥3scores)	Interstitial lung disease	3
	COPD	3
Psoriatic liver disease (≥3scores)	Liver fibrosis	3
	Abnormal liver function (needs to exclude drugs)	3
	cholecystitis	3
Psoriatic uveitis (≥3 scores)	Inflammation of iris, ciliary body or choroid tissue	3
P**soriatic lupus erythematosus** (≥3 scores)	ANA positive	1
	anti-ds-DNA or anti-Smith antibody Positive	2
	EULAR/ACR Classification criteria for systemic lupus erythematosus[54,55]	10
Psoriasis with malignant tumors[29] (≥3 scores)	Squamous cell carcinoma/basal cell carcinoma	3
	Malignant melanoma	3
	Cutaneous T cell lymphoma	3
	Hematological malignancies	3
	Other malignant tumors	3

CPRWERG: The Chinese Psoriasis Real-World Evidence Research Group;

THERAPY FOR PSORIASIS

Choice of treatment for psoriasis depends on many factors, including the patients themselves and the drugs. The former including the onset age, the duration, extent of disease, site of the lesions, the age of the patient, the type of psoriasis (cutaneous or systemic), pregnancy or not, infection (especially tuberculosis or HBV) or not, medical insurance covered or not, past therapy history and the patient's perception of their illness. The latter includes the drug's efficacy, safety, price, response time, maintenance, frequency and resistance or not. For moderate-to-severe cutaneous psoriasis and systemic psoriasis, we now have biological therapies, which have been approved since 2004[1]. Biologics are proteins or antibodies that target specific molecules thought to be essential in psoriasis pathogenesis, such as TNFα, IL-17, IL-23 and IL-12. Cutaneous psoriasis could be fully reversible by administration of appropriate therapies targeted to specific immune molecules.

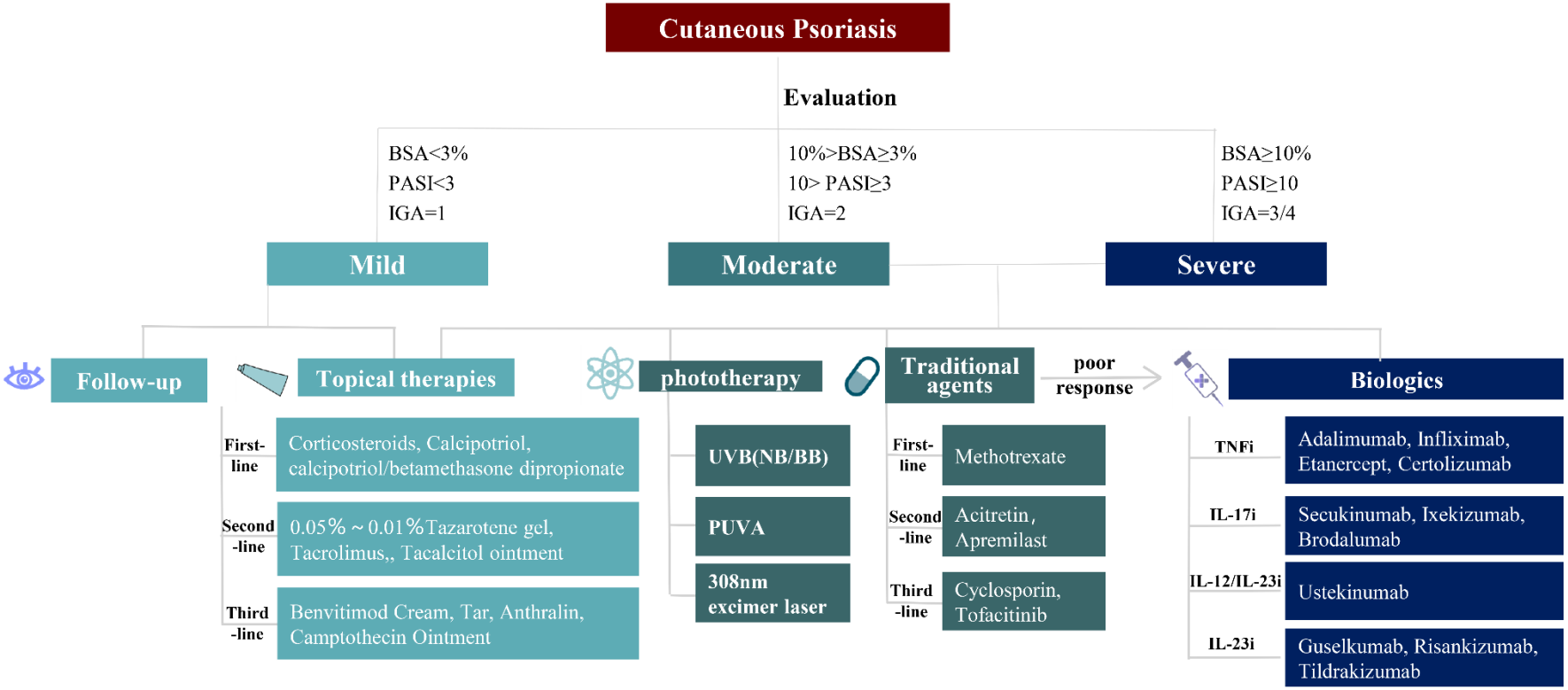

Figure 1. Therapies for cutaneous psoriasis.

