UPDATE OF ATOPIC DERMATITIS: WHAT’S NEW IN SYSTEMIC TREATMENT FOR CHILDREN WITH SEVERE AD

DERMATITA ATOPICĂ MODERAT – SEVERĂ LA COPII: NOUTĂȚI ÎN TERAPIA SISTEMICĂ

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Abstract

Atopic dermatitis affects more often the children than the adults and its prevalence is increasing in the last years, especially in the developed countries. In the cases of patients with moderate – severe atopic dermatitis, sometimes a systemic treatment is necessary in order to manage the disease. This article presents a synthesis of the recent data from the literature, regarding the safety and the efficacy of various systemic therapies for children with moderate – severe atopic dermatitis.

INTRODUCTION

Atopic dermatitis (AD) is a pruritic chronic inflammatory skin disease, which affects 10-20% of children and 1-3% of adults. The incidence of the condition is higher in the developed countries and it has been increasing in the last years (1). Children’s AD presents many differences compared to adults regarding clinical aspects, physiopathology and therapy management. Sometimes the topical therapy is not enough to manage the disease. Because AD affects more often the children, it is important to know the efficacy and safety of systemic treatment. The dermatologists are not always so confident when using systemic drugs as an alternative for children with AD unresponsive to topical therapy. More information about this subject can improve their experience and, in the same time, can increase their comfort when using systemic drugs for pediatric patients. The objective of this...
article is to offer a better knowledge regarding the use of systemic treatment in younger patients with moderate to severe AD. This article presents the news published in the past years in the literature concerning the safety and efficacy of systemic drugs in children with AD between 2 - 18 years old.

**IMMUNOSUPPRESSIVE THERAPY**

Severe and refractory AD has a significant impact upon QOL (quality of life) of the patient or the family and represents a real challenge for doctors. Immunosuppressive drugs could be an alternative choice for these cases, but their results depends on dosage, patient’s body surface area and the doctor’s experience. The age of patients, body mass and surface, general health and co morbidities play an important role in the evaluation of the clinical response.

1. Methotrexate (MTX) is mentioned in various studies and articles for its beneficial effects in adults with severe or refractory AD, but for children this type of data is few and limited. Thereby, in the European Journal of Paediatrics, a group of scientists from Egypt published the first randomized comparative study between MTX and cyclosporine in children with severe AD. 40 patients were included with ages between 7 - 14 years old, divided in 2 groups of 20. The first group received 7,5 mg/week of MTX and the second group 2,5 mg/kg/day of cyclosporine. After 12 weeks, the results showed a similar efficacy for both drugs - 50% improved and an equal reduction of severity scoring for atopic dermatitis (SCORAD) [2].

2. The efficacy of clinical response to azathioprine (AZT) was also observed in 12 children with severe atopic dermatitis. In this study side effects were evaluated and they included laboratory tests, such as thiopurine methyltransferase (TPMT) activity. The study demonstrated the importance of measuring TPMT activity repeatedly during the treatment in order to evaluate unresponsive patients or changes in response [3]. The European treatment of severe atopic eczema in children taskforce (TREAT) survey, published in the British Journal of Dermatology, concluded that cyclosporine (43%), oral corticosteroids (30,7%) and AZT (21,7%), should be the first-line treatment in children with severe AD [4].

3. In 2014, the American Academy of Dermatology published the Guidelines of care for the management of atopic dermatitis, which were divided in 4 parts. The third section was dedicated to the management and treatment of AD with phototherapy and systemic agents. The indications of systemic immunomodulators have been evaluated, in association with dosage regimens and treatment monitoring. Each systemic drug was presented for both categories of patients, adults and children with severe AD. Regarding the use of cyclosporine for children with severe AD, the authors of this guideline suggested that it is more suitable to use a continuous dosage, because it is associated with a higher efficacy in comparison with an intermittent use of the same drug. AZT was recommended to be used for children with severe AD, but also for cases with a significant impact upon QOL (quality of life) of patients or of their families. The recommendation was to regularly monitor the TPMT activity, according to the results of the guideline. The scientists suggested that pediatric patients with lower TPMT levels might have a better clinical response on a lower dosage, but, in the same time, they might be at a higher risk of myelosupression.

