Systemic treatment of psoriasis in special population

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Abstract

Psoriasis is a common skin disorder affecting approximately 1% of the general population. The treatment of psoriasis depends on the body surface area involvement, quality of life impairment and associated co-morbidities. Special population comprising of pregnant women, lactating mothers, elderly individuals and children, is more vulnerable. They are not included in drug trials; rendering the data for use of systemic treatment scant and is mainly based on anecdotal evidence. In this narrative review, we discuss systemic treatment options in this special population. Though couples planning a family are not considered a special population, they form a subset that require special therapeutic consideration and have also been included in this review.

Key words: psoriasis, treatment, elderly, paediatrics, pregnancy, lactation, fertility

Introduction

Psoriasis is a T-cell-mediated disorder of uncertain aetiology, primarily affecting the skin, nails and joints. It can occur at any age; however, it has bimodal peaks, the first between 16 and 22 years and the second between 57 and 60 years of age. The mean age of onset of psoriasis is 33 years.[1] Its prevalence varies from 0.7% in China to 4.6% in the United States of America, and it affects 0.4–2.2% of Indians.[2] The treatment of psoriasis depends on its severity which is determined by the body surface area involvement, quality-of-life impairment, and associated co-morbidities. The varied treatment options include topical therapy, phototherapy, conventional systemic agents, small molecules, and biologics. The treatment options in the special population are limited due to scant data. The special population is defined in terms of age, gender, ethnicity or health status. This population is more vulnerable and includes pregnant women, lactating mothers, paediatric and elderly population.[3] This population is generally not included in the trials, due to the physiological differences and legal concerns arising out of issues such as consent and teratogenicity. The evidence for treatment in this population remains anecdotal and accumulates slowly after the drug is available in the market for many years. In this narrative review, we will discuss systemic treatment of psoriasis in the above considered special population. Couples planning families also require special therapeutic consideration and is a common clinical dilemma to decide upon the specific treatment plan. We will discuss this clinical scenario also in our review.

Paediatric population: Psoriasis affects 0.5–1% of children. Guttate, palmoplantar and inverse psoriasis are more common in children than in adults.[4] Napkin psoriasis accounts for 40–50% of cases in less than two years and nail involvement occurs in 20–40% patients.[5] Psoriatic arthritis and pustular psoriasis are uncommon in children.[6] The paediatric population requires an early intervention due to the severe impact on quality of life caused by poor social interaction and parental anxiety.

A. **Systemic therapies:** None of the agents is approved for childhood psoriasis; however, enough safety and efficacy data are available. Initiation of systemic therapy should be critically thought of keeping in mind the risk versus

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benefit.[7] The dose and common adverse effects are discussed in Table 1.

Methotrexate: It is the most used agent in moderate to severe childhood psoriasis including psoriatic arthritis and pustular psoriasis with a favourable safety profile. The dose is 0.3 mg/kg/week. There is no consensus regarding the total treatment duration; however, gradual tapering after 2–3 months of sustained remission is advised. Giving a test dose of 1.25–5 mg is recommended. Liver biopsy is rarely indicated in children and dose adjustment may be required in renal dysfunction. Due to higher bone marrow reserve, haematological complications are less in children.[7]

Cyclosporine: It is used for the rapid control of severe psoriasis. Children require higher dosages due to reduced absorption and increased clearance. It should be initiated at 4–5 mg/kg/day and reduced subsequently to the lowest effective dose after disease control. Gradual tapering and combination with another safer agent for long-term treatment along with blood pressure monitoring at every visit is advised.[7] It has also been used in infantile pustular psoriasis at 1 mg/kg/d.[8] Long-term use is best avoided especially with present or previous PUVA treatment, due to the risk of non-melanoma skin cancers and lymphoproliferative malignancies. Live vaccines are contraindicated during its use.

