SYSTEMATIC REVIEW OF THE SAFETY AND EFFICACY OF JAK1 AND JAK2 INHIBITORS COMPARED WITH ORAL CORTICOSTEROIDS FOR THE TREATMENT OF ALOPECIA AREATA

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INTRODUCTION

- Alopecia areata (AA), an autoimmune hair loss condition, has a global lifetime risk of 2% with no gender preference as well as presents in young adulthood and disproportionately affects Blacks and Asians
- While treatment options exist, JAK1/JAK2 inhibitor therapies were recently FDA-approved in June 2022
- Inhibition of JAK proteins blocks the intracellular pathways responsible for inflammation at the site of the hair follicles as seen in AA
- Due to significant cost differences and side effect profiles, it is important to compare JAK inhibitors and traditionally-used oral steroids for efficacy
- The aim of this study is to compare oral JAK inhibitors with oral steroids

OBJECTIVES

- The primary objective of this study was to assess and compare oral JAK1/JAK2 inhibitors and oral corticosteroids across the following criteria:
  - Mean percent change between baseline Severity of Alopecia Tool (SALT) score and post-treatment SALT score
  - Mean percent of treatment groups with greater than 95% of hair regrowth
  - Safety profile in terms of reported adverse events (AEs)

METHODS

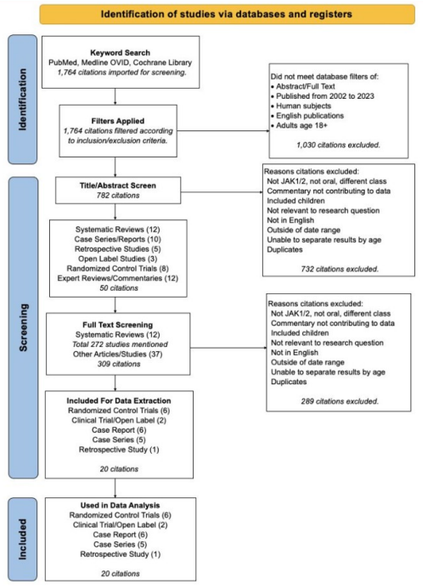

Figure 1. PRISMA schematic identifying literature review and selection process

- Total of 20 studies included in data extraction
- **Search terms:** "alopecia areata," "steroids," "oral administration," "janus kinase inhibitor," "treatment outcome" and "systematic review"
- **Inclusion criteria:** publications in English between Jan. 2002 and May 2023, human subjects, ages 18 and older
- **Exclusion criteria:** other types of alopecia, hair loss in other areas besides the scalp, concurrent use of other systemic or topical medications, other classes of JAK inhibitors, non-idiopathic alopecia areata

RESULTS

Table 1. Study characteristics

Author(s)	Type of Study	n	Mean Age (+/- SD)	Age Range (years)	Duration Since Diagnosis of AA
King et al (2022)- BRAVE-AA1	RCT	Total: 654 T1: 184 T2: 281 Placebo: 189	Overall NR T1:38.0(+/-12.8) T2: 36.3(+/-13.3) Placebo: 37.4(+/-12.9)	18-70	Overall NR T1: 12.1(+/-9.8) T2: 11.8(+/-11.1) Placebo: 12.6(+/-11.2)
King et al (2022)- BRAVE-AA2	RCT	Total: 546 T1: 156 T2: 234 Placebo: 156	Overall NR T1: 39.0(+/-13.0) T2: 38.0(+/-12.7) Placebo: 37.1(+/-12.4)	18-70	Overall NR T1: 13.1(+/-11.8) T2: 11.9(+/-11.1) Placebo: 11.8(+/-10.2)
King et al (2021)	RCT	Total: 110 T1: 28 T2: 27 T3: 27 Placebo: 28	Overall NR T1: 38.6 (11.3) T2: 42.5 (13.8) T3: 42.4 (14.9) Placebo: 40.5 (14.2)	27-56	Overall NR T1: 12.5 (12.5) T2: 16.9 (12.8) T3: 12.3 (10.1) Placebo: 16.8 (13.0)
Olamiju et al (2019)	CR	1	60	NA	9 years
Pestana et al (2022)	CR	1	31	NA	NR
Wang et al (2022)	CS	9	27.3	18-43	3-41 years
Almutairi et al (2019)	CT	38	35.5 (+/- 13.8)	18-54	29.6 (+/- 11.5) months
Mackay-Wiggan et al (2016)	CT, OL	12	43.67 (+/- 14.41)	NR	NR
Harris et al (2016)	CR	1	35	NA	19 years
Vandiver et al (2016)	CR	2	NR	45-59	NR
Ramot and Zlotogorski (2018)	CS	1	33	NA	11 years
Xing et al (2014)	CS	3	NR	NR	NR
Pieri (2015)	CR	1	24	NA	12 years
Higgins (2015)	CR	1	28	NA	2 years
King et al (2022)	RCT	Total: 149 T1: 30 T2: 38 T3: 37 Placebo: 44	36.8 (+/- 12.85)	NR	NR
Kar (2005)	RCT	Total: 36 T1: 20 Placebo: 16	26.3 (+/- 7.3)	19-40	9 months-4 years
Sato-Kawamura (2002)	CS	6	34.8	22-63	NR
Gupta et al (2019)	RCT	21	25.90 (+/- 1.17)	NR	1-7 years
Jang et al (2016)	Retrospective CS	37	38.7	NR	NR
Lobato-Berezo (2022)	Retrospective†	45	42.8	20-78	80.2 (+/-98.3) months
Overall	6 RCTs 6 CRs 5 CSs 3 non-RCTs	1,674	--	18-78	--

