INTERNATIONAL SEVEN JOURNAL
OF MULTIDISCIPLINARY
ISSN: 2764-9547

Safety and efficacy of JAK inhibitors in the treatment of alopecia areata: A systematic review

Segurança e eficácia do uso de inibidores de JAK no tratamento da alopecia areata: Uma revisão sistemática

DOI: 10.56238/isevmjv3n2-026
Receipt of originals: 04/03/2024
Acceptance for publication: 04/23/2024

Alice Borem Camargos[1], Gabriela Bicalho Cordier[2], Luna Braga Bello Lisboa[3], Marco Túlio Andrade Silva[4].

ABSTRACT

Objective: To carry out a literature review on the safety and efficacy of using JAK inhibitor medications in the management of alopecia areata. Methods: A search was carried out in the PubMed , Scielo and LILACS databases using the keywords *alopecia in areas* and *JAK inhibitors* . Based on the inclusion and exclusion criteria, thirteen articles were selected from the 287 found. Results: The articles analyzed demonstrate that the use of JAK inhibitors, orally, resulted in a significant increase in favorable therapeutic responses, compared to the control group that received the placebo. Regarding therapeutic dosage, results were observed proportional to the duration of treatment. Regarding safety, the adverse events reported were mostly mild and controllable. Conclusion: The articles raise the possibility that orally administered JAK inhibitors may be among the most effective therapies for the treatment of alopecia areata .

Keywords: Alopecia in areas, JAK Inhibitors, Janus Kinases, Efficiency, Safety.

INTRODUCTION

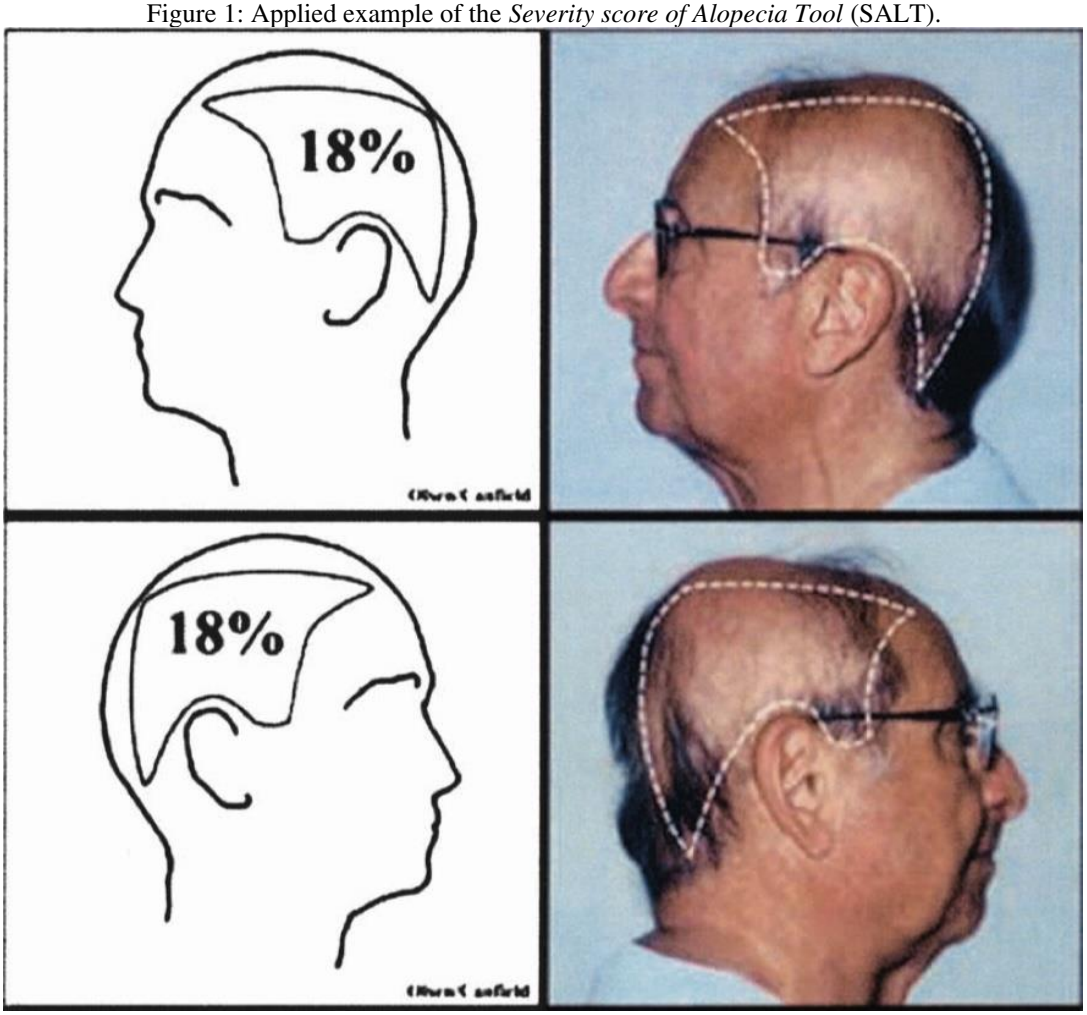
Alopecia areata (AA) is a chronic and relapsing autoimmune disease characterized by scarless hair loss and sparing of the hair follicle (LIU, *et. al.* , 2023). AA affects 2% of the world population, which can be adults and pediatrics, and without gender predilection (WINNETTE, *et. al.* , 2022). AA often presents as a cyclical disorder marked by unpredictable periods of hair loss and spontaneous regrowth and can result in varying degrees or patterns of hair loss (KING, *et. al.* , 2023). Hair loss can be partial (irregular AA), complete hair loss on the scalp (alopecia totalis) or total hair loss over the entire body (alopecia universalis) (KING, *et. al.* , 2023). Although patients with localized AA often resolve spontaneously, those with moderate hair loss or the severe phenotype often experience more recalcitrant disease, which can significantly affect