Retinoids: Acitretin has an anti-inflammatory action and regulates keratinocyte maturation and turnover. It is most efficacious in pustular, palmoplantar and guttate psoriasis, even in very young children (≥6 weeks) with maximal effect seen in 2–3 months except pustular psoriasis which responds within 1–3 weeks.[9,10] Isotretinoin may be used in adolescent females due to a longer half-life of acitretin.[11] Long-term high dose use may cause bone abnormalities which are unusual at lower doses (<1 mg/kg/d) and/or short duration. No consensus exists regarding bone monitoring; however, periodic radiography is advised in long-term use or if symptomatic (bone/joint/back pain, myalgia, sensory loss in hands/feet). Concomitant vitamin A administration >5000 IU/d must be avoided.

Apremilast: Limited data restricted to a phase-2 trial showing good efficacy and safety profile is available. A weight-based dosing is preferred with 20–30 mg twice daily in ≥6 years children.[12]

Tofacitinib: Validated larger-multicentre trials are lacking. A recent open-label trial found 5 mg twice daily dose to be safer and effective without any major side effects.[13]

B. Biologics: Etanercept, adalimumab, secukinumab, ixekizumab and ustekinumab are approved for moderate-to-severe childhood plaque psoriasis. Off-label indications include pustular and erythrodermic psoriasis. Data is lacking regarding its use in nail, scalp and palmoplantar psoriasis.[14–17] The dose and approval are mentioned in Table 2.

Pregnancy: Pregnancy is marked by complex hormone-mediated immunosuppression where the maternal immune

Table 1: Systemic agents used in childhood psoriasis

Drug	Dose	Important side effects	Remarks
Methotrexate	0.2–0.3 mg/kg/week	Haematological and hepatotoxicity	Less risk of haematological and hepatotoxicity
Cyclosporine	2–5 mg/kg/d in two divided doses	Nausea, hypertrichosis, more common than hypertension and nephrotoxicity	Higher dosage required Live vaccines contraindicated; Phototherapy should not be used in combination with CsA
Acitretin	0.1 to 1 mg/kg/d	Dryness, dyslipidaemia, epiphyseal closure	Isotretinoin - substitute in female adolescents
Apremilast	Weight >35 kg – 20 or 30 mg twice daily >15 kg – 20 mg twice daily	Hypersensitivity, gastrointestinal disturbance	Less data available, age more than 6 years only
Tofacitinib	5 mg twice daily	Nasopharyngitis, upper respiratory tract infections, headache, GIT disturbance	Age ≥8 years No relation with food

Table 2: Biologics in childhood psoriasis

Drug	FDA approved	Dose	Side effects
Etanercept	≥4 years	0.8 mg/kg/week (max 50 mg/week)	Injection site reactions, hypersensitivity, infection reactivation of chronic infection
Adalimumab	≥4 years (EMA approved; not approved by FDA)	0.4–0.8 mg/kg alternate weeks	
Secukinumab	≥6 years	75 mg for <50 kg; 150–300 mg for ≥50 kg	Infections (esp. candida), Inflammatory bowel disease flare
Ixekizumab	≥6 years	40 mg at 0 week and 20 mg subsequently every 4 weeks for <25 kg	
Ustekinumab	≥12 years	0.75 mg/kg at 0, 4, 16 weeks and every 12 weeks thereafter	Hypersensitivity, infections

system shifts from a Th1 response to a Th2 response. The course of psoriasis in pregnancy is unpredictable; however, approximately 55% patients improve, 23% worsen and the rest remain static. Pregnancy may also trigger psoriatic arthritis in the postpartum period in 30–40% cases.[18–19] The pregnancy outcome may be worse and there is an increased incidence of preterm birth, low birth weight, recurrent miscarriage and an increase in caesarean delivery.[20] Foetal risks are dependent on maternal disease activity. The treatment of severe psoriasis in pregnancy is challenging as drugs used in pregnancy create a sense of fear, primarily due to the unknown effect on developing organs of the foetus. The clinical scenarios which may be encountered and require treatment are as follows:

A. Unplanned pregnancy – When a patient has unplanned conception while being on systemic anti-psoriatic treatment, the treatment should be stopped. Patients should be counselled regarding the risk and referred to an obstetrician for further management. Methotrexate and acitretin being teratogenic are incompatible with pregnancy while cyclosporine and apremilast are compatible.[21] Most biologics have a favourable pregnancy outcome and risk versus benefit should be discussed with parents.[22]

