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Biologics and small molecules treatment for moderate-to-severe atopic dermatitis patients with comorbid conditions and special populations: an Italian perspective

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Abstract

This comprehensive review offers a detailed look at atopic dermatitis (AD) treatment in Italy, focusing primarily on the use of biologics and small molecules.

In response to advancing knowledge of AD's causes and treatments, there's a global need for updated guidelines to provide physicians with a more comprehensive clinical perspective, facilitating personalized treatment strategies.

Dupilumab, a groundbreaking biologic, gained approval as a significant milestone. Clinical trials demonstrated its ability to significantly reduce AD severity scores, with an impressive 37% of patients achieving clear or nearly clear skin within just 16 weeks of treatment. Real-world studies further support its efficacy across various age groups, including the elderly, with a safety profile akin to that of younger adults.

Tralokinumab, a more recent approval, shows promise in clinical trials, particularly among younger populations. However, its real-world application, especially in older individuals, lacks comprehensive data.

JAK inhibitors like Upadacitinib, baricitinib, and abrocitinib hold substantial potential for AD treatment. Nevertheless, data remains limited for patients over 75, with older adults perceived to carry a higher risk profile. Integrated safety analyses revealed individuals aged 60 and above experiencing major adverse cardiovascular events and malignancies, underscoring the need for cautious consideration.

While these therapies offer promise, especially among younger patients, further research is essential to determine their safety and efficacy in various populations, including pediatric, geriatric, and those with comorbidities. This review highlights the evolving landscape of AD treatment, with biologics and small molecules emerging as potent tools to enhance the quality of life for AD-affected individuals.

Introducion

Atopic dermatitis (AD) is a chronic relapsing and remitting, pruritic, inflammatory skin disease affecting both children and adults. Patients with moderate-to-severe AD who fail first-line systemic traditional therapies, such as cyclosporine A, may be considered for biologic or small molecules therapy. Biologics and small-molecules currently approved in Italy for the treatment of moderate-to-severe AD include Dupilumab (DUP), Tralokinumab (TRA), Upadacitinib (UPA), Abrocitinib (ABR) and Baricitinib (BAR).

Data from clinical trials, real-world studies, and case-series provide information on the safety and efficacy of these treatments also in special populations of patients (1) .

This paper aims to summarize the literature and create an evidence-based treatment algorithm for moderate-to-severe AD in patients with comorbidities and in special populations (Table 1), including those with Th2 atopic comorbidities **(1)**, past and current infections **(2)**, arthritis and inflammatory bowel diseases **(3)**, other autoimmune or inflammatory skin diseases **(4)**, previous history of cancer **(5)**, childbearing and breastfeeding potential **(6)**, pediatric and adolescent patients **(7)**, and elderly patients **(8).**

TH2 atopic comorbidities

Type 2 inflammation is driven by Th2 cells and group 2 innate lymphoid cells, which produce the type 2 cytokines, like interleukin IL-4, IL-5 and IL-13 and other inflammatory mediators. A number of atopic conditions, including AD, rhinitis, asthma and chronic rhinosinusitis with nasal polyps, are characterized by type 2 inflammation. For appropriate disease treatment and improving overall patient outcomes, identifying AD comorbidities is important.

Asthma

AD is typically the initial manifestation of an atopic diathesis, which affects people with a hereditary predisposition and also includes asthma and rhinitis. Asthma or rhinitis could develop in children with AD up to 80% of the time (2). The worldwide prevalence of asthma symptoms caused by atopic sensitization in was 30% in adults and ranged with a large international variation from 0% to 93.8% in children. In Italy, the fraction of current asthma attributable to atopy in pediatric patients was 56.2 %. (3–5). For the treatment of asthma, various biologics that target Th2 pathways have been approved. The most appropriate biologic for treating asthma depends on age, comorbidities, treatment objectives and exacerbation triggers (6) . Due to the overlapping functions of IL-4 and IL-13, biologics that target just one of these molecules have not shown to be effective in treating asthma (7). TRA , selective IL-13 inhibitor, did not show efficacy in phase 3 clinical trials in asthma (8). Through multiple studies, DUP has shown effectiveness in the treatment of asthma(9,10) . DUP is the only medication licensed to treat people with AD and concomitant asthma(11). A post-hoc subgroup analysis of DUP use in patients with AD and concomitant asthma demonstrate a significant improvements in AD-related outcomes and asthma(12) . In the analysis the effectiveness of DUP in AD outcomes is equivalent to that of the overall study population and there are no safety differences between AD patients with concomitant asthma and those with AD alone. It would be an interesting issue to explore if early treatment with DUP could prevent subsequent asthma development in children with AD.

