Optimal Use of Jak Inhibitors and Biologics for Atopic Dermatitis on the Basis of the Current Evidence

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Recently, Jak inhibitors such as baricitinib, upadacitinib, and abrocitinib were approved for the treatment of atopic dermatitis (AD) in addition to biologics, including dupilumab, tralokinumab, and nemolizumab. The increase in treatment options can be a benefit to patients with AD. Meanwhile, it could make it difficult for physicians to choose the best treatment among those treatment options. Biologics and Jak inhibitors differ in efficacy, safety, route of administration, and whether or not there is a concern about immunogenicity in addition to the evidence on comorbidities. Among the three Jak inhibitors, the degree of inhibition of signal transducer and activator of transcription differs in each Jak inhibitor. Therefore, the efficacy and safety profiles of the three Jak inhibitors are different. Physicians who treat patients with AD with Jak inhibitors and biologics need to understand the current evidence and choose the best treatment for individual patients. In this review, we discuss how integrating knowledge of the mechanisms of action of Jak inhibitors and biologics, the potential significant adverse events of these drugs, and the age and comorbidities of the patient can help achieve optimal clinical benefit for patients with moderate-to-severe AD refractory to topical agents.

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INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease with pruritus, characterized by recurrent eczema with exacerbations and remissions, impairs patients' QOL, and places a heavy burden. Although most of the patients are successfully treated with topical therapy, including corticosteroids, tacrolimus (a calcineurin inhibitor) (Nakagawa et al., 1994), delgocitinib (a Jak inhibitor) (Nakagawa et al., 2021), and difamilast (a phosphodiesterase-4 inhibitor) (Saeki et al., 2022), some of the patients need phototherapy or systemic therapy such as oral corticosteroid, cyclosporine, and methotrexate. However, the effectiveness of phototherapy and these conventional systemic treatments is insufficient in certain patients. Furthermore, owing to safety concerns, some of them are not approved for the treatment of AD in some countries, and even in the countries where they have been approved, they are recommended to be used for the short term (Katoh et al., 2020). Insufficiency of effectiveness and safety concerns of conventional systemic therapy were unmet needs in AD treatment.

Recently, new biologics and oral drugs with high efficacy and tolerable safety have been approved for the treatment of AD. At present, Jak inhibitors such as baricitinib, upadacitinib, and abrocitinib are available for patients with AD in addition to dupilumab, an anti−IL-4Rα antibody; tralokinumab, an anti−IL-13 antibody; and nemolizumab, an anti−IL-31RA antibody. The increase in treatment options can be of benefit to patients with AD. Meanwhile, it could make it difficult for physicians to choose the best treatment among those treatment options. Biologics and Jak inhibitors differ in efficacy, safety, route of administration, and whether or not there is a concern about immunogenicity in addition to the evidence on comorbidities. Among the three Jak inhibitors, the degree of inhibition of signal transducer and activator of transcription (STAT) differs in each Jak inhibitor. Therefore, the efficacy and safety profiles are different among the Jak inhibitors. Physicians who treat patients with AD with Jak inhibitors and biologics need to understand the current evidence and select the best treatment for individual patients. In this review, we discuss how integrating knowledge of the mechanisms of action of Jak inhibitors and biologics, the potential significant adverse events of these drugs, and the age and comorbidities of the patient can help achieve optimal clinical benefit for patients with moderate-to-severe AD.

Cytokines and Jaks in the pathogenesis of AD, the immune response, and homeostasis

AD is characterized by complex interactions between genetic and environmental factors, such as skin barrier dysfunction, allergy/immunity, and pruritus (Otsuka et al., 2017). A variety of cytokines are involved in the pathogenesis of AD. IL-4 and IL-13 suppress the expression of FLG, resulting in skin barrier dysfunction. IL-31, thymic stromal lymphopoietin, IL-4, and IL-13 are involved in pruritus. IL-5 activates eosinophils.

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Abbreviations: AD, atopic dermatitis; CI, confidence interval; CPK, creatine kinase; EASI, Eczema Area and Severity Index; HR, hazard ratio; IGA, Investigator's Global Assessment; NMSC, nonmelanoma skin cancer; NRS, numerical rating scale; PP-NRS4, 4-point improvement in Peak Pruritus Numerical Rating Scale; RA, rheumatoid arthritis; STAT, signal transducer and activator of transcription; VAS, visual analog scale

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IL-22 drives the proliferation of keratinocytes in the chronic phase. Those cytokines bind to specific receptors and allow activation of Jak, inducing the phosphorylation of STAT (Jak–STAT signaling pathway). Because Jak1 is involved in the signaling pathway of those key cytokines for AD (Chovatiya and Paller, 2021), inhibition of Jak1 leads to improvement of AD. Jak inhibitors inhibit a wider range of signaling pathway of these AD-associated cytokines, whereas dupilumab, tralokinumab, or nemolizumab does so of only IL-4 and IL-13, IL-13, or IL-31, respectively (Figure 1). However, Jak is expressed not only in receptors of cytokines associated with AD but also in receptors of cytokines that contribute to homeostasis and the immune response (Traves et al., 2021). For instance, IFN-α plays an important role in the innate immune response, and its receptor harbors Jak1 and TYK2. IFN-γ is associated with innate antiviral defense, and its receptor harbors Jak1 and Jak2. GM-CSF and erythropoietin are involved in erythropoiesis, myelopoiesis, and platelet production, and their receptors harbor Jak2. Therefore, strong inhibition of Jak1 and Jak2 could cause adverse events, including herpes and anemia, in addition to amelioration of AD.

Differences among Jak inhibitors for AD

The three Jak inhibitors are not the same. First, the selectivity of inhibition of Jak is different. Baricitinib is a Jak1/2-selective inhibitor, whereas upadacitinib and abrocitinib are Jak1-selective inhibitors. However, we should be aware that the selectivity of inhibition of Jak is relative. Increased dose of administration can inhibit other Jaks. For instance, although upadacitinib is a Jak1-selective inhibitor, clinical trials showed that the incidence of anemia, which is one of the adverse effects of Jak2 inhibition, was higher in patients treated with 30 mg of upadacitinib (1.4%) than in those treated with 15 mg of upadacitinib (0.3%) or placebo (0.4%) during 0–16 weeks (AbbVie, 2021). Furthermore, the degree of Jak–STAT inhibition is not the same among these Jak inhibitors. Traves et al. (2021) compared the degree of Jak–STAT inhibition by Jak inhibitors, utilizing PBMCs and whole blood from healthy donors and patients with rheumatoid arthritis (RA). Inhibition of STAT was generally stronger in cells treated with upadacitinib than in those treated with baricitinib, indicating that the degree of STAT inhibition by individual Jak inhibitors is different. Indeed, reflecting these results, the efficacy for AD and safety profiles were different in clinical trials of each Jak inhibitor (Tables 1 and 2). Although baricitinib inhibits Jak2 in addition to Jak1, the degree of inhibition is relatively mild. Clinical trials of baricitinib showed mild efficacy with tolerable safety. Regarding anemia, one of the possible adverse effects caused by Jak2 inhibition, severe anemia (grade 3 or more), was not observed in the pooled safety data from eight clinical trials of baricitinib (Bieber et al., 2021b). In addition to the selectivity of inhibition of Jak, the degree of inhibition is also important in understanding the differences among Jak inhibitors.