B. Planning pregnancy: Couples planning a family should plan pregnancy when maternal psoriasis is under good control. The treatment should be switched to topical and narrow band ultraviolet B treatment when pregnancy is planned. Narrow band ultraviolet B can degrade folic acid and should be supplemented to prevent the risk of neural tube defects.[22]

C. Onset of disease/flare during pregnancy: Systemic treatment may be required in patients with new onset severe psoriasis such as generalised pustular psoriasis, erythrodermic psoriasis or flare of pre-existing disease. The patients with stable chronic plaque psoriasis may be managed with topical therapy and narrow band ultraviolet B. Cyclosporine may be used in case of unstable disease or in those not responding to first-line management. Generalised pustular psoriasis of pregnancy is a challenging condition to treat, where cyclosporine and oral steroids alone or in combination can be used for its management.[23] Infliximab and secukinumab has also been used successfully.[24,25]

Foetal exposure to biologics is directly proportional to the transport of immunoglobulin across the placenta. During the first trimester, the foetal immunoglobulin levels are low whereas in the third trimester, these levels are almost equal to maternal levels. This increased transplacental transfer of biologics in late pregnancy may result in impaired immune response in the new-born, thereby warranting cessation of biologics before term and avoiding live vaccination to the infant for the first six months. TNF alpha inhibitors are generally considered safe in the first half of pregnancy.[26] Certolizumab pegol is a pegylated antigen-binding fragment (Fab) antibody that lacks an Fc region and cannot be actively transported across the placenta by the FcRn receptor. It is considered safe for use in pregnant women.[27] The safety of other biologics in pregnancy is not established and should be used only after careful risk–benefit analysis. Systemic and biologics drugs in pregnancy are discussed in Tables 3 and 4.

Lactation: Mammary epithelial cells form a semipermeable membrane. The intercellular spaces are large during the first week (colostral phase) allowing immunoglobulins to pass through. After one week, molecules less than 200 Daltons can pass through the intercellular space and larger molecules through diffusion. The data on apremilast and acitretin are scant and are not advisable in nursing mothers. Methotrexate has low risk to foetus and can be used during lactation. Withholding breastfeeding for 24 hours after weekly doses of methotrexate may decrease infant dose by 40%.[28] Cyclosporine levels in breast milk vary in various case reports. Expert guidelines suggest cyclosporine to be safe during breast feeding; however, the child should be monitored closely when the lactating mother is on cyclosporine.[29] Large protein molecules such as biologics are secreted in breast milk in very small quantity and are also destroyed in the gastrointestinal system of the infant. Most prescribing information warns against breastfeeding but overall, it appears that biologics are compatible with lactation. Very low levels of TNF alpha inhibitors can be detected in breast milk

Table 3: Systemic drugs in pregnancy

Drugs	Pregnancy category	Effects	Role in treatment	Unplanned pregnancy
Methotrexate	**X**	Miscarriage; congenital malformation	Stop 3 months prior to conception	Stop immediately; start folic acid supplements Refer to OBG
Cyclosporine	**C**	Low birth weight; preterm delivery; gestational diabetes; hypertension	Useful, if benefit outweighs the risk	Regular follow-up by OBG
Acitretin	**X**	Major malformation – retinoic acid embryopathy (CNS, heart);	Stop 3 years prior to conception	Stop immediately; Refer to OBG
Apremilast	**C**	Not enough data; low birth weight		Not enough data; low birth weight Referral to OBG

