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A systematic review of ustekinumab in the treatment of atopic dermatitis

Running Head: A systematic review of ustekinumab in AD

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Abstract

Ustekinumab is a human monoclonal IgG1 antibody targeting the p40 subunit shared by IL-12 and IL-23. We reviewed the published literature by searching from PubMed, EMBASE, Web of Science and ClinicalTrial.gov to evaluate the efficacy and safety of ustekinumab in the treatment of AD. Ten studies including eight cases and two RCT, comprising 107 patients, were included in the systematic review. Analysis all studies, a total of 58 patients (54.2%) gained an effective treatment with little adverse events. Ustekinumab is a well-tolerated and safe treatment with no significant difference in effect from placebo in patients with AD. Further larger randomized controlled trials need to be conducted to identify a suitable regimen for AD and provide more evidence for clinical application.

Keywords

atopic dermatitis; ustekinumab

Introduction

Atopic dermatitis(AD) is a chronic inflammatory skin disease, which could influence almost up to 20% of children and 1-3% of adult over the world, and it could be a financial burden for treatment and care both on family and society. Besides, it has a significant influence on the quality of life[1, 2]. AD is the first step of the so called “atopy march” which followed by asthma and allergic rhinitis in later life[3].

The conventional treatments include emollients, phototherapy, topical steroids, calcineurin inhibitors, trigger elimination, systemic immunosuppressive agents[4]. However they are not so effective to provide long-term relief or remission for those severe refractory atopic dermatitis[5]. New therapies which using biologic agents targeting specific immune responses offer a promising and effective method for severe AD treatment[6]. AD is thought to be a predominantly T-helper (Th)2-driven disease with a switch to Th1 in the chronic phase, but Th17 and Th22 cell subsets are increasingly recognized to take part in inflammatory responses in AD[5, 7]. Ustekinumab, which has been approved for the treatment of moderate-to-severe plaque psoriasis, is a human monoclonal IgG1 antibody that targets the p40 subunit shared by IL-12 and IL-23[8]. As ustekinumab inhibits the Th1 and Th17 inflammatory pathway by blocking IL-12 and IL-23, it represents a potential treatment for AD[8, 9]. In this article, we reviewed 8 case reports and 2 clinical trials about the efficacy and safety of ustekinumab in AD.

Methods

We searched the published literature from PubMed, EMBASE, Web of Science and ClinicalTrial.gov with the search terms including "atopic dermatitis", "eczema", "Ustekinumab". Studies published before September 2017 and written in English were included. Articles were selected if they concern the efficacy and safety of ustekinumab in the treatment of AD. Several variables retrieved from patient records were as follows: serum total IgE, systemic comorbidities, duration on therapy, eczema baseline, side effects.

Results

The outcomes of the search included eight case studies and two randomized, placebo-controlled pilot studies. It comprised 107 patients with moderate-severe atopic dermatitis. There were 58 patients gaining an effective treatment, while 49 patients reported not obvious response.

A total of 85 patients treated with ustekinumab in two randomized placebo-controlled trials were identified. Saeki H et al.[10] showed an effect with -38.2% reduction of EASI score in 45mg group and -39.8% in 90 mg group. However it was not significant compared to placebo group which have -37.5% reduction. They found common adverse events were nasopharyngitis and worsened AD. Similarly, Khattri et al.[11] showed the difference between ustekinumab-placebo and placebo-ustekinumab groups was not statistically significant. No severe adverse events were observed.

Puya et al.[12] reported the first case of the successful management of a patient suffering from severe refractory AD. Doris Weiss, et al.[7] showed 3 patients had significant reduction of EASI score (50% reduction) and pruritus after 16 weeks treatment. The only adverse event was a common cold of moderate intensity. Similar, a case report showed 4 patients had a comparable improvement both in clinical and SCORAD index without adverse effects, infections or other complications[13]. In another case, a patient was treated with standard dose while given in shorter time intervals with obvious alleviation. They found AD patients tends to exacerbate 1-2 weeks before the expected ustekinumab, and intended to evaluate shorter dosing intervals[14]. On the contrary, samorano et al.[15] reported two patients did not experience therapeutic benefits from the ustekinumab. One of the explanations could be that ustekinumab block the Th17 pathway in patients, and they were prone to staphylococcal skin infection which may inhibit response or cause a persistent flare. There were 2 cases concerned the application in adolescent patients, Agusti-Mejias et al.[16] reported the use of ustekinumab in an 16-year-old patient who completely recovered without any skin lesions as well as any side effect. Wlodek et al.[17] presented a case of a 13-year-old patient cured with the ustekinumab although she experienced flares 3-4 weeks before the next injection. A report of 10 patients by Nic Dhonncha et al.[18] showed 1 patients complete response and 3 patients almost complete response while 6 patients demonstrated no response. They found no adverse effects except that one patient developed an elevated alanine transferase.

