Review Article

Psoriasis and its Variants

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Abstract: Background: Psoriasis is a chronic, immune-mediated, inflammatory illness of the skin which is quite common. The typical lesions are well demarcated, flaky and erythematous plaques that are frequently observed on the extensor regions. Psoriasis causes vasodilatation and hyper proliferation of keratinocytes expressed as thickened and erythematous skin, generally covered with silver gray scales. Although the etiology of this disease is not very clear, yet there may be genetic and environmental implications. There are a number of variants of psoriasis which include palm plantar, pustular, erythrodermic, and guttate types. Psoriasis is related to several systemic impediments and coexisting illnesses rendering a great effect on patients. Psoriasis displays coexistence of both autoimmune and auto inflammatory reactions and the stability between the two is important for clinical and histopathological demonstration. Chronic plaque psoriasis shows adaptive immune responses whereas pustular psoriasis displays innate and auto inflammatory responses. Histopathological analysis is the main diagnostic tool for atypical and controversial situations which aids in discerning psoriasis from other dermatoses; biopsy is seldom required for typical psoriasis.

Keywords: Psoriasis, Inflammatory skin disease, Immune mediated disease, Histopathology, Variants, Dermatology.

INTRODUCTION

Psoriasis is a chronic, inflammatory, immune-mediated and proliferative skin condition that principally encompasses the nails, skin, and joints [1-3]. Psoriasis is also named as Willan'slepra after Robert Willan, the father of modern dermatology, who presented the first comprehensive clinical account of psoriasis [4, 5]. Psoriasis has not curable, and it increases and decreases with exacerbation. Depression is common in patients with psoriasis due to poor quality of life. There are quite a lot of forms of psoriasis among which the plaque form is the most common which is found on the trunk, extremities, and scalp. White silvery scales can be seen on close inspection of the plaques. The eye is involved rarely but in women mostly, comprising approximately 10% of the patients; it is practically at all times linked with skin [6].

In 1818, the relationship between arthritis and psoriasis was defined by Alibert for the first time and in 1964, the American Rheumatology Association acknowledged it as a distinct form [4]. Psoriasis is considered as a chronic and heterogeneous skin disorder, affecting 2-3% of the universal populace [7-9] with varying incidence in different regions. This ailment appears to arised due to a decontrolled interaction between immune cells, skin keratinocytes and the environment rendering an insistent inflammatory course regulated by activated T-cells and proinflammatory cytokines. Psoriasis is described as hyper proliferation of keratinocytes owing to an escalated turnover and vasodilatation, causing a thickened and swollen skin which is enclosed by layers of silvery scales. Like with many other multifactorial illnesses, the clinical phenotype of psoriasis may be noticeable in a number of clinically diverse forms that are driven by typical autoimmune or auto inflammatory processes [10, 11]. Although psoriasis is considered to be an immune mediated disease in which intralesional T lymphocytes and their proinflammatory signals trigger primed basal layer keratinocytes to rapidly proliferate, debate and research focus on the stimulus that incites this inflammatory process. Our current understanding considers psoriasis to be triggered by exogenous or endogenous environmental stimuli in genetically susceptible individuals. Such stimuli include group A streptococcal pharyngitis, viremia, allergic drug reactions, antimalarial drugs, lithium, beta-blockers, IFN-α, withdrawal of systemic corticosteroids, local trauma (Köbner phenomenon), and emotional stress. These stimuli correlate with the onset or flares of psoriatic lesions. Psoriasis

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genetics centers on susceptibility loci and corresponding candidate genes, particularly the psoriasis susceptibility (PSORS) 1 locus on the major histocompatibility complex (MHC) class I region [12, 13].

