JAK Inhibitors for the Treatment of Pediatric Alopecia Areata

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Alopecia areata is a common autoimmune condition that disproportionately affects children and can significantly hinder quality of life. Few safe and effective therapies are available for the treatment of severely affected pediatric patients. JAK inhibitors have been recently established as an effective and well-tolerated therapy in adults, but there are limited data regarding the use of JAK inhibitors to treat alopecia areata in children. Here, we review the available literature regarding the use of JAK inhibitors in children in dermatology and across other medical disciplines.

INTRODUCTION

Alopecia areata (AA) is a common autoimmune condition characterized by nonscarring hair loss. Severity of presentation ranges from small, well-circumscribed patches of alopecia to complete loss of hair on the scalp (alopecia totalis, AT) or the body (alopecia universalis, AU). The prevalence of AA in the United States is 0.1–0.2% (Safavi, 1992) with 5% of patients progressing to AT or AU (Safavi et al., 1995).

Although not an exclusively pediatric condition (Strazzulla et al., 2018), AA disproportionately affects a younger subset of patients (Kyriakis et al., 2009; Muller and Winkelmann, 1963) with studies reporting 31–48% of patients developing the condition before the age of 20 years (Shellow et al., 1992; Tan et al., 2002). Of note, pediatric-onset AA tends to be more severe and carries a worse prognosis than adult-onset disease (De Waard-van der Spek et al., 1989; Xiao et al., 2006). Early age of onset and concomitant atopy are both strong negative prognostic factors (Goh et al., 2006; Muller and Winkelmann, 1963). Survey studies, although inherently biased toward severe phenotypes, suggest that up to half of pediatric patients presenting with localized AA could progress to AT or AU (Goh et al., 2006; Tosti et al., 2006). AA can severely affect mental health and quality of life in pediatric patients. Children with AA have higher rates of psychiatric disorders, and an AA diagnosis in a child is correlated with a reduction in health-related quality of life for both the child, driven by feeling of self-consciousness, and for caregivers, driven by emotional distress and financial burden (Bilgiç et al., 2014; Liu et al., 2018; Putterman et al., 2019).

Despite the prevalence of AA in children and the negative impact on the quality of life for patients and families affected, there is a relative paucity of literature focusing on therapy for AA in pediatric patients. Common therapies include topical, subcutaneous or systemic corticosteroids, topical minoxidil, topical contact-sensitizing agents, and rarely, nonsteroidal systemic immunosuppressants such as methotrexate (reviewed in Peloquin and Castelo-Soccio, 2017). Although a subset of patients will respond favorably to these regimens (response rates in studies focused on children ranged from 13% to 64%), patients with severe disease often have limited benefit and rate of relapse in responders is high, ranging from 70% to 100% at 1 to 2 years after treatment (Peloquin and Castelo-Soccio, 2017). In younger children, treatment is hindered by poor tolerance of painful procedures or irritating topical formulations. The use of systemic immunosuppressants, particularly systemic steroids, is further limited by side effects and concern regarding the long-term consequences of these regimens on developing children. Given these challenges of treating AA in children, some practitioners prefer to focus care on education, counseling, and psychological support for affected children and their families rather than resolution of disease.

In the last few years, the JAK-signal transducer and activator of transcription (JAK-STAT) pathway has been implicated in the pathogenesis of a number of inflammatory dermatoses, sparking interest in investigating inhibitors of the JAK receptor family (JAK1, JAK2, JAK3, and tyrosine kinase 2) in the treatment of dermatological conditions.

