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RECOMMENDATION

Portuguese recommendations for the treatment of atopic dermatitis with biologic therapy and JAK inhibitors in adult patients

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Abstract

Atopic dermatitis is a highly prevalent chronic, immune-mediated inflammatory skin disease with a significant burden on patients, families and healthcare systems. This article presents recommendations developed by the Atopic Dermatitis Group of the Portuguese Society of Dermatology and Venereology addressing several clinical questions that arise in the management and care of moderate-to-severe atopic dermatitis with biologic agents and Janus kinase (JAK) inhibitors based on the available evidence. The recommendations were generated after a thorough evaluation of existing guidelines on the treatment of atopic dermatitis, publications concerning new biologics and JAK inhibitors not yet incorporated into existing guidelines, and expert-based recommendations. It also includes considerations on atopic dermatitis severity, indications for initiating biologic agents and JAK inhibitors, parameters to be considered in the treatment choice, in particular treatment goals, and recommendations for the use, screening and monitoring of these therapies.

Keywords: atopic dermatitis, biologic therapy, guidelines, JAK inhibitors, recommendations, treatment goals.

Citation

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Introduction

Atopic dermatitis (AD) is a highly prevalent disease with a profound impact on all dimensions of a patient's life as well as on the healthcare system.[1] In recent years, understanding of AD pathogenesis has significantly improved and treatment options have expanded.[1] Pathogenic mechanisms, such as dysregulated T helper 2 immune response, impaired maturation of keratinocytes, skin barrier disruption and abnormal microbial colonization, have been identified,[2] leading to the development of biologic agents and small molecules specifically targeting key pathogenetic mechanisms.[3,4]

AD may be frequently under-treated, especially in a long-term perspective, leading to the need for treatment recommendations based on the best available evidence.[5] New therapies with unique mechanisms of action have been approved for moderate-to-severe AD, bringing significant opportunities for better disease control with lesser toxicity compared to conventional systemic immunosuppressants.[6,7] Recent approval of the IL-4/IL-13 inhibitor dupilumab (for adults and adolescents above 12 years of age and recently for children 6–11 years of age), the IL-13 inhibitor tralokinumab (for adults) and the Janus kinase inhibitors (JAKi), baricitinib (JAK1/2 inhibitor, for adults), and upadacitinib (JAK1 inhibitor, for adults

and adolescents 12 years and older) offers a great opportunity for the effective and safe treatment of patients with moderate-to-severe AD.[6,7] In the near future, other biologics (such as the IL-13 inhibitor lebrikizumab) and JAKi (such as abrocitinib, a JAK1 inhibitor) are likely to be licensed for the treatment of AD.[3,4] Therefore, appropriate patient management is very important as is the use of all available therapeutic resources.

Management of AD in daily clinical practice is highly variable as many issues are still controversial and not definitely addressed by evidence-based medicine. The Summaries of Product Characteristics provided by the European Medicines Agency (EMA) provide information on the use of various drugs but do not fully resolve various challenges in daily clinical practice. National guidelines/recommendations for the evaluation, management and treatment of patients with AD with new targeted therapies in routine clinical practice are helpful for optimizing patient care. Additionally, the need for national guidelines/recommendations arises from the varying availability and reimbursement practices of drugs in each country.

No Portuguese recommendations for the treatment of AD have been published to date. With the recent development and approval of highly effective and safer biologic agents and small molecules for the treatment of moderate-to-severe AD, these national recommendations are now crucial.

Aim

These recommendations were developed to assist dermatologists and provide useful indications for the management of moderate-to-severe AD in adult patients with biologic and JAKi therapy in clinical practice. These are consensus-based recommendations, considering available evidence from other guidelines, systematic reviews, published studies and expert opinion. Additionally, peculiarities of the medical and legal context in Portugal were included such as reimbursement issues.

Considerations regarding AD severity, the indications for initiating biologic/JAKi therapy, the parameters to be considered in the treatment choice, treatment goals to be achieved, and recommendations for the use, screening and monitoring of these therapies were also incorporated.

These recommendations include the current biologic agents and JAKi approved by the EMA for the treatment of moderate-to-severe AD. Most recommendations fall within licensed indications; exceptionally, and only if clearly supported by evidence, off-label use may be recommended.

Nevertheless, therapeutic recommendations are not intended to replace clinician knowledge, experience and skills. Therapeutic recommendations are not able to encompass therapy specifications for all medical decision-making situations. As such, in specific situations, deviations from these recommendations may be not only justifiable but also inevitable.

Methods

An initial working group, constituted by two independent Portuguese dermatologist experts in the field (TT, PF), determined the scope of the therapeutic recommendations, and these were further discussed in virtual meetings with all members of the Atopic Dermatitis Group of the Portuguese Society of Dermatology and Venereology (GRADA-SPDV), which includes dermatologists from different areas of Portugal with large experience in the management of AD in children and adults.

