Hot Topics in Dermatology

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Methotrexate versus Biologic Agents in Pediatric Psoriasis: Not Yet the Time to Move-On

A recent study by Bronckers *et al*.[1] compared methotrexate and biologic agents in children from North America and Europe with plaque psoriasis. This retrospective study analyzed 234 children with moderate-to-severe psoriasis who received at least 3 months of either therapy. The mean age at the start of systemic therapy was 11.6 years in the methotrexate-only group and 13.3 years in the biologic agent-only group. Treatment response was assessed using Psoriasis Area and Severity Index (PASI) and Physician Global Assessment (PGA) at the baseline and within the next 6 months. Methotrexate was used in 69.7%, while biologics were administered to 20.1% of the patients. In 10.2% of patients, two treatment modalities were given sequentially (methotrexate followed by biologics in all but one patient). Patients receiving methotrexate were younger at treatment initiation and had a shorter interval between diagnosis and initiation of systemic therapy. Etanercept was the most frequently used biologic (in 73.2% of the patients who received biologics). More than 75% reduction in PASI (PASI75) was achieved in 40% of the patients on methotrexate and 71.4% of the patients on biologics. For those who were prescribed single-agent methotrexate treatment, the mean start and maximum dose of methotrexate were 0.28 mg/kg and 0.36 mg/kg, respectively. The mean start and maximum dose were 0.24 mg/kg and 0.29 mg/kg, respectively, in those who received methotrexate as sequential therapy. Clear or almost clear PGA was achieved in 35.6% of the patients who received methotrexate and 48.6% of the patients on biologic agents. Decreased mean PASI and PGA scores were associated with biologics more than with methotrexate (PASI effect: −3.13 and PGA effect: −0.31). After 5 years of use, drug survival rates were 35.9% and 57.1% for methotrexate and biologics, respectively. Better confounder-corrected drug survival was associated with biologics than methotrexate (hazard ratio [HR]: 2.23). Discontinuation owing to the lack of response was comparable with both the modalities (HR: 1.64).

Comments

Psoriasis is a chronic, immune-mediated, polygenic skin disorder. The prevalence of the disease in the pediatric population is 0%–1.37%.[2] The most common variant seen in children is chronic plaque psoriasis followed by guttate and pustular psoriasis. The disease can be managed with topical medications in most patients, but those with moderate-to-severe disease require systemic agents. Several treatment options are available, most of them lacking approval and efficacy data in this population. Methotrexate is approved for the treatment of chronic plaque psoriasis in patients aged more than 18 years. It is the most commonly used systemic immunosuppressant in the pediatric population.[3] Several biologics are also available in India now, but the clinical experience with these agents is limited. Etanercept and ustekinumab are approved by the Food and Drug Administration in children over 4 and 12 years of age, respectively, while adalimumab is approved by the European Medical Association in children over 4 years of age. In a randomized, double-blinded trial, methotrexate was found to be inferior to adalimumab for severe chronic plaque psoriasis in children.[4] Rates of infection were similar in two groups in this study. Similar to the findings of Bronckers *et al*.,[1] PASI75 was achieved in only 40% of children in the methotrexate group, while response rates were much higher with biologics. An important limitation of both these studies was that a lower dose of methotrexate was used (average-0.15 mg/kg) as compared to real-world setting. Several studies have documented impairment of quality of life (QoL) in pediatric psoriasis, and the maximum improvement in QoL is seen with treatment modalities able to

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achieve PASI90.[5] Considering the excellent response rates as well as paucity of evidence-based treatment options in pediatric psoriasis, biologics like etanercept may be a welcome addition to our therapeutic armamentarium. Even though biologics require lesser monitoring and have fewer adverse effects, faster onset of action, and higher response rates, methotrexate is far from being dismissed as a drug of the past just yet. It offers several advantages including a long history of use, oral formulation, low cost, and easy availability, all of which are important in our setting. It might be prudent to await further prospective studies with larger sample size and higher methotrexate doses before biologics can be unequivocally placed above methotrexate in the therapeutic ladder for pediatric psoriasis.

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Conflicts of interest

There are no conflicts of interest.