AA = alopecia areata, RCT = randomized control trial, CR = case report, CS = case series, CT = clinical trial, OL = open-label study, Non-RCTs = CT, OL, retrospective CS, multicentric retrospective study†, T = treatment group, NR = not reported, NA = not applicable, SD = standard deviation

- Total of 1,674 study subjects (1,516 from RCTs, seven from CRs, 56 from CS, 50 from clinical trials, and 45 from a retrospective study)
- The studies were distributed as: six RCTs, six case reports, five case studies, and three non-RCTs
- There were variable age ranges and duration since diagnosis of AA across the studies

Table 2. Pooled study results with treatment outcome of $SALT_{80}$ or greater, average time to regrowth, mean percent change of SALT, and mean percent of treatment groups with greater than 95% hair regrowth by medication class

Type of Study	JAK1/2 Inhibitors			Steroids			
	BARI	RUXO	CTP-543	PSL	PDN/MP	BETA	DEXA
RCT (N= 6)							
Total in treatment:	909	-	95	20	-	21	-
n with $SALT_{80-100}$	308	-	25	5	-	7	-
% with $SALT_{80-100}$	33.89	-	26	25	-	33.33	-
n with $SALT_{<80}$	601	-	70	15	-	14	-
Avg. time to regrowth	NR	-	NR	NR	-	4 months	-
CS/CR (N= 11)							
Total in treatment:	11	6	-	-	3	37	-
n with $SALT_{80-100}$	2	5	-	-	NR	*	-
% with $SALT_{80-100}$	18.18	83.33	-	-	NR	*45.90	-
n with $SALT_{<80}$	9	1	-	-	NR	NR	-
Avg. time to regrowth	NR	NR	-	-	NR	NR	-
Non-RCT (N= 3)							
Total in treatment:	-	47	-	-	-	-	45
n with $SALT_{80-100}$	-	15	-	-	-	-	11
% with $SALT_{80-100}$	-	31.91	-	-	-	-	25.00
n with $SALT_{<80}$	-	32	-	-	-	-	34
Avg. time to regrowth	-	NR	-	-	-	-	NR
Mean % Change of SALT Scores	N=5 Mean: 52.03 (+/-24.39)			N=1 Mean: 21.10 p= 0.52			
Mean % of Treatment Groups with >95% Hair Regrowth	N=13 Mean: 55.58 (+/-40.86)			N=4 Mean: 32.31 (+/-9.88) p= 0.076			

BARI= baricitinib, RUXO= ruxolitinib, CTP-543= cytochrome p-543, PSL= prednisolone, PDN/MP= prednisone/methylprednisone, BETA= betamethasone, DEXA= dexamethasone, RCT= randomized control trial, CS/CR= case series/case reports, non-RCTs= any study that is not either an RCT or a CS/CR, N= total number of studies, n= number of participants, *percent of hair regrowth not specified, NR= not reported

- Baricitinib had the highest percent (33.89%) of participants achieving a $SALT_{80}$ or greater
- For greater than 95% hair regrowth, JAK inhibitors yielded 55.58%(±40.86) compared to steroids at 32.31%(±9.88)
- The range of $SALT_{80}$ to $SALT_{100}$ captured the highest categories of hair regrowth and was used to illustrate response in treatment groups across different types of studies by medication