In general, low-molecular-weight compounds inhibit a wide range of signaling pathways, whereas biologics inhibit specific cytokine signaling pathways. Therefore, strong potency or a high dose of low-molecular-weight compounds is associated with safety concerns, which is applicable to Jak inhibitors for AD. Jak inhibitors with high efficacy showed higher incidences of specific adverse events, including herpes zoster (Tables 1 and 2). Regarding efficacy, a network meta-analysis showed that 30 mg of upadacitinib had the highest efficacy, followed by 200 mg of abrocitinib and 15 mg of upadacitinib, then 100 mg of abrocitinib, 4 mg of baricitinib, and 2 mg of baricitinib in terms of the Eczema Area and Severity Index (EASI)-75 at weeks 12–16 (Pereyra-Rodriguez et al., 2021). Although dupilumab or tralokinumab is not a Jak inhibitor, the efficacy of dupilumab was similar to that of 15 mg of upadacitinib, and that of tralokinumab was to that of baricitinib. As for adverse events observed in clinical trials of monotherapy, the incidence of any adverse event was higher in clinical trials of upadacitinib and abrocitinib than in clinical trials of baricitinib and biologics. A similar trend was observed in other network meta-analyses (Drucker et al., 2022; Silverberg et al., 2022; Wan et al., 2022). In contrast, biologics such as dupilumab and tralokinumab specifically inhibit IL-13 and/or IL-4 and showed relatively high efficacy with good safety profiles, although they have other concerns, including conjunctivitis.

RESULTS

Efficacy and safety of Jak inhibitors for AD

Before focusing on the characteristics of individual Jak inhibitors, we mention the safety of Jak inhibitors. Baricitinib and upadacitinib are also used for the treatment of RA. However, their safety profiles in clinical trials of patients with AD were different from their safety profiles in clinical trials of those with RA probably owing to the differences in age and immune conditions of the patients. Generally, the safety profiles of drugs in patients with AD are better than those in patients with RA when the same drugs are administered. When explaining the characteristics of Jak inhibitors to patients with AD, the explanation should be based on the evidence of clinical trials in patients with AD (real-world data are lacking as of now) instead of those in patients with RA or other diseases. Clinical trials of tofacitinib, a Jak1, 2, 3 inhibitor, raised potential safety concerns of increased risks of serious infection, malignancy, cardiovascular events, thrombosis/embolism, and gastrointestinal perforation (Cohen et al., 2020; Wollenhaupt et al., 2019; Ytterberg et al., 2022). However, increased risks of these events have not been reported in clinical trials of baricitinib, upadacitinib, or abrocitinib in patients with AD to date, although a few cases were observed. It is important not to choose Jak inhibitors for patients who are at risk for these diseases, but deprival of the benefits of Jak inhibitors by overestimating the risks should be avoided. We should understand the safety evidence of individual Jak inhibitors, know which patients are at high risk for adverse events, and not administer Jak inhibitors as a first-line therapy for those patients. The right choice of drugs leads to maximizing benefits and minimizing risks. However, safety data on the long-term use of Jak inhibitors in patients with AD are limited. Only safety data on the administration of Jak inhibitors to patients with AD for a period of approximately 1 year have been published to date. Meanwhile, safety data on the administration of upadacitinib and baricitinib to patients with RA for a longer period of time are available. Considering that the safety profiles in patients with AD are better than

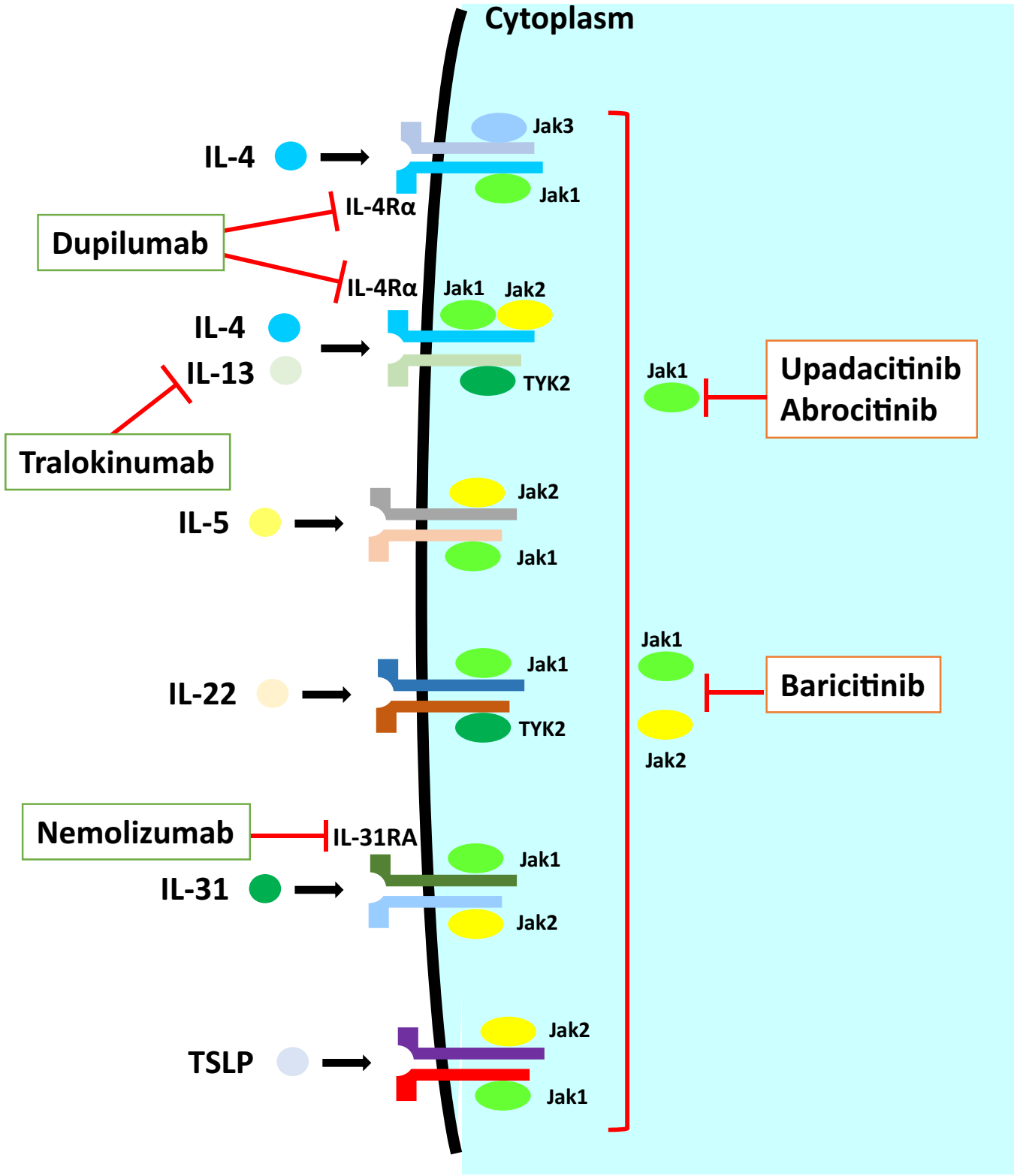

Figure 1. Different mechanisms of action of Jak inhibitors and biologics in the treatment of atopic dermatitis. Jak inhibitors inhibit a wider range of signaling pathways of atopic dermatitis–associated cytokines, whereas dupilumab, tralokinumab, or nemolizumab do so of only IL-4 and IL-13, IL-13, or IL-31, respectively

those in patients with RA, the safety profiles in patients with RA could be useful for dermatologists who treat patients with AD with the same Jak inhibitor, especially for long-term use.