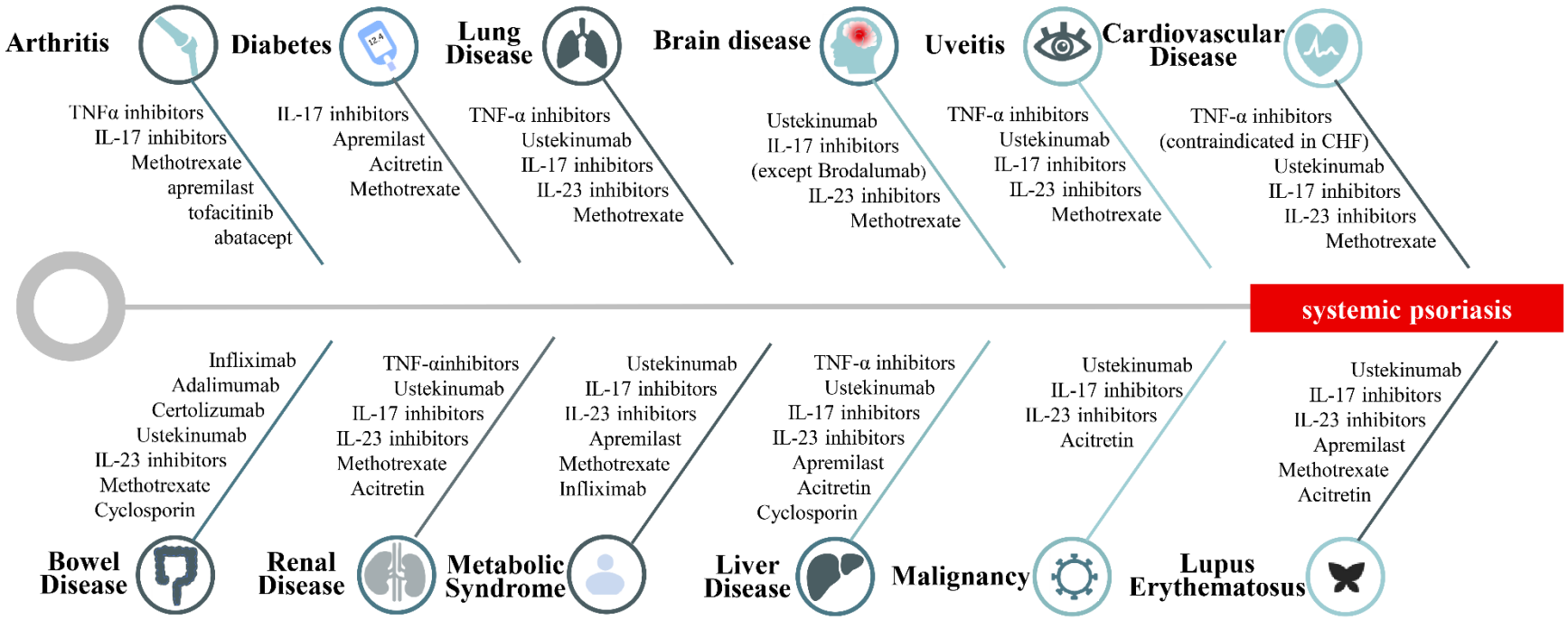

Figure 2. Therapies for systemic psoriasis.

Figure 1 lists selected therapeutics for mild, moderate and severe adult cutaneous psoriasis. For mild psoriasis, dermatologists may recommend topical agents or let the patient wait-and-see. For moderate and severe cutaneous psoriasis, topical agents, phototherapy, systemic non-biological therapy and/or biologics could be chosen. See refs [1,13,56] for recent comprehensive reviews. Comorbidities have a significant impact on the decision to use one therapy over another[13]. Figure 2 lists selected therapeutics for adult systemic psoriasis with comorbidities. Treatment plans should be tailored to meet their different needs (Figure 2).

For the therapy of pediatric psoriasis patients younger than 18 years, AAD/NPF jointly published a comprehensive review recently[2]. Briefly, pediatrics failure to topical therapy may undergo phototherapy and systemic therapy (Figure 3). Long-term maintenance at the lowest effective dose with the least toxic therapy is the preferred approach[2]. Till now, four biologics, etanercept, adalimumab, ustekinumab and ixekizumab, were approved by FDA or EMA for pediatric psoriasis, which may be considered as first-line systemic agents[2].

