Safety and efficacy of JAK inhibitors in alopecia areata, alopecia totalis, and alopecia universalis in the pediatric population: A systematic review and meta-analysis

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Background

Alopecia areata (AA) is the third most common dermatologic disorder in children[1]; disease heterogeneity and limited therapeutic options make treatment challenging.[2] Clinical trials have demonstrated benefit of Janus kinase (JAK) inhibitors in adults with AA.[2] We performed a systematic review and meta-analysis examining the safety and efficacy of JAK inhibitors in pediatric patients with AA.

Methods

A search was conducted on EMBASE, PubMed, Web of Science, and Google Scholar using the terms "alopecia AND janus kinase inhibitor," "alopecia AND JAK inhibitor," "alopecia AND tofacitinib," "alopecia AND ruxolitinib," and "alopecia AND baricitinib." Two independent reviewers identified studies and performed data extraction. Treatment response was defined as ≥5% improvement or any hair regrowth.

Results

Fourteen studies containing 51 patients (11 with AA and 45 with alopecia totalis or alopecia universalis) with a mean age of 12.6 years were included. Study and patient characteristics are detailed in Table 1. The pooled response rate to systemic JAK inhibitors was 80.3% (95% CI: 59.9%-91.8%; *p=0.006;* Figure 1A). Topical JAK inhibitors were associated with a pooled rate of response of 31.6% (95% CI 9.6%-66.9%; *p=0.31*) (Figure 1B).

Figure 1A. Meta-Analysis of Systemic JAK Inhibitors

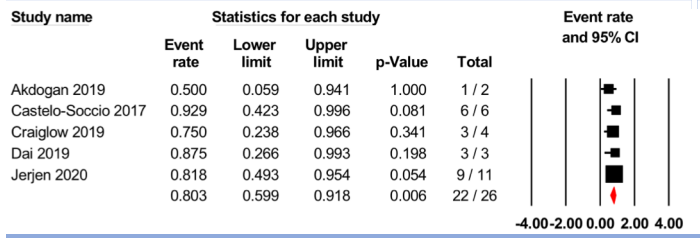

Figure 1B. Meta-Analysis of Topical JAK Inhibitors

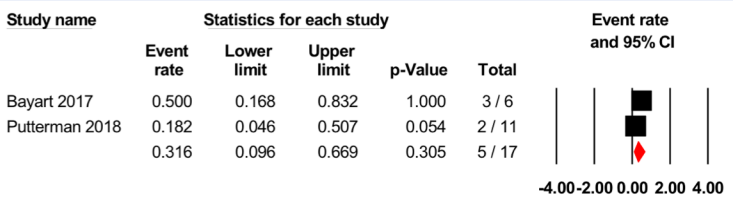

Table 1. Study and Patient Characteristics

STUDY	PATIENT		JAK INHIBITOR					
Author Year	**No.**	**Age (y)**	**Diagnosis**	**Name**	**Dose**	**ROA**	**Frequency**	**Adverse Events**
Akdogan 2019[4]	2	13-16	2 AT/AU	Tof	7.5 - 10 mg	Oral	QD	One patient experienced proteinuria at 2 months which did not require drug discontinuation
Bayart 2017[5]	6	3-17	6 AA	Tof & Rux	1% - 2%	Topical	BID – QOD (Tof) BID (Rux)	Two patients experienced mild laboratory abnormalities, which could not definitively be attributed to treatment; their condition normalized after 3 months of ongoing treatment
Castelo-Soccio 2017[6]	8	12-19	8 AT/AU	Tof	5 mg	Oral	BID	None
Chiang 2018[7]	1	17	1 AT/AU	Tof	5 mg	Oral	BID	Patient had an episode of herpes zoster at month 5, and drug was discontinued for 3 days. At month 8, a new alopecic patch formed and continued to expand after drug discontinuation
Craiglow 2016[8]	1	Late teens	1 AT/AU	Rux	0.60%	Topical	BID	None
Craiglow 2019[9]	4	8-10	4 AT/AU	Tof	5 mg	Oral	QD - BID	None
Dai 2019[10]	3	4-5	3 AT/AU	Tof	2.5 - 5 mg	Oral	QD - QID	Two patients experienced diarrhea and one patient experienced URTI, all of which spontaneously resolved without drug discontinuation.
Ferreira 2019[11]	1	13	1 AT/AU	Tof	5 mg	Oral	BID	None
Hosking 2018[12]	1	17	1 AT/AU	Tof	5 mg	Oral	BID	Patient experienced suspected herpes zoster-associated encephalitis which resolved without lasting sequelae with oral valacyclovir for 7 days and drug discontinuation
Jerjen 2020[13]	13	7-11	7 AA 6 AT/AU	Tof	2.5 - 7.5 mg	Oral	QD	Elevated AST and ALT (n = 5), eosinophilia (n = 5), hypercholesterolemia (n = 3), elevated urea (n = 3), hyperkalemia (n = 3), low total protein (n = 1), elevated triglycerides (n = 1), persistent, asymptomatic hyperbilirubinemia (n = 1), mild URTI (n = 3), none of which required drug discontinuation. One patient discontinued drug due to self-limiting unilateral lower leg pain although tofacitinib was not considered to be implicated
Liu 2019[14]	4	18-20	3 AT/AU 1 AA	Tof & Rux	10 - 15 mg (Tof) 10 - 20 mg (Rux)	Oral	QD – BID (Tof) BID (Rux)	The adverse effects of ruxolitinib were mild and included URTIs, weight gain, worsening of or development of new acne, easy bruising, and fatigue
Patel 2018[15]	1	17	1 AA	Tof	5 mg	Oral	BID	None
Peterson 2020[16]	1	9	1 AT/AU	Rux	20 mg	Oral	BID	None
Putterman 2018[17]	11	4-16	1 AA 10 AT/AU	Tof	2%	Topical	QD - BID	None

Results

Subgroup analysis of response to systemic JAK inhibitor based on disease duration of <3 years versus >3 years trended towards better response in patients with shorter (77.5%; 95% CI 39.3%-94.8%; *p=0.15*) compared to longer disease duration (75.5%; 95% CI 36.3%-94.3%; *p=0.19*) (Figure 1B). The most common adverse events (AEs) included mild upper respiratory tract infections, elevated liver enzymes, and eosinophilia.

Conclusions & References

- We found evidence to support the safety and efficacy of systemic JAK inhibitors for pediatric AA
- Oral JAK therapy was more effective than topical JAK inhibitor therapy, potentially due to the lower penetrability of topical medications
- The observed trend of better response in patients with shorter disease duration is not surprising given longer disease duration often portends a poorer prognosis and refractoriness to treatment.
- Our results show that JAK inhibitors appear to be safe in this population with the majority of AEs being mild and not requiring treatment discontinuation.
- Additional studies are needed to determine the optimal dosage and frequency as well as the long-term safety and efficacy.

[1]Afford R, Leung AKC, Lam JM. Pediatric alopecia areata. *Curr Pediatr Rev.* 2020.

[2]Phan K, Sebaratnam DF. JAK inhibitors for alopecia areata: a systematic review and meta-analysis. *J Eur Acad Dermatol Venereol.* 2019;33(5):850-856.