Several clinical trials of Jak inhibitors have been conducted. In this paper, we mainly mention the results of monotherapy clinical trials (without topical corticosteroids). The

Table 1. Efficacy of Jak Inhibitors for Atopic Dermatitis in Clinical Trials at 12–16 Weeks

	Baricitinib Versus Placebo (16 wk) BREEZE-AD1 (Simpson et al., 2020a)			Abrocitinib Versus Placebo (12 wk) JADE MONO-1 (Simpson et al., 2020b)			Upadacitinib Versus Placebo (16 wk) Measure Up 1 (Guttman-Yassky et al., 2021)		
	Placebo	2 mg	4 mg	Placebo	100 mg	200 mg	Placebo	15 mg	30 mg
vIGA-AD response[1] (%)	4.85	11.4	16.8	8	24	44	8.4	48.1	62.0
EASI-75 (%)	8.8	18.7	24.8	12	40	63	16.3	69.6	79.7
EASI-90 (%)	4.8	10.6	16.0	5	19	39	8.1	53.1	65.8
EASI-100 (%)	ND	ND	ND	ND	ND	ND	1.8	16.7	27.0
Pruritus NRS response[2] (%)	7.2	12.0	21.5	15	38	57	11.8	52.2	60.0

Abbreviations: EASI, Eczema Area and Severity Index; ND, not described; NRS, numerical rating scale; vIGA-AD, validated Investigator Global Assessment for Atopic Dermatitis.
[1]Defined as a vIGA-AD score of 0 (clear) or 1 (almost clear) with ≥2 grades of reduction from baseline.
[2]Defined as a 4-point improvement in pruritus NRS score.

results described below are all from multicenter, double-blind, randomized, placebo-controlled phase III trials.

Baricitinib. Adult patients with moderate-to-severe AD were enrolled in the BREEZE-AD1 trial of baricitinib. The percentage of patients with AD achieving Investigator's Global Assessment (IGA) score of 0 of 1 at 16 weeks was 16.8% among patients receiving 4 mg of baricitinib, 11.4% among those receiving 2 mg of baricitinib, and 4.85% among those receiving the placebo (Simpson et al., 2020a). The percentage of patients achieving EASI-75 was 24.8, 18.7, and 8.8%, respectively. Reduction rates of numerical rating scale (NRS) scores of pruritus were 36.6, 29.4, and 12.0%, respectively. Baricitinib significantly improved dermatitis and pruritus in patients with AD. In addition, amelioration of sleep disorder and pain was observed. Another clinical trial, the BREEZE-AD2 trial, showed similar results as the BREEZE-AD1 trial. Improvement of depression and anxiety at 16 weeks in patients receiving baricitinib has been reported (Thyssen et al., 2022). Regarding long-term efficacy, data on patients with AD receiving baricitinib for 68 weeks have been reported with maintained efficacy (Silverberg et al., 2021).

As for safety, the results of pooled safety analysis of baricitinib from eight clinical trials are available (Bieber et al., 2021b). A total of 2,531 patients (2,247 per person-year;

Table 2. Incidence of AEs of Interest in Patients with Atopic Dermatitis Treated with Jak Inhibitors (Events per 100 Patient-y)

	Baricitinib 2 mg/4 mg Pooled	Abrocitinib 100 mg	Abrocitinib 200 mg	Upadacitinib 15 mg	Upadacitinib 30 mg
Number of patients	2,531	1,023	2,105	1,239	1,246
Person-y	2,247	849.9	1,238.9	1,373.4	1,414.2
Duration of exposure (days)	310 (median)	ND	ND	405 (mean)	415 (mean)
Severe AEs	ND	ND	ND	12.4	15.2
Serious AEs	6.1	6.7	7.1	7.1	7.7
AEs leading to discontinuation	4.6	10.9	14.3	4.4	5.7
Herpes zoster (global population)	2.3	2.1	4.3	3.5	5.2
Oral herpes/herpes simplex	4.9/4.0	ND/7.1	ND/11.1	5.0/ND	8.8/ND
Acne/Folliculitis	ND/3.2	4.9/ND	13.1/ND	13.3/3.7	20.2/4.1
Headache	7.6	7.5	16.7	7.4	6.6
Nausea	2.1	7.3	30.7	3.0	3.1
Vomit	ND	2.9	6.3	ND	ND
CPK elevation	2.1 (≥10 × ULN)	5.3	7.5	7.1	10.8
Anemia	0.9 (<10 mg/dl), 0 (<8 mg/dl)	0.8	4.8	1.3	3.3
Neutropenia	0.2 (<1000 cells/mm^3)	0.1	1.2	1.8	3.2
Lymphopenia	1.0 (<500 cells/mm^3)	0.6	2.1	0.4	0.6
Thrombocytopenia	1.0 (>600 billions/l)	0.2	4.1	ND	ND
Pancytopenia	ND	0.1	0.2	ND	ND
Hepatic disorders	Few[1]	2.8	4.5	6.1	7.5
References	(Bieber et al., 2021b)	(Pharmaceuticals_and_Medical_Devices_Agency, 2021b)		(Guttman-Yassky et al., 2023)	

Abbreviations: AE, adverse event; CPK, creatine kinase; ND, not described; ULN, upper level of normal.
[1]The number was not described.

median time of observation of 310 days) were analyzed. The incidences of serious adverse events were almost the same between patients receiving baricitinib and those receiving placebo during 0–16 weeks. Under long-term administration, the incidence of herpes zoster was 2.3 events per 100 person-year, indicating a slightly increased risk of herpes zoster. In the Japanese population, it was 2.7 events per 100 person-year (Pharmaceuticals_and_Medical_Devices_Agency, 2022c). Laboratory tests showed slightly elevated serum levels of creatine kinase (CPK), low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol and slightly decreased hemoglobin. Elevated liver enzymes were observed in less than 2% of patients. Although severe adverse events are rare except in patients with renal dysfunction and elderly patients, regular monitoring is necessary, especially in patients taking baricitinib over a long period of time.

As for long-term use of baricitinib, the safety of baricitinib in 3,770 patients with RA over a median of 4.6 years and up to 9.3 years of treatment has been published (Taylor et al., 2022), although there are no data on patients with AD. Baricitinib maintained a similar safety profile as that in earlier analyses. No new safety signals were identified. Analysis of the Japanese RA population revealed that age >50 years was a risk factor for the development of herpes zoster during treatment with baricitinib (hazard ratio [HR] = 1.94, 95% confidence interval [CI] = 1.49–2.52) (Harigai et al., 2021), which is compatible with reports in the general population (Chen et al., 2017; Kawai et al., 2014). Furthermore, Harigai et al., 2021 showed that the live vaccine against herpes zoster did not have any preventive effect on the development of herpes zoster while patients with RA were receiving baricitinib. No evidence of the preventive effect of the subunit vaccine against herpes zoster has been reported yet.