Janus Kinases mediate activity of many asthma-relevant cytokines. Theoretically and based on animal models they might be used to treat asthma. GDC-0214 and GDC-4379, inhaled small molecule JAK1 inhibitors, demonstrated dose-dependent reductions of fractional exhaled nitric oxide and peripheral biomarkers of inflammation in patients with mild asthma(13,14) .

JAK1/2 inhibitor BAR demonstrated a promising treatment for severe eosinophilic asthma(15) . To evaluate the impact JAKis can have on treating asthma, more research must be done.

Allergic rhinitis and chronic rhinosinusitis with sinonasal polyposis

Allergic rhinitis and Chronic Rhinosinusitis with Sinonasal Polyposis (CRSwNP) are diseases frequently characterized by type 2 inflammation, with release of pro-inflammatory cytokines such as IL-4, IL-5, IL-9 and IL-13. 10% of patients with CRSwNP have a diagnosis of non-steroidal anti-inflammatory drug-exacerbated respiratory disease (NSAID-ERD) (16) . According to the findings of two randomized placebo-controlled phase 3 trials in patients with CRSwNP and NSAID-ERD, DUP improved symptoms, endoscopic and radiologic outcomes, and airway function with suppressing underlying type 2 inflammation (17) . A post-hoc subgroup analysis of DUP use in patients with AD and chronic sinonasal conditions demonstrated a significant improvement in AD-related outcomes and sinonasal diseases (12). The effectiveness and safety of anti-IL13 drugs such as TRA in treating rhinitis are not at this time being studied in randomized controlled trials. Also, there are currently no studies proving the efficacy of JAKi therapy in rhinitis.

Ocular surface diseases

Minor Hanifin and Rajka criteria for AD include keratoconus, recurrent conjunctivitis and anterior subcapsular cataract, underlining the evidence that ocular disease is a component of the AD syndrome. A systematic review revealed that allergic conjunctivitis was the most common subtype in patients with AD, while atopic keratoconjunctivitis and infectious conjunctivitis were substantially less common. Conjunctivitis was prevalent in patients with AD at 31.7%, compared to 13.3% in controls(18) . Blepharitis affected 22.0%, dry eye disease 9.1%, keratitis 1.4% and keratoconus affected less than 1% (19) . Medication-induced ocular surface disease (mOSD) is the term used to characterize patients who have a new onset of OSD or an exacerbation of an existing OSD following the start of a new medication. In AD populations, this is noticeable with IL-4 and/or IL-13 inhibitors. A higher incidence of mOSD correlates with certain baseline AD-related factors, such as the severity of AD and a previous conjunctivitis history(20) .

Although no mOSD-specific predictive factors have been established, higher baseline AD severity and a history of conjunctivitis were linked to an increased incidence of ocular AEs in DUP clinical

trials(20,21) . Clinical trials of DUP for other diseases, such as asthma and CRSwNP, have not revealed this elevated prevalence (22).

According to an analysis of 5 TRA randomized controlled trials, an increased risk of conjunctivitis was found in both the placebo and treatment groups and it was linked to more severe baseline AD, a history of allergic conjunctivitis or atopic keratoconjunctivitis and a higher number of atopic comorbidities (23). Most of reported cases of conjunctivitis were mild-to-moderate in severity, resolved during the clinical trial and did not lead to treatment discontinuation (22,23) .

The pathophysiological mechanisms of DUP/TRA induced AOEs are not fully understood. According to some studies, by blocking IL-4 and IL-13, these monoclonal antibodies prevent the activation of conjunctival goblet cells, which would result in hypoplasia and a decrease in mucin synthesis, which would have an impact on the mucosal epithelial barrier function (24). Lower incidence of ocular adverse events was observed in the JAKi-treated patients in head-to-head studies comparing ABR and UPA to DUP, in some cases lower than placebo (25,26) . Randomized clinical trials on BAR showed that the proportion of patients with a conjunctival disorder was lower in the BAR vs. placebo groups (27) .

Of note, Th2 blockage with IL-4 and IL-13 inhibitors can promote a shift towards the Th1 phenotype, which is associated with atopic keratoconjunctivitis (28). One explanation is that JAKis' more extensive immunomodulatory impact (targeting both Th2 and Th1) may prevent OSD by reducing this Th1 shift (11).

Patients with a history of severe OSD should start Jaki therapy rather than biologics to prevent the possibility of severe OSD recurrence. Conjunctivitis incidence during TRA treatment was comparable with placebo and further studies in a real life setting are needed. An ophthalmological examination may be helpful if treatment with IL-13/IL-4 inhibitor has to be initiated.

