

Comparison of treatment standards in Atopic Dermatitis management across selected geographies prior to emerging targeted therapies onset

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ABSTRACT

Atopic Dermatitis (AD) is a chronic inflammatory disease persisting predominantly in the pediatric population. Treatment is generally supervised by various medical specialists, including primary care practitioners, allergists, and dermatologists. This divergence in disease management allows various therapeutic approaches to be administered to patients by supervised physicians. This article covers etiology of the disease and summarizes dermatologic treatment standards of selected countries binding prior to the registration of dupilumab by both the European Medicines Agency (EMA) and Federal Drug Administration (FDA) in 2017. Before recent development in targeted therapies (small molecules and biologic agents), standards in AD treatment remained unchanged for years with extensive similarities across a sample group of countries in particular geographic and economic regions. The spectrum of available and popular therapeutic options can be categorized into three dominating groups: non-pharmacologic, pharmacologic, and systemic interventions. Their prescription, in principle, was historically driven by disease severity and previous treatment history. However, advances in targeted therapies may change AD management guidelines and medical care standards.

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Introduction to Atopic Dermatitis

Atopic Dermatitis (AD), interchangeably called Atopic Eczema, is a chronic pruritic inflammatory disease commonly affecting children, and, to a lesser extent, adults. AD diagnoses are continuously on the rise, oscillating between 10% and 20% of the pediatric population. The condition develops predominantly in early childhood:

- In 45% of children, symptoms appear prior to 6 months of age;
- In 60% of patients, symptoms appear before reaching 1 year of age;
- In 30% of children diagnosed with AD, the disease will present itself before the age of 5; and
- In the remaining 10% of the population with AD, symptoms manifest between 6–20 years of age.

In the absence of a specific diagnostic laboratory marker, AD diagnosis is performed clinically, based on the patient's medical history, specific clinical symptoms, and exclusion of other non-inflammatory skin disorders¹. The most distinct features of the disease include pruritus, skin dryness, and other skin lesions such as serous exudate, excoriation, papules, and lichenification. Moreover, ~60% of children with

AD are predisposed to develop one or more atopic comorbidities such as asthma, allergic rhinitis, or food allergies. This phenomenon is termed “atopic march”, and its causes are being further researched. Although AD is not a life-threatening condition, it significantly lowers patients' quality-of-life and can lead to anxiety and depression².

The pathogenesis of AD is multifactorial, and presumably originates from the interplay of genetic, immunologic, environmental factors, infections causing dysfunctions of the skin barrier, and inflammation³. Additionally, structural disorders of certain proteins (i.e. filaggrin) and ceramides are relevant to the development of AD. An allergen stimulates dendritic cells of the skin, which triggers Th2 lymphocytes to release pro-inflammatory cytokines (IL-4, IL-5, and IL-13). High concentrations of cytokines activate serine proteases, causing further functional impairments of the skin barrier. Th1 lymphocytes are also involved in this pathogenic process at the chronic stage of AD. It is speculated that the Th17 and Th22 lymphocytes might also participate⁴.

The pruritus exacerbates AD and can trigger an itch/scratch cycle. The current focus of research is on biological therapy targeting interleukins IL-4/13 and IL-31 associated with pruritus. Treatment options for AD are outlined in greater detail below.

Management of Atopic Dermatitis

Standard of care

AD treatment is generally supervised by primary care practitioners as well as various medical specialists, including allergists and dermatologists, allowing for varied therapeutic approaches to be administered to patients by attending physicians. The treatment guidelines outlined below have been recommended by various dermatologic associations. The guidelines comparison has been focused on juxtaposing treatment standards of US and selected European countries representing various geographic and economic zones of Europe: Germany (Western Europe), Poland (Central Europe), and the Ukraine (Eastern Europe).