Real-world data of short-term use of baricitinib (Uchiyama et al., 2022; Vittrup et al., 2022) showed effectiveness and tolerable safety similar to the results of clinical trial data, although they are limited. Concomitant strong topical corticosteroid and/or previous use of dupilumab in certain patients could account for the subtle difference in the effectiveness of real-world data from the efficacy of clinical trials.

Baricitinib is mainly excreted by the kidneys. In patients with renal impairment, dose reduction of baricitinib or avoiding baricitinib is recommended according to the severity of renal impairment (Pharmaceuticals_and_Medical_Devices_Agency, 2022b).

Abrocitinib. Patients with moderate-to-severe AD aged >12 years were enrolled in the JADE MONO-1 trial of abrocitinib. The percentage of patients achieving EASI-75 at week 12 was 63% among patients treated with 200 mg of abrocitinib, 40% among those treated with 100 mg of abrocitinib, and 12% among those treated with placebo (Simpson et al., 2020b). The percentage of patients achieving EASI-90 at week 12 was 39, 19, and 5%, respectively. Abrocitinib significantly improved pruritus. Similar results were observed in the JADE MONO-2 trial (Silverberg et al., 2020).

In a head-to-head trial of abrocitinib versus dupilumab (Bieber et al., 2021a), the percentage of patients achieving EASI-75 at week 12 was 70.3% among patients treated with 200 mg of abrocitinib, 58.7% among those treated with 100 mg of abrocitinib, 58.1% among those treated with dupilumab, and 27.1% among those treated with placebo. Although statistical evaluation was not conducted, 200 mg of abrocitinib could be superior in efficacy to dupilumab. Furthermore, another article (Reich et al., 2022) reported that 200 mg of abrocitinib induced earlier reduction of itch and AD signs than dupilumab (proportions of patients reaching a 4-point improvement in Peak Pruritus Numerical Rating Scale [PP-NRS4] at week 2 was 48% in patients treated with abrocitinib and 26% in those treated with dupilumab; EASI-90 at week 4 was 29 and 15%, respectively). The efficacy of these indexes reached almost the same levels at week 26 (PP-NRS4 of 68 and 63% and EASI-90 of 55 and 48%, respectively (Table 3).

Regarding the safety of abrocitinib for AD, integrated safety analysis on data from 2,856 patients with AD (1,614 patient-year) has been reported (Simpson et al., 2021). Nausea (14.6% in patients treated with 200 mg of abrocitinib, 6.1% in those treated with 100 mg of abrocitinib, and 2.0% in those treated with placebo), headache (7.8, 5.9, and 3.5%), and acne (4.7, 1.6, and 0%) were observed in a dose-dependent manner. The incidence of herpes zoster was 4.34 per 100 patient-year in those treated with 200 mg of abrocitinib and 2.04 in those treated with 100 mg of abrocitinib. Multivariate analysis found that 200 mg abrocitinib, age ≥65 years, and severe disease at baseline were associated with a higher risk of herpes zoster (Simpson et al., 2021). In the Japanese population, the incidence of herpes zoster was 9.80 and 5.36 in those treated with 200 mg and 100 mg of abrocitinib, respectively (Ito et al., 2022). Five venous thromboembolism events occurred (0.30 per 100 patient-year), all in the 200-mg group. Laboratory

Table 3. Comparison of 200 mg of Abrocitinib with Dupilumab

	Abrocitinib (n = 362)	Dupilumab (n = 365)
Efficacy (%)		
PP-NRS4 at week 2	48	26
EASI-90 at week 4	29	15
PP-NRS4 at week 16	68	63
EASI-75 at week 26	73	72
EASI-90 at week 26	55	48
EASI-100 at week 26	23	14
Safety: TEAE through week 26 and up to 28 days after the last dose of the study drug (%)		
Severe AE	3	2
Serious AE	2	2
Nausea	19	2
Headache	13	7
Acne or folliculitis	13	3
Conjunctivitis	3	11
Herpes Zoster	2	<1

Abbreviations: AE, adverse event; EASI, Eczema Area and Severity Index; PP-NRS4, 4-point improvement in Peak Pruritus Numerical Rating Scale; TEAE, treatment-emergent adverse event.
Data are presented as per Reich et al. (2022).

findings showed a slight decrease in platelets and increases in serum levels of CPK, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol, without any clinical consequences. The incidence of serious adverse events was higher in elderly patients (aged ≥65 years, 22.8 per 100 patient-year in patients treated with 200 mg of abrocitinib, 16.5 in those treated with 100 mg) than in younger patients (aged <18 years, 5.1 and 6.3 for 200 mg and 100 mg of abrocitinib, respectively; aged 18–64 years, 6.4 and 6.4 for 200 mg and 100 mg of abrocitinib, respectively) (Pharmaceuticals_and_Medical_Devices_Agency, 2021b). In the clinical trial of 200 mg of abrocitinib versus 300 mg of dupilumab (Reich et al., 2022), the incidences of adverse events of nausea, headache, and acne/folliculitis were higher in patients receiving abrocitinib than in those treated with dupilumab (Table 3). The incidence of conjunctivitis was higher in patients receiving dupilumab.

The primary route of elimination of abrocitinib is through cytochrome P450 hepatic metabolism. Abrocitinib is not indicated for patients with severe hepatic impairment. In addition, dose reduction should be considered for patients with renal dysfunction (Pharmaceuticals_and_Medical_Devices_Agency, 2021a).

Upadacitinib. Patients with moderate-to-severe AD aged >12 years were enrolled in the Measure Up 1 trial of upadacitinib. The percentage of patients achieving EASI-75 at 16 weeks was 79.7% in patients treated with 30 mg of upadacitinib, 69.6% in those treated with 15 mg of upadacitinib, and 16.3% in those treated with placebo (Guttman-Yassky et al., 2021). The percentage of patients achieving EASI-90 was 65.8, 53.1, and 8.1%, respectively, and the percentage of patients achieving EASI-100 was 27.0, 16.7, and 1.8%, respectively. Significant improvement in pruritus was observed. The results of another clinical trial, Measure Up 2, were similar to those mentioned earlier. In the head-to-head trial of 30 mg of upadacitinib versus 300 mg of dupilumab (Blauvelt et al., 2021), 61.1, 38.7, and 7.6% of patients treated with dupilumab showed EASI-75, EASI-90, and EASI-100, respectively, whereas 71.0, 60.6, and 27.9% of those treated with upadacitinib did so (Table 4). The percentage change from baseline of worst pruritus NRS was −8.8% in the dupilumab group and −31.4% in the upadacitinib group at 1 week and −49.0 and −66.9%, respectively, at 16 weeks. This clinical trial revealed the superiority of upadacitinib to dupilumab in efficacy toward eruption and pruritus and rapid onset of efficacy of upadacitinib.