Methodology

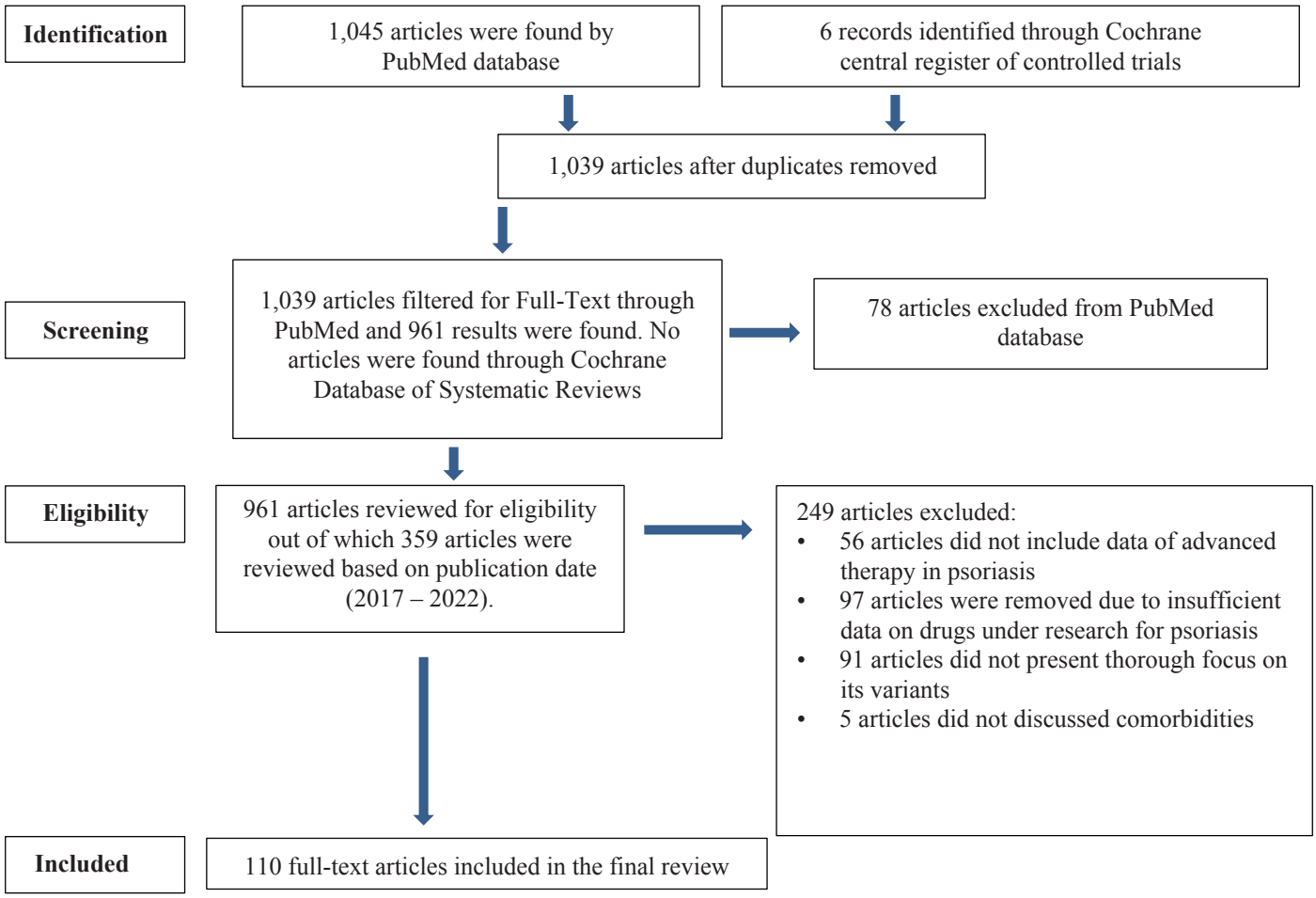

Fig. (1). Article Selection Flow Diagram.

RESULTS

A total of 1,039 articles were found with the keyword psoriasis and its variants by regular search in PubMed and Cochrane database. Out of these 359 articles were found in the period of 2017 – 2022. Among the 359 articles, 110 full-text articles were considered significant for our review article.

DISCUSSION

Pathogenesis and Pathophysiology of Psoriasis

Genes and single nucleotide polymorphisms linked with psoriasis have been identified by studies of genetic linkage. The contact amid environmental stimulants and the innate and adaptive immune systems ensue keratinocyte hyper proliferation. Psoriatic inflammation is associated with important cytokines like Tumor necrosis factor (TNF), interleukin (IL) 17 and IL-23 leading to oxidative stress and endothelial cell flaws. Communal pathways of inflammation exist for psoriasis and cardiovascular disease both. An early initiation of psoriasis is linked with human leukocyte antigen (HLA)-Cw6 in 90% patients [14, 15] and modifications in skin microbiome may add up as decreased microbial miscellany has been detected in psoriatic lesions [16].

The innate immune pattern seems to have a very noticeable part in the pustular psoriasis types, though the TNF α–IL23–Th17 axis has a dominant part in plaque psoriasis that is T cell-mediated [11]. Diverse pathological processes are related to distinct psoriasis subcategories. In guttate psoriasis, the increase of skin T cells are thought to be stimulated by streptococcal superantigens [17]. A significant sequence