Patients with past and current infections

Infectious complications during biological and small molecules therapies depend on the immune cell or cytokine inhibited. Most infections arise during the first year of biological therapy and the main ones are bacterial infections, mycobacterial and fungal diseases, herpes zoster and hepatitis B virus (HBV) reactivation. (29)

Herpes simplex virus

AD is associated with increased risk of herpes virus infections. Eczema herpeticum (EH) is a severe disseminated HSV infection, reported to occur in approximately 3% of patients with AD (30), and can cause life-threatening complications (31) . The incidence rates of herpesvirus infection was

slightly (1%) higher in the DUP groups than in the placebo groups (32), however these were not serious and should not influence treatment choices (33) .

A meta-analysis of eight randomized controlled trials revealed decreased risks of EH in patients who received DUP compared with placebo (33). TRA-treated patients had lower rates of HSV infection and EH vs. placebo in ECZTRA 1 and ECZTRA 2 studies (23) .UPA and ABR showed increases in the overall prevalence of HSV infections compared to placebo in pooled analyses of clinical trials (25,34) . Incidences of HSV, but not EH, were dose-dependent with ABR (35) .

HSV infection was reported more frequently for BAR 4 mg compared to BAR 2 mg and placebo. However, HSV incidence in the extended data set was higher in placebo group suggesting that prolonged treatment with BAR does not result in a continuous increase of HSV incidence. EH infection incidence was higher in BAR 4 mg group and correlate with AD severity, while there was no increase of HE incidence in BAR 2 mg group (27).

Systemic medication may change the frequency of HSV in AD patients. Patients with a history of recurrent or severe HSV infection should be screened for the virus and physicians should consider prophylactic or prompt antiviral treatment (11). In conclusion, therapy with DUP and TRA may be preferable to JAKis .

Herpes zoster

AD is associated with an increased risk of HZ (36) . Compared to placebo, the rate of HZ was lower in patients receiving DUP (32). The published phase 3 clinical trial data for TRA does not identify HZ as an adverse event (23).

In comparison to placebo, JAKis showed increases in the overall frequency of HZ infections (25,35). In head-to-head studies of DUP versus ABR and UPA, the reactivations of VZV were numerically higher for patients treated with UPA and ABR than those treated with DUP, all at generally low levels. All HZ events were mild or moderate in severity (25,26) . More events of HZ were reported in the BAR 2 mg group than placebo or BAR 4 mg groups (27) .

Therapy with DUP and TRA may be preferable to JAKis in patients who have HZ risk factors. Before beginning systemic treatment with JAKis , the HZ vaccine should be taken into consideration(11). In conclusion, therapy with DUP and TRA may be preferable to JAKis.

Hepatitis B virus

Hepatitis B virus (HBV) reactivation can be a serious complication for patients with chronic or resolved HBV infection when treated with biologics.

Due to the exclusion criteria (37) HBV-positive individuals were not included in DUP clinical studies, and there is no published data indicating that DUP is safe for HBV infection.

Only one case report on two patients with chronic HBV infection in treatment with entecavir and DUP shows no viral reactivation (38) . Furthermore, in a prospective report of five patients treated with DUP who were HBV surface antigen positive and did not receive HBV medication no viral reactivation was detected (39) .

TRA phase 3 clinical studies have not reported any cases of HBV reactivation, potentially reflecting trial exclusion criteria for patients with a history of HBV (11)

DUP and TRA specifically inhibits Th2 immune responses while having limited effect on Th1 immune responses (40). Given that HBV suppression occurs primarily through a Th1 immune response, DUP and TRA are unlikely to cause HBV reactivation.

There are no published data of HBV-positive patients receiving JAKis for AD. Despite this, cases of HBV reactivation after therapy with JAKis for rheumatoid arthritis are reported in the literature (41–43). JAKi may enhance the risk of viral reactivation according to their mechanism of action on lymphocytes and interferon signaling. Before beginning any systemic therapy for AD, patients with HBV infection who have surface antigen positivity should be investigated for concomitant HBV therapy (11) .

If HBV therapy cannot be started, therapy with DUP and TRA may be preferable to JAKi.

Human immunodeficiency virus

History of HIV is one of the exclusion criteria for studies of DUP, TRA, UPA, BAR and ABR.

For these reasons there are no safety data for these therapies. Several cases of HIV patients treated with DUP are reported in the literature(44,45) . According to all published cases, DUP is safe in individuals with HIV who have stable CD4 counts and low viral loads (46).

Tuberculosis

A third of the world's population is exposed to Mycobacterium tuberculosis in their lifetime (47) .

Treatment with biologic agents is associated with an increased risk of tuberculosis (TB) and this risk is highest with the tumor necrosis factor-alpha inhibitors (48)

Currently, no TB screening is necessary for biologics licensed for AD (49) . Based on their mode of action, biologics that target the IL-13/IL-4R axis would not disrupt granulomas and cause unregulated TB proliferation (50) (48). Clinical trials for AD patients often exclude those with a history of TB. JAKi should not be administered to patients with latent TB until the latent TB has been treated (51–53) . They might increase the risk of TB infections, through down-regulating Th-1 responses and

production of IFN-γ involved in protective immunity against *M. tuberculosis* (54). Patients with latent TB should not be treated with JAKi until latent TB is treated. In patients with untreated latent TB therapy with DUP and TRA may be preferable to JAKi.

