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Review Article

Efficacy of Janus kinase inhibitors in adult patients with alopecia areata

Andrea Sierra Franco[1]*, Paulina García De León Flores[2], Paola Scarlett Díaz De Alba[3], María Jimena Talamante Madrid[4], Cassandra Espinosa Rodríguez[4], Renata Monserrat Espejo Nuño[2]

[1]Hospital General Regional #45 IMSS, Guadalajara, Jalisco, México
[2]Universidad Autonoma de Guadalajara, Guadalajara, Jalisco, México
[3]Hospital General Regional #46 IMSS, Guadalajara, Jalisco, México
[4]Hospital General de Zona #2 IMSS, Hermosillo, Sonora, México

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***Correspondence:**
Dr. Andrea Sierra Franco,
E-mail: felixosuna10@hotmail.com

ABSTRACT

Alopecia areata (AA) is a chronic, immune-mediated disorder resulting in localized hair loss due to targeting hair follicle epithelium. The authors aimed to summarize the existing literature on patients with AA who underwent treatment with Janus kinase inhibitors (JAKis) and discuss the current evidence regarding their efficacy and safety. An extensive scientific literature search was conducted between January 1, 2017, and April 16, 2023, using a recognized medical and scientific database. The extracted data were synthesized and analyzed, focusing on the effect of JAKis in reducing hair loss in adult patients with AA. The evidence suggests that oral JAKis such as tofacitinib, ruxolitinib, and Baricitinib show promise in treating AA regarding both efficacy and safety. The group of drugs JAKis are a good treatment option even in severe clinical conditions of AA, further investigation should be taken to consideration including dosage and treatment duration

Keywords: AA, Hair loss, JAKis

INTRODUCTION

Alopecia areata (AA) is a prevalent autoimmune condition characterized by hair loss. It ranks as the third most common dermatologic presentation in children, with a lifetime risk of 1-2%. The global population is affected by AA at a rate of 2.11%, with a lower prevalence in adults (1.47% [1.18-1.80]) compared to children (1.92% [1.31-2.65]). The prevalence of this condition increases over time and varies by geographical region (Lee et al). In the UK, the prevalence of AA among adults was recorded as 0.58% in 2018, while in the US, the age-and-sex standardized prevalence among adults was observed to be 0.18%. AA can manifest as patchy, non-scarring hair loss on the scalp, affecting any hair-bearing area of the body. Microscopic examination typically reveals characteristic features such as "exclamation point hairs," "yellow dots," and nonspecific nail changes. The association between AA and hair color is influenced by natural hair color, with a preference for targeting darker hair. This phenomenon can be explained by an immune response directed against melanogenesis-associated proteins during the anagen phase of hair follicles.[1-4]

The use of JAKis has demonstrated promising results in the treatment of AA. These targeted therapies utilize small molecules to block the inflammatory pathway believed to contribute to the pathogenesis of the condition. Studies have reported high response rates and significant hair regrowth with the use of JAKis. Despite

the development and testing of several therapies, no specific treatment has been approved for AA, leading to the utilization of off-label treatment options with limited efficacy.[6] JAKis offer a potential solution and may serve as a more effective treatment option for patients with AA, addressing the unmet needs of this patient population. However, further research, including large-scale randomized studies, is necessary to validate these findings and determine the long-term safety and efficacy of JAK inhibitors for the treatment of AA.[5-8]

LITERATURE REVIEW

A review was conducted using the PICO format (P: Patient or problem, I: Intervention, C: Control, O: Outcome) for the research question, "Are JAKis more effective than standard treatments or placebo in improving follicular repopulation and reducing hair loss in adult patients with AA?".

PICO question: P: Adult patients with alopecia Areata, I: JAKis, C: Placebo or standard treatment and O: Follicular repopulation, reduction of hair loss.

An extensive scientific literature search was conducted between January 1, 2017, and April 16, 2023, using a recognized medical and scientific database. These databases included PubMed. Search strategy: The search strategy consisted of controlled MeSH vocabulary and accessible language using the following keywords. Syntax was complemented using Boolean and proximity operators. This strategy was adapted to all databases. Language filters (English and Spanish), clinical trials, meta-analyses, and reviews were used whenever possible in the databases.