As an initial step, TT and PF identified important clinical questions regarding biologic and JAKi treatment of AD in adult patients and conducted a systematic search of the literature using the Cochrane Library, MEDLINE and EMBASE databases (January 2015 to March 2021) for articles with the specific keywords "atopic dermatitis", "dupilumab", "tralokinumab", "JAK inhibitors", "upadacitinib", "baricitinib", "treatment recommendations" and "guidelines" present in the title, abstract or body. The reference lists of those articles were examined to retrieve other studies that were considered relevant and contributed to the scientific purpose of the present manuscript but had not been retrieved by the database search. Articles that presented duplicate information were excluded.

The first version of the manuscript was collegially evaluated and updated by the members of the GRADA-SPDV. In virtual meeting rounds, discussion proceeded until a >90% consensus was reached for each item and the final version of the document was approved by all.

Clinical recommendations were developed based on the best available evidence. In situations in which documented evidence-based data were not available, expert opinion was used to generate the clinical recommendations. The strength of recommendations was not expressed.

Recommendations

Considerations on biologic/JAKi therapy

- Biologic agents and JAKi currently approved by EMA for the treatment of moderate-to-severe AD are dupilumab, a fully human monoclonal antibody against IL-4Rα that blocks both IL-4 and IL-13 signalling; tralokinumab, a humanized monoclonal antibody that blocks IL-13 from binding to IL-13Rα1 and IL-13Rα2; baricitinib, an oral selective JAK1 and JAK2 inhibitor; and upadacitinib, an oral selective JAK1 inhibitor.[8–11] In the near future, the approval of another IL-13 inhibitor, lebrikizumab, and another JAK1 inhibitor, abrocitinib, is expected.
- Although all agents are approved in Europe for the treatment of moderate-to-severe AD in patients who are candidates for systemic therapy, in Portugal, biologic agents and JAKi are not reimbursed as first-line systemic therapies for the treatment of AD; however, once a patient meets the conditions for

drug approval, these agents can be prescribed within the National Health System Institutions and are fully reimbursed.
- Initiation and supervision of biologic and JAKi therapy should be undertaken by dermatologists experienced in the diagnosis and treatment of AD. AD is a heterogeneous disease with a broad spectrum of clinical presentations and differential severity (phenotypes).[1] AD diagnosis is based essentially on the clinical signs and symptoms and no diagnostic markers are currently available; thus, clinician experience is fundamental for a proper differential diagnosis (which includes contact dermatitis, skin infections, neurodermatitis, immunodeficiency disorders, drug eruptions, cutaneous T cell lymphoma and other skin diseases).[1]
- Patients with significant atopic comorbidities should be managed with the support of relevant specialized healthcare professionals (such as allergists, pulmonologists, ear, nose and throat specialists, ophthalmologists, or other medical specialties).

Indications for biologic/JAKi therapy

Although the decision to initiate systemic therapy with a biologic or a JAKi needs to be evaluated on an individual basis, the group has reached the following consensus criteria to recommend initiation of therapy.

- Biologic and JAKi therapy should be proposed to patients with any form of AD meeting one of the following criteria:
  - the disease is considered moderate-to-severe and persistent for >3 months, defined as AD with an Eczema Area and Severity Index (EASI) score of ≥16, or
  - with an EASI score <16 but at least one of the following conditions:
    - Localization on the face, hands or genitals
    - Pruritus with numeric rating scale (NRS) score >7
    - Sleep disturbances with NRS score >7
    - Significant negative impact on physical, psychological or social functioning (Dermatology Life Quality Index (DLQI) >10)

And one of the following:

  - Patients who (1) have not responded to at least one conventional systemic therapy, such as systemic corticosteroids (on-label in Portugal), cyclosporin (on-label in Portugal), methotrexate, azathioprine and mycophenolate mofetil (all off-label in Portugal), or (2) are only controlled with therapy that cannot be continued in the long term (e.g. corticosteroids or cyclosporin), or (3) if the patient is intolerant or has a contraindication to these treatments, or (4) is unwilling to consent to start an off-label systemic treatment.
    - Patients are considered as non-responders when at least a 50% improvement of the considered severity indices has not been achieved within a reasonable time frame (according to EMA, up to 3 months).
- In the exceptional severe case of AD where a rapid response is desirable and conventional online systemic therapies are contraindicated, biologic and JAKi therapy may be considered earlier as first-line treatment in the treatment ladder as this indication has been approved by EMA and is present in their own Summaries of Product Characteristics (Table 1).[8–11]