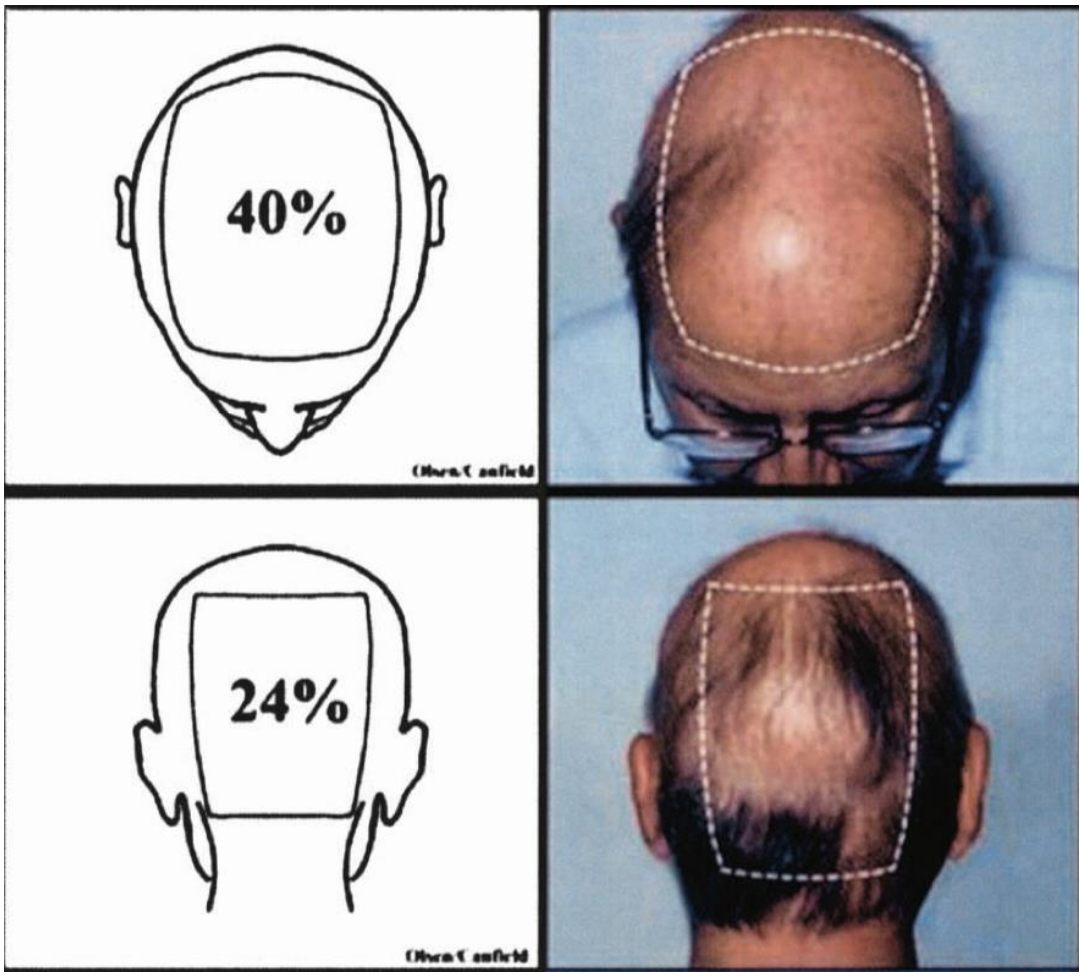
1 E-mail: aliceborem15@gmail.com
2 E-mail: gabriela.cordier@hotmail.com
3 E-mail: luna.medicina@icloud.co
4 E-mail: mtuliodermato@gmail.com

