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Title of paper: Treatment of chronic alopecia areata with tildrakizumab: an open-label pilot study

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Alopecia areata (AA) is a common autoimmune disease with an estimated lifetime risk of 2.0%.¹ Most patients experience acute AA with 1-5 circular patches of alopecia that develop in close succession and spontaneously regrow within 6-12 months.¹ When AA persists beyond 12 months it is defined as chronic.¹ Approximately 30% of patients develop chronic AA with the serial development of multiple patches of alopecia over many years.¹

A systematic review of systemic treatment for AA did not identify any reliably effective evidence-based treatments for chronic AA, and a significant number of patients are refractory to all treatment.²

Tildrakizumab is a high-affinity monoclonal antibody targeting interleukin (IL)-23 p19.³ IL-23 induces T-helper 17 (Th17) cell proliferation that produce IL-17, a proinflammatory cytokine linked to the pathogenesis of several autoimmune conditions.^{3,4} Janus kinase (JAK) 2 has also been demonstrated to be an intracellular mediator of IL-23 cell surface receptor binding.³ Recent evidence support the role of IL-17 in the pathogenesis of AA, highlighting the potential therapeutic role by targeting IL-23.⁴

To study the efficacy of tildrakizumab in chronic AA, patients with moderate to severe AA, refractory to systemic therapy, were enrolled in a prospective, open-label pilot study. All had a baseline Severity of Alopecia Tool (SALT) score > 35%. Prior to first dose, all patients had negative serology for human immunodeficiency virus, hepatitis B and C viruses, and for *Mycobacterium tuberculosis*. Tildrakizumab, 100mg, was administered subcutaneously at weeks 0, 4 and 16. Response was assessed by calculating the percent change in SALT score at week 28: no response (0%), minimal (1%-15%), partial (16%-99%), or complete (100%). Patient demographics and treatment courses are detailed in Table 1.

Five females and 4 males aged between 17 and 48 years received 3 doses of tildrakizumab. The mean age at AA onset was 14.1 years (standard deviation [SD] 7.9; range 5-33 years). The mean duration of the current episode of AA was 9.4 years (SD, 6.4; range, 2-21 years). Two patients had patchy AA, 4 had alopecia totalis (AT), and 3 patients had alopecia universalis (AU). All patients were refractory to multiple previous treatments including oral prednisolone, tofacitinib, azathioprine, intralesional steroid, and diphenylcyclopropenone (DPCP). Two patients had a partial response (Fig.1), and 8 patients had no regrowth. One

patient withdrew after 2 injections due to lack of efficacy. Adverse effects of tildrakizumab were mild and included upper respiratory tract infection and acne.

The partial response to tildrakizumab seen in 2 out of 9 participants adds to the existing literature supporting the role of IL-17 in the pathogenesis of AA.⁴ The response rate to tildrakizumab is similar to that seen with cyclosporin 4mg/kg.⁵ Limitations of this pilot study include small sample size, lack of control group, and that only patients refractory to multiple other therapies were included. The treatment protocol selected was that used to treat psoriasis which is lower than the dose used to treat hidradenitis suppurativa. Adequately powered, randomized, placebo-controlled, dose-ranging trials would be required to further examine the efficacy of tildrakizumab in AA.

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Figure legends

Figure 1. Patient 5. Baseline Severity of Alopecia Tool (SALT) score 86 (left). SALT score 68 at week 28. Significant improvement not fully reflected in SALT score due to pre-existing androgenetic alopecia (right). Treatment was continued for a further 6 months, and the response maintained.

Table 1. Summary of individual demographics and treatment record of patients with alopecia areata on tildrakizumab

	Patient								
Characteristic	1	2	3	4	5	6	7	8	9
Age, y	22	17	42	35	48	28	20	20	30
Sex	M	M	F	F	M	M	F	F	F
Age of onset of AA, y	10	5	11	12	33	13	13	18	12
Duration of current episode of AA, y	6	3	21	8	15	10	5	2	15
Autoimmune/atopic comorbidities	–	AD	AD	–	–	–	AR	AD, asthma	Thyroid disease
Family history	–	–	AA	–	–	AD	AA, AD, Thyroid disease	AA	AD
Pattern of scalp AA	Totalis	Patchy	Universalis	Totalis	Patchy	Universalis	Totalis	Universalis	Totalis
Baseline SALT score, %	100	38	100	95	86	100	100	100	100
SALT score at week 28, %	100	29	100	100#	68	100	100	100	100
Response to treatment*	None	Partial	None	None	Partial	None	None	None	None
Follow-up duration, weeks/outcome	28/ceased	28/ceased	28/ceased	12/ceased	28/4 th injection administered	28/ceased	28/ceased	28/ceased	28/ceased
Adverse event(s)	URTI	Acne	–	–	–	–	–	–	–

Abbreviations: AA, Alopecia areata; AD, Atopic dermatitis; AR, Allergic rhinitis; F, Female; M, Male; URTI, upper respiratory tract infection; y, year

#SALT score calculated at week 12 for patient 4

*No response (0%), minimal (1%-15%), moderate (16%-99%), complete (100%).

1

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