Various first-generation JAK inhibitors, which include ruxolitinib (JAK1/2 inhibitor), tofacitinib (JAK1/3 >2 inhibitor) and baricitinib (JAK1/2 inhibitor), have been found to be highly efficacious and well tolerated in patients with psoriasis, atopic dermatitis, vitiligo, and AA among others (reviewed in Damsky and King, 2017). Studies of AA mouse models revealed the importance of JAK-STAT signaling for development of autoreactive cluster of differentiation 8 (CD8^{+}) T-cell targeting of the hair follicle and confirmed that JAK inhibitors promoted hair regrowth in affected animals (Xing et al., 2014). The first patient with AA treated with tofacitinib was reported in 2014 (Craiglow and King, 2014), and since then, a number of case series (Ibrahim et al., 2017; Liu and King, 2019; Liu et al., 2017; Park et al., 2017) and a few small clinical trials (Almutairi et al., 2019; Jabbari et al., 2018; Kennedy Crispin et al., 2016; Mackay-Wiggan et al., 2016) have demonstrated hair regrowth in adult patients with moderate to severe AA treated with JAK inhibitors. Responses were muted in patients with long-standing disease and relapse often occurred upon cessation of therapy. Topical formulations of JAK inhibitors, while less effective for severe

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Abbreviations: AA, alopecia areata; AT, alopecia totalis; AU, alopecia universalis; JAK-STAT, JAK-signal transducer and activator of transcription

presentations (Bokhari and Sinclair, 2018; Craiglow et al., 2016; Phan and Sebaratnam, 2019) have been found to be a useful adjunct therapy for patients with limited disease or distinct areas of desired regrowth (e.g., eyebrows and eyelashes [Craiglow, 2018]).

The safety of long-term JAK inhibitor use has been a major focus of investigation as the utility of this drug class has been established in dermatology. Use of tofacitinib and ruxolitinib is associated with increased rates of infection (most commonly urinary tract infection and varicella zoster virus reactivation), lipid abnormalities, and rarely cytopenias and treatment-associated malignancies (reviewed in Damsky and King, 2017). Although associated with serious adverse events in the setting of treatment of hematological malignancy (cytopenias) or transplant immunosuppression (malignancy), at the lower doses required for efficacy in inflammatory dermatoses, JAK inhibitors have been well tolerated. A recent meta-analysis of 313 patients treated with JAK inhibitors for AA reported overall low complication rates associated with treatment (Phan and Sebaratnam, 2019). The most common adverse events were mild infections (24.6%), lipid abnormalities (11.8%), transaminitis (1.6%), and leukopenia (1.0%). No malignancies or tuberculosis reactivation events were observed. Several clinical trials exploring the use of JAK inhibitors for AA are currently underway to more systematically assess safety in larger patient cohorts.

In contrast, there is substantially less data describing the use of JAK inhibitors in children (Table 1). We reviewed the available literature regarding JAK inhibitors in the pediatric population, both for the treatment of AA as well as other conditions. A search was performed in PubMed using combinations of the following search terms: "ruxolitinib," "baricitinib," "tofacitinib," "JAK inhibitor," "janus kinase inhibitor," "child," "adolescent," "children," "pediatric" along the MeSh terms: "child" and "adolescent,"

producing a list of 170 publications. These were then screened to remove duplicates, retaining only those studies that described the direct treatment of a child (<18 years) with a JAK inhibitor, were in English, and were in full publication form (i.e., not simply an abstract with limited supporting information).

RESULTS

Only a handful of case series and reports have investigated the safety and efficacy of JAK inhibitors for AA in children and adolescents. In two case series of patients aged 12−17 years with AA treated with tofacitinib, 9 of 13 (Craiglow et al., 2017) and 6 of 6 treated patients (Castelo-Soccio, 2017) experienced clinically significant hair regrowth. Both studies dosed tofacitinib at standard levels of 5 mg twice daily, although one patient required an increased dose of 5 mg in the morning and 10 mg in the evening to achieve optimal regrowth after relapse (Craiglow et al., 2017). A small case series also investigated the use of tofacitinib in preadolescent children and included four patients with AT or AU aged 8 to 10 years dosed at 5 mg twice daily (Craiglow and King, 2019). Two patients experienced complete regrowth at 3 and 6 months, respectively, and a third demonstrated 62% regrowth at 6 months of treatment. Most recently, a small report investigated the use of tofacitinib in three younger children aged 4 to 5 years with AT or AU (Dai and Chen, 2019). Drug dosing was initiated at 2.5 mg daily. At this dose, two patients experienced clinically significant regrowth with >90% improvement after 12 months. The third patient required a dose increase to 2.5 mg 4 days per week and 5 mg 3 days per week at 6 months, ultimately achieving full regrowth of eyebrows and eyelashes and 50% regrowth of scalp hair at 21 months. Several individual cases of children treated with JAK inhibitors for AA have also been reported with similar results (Table 1). Taken as a whole, these studies