Patients with arthritis and inflammatory bowel diseases

The association of AD with autoimmune disorders has been extensively investigated. A recent meta-analysis demonstrated that AD increases the risk of developing rheumatoid arthritis (RA), ulcerative colitis (UC) and Crohn's disease (CD) (55) . Considering the presence of these comorbidities in patients with AD, the choice of therapy should be carefully evaluated to ensure a safe and potentially pleiotropic treatment option.

Arthritis

Regarding AD and arthritis, the Italian Medicines Agency (AIFA) has approved the use of UPA in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) and approved the use of BAR in patients with RA. An integrated safety analysis of UPA, which included clinical trials involving patients with RA, PsA, AS, and AD, confirmed an acceptable safety profile with no new safety risks. UPA and BAR may represent two suitable option for AD patients with arthritis (56–58).

However, there is currently no available data on the effects of TRA and ABR on arthritis. DUP-associated enthesitis and arthritis have been described in literature. In most cases, the symptoms were mild and did not require discontinuation of DUP. However, in cases of moderate-to-severe arthritis, administration of nonsteroidal anti-inflammatory drugs or discontinuation of DUP was necessary (59–65). Bostan et al. reported a case of reactivation of inflammatory monoarthritis during DUP therapy (66).

Bridgewood et al. conducted a pharmacovigilance analysis using VigiBase and observed an association between DUP and seronegative arthritis and enthesitis/enthesopathy. The proposed pathogenetic mechanism involved the induction of IL-17- driven inflammation secondary to downregulation of the IL-4/IL-13 axis. (67,68)

Inflammatory bowel diseases

There are concerns regarding the potential onset or exacerbation of inflammatory bowel disease (IBD) with IL-4/IL-13 blockade (69) and limited data exist on the use of DUP in patients with IBD (70). Spencer et al. conducted a study involving seventeen IBD patients who were receiving DUP for severe AD, as well as AD or psoriasiform dermatitis induced by anti-TNF therapy for IBD management.

Among these patients, eight received a combination of biologics, including DUP and anti-TNF, ustekinumab, or vedolizumab. All patients showed a positive response to DUP for AD, and no adverse events were reported, including no increase in IBD activity(71) .

Studies have presented contrasting results regarding the effects of IL-13 cytokine in ulcerative colitis (UC) and Crohn's disease (CD) (72). TRA has been evaluated in moderate-to-severe UC, but it did not significantly improve clinical response compared to placebo. However, TRA was associated with a higher remission rate, suggesting potential benefits for certain UC patients (73) .

Clinical trials have demonstrated the efficacy and tolerability of UPA in IBD patients, leading to its approval by AIFA for the induction and maintenance therapy of moderate-to-severe UC and CD (73–82).

Grieco et al. reported a case of a patient with overlapping AD and UC who was successfully treated for both conditions with UPA 15 mg (77). UPA may hold promise as a treatment option for patients with concurrent AD and IBD.

Currently, there is no available data on the effect of ABR and BAR on patients with IBD. Further research is needed to assess their potential impact in this patient population.

Patients with concomitant autoimmune or inflammatory skin diseases

Patients with AD are at higher risk of developing multiple autoimmune skin diseases, including alopecia areata and vitiligo (55). Moreover, patients with overlapping AD and psoriasis have been increasingly reported and this association represents a therapeutic challenge (83)

Alopecia areata

In patients with concomitant AD and alopecia areata (AA), DUP demonstrated controversial effects (84) . Several authors reported AA onset or worsening during DUP therapy for AD (82,85–94) . However, there have also been observations of hair regrowth in both adult and pediatric patients receiving DUP (95–100). Recent evidence suggests that the Th2 immune axis may play a role in the pathogenesis of AA (101) . Patients with more severe and long-standing histories of AD and atopic comorbidities have shown greater improvement in AA with DUP treatment (102,103). A phase 2 randomized clinical trial (NCT03359356) investigating DUP for AA patients demonstrated a higher response in atopic patients with baseline serum IgE levels ≥ 200 IU/ml (104) .

