Management of Psoriasis in Children: a Narrative Review

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Psoriasis is an inherited chronic inflammatory papulosquamous disorder with a variable clinical spectrum affecting about 0.5% to 2% of children and adolescence (1). The disease affects 4% of all children younger than 16 years with all types of dermatological disorders (2-4). The onset of disease in one third of all patients in childhood is in the first and second decades of life and there is a strong association between early onset of disease and HLA-Cw6 (5). At present, the risk of disease can be recognized by genetic consultation. The lifetime risk of getting psoriasis if no parent, one parent, or both parents have involved, are 0.04%, 0.28% and 0.65%, respectively. If no sibling, one sibling or both siblings affected, the corresponding risks are 0.24%, 0.51% and 0.83%, respectively (6). The onset of disease in girls is earlier than boys (7, 8). Psoriasis is a chronic cell mediated inflammatory disease characterized by keratinocyte hyperproliferation, vascular endothelial proliferation and inflammatory cell infiltration of dermis and epidermis, with many of pathogenic mechanisms not fully cleared yet (1-4). Several factors are contributed as causative agents of disease including genetic, environmental and immunologic factors (9). Predisposing factors include trauma, infections such as staphylococci, streptococci, HIV and candida species, medications, stresses, cigarette smoking and alcohol. Each type of trauma such as physical, chemical, thermal, surgical and/or inflammatory injuries are thought to play a role in the progression of disease (7). Streptococcal pharyngitis or perineal streptococcal dermatitis often predisposes the development of Guttate psoriasis. Although prophylactic antibiotic therapy or tonsillectomy have been recommended in children with recurrent Guttate psoriasis, there are no clinical trials about it (10). HIV infection is also thought to play a role in the development and progression of psoriasis (10, 11). Therapeutic agents including beta-blockers, lithium, antimalaria, NSAID, withdrawal oral or topical potent steroids play an important role in development or rebound of psoriasis. In addition, psychological and psychosomatic factors like stress and lack of social support play effective role in the disease prognosis (7). Clinical features of disease in children are different from adults. All of the forms identified in adults are observed in childhood including plaque, Guttate, erythrodermic and pustular. However, Guttate and flexural forms are particularly common in children and characterized by pruritic plaque lesions that are thinner, softer and less scaly than those seen in adults with most involvement of face and flexural area (5, 12). The diagnosis of disease is mainly based on clinical manifestations. Nevertheless, it may be challenging if the disease is mild or presented atypical. In this situation, histopathology finding can be helpful in diagnosis of disease. Treatment of childhood psoriasis is different from those used in the adult population. Childhood psoriasis is considered as a therapeutic challenge. In spite of various available therapies, many of them are not licensed for use in children (12). Therapies for childhood psoriasis are varied from moisturizing in infants to systematic medications in severe cases of disease in children and teenagers (13). Due to lack of approved therapies and standardized methodology, this paper provided a review on the management of psoriasis in children.