homology amid streptococcal M proteins and human keratin 17 proteins has been shown. As CD8(+) T cell IFN-γ responses were stimulated by K17 and M6 peptides in sufferers with the chief histocompatibility HLA-Cw6 allele, molecular impression may have a part in such patients [18, 19]. As compared to psoriasis vulgaris, pustular psoriasis is described by enhanced IL-1β, IL-36α, and IL-36γ transcripts' expression [20] . On the other hand, IL-17 signaling is related to pustular psoriasis also and sufferers of generalized pustular psoriasis lacking IL-36R mutations reacted to anti-IL-17 therapies [21]. In psoriatic arthritis (PsA) and nail psoriasis, there is an enlarged expression of TNF-α, NFκB, IL-6 and IL-8 in nails affected due to psoriasis which is steady with the markers of inflammation observed on injured psoriatic skin [22]. The pathophysiology of psoriasis and PsA is pooled as synovial tissue in psoriatic arthritis expressing pro-inflammatory cytokines: IL-1, IFN-γ and TNFα [23, 24]. A great clonal development of CD8+ T cells is exposed due to the infiltrating cells in PsA, tissues and synovial fluid. Pathology of the joint, especially destruction of bone, is partially facilitated through signaling of IL-17A, thereby inducing the activator of receptor of nuclear factor kappa b ligand (RANKL), and thereby stimulating osteoclasts. Pro-inflammatory cytokines IL-1β and TNF-α perform in collaboration with the local setting [25].

Epidemiology of Psoriasis

As per the big population-based Multinational Assessment of Psoriasis and Psoriatic Arthritis (MAPP) survey, there is overall 1.9% prevalence of psoriasis i.e. with 1.4% in Spain and 3.3% in Canada [15]. The prevalence is bit higher at 2.2% in the USA [26, 27]. The prevalence is variable globally both regionally and amongst diverse ethnicities within the same area; it is generally stated at higher rates in regions far from the equator [28, 29]. WHO in 2014 reported psoriasis as a significant non-communicable illness and emphasized over the suffering associated to misdiagnosis, insufficient management and stigma related to this ailment [30]. The Global Burden of Disease Study in 2016 assessed that psoriasis accounted for 5.6 million all-age disability-adjusted life-years (DALYs) i.e. at least three-fold that of inflammatory bowel disease [31].

Clinical Presentation of Psoriasis

Psoriasis can occur at any time of life. However, the disease follows a bimodal pattern i.e. reaching the peak in about 20–30 years age wise and then in about 50–60 years of age [27, 32]. Generally there is a family history of psoriasis. A first-degree relative is found in almost 30% patients with psoriasis and the possibility of this illness rises with the count of affected relatives [33, 34]. Certain researches propose that the bimodal pattern signifies two separate types of psoriasis: the patients having early onset probably have a much more genetic marker which is considerably related to psoriasis and to have a parent affected with psoriasis in comparison to patients having psoriasis in life later. Psoriasis with early commencement is moreover linked with further severe illness [27]. Mostly, the ailment increases or decreases all through the life of the patient, and spontaneous remission deprived of therapy is improbable [35].

Psoriasis plaques can be damaging and sternly pruritic and/or painful. The most troublesome symptom of psoriasis is itching [27]. Quality of life can be influenced significantly, and several affected patients complain of a substantial social and emotional problem inclusive of the adverse impact of this ailment on their physical health [36, 37]. Practical disability owing to psoriasis is even more in comparison to the persons having other severe ailments like cancer and heart disease [38]. The MAPP survey revealed a 2-year median interval from symptom initiation to period of diagnosis. It was noted that around 30% of psoriatic patients and 50% having both psoriasis and psoriatic arthritis ranked their illness as severe. Despite of this, almost half of psoriatic patients did not see a doctor in the former year and a lot of patients were either not taking treatment or were on topical treatment only. One of the causes of under treatment was deficiency of tolerability or effectiveness of existing oral or biologic therapies. These facts focus towards the significance of refining diagnosis of psoriasis and requirement of better healing options [27].

Comorbidities with Psoriasis

For diabetes, Psoriasis is considered as an independent risk element and accounts for chief adverse cardiovascular effects. Various other morbidities like hypertension, chronic kidney disease, inflammatory bowel disease, nonalcoholic fatty liver disease, lymphoma (particularly cutaneous T-cell lymphoma), etc. are related to psoriasis too [39]. Psoriatic arthritis is often faced with cutaneous psoriasis but it is identified late in the disease course. An association amid psoriasis, dietary elements and celiac disease may also exist [40-42]. A gluten-free diet should be prompted if analysis for IgA anti-endomysial antibodies and IgA tissue transglutaminase antibodies is positive; it has exhibited improvement in psoriatic lesions [42]. Cutaneous psoriasis frequently affects mental health apart from physical health; augmented anxiety, depression, and sleep disorders are usually faced by the patients. The persistent itch related to psoriasis is a lot disturbing and adversely affects the quality of life of affected individuals [15].

Variants of Psoriasis

Psoriasis typically presents persistent plaques with silvery scales on extensor regions i.e. elbows and knees. Disease severity links to the size of affected body surface area. Psoriasis with plaques is the most common one, yet, other forms are also present; patients may display one main form or various variants at the same time. Mostly, different forms of psoriasis

exhibit three typical aspects: erythema, skin congealing, and scaly skin. Patient's history and some physical indications can help to diagnose psoriasis e.g. the Koebner phenomenon, the Auspitz sign, and the Woronoff ring [15]. The Koebner phenomenon denotes formation of psoriatic lesions in an traumatized area, often ensuing a lined streak-type form [43]. The Auspitz sign refer to identify bleeding that might come across with the elimination of a psoriatic plaque. The Woronoff ring is blanching that may frame a psoriatic lesion [15].