Conversely, patients with a shorter duration and later onset of AD, as well as those without atopic comorbidities, may exhibit less prominent Th2 skewing. The downregulation of Th2 immune response following DUP use in these individuals may lead to an abrupt skewing towards Th1, potentially promoting the pathogenesis of AA and subsequent hair loss.(103)

Baricitinib has recently been approved by the AIFA (105) for the treatment of AA with Severity of Alopecia Tool (SALT) score >50, based on the results of two randomized, placebo-controlled Phase 3 trials (BRAVE-AA1 and BRAVE-AA2) (106) . BRAVE-AA1 trial, focusing on patients with severe AA, showed that at week 36, the percentage of patients achieving a SALT score of 20 or less was 38.8% for 4-mg BAR, 22.8% for 2-mg BAR, and 6.2% for placebo. Similarly, in BRAVE-AA2, the corresponding figures were 35.9%, 19.4%, and 3.3%, respectively. Although there is currently no post hoc analysis on trials involving patients with both AA and AD, such an analysis could provide valuable insights into the efficacy of BAR as a simultaneous treatment for both conditions. A case series involving three adult patients affected by both AA and AD reported the efficacy of BAR in leading to clinical improvement of diseases(107). A single patient case report highlighted the efficacy of switching from 2 mg to 4 mg of daily BAR in improving AD signs in a 45-year-old male treated for his patchy AA (108)

A randomized, double-blind, placebo-controlled pilot study (NCT02684097) was started to evaluate the efficacy of TRA in AA. The study enrolled a total of 30 participants with moderate to severe AA, with 50% expected to have concomitant AA and AD. The TRA group received subcutaneous injections every two weeks for 24 weeks, while the placebo group received saline injections as a control. Of the enrolled participants, 2 in the TRA group and 1 in the placebo group completed the study, while the remaining participants discontinued due to lack of efficacy (109).

The use of UPA in the treatment of AA and related conditions has shown promising results, as highlighted in recent studies. In a multicenter retrospective study by Chiricozzi et al. (110) UPA demonstrated beneficial effects on AA associated with AD, with a significant reduction in mean baseline SALT score from 95.1 ± 9.6 to 77.6 ± 28.2 after 4 weeks of treatment. The study also reported incremental decreases in SALT score over time, with a higher percentage of patients achieving SALT50, SALT75, SALT90, and SALT100 responses. Previously, Cantelli et al reported the case a 24-year-old patient with a history of AD and severe AA who was treated with UPA after the failure of previous therapies. After 3 months of UPA therapy, significant clinical improvement was observed in both AD and AA, with regrowing hair all over the scalp and no signs of disease activity (111). More data regarding the pediatric populations are coming from case series. The study by Dianhe Yu and Yunqing Ren reported a case of successful treatment with UPA in a child with alopecia universalis (AU) and mild AD (EASI 2.5) (112). The patient experienced substantial hair regrowth after 4 weeks of UPA treatment, with a marked improvement in the SALT score from 100% at baseline to 0% at week 12. Similarly, Bourkas and Sibbald (113) reported a pediatric patient with AA and severe AD achieving a reduction in the SALT score from 95.1 ± 9.6 at baseline to 77.6 ± 28.2 at week 4, indicating a positive response to UPA therapy. The role of ABR in the treatment of

AA has been investigated only in case reports up to now. In the study by Bennett et al.(114), a 33-year-old male with severe AD and chronic universal AA achieved complete remission of AA with ABR. Similarly, Zhao et al. (115) reported a case of a 14-year-old girl with AD and AU who experienced thick regrowth of terminal hairs on various body parts after ABR treatment. Huang et al (116) presented a case of refractory AA in an 11-year-old boy, where ABR led to significant hair regrowth after 4 months of therapy. These case reports provide valuable insights into the potential efficacy of ABR for the treatment of AA, including in pediatric patients.

Vitiligo

Biologics and vitiligo: DUP and TRA

Vitiligo onset or exacerbation represent a rare cutaneous adverse event reported during DUP therapy. Non-segmental vitiligo with facial involvement represented the most common type. DUP-associated vitiligo showed a good prognosis in most of the cases with response to topical treatments or narrow-band UVB phototherapy. However, DUP discontinuation was necessary in three patients with non-responsive and rapidly worsening vitiligo (117–120). Currently no data are available on association between TRA administration and vitiligo.

JAK inhibitors and vitiligo: UPA, BAR and ABR

The JAK/STAT signaling pathway is involved in vitiligo pathogenesis. Ruxolitinib and tofacitinib lead to vitiligo improvement in most of cases. However less is known about the effect of other type of JAKi. Pan et al. reported a 16-year-old boy with both AD and vitiligo successfully treated for both conditions with UPA 15 mg (121). Preliminary data showed that BAR was effective in vitiligo treatment (122–124). No data are available about ABR effects on patients affected by vitiligo.