Treatment goals

- Treatment goals are important to optimize the management of patients with AD and to help dermatologists decide when and how to progress along treatment algorithms, improving patient care and, as such, avoiding suboptimal or unnecessary treatments.
- Overall, both objective and subjective symptoms should be evaluated to assess disease activity as both contribute to clinical severity: using validated instruments, the severity of skin signs and symptoms (particularly pruritus), the impact of disease on the quality of life (physical, psychological and social well-being of the patient), and the patient's point of view and level of satisfaction should be considered.[12] Treatment safety and tolerability should also be considered at each decision point.
- Medical management of other atopic and non-atopic comorbidities associated with AD, particularly asthma and allergic rhinitis, should also be considered (in consultation with an allergist, pulmonologist or other medical specialties).
- The objective is to achieve disease control or at least clinically meaningful improvement of disease activity as defined below (consensus definition).
- Evaluation of the treatment effectiveness (clinically meaningful improvement) must be carried out, considering as therapeutic objectives:
  - EASI 50 response at 3 months
  - EASI 75 response at 6 months
  - Reduction of at least 3 points of Pruritus NRS at 3 months
  - Pruritus NRS ≤4 at 6 months
  - Reduction of at least 4 points of DLQI at 3 months
  - DLQI ≤5 at 6 months
- Primary treatment failure is defined as not achieving treatment goals at 3 months. In patients with initial partial response (achieving goals in EASI response but not in symptomatic and quality of life goals or vice versa), consider treatment continuation/treatment optimization.
- During maintenance treatment, an assessment of treatment goals should be made at regular intervals oriented by clinical monitoring (every 3–6 months); safety monitoring should also be performed.

Table 1. Summary of characteristics of approved biologic therapies for atopic dermatitis.

Therapy	EMA's therapeutic indication in adults	Dosing (summaries of product characteristics)	Administration route	Year of EMA approval for atopic dermatitis	Approval for other atopic diseases	Approval for other diseases	Main contraindications (relative or absolute) or safety signals
Biologic agent							
Dupilumab (IL-4/13i)	Moderate-to-severe atopic dermatitis in adults who are candidates for systemic therapy	Initial dose of 600 mg (two 300 mg injections), followed by 300 mg every other week	Subcutaneous	2017	Asthma; chronic rhinosinusitis with nasal polyposis	No	Conjunctivitis and keratitis
Tralokinumab (IL-13i)	Moderate-to-severe atopic dermatitis in adults who are candidates for systemic therapy	Initial dose of 600 mg (four 150 mg injections), followed by 300 (two 150 mg injections) mg every other week	Subcutaneous	2021	No	No	Conjunctivitis and keratitis
JAK inhibitor							
Baricitinib (JAK1/JAK2i)	Moderate-to-severe atopic dermatitis in adults who are candidates for systemic therapy	4 mg once day (qd) 2 mg qd for patients ≥75 years of age and/or history of chronic or recurrent infections 2 mg qd as dose tapering for patients with sustained disease control with 4 mg qd	Oral	2020	No	Rheumatoid arthritis	Tuberculosis reactivation; haematological abnormalities; viral reactivation (herpes simplex and zoster); venous thromboembolism; lipids increase; hepatic transaminase elevations; severe hepatic disease (Child–Pugh C); severe renal disease (CrCl <30 mL/min)
Upadacitinib (JAK1i)	Moderate-to-severe atopic dermatitis in adults who are candidates for systemic therapy	15 mg or 30 mg qd based on individual patient presentation (30 mg qd may be appropriate for patients with high disease burden or patients with an inadequate response to 15 mg qd) 15 mg qd for patients ≥65 years of age	Oral	2021	No	Rheumatoid arthritis; psoriatic arthritis; ankylosing spondylitis	Tuberculosis reactivation; haematological abnormalities; viral reactivation (herpes simplex and zoster); lipids increase; hepatic transaminase elevations; venous thromboembolism; severe hepatic disease (Child–Pugh C)

EMA, European Medicines Agency; JAKi, Janus kinase inhibitor.

- Secondary failure (loss of response in patients who had previously achieved an adequate response during the induction phase) is defined as follows:
  - failure to attain the treatment goal at any time during the course of therapy even after treatment optimization;
  - a response that is no longer considered sufficient by both clinician and the patient.
- In the case that treatment goal is not achieved or is lost during treatment, several strategies may increase efficacy and should be chosen by the clinician on a case-by-case approach:
  - Evaluate, treat or advise about modifiable factors contributing to poor response (e.g. infections, allergies, psychosocial factors, poor compliance, contact dermatitis); identifying and avoiding possible triggers may reduce the severity of AD signs and symptoms, increasing the duration of the periods with complete remission.
  - Add another drug (combination therapy – topical, phototherapy or systemic therapy); topical anti-inflammatory drugs (topical corticosteroids or topical calcineurin inhibitors) may be combined with biologic and JAKi treatment as needed; phototherapy or systemic therapy may improve treatment response; however, drug interactions, an increased risk of infection or other side effects have to be considered.
    - A short-term course of rescue therapy with systemic corticosteroids in association with biologic or JAKi therapy may be an option to treat an acute flare or if a patient fails to improve; its use should be restricted to short-term therapy due to significant adverse events associated with long-term use.[13]
    - Dupilumab and tralokinumab may be associated with any conventional systemic immunosuppressants.
    - JAKi are not recommended in combination with potent immunosuppressive agents, such as cyclosporin, because of the possibility of additional immunosuppression and increased risk of infection or lymphoma. JAKi may be associated with methotrexate, based on safety data from their use in rheumatology.[14]
  - Changing/switching drugs is indicated whenever adjustments have proven ineffective or inappropriate, and EASI, pruritus and DLQI treatment goals are no longer achieved.