Table 1. JAK Inhibitor Use in Pediatric Alopecia Areata

Publication	Drug	Route	Dose	Patients (n)	Age (y)	Response	Reported Side Effects
Dai and Chen (2019)	Tofacitinib	Oral	2.5 mg QD; 2.5, 5 mg alt QD	3	4−5	50−90% regrowth	Mild: diarrhea, URI
Liu and King (2019)	Ruxolitinib	Oral	10 mg BID	1	14	91% change in SALT	Mild: URI, weight gain, acne, drop in WBC[1]
Brown and Skopit (2018)	Tofacitinib	Oral	5 mg BID	14	8	100% change in SALT	Treatment limiting HA
Craiglow and King (2019)	Tofacitinib	Oral	5 mg BID		8−10	0−100% regrowth	None
Patel et al. (2018)	Tofacitinib	Oral	5 mg BID	1	17	85% change in SALT	Weight gain
Castelo-Soccio (2017)	Tofacitinib	Oral	5 mg BID	6	12−16	52−79% change in SALT	None
Craiglow et al. (2017)	Tofacitinib	Oral	5 mg BID; 5, 10 mg alt BID	13	12−17	1−100% change in SALT	Mild: HA, URI, transaminitis
Putterman and Castelo-Soccio (2018)	Tofacitinib	Topical	2%	11	4−16	32.3% average change in SALT	Application site irritation
Bayart et al. (2017)	Tofacitinib, ruxolitinib	Topical	1%, 2%	6	1−16	4 of 6 patients; 20−95% regrowth	Mild laboratory abnormalities
Craiglow et al. (2016)	Ruxolitinib	Topical	0.60%	1	Late teens	100% growth eyebrows; 10% scalp	Mild drop in WBC

Abbreviations: alt, alternating; BID, twice daily; HA, headache; QD, daily; SALT, Severity of Alopecia Tool; URI, upper respiratory infection; WBC, white blood cell count.

[1]Side effects listed for all patients in study but only one was an adolescent. Specific side effects experienced by this patient were not listed.

demonstrated success rates for systemic JAK inhibitors in children comparable with those found in adults, with a number of dramatic responses and a smaller subset of poor responders. Side effects were minimal and included mild infections, diarrhea, and transient laboratory abnormalities. Although suggestive of JAK inhibitors being a well-tolerated treatment of AA in children, these small case series must be followed with randomized controlled trials to reach definitive conclusions.

Given the concern regarding long term consequences of JAK inhibitors in developing children, a few studies have focused on the use of topical JAK inhibitors for AA in the pediatric population. A series of six patients aged 3−17 years treated with application of 2% tofacitinib or 1−2% ruxolitinib found variable responses (20−95% improvement) in 4 of 6 patients (Bayart et al., 2017). One patient who did not respond to 2% tofacitinib in a nonliposomal base experienced complete regrowth when switched to a liposomal vehicle, demonstrating the importance of the vehicle composition in drug penetration. Another series of 11 pediatric patients ranging from 4 to 11 years treated with 2% tofacitinib experienced an average of 32.3% change in