The analysis of integrated safety data from the phase 2 clinical trials and phase 3 trials (Measure Up 1, Measure Up 2, AD Up, and Rising Up) (AbbVie, 2021; Katoh et al., 2021; Reich et al., 2021b; Simpson et al., 2022) showed no significant difference in the incidence of serious adverse events during 0–16 weeks between placebo and upadacitinib. Acne was observed in 15.5% of patients treated with 30 mg of upadacitinib, 9.9% of those treated with 15 mg of upadacitinib, and 2.5% of those treated with placebo. Elevated serum CPK levels (5.2, 4.2, 2.1%), anemia (1.4. 0.3, 0.4%), and neutropenia (3.0, 1.1, 0.3%) were reported in a dose-dependent manner (AbbVie, 2021). Long-term safety data pooled from phase 3 clinical trials (Measure Up 1, Measure Up 2, AD Up, Rising Up, and Heads Up) up to 52 weeks (AbbVie, 2021; Blauvelt et al., 2021; Katoh et al., 2021; Reich et al., 2021b; Simpson et al., 2022) showed that the incidence of acne was 23.2 events per 100 person-year in patients treated with 30 mg of upadacitinib and 14.5 in those treated with 15 mg of upadacitinib. The incidence of CPK elevation was 10.0 and 7.4, respectively, and that of herpes zoster was 5.8 and 3.7, respectively. The incidence of herpes zoster in the Japanese population of patients with AD treated with 30 mg or 15 mg of upadacitinib was 14.7 or 7.2, respectively (Katoh et al., 2021). Elevated liver enzymes, anemia, and neutropenia were also reported in a few patients in the analysis of long-term safety data. In the clinical trial of 30 mg of upadacitinib versus 300 mg of dupilumab (Blauvelt et al., 2021), the incidences of adverse events of serious infection, herpes simplex, herpes zoster, and abnormality in laboratory data were higher in patients receiving upadacitinib than in those treated with dupilumab (Table 4). The incidence of conjunctivitis was higher in patients receiving dupilumab. A few patients injected with dupilumab showed injection-site reactions.

Regarding long-term use of upadacitinib, safety data in patients with RA treated with 15 mg of upadacitinib (7,023.8 person-year; median period of observation = 136 weeks) or 30 mg of upadacitinib (3,091.6 person-year; median period of observation = 160 weeks) were presented (Cohen et al., 2021). Serious infection (5.1 events per 100 person-year in patients treated with 30 mg of upadacitinib and 3.3 in those treated with 15 mg of upadacitinib), herpes zoster (5.9 and 3.3, respectively), anemia (4.2 and 3.3, respectively),

Table 4. Comparison of 30 mg of Updacitinib with Dupilumab

	Upadacitinib (n = 348)	Dupilumab (n = 334)
Efficacy (%)		
% change from baseline in worst pruritus NRS at week 1	−31.4	−8.8
EASI-75 at week 2	43.7	17.5
Worst pruritus NRS improvement ≧4 points at week 16	55.3	35.7
EASI-75 at week 16	71.0	61.1
EASI-90 at week 16	60.6	38.7
EASI-100 at week 16	27.9	7.6
Safety: TEAE through week 16 (%)		
Severe AE	7.2	4.1
Serious AE	2.9	1.2
Serious infection	1.1	0.6
Acne	15.8	2.6
Herpes Zoster	2.0	0.9
Conjunctivitis	1.4	8.4
Anemia	2.0	0.3
Neutropenia	1.7	0.6
Lymphopenia	0.6	0
Creatine phosphokinase elevation	6.6	2.9
Hepatic disorder	2.9	1.2

Abbreviations: AE, adverse event; EASI, Eczema Area and Severity Index; NRS, numerical rating scale; TEAE, treatment-emergent adverse event.
Data are presented as per Blauvelt et al. (2021).

neutropenia (4.6 and 2.3, respectively), elevation of CPK (8.4 and 4.9, respectively), and nonmelanoma skin cancer (NMSC) (1.1 and 0.3, respectively) were observed dose dependently. The high incidence of NMSC in the 30 mg upadacitinib group was due in part to recurrent events (34%). The incidence of gastrointestinal perforation was 0.2 in patients treated with 30 mg of upadacitinib and 0.1 in those treated with 15 mg of upadacitinib (0.0 in those treated with methotrexate and 0.0 in those treated with adalimumab and methotrexate). The incidence of major adverse cardiac events was 0.6 in patients treated with 30 mg of upadacitinib and 0.4 in those treated with 15 mg of upadacitinib (0.3 in those treated with methotrexate and 0.3 in those treated with adalimumab and methotrexate). The incidence of those adverse events increased or seemed to increase in a dose-dependent manner. Further accumulation of evidence on the adverse effects of long-term use of Jak inhibitors in patients with AD is definitely needed.

Data from patients with RA (Yamaoka et al., 2021) showed that age >50 years and a history of herpes zoster were risk factors for the development of herpes zoster during upadacitinib treatment (HR = 1.78, 95% CI = 1.23−2.57 and 18.20, 95% CI = 1.23−2.57). Furthermore, a history of live vaccine against herpes zoster did not reduce the incidence of herpes zoster during upadacitinib treatment (HR = 1.08, 95% CI = 0.59−1.98), similar to the data from patients with RA treated with baricitinib. No data on the subunit vaccine against herpes zoster have been reported yet.

Real-world data of short-term use of upadacitinib (Chiricozzi et al., 2022; Hagino et al., 2022; Napolitano et al., 2022; Pereyra-Rodriguez et al., 2023) showed effectiveness and tolerable safety similar to the results of clinical trial data, although they are limited. Hagino et al. (2022) revealed that baseline total eosinophil count was positively correlated with the percent reduction of EASI at week 4, suggesting that baseline total eosinophil could be a biomarker reflecting therapeutic effects in upadacitinib treatment for AD. Napolitano et al. (2022) reported that the decrease of pruritus at week 16 was higher in their patient population (96.62%) than that reported in clinical trials for 30 mg upadacitinib. Chiricozzi et al. (2022) confirmed elevated effectiveness and favorable safety of upadacitinib in patients unresponsive to dupilumab.

Upadacitinib is metabolized mainly by cytochrome P450 3A hepatic metabolism (Pharmaceuticals_and_Medical_Devices_Agency, 2022). Upadacitinib is not indicated for patients with severe hepatic impairment. Dose reduction should be considered for patients with severe renal dysfunction.

Efficacy and safety of biologics for AD

Dupilumab. The efficacy and safety of dupilumab in clinical trials and effectiveness and safety profiles in real-world settings are described in our previous article (Kamata and Tada, 2021).

Tralokinumab. Patients with moderate-to-severe AD aged ≥18 years were enrolled in the ECZTRA 1 and ECZTRA 2 trials of tralokinumab (Wollenberg et al., 2021). The percentage of patients achieving an IGA score of 0 or 1 at 16 weeks was 15.8% in patients treated subcutaneously with 300 mg tralokinumab every 2 weeks versus 7.1% in those with placebo in ECZTRA 1 and 22.2 versus 10.9% in ECZTRA 2. The percentage of patients achieving EASI-75 at 16 weeks was 25.0 versus 12.7% and 33.2 versus 11.4%, respectively. Reduction of weekly average worst daily pruritus NRS by ≥4 points from baseline to week 16 was achieved by 20.0% with tralokinumab versus 10.3% with placebo in ECZTRA 1 and by 25.0% versus 9.5% in ECZTRA 2. With 2 years of tralokinumab with topical corticosteroid, improvements in the extent and severity of AD were sustained, with EASI-75 in 82.5% of participants (Blauvelt et al., 2022b).