Before starting biologic or JAKi therapy (Table 2)

- Due to different mechanisms of action and safety profiles, the contraindications, risks, pretreatment screening, adverse events, and laboratory and clinical follow-up differ between biologic agents and JAKi.
- For all patients starting biologic or JAKi therapy:
  - Patient history and physical examination
    - Assess patients with AD prior to biologic and JAKi therapy with respect to risk factors for infection (e.g. comorbidities, co-therapy, lifestyle and travel); known infections (past or current) and signs or symptoms suggestive of infection.
    - Assess patients prior to biologic and JAKi therapy with respect to their past or current history of cancer and/or any personal/family risk factor of cancer; provide information regarding the importance of participating in national cancer screening programmes; consult a specialist if history of cancer, particularly if diagnosed and treated in the previous 5 years and/or when the baseline risk of skin cancer is increased.
  - When possible, complete all required vaccinations prior to initiation of biologic or JAKi therapy; in the case of live vaccines and attenuated live vaccines, biologic and JAKi therapy can be started 4 weeks after vaccine administration. Efficient immune responses for tetanus and meningococcal vaccines, IgE seroconversion to tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis have been reported with dupilumab treatment[15] and tetanus/diphtheria/pertussis and meningitis with tralokinumab[16]; and satisfactory humoral response to pneumococcal vaccination was observed in patients with rheumatoid arthritis treated with baricitinib or upadacitinib in association with methotrexate.[8,9]
  - In women planning conception or who are pregnant or breastfeeding, the available evidence of the use of biologic and JAKi is very limited. Biologic agents should be used during pregnancy only if the benefit outweighs the risk. Available data from use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.[10,11] However, human IgG antibodies are known to cross the placental barrier; therefore, this drug may be transmitted from the mother to the developing fetus. In animal studies, no adverse developmental effects were observed in offspring after maternal subcutaneous administration of a homologous antibody against IL-4Rα during organogenesis through parturition at doses up to 10 times the maximum recommended human dose.[11] JAKi use is contraindicated during pregnancy or breastfeeding.[8,9] In animal studies, oral administration to pregnant animals at exposures equal to and greater than approximately 20 and 84 times the maximum recommended human dose, respectively, resulted in reduced fetal body weights, increased embryolethality and dose-related increases in skeletal malformations.[9]
- For patients starting biologic therapy (dupilumab or tralokinumab):
  - No routine pretreatment laboratory screening is recommended for patients starting dupilumab or tralokinumab for AD. A baseline full blood count (including a differential white cell) may be considered

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Table 2. Suggestion for screening and monitoring of patients with atopic dermatitis on biologic/JAKi therapy.

All patients			
Patient history and physical examination		**Baseline**	**Monitoring**
Atopic dermatitis	Disease phenotype; stable/unstable course; clinical response and adverse effects to prior therapies	Yes	Ongoing
Atopic dermatitis severity assessment	EASI, Pruritus NRS, DLQI	Yes	Every visit (at least every 6 months)
	Evaluate whether therapy goal has been attained	N/A	Every visit (at least every 6 months)
Atopic comorbidities	Screen for atopic comorbidities[a]	Yes	Every visit (at least every 6 months)
Identification of contraindications to therapy and/or development of therapy-induced toxicity/side effects	Thorough history (symptom enquiry), co-medication, family history, lifestyle (e.g. risk of infections, conception plans); general physical examination	Yes	As indicated by history/symptom enquiry (at least every 6 months)
Malignancy	Assess past or current history of cancer and/or any personal/family risk factor of cancer	Yes	As indicated by history/general physical examination and national cancer screening programmes; in consultation with cancer specialist if past or current malignancy
Vaccination	Assess patient vaccination	Yes	As national vaccination programme
Non-atopic comorbidities (infections, neuropsychiatric disorders, diabetes, autoimmune diseases, skin cancer, obesity, cardiovascular disease)	Screen for non-atopic comorbidities[b]	Yes	At least every 6 months
Biologic therapy			
Patient history and physical examination		**Baseline**	**Monitoring**
Eye inflammation (conjunctivitis, keratitis or other eye conditions)	Enquiry for history of recurrent or moderate-to-severe eye inflammation[c]	Yes	Every visit (at least every 6 months)
Analytic control			
Blood tests	Full blood count	Yes (no routine pretreatment laboratory screening is recommended but a baseline full blood count may be considered)[d]	If clinically indicated (no routine laboratory monitoring is recommended but it may be considered during the first 3–6 months of therapy)[d]
	Other laboratory tests	Only if clinically indicated	Only if clinically indicated

(Continued)

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Table 2. (*Continued*)