their quality of life (GUTTMAN-YASSKY, *et. al., 2021*). The condition is also frequently associated with a significant impact on patients' mental health-related quality of life and adverse psychological effects, such as anxiety disorders and depression (WINNETTE, *et. al.* , 2022).

Given the clinical picture of AA, the *Severity scale of Alopecia Tool* (SALT), in free translation “tool for assessing the severity of alopecia”, is a validated instrument for measuring the degree of hair loss and divides an individual's scalp into four quadrants: posterior, superior, and lateral left and right representing 24%, 40% and 18% of the total surface area, respectively. Summing the scores from the four quadrants provides an overall SALT score that ranges from 0% (no scalp hair loss) to 100% (complete scalp hair loss) (WINNETTE, *et. al.* , 2022).

Figure 1: Applied example of the *Severity score of Alopecia Tool* (SALT).





The percentage of hair loss in any of the four views (areas) of the scalp = the percentage of hair loss in 3% of the scalp surface area in that area. The SALT score is then equal to the sum of the percentage of scalp hair loss in each area.
(a) Left lateral quadrant = 95% x 0.18 = 17.1
(b) Right lateral quadrant = 90% x 0.18 = 16.2
(c) Upper quadrant = 95% x 0.40 = 38
(d) Lower quadrant = 55% x 0.24 = 13.2
a+b+c+d = 17.1 + 38 + 16.2 + 13.2 = 84.5% hair loss or SALT score 84.5.
Source: Adapted from Olsen EA *et. al.,* 2004.

Currently, there is no cure for AA and topical, intralesional and systemic corticosteroids , glycyrrhizin, minoxidil , diphenylcyclopropenone and systemic agents such as methotrexate are used to alleviate AA in patients with the disease. Furthermore, systemic corticosteroid therapy , the strategy most used in clinical practice, is associated with side effects such as acne, weight gain and endocrine disorders, while topical corticosteroid therapy is related to significant skin atrophy at the site of application. (WEI, *et. al.* , 2023). Recent studies have shown that Janus Kinase (JAK) enzyme inhibitor medications can block the T lymphocyte-mediated immune response in hair follicles, promote the formation of hair follicle stem cells, and trigger angiogenesis, both of which occur during the hair growth phase. JAK inhibitors can also accelerate the transition of hair follicles from the telogen phase to the anagen phase . Many

clinical studies have demonstrated that the use of JAK inhibitors to treat AA achieved satisfactory results with an acceptable side effect profile, through local inflammatory remission and consequent hair growth (JABBARI A, et al., 2015; SEDEH, *et. al* ., 2023). These inhibitors target several cytokines, including IL-2, IL-7, IL-15, IL-21, and IFN-γ, which appear to be involved in the pathogenesis of AA. Furthermore, the JAK/STAT signaling pathway is involved in the hair cycle and is supposedly upregulated in the catagen and telogen phases of the hair cycle, but suppressed in the anagen phase (SEDEH, *et. al* ., 2023).

The objective of this study was to carry out a literature review on the use of JAK inhibitor medications in the management of alopecia areata , highlighting the safety and efficacy aspects of the medications in treating the disease.