Keywords: Psoriasis; Papulosquamous Disorders; Treatment; Children

1. Context

Psoriasis is a common chronic inflammatory cutaneous disease affecting 0.5% to 2% of children and adolescence (1). The disease affects 4% of all children younger than 16 years with all types of dermatological disorders (2-4). The onset of disease in one third of all patients in childhood is in the first and second decades of life and there is a strong association between early onset of disease and HLA-Cw6 (5). At present, the risk of disease can be recognized by genetic consultation. The lifetime risk of getting psoriasis if no parent, one parent, or both parents have involved, are 0.04%, 0.28% and 0.65%, respectively. If no sibling, one sibling or both siblings affected, the corresponding risks are 0.24%, 0.51% and 0.83%, respectively (6). The onset of disease in girls is earlier than boys (7, 8). Psoriasis is a chronic cell mediated inflammatory disease characterized by keratinocyte hyperproliferation, vascular endothelial proliferation and inflammatory cell infiltration of dermis and epidermis, with many of pathogenic mechanisms not fully cleared yet (1-4). Several factors are contributed as causative agents of disease including genetic, environmental and immunologic factors (9). Predisposing factors include trauma, infections such as staphylococci, streptococci, HIV and candida species, medications, stresses, cigarette smoking and alcohol. Each type of trauma such as physical, chemical, thermal, surgical and/or inflammatory injuries are thought to play a role in the progression of disease (7). Streptococcal pharyngitis or perineal streptococcal dermatitis often predisposes the development of Guttate psoriasis. Although prophylactic antibiotic therapy or tonsillectomy have been recommended in children with recurrent Guttate psoriasis, there are no clinical trials about it (10). HIV infection is also thought to play a role in the development and progression of psoriasis (10, 11). Therapeutic agents including beta-blockers, lithium, antimalaria, NSAID, withdrawal oral or topical potent steroids play an important role in development or rebound of psoriasis. In addition, psychological and psychosomatic factors like stress and lack of social support are effective role in the disease prognosis (7). Clinical features of disease in children are different from adults. All of the forms identified in adults are observed in childhood including plaque, Guttate, erythrodermic and pustular. However, Guttate and flexural forms are particularly common in children and characterized by pruritic plaque lesions that are thinner, softer and less scaly than those seen in adults with most involvement of face and flexural area (5, 12). The diagnosis of disease is mainly based on clinical manifestations. Nevertheless, it may be challenging if the disease is mild or presented atypical. In this situation, histopathology finding can be helpful in diagnosis of disease. Treatment of childhood psoriasis is different from those used in the adult population. Childhood psoriasis is considered as a therapeutic challenge. In spite of various available therapies, many of them are not licensed for use in children (12). Therapies for childhood psoriasis are varied from moisturizing in infants to systematic medications in severe cases of disease in children and teenagers (13). Due to lack of approved therapies and standardized methodology, this paper provided a review on the management of psoriasis in children.
2. Evidence Acquisition

We conducted a narrative review of literature by searching of PubMed in Medline area and Google scholar, and Cochrane library to answer clinical questions on the management of psoriasis in children by use of the following keywords: Psoriasis, Papulosquamous Disorders, Children, Treatment, and inherited. Following reading the titles and abstracts of the retrieved articles by two independent reviewers, full text articles written in English language related to management of psoriasis in children were selected. Articles were excluded if were not related to childhood psoriasis. Here in, the qualitative data are discussed as results of the review.

3. Results

3.1. Clinical Features

Diagnosis of psoriasis is more difficult in children due to atypical characteristics and limited involvement of skin. Various kinds of disease may be presented in different lifetime of an individual. Among all types of psoriasis, congenital psoriasis appears to be rare (14). Plaque psoriasis is the most common type of psoriasis seen during childhood. The diameter of psoriatic plaques is 5-10 cm affecting the extensor of limbs symmetrically. Face involvement occurs in children more frequently than adults. Plaques formation on the scalp is common and should be differentiated from seborrheic dermatitis and Tinea capitis. In addition, various types of psoriasis including follicular, papules, annular or figurate lesions may be seen in plaque psoriasis. Inverse psoriasis affecting flexural area and skin folds are common in infants. Erythematous patches without exfoliation frequently appear around the napkin area. In a study performed on 1262 patients with psoriasis, about 4% of patients had localized psoriasis around the napkin area. This form of psoriasis should be differentiated from inflammatory linear verrucaous epidermal nevus (ILVEN), (10, 11, 15, 19, 20). Zonal form of the disease presents at the site of herpes zoster lesions following the Koebner phenomenon (10, 11, 15, 19, 20).

3.2. Atypical Forms of Psoriasis

Atypical forms of psoriasis are characterized by unusual localized lesions including digital and interdigital forms and occasionally found on knee as verrucous lesions. Follicular form is specially misdiagnosed with pityriasis rubra pilaris (10, 11, 15, 19, 20).

3.3. Linear and Zonal Lesions

Linear type lesions occur at present of typical psoriasis following the Koebner phenomenon. The real linear type without typical psoriatic lesions plaques is very rare and should be differentiated from inflammatory linear verrucous epidermal nevus (ILVEN), (10, 11, 15, 19, 20). Zonal form of the disease presents at the site of herpes zoster lesions following the Koebner phenomenon (10, 11, 15, 19, 20).

