Minireview

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Characterization of the effects on pruritus by novel treatments for atopic dermatitis

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Summary

Chronic pruritus is a common and debilitating symptom in patients with atopic dermatitis and contributes to impairment of quality of life. Effective treatment of pruritus should therefore be one of the main treatment goals in patients with atopic dermatitis. Pathophysiologically, the histamine-independent pruritogens interleukin-31, interleukin-13, and interleukin-4, have been shown to play a major role in atopic dermatitis. All three cytokines can mediate chronic pruritus via Janus kinase 1/2 signaling pathways. Novel drugs target these pathways and have shown rapid and sustained reduction of pruritus in patients with atopic dermatitis in clinical use and in phase II and III clinical trials. Here we summarize the published data on the effects of these drugs on itch parameters such as overall reduction in pruritus intensity and percent of patients with atopic dermatitis achieving a relevant reduction in itch. Each of the novel drugs shows very good effects on pruritus. These data offer hope for an even better and possibly more specific treatment of pruritus in patients with atopic dermatitis in the future. In addition, the different pharmacological approaches give us the chance to learn more about the pathophysiology of pruritus in atopic dermatitis.

Introduction

Chronic pruritus (CP) is a very common and often debilitating symptom in many dermatological and non-dermatological diseases [1, 2]. In dermatological conditions, CP is not only one of the most common symptoms, but also often the main factor affecting quality of life impairment. For example, 47 % of patients presenting to the emergency dermatological unit of a university hospital in Germany suffered itching [3] and dermatological patients with "very strong" pruritus reportedly have very severely impaired sexual activities and a high rate of suicidal ideation (17.9 % vs. 4.1 % in patients with "mild" pruritus) [4].

In atopic dermatitis (AD) rapid and effective treatment of pruritus is one of the main goals, as most patients suffer from moderate or severe pruritus, leading for example to sleep disturbances in the vast majority of AD patients [5–7]. Within the last years, a number of novel therapeutic options for AD have been introduced or are in late stages of clinical development [8]. Here, we summarize the reported efficacy on pruritus of these novel agents.

Pathogenesis of pruritus in atopic dermatitis

The exact underlying mechanism of pruritus in AD is not yet fully understood. Recent evidence indicates that histamine-independent pruritogens such as interleukin (IL)-31 [9], IL-13 and IL-4 [10] are implicated in CP in AD patients. Interleukin-31 is a cytokine that is predominantly produced by Th2 cells. It evokes itch via a receptor complex on C-fibers that consists of IL-31 receptor A (IL-31RA) and oncostatin M receptor β (OSMRβ). Binding of IL-31 to its receptors activates three pathways: ERK1/2 MAP kinase, PI3K/AKT, and Janus kinase (JAK) 1/2 signaling pathways [11]. In addition, IL-13 and IL-4 are Th2-specific cytokines that are thought to be involved in the pathogenesis of AD. Both cytokines share

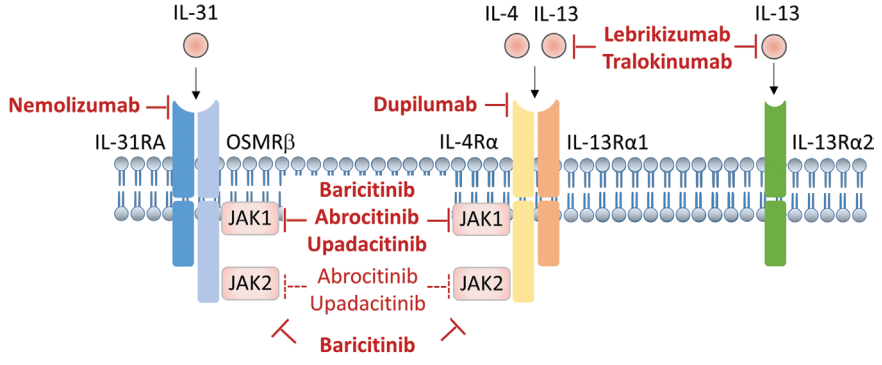
the IL-4/IL-13 receptor (formed by IL-4Rα and IL-13Rα1) on sensory neurons and can mediate CP through JAK1/2 signaling. Interleukin-13 also binds with high affinity to the IL-13 Rα2 receptor [12]. Its role in AD is still under investigation but preliminary studies have indicated a possible role of IL-13 Rα2 as a decoy receptor with anti-inflammatory properties [13]. Other pruritogens that have been associated with itch in AD are histamine (via histamine type 1 and 4 receptors), tryptase (via mas-related G protein-coupled receptor X2), IL-33, and thymic stromal lymphopoietin (TSLP) [14]; their clinical relevance in inducing itch in AD, however, remains unclear (Figure 1). Overall, pruritus in moderate and severe AD has been reported to be closely associated with AD severity [5], indicating that similar mechanisms may be responsible for both itch and skin inflammation. However, many AD patients report generalized pruritus which is not restricted to the lesional skin [4], and a subset of patients with mild atopic dermatitis report severe itch [15]. Therefore, other factors than those directly associated with inflammation may contribute to the pathomechanism and severity of pruritus.