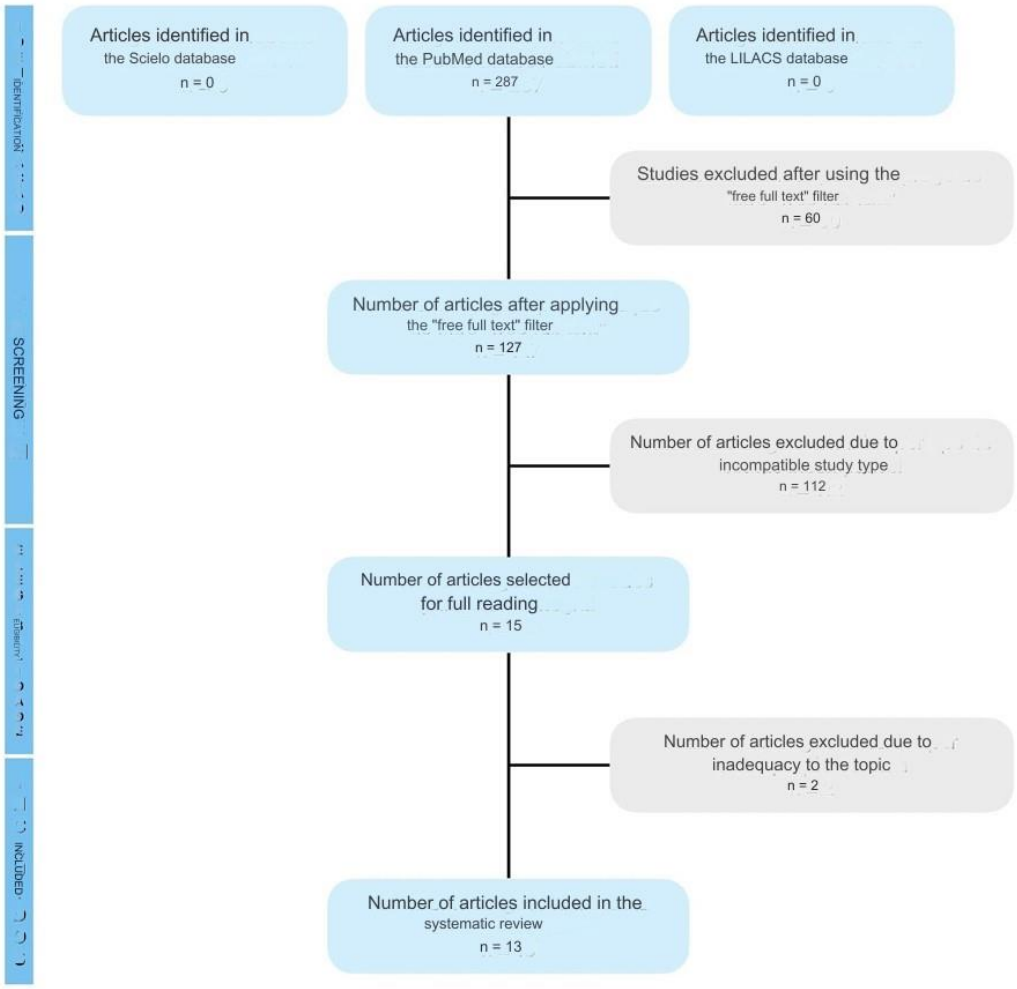
MATERIALS AND METHODS

Articles published in indexed journals were selected, using the search platforms PubMed , Scielo and LILACS, with classification. The search was carried out in Portuguese, English and Spanish, between 2013 and 2023, using the descriptors *"area alopecia"* and *"JAK inhibitors"* .

RESULTS

With the descriptors alopecia in areas and JAK inhibitors, no articles were found in Scielo nor in LILACS. In PubMed , using *Medical Subject Headings* (MeSH), 287 articles were found. By applying the "free full text" filter, 60 articles were excluded. Of the remaining 127 articles, 112 articles that did not fit into any of the categories of clinical trial, meta-analysis or randomized controlled study were excluded. No article was excluded based on "year of publication". After reading the articles in full, only 13 were kept for analysis and data collection by the authors. This article selection process was illustrated in the following flowchart:

Figure 2: Flowchart of articles selected in the systematic literature review.



Source: The authors (2023).

After exclusions, a total of 13 articles were used as theoretical references. The analysis of these was organized in the table below:

Table 1: General aspects of the articles evaluated.