3.4. Seborrheic Psoriasis

The seborrheic lesions in this form of psoriasis manifests in scalp, eyebrow and post auricular skin associated with signs of both the two types of diseases (10, 11, 15, 19, 20).

3.5. Mucosal Involvement

Although, mucosal involvement is rare in psoriasis, it has been reported in pustular, erythematous and plaque types of psoriasis. Multiple lesions include white or grey-yellow plaques, annular lesions and erythema diffuses of tongue and geographic tongue (10, 11, 15, 19, 20).

3.6. Ophthalmic Lesions

Ophthalmic lesions such as blepharitis, conjunctivitis, keratitis, eye dryness, symblepharon and trichiasis have been reported (15).

3.7. Treatment

In most cases, psoriasis is a mild disease and can be controlled easily by topical therapy. Control of disease is diffi-
cult in some cases. Age of patient, extended and severity of lesions and the site of involvement should be considered in long-term treatment. Control of disease, not eradication must be considered as a main goal and ultimate outcome at the beginning of treatment. Predisposing factors such as infections, stress and trauma should always be noted. Most pediatric patients with childhood psoriasis can be effectively treated by topical therapies at home under supervision of their parents. In severe cases with extended lesions or in patients with low therapeutic response, hospitalization is required (12). Whereas no cure is available for psoriasis, a wide range of therapeutic options are existed including; topical therapy, phototherapy, chemotherapy, systemic therapies and biologic therapies (19). Therapeutic options must be weighed with extreme care in children. Physical and psychological conditions should be considered in selecting therapeutic options. Table 1 shows the available remedies for pediatric papulosquamous diseases including psoriasis (21).

3.8. Topical Therapies

3.8.1. Moisturizers

Moisturizing can decrease desquamation and relieve itching. Moisturizers are low cost and used easily. Moisturizers can be the only treatment in mild psoriasis (14).

3.8.2. Steroids

Steroids were one of the main treatments of psoriasis at the beginning of 1950. Topical corticosteroids can be effective agents, especially when itching is the main manifestation of disease. Being odorless and easy availability are great benefits of topical steroids and making them suitable for use by patients. Topical steroids are anti-proliferative and anti-inflammatory agents and alleviate redness and decrease desquamation of psoriatic plaques. Topical corticosteroids are the first line therapeutic agents for mild to moderate psoriasis, especially for the flexural affected sites and genital area, in which other therapeutic agents cause irritabilities. Topical corticosteroid preparations are marketed as different forms such as ointments, cream, lotions, jelly, foam and shampoo. However, the ointment has the most therapeutic effect. Use of potent corticosteroids should be avoided in children, especially with psoriatic lesions at the flexural sites and genital area. Long-term steroid therapy can lead to steria and atrophic telangiectasia, and even in rare cases, suppression of Adreno-hypophyseal-hypothalamic axis occurs. Although the use of topical steroids beneath dressing may be effective, increasing penetration of agent may increase the adverse effects (7, 14). Halobetasol cream 0.05% and clobetasol propionate emulsion 0.05% seem to be efficacious treatments in childhood plaque psoriasis for two weeks. Sudden discontinuation of topical steroids causes exacerbation of disease. For this reason following improvement of lesions, the medicine should be tapered gradually.

3.8.3. Vitamin D Analogs

From 1990, Vitamin D3 was used for topical treatment of psoriasis. Vitamin D inhibits epidermal proliferation and improves epidermal differentiation. Vitamin D modulates immune system. Furthermore, Vitamin D consumption has been limited due to its effect on homeostasis of calcium. Calcipotriol as an analogue of Vitamin D found to be less effective on calcium homeostasis. Due to cleansing and being odorless, patients’ tolerability to use this agent is very good. In a double-blind clinical trial, 77 pediatric patients received Calcipotriol ointment 50 µg/gr twice daily for eight weeks compared to placebo. The results confirmed acceptability of treatment and there was

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<tr>
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<td>α-Bisabolol</td>
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Occlusive dressings