Chronic Plaque-Type Psoriasis

It is the utmost common form which is described by well-defined pink papules and plaques with silvery scales in a symmetry on the extensor regions, trunk, scalp and lumbosacral parts [15, 44]. Primary cause of psoriasis is a dysregulation of immune responses, which manifests in individuals carrying one or more psoriasis susceptibility genes, either skin specific or related to immune functions, and after their exposure to certain environmental triggers. The latter include physical trauma (Koebner phenomenon) and infections, which trigger innate immune responses by promoting the formation and the release of nucleic acid/autoantigen complexes by injured skin cells. In particular, complexes formed by the cathelecidin LL37 and self-DNA/RNA fragments activate plasmacytoid dendritic cells (pDCs), a subset of DC releasing high IFN-α and TNF-α [45].

Guttate Psoriasis

Guttate psoriasis, the word derived from the Greek word gutta meaning a droplet, defines the sensitive inception of a countless of tiny, 2–10 mm diameter lesions of psoriasis. These are generally distributed in a centripetal approach while guttate lesions can also involve head and limbs. It is defined by minor (often < 1 cm) scaly and pink papules with sudden appearance. It is much common in youngsters commonly headed by an upper respiratory tract infection, usually with Streptococcus. If streptococcus analysis is affirmative, then rational antibiotic therapy can improve guttate psoriasis [46, 47]. The number of lesions is up to 100 and commonly 5 or 10 will be seen. Guttate psoriasis accounts for 2% of the whole cases of psoriasis. In children, a delicate period of guttate psoriasis is usually self-limiting in adults, guttate flares may confuse chronic plaque disease. Although a trivial number of studies have been done on long-term prediction of children with acute guttate psoriasis, one study shown that 33% of patients with acute guttate psoriasis ultimately developed chronic plaque disease [48].

Erythrodermic Psoriasis

Erythrodermic psoriasis (EP), which accounts for 1% to 2.25% of all psoriasis, 2 is a form of the disease clinically characterized by a generalized erythema covering ≥90% of the body surface area (BSA). It represents a rare event that occurs in a small percentage (<3%) of psoriatic patients, who are usually affected by an unstable plaque psoriasis. Triggering factors include also drug reactions, withdrawal of systemic therapy and systemic infections. The management of EP is challenging, as the condition is severe, potentially life-threatening and patients can experience systemic symptoms such as dehydration, lymphadenopathy, or arthralgia, too It encompasses minimum 75% of the body with erythema and scales [49, 50]. Various conditions may induce erythroderma like a drug reaction, Sezary syndrome, atopic dermatitis, seborrheic dermatitis, and pityriasis rubra pilaris. Management of further disorders in the differential diagnosis can possibly lead to worsening of psoriasis. Careful clinical analysis is essential for correct diagnosis as the results of skin biopsy are usually nonspecific [15, 51].

Pustular Psoriasis

This can arise in localized (palmoplantar) or generalized forms. Generalized pustular psoriasis, a cruelest form of erythrodermic psoriasis with severe systemic departure in which sterile pustules and scaling expand over the trunk and limbs (Fig. **1**). It causes extensive inflammation with malaise, pyrexia and circulatory interruption. It can be toxic, as the skin loses its capacity to maintain well-organized thermoregulation and liquid balance. It can develop instinctively or sometimes as an obstacle of potent corticosteroid therapy (particularly when high-dose systemic steroids are quickly withdrawn). Management is like to that of blisters in burn patients, as the interference to the skin's functions must be minimized and controlled. Palmoplantar psoriasis is restricted to sterile pustule formation on the palms and soles without systemic indications. It is familiar in cigarette smokers, usually in middle-aged women and few of classic plaque psoriasis patients [48]. It is described through appearance of vivid erythema and sterile pustules. This disease can be initiated by pregnancy, suddenly tapered corticosteroids, hypocalcemia, and infections. The palms and soles can be involved with grave desquamation that may extremely affect the quality of life [52].