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Treatment of Head Lice Infestation: Old is Gold

Head lice infestation (pediculosis capitis) is a common problem that affects people of all ages worldwide. Several treatment options are available, and the efficacy of various agents has to be balanced against the potential toxicity. Topical neurotoxic pediculicides and occlusive agents are two major classes of therapy. Increasing resistance to insecticides has been observed, clinical efficacy of such agents falling below 50% since 2004. The occlusive agents are broadly of two types – natural oils like coconut oil and synthetic compounds like silicone oil. Other neurotoxic chemicals like eucalyptus oil or nonneurotoxic chemicals like benzyl alcohol or surfactant may be added to the occlusive agents. A systematic review and meta-analysis by Flores-Genuino *et al*.[1] compared these agents in the treatment of head lice infestation. The authors included randomized controlled trials that compared neurotoxic and occlusive agents in patients with head lice infestation. Primary outcomes assessed were the final cure rate and adverse effects, while secondary outcomes included initial cure rate (after one treatment) and quality-of-life scores. A total of 17 studies were included in systematic review of which 16 studies were included in meta-analysis. The risk of bias was deemed to be moderate and was mainly due to the lack of blinding. Occlusive agents had a higher final cure rate (70%) as compared to neurotoxic agents (61%) ($P < 0.00001$). *Post hoc* analysis suggested that the better efficacy was seen in studies that used synthetic combination occlusive agents or where comparator neurotoxic agent had low cure rate. Although incidence of adverse effects was lesser with the former (3.1% for occlusive agents vs. 7.3% for neurotoxic agents), the difference was not found to be statistically significant ($P = 0.27$). Initial cure rate between the two groups were similar, and validated patient satisfaction questionnaires were not used in any of the studies except one. The authors concluded that occlusive agents may be superior to or as efficacious as neurotoxic pediculicides in treatment of head lice infestation.

Comment

Despite the concerns regarding toxicity, increasing resistance, and prolonged chemical persistence in environment, pediculicides remain the mainstay of therapy for head lice infestations. Alternative, nonpesticidal agents such as petroleum jelly, olive oil, mayonnaise, pomade, and dimeticone are generally considered unsubstantiated agents lacking high-quality evidence. They act by slowing the movement of lice and aid combing them out of the hair. Although not directly lethal to the lice, they can block the excretory system of lice or may cause death by suffocation. Immersion of lice in dimeticone has been shown to result in complete obstruction of the respiratory system within 30 min leading to death of 100% of the lice.[2] The excellent ovicidal activity has been observed with a combination of essential oils.[3] These are especially beneficial in regions where insensitivity to neurotoxic pediculicides has been recorded. Since both the classes of agents require multiple applications, occlusive agents might be a welcome addition to our therapeutic arsenal for head lice, with the added advantage of being nontoxic and having no risk of resistance. This study is relevant as it adds high-quality evidence supporting the usage of

occlusive agents in head lice infestation, although the authors do comment that the efficacy may be limited to studies using combination products and to patients who have already developed resistance to neurotoxic pediculicides. The American Academy of Pediatrics still recommends pyrethroids as the first line for treatment of pediculosis capitis in areas where widespread resistance to these agents is not reported.[4] Data on the prevalence of pediculicide resistance are not available from India. The final choice of treatment should take into account availability, cost, and convenience as well as efficacy and tolerability.

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Conflicts of interest

There are no conflicts of interest.

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Ultraviolet Light Exposure is Associated with Reduced Risk of Eczema Development

The role of Vitamin D in pathogenesis of atopic dermatitis (AD) has been a subject of research for long. Suboptimal sun exposure at higher altitudes has been hypothesized to be a causative factor in higher prevalence of allergic diseases in these regions. A double-blinded, randomized controlled study from Australia by Rueter *et al*.[1] aimed to determine the effects of Vitamin D supplementation in infancy on eczema and immune development. The study recruited 195 neonates having a first-degree relative with atopy who were randomly assigned to receive either Vitamin D supplementation (400 U/day) or placebo drops (coconut and palm kernel oil) till 6 months of age. Trial product was not given if the infant was consuming 1000 mL/day of Vitamin D-fortified infant formula. Infants whose mother had smoked during pregnancy, whose mother had autoimmune disease or immunodeficiency, or those with very high or very low maternal 25-hydroxyvitamin D level were excluded from the study. Since ultraviolet (UV) light exposure is the predominant natural source of Vitamin D and has independent immunomodulatory functions, the UV light exposure during the first 3 months of life was measured using a UV dosimeter in a subset of the infants (n = 86). Eczema, wheeze, and immune function were assessed at 6 months of age and Vitamin D levels were measured at 3 and 6 months of age. Significantly higher levels of Vitamin D were noted in the intervention group both at 3 and 6 months ($P < 0.01$ and $P = 0.02$, respectively). However, this did not translate into clinical improvement as the incidence of eczema at 6 months did not differ between the two groups ($P = 0.68$). The somewhat riveting finding in this study was that infants who developed eczema had a lower cumulative UV exposure (median-555 J/m$^{2)}$ as compared to those who did not (median – 998 J/m^2), P =0.02. UV light exposure was also found to be inversely proportional to interleukin-2, granulocyte-macrophage colony-stimulating factor, and eotaxin levels.