Abbreviations: PULVA; Psoralen and Ultra Violet A, UVB, Ultraviolet Light B.
UVB used in the Goeckerman regimen can be helpful in pruritic properties. Combination therapy with Tar and of tar by patients. Tar has anti-proliferative and anti-odor, coloration and photo toxicity limited acceptance and Guttate psoriasis. Few adverse effects such as bad unfavorable effects. Topical tacrolimus for the treatment of atopic dermatitis, especially in children due to no sterias and no atro-eral studies regarding the successful treatment by topical Calcineurin inhibitors for psoriasis in adults (23-25). Calcineurin inhibitors can be used safely in inverse psoriasis, especially in children due to no steric and no atrophic adverse effects (25). In a study, topical tacrolimus 0.1% twice daily for four weeks was effective in the treatment of plaque-type psoriasis in all age groups of the patients. Ditranol has been reported to be effective in the treatment of psoriasis in 81% of children aged 5-10 years (27). Therapeutic efficacy and alleviating of adverse effects are saved by using Ditranol 1-3% for 30-45 minutes. Ditranol cream is available for use at home. Coloration of skin and clothes occurs following use of Ditranol. Ditranol causes irritation of flexural area, face and genitalia and leads to burning of normal skin surrounded the rashes. Supervision of parents is recommended for proper use of medicines and applying oily moisturizing agents around the plaque. Combination therapy with Anthralin and UVB or other topical medicines can enhance its therapeutic properties. Limited and large plaques can be treated by Anthralin as a form of Zink paste (14).

3.8.7. Ditranol (Anthralin)

Ditranol is a traditional approved treatment of plaque-type psoriasis in all age groups of the patients. Ditranol has been licensed for use in children younger than six years due to systemic absorption and increasing the risk of toxicity (28).

3.9. Phototherapy

There are three types of ultra violet (UV) light including UVA (320-400 nm), UVB (290-320 nm) and UVC (200-290 nm). UVA is subdivided into UVAI (340-400 nm) and UVAII (320-340 nm). The term narrow-band UVB is referred to UVB (311-313 nm) (26). About 90% of UVB radiation is absorbed by ozone. UVA radiation is the largest UV light reaching the earth's surface. The shorter wavelength had more radiation energy. UVA penetrates both epidermal and dermal layers, while UVB affects only the epidermis. Phototherapy is a therapy using light for treatment of skin disorders. Photochemotherapy is a combination therapy of a photosensitizer such as Psoralen and UVA phototherapy (PUVA). Psoralen is a family of natural products known as furocou-marins, which absorbs UV. The available psoralens include 8-methoxy Psoralen, 5-methoxy Psoralen and 4, 5, 8-trimethoxy Psoralen. Psoralens may be used orally or applied as a form of cream, ointment, lotion or bathwater-delivered Psoralen. The gastrointestinal adverse effects of oral or bath immersion of Psoralen is lesser than other routes of administration (29, 30). Recently, Xenon Chloride gas Excimer; a novel mode of phototherapy has been available, which can produce fluency wavelengths higher than UVB light used in localized dermatologic lesions and minimizing contact of body with UV radiation. As a theory, it can impose a low rate of malignancy in this mode of phototherapy. There are two sources of producing xenon chloride gas Excimer including Excimer laser and (Excimer light) non-laser technology (31).
3.10. Phototherapy Mechanism of Action

Phototherapy acts through a combination of pathways including anti-inflammatory, anti-proliferative and immunosuppressive effects in the treatment of psoriasis and its successful therapeutic effects are due to combination of these three mechanisms of actions (32, 33). There are several published articles regarding phototherapy in childhood psoriasis, in which NB UVB was often used as radiation therapy. More therapeutic effects were seen in Guttate and plaque types of psoriasis (34). Recovery period varies among these patients and might be prolonged for months and years. Treatment is usually given three times weekly for six weeks with increasing doses as tolerated. Topical preparations such as tar or Calcipotriol and Anthralin are also useful in combining with UVB. Acute phototoxicity including erythema and blister manifested 4-6 hours with a pick of 12-24 hours after UVB contact are complications of UVB (12). Prolonged complications of this method are photoaging and carcinogenicity (33). Absolute contraindications of phototherapy include xeroderma pigmentosa (XP), systemic lupus erythematosus (SLE) and basal cell nevus. In addition to abovementioned contraindications, age below 10 years, pregnancy and lactation, positive history of melanoma and hypersensitivity to light are other absolute contraindications of PUVA therapy (33). In a number of children with hand and palm pustular psoriasis, psoralen combined with UVA (PUVA) may be indicated. In such cases, using psoralen bath is preferred to oral route (7). Although the safety of long-term use of phototherapy and chemotherapy has not been cleared in childhood psoriasis, it plays an important role in the treatment of older children with psoriasis resistant to conventional treatment, and patients with moderate to severe psoriasis with 15-20% of body surface involvement by plaque psoriasis, and in patients with palmar and plantar debilitating involvement (3).