As depicted in [Table 1](#), treatment guidelines are, to a large extent, consistent across sampled countries. No significant disparities have been identified apart from the American Academy of Dermatology's (AAD) acknowledgment of emerging biological therapy. In general, topical corticosteroids (TCS) are indicated for first-line therapy to be followed by topical calcineurin inhibitors (TCI) as a second-line regimen. In cases of severe disease manifestations, more aggressive therapies are recommended, but often present a less favorable safety profile for patients. Moreover, it is estimated that more than 19% of patients with AD present resistance to TCS, and in the remaining population the "steroid phobia" is consistently growing and has reached ~50%. Noteworthy, the therapeutic options listed in [Table 1](#) appeared in below juxtaposition as they were cited in the respective guidelines at the time of this comparative analysis performance. Thus, it should be considered that certain options which have been recently registered in AD and are progressively entering the medical practice might not have made it to the listing at the time of analysis as they are in the process of paving their way into the treatment guidelines. For example, crisaborole recently approved by FDA is already indicated as the upcoming topical therapeutic. However, its registration status in the European Union is not concluded, therefore this substance is yet to be marked as the standard of care in respective guidelines⁵.

Another factor of relevance in terms of access to treatment is the reimbursement status of recommended therapeutic substances in countries with universal healthcare. In general, Western European countries offer comprehensive coverage for AD treatment. In the Central and Eastern European region, the national insurance systems reimburse only select options. For example, in Poland two TCSs in AD treatment are fully covered by the National Health Fund, while TCI is not. In the Ukraine, there is no reimbursement for any therapeutic option. Treatment costs often pose financial challenges and burdens for patients and their families, driving them to choose more affordable therapeutic options in management of this life-long condition.

The standards of treatment in other European countries remain aligned with European guidelines. Similar to national guidelines presented in [Table 1](#), the core of therapy in these countries is based on emollients, use of TCS and TCI, and, in the case of systemic treatment, immunosuppressants as well

as antihistamines. No biologics were authorized or reimbursed in Europe in AD treatment (as for mid-2017).

Exemplary targeted therapies investigated in atopic dermatitis management

As therapeutic needs of patients with AD are still widely unmet, and disorder prevalence is constantly growing, the search for new, effective, and safe solutions is welcome and gathering momentum. Current research and development indicate that the era of biological therapy is not only revolutionizing the oncology, but also having a great impact on other immune disorders such as AD, asthma, and psoriasis. The first evidence of a promising breakthrough surfaced in 2017 when the AAD endorsed the use of Dupilumab (Dupixent, Sanofi) in treatment of moderate-to-severe AD "not adequately controlled with topical prescription therapies or when those therapies are not advisable"⁶. Dupilumab is a human monoclonal antibody targeting IL-4/IL-13 for subcutaneous injections administered once a week. Dupixent was granted marketing authorization by EMA and FDA in 2017, and is now available within the European Union and US as a first immunotherapeutic agent in AD management.

Success of Dupilumab use in AD treatment potentially heralds the arrival of similar, new therapeutics. Clinical research dedicated to biologics in AD management is very active, and more studies are being registered in Europe and the US. For instance, Lebrizikumab and Tralokinumab, both targeting IL-13 in phase III trials, and fezakinumab, targeting IL-22 in the phase II trial. There are ongoing trials on Omalizumab (anti-IgE) among asthma and AD populations. Another Nemolizumab antibody is also being tested in clinical studies. This human monoclonal antibody targets the receptor for IL-31, a cytokine produced by active T lymphocytes, in response to IL-4, which promotes Th2-dependent inflammatory reaction and induces pruritus. Its application may extend to all conditions associated with itching. Promising results in the AD treatment also shows JAK inhibitors: tofacitinib, baricitinib, and abrocitinib investigated in III phase trials.

Conclusions

The intention of this article is to enable easy comparison of the standards of AD care across various countries of interest, representing diverse economic and geographic regions. This comparison exercise revealed that, despite various healthcare settings and financial potential due to a therapeutic plateau in the development of new therapies for AD management, the standards of care were widely comparable or overlapping. As immune mechanisms underlying inflammatory diseases are being more widely harnessed or modulated for treatment benefit, caregivers seek to replace standard therapeutic treatments with new targeted therapies. The revolution in AD treatment will first be realized in countries in good economic standing, as the cost of biologics may be out of reach for patients from less financially affluent countries.