4. Mycophenolat mofetil (MM) is also an alternative systemic drug in children with severe AD, with a dosage that varies between 40- 50 mg/kg/day. The results showed a benefit for using MM in monotherapy, for children above 2 years old [5]. Besides that, in the same year - 2014 - a review on systemic treatment for patients with moderate-severe AD has been presented. In this case, the data was collected from 34 randomized controlled trials (RCTs), with strong arguments in the literature regarding the use of cyclosporine as a first-line treatment, but only for a short-term. The 2nd line was AZT, but with a lower comparative efficacy and MTX represented the 3rd line choice for the therapy [6]. Dermatologists who treat children with this kind of pathology should know more details about the risk of relaps after systemic treatment. In addition, in a retrospective study, cyclosporine was suggested to be an alternative for relapse risk reduction in pediatric patients with severe AD. This was the case only when it was used for a longer period of time at a lower dosage [7]. MTX was analysed in a 5-year retrospective study, in New Zealand, for children and also for adolescents. The results were in favour of using this drug in a lower-dose with a good safety and efficacy for children and adolescents [8].

**PROBIOTICS THERAPY**

Probiotics are living organisms, with beneficial effects on the patient’s health. During the time, the treatment with probiotics showed beneficial effects in various diseases, including AD. Modulation of the immune response, competitive inhibition of invading flora in the gut, modification of pathogenic toxins and host products and enhancement of epidermal barrier function represent some of the mechanisms of action of probiotics, which could influence the clinical response [9,10,11]. According to the published articles from the literature, probiotics like bifidobacteria, lactobacilli and enterococcus do not have adverse reactions and are recognized as being safe [12]. Regarding the efficacy of probiotics for patients with AD, the results are controversial. For pediatric patients, this therapy showed no beneficial effects [12].
In 2014, JEADV published a meta-analysis in probiotics, which showed a protective role of this therapy in prevention of AD (13). These contrary results demonstrate the necessity of future research and studies, for evaluation of the effects of probiotics on patients with AD. Probiotics have many effects on the immune system, especially upon T helper cells. Some of these effects are inhibition of TH2 and stimulation of TH1 (12) or upregulation of regulatory T cells and influence on T helper cytokine activation. Other effects of probiotics include modulation of intestinal flora and dropping the fermentation products, improvement of barrier function both in skin and mucosa, and reduction of adherence of Staphylococcus aureus. According to some authors (13), the uses of probiotics in AD have not been evaluated in large and homogenous trials and we cannot draw a conclusion this moment, although some patients benefit from this treatment.

CONCLUSIONS

In the past several years, many publications concluded that immunosuppressive therapy offers a great possibility of treatment for young patients with severe or unresponsive AD. These drugs can improve the clinical aspects of the disease and can increase QOL of patients and their families, when they are being used with a right dosage and adequately monitored. Cyclosporine is recommended as the first-line therapy for recalcitrant pediatric AD, it is well tolerated and it is associated with a decrease of relapse disease. The efficacy of the drug is similar for children and adults with severe AD, but the tolerability seems to be higher in children’s case (14). Hypertension and renal dysfunction are the most frequent adverse effects associated with the use of cyclosporin and they are usually reversible after drug discontinuation. These results represent a big advantage for doctors and their comfort using immunosuppressive drugs. For patients who cannot tolerate cyclosporine, AZT and MTX could be the alternative choice of refractory AD treatment. Otherwise, AZT was presented like an effective treatment for pediatric severe AD, with low important side effects (15). Gastro-intestinal symptoms, such as nausea, stomatitis and vomiting were the most common side effects for children treated with MTX (16). Prevention and treatment of AD with probiotics represents a new perspective therapy, of increasing interest in the last years for health care professionals. Their clinical effects depend on the type of bacteria, dosing regimen, delivery method and other host factors, such as age and diet (17). In the present, the data from the literature is contradictory and a possible cause could be the patient characteristics, dosage of probiotics, duration of supplementation, use of a single strain or a mixture of strains. Future studies and recommendations are needed to determine the clear indications and efficacy of probiotics for patients with AD.

BIBLIOGRAPHY