Treatment Approaches

Biologics

Dupilumab: Dupilumab is a fully human Immunoglobulin (Ig) G4κ monoclonal antibody that inhibits IL-4 and IL-13 signaling via inhibition of IL-4Rα (Figure 1). A recent analysis of four randomized phase III clinical trials focuses on the effects of dupilumab on pruritus in patients with moderate to severe AD. The authors specifically analyzed the time course (onset, duration, magnitude) of reduction of itch in those patients. Dupilumab treatment led to a rapid and statistically significant improvement vs. placebo in daily peak pruritus (percent change, numerical rating scale [NRS]) as early as day 2 in adult and day 5 in adolescent patients. Furthermore, there was a rapid improvement (defined as patient proportion with at least 3-point improvement from baseline) of itch from day 4 in adult and day 13 in adolescent patients. Over the course of the respective studies, itch intensity was significantly reduced in all studies compared to placebo and showed a progressive reduction over time (Table 1) [16].

Lebrikizumab: Lebrikizumab is a humanized monoclonal IgG4κ anti-IL-13-antibody which prevents heterodimerization of the IL-13Rα1/IL-4Rα complex and therefore selectively inhibits IL-13 signaling (Figure 1). Recently, efficacy and safety of lebrikizumab has been explored in adult patients with moderate to severe AD in a phase IIb trial. Subcutaneous lebrikizumab injections showed a dose-dependent clinical efficacy in AD patients compared to placebo during the 16-week treatment phase. In regard to the effect on pruritus, lebrikizumab treatment resulted in a dose-dependent improvement in pruritus NRS score with significant difference for all three dosing options compared to placebo. First differences in NRS score changes of at least four points compared to placebo were observed at day 2 for the high dosed groups, without further statistical analysis [17]. The currently ongoing phase III studies will provide more detailed information on the specific effects on pruritus (Table 1).



Compound	Primary target(s)	IC_{50} in cell free assay (nM)		
		JAK1	JAK2	JAK3
Baricitinib	JAK1 and JAK2	5.9	5.7	560
Abrocitinib	JAK1	29	803	>10,000
Upadacitinib	JAK1	43	200	2,300

Obtained from MedChemExpress

Figure 1 Schematic representation of signaling pathways of pruritus in atopic dermatitis. The solid red lines indicate selective inhibition of the respective molecule, the dashed red lines indicate that the Janus kinases are also inhibited at higher doses of the respective drugs.
Abbr.: IC_{50}, half maximal inhibitory concentration; IL, Interleukin; JAK, Janus kinase; OSMβ, Oncostatin M receptor β; R, Receptor.

Table 1 Overview of pruritus efficacy of novel treatments for atopic dermatitis in adult patients. Data shown for adult patients.