Search protocol

Identification of keywords were a. Alopecia areata, hair loss, b. Janus kinase inhibitors, JAK inhibitors, c. Placebo, standard therapy, d. Follicular repopulation, hair regrowth, e. Reduction of hair loss, f. Randomized controlled trials, controlled clinical trials, clinical trials, clinical study.

Combination of keywords

They were-a. Alopecia areata and Janus kinase inhibitors, b. Alopecia areata and placebo or standard therapy, c. Janus kinase inhibitors and placebo or standard therapy, d. Alopecia areata and Janus kinase inhibitors and placebo or standard therapy, e. Alopecia areata and Janus kinase inhibitors and placebo or standard therapy and follicular repopulation, f. Alopecia areata and Janus kinase inhibitors and placebo or standard therapy and reduction of hair loss, g. Alopecia areata and Janus kinase inhibitors and placebo or standard therapy and follicular repopulation and reduction of hair loss and h. Randomized controlled trials and alopecia areata and Janus kinase inhibitors and placebo or standard therapy and follicular repopulation and reduction of hair loss,

PubMed search

(\"Janus kinase inhibitors\" AND \"Alopecia Areata\" AND \"hair loss\") OR (\"Tofacitinib\" AND \"Alopecia Areata\" AND \"follicular repopulation\") OR (\"Baricitinib\" AND \"Alopecia Areata\" AND \"efficacy\") OR (\"Janus kinase inhibitors\" AND \"Alopecia Areata\" AND \"clinical trial\") OR (\"Ruxolitinib\" AND \"Alopecia Areata\" AND \"hair regrowth\")

After the search protocol was established, an initial screening of the identified articles was performed by two independent reviewers, who assessed the titles and abstracts for relevance to the research question. Any reviewer disagreements were resolved by consensus or involving a third reviewer if necessary. The full text of potentially relevant articles was then obtained and assessed for eligibility based on predefined inclusion and exclusion criteria.

Inclusion criteria

Studies involving patients with a diagnosis of AA, studies comparing the use of JAKis with placebo or standard treatment, studies report outcomes related to follicular repopulation and reduction of hair loss, randomized controlled trials, controlled clinical trials, and clinical studies and articles published in English or Spanish between January 1, 2014, and April 16, 2023 were included in study.

Exclusion criteria

Studies focusing on other types of alopecia or hair loss disorders, studies that did not compare the use of JAKis with placebo or standard treatment, case reports, case series, editorials, letters to the editor, and narrative reviews and articles published in languages other than English or Spanish were excluded.

Data extraction and synthesis

Data extraction was performed using a standardized data collection form, which included information on study design, population characteristics, interventions, comparators, and outcomes. The extracted data were then synthesized and analyzed, focusing on the effect of JAKis on follicular repopulation and hair loss reduction in adult patients with Alopecia Areata. The results were presented as a narrative synthesis.

MECHANISM OF ACTION OF JAK INHIBITORS IN AA

AA a condition characterized by unpredictable hair loss, has attracted the attention of the medical community to a

new type of drugs called JAK inhibitors. Tofacitinib, ruxolitinib, and baricitinib are notable members of this drug class due to their potential effectiveness in treating this disease.[9-13]

The underlying basis for their potential lies in the JAK-STAT pathway, a biochemical process involved in various autoimmune diseases that affect hair growth. AA specifically relies on a critical disruption of this pathway. The interferon-γ/interleukin-15 feedback loop, which signals through the JAK-STAT pathway, is implicated in breaching the protective mechanism of the hair follicle called the follicular immune privilege, ultimately resulting in hair loss.[14]

The objective of JAKis is to halt this destructive process. By inhibiting the JAK-STAT signaling pathway, these medications are believed to impede the T-cell mediated inflammatory response, which is a key driver behind the development of AA. This could potentially lead to the reversal of hair loss in affected individuals.[15]