Discussion

The pathogenic mechanism of AD is complex, and the conventional therapies fail to systemically modulate pathways driving AD[2]. Ustekinumab, which block Th1 and Th17 pathways by specifically binds IL-12 and IL-23, antagonizes the activation of Th1, Th17, Th22 in AD. This paper studies literature concerning the efficacy and safety of using ustekinumab in the treatment of AD.

In general, the observational studies of ustekinumab for AD have more clinically meaningful efficacy compared to the RCTs, in which the difference in effect is not statistically significant from placebo. This could be publication bias and the results of clinical trials are more convincing compared to case reports. As the ustekinumab was approved for treatment in psoriasis, the regimen, injections in weeks 0 and 4 and then every 12 weeks, employed in psoriasis may be not suitable for patients with AD. The disease severity was assessed by many scoring systems including VAS, EASI, DLQI, SCORAD. SCORAD was the most widely used while 2 studies did not provide any scoring data. There were 2 cases of patients who had been observed flares before the expected injection, indicating the shorter dosing intervals maybe an effective way to elevate the effect of ustekinumab. There were none or few mild adverse events reported in those studies. Only 2 studies reported side effects including nasopharyngitis, worsen AD, erysipelas, an elevated alanine transferase. So ustekinumab is generally well tolerant in the treatment of AD.

In conclusion, ustekinumab is a safe treatment, while RCTs show no significant difference in effect from placebo in patients with AD. The regimen employed in

psoriasis maybe not suitable for patients with AD. A suitable regimen of ustekinumab for AD need identified by further larger randomized controlled trials which provided more evidence for clinical application.

References

1. Boguniewicz, M., D.Y. Leung. *Atopic dermatitis: a disease of altered skin barrier and immune dysregulation*. Immunol Rev, 2011. **242**(1): p. 233-46.
2. Eyerich, K., N. Novak. *Immunology of atopic eczema: overcoming the Th1/Th2 paradigm*. Allergy, 2013. **68**(8): p. 974-82.
3. Plotz, S.G., Markus Wiesender, Antonia Todorova, et al. *What is new in atopic dermatitis/eczema?* Expert Opin Emerg Drugs, 2014. **19**(4): p. 441-58.
4. Lio, P.A., Margaret Lee, Jennifer LeBovidge, et al. *Clinical management of atopic dermatitis: practical highlights and updates from the atopic dermatitis practice parameter 2012*. J Allergy Clin Immunol Pract, 2014. **2**(4): p. 361-9; quiz 370.
5. Guttman-Yassky, E., N. Dhingra, D.Y. Leung. *New era of biologic therapeutics in atopic dermatitis*. Expert Opin Biol Ther, 2013. **13**(4): p. 549-61.
6. M. D. Howell, M. L. Parker, T. Mustelin, et al. *Past, present, and future for biologic intervention in atopic dermatitis*. Allergy, 2015. **70**(8): p. 887-96.
7. Doris Weiss, Michaela Schaschinger, Robin Ristl, et al. *Ustekinumab treatment in severe atopic dermatitis: Down-regulation of T-helper 2/22 expression*. J Am Acad Dermatol, 2017. **76**(1): p. 91-97 e3.
8. Heratizadeh, A., T. Werfel. *Anti-inflammatory therapies in atopic dermatitis*. Allergy,

2016. **71**(12): p. 1666-1675.

9. Werfel, T., T. Biedermann. *Current novel approaches in systemic therapy of atopic dermatitis: specific inhibition of cutaneous Th2 polarized inflammation and itch*. Curr Opin Allergy Clin Immunol, 2015. **15**(5): p. 446-52.
10. H. Saeki, K. Kabashima, Y. Tokura, et al. *Efficacy and safety of ustekinumab in Japanese patients with severe atopic dermatitis: a randomized, double-blind, placebo-controlled, phase II study*. Br J Dermatol, 2017.
11. Saakshi Khattri, Patrick M. Brunner, Sandra Garcet, et al. *Efficacy and safety of ustekinumab treatment in adults with moderate-to-severe atopic dermatitis*. Exp Dermatol, 2017. **26**(1): p. 28-35.
12. Puya R, Alvarez-Lopez M, Velez A, et al. *Treatment of severe refractory adult atopic dermatitis with ustekinumab*. Int J Dermatol. 2012 Jan;**51**(1):115-6.
13. M.C. Fernandez-Anton Martinez, F. Alfageme Roldan, C. Ciudad Blanco, et al. *Ustekinumab in the treatment of severe atopic dermatitis: a preliminary report of our experience with 4 patients*. Actas Dermosifiliogr, 2014. **105**(3): p. 312-3.
14. Shroff, A., E. Guttman-Yassky. *Successful use of ustekinumab therapy in refractory severe atopic dermatitis*. JAAD Case Rep, 2015. **1**(1): p. 25-6.
15. L.P. Samorano, J.M. Hanifin, E.L. Simpson, et al. *Inadequate response to ustekinumab in atopic dermatitis – a report of two patients*. J Eur Acad Dermatol Venereol. 2016 Mar;**30**(3):522-3.
16. Anna Agusti-Mejias, Francesc Messeguer, Ramon Garcia, et al. *Severe refractory atopic dermatitis in an adolescent patient successfully treated with ustekinumab*. Ann

Dermatol, 2013. **25**(3): p. 368-70.