Reference	Article type	Results and conclusion
GUTTMAN-YASSKY, *et. al.* , 2021	Clinical trial.	In the 24th week of the study, both ritlecitinib and brepocitinib demonstrated an improvement in the sample collected for biopsy greater than 100% in the transcriptome lesional profile of the scalp towards a non-lesional profile . At week 12, improvements in scalp tissue were greater with brepocitinib than with ritlecitinib , however, at week 24, improvements were greater with ritlecitinib . For both ritlecitinib and brepocitinib , improvement in SALT scores was positively associated with the expression of TH1 markers and negatively associated with the expression of hair keratins. Larger, longer-term clinical trials are needed.
JABBARI, *et. al.* , 2018.	Clinical trial.	The use of tofacitinib was instituted in 12 patients with moderate to severe AA, of which 11 patients completed the full cycle of treatment with minimal adverse events. After limited response to the initial dose (5 mg twice daily), the dose was increased (10 mg twice daily) for subjects who

		did not respond. Eight of the 12 patients demonstrated 50% hair growth, while three patients demonstrated <50% growth, as measured by the SALT score. Only one patient did not show growth. Gene expression profiles and AASIS scores correlated with the observed clinical response, converging to a positive outcome for the use of JAK inhibitor medication in the treatment of AA. Further studies are encouraged.
KING, *et. al.* , 2021.	Clinical trial.	Treatment with brepocitinib and ritlecitinib for 24 weeks was effective in treating AA and generally well tolerated, as significant hair growth was observed. In patients whose baseline SALT score was 50%+. Additional clinical trials are needed to confirm these results.
KING, *et. al.* , 2021.	Clinical trial.	The effectiveness of using baricitinib in the treatment of AA at a dosage of 1mg once a day was significantly lower compared to the use of 2mg and 4mg a day. In the 36th week of treatment, the effectiveness of using dosages of 2mg (33.3%, p = .016) and 4mg (51.9% p = .001) in relation to placebo (3.6%) was significant. The results converge, therefore, to the efficacy and safety of the use of baricitinib in patients with a SALT score 50%+.
KING, *et. al.* , 2022.	Clinical trial.	A dose-related increase in the efficacy of treating AA patients with CTP-543 was observed at week 24 (9% placebo, 21% 4 mg twice daily, 47% 8 mg twice daily, and 58% 12 mg twice daily), with statistical significance versus placebo (P = 0.001) observed for the 8 mg twice daily and 12 mg twice daily groups, with differences compared to placebo observed as early as 12 weeks after the start of treatment . The safety results were consistent with the known safety profiles of JAK inhibitors.
KWON *et. al.* , 2023.	Clinical trial.	The efficacy of using oral baricitinib once a day, at a dose of 2-4mg in the treatment of adults with severe AA (SALT score 50%+) without spontaneous improvement was shown to be significantly effective in continuous treatment over 52 weeks, with progressive improvement. The improvement was greater in patients using the 4mg dose compared to the 2mg dose. Adverse effects were observed in approximately 58.5%-69.6% of patients using oral baricitinib 2-4mg, most of which were mild or moderate. The study confirms the great potential for using baricitinib in the treatment of AA.
LIU, *et. al.* , 2023.	Systematic review and meta-analysis.	Evidence suggests that the use of JAK inhibitors was successful in the treatment and hair growth of patients with AA compared to the placebo group. Oral use of JAK inhibitors. proved to be superior in relation to the topical use of medication from the same class. The reported adverse effects were similar between the drug treatment groups and the placebo group, but further studies are needed to confirm this result. The use of JAK inhibitors was not associated with more severe grades of AA. Data were extracted from randomized controlled trials.
MAO, *et. al.* , 2023.	Systematic review and meta-analysis.	The evidence converges towards a positive outcome of the use of JAK inhibitors in the treatment of AA, with a significant improvement in the SALT score. Furthermore, ruxolitinib was superior to tofacitinib in the treatment of AA. The reported adverse effects were classified by patients as “tolerable”. Additional quality studies are necessary to identify the best dose and drug for therapeutic optimization. Data were extracted from observational studies and randomized controlled trials.
SEDEH, *et. al* ., 2023.	Systematic review and meta-analysis.	The primary result of the systematic review included an improvement of 30%, 40%, 50%, 75% and 90% in the SALT score (*Severity of Alopecia Tool*) after JAK inhibitor treatment. The meta-analysis converged on a result of maximum efficacy in the oral use of 4 mg of baricitinib once a day, while the oral use of ruxolitinib required a dose of 12 mg twice a day for