		JAKi therapy	
Patient history and physical examination		**Baseline**	**Monitoring**
Infection	Enquiry for any past or current chronic infection, including tuberculosis, zoster or other	Yes	At least every 6 months
	Identify risk factors for hepatitis B, C, HIV or other infections	Yes	Annually in people belonging to a group with increased infection risk
	Identify risk factors for tuberculosis	Yes	Annually
	Identify risk factors for anti-tuberculosis drugs toxicity	Yes	Only if anti-tuberculosis is needed during treatment
Venous thromboembolism	Evaluate for risk factors of VTE	Yes	Annually
Analytic control			
Blood test	Full blood count, liver enzymes, renal function, lipid levels	Yes	At 3 months and then periodically according to routine patient management
	Hepatitis B (surface antigen and surface and core antibody) hepatitis C (IgG)	Yes	If clinically indicated or annually in people belonging to a group with increased infection risk
	Human immunodeficiency virus (HIV-1 and HIV-2 antibody and HIV-1 antigen)	Yes	If clinically indicated or annually in people belonging to a group with increased infection risk
Tuberculosis	IFNγ release assay, Mantoux test and chest X-ray (as local guidelines)	Yes	If clinically indicated, e.g. symptoms or signs of tuberculosis, new exposure to tuberculosis or at least every year (depending on baseline results)
Varicella/zoster infection	Evaluate for infection or immunization status	Yes	If clinically indicated

DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; JAKi, Janus kinase inhibitors; NRS, Numerical Rating Scale; VTE, venous thromboembolism.
[a]Patients with atopic comorbidities should be managed in consultation with the relevant specialized healthcare professionals (such as allergists, pulmonologists); [b]In the presence of comorbidities, a multidisciplinary management is recommended; [c]In the presence of moderate-to-severe eye inflammation, consultation with an ophthalmologist should be considered; [d]As eosinophilia and mild decreases in platelets and neutrophils have been reported during dupilumab and tralokinumab treatment.

as eosinophilia and mild decreases in platelets and neutrophils have been reported during dupilumab and tralokinumab treatment.[10,17]
    - In patients with a history of recurrent or moderate-to-severe eye inflammation (conjunctivitis, keratitis or other eye conditions), consultation with an ophthalmologist should be considered.
- For patients starting JAKi therapy:
    - Routine pretreatment laboratory screening is recommended for patients starting a JAKi for AD: baseline full blood count (including a differential white cell count), liver enzymes (in particular transaminases), renal function and lipid levels (unless if recently checked); no creatine phosphokinase testing is recommended.
    - Test for hepatitis B (surface antigen and surface and core antibody), hepatitis C (IgG) and HIV (HIV-1 and HIV-2 antibodies and HIV-1 antigen) infection; consult a specialist if any positive test.
    - Tuberculosis (TB) screen according to local guidelines:
        - Epidemiological inquiry, IFNγ release assay (IGRA) alone, Mantoux test and plain chest radiograph.
        - If positive, assess for active TB and/or management of latent TB in consultation with a TB specialist.
        - Initiate JAKi treatments only after completion of 1–2 months of TB treatment (upadacitinib therapeutic effect may be reduced if coadministered with rifampin, a strong CYP 3A4 inducer).[8]
    - Evaluate for varicella/zoster infection or immunization status. Currently, zoster vaccination is not recommended prior to JAKi therapy in all patients. The evidence for efficacy of the live vaccine is still questionable in addition to the 3–4 weeks postvaccination delay to start a JAKi; the non-live vaccine is not contraindicated, although no data on safety and protective immunogenicity of this vaccine in patients treated with JAKi is available; it is recommended that patients be vaccinated in agreement with current immunization guidelines.
    - Evaluate for risk factors for venous thromboembolism (VTE) by clinical history and/or laboratory study for potential clotting abnormalities. Consider as risk factors for VTE: past history of VTE (most important); increasing age (patients older than 65 years); obesity; prolonged immobility (i.e. long travel, lower-extremity paralysis due to spinal cord injury, trauma with reduced mobility); hereditary (i.e. factor V Leiden, prothrombin mutation 20210) and acquired thrombophilia (i.e. antiphospholipid syndrome, malignancy); COX2 inhibitor therapy; prednisolone of ≥7.5 mg/d and above; and major surgical interventions such as neurosurgery, urologic, gynaecologic and orthopaedic surgery.