Table 1. The summary of guidelines for AD treatment in the US, Europe, Poland, Germany, and Ukraine.

Selected treatment methods for AD	ETFAD/EADV ²			Polish guidelines ^{6,7}		German guidelines ⁸		Ukrainian guidelines ⁹	
	AAD	Basic therapy Basic therapy	Basic therapy Basic therapy	Not discussed	Basic therapy Basic therapy	Basic therapy Basic therapy	Not determined		
<i>Non-pharmacologic interventions</i>									
Bathing practices									
Moisturizers									
<i>Pharmacologic interventions</i>									
Topical pharmacotherapies									
Topical corticosteroids (TCS)	1st line treatment	Mild AD	Mild AD	1st line treatment	Short-term use; 1st line treatment	Short-term use; 1st line treatment	Not determined		
Topical calcineurin inhibitors (TCI)	2nd line treatment (i.a. tacrolimus, pimecrolimus)	Mild and moderate AD	Mild and moderate AD	2nd line treatment (not reimbursed)	2nd line treatment	2nd line treatment	Tacrolimus		
Wet wrap therapy	In combination with TCS for refractory AD	In combination with TCS for moderate AD	In combination with TCS for moderate AD	Alternative treatment	Discussed—in combination with TCS	Discussed—in combination with TCS	Not discussed		
Topical antimicrobials	To be avoided due to widespread antimicrobial resistance	Mild AD	Mild AD	Adjuvant therapy	In serious infection; Short-term use	In serious infection; Short-term use	Not determined		
Systemic therapy									
Phototherapy	In AD refractory to topical treatments	AD chronic phase in adults	AD chronic phase in adults	3rd line treatment	Adjuvant treatment	Adjuvant treatment			
Systemic immunosuppressants	In severe AD refractory to topical treatments and phototherapy (i.a. cyclosporine, methotrexate, mycophenolate mofetil, azathioprine)	Severe AD (i.a. cyclosporine, methotrexate, mycophenolate mofetil, azathioprine)	Severe AD (i.a. cyclosporine, methotrexate, mycophenolate mofetil, azathioprine)	3rd line treatment in severe AD (cyclosporine) Off-label use: • methotrexate, • Mycophenolate mofetil • Azathioprine	Chronic, severe AD (cyclosporine) Off-label use: • mycophenolate mofetil • Methotrexate • azathioprine	Chronic, severe AD (cyclosporine) Off-label use: • mycophenolate mofetil • Methotrexate • azathioprine	i.a. ciclosporin, mycophenolate mofetil		
Systemic corticosteroids	To be avoided in acute severe exacerbations or as a bridge therapy	Short course for severe AD	Short course for severe AD	Short course for severe AD	Short course for severe AD	Short course for severe AD	In case of ongoing therapy is ineffective		
Systemic antihistamines	To be avoided; short-term use in patients with disturbed sleep	To decrease pruritus in patients with disturbed sleep; long-term use not recommended	To decrease pruritus in patients with disturbed sleep; long-term use not recommended	Not discussed	Generally not recommended	Generally not recommended	(2nd generation recommended)		
Systemic antimicrobials	In case of bacterial infection only; alongside other therapies	Overt secondary infection	Overt secondary infection	In infections with clinical symptoms	In infections with clinical symptoms	In infections with clinical symptoms	In case of AD complications or overt secondary bacterial infection		
Immunotherapy	Dupilumab	Discussed; dupilumab—promising efficiency and safety profile	Discussed; dupilumab—promising efficiency and safety profile	Not authorized, not reimbursed, not discussed	Dupilumab: not authorized, not reimbursed, not discussed omalizumab: Not recommended	Dupilumab: not authorized, not reimbursed, not discussed omalizumab: Not recommended	Not authorized, not reimbursed, not discussed		
Other	N/A	N/A	N/A	N/A	N/A	N/A	• Plasmapheresis • Antidepressants		

Abbreviations. AAD, American Academy of Dermatology; AD, atopic dermatitis; ETFAD/EADV, European Task Force on Atopic Dermatitis (ETFAD)/European Academy of Dermatology and Venereology (EADV).

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