		maximum efficacy in the treatment of alopecia areata (AA) with 50%+ scalp involvement. The response to treatment is directly related to the dose. More studies are needed to confirm these results.
TAYLOR, *et. al.,* 2023 .	Clinical trial.	The low-risk population (under 65 years of age without comorbidities) had a low incidence of adverse effects resulting from the use of JAK inhibitor medication (baricitinib). The dermatological indication for the use of the medication also favors a lower incidence of adverse effects in at-risk patients (patients aged 65+, cardiovascular atherosclerotic disease , diabetes mellitus, hypertension, smoking, HDL cholesterol < 40 mg/ dL , BMI > 30 kg /m2, reduced mobility or history of malignancy). Furthermore, risk factors, response to treatment and patient individualities must be considered when choosing treatment with baricitinib . Data were collected from long-term clinical trials and included patients with moderate to severe rheumatoid arthritis, moderate to severe atopic dermatitis and alopecia in severe areas.
WEI, *et. al.* , 2023.	Meta-analysis.	In terms of efficacy, the use of baricitinib , ruxolitinib , and oral tofacitinib significantly improved treatment response compared to placebo. Oral use of baricitinib significantly improved treatment response compared to topical use of the JAK inhibitor. In terms of safety, treatment with oral baricitinib and ruxolitinib significantly reduced the rates of adverse effects arising from the treatment compared to conventional treatment with corticosteroids . Additional studies are needed to identify the best therapeutic dose. Data were extracted from prospective and retrospective studies and randomized controlled trials.
WINNETTE, *et. al.* , 2022.	Clinical trial.	The evaluation of AASIS scores (*Alopecia Areata Symptom Impact Scale*) and SALT were similar in patients treated with ritlecitinib and brepocitinib , with significant improvement compared to the placebo group at week 24 of treatment.
YU, *et. al.* , 2021.	Systematic review. and meta-analysis.	Both oral tofacitinib and ruxolitinib are effective and well tolerated in the treatment of alopecia areata . Clinicians should be aware of the expected efficacy, adverse events, and high recurrence rate of AA when using oral JAK inhibitors. The analysis revealed that drug choice, average age, sex ratio, and proportion of alopecia areata subtype did not significantly affect treatment response. Patients treated for more than six months had a higher frequency of laboratory changes compared to those treated for shorter periods (24% versus 7%; P = 0.04). Recurrence of alopecia areata was observed three months after discontinuation of treatment in the majority of patients (74%).

Source: The authors (2023).

The variables observed in the studies were included in Table 2.

Table 2: Variables observed in the studies.

Reference	**Indicated drug**	**Efficiency**	**Adverse effects**
GUTTMAN-YASSKY, *et. al.* , 2021	Oral Ritlecitinib and Brepocitinib	Good.	Tolerable
JABBARI, *et. al.* , 2018	Oral tofacitinib	Good; Dose dependent.	Tolerable

KING, *et. al.* , 2021	Oral Ritlecitinib and Brepocitinib	Good.	Tolerable
KING, *et. al.* , 2021	Oral baricitinib	Good; Dose dependent.	Tolerable
KING, *et. al.* , 2022	oral CTP-543	Good; Dose dependent.	Tolerable
KWON *et. al.* , 2023	Oral baricitinib	Good; Progressive; Dose dependent.	Tolerable
LIU, *et. al.* , 2023	—*	Good; Oral use superior to topical use.	Tolerable
MAO, *et. al.* , 2023	Baricitinib and oral ruxolitinib	Good; Superior compared to other drugs; Dose- dependent.	Tolerable
SEDEH, *et. al* ., 2023	Baricitinib and oral ruxolitinib	Good; Superior compared to other drugs.	Tolerable
TAYLOR, *et. al., 2023*	Oral baricitinib	—*	Tolerable
WEI, *et. al.* , 2023	Baricitinib and oral ruxolitinib	Good; Superior compared to other drugs; Oral use superior to topical use.	Tolerable
WINNETTE, *et. al.* , 2022	Oral Ritlecitinib and Brepocitinib	Good.	—*
YU, *et. al.* , 2021	Tofacitinib and oral ruxolitinib	Good.	Tolerable

*The variables were not specifically mentioned in the studies.
Source: The authors (2023).