17. C. Wlodek, H. Hewitt, C.T. Kennedy. *Use of ustekinumab for severe refractory atopic dermatitis in a young teenager*. Clin Exp Dermatol, 2016. **41**(6): p. 625-7.
18. E. Nic Dhonncha, J. Clowry, M. Dunphy, et al. *Treatment of severe atopic dermatitis with ustekinumab: a case series of 10 patients*. Br J Dermatol, 2016.

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Table 1

References	Time	Pt.	Men	Age	Comorbidities	IgE Mean	Dose	Time on Therapy	Eczema (baseline)	Effect	Side effects	Comments
Puya R et al.[12]	2012	1	0/1	21	ACD		45mg at weeks 0,4 and then every 12 weeks	12mo	VAS 9	1x ↑ ↑ ↑	None	first case of successful control
Weiss D et al.[7]	2016	3	2/3	42.7(27-55)	AR, Asthma	> 5000	45mg at weeks 0,4 and 12 and subsequently every 8 weeks	16wk	Mean SCORAD 68.4±16.1	3x ↑ ↑	None	a distinct clinical and immunologic response
Fernández-Antón Martí nez MC et al.[13]	2014	4	4/4	27.25(23-29)	Asthma	11522	45mg at weeks 0,4 and every 12 weeks	16wk	Mean SCORAD 77.75	4x ↑ ↑	None	a good clinical response
Shroff A et al.[14]	2014	1	0/1	70	ACD		45mg at weeks 0,3,11,19	19wk	SCORAD 50	1x ↑ ↑ ↑	None	may require shorter dosing intervals
Samorano LP et al.[15]	2016	2	1/2	33.5(20-47)	1 with psoriasis	> 5000 2152	45mg at weeks 0 and 4 then every 12 weeks; 45mg at weeks 0,12 and 24 , restarted at weeks 0,6 and 12	4mo 4mo 24wk		1 flare 1x→	None	1 flared after 4 month cleared, 1 psoriasis improved while did not experience therapeutic benefits with AD the benefit has waned as treatment continued
Wlodek C et al.[17]	2016	1	0/1	13		7443	45mg at weeks 0,4,16,28 and 40	40wk	SCORAD 71.6	1x ↑	None	
Nic Dhonncha E et al.[18]	2016	10	8/10	32.9(20-50)	Asthma, AR		45mg or 90mg (who weighed between 90-95 kg) at weeks 0,4 and every 12 weeks	mean=1 9.2mo(4-71)		1x ↑ ↑ ↑ 3x ↑ ↑ ↑ 6x→	1 developed an elevated alanine transferase	the largest retrospective case series
Agusti-Mejias A et al.[16]	2013	1	0/1	16	Asthma, AR	752	45mg at weeks 0,4 and then every 12 weeks	14mo	SCORAD 23	1x ↑ ↑ ↑	None	a case in an adolescent patient successfully treated

Table 1 continued

References	Time	Pt.	Men	Age	Comorbidities	IgE Mean	Dose	Time on Therapy	Eczema (baseline)	Effect	Side effects	Comments
Khatti S et al.[11]	2016	32	20/32	37	(group 1);	9422(gr oup 1);7443(	45mg or 90mg (weight $\leq$ 100 or > 100kg) at weeks 0.4 and 16 (group 1) or weeks 16,20 and 32 (group 2)	40wk	SCORAD 69.73(group 1);65.40(group 2)	group 1: 9x $\uparrow$ group 2: 8x $\uparrow$	No serious adverse events	design two group received subcutaneous ustekinumab or placebo with a crossover to the other agent (either ustekinumab or placebo)
Saeki H et al.[10]	2017	52	36/52	45mg	(group 34(grou p 90mg)	7455 (group 45mg) 5575(gr oup 90mg)	45mg or 90mg at weeks 0.4 and a follow-up until week 24	24wk	EASI 38.0 (group 45mg) 36.5(group 90mg)	group 45mg: 9x $\uparrow$ 2x $\uparrow$ group 90mg: 10x $\uparrow$ 5x $\uparrow$	nasopharyn gitis, worsen AD, erysipelas	randomized(1:1:1) to receive ustekinumab 45mg, 90mg or placebo

group 1, placebo -ustekinumab group; group 2, ustekinumab -placebo group; $\uparrow$, mild; $\uparrow$, partial; $\uparrow$, complete; $\rightarrow$, none; ACD, allergic contact dermatitis; IgE, baseline mean serum total immunoglobulin level(IU/mL); SCORAD, scoring atopic dermatitis; VAS, visual analogue scale; wk, week; mo, month.