	Biologicals				JAK-Inhibitors		
Drug	**Dupilumab**	**Lebrikizumab**	**Tralokinumab**	**Nemolizumab**	**Baricitinib**	**Abrocitinib**	**Upadacitinib**
Therapeutic target	Interleukin-4-Receptor α	Interleukin-13	Interleukin-13	Interleukin-31-Receptor A	Janus kinase 1 and 2	Janus kinase 1	Janus kinase 1
Formulation and Dosing (adult patients)	s.c. injection; 300 mg every 2 weeks (LD 600 mg)	s.c. injection; 125mg every 4 weeks (LD 250 mg); 250mg every 4 weeks (LD 500 mg) 250mg every 2 weeks (LD 500 mg)	s.c. injection; 300 mg every 2 weeks*	s.c. injection; 60 mg every 4 weeks*	oral; 4 or 2 mg 1 x/day*	oral; 100 mg or 200 mg 1 x/day	oral; 15 mg 1 x/day 30 mg 1 x/day
Most advanced study phase published	Phase III [16] Approval for atopic dermatitis 2018 (EU)	Phase IIb [17] Phase III ongoing (NCT04146363, NCT04178967)	Phase III [19] Approval for atopic dermatitis 2021 (EU)	Phase III [20]	Phase III [23] Approval for atopic Dermatitis 2020 (EU)	Phase III, comparison to dupilumab treatment [25]	Phase III [26] Approval for atopic dermatitis 2021 (EU)
Effect on pruritus	Significant effect compared to placebo	Significant effect compared to placebo (all 3 dosing options)	Significant effect compared to placebo	Significant effect compared to placebo	Significant effect compared to placebo	Significant effect compared to placebo (both dosing options) and compared to dupilumab	Significant effect (both dosing options) compared to placebo
Mean change from baseline in daily peak pruritus NRS/VAS at week 16	Dupilumab[#] –47.4 % Placebo –20.5 %	Lebrikizumab –35.9 % (125 mg) –49.6 % (250 mg/4w) –60.6 % (250 mg/2w) Placebo 4.3 %	Tralokinumab –4.1 Placebo –2.9	Nemolizumab –42.8 % Placebo –21.4 %	Baricitinib –43.4 % (2 mg) –51.2 % (4 mg) Placebo –27 %	Not reported	"Measure Up 1" Upadacitinib –62.8 % (15 mg) –72.0 % (30 mg) Placebo –26.1 % "Measure Up 2" Upadacitinib –51.2 % (15 mg) –66.5 % (30 mg) Placebo –17 %

Continued

Table 1 Continued.

	Biologicals				JAK-Inhibitors		
Drug	**Dupilumab**	**Lebrikizumab**	**Tralokinumab**	**Nemolizumab**	**Baricitinib**	**Abrocitinib**	**Upadacitinib**
Proportion of patients with meaningful response at week 16 ≥ 4-point improvement in daily peak pruritus NRS scores from baseline	Dupilumab[#] 38.4 % Placebo 10.9 %	Lebrikizumab 41.8 % (125 mg) 47.4 % (250 mg/4w) 70.0 % (250 mg/2w) Placebo 27.3 %	Tralokinumab 45.5 % Placebo 34.1 %	Not analyzed	Baricitinib 38 % (2 mg) 44 % (4 mg) Placebo 20 %	Abrocitinib 38 % (100 mg) 57 % (200 mg) Placebo 15 % *at week 12*	"Measure Up 1" Upadacitinib 52.2 % (15 mg) 60.0 % (30 mg) Placebo 11.8 % "Measure Up 2" Upadacitinib 41.9 % (15 mg) 59.6 % (30 mg) Placebo 9.1 %
Onset of first significant itch reduction	Day 2	Not analyzed; first differences compared to placebo at day 2	Changes from baseline of daily peak pruritus compared to placebo from week 1 onwards	Not analyzed	Day 2	Day 1	Day 2
Most common adverse events	Injection site reactions, conjunctivitis	Injection site reactions, herpesvirus infections, conjunctivitis	Upper respiratory tract infections, conjunctivitis	Injection site reactions, worsening of atopic dermatitis	Upper respiratory tract infections, hyperlipidemia, herpes virus infection	Nausea, upper respiratory tract infections	Acne, upper respiratory tract infections, nasopharyngitis, headache

Abbr.: IL, Interleukin; LD, loading dose; NRS, numerical rating scale; s.c., subcutaneous; VAS, visual analogue scale.
[#]Data from patients with dupilumab monotherapy: studies LIBERTY SOLO AD 1 and 2 *study medication/placebo in combination with topical corticosteroid treatment. NRS and VAS are highly correlated and are thus considered comparable.