DISCUSSION

Alopecia Areata (AA) is a T cell-mediated autoimmune disease, which is manifested phenotypically by hair loss and, histologically, through T cell infiltration around hair follicles. Although steroid drug therapy has historically been the predominant treatment strategy, advances in the mechanistic understanding of possible T cell inflammatory pathways have caused a new target to emerge. In this sense, by discovering interferon-gamma (IFN-g) as a fundamental pathogenic cytokine, the JAK-STAT pathway emerged as a promising new therapeutic target, leading to the introduction of JAK inhibitors as a new alternative for the treatment of Alopecia Areata. (WEI, *et. al.* , 2023).

Several scientific studies have documented that the use of baricitinib and ruxolitinib , orally, resulted in a significant increase in favorable therapeutic responses, compared to the control group that received the placebo. It is worth mentioning that baricitinib is a dual JAK1/JAK2 inhibitor, due to its substantial binding interactions with both proteins. On the other hand, ruxolitinib is a JAK1/JAK2 inhibitor, capable of inhibiting both JAK1/JAK3 family cytokine signaling and interferon-gamma (IFN-gamma) (JAK1/JAK2) signaling (WEI, *et. al* . , 2023).

In addition to the drugs already mentioned, baricitinib and ruxolitinib , a variety of JAK inhibitors are being tested in clinical trials for the treatment of AA. The study conducted by King, et. al, for example, consisted of a randomized, placebo-controlled clinical trial, aimed at evaluating the efficacy and safety of ritlecitinib and brepocitinib (KING, et. al., 2023). In this clinical trial, substantial improvements were recorded in both the favorable response rate and the complete response rate in patients undergoing treatment. Another study was carried out by Guttman-Yassky *et. al,* which conducted an investigation of biomarkers associated with scalp Alopecia Areata in patients who participated in the clinical trial (GUTTMAN-YASSKY, *et. al., 2021*). This research revealed that, although brepocitinib can exert a direct inhibition on interferon-gamma (IFN-gamma) signaling through the activation of JAK1/2, ritlecitinib can indirectly influence the production of IFN-gamma, through inhibition of kinases belonging to the TEC family (WEI, *et. al.* , 2023).

Regarding therapeutic dosage, a trend of increasing results was observed with the duration of treatment in the included studies. However, it is crucial to highlight that increasing the dose of JAK inhibitors can lead to an increase in adverse events (WEI, *et. al.* , 2023).

The adverse events reported were, to a large extent, mild and relatively manageable. The most common unwanted effects included upper respiratory tract infections, headache, acneiform rashes and biochemical changes. Among these, infections of a mild nature had the highest prevalence. It is notable that, despite the inherent selectivity of the routes of action of different JAK inhibitors, there is an overlap in their safety profiles. Therefore, although the frequency of serious adverse events related to JAK inhibitors has been shown to be low in previous studies, it is recommended that patients with Alopecia Areata who undergo this treatment undergo regular monitoring of liver function, complete hematological analyzes and other laboratory markers throughout the therapeutic process." Finally, it is important to highlight that the findings regarding therapeutic safety revealed that the incidence of side effects was reduced in patients who received oral JAK inhibitors, compared to those undergoing conventional therapy based on corticosteroids (WEI, *et. al.* , 2023).

Given this context, the articles raise the possibility that orally administered JAK inhibitors could be among the most effective therapies currently available for the treatment of Alopecia Areata (AA). This highlight becomes particularly relevant when considering those patients in whom conventional therapeutic approaches, such as corticosteroids , have proven ineffective (WEI, *et. al.* , 2023).

CONCLUSION

Through this literature review, it was possible to make a comparison between the articles and analyze the main medications that are being used and tested in the treatment of alopecia areata . Regarding therapeutic efficacy, it was observed that the oral administration of baricitinib , ruxolitinib , tofacitinib , ritlecitinib and brepocitinib showed a notable improvement in the response to treatment, when compared to the use of a placebo (GUTTMAN-YASSKY, *et. al., 2021*). It is also important to highlight that the evaluation of the results was carried out mainly through the AASIS scores (Alopecia Areata Symptom Impact Scale) and SALT (Severity of Alopecia Tool).