3.11. Systemic Treatment

Systemic treatment of psoriasis disorders are indicated if the disease cannot be controlled by topical therapy and phototherapy. Retinoids like acitretin, methotrexate, cyclosporine, hydroxyurea and Dapsone are classical antipsoriatic agents used in adult psoriasis. These drugs are used only in severe psoriasis (pustular, erythrodermic, exfoliative and plaque psoriatic lesions resistant to topical therapy). There is no enough information regarding the use of systemic antipsoriatic drug therapy in children. Systemic antipsoriatic drugs should be administered only by experienced dermatologists and parents should be informed about possible adverse effects of drugs and requirement of close monitoring during the treatment (14).

3.11.1. Retinoids

Retinoids are effective in the treatment of pustular and erythrodermic psoriasis in children despite their numerous adverse effects. Acitretin in a dosage of 0.25 to 0.6 mg/kg/d is the most common used drug. Although retinoids have been used widely in inherited disorders of keratinization, there are a few case reports and case series regarding the administration of Acitretin in the treatment of childhood psoriasis. Measurement of baseline lipid profile and liver enzymes and repeating at 3-month intervals are required for the administration of retinoids. Absolute necessity of avoiding pregnancy must be recommended to girls of childbearing age during and for two years after cessation of drug. The most common adverse effects of this drug are dry skin and mucous membranes and malaise (14, 34). Premature epiphyseal closure is another adverse effect of using retinoids in children. Decreasing the dosage of acitretin to 0.25-0.6 mg/kg minimizes the risk of this adverse effect. Although sometimes, the higher dose up to 1 mg/kg may be used. Monitoring by bone scan every 12-18 months has been recommended (35, 36). Overall, Retinoids are used for the treatment of pustular and erythrodermic psoriasis in infant and male adolescence.

3.11.2. Methotrexate

Methotrexate has a direct effect on T lymphocytes and keratinocyte cell cycle as well. There is few evidence regarding its use in childhood psoriasis. Although methotrexate is used in some of skin diseases, its safety and efficacy have not been approved in children except for cancer chemotherapy (37). If it should be administered, carefully monitoring is needed and the lowest possible dosage should be prescribed, usually in the range of 0.2-0.7 mg/kg per week and preferably 0.2-0.4 mg/kg. The most common adverse effect of methotrexate is gastrointestinal disturbance and bone marrow suppression is dose-dependent and arises early. Hepatic toxicity is related to the drug accumulation dosage. During the treatment by methotrexate, evaluation of hepatic enzymes, renal function and white Blood cell (WBC) counts should be performed at first, weekly, monthly and finally every three months. Repeated liver biopsy has been recommended by some guidelines, because of the lack of sensitivity of liver enzymes in detecting hepatic fibrosis. Noninvasive techniques such as serial measurements of serum procollagen III peptide are also investigated for further evaluation (14, 38). Up to now, safety and efficacy of methotrexate in the treatment of childhood psoriasis was not investigated. However, Methotrexate was used in long-term treatment of juvenile idiopathic arthritis as the second therapeutic line. In cases of moderate to severe plaque psoriasis resistant to topical therapy and phototherapy, methotrexate is considered a choice treatment.