Further emphasizing the importance of this pathway, the pathogenesis of the disease involves a complex interplay of genetic, environmental, and immune factors regulated by specific cytokines, namely interferon-γ and interleukin (IL)-15, as mentioned earlier. The observation of hair regrowth following JAKis further underscores the critical role of the JAK-STAT signaling pathway in this context.[16,17]

While these findings shed significant light on the disease's molecular underpinnings, the complete picture of how JAKis exert their action in AA remains unclear. This knowledge gap underscores the need for further research, paving the way for optimized treatment strategies and bringing hope to those dealing with AA.[16]

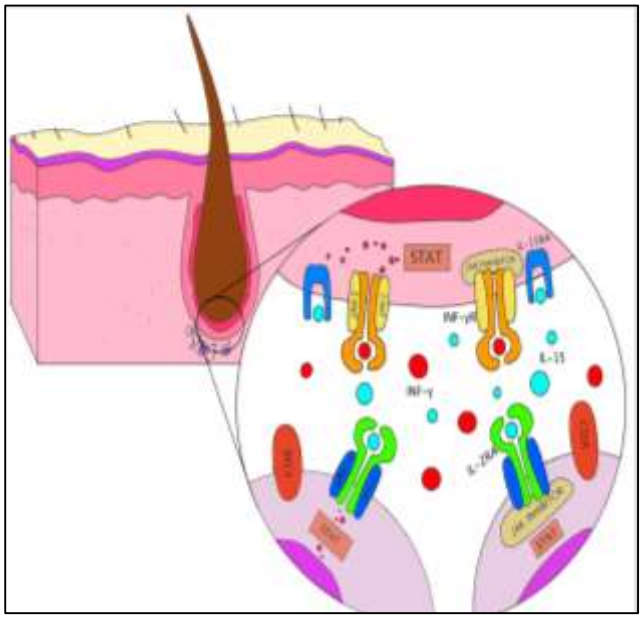

Figure 1: JAK-STAT kinase pathway.

On the left side of the zoomed image the cytoplasmic JAK kinase activates the signaling pathway on both the CD8+T cell and the air follicle epithelium induced by INF-Y and IL 15 leading to hair loss. On the right side the JAK inhibitor blocks the STAT binding therefore the catatonic process of the hair follicle.

EFFICACY OF JAK INHIBITORS IN TREATING AA

The effectiveness of JAKis in the treatment of AA has been supported by multiple reviews, meta-analyses, and comparative studies. These investigations have demonstrated promising response rates among AA patients who received JAKis therapy.[16]

A comprehensive meta-analysis, encompassing 30 studies and 289 cases, revealed that 72.4% of patients responded positively to JAKis treatment. Among these responders, 45.7% were classified as good responders, while 21.4% exhibited partial responses. Another analysis specifically focusing on pediatric patients reported an even higher response rate of 81.9%, with the majority of patients being good responders (68.5%) and a smaller portion demonstrating partial responses (7.7%).[17]

Furthermore, an open-label comparative study that evaluated two notable JAKis, ruxolitinib and tofacitinib, in severe AA patients demonstrated significant hair regrowth with both medications. The efficacy of treatment was assessed using the severity of alopecia tool (SALT) score, which indicated a remarkable mean change in both the ruxolitinib group (93.8±3.25) and the tofacitinib group (95.2±2.69).[18]

Likewise, a network meta-analysis involving randomized controlled trials and cohort studies found that oral baricitinib and ruxolitinib showed significant superiority over the placebo in improving response rates among AA patients. In particular, oral baricitinib exhibited higher response rates compared to non-oral JAKis.[19]

Despite the promising results, it is crucial to remember that there is variability in efficacy and safety among different JAKis. An integrated safety analysis of baricitinib in patients with severe AA showcased an overall favorable safety profile with ruxolitinib; they have demonstrated consistent positive results.[18] Further studies are needed to determine optimal dosing for AA therapy, standardize the use of these drugs in dermatology, and gather conclusive data on long-term safety and efficacy, which is currently lacking due to limited randomized clinical trials.[20]