Pooled safety analysis of patients with tralokinumab every 2 weeks (n = 1,605; 473.19 patient-year) and those with placebo (n = 680; 193.1 patient-year) revealed tolerable safety (Blauvelt et al., 2021). As safety concerns of interest, the incidence of eye disorders, including conjunctivitis, keratoconjunctivitis, and keratitis, was higher in patients treated with tralokinumab than in those with placebo (7.9%, 31.1 events per 100 person-year vs. 3.4%, 12.9, respectively) in addition to injection-site reaction (3.5%, 22.9 vs. 0.3%, 4.0). That of eczema herpeticum was lower (0.3%, 1.2 vs. 1.5%, 5.2). That of skin infections requiring systemic treatment was also lower (2.6%, 9.7 vs. 5.5%, 22.8). Long-term use of tralokinumab (over 2 years) was well-tolerated with a safety profile (n = 1,174; 1,235.7 patient-year). The incidences of eye disorders, eczema herpeticum, and skin infections requiring systemic treatment were 6.6%, 7.8 events per 100 patient-year; 0.9%, 0.8 events per 100 patient-year; and 1.8%, 2.2 events per 100 patient-year, respectively. Regarding conjunctivitis, results from five tralokinumab clinical trials including 2,285 adult patients with AD up to 16 weeks were analyzed (Wollenberg et al., 2022). The incidence of conjunctivitis was higher (7.5%) with tralokinumab than with placebo (3.2%). Most events were mild or moderate in severity. An increased incidence of conjunctivitis, regardless of treatment group, was associated with more severe baseline AD and a history of allergic conjunctivitis/atopic keratoconjunctivitis as well as the number of atopic comorbidities.

Nemolizumab. Patients with AD aged ≥18 years with inadequate pruritic response to topical corticosteroids for at least 4 weeks and to oral antihistamines administered for at least 2 weeks and with pruritus visual analog scale (VAS) score of 50 or more (maximum 100) and an EASI score of 10 or more were included in the clinical trial of nemolizumab (Kabashima et al., 2020). At week 16, the mean percentage change in the VAS score was −42.8% in patients treated subcutaneously with 60 mg nemolizumab every 4 weeks and −21.4% in those treated with placebo. The mean percentage change in the EASI score was −45.9% with nemolizumab and −33.2% with placebo. The percentage of patients with a dermatology life quality index score of 4 or less was 40% in the nemolizumab group and 22% in the placebo group. The incidence of injection-site reactions was greater with nemolizumab than with placebo (8%, 3%).

MATERIALS AND METHODS

To evaluate efficacy and safety, we identified articles on clinical trials of baricitinib, abrocitinib, upadacitinib, dupilumab, tralokinumab,

and nemolizumab for AD from the PubMed database. Regarding efficacy, we mainly selected the clinical trials of those drugs in which patients did not use topical agents. Head-to-head comparison clinical trials were also included. In terms of safety, articles on analyses of data pooled from some clinical trials were selected preferentially. Data on safety were also collected from new drug application review reports issued by the Pharmaceuticals and Medical Devices Agency in Japan and proper use guides from pharmaceutical companies. In addition, the latest data presented at international conferences were collected. Real-world evidence was also identified from the PubMed database.

DISCUSSION

Differences between biologics and Jak inhibitors

Because the difference in the mean percentage change in the EASI score at week 16 between nemolizumab and placebo was subtle, we would not expect so much improvement in AD signs from nemolizumab as from other biologics and Jak inhibitors, although nemolizumab showed significant improvement in pruritus. In this point of view, the characteristics of nemolizumab are different from those of other biologics and Jak inhibitors. Therefore, in this section, we mainly discuss the differences between Jak inhibitors and biologics except for nemolizumab, namely, dupilumab and tralokinumab. We include nemolizumab in the discussion section optimal use of biologics and Jak inhibitors.

There are some differences between biologics and Jak inhibitors in addition to the route of administration (subcutaneous vs. oral) and mode of action (Figure 1).

Biologics have possible concerns about immunogenicity (Kamata and Tada, 2021). Although the incidence was quite low (<0.6% of patients), antidrug antibodies could affect the pharmacokinetics and effectiveness of dupilumab in patients with a high titer of over 10,000 (Pharmaceuticals_and_Medical_Devices_Agency, 2022a). Because low trough plasma dupilumab levels are associated with the development of anti-drug antibodies (Worm et al., 2020), short-term use and a repeat of introduction and withdrawal are not recommended in terms of immunogenicity (Kamata and Tada, 2021). Dupilumab and tralokinumab are suitable for maintaining remission in addition to inducing remission. In contrast, oral Jak inhibitors do not have issues of immunogenicity, which allows for short-term use. The flexibility of administration of Jak inhibitors, for example, temporary use, withdrawal, and reinitiation, is one of the strong points of Jak inhibitors. Discontinuation after short-term use could result in rapid loss of efficacy (Guttman-Yassky et al., 2018; Reich et al., 2021a). However, reinitiation brings efficacy to the same extent (Guttman-Yassky et al., 2019; Reich et al., 2021a). To date, data on whether efficacy will be maintained after the withdrawal of Jak inhibitors that have been administered for a long period of time have not been reported yet.

The elimination half-life of biologics, for instance, dupilumab (5.13 ± 1.42 days) (Pharmaceuticals_and_Medical_Devices_Agency, 2022a), is much longer than that of Jak inhibitors (several hours) (Pharmaceuticals_and_Medical_Devices_Agency, 2022b, 2022d, 2021a). Regarding the occurrence of adverse events, discontinuation of Jak inhibitors results in a rapid reduction of the adverse effects of these drugs, whereas adverse effects could last for a while even after withdrawal of dupilumab. Although on the basis of our personal experience, when switching from a Jak inhibitor to dupilumab or tralokinumab, careful attention needs to be paid owing to the differences in elimination half-times and rapidity of onset of efficacy; this needs to be confirmed by clinical trials. Because the effects of Jak inhibitors wear off rapidly and because it usually takes several days or a few weeks for dupilumab and tralokinumab to exert their effects, a temporary flare can occur. Therefore, strengthening topical therapy, concomitant administration of a Jak inhibitor and biologics for a short period of time, or temporary use of cyclosporine for the flare should be considered. Regarding the safety of concomitant administration of a Jak inhibitor and biologics, although it is considered tolerable, a Jak inhibitor and biologics should be administered concomitantly for only a short period of time because data are limited. Conversely, switching from dupilumab or tralokinumab to a Jak inhibitor can usually be performed without inducing flares. During the first few weeks after switching from dupilumab or tralokinumab to a Jak inhibitor, both drugs are having an effect owing to the long elimination half-life of biologics. Immunologically, IL-13 and/or IL-4 are inhibited strongly and/or for a long period of time by dupilumab or tralokinumab in addition to short-term inhibition of a wider range of cytokines by a Jak inhibitor, which might affect the immune response to parasites regarding safety. However, parasitic infection rarely becomes a problem in countries where a Jak inhibitor is approved owing to good hygienic environments. It is speculated that short-term concomitant administration of a Jak inhibitor and biologics such as dupilumab and tralokinumab would not cause serious adverse events, which is supported by the fact that no additional adverse events were observed in patients who switched from dupilumab to upadacitinib at 24 weeks in a clinical trial (Blauvelt et al., 2022a). Furthermore, in this trial, intriguingly, the percentage of patients achieving EASI-90 was numerically higher in those who switched from dupilumab to upadacitinib at 24 weeks than in those treated with only upadacitinib (87.8 and 73.4% at 4 weeks after switching or 28 weeks after initiation of upadacitinib; 89.1 and 71.8% at 8 weeks after switching or 32 weeks after initiation of upadacitinib; 87.7 and 73.6% at 16 weeks after switching or 40 weeks after initiation of upadacitinib). This additional effectiveness suggests that the inhibition of IL-4 and IL-13 signaling pathways by dupilumab could be longer and/or stronger than the inhibition of Jak1/2 by Jak inhibitors. Further research is needed to elucidate this.