Table 3. Summary of adverse events (AEs) reported by medication

Author(s)	n (%)							
	GI *	Infections †	Neuro ‡	Skin §	Metabolic ±	Malignancy ¶	Other **	Total AEs
Baricitinib								
King et al (2022)- BRAVE-AA1	0 (0)	80 (38.83)	31 (15.05)	27(13.11)	0 (0)	0 (0)	68 (33.01)	206
King et al (2022)- BRAVE-AA2	0 (0)	86(53.09)***	43 (26.54)	23(14.20)	0 (0)	0 (0)	10 (6.17)	162
King et al (2021)	0 (0)	29(100.00)***	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	29
Olamiju et al (2019)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0
Pestana et al (2022)	0 (0)	0 (0)	0 (0)	1(100.00)	0 (0)	0 (0)	0 (0)	1
Wang et al (2022)	1 (25.00)	0 (0)	0 (0)	2(50.00)	0 (0)	0 (0)	1 (25.00)	4
Ruxolitinib								
Almutairi et al (2019)	2 (9.52)	8 (38.10)	2(9.52)	1(4.76)	1(4.76)	0 (0)	7 (33.33)	21
Mackay-Wiggan et al (2016)	0 (0)	10 (66.67)	0 (0)	3(20.00)	0 (0)	0 (0)	2 (13.33)	15
Harris et al (2016)	-	-	-	-	-	-	-	-
Vandiver et al (2016)	1 (33.33)	0 (0)	0 (0)	0 (0)	1(33.33)	0 (0)	1 (33.33)	3
Ramot and Zlotogorski (2018)	-	-	-	-	-	-	-	-
Xing et al (2014)	0 (0)	8 (72.73)	0 (0)	2(18.18)	0 (0)	0 (0)	1 (9.09)	11
Pieri (2015)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0
Higgins (2015)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0
CTP-543								
King et al (2022)	20 (16.67)	18 (15.00)	26 (21.67)	22(18.33)	4 (3.33)	0 (0)	30 (25.00)	120
Prednisolone								
Kar (2005)	-	0 (0)	0 (0)	-	-	0 (0)	-	11††
Prednisone/Methylprednisone								
Sato-Kawamura (2002)	-	-	-	-	-	-	-	-
Betamethasone								
Gupta et al (2019)	5 (13.89)	0 (0)	0 (0)	8 (22.22)	23 (63.89)	0 (0)	0 (0)	36
Jang et al (2016)	4 (9.52)	0 (0)	4 (9.52)	8 (19.05)	20 (47.62)	0 (0)	6 (14.29)	42
Dexamethasone								
Lobato-Berezo (2022)	5 (12.20)	4 (9.76)	1 (2.44)	8 (19.51)	7 (17.07)	0 (0)	16 (39.02)	41
Overall	38 (5.41)	242 (34.47)	107 (15.24)	105 (14.96)	56 (7.98)	0 (0)	142 (20.23)	702

n= single reported adverse events
*Gastrointestinal sxs: nausea, abdominal pain, diarrhea, weight gain, bloating, gastric reflux
† Infections: upper respiratory infection, urinary tract infection, herpes zoster, herpes simplex, pneumonia
‡ Neuro sxs: headache, dizziness
§Skin sxs: acne, seborrhea, folliculitis, striae distensae, dermatophytic infection, skin atrophy, hirsutism, hypertrichosis
±Metabolic sxs: weight gain, facial edema, hypertriglyceridemia, increased low-density lipoprotein, Cushing syndrome
¶Malignancy: none reported
**Other: nasopharyngitis, increased serum creatinine kinase, major CV event (unspecified), venous thromboembolism, increased serum liver transaminases, leukopenia, fatigue, conjunctival hemorrhage status post-surgery, hemoglobinemia, bruising, sleep disorders, hypertension, psychiatric disorders, arthromyalgias, cough
***At least one infection requiring discontinuation of medication
†† Distribution not specified: Acneiform eruption, gastrointestinal upset, weight gain, facial mooning, oligomenorrhea

- Infection was the most common side effect accounting for 34.47%
- Baricitinib had the largest number of reported side effects (402) compared with ruxolitinib (50), CTP-543 (120), prednisolone (11), betamethasone (78), prednisone/methylprednisone (0), and dexamethasone (41)
- Betamethasone had the most side effects (78) reported for all steroids

DISCUSSION

- First systematic review to compare oral steroids with oral JAK inhibitors focusing on mean SALT score percent changes, mean percent of treatment groups with 95% regrowth, and summarizing treatment outcomes for patients with $SALT_{80}$ or greater by study type
- No statistical significance between JAK inhibitors and steroids with mean percent change of SALT scores and mean percent of treatment groups of greater than 95% hair regrowth
- Consistent with existing studies, baricitinib had the greatest number of reported side effects (402) compared with ruxolitinib (50), CTP-543 (120), prednisolone (11), prednisone/methylprednisone (0), betamethasone (78), dexamethasone (41)
- **Strengths:**
  - Inclusion of 6 randomized control trials which provided high quality evidence
  - Unique analysis of results based on means of included studies
- **Limitations:**
  - Lack of standardization in reporting of results across studies
  - Not all data points of interest were reported in every study
  - Data obtained from case series and case reports that are at risk of selection and publication bias
  - The data contained confounders due to summarized means from studies
  - Only one steroid study was included in the comparison of mean percent change of SALT score

CONCLUSION

- Results suggests that there are no significant differences between the efficacy of JAK1/JAK2 inhibitors compared to oral steroids in terms of 95% regrowth and percent mean change of SALT
- Adverse events reported suggests that JAK1/JAK2 inhibitors have the greatest likelihood of minor infections while oral steroids have the greatest likelihood of increasing metabolic dysfunction
- To our knowledge, no existing study solely compares oral steroids and JAK inhibitors; therefore, there is no result comparison available
- **Variables of interest in future studies:**
  - Quality of life measures such as emotional well-being, interpersonal relations, and social inclusions as primary outcomes
  - Social determinants of health measures due to an increase disease burden for people of color
  - JAK inhibitors are an expensive class of medication with a unique side effect profile that require close follow-up with healthcare providers

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