Choosing the biologic and JAKi therapy

- Currently, dupilumab and tralokinumab are the only biologic agents and baricitinib and upadacitinib are the only JAKi approved by EMA for the treatment of moderate-to-severe AD.
- Treatment decisions should be based on a patient's medical profile, as long as no predictive efficacy or safety biomarkers are identified. Eventually, patient preference based on the different route of administration (oral *versus* subcutaneous) can also be considered.
- Consider both AD and the presence and severity of atopic comorbidities, in particular asthma, before initiating or making changes to biologic and JAKi therapy. Consider managing atopic comorbidities in consultation with an allergist, pulmonologist or other medical specialty.
- Main factors to consider that may influence the choice of biologic and JAKi therapy:
    - Probability of achieving the treatment goals:
        - on cutaneous lesions severity
        - on pruritus severity
    - Overall safety profile
    - AD phenotype and pattern of activity
    - Location of lesions, disease severity and psychosocial impact
    - Presence and severity of atopic comorbidities, that may also benefit from therapy, according to previous clinical trials/studies (e.g. asthma, allergic rhinitis, chronic rhinosinusitis with nasal polyposis, food allergies)
    - Concomitant diseases that may also benefit from therapy, according to previous clinical trials/studies (e.g. alopecia areata, prurigo nodularis, vitiligo, psoriasis, inflammatory bowel disease or others)
    - Past or current comorbid conditions (e.g. laboratory abnormalities, risk factors for VTE, chronic infectious disorders, impaired renal or hepatic function, eye disorders, cancer)
    - Risk of TB or herpes zoster infection
    - Other medications (risks of drug interactions and immunosuppression)
    - Body weight, body mass index
    - Conception plans
    - Patient's views and stated preference on administration route or frequency
    - Likelihood of adherence to treatment
    - Drug costs and availability
- In patients with no known contraindications for any agent or with no special conditions mentioned below, all biological agents and JAKi may be considered as first-line treatment; consider the probability of achieving the treatment goals on cutaneous lesions severity and on pruritus severity.[18]
- In patients with moderate-to-severe AD and certain forms of severe asthma or severe chronic rhinosinusitis with nasal polyposis, dupilumab should be considered due to its approval by the EMA for these atopic diseases.[11]
- In patients with moderate-to-severe AD and prurigo nodularis, dupilumab should be considered due to the efficacy shown in phase III clinical trials.

- In patients at high risk of contact with TB (professionally or otherwise) or at high risk of toxicity to anti-TB drugs, the option should fall for dupilumab or tralokinumab due to its minimal to no risk of TB reactivation.[19]
- In patients with moderate-to-severe hepatic, renal insufficiency or taking drugs with known interactions with JAKi (as per individual product information), dupilumab or tralokinumab should be preferred.
  - In cases of severe hepatic disease (Child–Pugh C), JAKi should not be used.
  - In patients with severe renal disease (CrCl <30 mL/min), baricitinib is not recommended; with CrCl 30–60 mL/min baricitinib should be used at 2 mg daily.
  - No dose reduction is recommended for modest renal impairment with upadacitinib.
- In patients with higher risk of infections, dupilumab or tralokinumab should be preferred.
- In patients with a high risk of VTE or previous episode of VTE, mainly if not anticoagulated, dupilumab and tralokinumab should be preferred.
  - In patients with a history of VTE initiation of a JAKi should be carefully evaluated; anticoagulation treatment likely counteracts the risk – consulting a specialist should be considered.
- In patients in whom a rapid improvement of pruritus is required, JAKi should be preferred due to its fast-acting action on pruritus.
- In patients preferring oral administration and dose flexibility, JAKi should be preferred.
- In patients with a history of recurrent or moderate-to-severe eye inflammation (conjunctivitis, keratitis or other eye conditions), JAKi should be preferred.
- In patients with concurrent disease with known efficacy of JAKi, such as alopecia areata, vitiligo, psoriasis, rheumatoid arthritis or inflammatory bowel disease, JAKi should be preferred.
- In patients with a previous history of eosinophilic-associated complications, such as pneumonitis, myositis or vasculitis, JAKi should be preferred.
- When transitioning from conventional systemic therapy to biologic or JAKi therapy consider:
  - Start biologic therapy (dupilumab or tralokinumab) with no drug washout period in patients taking conventional systemic therapies (e.g. corticosteroids, methotrexate or cyclosporin).
  - Start JAKi with no drug washout period in patients taking methotrexate or in patients on corticosteroids or cyclosporin if discontinuation leads to unstable disease (stopping when a minimum response has been achieved).
  - Clinician decisions should always be on a case-by-case basis.
- Note that the recommended first-line choice of biologic therapy may not be appropriate for every individual patient.

Switching biologic and JAKi therapy

- Consider switching to another agent (biologic agent or JAKi) if any of the following applies:
  - Primary failure – the recommended option is switching to a different drug class (switching between biologic agents or between JAKi may also be considered).
  - Secondary failure – the recommended option is also switching to a different drug class (switching between biologic agents or between JAKi may also be considered).
  - If patients develop any adverse event to the biologic or JAKi therapy, treatment cannot be tolerated or becomes contraindicated – the recommended option is switching to a different drug class.
- A 1-month washout period should be considered when switching to a new therapy due to safety reasons; no washout period needs to be considered whenever switching is due to efficacy failure (clinician decisions should always be on a case-by-case basis).