Inverse or Flexural Psoriasis

This is present as gleaming, pink-to-red well defined plaques encompassing intertriginous regions, usually the inguinal crease, groin, axilla, infra-mammary areas, and intergluteal cleft [53]. According to different studies and populations, the prevalence of IP is highly variable, ranging from 3 to 36%, because of the lack of precise diagnostic criteria and of the consensus whether genital localization is considered part of the disease. IP is typical in children, especially in young infants with involvement of the diaper area configuring the

"napkin psoriasis". The pathogenesis of IP does not differ from that of plaque psoriasis, and the possible role of fungal and/or bacterial colonization of the folds as possible trigger factor is still debated.1 Although IP may involve a limited percentage of skin body areas, it may have a significant impact on the quality of life, especially on sexual function, embarrassment, and shame, as demonstrated by a study using a specific tool to measure the burden of disease called Inverse Psoriasis Burden of Disease (IPBOD) questionnaire. It has also been suggested that the sudden onset of IP in adults might be an indicator of HIV infection [53].

Geographic Tongue

This is designates psoriasis of the tongue. Geographic tongue, also known as benign migratory glossitis, is a benign chronic inflammatory condition of the tongue. The mucosa of the tongue is presented with white plaques having a geographic border. There are no scales and the wetness on the tongue creates zones of hyperkeratosis that look white [15, 54]. It is characterized by erythematous lesions with filiform papillae atrophy, surrounded by white limited areas in the dorsal and lateral aspects of the tongue, producing a map-like aspect. This lesions change in size and shape with time, and are characterized by periods of exacerbation and remission without scaring. Although the cause of geographic tongue is still unknown, most patients report family history of the condition, suggesting then a possible genetic predisposition. Prevalence of this condition among parents and siblings of these patients is significantly higher than general population [55].

Nail Psoriasis

This is a refractory disease that affects 50–79% skin psoriasis patients and up to 80% of patients with psoriatic arthritis (PsA). The pathogenesis of nail psoriasis is still not fully illuminated, although some peculiar inflammatory cytokines and chemokines seems to be the same as described in psoriatic skin lesions. Psoriatic nail involving matrix can cause pitting, leukonychia, red spots in lunula, and nail plate crumbling, while nail bed involvement can result in onycholysis, oil-drop discoloration, nail bed hyperkeratosis, and splinter hemorrhages. The common assessment methods of evaluating nail psoriasis includes Nail Psoriasis Severity Index (NAPSI], Nail Assessment in Psoriasis and Psoriatic Arthritis (NAPPA], Nail Psoriasis Quality of life 10 (NPQ10], and so on. It can be evident as nail pitting, oil staining, onycholysis and subungual hyperkeratosis. This variant of psoriasis is reasonably upsetting for affected persons and can be tough to cure [56].

Palmoplantar Psoriasis

This involves the hand palms and feet soles. Lesions are either like other psoriatic plaques with sharp erythematous scaling lesions or encompass congealing and scaling deprived of erythema [47, 57]. Palmoplantar psoriasis (PP) accounts for about 12–16% of psoriasis cases. Palmoplantar psoriasis is often resistant even to strong local treatment; it should be classified as severe psoriasis. Patients with this disease report significant functional impairment and the occurrence of symptoms such as burning or pain, and worse health-related quality of life than in patients with other forms of psoriasis. Morphology may vary from thick, hyperkeratotic plaques with fissuring to pustular lesions. Although palm and sole involvement is less than 5% of body surface area, patients may suffer from greater physical constraints than people with psoriasis localized in other areas. Diagnosis of psoriasis of palms and soles is not always straightforward, considering frequent clinical overlap with chronic eczema and frequent co-occurrence of these two conditions. Due to the fact that their treatment will vary, proper diagnosis is essential for a successful outcome. Despite the relatively small BSA, quality of life can be poor for patients with psoriasis of hands and feet due to pain and its visibility. Treatment should focus on alleviating pain as well as cosmetic improvement, as pain reduction and improvement in daily activities may be more important for patients than the total remission of skin lesions [58].

Psoriatic Arthritis

This can significantly harm joint and cause incapacity. Mostly, patients with this disease have a history of previous skin illness [59]. There is no particular lab test available for psoriasis but the radiologic investigation can exhibit bulky syndesmophytes, central and marginal destructions and periostitis. There are variable forms of involvement of joint. This disease is expected to impact the metacarpophalangeal joints more than osteoarthritis and probably impacts the distal interphalangeal joints more than rheumatoid arthritis [60]. Psoriatic arthritis frequently grows slowly generally causing uneasiness but no acute pain. Swelling at the place where tendons or ligaments fit into the bone (enthsitis) frequently exists. Joint damage might result in telescoping "opera glass" digit [61-63]. PsA is an inflammatory musculoskeletal disease associated with cutaneous psoriasis. It affects men and women almost equally between the ages of 40 and 50 years . The diversity of affected organ systems includes peripheral and axial joints, entheses, skin, and nails. PsA is associated with comorbidities such as osteoporosis, uveitis, subclinical bowel inflammation, and cardiovascular disease . Given this heterogeneity, its diagnosis has been difficult. However, classification criteria such as CASPAR (classification criteria for PsA) and several screening tools have facilitated the recognition of this disease among family physicians, dermatologists, and rheumatologists [64].