The differences in efficacy and onset of action between Jak inhibitors and biologics are described earlier. Abrocitinib and upadacitinib are superior in rapid onset of efficacy to dupilumab. Dupilumab has concerns of conjunctivitis and facial redness, the details of which are described in our previous article (Kamata and Tada, 2021), whereas Jak inhibitors do not increase the risks of conjunctivitis. Dupilumab reduces the risks of cutaneous infections, including eczema herpeticum (Fleming and Drucker, 2018; Ou et al., 2018). Dupilumab is efficacious for asthma, eosinophilic esophagitis, and chronic rhinosinusitis with nasal polyps (Bachert et al., 2019; Castro et al., 2018; Hirano et al., 2020). Tralokinumab also has concerns of conjunctivitis (Blauvelt et al., 2022b; Wollenberg et al., 2022). Tralokinumab showed the tendency

of reduced risks of cutaneous infection, including eczema herpeticum, although statistical analysis has not been conducted. The ages of patients for whom Jak inhibitors and biologics are approved differ according to the drug and country. In Japan, dupilumab, tralokinumab, baricitinib, and 30 mg of upadacitinib are approved for patients with moderate-to-severe AD who are not aged <15 years; nemolizumab is approved for those who are not aged <13 years; and abrocitinib and 15 mg of upadacitinib are approved for those who are not aged <12 years, as of December 2022.

Optimal use of biologics and Jak inhibitors

Nemolizumab showed significant efficacy for pruritus in patients with AD. However, its efficacy for AD signs was not strong. Therefore, other biologics or Jak inhibitors should be considered for patients with AD with severe AD signs. Other biologics and Jak inhibitors are efficacious for both pruritus and AD signs. In Japan, nemolizumab has been approved for patients with AD with an EASI score of 10 or above who suffer from severe pruritus, whereas other biologics and Jak inhibitors can be prescribed to patients with AD with an EASI score of 16 or above. Patients with AD have heterogeneous clinical phenotypes, including different combinations of itch and lesional severity (Chovatiya et al., 2021). Some patients suffer from severe pruritus with mild-to-moderate AD signs. Nemolizumab can be considered for those patients, for instance, patients with an EASI score of 10−16 and severe pruritus (Figure 2). EASI scores in some patients with prurigo nodularis−like phenotype in AD are low because of small areas of affected lesions. These patients are also candidates for nemolizumab.

Dupilumab, tralokinumab, and Jak inhibitors are treatment options, apart from patients suitable for nemolizumab. Although oral medicine is generally preferred to injection, Jak inhibitors have some safety concerns compared with dupilumab and tralokinumab. First, dupilumab or tralokinumab is preferred for patients who had or have risks of malignancy, cardiovascular diseases, deep vein thrombosis, pulmonary embolism, gastrointestinal perforation, or diverticulitis. Patients with renal or hepatic impairment can receive Jak inhibitors at reduced doses according to the degree of impairment, or physicians can choose the appropriate drugs considering their metabolism and excretion; however, dupilumab or tralokinumab is a better option for patients with severe comorbidities in terms of safety. Among patients treated with upadacitinib, the incidences of serious or severe adverse events and anemia were higher in elderly patients than in younger patients (AbbVie, 2021). Among patients treated with abrocitinib, the incidences of serious adverse events were also higher in elderly patients than in younger patients (Pharmaceuticals_and_Medical_Devices_Agency, 2021b). Therefore, in elderly patients and those in whom safety is prioritized, dupilumab or tralokinumab can be the first line as systemic therapy for AD. As stated earlier, age >50 years is one of the risk factors for the development of herpes zoster in patients with RA treated with baricitinib (Harigai et al., 2021). Age >65 years and severe AD are risk factors for the development of herpes zoster in patients with AD treated with abrocitinib (Simpson et al., 2021). Elderly patients and a history of herpes zoster are risk factors for the development of herpes zoster in patients with RA treated with upadacitinib (Yamaoka et al., 2021). Dupilumab or tralokinumab is recommended in patients at higher risk of herpes zoster such as elderly patients and those with a history of herpes zoster. Because dupilumab was shown to be associated with a reduced risk of cutaneous infections (Fleming and Drucker, 2018; Ou et al., 2018) and tralokinumab showed the same trend (Blauvelt et al., 2022b), dupilumab or tralokinumab should be considered instead of Jak inhibitors in patients with AD with repeated skin infections, including eczema herpeticum. Dupilumab is preferred in patients with AD with asthma, eosinophilic esophagitis, and/or chronic rhinosinusitis with nasal polyps owing to the efficacy of dupilumab for patients with these conditions. Dupilumab can be the first-line option of treatment for patients with AD with the conditions mentioned earlier (Figure 2).

A Jak inhibitor is one of the systemic treatment options in patients without the conditions mentioned earlier (Figure 2). Jak inhibitors are favored, especially for patients with a fear of needles (trypanophobia) or who prefer oral medicine to injection. Because Jak inhibitors showed significant improvement in pruritus from 1 day after initiating the drug and rapid onset of efficacy in eruption, Jak inhibitors are suitable for patients who suffer from severe pruritus and/or who wish for a rapid onset of efficacy. Jak inhibitors should also be considered for patients who cannot continue systemic therapies for a long period of time owing to economic reasons; those who experience a temporary exacerbation, for instance, at a certain season; and those who need or want to receive systemic therapy over the short term for any reason. Patients with a history of conjunctivitis and/or elevated serum levels of thymus and activation-regulated chemokine (over 3,000 pg/ml) and IgE (over 11,000 IU/ml) are at high risk for developing conjunctivitis during dupilumab treatment (Kamata and Tada, 2021; Uchida et al., 2020), although the results vary depending on the report. Jak inhibitors could be considered first for those patients. In patients with AD treated with dupilumab or tralokinumab who suffer from severe or persistent conjunctivitis and/or facial redness, switching to a Jak inhibitor is one of the options. Cases successfully treated by switching from dupilumab to a Jak inhibitor have been reported (Hayama and Fujita, 2022; Licata et al., 2022). The superiority of 30 mg of upadacitinib to 300 mg of dupilumab (Blauvelt et al., 2021) gives a choice of switching to upadacitinib in patients who are refractory to dupilumab. Although it is rare, there are a few cases who developed alopecia areata or arthritis/enthesitis during dupilumab treatment (Kamata and Tada, 2021). Changing dupilumab to a Jak inhibitor should be considered in those patients.