Table 2. JAK Inhibitor Use in Nondermatological Pediatric Disciplines

Discipline	Condition	Publication	Drug	Dose	Patients (n)	Age (y)	Notable Adverse Events
Oncology							
	GVHD	Bauters et al. (2019)	Ruxolitinib	Unspecified	1	10	Hypertriglyceridemia with sirolimus
		González Vicent et al. (2019)	Ruxolitinib	Infants: 2.5 mg QD; Children: <25 kg−2.5 mg BID; ≥25 kg−5 mg BID; Adolescents: 10 mg BID	22	0.4−18	Grade 3 liver toxicity, unrelated to drug; Viral, fungal, bacterial infections; Mild thrombocytopenia
		Schoettler et al. (2019)	Ruxolitinib	5 mg−10 mg BID; 1 patient 2.5 mg TIW	5	7−21	Grade 3 fungal infection while also on corticosteroid
		Khandelwal et al. (2017)	Ruxolitinib	<25 kg: 2.5 mg BID; ≥25 kg: 5 mg BID	11	1−16	Grade 3−4 elevated transaminases; Grade 3−4 neutropenia, grade 4 thrombocytopenia; infections: EBV, adenovirus, BK, bacterial, fungal
	ALL	Ding et al. (2018)	Ruxolitinib	40 mg/m²/dose twice daily	1	10	Grade 4 transaminitis, transient; No further cytopenia or toxicities beyond typical chemotherapy
		Mayfield et al. (2017)	Ruxolitinib	40 mg/m²/d split twice daily	1	17	Persistent thrombocytopenia and neutropenia
	CML	Freedman et al. (2016)	Ruxolitinib	50 mg/m²/d	1	11	
	Lymphoma	Hanna et al. (2014)	Tofacitinib	15 mg BID	1	14	
	PV	Coskun et al. (2017)	Ruxolitinib	5 mg BID titrated up to 25 mg BID	1	2	None
	Various cancers	Loh et al. (2015)	Ruxolitinib	15, 21, 29, 39, 50 mg/m²/dose, BID	49	1−22	1 grade 5 multiorgan failure at 21 mg/m²/dose; 2 grade 4 neutropenia events at 29 and 39 mg/m²/dose; 1 grade 4 CK elevation at 50 mg/m²/dose
Rheumatology							
	CMC	Bloomfield et al. (2018)	Ruxolitinib	10 mg BID (20 mg/m²/d)[1]	1	12	URI
	Interferonopathy	Kim et al. (2018) [2]	Baricitinib	0.1−17 mg/d (0.01−0.82 mg/kg/d); PK analysis to establish dosing	18	1−24	Kidney disease secondary to BK infection; Viral infections: URI, VZV, BK viruria, and viremia; Osteonecrosis
		Saldanha et al. (2018)	Ruxolitinib	5 mg daily	1	3	Partial response leading to nasal septal destruction
		Sanchez et al. (2018) [2]	Baricitinib	0.1−17 mg/d (0.01−0.82 mg/kg/d)	18	1−24	Kidney disease secondary to BK infection; Viral infections: URI, VZV, BK viruria, and viremia; Osteonecrosis
		Frémond et al. (2016)	Ruxolitinib	Not specified	3	5−12	Papillary edema
	JIA	Ruperto et al. (2017)	Tofacitinib	2−5 mg BID	26	2−18	Fatigue
	Juvenile DM	Papadopoulou et al. (2019)	Baricitinib	6 mg BID	1	11	None
		Aeschlimann et al. (2018)	Ruxolitinib	10 mg BID (0.5 mg/kg/d)	1	13	None

Abbreviations: ALL, acute lymphocytic leukemia; BID, twice daily; CK, creatine kinase; CMC, chronic mucocutaneous candidiasis; CML, chronic myeloid leukemia; DM, dermatomyositis; GVHD, graft-versus-host disease; JIA, juvenile idiopathic arthritis; PK, pharmacokinetic; PV, polycythemia vera; QD, daily; SALT, Severity of Alopecia Tool; TIW, three times weekly; URI, upper respiratory infection; VZV, varicella zoster virus.

[1]Dose was later decreased by 50% owing to drug interactions.

[2]These works analyze the same cohort of patients.