Drug-Provoked Psoriasis

This can be induced or aggravated by the drug. Drug-induced form gets better after cessation of the offending drug and be likely to come about in individuals with no personal or family history of the disease. Drug aggravated form progresses even after the cessation of the causative drug and is much frequently perceived in patients having a history of the disease [65]. Medications that usually aggravate psoriasis include beta-blockers, lithium, and antimalarial while others are antibiotics, digoxin, and NSAIDs [46, 66].

Therapy of Psoriasis

Psoriasis often needs a long-term treatment as it is a chronic and recurring disease. The severity of illness, comorbid conditions and contact to health care setting determine the selection of therapy for psoriasis. Psoriatic patients are often classified as mild or moderate to severe groups, subject to sternness of the lesions clinically, the influenced body surface area and patients quality of life [33, 67]. Clinical severity of disease and therapy response can be rated via several different scores. The Psoriasis Area Severity Index (PASI) score is widely used in clinical trials, mainly in the ones concerning to the formation of the biologic drugs. Psoriasis which is mild to moderate can be managed by topical agents, with a blend of glucocorticoids, vitamin D analogues and phototherapy [68]. Moderate to severe disease frequently necessitates systemic therapy. The existence of comorbid conditions like psoriasis arthritis is extremely important as well in deciding for therapeutic options [33, 69-71].

Small-Molecule

Advancements in psoriasis treatments have given rise to progressive targeted biological agents. Methotrexate (MTX), retinoids and cyclosporine A are customary therapeutic preferences for psoriasis. Dimethyl fumarate and apremilast are latest medications accepted to treat psoriasis. MTX is an analogue of folic acid that deters DNA production by inhibiting biosynthesis of thymidine and purine. The preliminary suggested dosage is 7.5–10 mg per week to 25 mg per week at maximum [72-74]. A retrospective study stated positive response (defined by PASI decline of 50% to 75% and absolute DLQI value) extended up to 33%, 47%, and 64% of patients at 3, 6 and 12 months, correspondingly [75]. A contradictory indication exists on psoriatic arthritis for MTX efficacy. A publication conveyed that 22.4% patients attained least activity of arthritic disease and 27.2% reached a PASI 75 at 12th week [76]. HLA-Cw6 has been proposed as a capable marker for patients getting benefit from MTX therapy [77]. Cyclosporine is a short-term and intermittent treatment for psoriasis and the dose is 2.5 - 5.0 mg per kg of body weight for 10 - 16 weeks. Drug should be tapered to avoid recurrence [78].

Retinoids are vitamin A-related molecules (natural or synthetic) and Acitretin is employed to treat psoriasis. Acitretin impacts transcriptional systems by acting via nuclear receptors and regularizes keratinocyte proliferation and differentiation [79]. For Acitretin, the maximum dose is 1 mg/kg body weight/ day and initial dose is 0.3–0.5 mg per kg body weight/ daily. Fumaric acid esters (FAEs) are tiny molecules with anti-inflammatory and immunomodulatory actions [33, 80]. The precise process for activity is unclear, yet it is assumed to have an interaction with glutathione, inhibiting the transcriptional action of NF-κB apart from other mechanisms. FAEs were primarily a blend of dimethyl fumarate (DMF) and monoethyl fumarate (MEF), dimethyl fumarate being the chief active compound. DMF decreases the migratory capability of slan+ (6-sulfo LacNAc) monocytes and also inhibits initiation of Th1/Th17 responses. Slan+ cells are common dermal inflammatory dendritic cell types that are derivative of blood circulating slan+ nonclassical monocytes. FAE preparation with exclusively DMF was permitted for psoriasis management in the European Union, Norway and Iceland in 2017. A noticeable progress was observed by use of this therapy for psoriatic arthritis and also nails psoriasis. It is suggested to have a complete blood picture prior to therapy commencement and on monthly basis for DMF/MEF or every three months for DMF because FAEs may reduce counts of lymphocytes and leukocytes [33].

Apremilast (phosphodiesterase-4 inhibitor) impedes the hydrolyzation of cAMP (second messenger) leading to enhanced levels of IL-10 and reduction in expression of TNF-α, IL-12 and IFN0γ (pro-inflammatory cytokines). Extensive anti-inflammatory actions on fibroblasts, endothelial cells and keratinocytes have been displayed by Apremilast [81, 82]. Apremilast was investigated in the context of slan+ cells where it intensely diminished TNF-α and IL-12 formation; on the other hand, it enhanced IL-23 secretion and IL-17 formation in T cells triggered by apremilast-treated slan+ monocytes [83]. This twofold effect on slan+ antigen-presenting cells can limit treatment responses. A key benefit for apremilast is that it does not necessitate routine observation of hematologic factors in comparison to other small molecule agents [82]. At week 16, a 33.1% PASI 75 response was displayed by Apremilast. In addition to psoriatic arthritis, this agent is beneficial for scalp, palmoplantar and nail psoriasis also [21,84, 85].