Psoriasis

DUP-associated psoriasis and psoriasiform manifestations include plaque, guttate, erythrodermic, pustular and reverse psoriasis (85,125–141) . DUP downregulates the Th2 pathway, and might lead to Th17 subsets shift and the activation of IL-23/Th17 axis in psoriasiform lesions (142,143) . In patients affected by psoriatic arthritis UPA 15 mg provided a positive response on plaque psoriasis in 52.3% of cases (144) . Gargiulo et al reported four patients with concomitant psoriasis and AD successfully treated with UPA for both conditions(145). Moreover UPA demonstrated effective in a 58-year-old female with psoriasiform dermatitis induced by DUP (146) .

However, the phenotypic switch from AD to psoriasis during treatment with UPA was recently described(147). In a randomized phase 2b trial of BAR a positive clinical response was documented

in patients with moderate-to-severe psoriasis (148). Moreover, BAR was successfully administered in AR patients with psoriasis induced by bDMARDs (149). Currently no data are available on TRA and ABR in psoriatic patients.

Patients with neoplasm history

The associations between AD and cancer are not yet well understood. Two cohort studies from England and Denmark did not find evidence of an association between AD and most cancers , except for lymphomas(150,151). However, it was observed that AD patients with severe long-term disease have a higher risk of developing lymphoma in adulthood, (1,150) and there have also been reports of pediatric cases (152).

DUP and TRA in patients with neoplasm history

Patients with a history of malignancy are generally excluded from biologics clinical trials. However, real-life studies have shown that DUP is not associated with an increased risk of malignancy (153) and can be considered a safe option for patients with a history of solid neoplasms(154–156) .

The relationship between DUP and the risk of developing lymphomas, particularly cutaneous T-cell lymphomas (CTCL), is controversial. While Th2-cytokines, including IL-4 and IL-13, are overexpressed in advanced CTCL, (157) the use of DUP has been associated with the onset or progression of CTCL in several cases (158–164).

Furthermore, other types of lymphomas such as the anaplastic large-cell lymphoma, cytotoxic T-cell lymphoma, angioimmunoblastic T-cell lymphoma, and Hodgkin lymphoma have been reported during DUP therapy (165–169). The current available published data provide reassurance regarding the use of DUP in patients with a history of solid tumors, but caution must be exercised in the case of hematological malignancies.

There is a lack of real-life studies examining the risk of cancer in patients treated with TRA. In the ECZTEND safety analysis, the occurrence of tumors diagnosed after randomization was very rare (0.8%) (170) .

Despite the limited evidence, biologics, including DUP and TRA, are considered the preferred treatment options for patients with AD and a history of cancer based on their mechanism of action and expert opinion (11).

A case-by-case approach and multidisciplinary discussion involving oncologists and hematologists are recommended to guide treatment decisions in these patients.

5.2 UPA, ABR and BAR in patients with neoplasm history

Patients with active cancer or a history of several cancers are generally not suitable candidates for treatment with JAKis (171) .

EMA has formulated some measures to minimize the risk of serious side effects, and JAKis should be considered in patients with malignancy risk factors, only if anti-IL therapies are no suitable options (172).

It is important to note that most of the safety concerns regarding JAKis, particularly tofacitinib, have emerged from post-marketing studies conducted in RA patients. (173). A study by Burmester et al. evaluated the safety profile of UPA in a large cohort of 6,991 patients, including 2,693 patients with AD. In AD patients, the rates of malignancy were higher with UPA 30 mg compared to UPA 15 mg. It is worth noting that four out of the nine malignancies observed with UPA 30 mg occurred within 6 months after starting the treatment. Overall, this analysis confirmed the known safety profile of UPA without identifying any new safety risks (56). Regarding ABR treatment, cancer events reported during phase 2 and 3 studies were rare, with cases of non-melanoma skin cancer (NMSC) and lymphoma being reported (35). Malignancies reported during BAR treatment were rare, and included NMSC, lymphomas, breast cancer and papillary thyroid cancer (27).

Caution should be exercised when considering JAKis in patients with a history of cancer or active cancer.

Patients with childbearing and breastfeeding potential

AD is the most frequent skin disease during the first and second trimesters of pregnancy. The onset or the recurrence of AD during gestation is called ‘‘atopic eruption of pregnancy’’ and should be distinguished from other pruritic eruptions(174). JAKis, including UPA, BAR e ABR, are contraindicated in pregnancy and breastfeeding based on animal studies that showed teratogenic effects (51–53). Therefore, women of child-bearing potential must be advised to use effective contraception during treatment and for 4 weeks following the last dose of JAKi. No data are available on the excretion of JAKis in human milk, but this is likely due to their pharmacokinetics. Regarding DUP, it appears to be safe for use during pregnancy. An analysis of the VigiBase pharmacovigilance database showed that DUP use was not associated with an increased risk of abortion, pre-eclampsia, or pre-term premature rupture of membranes. The only event with an odds ratio greater than 1 was the risk of ectopic pregnancy, although only one case was reported (175).