Maintenance treatment (Table 2)

- For all patients on biologic or JAKi treatment:
  - Along with the assessment of treatment goals, safety clinical monitoring should be performed periodically (every 3–6 months).
  - Assess patients with respect to risk factors for infection (e.g. comorbidities, co-therapy, lifestyle and travel) and signs or symptoms suggestive of infection.
  - Assess patients with respect to any risk of cancer; provide information regarding the importance of getting involved in national cancer screening programmes appropriate for their age and gender as well as regular, comprehensive dermatological assessment for skin cancer, including melanoma.
  - Inactivated vaccines may be administered during treatment with biologic and JAKi therapy; for the administration of live vaccines and attenuated live vaccines, consult with an infectious disease specialist as they should not be administered in patients being treated with biologic or JAKi therapy.
- For patients on biologic therapy (dupilumab and tralokinumab):
  - There is no need for routine laboratory monitoring during dupilumab and tralokinumab therapy; a full blood count (including a differential white cell) may be considered during the first 3–6 months of therapy as eosinophilia and mild decreases of platelets and neutrophils have been reported during treatment with these agents.
  - In case of symptomatic or persistent relevant hyper-eosinophilia (eosinophil blood count >2000/mm^3 for more than 3 months), which seems to have a higher prevalence in real-life studies than initially suggested by

clinical trials,[17] treatment discontinuation/switch should be considered.
    - Additional laboratory monitoring should be considered only if clinically indicated.
    - In the case of eye inflammation (conjunctivitis, keratitis or other eye problems), moisturizing the eye (artificial tears, lid rim hygiene) should be prescribed; consider a consultation with an ophthalmologist for exclusion of infectious causes; most cases of dupilumab and tralokinumab associated conjunctivitis are mild-to-moderate in severity respond well to topical treatment (corticosteroids, calcineurin inhibitors) and dupilumab and tralokinumab should not be discontinued. Consider discontinuation in severe cases or unresponsive to treatment.
- For patients on JAKi therapy:
    - Measurement of full blood count and differential, liver enzymes (particularly transaminases), renal function and lipid levels is recommended as a minimal laboratory monitoring, at 3 months and then periodically according to routine patient management.
        - Blood count: haemoglobin decrease of less than or equal to 20 g/L and haemoglobin levels greater than or equal to 90 g/L do not require dose adjustment; a reduction greater than 20 g/L or a haemoglobin value below 80 g/L (confirmed by repeat testing) should lead to dose interruption until normalization of haemoglobin values.
        - Absolute neutrophil counts over 1000/mm^3 require no dose adjustment; however, two sequential values between 500 and 1000/mm^3 dose reduction or temporary therapy cessation is recommended until counts are above 1000/mm^3. JAKi can then be resumed.
        - Absolute lymphocyte counts over 750/mm^3 require no dose adjustment, whereas two sequential values of 500–750/mm^3 suggest a dose reduction or temporary therapy cessation. Values above 750/mm^3 allow JAKi restart. Lymphocyte counts below 500/mm^3 may significantly increase the risk of opportunistic infection.
        - Increased levels of lipids should be managed according to national guidelines.
    - Routine creatine phosphokinase measurement is not needed unless clinically indicated.
    - Test annually for hepatitis B (surface antigen and core antibody), hepatitis C (IgG) and HIV (HIV-1 and HIV-2 antibodies and HIV-1 antigen) infection in patients who belong to a group at increased risk of infection.
    - Screen for latent tuberculosis annually as for local guidelines (may include IGRA, Mantoux test, plain chest radiograph and/or epidemiological inquiry, depending on baseline results).
    - If a patient develops herpes zoster, JAKi treatment should be temporarily interrupted until the episode resolves; a small proportion of patients can develop recurrent zoster; antiviral prophylaxis could be considered in such individuals.
- Consider actively screening and monitoring atopic and non-atopic comorbidities (infections, neuropsychiatric disorders, diabetes, autoimmune diseases and skin cancer, obesity, cardiovascular disease); in the presence of comorbidities, multidisciplinary management is recommended.
- Lifestyle interventions should be considered if needed in consultation with the relevant specialized healthcare professionals.
- There is good evidence of the benefit from patient education programmes[20,21]; physicians should explore patient eligibility for such programmes and, if possible, recommend their use.

Conclusion

This document has been prepared on behalf of the GRADA-SPDV and is based on the best available evidence at the time of document preparation. It provides useful and practical advice on the management and treatment of adult patients with moderate-to-severe atopic dermatitis with biologic and JAKi therapy. Currently available biologic and JAKi agents for AD are still considerably recent; thus, real-world data are still scarce. These recommendations may change once further pharmacovigilance and registry data become available. They may also change once more information becomes known regarding pathogenic pathways, endotypes and phenotypes to disease or pathways leading to adverse events.

Future studies and evidence in this fast-moving subject may require regular review and updating of these recommendations.