OBG – obstetrics and gynaecology

Table 4: Biologics in pregnancy

Biologics	Pregnancy category	Trimester	Remarks
Adalimumab	B	Recommended up to 28 weeks	No increased risk of low birth weight or congenital malformation
Etanercept	B	Can be given up to maximum 32 weeks	
Infliximab	B	Can be given up to maximum 20 weeks	Higher risk of spontaneous abortion and elective termination Avoid live vaccines for six months Unplanned pregnancy – reassure and regular follow-up
Certolizumab pegol	B	Safe in all trimesters	
Ustekinumab	B	Not recommended	Limited data No adverse maternal and foetal outcome reported
Secukinumab	B	Not recommended	Limited data No embryotoxicity in animals No adverse maternal or foetal outcome in limited reports
Guselkumab	B	Not recommended	Limited data available
Brodalumab, Ixekizumab, Tildrakizumab, Risenkizumab	Not assigned	Not recommended	Limited data available

Table 5: Systemic agents and biologics during lactation

Drug	Risk reduction	Remarks
Methotrexate	Withhold breast feeding for 24 hours after the dose	Safe for use
Cyclosporine	Lowest effective dose	Most reported data – safe in breastfed infants
Acitretin	Stop breast feeding	Limited data; not advisable
Apremilast	Stop breast feeding	Limited data; not advisable
Etanercept Adalimumab Infliximab Certolizumab	Minimum effective dose	Monitor for infections
Secukinumab, Ustekinumab, Brodalumab, Tildrakizumab, Risankizumab, Guselkumab	Insufficient data	Not advisable

and are considered safer. No specific data are available on the safety of breastfeeding and use of other biologic agents such as ixekizumab, ustekinumab and secukinumab currently and their use is not advisable. Mother and infant should be followed carefully when mother is on biologics.[30,31] Details are discussed in Table 5.

Systemic treatment in elderly: World Health Organization defines elderly as individuals above 65 years of age. Patients of age >65 years now represent an increasing proportion of psoriasis population with 15% of them having moderate to severe disease.[32] Psoriasis in this age group is difficult to manage due to factors including but not limited to presence of comorbidities, immunosenescence, polypharmacy and drug interaction, poor cognition level, lack of studies in this age group, frequent contraindications to systemic therapy, increased risk of infection and cancer vulnerability.[33] Phototherapy is also difficult to administer as it requires frequent visits and adequate patient mobility making the options limited for the treating physician.[34] With increasing age, the pharmacokinetic profile of many individuals undergo marked impairment due to limitation of absorption potential, decreased hepatic metabolic capacity and renal impairment. Hence, there will be an increased risk of potential interactions and adverse hepatic and renal outcomes. The systemic therapy and biologics may alter the immune status of a patient who is already having immunosenescence making the patient more vulnerable to serious infections such as latent tuberculosis and hepatitis B, hence making the treating physician more hesitant in initiating systemic therapy [Table 6].[35,36]

A. Systemic therapy:

Methotrexate: Lower dose of methotrexate should be used in the elderly as they are more susceptible to myelosuppression due to poor bone marrow reserve, coexisting renal impairment and folate depletion. Other antifolate medicines should be avoided or used with caution due to their synergistic adverse effects.[37]

Cyclosporin: Nephrotoxicity is a major adverse effect of cyclosporine. Elderly patients have often reduced renal function and hence dosing might be a challenge in this age group. Any concurrent use of nephrotoxic drugs should be avoided.[38] Since the drug is metabolised by Cytochrome P450 (CYP) 3A4, several drugs including but not limited to fluconazole, diltiazem, verapamil, phenytoin, carbamazepine, nicardipine and cotrimoxazole can have significant interactions. Adverse reaction rates are higher in cyclosporine as compared to methotrexate. The drug should be used with caution and frequent follow-ups in the elderly.[36,39]

Acitretin: The main advantage in the elderly is its lack of immunosuppressant action and the treating physician is devoid of the fear of teratogenicity while treating women of this age group. However, it is known to cause xerosis which is a major adverse effect in this age group. Acitretin is also known to alter liver enzymes and lipid levels and hence a stringent follow-up is required in case it is used.[40] Moreover, lower dose of acitretin has been shown to be effective in elderly patients as compared to their younger counterparts. It should be avoided in cases of hepatic or renal impairment.[41]

Apremilast: It is a newer phosphodiesterase-4 inhibitor which is effective, well tolerated and a convenient treatment option. No significant difference in terms of efficacy or safety profile was noted in the geriatric population as compared to younger population in various studies.[42] According to S3 guidelines, no dosage modification is required in the elderly population.[43] The pharmacokinetic exposure of apremilast is unaffected by mild to moderate renal impairment.[44] Table 5 summarises the systemic and biologic drugs in elderly patients with psoriasis.