Severity of Alopecia Tool score (Putterman and Castelo-Soccio, 2018). However, only 3 of 11 patients in this trial were deemed to have cosmetically acceptable growth. A final case report of a single patient in her late teens exhibited near full regrowth of eyebrows after 12 weeks of treatment with 0.6% ruxolitinib cream but only 10% regrowth of scalp hair (Craiglow et al., 2016). Of note, in all three studies investigating topical JAK inhibitors in children, minimal adverse effects were noted, consisting of mild laboratory abnormalities and application site irritation. Overall, topical JAK inhibitors in children appear to be best employed in the treatment of localized disease with limited utility in the treatment of more extensive AA, as is the case for adult patients.

JAK inhibitors have been investigated more extensively in pediatric patients in other medical disciplines, particularly rheumatology and oncology (Table 2). Although mostly consisting of small case reports and case series, there are three larger studies: a phase 1 trial of ruxolitinib in children with refractory solid tumors and hematological malignancies (Loh et al., 2015), a phase 1 trial of tofacitinib in children with juvenile idiopathic arthritis (Ruperto et al., 2017), and a compassionate use protocol using baricitinib in patients with the rare Mendelian interferonopathies (Kim et al., 2018; Sanchez et al., 2018). These larger studies provide important insight into the pharmacokinetics of JAK inhibitors in children, which can be vastly different than in adult patients. In patients under 40 kg baricitinib had a significantly shorter half-life than found in adults, necessitating 3−4 times daily dosing for optimal effect. Drug levels varied by renal function and weight, and given these complexities, the authors provided an extensive dosing table for baricitinib initial dosing and two dose escalations, organized by weight and glomerular filtration rate (Kim et al., 2018). Analysis of tofacitinib in patients with juvenile idiopathic arthritis also observed a similarly shorter half-life in children as well as a faster clearance rate than expected, requiring higher dosage than that suggested by adult pharmacokinetic studies (Ruperto et al., 2017). In contrast, in children with relapsed malignancies treated with escalating doses of ruxolitinib determined by surface area (15, 21, 29, 39, 50 mg/m^2/dose), pharmacokinetics were comparable with that in adults. Toxicities were comparable across all doses tested, and the highest dose (50 mg/m^2) was recommended for future trials in patients with cancer (Loh et al., 2015).

These studies also give insight into safety of this drug class in larger cohorts of children. As in adults, these drugs are well tolerated, with most adverse events resulting from increased susceptibility to mild infection, particularly viral infections, including Epstein Barr virus, BK virus, adenovirus, and varicella zoster virus, among others (Table 1). However, there were a few serious complications including instances of severe fungal infections and cytopenias, particularly when used to treat children with malignancy or graft-versus-host disease. As with adult safety data surrounding JAK inhibitor use in oncology, the direct relationship of these adverse events to JAK inhibitors is complicated by concomitant use of chemotherapeutic agents and other immunosuppressants, underlying bone marrow dysfunction, overall poor health of the patients treated, and substantially higher doses used to treat malignancy (for instance, up to 50 mg/m^2/d of ruxolitinib, equivalent to a dose of 70 mg/d in the average 10-year-old boy). In comparison, in the phase 1 study testing tofacitinib in children with juvenile idiopathic arthritis, a considerably healthier cohort of patients, only one mild adverse event (fatigue) was considered to be treatment related (Ruperto et al., 2017).

CONCLUSION

Although children develop AA at higher rates and with greater severity than adults, significantly affecting quality of life, few effective, tolerable, and safe treatment options are available to treat severe presentations of this disease in the pediatric population. JAK inhibitors have been identified as a largely safe and highly effective therapy for moderate to severe AA in adults, and a few small studies have suggested that similar results are to be expected in children. Phase 1 studies of JAK inhibitors for the treatment of malignancy and inflammatory conditions in children have supported the potential safety of these medications and have provided dosing guidance. Randomized controlled trials in children with AA are ultimately needed to fully establish the efficacy and safety of this drug class for this patient population.

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