Tralokinumab: Tralokinumab is a recombinant human IgG4λ monoclonal antibody targeting IL-13 by prevention of its binding to the IL-13Rα1 and IL-13Rα2 (Figure 1) and has very recently been approved for adults with moderate to severe atopic dermatitis in the European Union. Compared to lebrikizumab, tralokinumab binds a different epitope of soluble IL-13 but also with high affinity. In 2020, first results from phase III trials on tralokinumab monotherapy (ECZETRA1 and 2) as well in combination with topical corticosteroid treatment (ECZETRA 3) in patients with moderate to severe AD were published. At week 16, a reduction of weekly average daily peak pruritus (NRS ≥ 4) compared to baseline was achieved in a higher proportion of patients treated with Tralokinumab than compared to the placebo group. In addition, Tralokinumab-treated patients showed higher changes from baseline of daily peak pruritus NRS compared to placebo with significant difference from treatment week 1 onwards (Table 1) [18, 19].

Nemolizumab: Nemolizumab is a humanized monoclonal antibody targeting the IL-31RA (Figure 1) and is applied subcutaneously every 4 weeks. In a recent phase III study, treatment with nemolizumab in conjunction with topical corticosteroids showed an excellent effect on pruritus reduction in patients with moderate to severe AD compared to placebo with topical agents. At week 16, the mean percent change in the VAS score was significantly higher in the nemolizumab group (–42.8 %) as compared to placebo (–21.4 %) [20].

JAK-inhibitors

Baricitinib: Baricitinib is an oral JAK inhibitor with an equally high specificity for JAK-1 and -2 (Figure 1) and a lower specificity for Tyk2 [21]. It is the first of its class that received approval for the treatment of moderate to severe AD. In conjunction with topical corticosteroids, both 2 mg and 4 mg daily treatment with baricitinib resulted in a significant reduction of daily itch (mean NRS compared to baseline) at day 2. At week 16, a significant higher proportion of treated patients with AD (44 % for the 4 mg group, 38 % for the 2 mg group) compared to the placebo group (20 %) showed a clinical significant improvement of itch (defined as change compared to baseline NRS ≥ 4) (Table 1) [22, 23].

Abrocitinib: Abrocitinib is an oral selective JAK-1 inhibitor (Figure 1) and has been investigated as a daily treatment (100 mg and 200 mg 1 x/d) in a phase III trial in adults and adolescents with moderate to severe AD. Here, the proportion of patients who achieved a clinically relevant reduction of the peak pruritus was significantly higher for the abrocitinib treatment groups (57 % for the 200 mg group, 38 % for the 100 mg group) compared to the placebo group (15 %) at week 12 [24]. In another phase III head-to-head trial comparing abrocitinib in both doses to dupilumab, efficacy of abrocitinib was comparable to dupilumab in most endpoints, but was superior (in the 200 mg group) to dupilumab treatment in regard to itch response at week 2 (Table 1) [25].

Upadacitinib: Upadacitinib is an oral inhibitor of JAK-1 and has been shown to be effective in adult patients with moderate to severe AD in two replicate phase III trials (monotherapy) and in a phase III trial as a combination therapy with topical corticosteroids [26, 27]. At week 16, monotherapy with 15 mg or 30 mg 1 x/d resulted in significant improvement of pruritus as well as a significant, clinically relevant reduction of pruritus (defined as improvement compared to baseline NRS ≥ 4) in patients with AD compared to placebo (Table 1) [26]. In comparison to dupilumab treatment in a phase III head-to-head study in adult patients with AD, upadacitinib treatment was found to be superior in terms of improvement of pruritus [28].