Escolà et al published a case series of 13 women who were exposed to DUP during pregnancy and breastfeeding with no reported side effects and excellent maternal-fetal outcomes(176).

Moreover, DUP proved to be effective and safe during pregnancy in a woman affected by AD, hyper IgE syndrome and ulcerative colitis (177).

However, it is important to note that safety data on biologics, including DUP and TRA, during pregnancy are still limited and continuous surveillance is needed. (178)

Pediatric and adolescent patients

AD commonly develops in early childhood and affects up to 20% of children. AD can lead to anxiety, depression, and reduced quality of life, impacting on social life and school performance.

Dupilumab

DUP has shown significant improvement in AD signs, symptoms, and quality of life in adolescents and children with moderate to severe AD, with an acceptable safety profile.

A phase 3 clinical trial (NCT03054428) demonstrated the efficacy and safety of DUP in adolescents aged 12-17 years who had inadequate control with topical medications or for whom topical therapy was not advisable. The every-2-week regimen was more effective than the every-4-week regimen. Adverse events such as conjunctivitis, injection-site reactions, and non-herpetic skin infections were observed, but were generally of mild-to-moderate severity and resolved during the trial (179) .

DUP in combination with topical corticosteroids (TCS) also showed efficacy and safety in a phase 3 study (NCT03345914) on children aged 6-11 years with severe AD that was inadequately controlled with topical therapies. Injection-site reactions and conjunctivitis were the most notable adverse events during DUP treatment, but they were generally mild-to-moderate in severity and resolved during the trial (180).

A recent phase 3 study (NCT03346434) evaluated DUP in combination with low-potency TCS in children with moderate-to-severe AD aged from 6 months to less than 6 years, showing efficacy and an acceptable safety profile similar to older children, adolescents, and adults (179) .

In a real-life Italian study on 139 adolescents with moderate-to-severe AD, DUP confirmed its efficacy and safety profile (181). In Italy, DUP is approved and reimbursed in adolescent (12-17 years) and pediatric (6-11 years) patients.

Tralokinumab

TRA has demonstrated effectiveness in the phase 3 ECZTRA 6 trial on adolescents aged 12-17 years with moderate-to-severe AD. Most adverse events were non-serious and mild or moderate in severity, including conjunctivitis, which had a low incidence and similar occurrence between TRA and placebo arms at week 16. No increases in conjunctivitis were observed up to 52 weeks of treatment. Moreover, in the TRA 300 mg arm there were no cases of conjunctivitis, and fewer AD exacerbation compared to the TRA 150 mg arm(182). Currently in Italy TRA is still not yet approved for AD in adolescents.

Upadacitinib

UPA has demonstrated efficacy on adolescent aged 12-17 years in three phase 3 clinical trials: Measure Up 1 (NCT03569293), Measure Up 2 (NCT03607422), and AD Up (NCT03568318). In all these trials the benefit-risk profile was favorable, and the most common adverse events were acne, headache, upper respiratory tract infection, creatine phosphokinase level elevations, and nasopharyngitis(183–185). These data were confirmed by De Greef et al. in a case series including seven adolescent patients(186). In Italy, UPA is approved but not yet reimbursed (as of July 2023) for AD in adolescents aged 12-17 years.

Abrocitinib

In JADE MONO-1 (NCT03349060) and JADE MONO-2 (NCT0357587) phase 3 clinical trials, ABR 100 mg and 200 mg monotherapy were administered to adolescent and adult patients with moderate-to-severe AD (34,187). In JADE TEEN phase 3 study (NCT03796676), ABR 100 mg e ABR 200 mg in combination with topical therapy were administered to adolescent patients(188).

In all the studies both ABR doses resulted in significant improvement in AD signs and symptoms compared with placebo in adolescents. Most adverse events were mild and infrequently required interruption or permanent discontinuation of ABR therapy. The most common adverse events included nausea, nasopharyngitis, headache, upper respiratory tract infection and acne (35,188). Currently in Italy ABR is not yet approved for the treatment of AD in adolescents.

Baricitinib

A phase 3 randomized controlled trial (BREEZE-AD PEDS) evaluated the effectiveness of BAR in combination with TCS for treating moderate-to-severe AD in 438 children aged 2 to < 18 years. Participants were randomly assigned to receive placebo or daily doses of BAR (1 mg, 2 mg, or 4 mg) for 16 weeks. The primary endpoint, defined as achieving a ≥ 2-point improvement in the Investigator Global Assessment (vIGA-AD) with a final score of 0/1 at week 16, was met by 16.4%, 18.2%, and 25.8% of patients in the placebo, BAR 2 mg, and BAR 4 mg groups, respectively. Compared to placebo, the BAR 4 mg group demonstrated statistically significant improvements in secondary endpoints, including EASI-75, EASI-90, mean change in EASI score, SCORAD 75, and Itch NRS with 4-point improvement for patients aged ≥ 10 years (189).