Table 6: Systemic and biological drugs in elderly patients

Drug	Important points	Monitor
Methotrexate	Caution – Concomitant NSAID; Higher risk of bone marrow suppression and hepatotoxicity; Use with caution with folate antagonists; Contraindicated with hepatic or kidney impairment	CBC LFT RFT
Cyclosporine	Use with caution; nephrotoxicity; dyslipidaemia; hypertension	BP RFT Lipid profile
Acitretin	Safe	LFT Lipid profile
Apremilast	Presumably safe, data are less Should be tried in elderly patients	
Etanercept, adalimumab, infliximab	As effective as younger patients The risk of serious adverse events is more Higher rate of discontinuation Adverse events and discontinuation are less as compared to conventional systemic agents Etanercept has better safety profile and infliximab has minimum studies with worse safety profile	
Secukinumab	As effective as younger patients; the risk of discontinuation and adverse effect is more in the elderly	
Ustekinumab, Ixekizumab	Drug survival is the same as younger patients	
Guselkumab, Tildrakizumab, Risankizumab	Safety and efficacy – similar to younger patients	

Table 7: Systemic and biologics drugs and male fertility

Drug	Fertility	Teratogenicity	Remarks
Methotrexate	Conflicting studies, decreases sperm count	No conclusive data	Stop 3 months before conception Unplanned conception – no harm in continuation
Acitretin	No effect	None reported	Low risk, can be continued
Apremilast	No effect	None reported	Appears to be safe
Cyclosporine	Decreases male fertility in dose more than 4 mg/Kg	None reported	Appears to be safe
TNF-alpha inhibitors	May improve sperm quality. No need to stop	No risk	Safe
IL-17 inhibitors – Secukinumab, ixekizumab and brodalumab	No risk	No risk	Continue as per AAD – NPF guidelines According to the Australasian Psoriasis collaboration Secukinumab to be stopped 19 weeks prior to conception Ixekizumab to be stopped 9 weeks prior to conception
Ustekinumab	No risk	No risk	Continue as per AAD – NPF guidelines; Stop 15 weeks prior to conception as per Australian psoriasis collaboration
Tildrakizumab, Risankizumab, Guselkumab	Data scant	Data scant	No adverse effect in animal studies

B. Biologic therapy

TNF-alpha inhibitors: Among biologics, TNF-alpha inhibitors have been extensively used in the elderly. There is higher risk of infection in this age group which may sometimes prove fatal and hence, a good pre-biologic workup, immunisation and regular follow-up are required. In a study by Chiricozzi *et al*., out of 16 elderly and 101 young patients treated with adalimumab for psoriasis, the efficacy and adverse effect profile was found to be the same in both age groups. Haemorrhagic cystitis and Epstein–Barr virus infection was found to be unique in the elderly group.[45] Menter *et al*. compared 54 elderly patients with 760 young patients taking adalimumab for psoriasis and found nominal decreased efficacy in the elderly age group.[46] Militello *et al*. compared the safety and efficacy of etanercept between 77 elderly and 1158 young patients and found similar efficacy in both groups with higher adverse effects (AEs) in the elderly age group.[47] Esposito *et al*. also reported higher adverse effects with both adalimumab and etanercept in the geriatric population with 15 out of 61 in the etanercept group and 11 out of 28 in the adalimumab group withdrawing with higher adverse effects [Table 7].[48]

IL 17 inhibitors: Secukinumab is a commonly used biologic in the elderly age group. Korber *et al*. compared 67 elderly patients and 841 young patients on secukinumab and found similar efficacy in both age groups in terms of PASI 75, 90 and 100. However, the rate of adverse effect was more in the elderly and so was the rate of discontinuation.[49] A limited number of studies are available on ixekizumab and brodalumab in the elderly to comment on their safety and efficacy.