Discussion

In a recently published survey of 1,104 patients with AD, pruritus was considered by the vast majority of patients (95.4 %) to be very important in deciding whether or not a treatment is working [29]. Therefore, knowledge of the effects of novel drugs in AD on the improvement of pruritus is important. In recent years, pruritus assessments have become an important outcome parameter in clinical trials in AD. Itch parameters are commonly reported using standardized outcome measures, which makes it possible to compare novel drugs in terms of their effects on pruritus. It is important to note, however, that there are differences between the study designs, for example, in time points of assessment, allowed co-medications, the study population size and study specifics (for example, exclusion of patients with mild AD), so the comparisons presented here should be interpreted with caution. Particularly informative are therefore head-to-head trials, such as those already carried out and published for abrocitinib versus dupilumab and upadacitinib versus dupilumab [25, 28]. It is important to note that this review only describes effects on pruritus characteristics and does not address other efficacy outcomes such as improvement in eczema scores or safety aspects such as overall number of adverse events or suspected unexpected serious adverse reactions. In addition, the pipeline of potential treatments for patients with AD includes further drug candidates that are in earlier stages of development. Of special interest, and not discussed within this review, are novel topical treatment approaches such as the tyrosine kinase 2 (TYK2) inhibitor brepocitinib or the aryl hydrocarbon receptor modulating agent tapinarof [30, 31]. It will be interesting to compare the effects on pruritus of these topical treatments to those of the systemically applied drugs. All of the novel drugs in AD presented in this

review have shown promising data on improving itch, with a very rapid onset of itch relief often being reported. Although it is certainly debatable whether an improvement in pruritus occurring after two rather than ten days is relevant, the overall efficacy in reducing pruritus over the entire treatment period is of great importance to patients.

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Conflict of interest

HB received honoraria (advisory board, speaker) from Novartis and Sanofi-Aventis. MM received honoraria as a speaker and/or consultant for Amgen, Bayer, Galderma, Menlo, Novartis, Pfizer, Sanofi-Aventis. The other authors had no competing interests to declare.