Elderly patients

Based on the location and evolution of eczematous lesions at different ages, three groups of AD patients have been well-established: infantile-type, childhood-type and adolescent and adult-type. Elderly-type AD has recently been considered a fourth separate group (190). Studies estimate that 2 to 7% of the elderly population (> 65 years) is affected by AD (191). Elderly patients need more consideration in the therapeutic choice. A complete clinical history must include history of cancer, comorbidities, comedications, cognitive decline and ability to self-administer medications. Clinical evidence about the effectiveness and safety of biologics and small molecules in the elderly population is still limited. Clinical trials usually exclude older people due to upper age restrictions or exclusion criteria for common comorbidities (192).

To date 7 trials for DUP did not have explicit upper age limits, although only 4% of participants were over age 65 (192) . Four retrospective studies on the treatment of AD in patients aged ≥65 years on DUP demonstrated similar efficacy to younger adults (193–195). One of these studies showed that older people had a higher incidence of adverse events: injection-site reactions and conjunctivitis being the most common (194).

In TRA studies there was no safety or efficacy difference between the older and younger cohorts, with only 4.8% of the patients being over 65 (196). Currently, there is no specific data available for the use of TRA in the real-world setting in the elderly. However, we would assume that TRA safety and effectiveness profile in the elderly would be comparable to DUP due to similar mechanism of action. There are limited data in the literature on the use of JAKis in the elderly population, especially in patients over 75 years of age. According to the prescribing information for JAKis, older people may carry higher risks of adverse events compared with younger adult patients (51–53).

Before starting therapy with JAK inhibitors, it is currently recommended 1. to consider general risk factors for cancer (age > 65 and smoking) and to explore any history of cancer; 2. to assess risk factors for cardiovascular and thromboembolic events, and to rule out any history of these events; 3. to evaluate the serum lipid profile and to pay attention to dyslipidemia. Clinical trials on UPA treatment in moderate-to-severe AD included patients aged 12 to 75 years. Data from AD Up, Measure Up 1, and Measure Up 2 trials showed an exposure-adjusted rate of AEs higher in patients ≥65 years of age receiving UPA 30 mg compared to patients ≥65 years of age receiving UPA 15 mg and patients <65 years of age receiving either UPA 15 mg or 30 mg (197).

Simpson et al. published an integrated safety analysis of ABR for the Treatment of Moderate-to-Severe AD. Adults over 65 years receiving ABR were 5.1%. A multivariate analysis found that age ≥65 years was associated with higher risk of herpes zoster. Malignancies cases occurred in 71.4% of cases in patients ≥ 60 years old. Three patients aged ≥ 60 years old experienced a major adverse

cardiovascular event, including two events of myocardial infarction and one event of sudden death (35) . More data are needed on BAR safety in elderly patients with AD (198) .

We suggest that the first-choice therapy should be biologics because have the most data supporting its use in elderly patients, in particular on DUP use.

Conclusions

Treatment selection for patients with comorbidities and special populations affected by moderate to severe AD is complex, and the purpose of this review is to provide an algorithm for dermatologists to guide the choice of biologics and small molecules. Such an algorithm may undergo changes once new evidence become available.

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Table 1. Evidence-based treatment algorithm for moderate-to-severe AD in patients with comorbidities and in special populations.

	Biologics		Small-molecules JAK inhibitors		
	Dupilumab	Tralokinumab	Upadacitinib	Abrocitinib	Baricitinib
Asthma	↑↑				
Allergic rhinitis and CRSwNP	↑↑				
Ocular surface disease	↓		↑	↑	↑
Herpes simplex virus	↑	↑	↓	↓	
Herpes zoster	↑	↑	↓	↓	↓
HBV	↑	↑	↓	↓	↓
HIV	↑				
Latent/untreated TB	↑	↑	↓↓	↓↓	↓↓
Arthritis	↓		↑↑		↑↑
Inflammatory bowel disease	↑	↑	↑↑		
Alopecia areata			↑		↑↑
Vitiligo	↓				
Psoriasis	↓		↑		
Solid tumor	↑	↑	↓↓	↓↓	↓↓
Hematologic neoplasm	↓	↓	↓↓	↓↓	↓↓
Pregnancy breastfeeding			↓↓	↓↓	↓↓
Pediatric patients	↑↑				
Adolescent patients	↑↑		↑↑		
Elderly patients	↑	↑	↓	↓	↓

↑↑	Preferable choice
↑	Possible choice
	See the main text for specific recommendation
↓	Not recommended as first line choice
↓↓	Contraindicated or not advisable choice