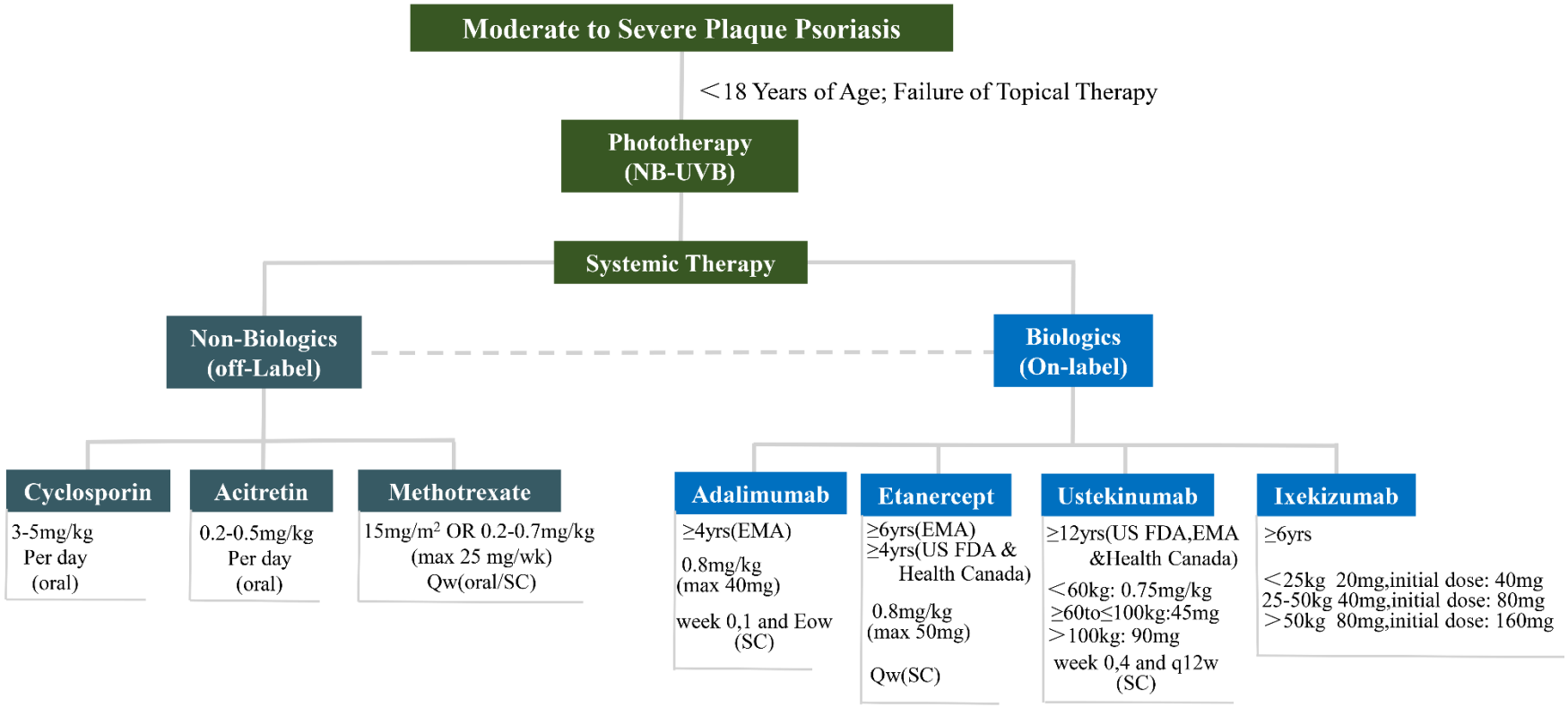

Figure 3. Therapies for pediatric psoriasis.

Limitations

The new point classification criteria for psoriasis provide a simple and direct method for classifying psoriasis. However, some criteria may not be so accurate, and no level of evidence and strength of recommendation are included. Some additional data should be included to define systemic psoriasis more accurately. Furthermore, the causality between psoriasis and systemic comorbidities does not build. It is definitely impossible to make that ALL these comorbidities are caused by psoriasis. Finally, this classification is just a recommendation, the sensitivity and specificity not being established. However, the quest to reduce medical risks of patients with cutaneous psoriasis and early identification of systemic psoriasis are areas that dermatologists and physicians can make a difference for the better of psoriasis patients.

Summary

In summary, psoriasis is systemic inflammation and can be classified as cutaneous psoriasis and systemic psoriasis. Cutaneous psoriasis can be subdivided into plaque, inverse, erythrodermic, pustular and guttate forms. In addition to cutaneous manifestations, systemic abnormalities may be present. Psoriasis patients should undergo a thorough history and physical examination including joints and other systemic disease. Optimal management depends on the form of psoriasis being cutaneous or systemic and their severity.

Conflict of interests

The authors declare no conflict of interest.

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