Optimal use of dupilumab and tralokinumab: Which to choose

Because evidence of tralokinumab is limited, it is difficult to compare dupilumab with tralokinumab at present. Because a head-to-head clinical trial has never been conducted, this discussion includes speculation and expectation. Tralokinumab seems to show a slower onset of efficacy than dupilumab but reaches almost the same levels after long-term use with topical corticosteroids. The incidences of conjunctivitis and facial redness might be lower in tralokinumab than in

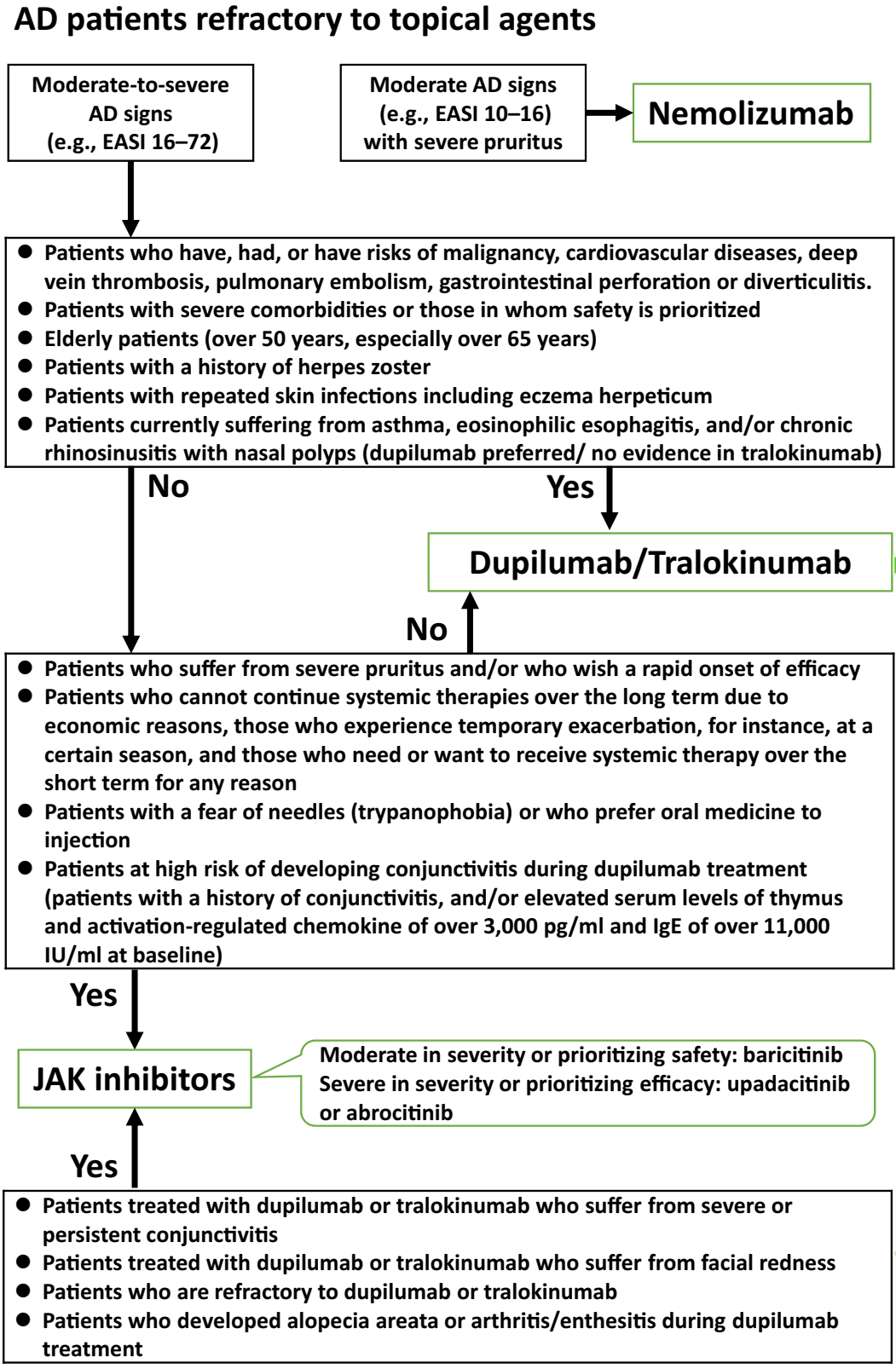

Figure 2. Optimal use of biologics and Jak inhibitors for AD. The schematic illustrates how to choose Jak inhibitors and biologics for patients with moderate-to-severe AD refractory to topical agents. AD, atopic dermatitis; EASI, Eczema Area and Severity Index.

dupilumab, although there is no evidence supporting this concept, and an accumulation of evidence is needed. Considering them, tralokinumab might be one of the good options for patients who prioritize safety over a rapid onset of efficacy. As stated earlier, dupilumab showed decreased risks of cutaneous infection, and tralokinumab showed the same

trend, although the evidence level is different between them. Dupilumab is efficacious for asthma, eosinophilic esophagitis, and/or chronic rhinosinusitis with nasal polyps, whereas tralokinumab has no evidence of it. Dupilumab should be considered for patients with AD with asthma, eosinophilic esophagitis, and/or chronic rhinosinusitis with nasal polyps instead of tralokinumab. Further accumulation of evidence is needed to clarify the differences between them.

Optimal use of Jak inhibitors: Which Jak inhibitor to choose

As stated earlier, Jak inhibitors with higher efficacy are accompanied by more safety concerns, including herpes zoster. Therefore, we should consider the balance of efficacy and safety, namely, the risks and benefits when choosing a Jak inhibitor. Because most patients with AD are young and have no comorbidities, even 30 mg of upadacitinib is relatively safe in most cases. However, in patients at high risk for the specific concerns discussed earlier, the choice of Jak inhibitor should be made carefully. In terms of efficacy, baricitinib can be considered for patients with moderate AD. In patients with severe AD, upadacitinib or abrocitinib is favored. Jak inhibitors are recommended for induction of remission. As for maintaining remission, safety data on the long-term use of Jak inhibitors in patients with AD are limited. Long-term use for up to 1 year can be considered on the basis of the results of clinical trials of Jak inhibitors for AD. The use of a Jak inhibitor for more than 1 year needs careful consideration owing to the lack of evidence. Because safety data of baricitinib in patients with RA over a median of 4.6 years showed that no new safety signals were identified (Taylor et al., 2022), baricitinib could be tolerable for long-term use. As of now, data on the long-term use of abrocitinib for more than 2 years have not been reported yet. According to the safety data of patients with RA treated with upadacitinib for a median of 2−3 years (Cohen et al., 2021), in treating patients with AD with 30 mg upadacitinib for the long term, we may want to consider reducing the dose to 15 mg once AD is well-controlled because the incidence of some adverse effects increased or seemed to increase in a dose-dependent manner. Further accumulation of evidence on the long-term use of Jak inhibitors is needed, especially in view of safety.

CONCLUSIONS

Understanding the characteristics of biologics and differences in the efficacy and safety profiles of Jak inhibitors is essential to choosing the right treatment option for individual patients with AD. Knowledge of the mechanisms of action of Jak inhibitors and biologics, the potential significant adverse events of these drugs, and the age and comorbidities of the patient can help achieve optimal clinical benefit for patients with moderate-to-severe AD. This article was written on the basis of the updated current evidence. We need to be informed of updated data and provide the best treatment for individual patients.

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CONFLICT OF INTEREST

MK received honoraria for lectures from AbbVie and Eli Lilly. YT received grants for research from AbbVie and Eli Lilly and honoraria for lectures from AbbVie and Eli Lilly.

AUTHOR CONTRIBUTIONS

Supervision: YT; Writing - Original Draft Preparation: MK; Writing - Review and Editing: YT.

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