Furthermore, it is essential to emphasize that the dose and duration of treatment are important factors in deciding on the best medication. It was demonstrated that the oral use of baricitinib had better treatment efficacy when compared to its topical application (WEI, *et. al.* , 2023). And the improvement was significantly greater in patients using the 4mg dose compared to the 2mg dose (KING, *et. al.* , 2021). In terms of safety, the reduction in the incidence of adverse effects associated with the oral administration of baricitinib and ruxolitinib is notable , when contrasted with the conventional approach that employs the use of corticosteroids (WEI, *et. al.* , 2023).

Finally, more prospective and comparative studies are needed to confirm the results on the treatment of alopecia areata .

REFERENCES

GUTTMAN-YASSKY E, et. al. Ritlecitinib and brepocitinib demonstrate significant improvement in scalp alopecia areata biomarkers. J Allergy Clin Immunol. 2022 Apr;149(4):1318-1328.

JABBARI A, et. al. An Open-Label Pilot Study to Evaluate the Efficacy of Tofacitinib in Moderate to Severe Patch-Type Alopecia Areata, Totalis, and Universalis. J Invest Dermatol. 2018 Jul;138(7):1539-1545.

KING B, et. al. A phase 2a randomized, placebo-controlled study to evaluate the efficacy and safety of the oral Janus kinase inhibitors ritlecitinib and brepocitinib in alopecia areata: 24-week results. J Am Acad Dermatol. 2021 Aug;85(2):379-387.

KING B, et. al. Efficacy and safety of the oral Janus kinase inhibitor baricitinib in the treatment of adults with alopecia areata: Phase 2 results from a randomized controlled study. J Am Acad Dermatol. 2021 Oct;85(4):847-853.

KING B, et. al. Phase 2 randomized, dose-ranging trial of CTP-543, a selective Janus Kinase inhibitor, in moderate-to-severe alopecia areata. J Am Acad Dermatol. 2022 Aug;87(2):306-313.

KWON O, et. al. Efficacy and Safety of Baricitinib in Patients with Severe Alopecia Areata over 52 Weeks of Continuous Therapy in Two Phase III Trials (BRAVE-AA1 and BRAVE-AA2). Am J Clin Dermatol. 2023 May;24(3):443-451.

LIU M, et. al. Janus Kinase Inhibitors for Alopecia Areata: A Systematic Review and Meta-Analysis. JAMA Netw Open. 2023 Jun 1;6(6):e2320351.

MAO MQ, et. al. The evaluation of JAK inhibitors on effect and safety in alopecia areata: a systematic review and meta-analysis of 2018 patients. Front Immunol. 2023 Jun 2;14:1195858.

OLSEN EA, et. al. Alopecia areata investigational assessment guidelines - Part II. National Alopecia Areata Foundation. J Am Acad Dermatol. 2004 Sep;51(3):440-7. doi: 10.1016/j.jaad.2003.09.032.

SEDEH F, et. al. Comparative Efficacy and Safety of Janus Kinase Inhibitors Used in Alopecia Areata: A Systematic Review and Meta-analysis. Acta Derm Venereol. 2023 Jan 25;103:adv00855.

TAYLOR PC, et. al. Baricitinib Safety for Events of Special Interest in Populations at Risk: Analysis from Randomised Trial Data Across Rheumatologic and Dermatologic Indications. Adv Ther. 2023 Apr;40(4):1867-1883.

WEI D, et. al. Efficacy and safety of different JAK inhibitors in the treatment of alopecia areata: a network meta-analysis. Front Immunol. 2023 Apr 17;14:1152513. doi: 10.3389/fimmu.2023.1152513.

WINNETTE R, et. al. Characterizing the relationships between patient-reported outcomes and clinician assessments of alopecia areata in a phase 2a randomized trial of ritlecitinib and brepocitinib. J Eur Acad Dermatol Venereol. 2022 Apr;36(4):602-609.

YU DA, et. al. Treatment outcome of oral tofacitinib and ruxolitinib in patients with alopecia areata: A systematic review and meta-analysis. Indian J Dermatol Venereol Leprol. 2021 Sep-Oct;87(5):621-627.