Lastly, it is worth noting that the efficacy of all approved JAK inhibitors in treating AA is typically observed rapidly and reaches its maximum effect by 12-14 weeks, with continued improvement thereafter. As for safety, the most frequently reported adverse events associated with JAK inhibitors for AA are infections and laboratory

abnormalities, particularly in patients receiving treatment for more than six months. However, the risk of major adverse cardiovascular events (MACE) and venous thromboembolism (VTE) linked to JAKis is dependent on the duration of exposure.[21]

Tofacitinib in treating AA

Tofacitinib, a JAKis has shown varying response rates in the treatment of AA, which can be influenced by study design and patient populations.[22]

In a prospective, open-label, observational, single-center cohort study involving 47 Arab-Asian patients with refractory AA, approximately 42% of the participants experienced complete regrowth of hair, while 25.58% achieved partial regrowth. On the other hand, 27.9% did not respond to the treatment. The study recommended a minimum treatment duration of 12 months before considering discontinuation or modification of treatment to avoid incomplete regrowth or treatment failure. Additionally, maintenance therapy after complete regrowth proved to be effective and safe in preventing hair loss recurrence. [22]

In a retrospective pilot study that examined 13 patients with severe AA, all three patients with AA responded well to treatment, while 50% of patients with alopecia universalis did not achieve successful treatment outcomes. [23]

Furthermore, a large retrospective study involving 90 AA patients found that among 65 potential responders (patients with alopecia totalis or alopecia universalis experiencing the current episode of the disease for ten years or less), approximately 77% achieved a clinical response. Nearly 58% of these patients demonstrated more than a 50% change in the SALT score over a treatment duration ranging from 4 to 18 months. [24]

In safety, a review and meta-analysis indicated that infections and laboratory abnormalities were the primary adverse events linked to tofacitinib in AA treatment. However, these side effects were generally mild and rare, with patients on treatment for over six months exhibiting a higher frequency than those on shorter treatment durations. Notably, recurrence of AA was observed in most patients within three months post-treatment discontinuation. [25]

A review and meta-analysis that included 14 studies (six clinical trials and eight observational studies) involving a total of 275 patients indicated that tofacitinib has a moderate level of effectiveness in treating AA (AA). The analysis revealed a pooled reasonable/complete hair regrowth rate of 54.0% and a partial response rate of 26.1%. The reported adverse effects were generally mild, with the most common events being upper respiratory infection, headache, and acne. [26]

Furthermore, an open-label comparative study comparing tofacitinib and ruxolitinib for severe AA suggested that both drugs can be considered appropriate treatments, with no significant difference observed in terms of hair regrowth and relapse rates Therefore, while tofacitinib has shown promising results in the treatment of AA, further studies are needed to determine the optimal dosages and confirm its efficacy and safety, particularly in pediatric patients. [27]

Ruxolitinib in treating AA

Ruxolitinib, a JAKis is used in the treatment of severe AA. As mentioned earlier, both ruxolitinib and tofacitinib have demonstrated effectiveness in treating AA, with no significant difference observed in terms of hair regrowth and relapse rates. Interestingly, ruxolitinib has shown a shorter duration for initial hair regrowth compared to tofacitinib. [28]

Similar to tofacitinib, the most commonly reported adverse events associated with ruxolitinib usage in AA patients are infections and laboratory abnormalities, with a higher frequency of adverse events observed with long-term treatment. However, ruxolitinib has shown potential efficacy in treating various autoimmune disorders and has maintained an acceptable safety profile. It is important for clinicians to be aware of the expected efficacy and potential adverse events when considering ruxolitinib for AA treatment. [29]

Furthermore, a study comparing the efficacy and safety of different JAKis, including ruxolitinib, tofacitinib, and baricitinib, in the treatment of AA revealed that ruxolitinib resulted in a faster onset of initial hair regrowth compared to the other two drugs. However, there were no significant differences observed between these groups in terms of hair regrowth at the end of the 6-month treatment period and relapse rate at the end of the 3-month follow-up. Therefore, it remains uncertain whether the duration of response to ruxolitinib significantly differs from other JAKis in the treatment of AA.