The most common adverse effects due to these small molecules are mild nausea, diarrhea and infections of upper respiratory tract including self-resolving nasopharyngitis. The customary systemic medications are immunomodulators requiring strict clinical observation owing to the frequent adverse effects encompassing primarily the liver and the kidney, except for apremilast. Methotrexate and cyclosporine

are the systemic treatments for psoriasis contained in Model List of Essential Medicines by WHO, even though there are signals of joint illness for the former agent and immunosuppression for the latter one [33].

Biologics

For the treatment of psoriasis, the term biologics denotes intricately engineered molecules together with receptor fusion proteins and monoclonal antibodies. Biologics are aimed for particular inflammatory pathways and are given through subcutaneous or intravenous route (like infliximab) on variable weekly schedules. At present, biologics are aimed for two pathways namely IL-23/Th17 axis and TNF-α-signaling are targeted by the biologics as they are critical for psoriatic plaque in terms of development and chronicity [68,74, 86].

TNF-α

TNF-α inhibitors are the first-generation biologics that have been available for over a decade and are useful in treating plaque psoriasis and psoriatic arthritis. TNF-α inhibitors are standards employed for evaluation of drug effectiveness in psoriasis. Etanercept, adalimumab, infliximab and certolizumab are the drugs in this class. Etanercept is distinctive in this class as it is both monoclonal antibody and recombinant human fusion protein; the receptor part for TNF-α ligand is bonded to Fc portion of an IgG1 antibody. The US FDA approved it as the first agent for psoriasis [87]. Infliximab (chimeric monoclonal IgG1 antibody) and adalimumab (human monoclonal IgG1 antibody) defuse TNF-α activity by attachment to its membrane-bound and soluble form. These agents are mainly used for treatment of psoriatic arthritis and demonstrate same effectiveness; they display dissimilar PASI 75 response rates i.e. 52% for etanercept, 59% for adalimumab and 80% for infliximab. It is reported that infliximab is superior in efficacy in comparison to other TNF-α inhibitors while it exhibited similar activity on comparison with ustekinumab [88]. The chimeric property of infliximab renders it having a greater immunogenic potential which consequently may impact drug persistence. PEGylation is recognized for several biopharmaceutical enhancements, together with better half-life and diminished immunogenicity. A pegylated Fab' fragment of a humanized monoclonal antibody is Certolizumab pegol used against TNF-α [89].

IL23/Th17 Axis

Ustekinumab (monoclonal antibody) targets the p40 subunit and is the first official biologic to treat psoriasis vulgaris after the TNF-α inhibitors. P40 is not limited to IL-23 and is communal with IL-12 which is a dimer comprising of p40 and p35. It differentiates simple T cells into Th1 cells. Ustekinumab inhibits 2 diverse T-cell stimulating processes: Th1 and Th17 options by targeting p40. Ustekinumab can effectively treat PsA (psoriatic arthritis) and Crohn's disease [2]. Ustekinumab is available as 45 mg and 90 mg, dependent on average 100 kg of body weight. This monoclonal antibody has wide-ranging safety data, diminished adverse effects, worthy clinical effectiveness and long term survival upon management. It presented a PASI 75 response in 72.4% at 90 mg, and in 61.2% at 45 mg respectively [90]. On comparison with the anti-TNF-α agents, ustekinumab established a significantly extended drug survival [91-93]. Common adverse effects reported are infections of upper respiratory tract, nasopharyngitis, fatigue and headache; infections are the serious adverse events noted on the label. There had been reports of TB in only a couple of psoriasis patients with ustekinumab administration [2, 94, 95]. The important character of IL-23 in modeling the Th17 response was accentuated by clinical effectiveness of ustekinumab and added elucidation of its mechanism of action [96]. Three completely human monoclonal antibodies having p19 specificity available are guselkumab, tildrakizumab and Risankizumab [33]. Guselkumab approved for psoriasis exhibited clinical lead in comparison to adalimumab; 85.1% patients demonstrated a PASI 75 and at week 16, 73.3% reached a PASI 90 response [97, 98]. Risankizumab displayed 88% PASI 75, 81% PASI 90, and 48% PASI 100 at 12th week. After the final injection at 16th week, patients were followed for 48 weeks showing that one-fourth sustained PASI 100 [99]. Whether or not IL-23 blockage has the capability to alter disease course following subsequent drug reclamation is under research.