Comments

AD is a chronic inflammatory skin disease with a complex pathogenesis involving the role of genetics, impaired cutaneous barrier, immune dysregulation, and environmental factors. Since Vitamin D has a role in both maintenance of skin barrier and immune function, the role of Vitamin D in AD has long been theorized. A recent meta-analysis found that Vitamin D supplementation resulted in a clinically meaningful reduction in the severity of AD.[2] The investigators of this study put forward the hypothesis that Vitamin D may in addition be useful in prevention of allergic disease and this randomized controlled trial was designed to assess this relationship. The usage of dosimeters to assess UV light exposure is a novel approach. The study design had several strengths, including randomized allocation, blinding of participants, study personnel as well as outcome assessors, intention-to-treat analysis with appropriate attrition reporting. Although Vitamin D did not prove to be beneficial, this is an important neutral study that paves the way for further trials and meta-analyses on this topic. However, a calculation of sample size and power was not provided by the authors. The association between UV light exposure and incidence of eczema, which has been stressed on throughout the article, was found only on *post hoc* analysis and was obtained from exploratory rather than randomized data. Further analysis to show that association between eczema and UV light exposure was independent of Vitamin D supplementation might have been a useful addition

to the study. The follow-up duration might not have been adequate to assess the development of atopy. The findings of this study encourage the practice of exposing infants to the sun, a more economical, feasible, and culturally acceptable practice as compared to Vitamin D supplementation. Larger studies with better study design and longer follow-up duration to explore the association between UV light exposure in neonatal period/infancy and development of eczema subsequently will be useful.

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Conflicts of interest

There are no conflicts of interest.

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Characteristics of Alopecia Areata in Children with Disease Onset below 4 Years of Age

A recent retrospective review by Rangu *et al*.[1] examined the epidemiology of alopecia areata (AA) in children aged 8 years or younger with disease onset under 4 years of age. Several epidemiological studies have been conducted on AA, but those highlighting the natural history of the disease in young children are rare. This study analyzed 125 children with disease onset before 4 years of age and those who had at least one follow-up visit. Patients on therapies that might have altered the natural course of the disease (systemic therapy or topical Janus kinase inhibitors) were excluded from the study. The data extracted included age, gender, growth parameters, ethnicity, age of onset, subtype of disease, past medical history, family history of AA, family history of thyroid or any autoimmune disease, and severity of alopecia tool (SALT) score. SALT scores were again recorded at 3–6-month follow-up, at 1-year follow-up, and 2 + year follow-up. A female predominance was observed in the study population (F: M ratio = 2.05:1). Majority of children (86.4%) had disease onset between 2 and 4 years of age. Among the disease subtype at onset, most common was AA in 72% of the patients, while alopecia totalis (AT) and alopecia universalis (AU) were diagnosed in 8.8% and 19.2% of the cases, respectively. A higher prevalence of AT/AU was seen in boys as compared to girls (39% in boys vs. 22% in girls). The most common comorbidity was atopic dermatitis (AD), seen in 40.8% of the cases. Other autoimmune conditions such as vitiligo, type 1 diabetes mellitus, and celiac disease were seen in 4% of the cases. Family history of AA was present in 28% of the cases, family history of autoimmune disease was positive in 27.2% of the cases, and 32% of the cases had a family member with hypothyroidism. Patients with mild alopecia (SALT u pto 24%) at presentation continued to have mild, patchy disease, while those with high SALT scores (SALT 50%–74%, 75%–99% and 100%) initially had a greater likelihood of high SALT scores at follow-up visits. Odds of having higher SALT scores increased with each subsequent visit (odds ratio: 1.44 at 3–6 months, 1.87 at 1 year, and 2.06 at 2 + years vs. initial visit).

Comments

AA is a common dermatosis that can affect all age groups but is more prevalent in children. Several studies have reported overall epidemiology of the disease, but clinical and epidemiological data pertaining specifically to pediatric age group are limited. A previous study from India analyzed 201 children with AA under 16 years of age.[2] Onset of disease before 5 years of age was seen in 67 cases (33.3%) and was found to be associated with higher disease severity. One of the largest population-based studies on AA found AD to be associated in only 5% of the total cases but noted a higher association with AD in children under 10 years of age while finding no association between autoimmune disease and AA in this age group.[3]

Study by Rangu *et al*.[1] is unique in that it focusses on disease pattern only in children with disease onset below 4 years of age, an aspect which has not been explored before. The higher overall prevalence in girls and more severe disease in boys have been reported in several previous studies. A rising trend in SALT scores was observed with a subsequent follow-up visit, which might either indicate an increase in disease severity over time or better adherence to follow-up in patients with more severe disease. Limitation of the study included retrospective design and low follow-up percentage: 2-year follow-up data were available in only 28 of 125 cases. Analysis of the association of disease severity with comorbid conditions and clinical characteristics could have been a useful addition. Similar studies in an Indian cohort will be useful for prognostication of the disease, in counseling the parents, and to anticipate the need for a more aggressive therapy.

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Conflicts of interest

There are no conflicts of interest.

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