IL 12/23 inhibitors: Ustekinumab is the only FDA-approved biologic in this group. Megna *et al*. and Hayashi *et al*. studied ustekinumab in 22 and 24 elderly patients of psoriasis and were found to have slower reduction in PASI 75 as compared to other biologics. However, no serious adverse effect and discontinuation of therapy was noted.[50,51]

Male fertility: The effect of psoriasis on male fertility is not understood completely. In inflammatory disease states like psoriasis, germ cells produce TNF-alpha in higher amounts that can reduce male fertility. Heightened inflammation has also been shown to decrease the amount of testosterone and sex binding hormone globulin (SHBG) in males which can lead to erectile dysfunction and loss of libido.[52–54] These organic causes in conjunction with psychological causes can compound sexual dysfunction in psoriatic individuals. The presence of systemic drugs in semen can also result in fear of teratogenicity. Therefore, advice regarding initiation of any treatment modality should factor in the alteration in fertility and teratogenicity.

a. Methotrexate: Methotrexate is a highly teratogenic drug, lethal to the developing embryos and is often used as an abortifacient. Spermatogenesis being a high cell turnover process is also negatively affected by methotrexate in the form of lowered sperm count. Although no teratogenic potential of the drug has been seen in males taking methotrexate at the time of conception, a three month washout period (duration of spermatogenesis) is still recommended in men with psoriasis planning conception. Fear of teratogenicity should be alleviated in case of unplanned pregnancy.[55,56]

b. Acitretin: It is a second-generation retinoid and foetal exposure is characterised by the classical retinoid syndrome which includes craniofacial, cardiac and CNS abnormalities. Out of the 13 pregnancies studied, where the father was taking acitretin at the time of conception only one was associated with foetal malformation and that too was not consistent with retinoid-induced-embryopathy.[57] The equivalent dose of acitretin transferred to the semen was 1/200,000 of a 25 mg capsule. Therefore, it is highly unlikely that acitretin exposure from semen at the time of conception will lead to any embryopathy as the critical period for organogenesis occurs 4–6 weeks later. The guidelines suggest that ongoing exposure to acitretin in males at the time of conception is low risk, though barrier contraceptives should be used post conception.

c. Apremilast: Though it is a thalidomide analogue; it lacks similar teratogenicity due to the absence of glutarimide moiety which is the culprit receptor behind teratogenicity. In animal studies, no teratogenicity and effect on fertility was seen, though no human studies outlining safety with respect to male fertility exist.[58]

d. Cyclosporine: The studies on rat testes with cyclosporine exposure showed decreased testosterone levels, increased gonadotrophin levels and overall decrease in spermatogenic process.[59] These effects were dose dependent, occurred two weeks after administration and resolved on stopping the drug. However, data from human studies are mixed. Out of nine post-kidney transplant patients who were administered cyclosporine, eight had no relevant sperm abnormality and partners of three of them conceived.[60] However, impregnation studies done in 26 men with renal transplant have shown significant differences in sperm motility and sperm head deformity at higher doses (4.1–6 mg/kg) of cyclosporine.[61]

e. Biologicals: They are large protein molecules and are not secreted in semen.

   i. TNF-alpha inhibitors: As psoriasis is associated with an inflammatory milieu in the genital tract, TNF alpha inhibitors are thought to be beneficial in psoriatic patients planning conception. In a prospective study of ten patients of psoriasis who were given TNF alpha inhibitors, no significant differences in sperm count or motility were noted.[62]

ii. IL-17 inhibitors: Currently, there is insufficient data exploring the effect of this group on male fertility. Ixekizumab also has been shown to have no effect on sperm in sexually mature cynomolgus monkeys.[63]

Conclusion

The systemic treatment of psoriasis is rapidly expanding, and many conventional agents, small molecules and biologics have been approved in adults. The treatment of psoriasis in the special population is challenging due to lack of adequate data and approvals. This population also deserves optimum management of severe psoriasis as per the best available evidence, keeping in mind the special therapeutic situation.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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