Three human monoclonal antibodies aimed at IL-17 are presented: Secukinumab, brodalumab and ixekizumab. Secukinumab and ixekizumab block IL-17A while brodalumab blocks IL-17 receptor A. Biologics targeting IL-17 perform faster, displaying substantial inconsistencies from placebo in the first week of management. Secukinumab was the first official IL-17A blocker for psoriasis which was approved in 2015. After one year, the permission was also made for PsA and ankylosing spondylitis. With secukinumab, 81.6% patients got a PASI 75 response and 28.6% had a PASI 100 response at 12th week [100]; more than 80% sustained PASI 75 at week 52. Secukinumab exhibited a swift onset of action, with a substantial probability of attaining PASI 75 in the week 1 of management in comparison to ustekinumab, and it was clinically superior at week 16 and 52 to ustekinumab [97, 101]. Ixekizumab also exhibited a considerably speedy commencement of action in the week 1 in comparison to placebo with a 50% PASI 75 response at 4th week and 50% PASI 90 by 8th week. The response rates noted were 89.1% for PASI 75 and 35.3% for PASI 100 at week 12 [102].

Scalp and nail psoriasis are the clinically resistant variants to customary topical treatments but secukinumab and ixekizumab have demonstrated effectiveness against them. Brodalum-

ab (human monoclonal antibody) is directed towards the IL-17 receptor type A. It consequently blocks the biological action of IL-17A, IL-17F, interleukin-17A/F and interleukin-17E (known as interleukin-25]. Brodalumab displayed an adequate safety profile and at week 12 it reached 83.3% PASI 75, 70.3% PASI 90 and 41.9% PASI 100 response [103]. Discontinuation of secukinumab demonstrated maintenance of response in 21% of patients after a year and after two years 10% was noted [104]. This outcome advocates that aiming IL-17 signaling put forth certain disease-modifying consequence recreating homeostasis of the inflammatory paths in a subcategory of psoriatic patients. Common adverse effects due to IL-17 inhibition are upper infections of respiratory tract, nasopharyngitis, headache and arthralgia. Additionally, IL-17 signaling is crucial for the acute protection counter to bacterial and fungal infections extracellularly. As compared to etanercept, Candida infections are further common in patients administered with secukinumab and ixekizumab [100]. However, candida infections are not severe and do not exhibit management disruption. There is very reduced risk of tuberculosis reactivation with biologic treatments other than anti-TNF-α [105].

Biosimilars in Psoriasis

A biosimilar is a biological formulation that must be extremely alike to an official biologic formulation and has no clinically significant dissimilarities in terms of potency, safety or purity on comparison with the reference formulation. Procedures for the formation and permission of biosimilars have been allotted by the WHO, European Medicines Agency and the FDA. There are at present two etanercept biosimilars, four infliximab biosimilars and eight adalimumab biosimilars official in Europe. By reducing the charges of systemic therapies for psoriasis management, biosimilar agents may also escalate the approach to biologics [106-108].

Drugs under Research for Psoriasis

Tofacitinib, which is an oral Janus kinase (JAK) blocker, was permitted for treating rheumatoid arthritis (RA) and psoriatic arthritis (PsA). This medication at week 16, exhibited a 59% PASI 75 and 39% PASI 90 response rate; it was effectual for nail psoriasis also yet, its production for psoriasis was ceased due to the causes that were not linked to safety. Upadacitinib is an additional JAK blocker going through clinical trials (phase III) to manage psoriatic arthritis. Piclidenoson (adenosine A3 receptor inhibitor), serlopitant (neurokinin-1 receptor antagonist) and RORγt inhibitors are being tried as oral therapies for psoriasis. There are two diverse biologics aimed at IL-17 and another aiming IL-23, are presently under the test. Moreover, there are 13 recently registered clinical trials (phase III) going on to test biosimilar agents for adalimumab (8), infliximab (3), and etanercept (2) [33, 86, 109].

Patient Education for Psoriasis

The patients should be educated by pharmacists especially about using moisturizers and management of dry skin. Additionally, patients' compliance with treatment is mandatory and above this it should be ensured that patients should avoid medicines that could be the source of flare-ups. The patients should also be educated on lifestyle changes by avoidance of alcohol, smoking, tension, and dry cold weather. Although the sun is helpful yet, excessive exposure should be evaded. If required, the patients should be monitored for self-harm and referred to the mental health therapist. Furthermore, the patients should be counseled to consume healthy items, workout on a regular basis and sustain a healthy weight. As relapses are common in psoriasis, so all such patients require constant follow-ups [110]. A professional interdisciplinary team can work for the management of psoriasis to produce better results [6].

CONCLUSION

Psoriasis is an inflammatory skin disorder which is principally genetically determined and is linked with substantial medical and psychosocial comorbidities. Improved understanding of its pathophysiology has steered to a number of therapeutic choices which could tremendously improve the lives of psoriatic patients. The therapy of psoriasis is not simple and generally involves a professional team to manage it. The fundamental objective is to enhance the quality of life of such patients, also by educating them about trigger avoidance.

CONFLICT OF INTEREST

Declared none.

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