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References

1. Langan S, Irvine A, Weidinger S. Atopic dermatitis. *Lancet*. 2020;396(10247):345–360. https://doi.org/10.1016/S0140-6736(20)31286-1
2. Werfel T, Allam J, Biedermann T, et al. Cellular and molecular immunologic mechanisms in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2016;138(2):336–349. https://doi.org/10.1016/J.JACI.2016.06.010
3. Ratchataswan T, Banzon T, Thyssen J, Weidinger S, Guttman-Yassky E, Phipatanakul W. Biologics for treatment of atopic dermatitis: current status and future prospect. *J Allergy Clin Immunol Pract*. 2021;9(3):1053–1065. https://doi.org/10.1016/J.JAIP.2020.11.034
4. He H, Guttman-Yassky E. JAK inhibitors for atopic dermatitis: an update. *Am J Clin Dermatol*. 2019;20(2):181–192. https://doi.org/10.1007/s40257-018-0413-2
5. Gisondi P, Girolomoni G. Undertreatment in adult patients with moderate-to-severe atopic dermatitis and other chronic inflammatory skin diseases. *J Eur Acad Dermatol Venereol*. 2020;34(10):2168–2169. https://doi.org/10.1111/JDV.16876
6. Ferreira S, Guttman-Yassky E, Torres T. Selective JAK1 inhibitors for the treatment of atopic dermatitis: focus on upadacitinib and abrocitinib. *Am J Clin Dermatol*. 2020;21(6):783–798. https://doi.org/10.1007/S40257-020-00548-6
7. Yang N, Chen Z, Zhang X, Shi Y. Novel targeted biological agents for the treatment of atopic dermatitis. *BioDrugs*. 2021;35(4):401–415. https://doi.org/10.1007/S40259-021-00490-X
8. European Medicines Agency. RINVOQ® (upadacitinib): EPAR product information. https://www.ema.europa.eu/en/documents/product-information/rinvoq-epar-product-information_en.pdf. Accessed July 27, 2021.
9. European Medicines Agency. OLUMIANT® (baricitinib): EPAR product information. https://www.ema.europa.eu/en/documents/product-information/olumiant-epar-product-information_en.pdf. Accessed July 27, 2021.
10. European Medicines Agency. ADTRALZA® (tralokinumab): EPAR product information. https://www.ema.europa.eu/en/documents/product-information/adtralza-epar-product-information_en.pdf. Accessed July 27, 2021.
11. European Medicines Agency. DUPIXENT® (dupilumab): EPAR product information. https://www.ema.europa.eu/en/documents/product-information/dupixent-epar-product-information_en.pdf. Accessed July 27, 2021.
12. De Bruin-Weller M, Biedermann T, Bissonnette R, et al. Treat-to-target in atopic dermatitis: an international consensus on a set of core decision points for systemic therapies. *Acta Derm Venereol*. 2021;101(2):adv00402. https://doi.org/10.2340/00015555-3751
13. Wollenberg A, Räwer H-C, Schauber J. Innate immunity in atopic dermatitis. *Clin Rev Allergy Immunol*. 2011;41(3):272–281. https://doi.org/10.1007/S12016-010-8227-X

14. Nash P, Kerschbaumer A, Dörner T, et al. Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors: a consensus statement. *Ann Rheum Dis*. 2021;80(1):71–87. https://doi.org/10.1136/ANNRHEUMDIS-2020-218398
15. Blauvelt A, Simpson E, Tyring S, et al. Dupilumab does not affect correlates of vaccine-induced immunity: a randomized, placebo-controlled trial in adults with moderate-to-severe atopic dermatitis. *J Am Acad Dermatol*. 2019;80(1):158–167.e1. https://doi.org/10.1016/J.JAAD.2018.07.048
16. Merola J, Bagel J, Almgren P, et al. Tralokinumab does not impact vaccine-induced immune responses: results from a 30-week, randomized, placebo-controlled trial in adults with moderate-to-severe atopic dermatitis. *J Am Acad Dermatol*. 2021;85(1):71–78. https://doi.org/10.1016/J.JAAD.2021.03.032
17. Marcant P, Balayé P, Merhi R, et al. Dupilumab-associated hypereosinophilia in patients treated for moderate-to-severe atopic dermatitis. *J Eur Acad Dermatol Venereol*. 2021;35(6):e394–e396. https://doi.org/10.1111/JDV.17177
18. Silverberg J, Thyssen J, Fahrbach K, et al. Comparative efficacy and safety of systemic therapies used in moderate-to-severe atopic dermatitis: a systematic literature review and network meta-analysis. *J Eur Acad Dermatol Venereol*. 2021;35(9):1797–1810. https://doi.org/10.1111/JDV.17351
19. Eichenfield L, Bieber T, Beck L, et al. Infections in dupilumab clinical trials in atopic dermatitis: a comprehensive pooled analysis. *Am J Clin Dermatol*. 2019;20(3):443–456. https://doi.org/10.1007/S40257-019-00445-7
20. Yoo JB, De Gagne JC, Jeong SHS, Jeong CW. Effects of a hybrid education programme for Korean mothers of children with atopic dermatitis. *Acta Derm Venereol*. 2018;98(3):329–334. https://doi.org/10.2340/00015555-2862
21. Siebert M, Qureshi Y, Chu T, Goff H. Validation of an evidence-based educational smartphone application for atopic dermatitis. *Dermatitis*. 2019;30(2):176–177. https://doi.org/10.1097/DER.0000000000000440