3.11.3. Cyclosporine

Cyclosporine is a potent IL-2 production inhibitor from T lymphocytes. Although, there is little evidence about its use in childhood psoriasis, there is considerable experience in childhood atopic eczema and adult psoriasis. Cy-
closporine is better to be used for remission rather than maintenance therapy. In a case report of a 9-year-old boy with generalized pustular psoriasis, closporine with a dosage of 3 mg/kg/day was effective (38). However, four patients with erythodermic or pustular psoriasis had no adequate response to closporine (2-5-7.5 mg/kg/day) (39). Cyclosporine has been suggested for transplant in pediatric population and may require a relatively higher dose than adults. Cyclosporine should not be suggested as a selective drug in childhood psoriasis.

3.12. Biologic Treatments

Biologic agents target specific portions of the immune system emerged as a new treatment for moderate to severe psoriasis failed to respond to systemic agents. Biologic agents used in the treatment of childhood and adolescent psoriasis belong to two categories; tumor necrosis factor (TNF)-α inhibitors including etanercept, infliximab and adalimumab and antagonist of human IL-12/23 called ustekinumab (40, 41).

3.12.1. Etanercept

Etanercept is a soluble TNF-receptor fusion protein, which competitively inhibits the binding of endogenous TNFα to its receptor. It was approved by the European Medicine agency (EMA) in 2009 for the treatment of children ≥ 6 years with severe, chronic plaque psoriasis refractory to or intolerant of other systemic agents or phototherapy. Infections are transient adverse effects during the treatment by etanercept. In a randomized double-blind placebo control trial performed on 211 patients with plaque psoriasis, etanercept 0.8 mg/kg with a maximum dosage of 50 mg was injected subcutaneously. At week 12, 27% of patients who received etanercept, achieved PASI 90% compared to 7% in the placebo group. In a study on children with pustular psoriasis, etanercept was prescribed at the dose of 25 mg twice weekly (0.4 mg/kg) for 3 to 31 months (40). Although its short-term consumption has been assessed in previous studies, there is no information regarding its adverse effects. Recently, etanercept has been used in the treatment of childhood psoriasis. The safety and efficacy of etanercept has been assessed in juvenile rheumatoid arthritis for eight years following treatment by etanercept.

3.12.2. Infliximab

Infliximab is a chimeric monoclonal antibody with strong activity against TNF-α. Infliximab is used in the treatment of childhood psoriasis with an infusion rate of 3.3-5 mg/kg. Infusions were given at 0, 2 and 6 weeks and repeated every eight weeks continually. Duration of treatment was different from one session to 10 months and therapeutic response of all patients was considerable. Treatment was discontinued in patients who received infliximab for 10 months due to lack of therapeutic effect in long-term therapy (37, 41-44).

3.12.3. Antibiotics

In a study on two patients, thiamphenicol 20 mg/kg/day was used and clearance of less than 50% of lesions occurred. In a case-series on four patients, erythromycin 50 mg/kg/day was administered for two weeks and all the lesions were disappeared. Other studies reported the effectiveness of amoxicillin, clavulanic acid, rifampin and penicillin v in childhood psoriasis, especially in Guttate psoriasis (45-47). However, there is controversy regarding the efficacy of antibiotic in childhood psoriasis, and unfortunately there are no clinical trials about antibiotic therapy and tonsillectomy in children with psoriasis (48-50).

4. Conclusions

Management of psoriasis in children is different from adults. Childhood psoriasis can be managed by topical therapy. Current therapies are more suppressive than curative. Calcipotriene is the choice treatment in mild to moderate childhood psoriasis and can be administered in combination with mild to moderate steroids if necessary. In cases of flexural psoriasis resistant to topical treatment, tacrolimus cream 1% can be added to the therapeutic regimens. If therapeutic regimens are not effective or in moderate to severe psoriasis, Ditranol would be recommended. Phototherapy for a short period is considered when all other therapeutic methods were ineffective. Although there is a controversy regarding the use of antibiotics, they are indicated in Guttate psoriasis and in cases of suspected streptococcal infections. Methotrexate is a choice among systemic treatments of psoriasis. Retinoids should be considered as a therapeutic approach in cases of pustular and erythodermic psoriasis. Treatment by Cyclosporine must be used in exceptional cases; it has a relatively rapid onset of action. Etanercept as a new therapeutic approach is the third line of treatment when other therapies are not tolerated by patients (50). Recently, Etanercept has been approved by the European Medicines Agency as the first and only biological drug available for children.

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