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References

1 Cassano N, Tessari G, Vena GA, Girolomoni G. Chronic pruritus in the absence of specific skin disease: an update on pathophysiology, diagnosis, and therapy. Am J Clin Dermatol 2010; 11(6): 399–411.
2 Metz M. Are we facing a change in the treatment of chronic pruritus? Br J Dermatol 2019; 181(5): 877–8.
3 Ansorge C, Miocic JM, von Bubnoff D, Technau-Hafsi K. Dermatological conditions presenting to the emergency dermatological unit of a university hospital in Germany. J Dtsch Dermatol Ges 2018; 16(12): 1451–6.
4 Hawro T, Przybylowicz K, Spindler M et al. The characteristics and impact of pruritus in adult dermatology patients: A prospective, cross-sectional study. J Am Acad Dermatol 2021; 84(3): 691–700.
5 Huet F, Faffa MS, Poizeau F et al. Characteristics of pruritus in relation to self-assessed severity of atopic dermatitis. Acta Derm Venereol 2019; 99(3): 279–83.
6 Kage P, Simon JC, Treudler R. Atopic dermatitis and psychosocial comorbidities. J Dtsch Dermatol Ges 2020; 18(2): 93–102.
7 Ständer S. Atopic Dermatitis. N Engl J Med 2021; 384(12): 1136–43.
8 Bieber T. Novel therapies based on the pathophysiology of atopic dermatitis. J Dtsch Dermatol Ges 2019; 17(11): 1150–62.
9 Dillon SR, Sprecher C, Hammond A et al. Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice. Nat Immunol 2004; 5(7): 752–60.
10 Zheng T, Oh MH, Oh SY et al. Transgenic expression of interleukin-13 in the skin induces a pruritic dermatitis and skin remodeling. J Invest Dermatol 2009; 129(3): 742–51.
11 Zhang Q, Putheti P, Zhou Q et al. Structures and biological functions of IL-31 and IL-31 receptors. Cytokine Growth Factor Rev 2008; 19(5-6): 347–56.
12 McCormick SM, Heller NM. Commentary: IL-4 and IL-13 receptors and signaling. Cytokine 2015; 75(1): 38–50.
13 Ranasinghe C, Trivedi S, Wijesundara DK, Jackson RJ. IL-4 and IL-13 receptors: Roles in immunity and powerful vaccine adjuvants. Cytokine Growth Factor Rev 2014; 25(4): 437–42.
14 Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. Lancet 2020; 396(10247): 345–60.
15 Chovatiya R, Lei D, Ahmed A et al. Clinical phenotyping of atopic dermatitis using combined itch and lesional severity: A prospective observational study. Ann Allergy Asthma Immunol 2021; 127(1): 83–90e2.
16 Silverberg JI, Yosipovitch G, Simpson EL et al. Dupilumab treatment results in early and sustained improvements in itch in adolescents and adults with moderate to severe atopic dermatitis: Analysis of the randomized phase 3 studies SOLO 1 and SOLO 2, AD ADOL, and CHRONOS. J Am Acad Dermatol 2020; 82(6): 1328–36.
17 Guttman-Yassky E, Blauvelt A, Eichenfield LF et al. Efficacy and Safety of lebrikizumab, a high-affinity interleukin 13 inhibitor, in adults with moderate to severe atopic dermatitis: a phase 2b randomized clinical trial. JAMA Dermatol 2020; 156(4): 411–20.
18 Wollenberg A, Blauvelt A, Guttman-Yassky E et al. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). Br J Dermatol 2021; 184(3): 437–49.
19 Silverberg JI, Toth D, Bieber T et al. Tralokinumab plus topical corticosteroids for the treatment of moderate-to-severe atopic dermatitis: results from the double-blind, randomized, multicentre, placebo-controlled phase III ECZTRA 3 trial. Br J Dermatol 2021; 184(3): 450–63.
20 Kabashima K, Matsumura T, Komazaki H et al. Trial of nemolizumab and topical agents for atopic dermatitis with pruritus. N Engl J Med 2020; 383(2): 141–50.
21 Nezamololama N, Fieldhouse K, Metzger K, Gooderham M. Emerging systemic JAK inhibitors in the treatment of atopic dermatitis: a review of abrocitinib, baricitinib, and upadacitinib. Drugs Context 2020; 9: 8–5.
22 Simpson EL, Lacour JP, Spelman L et al. Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. Br J Dermatol 2020; 183(2): 242–55.
23 Reich K, Kabashima K, Peris K et al. Efficacy and safety of baricitinib combined with topical corticosteroids for treatment of moderate to severe atopic dermatitis: a randomized clinical trial. JAMA Dermatol 2020; 156(12): 1333–43.
24 Simpson EL, Sinclair R, Forman S et al. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet 2020; 396(10246): 255–66.

25 Bieber T, Simpson EL, Silverberg JI et al. Abrocitinib versus placebo or dupilumab for atopic dermatitis. N Engl J Med 2021; 384(12): 1101–12.
26 Guttman-Yassky E, Teixeira HD, Simpson EL et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. Lancet 2021; 397(10290): 2151–68.
27 Reich K, Teixeira HD, de Bruin-Weller M et al. Safety and efficacy of upadacitinib in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis (AD Up): results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2021; 397(10290): 2169–81.
28 Blauvelt A, Teixeira HD, Simpson EL et al. Efficacy and safety of upadacitinib vs dupilumab in adults with moderate-to-severe atopic dermatitis: a randomized clinical trial. JAMA Dermatol 2021; 157(9): 1047–55.
29 Kobyletzki LB, Thomas KS, Schmitt J et al. What factors are important to patients when assessing treatment response: an international cross-sectional survey. Acta Derm Venereol 2017; 97(1): 86–90.
30 Jo CE, Gooderham M, Beecker J. TYK 2 inhibitors for the treatment of dermatologic conditions: the evolution of JAK inhibitors. Int J Dermatol 2021 Apr 30. [Epub ahead of print].
31 Paller AS, Stein Gold L, Soung J et al. Efficacy and patient-reported outcomes from a phase 2b, randomized clinical trial of tapinarof cream for the treatment of adolescents and adults with atopic dermatitis. J Am Acad Dermatol 2021; 84(3): 632–8.

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