In summary, while ruxolitinib shows promising effectiveness in treating AA, further research is needed to explore optimal dosing, as well as confirm its long-term safety and efficacy. [30]

Baricitinib in treating AA

Baricitinib, another JAKis, has shown significant promise in the treatment of AA. According to a network meta-analysis, oral baricitinib has demonstrated a notable improvement in patient response rates compared to a placebo, surpassing non-oral JAK inhibitor treatments as well. Furthermore, oral baricitinib has proven to be more effective in achieving complete response rates compared to a placebo and has shown greater safety compared to conventional steroid treatments. [30]

The efficacy and safety of baricitinib in treating AA are well-supported by various studies. For instance, a review and meta-analysis concluded that baricitinib is an effective and well-tolerated medication for AA, exhibiting improvement in SALT scores compared to a placebo. A phase 2 study demonstrated the safety and efficacy of baricitinib in patients with 50% or more scalp hair loss. Additionally, a phase III study revealed continuous improvement in hair regrowth over 52 weeks of baricitinib treatment in adults with severe AA, with no new safety concerns emerging. Two phase 3 trials involving patients with severe AA found oral baricitinib to be superior to a placebo in terms of hair regrowth at 36 weeks. [31]

The most frequent adverse events reported in adults receiving continuous therapy for 52 weeks include upper respiratory tract infection, headache, nasopharyngitis, acne, urinary tract infection, creatine phosphokinase elevation, and COVID-19 infection. However, an integrated safety analysis from two randomized clinical trials involving adults with severe AA reported no new safety concerns with baricitinib over a median exposure of 532 days with 1868 patients. The incidence rate of serious infections, malignancies, and major adverse cardiovascular events was low. Nevertheless, further studies with larger sample sizes are necessary to thoroughly evaluate the long-term safety of the baricitinib. [32]

TREATING MORE SEVERE FORMS: ALOPECIA TOTALIS AND ALOPECIA UNIVERSALIS

The treatment of severe forms of AA, specifically alopecia totalis and alopecia universalis, can be challenging due to the significant hair loss associated with these conditions. JAKis, such as tofacitinib, ruxolitinib, and baricitinib, have shown promise in addressing these difficult-to-treat variants. Several studies have demonstrated their efficacy in adults and children with severe forms of the condition.[33]

In one study, the application of a 2% tofacitinib ointment twice daily resulted in partial hair regrowth in six patients with alopecia universalis. Similarly, a 1% ruxolitinib ointment led to partial hair regrowth in five patients.[31] These findings provide preliminary evidence of the potential of topical JAK inhibitors in the treatment of severe forms of AA.[34]

For oral JAKis, a review and meta-analysis of 30 studies involving 289 cases found that approximately 72.4% of patients responded to the treatment, with approximately 45.7% experiencing good responses and 21.4% experiencing partial responses. It was also observed that all 37 cases of relapse occurred when treatment was discontinued after an average of 2.7 months.[35]

A comparative study revealed that oral tofacitinib was more effective than diphenylcyclopropenone immunotherapy and better tolerated than conventional oral treatment for refractory cases of alopecia totalis and universalis.[32] Another open-label study demonstrated significant hair regrowth in all six patients with alopecia universalis who received tofacitinib.[36]

Furthermore, a retrospective study comparing ruxolitinib and tofacitinib found that both drugs led to remarkable hair regrowth in patients with AA, with no statistically significant difference in terms of hair regrowth and relapse rate. [37]

These promising results highlight the importance of continuous treatment to maintain the achieved gains, as there is a risk of relapse after treatment discontinuation. However, extensive randomized studies are needed to confirm these findings and establish the optimal dosage and duration of treatment for each patient.[35]

DISCUSSION

AA, an autoimmune condition causing hair loss, is part of its pathophysiology in the JAK-STAT pathway, a biochemical cascade, specifically on the disruption of this pathway. The interferon-γ and interleukin-15 are implicated in breaching the follicular immune privilege, a protective mechanism of the hair follicle, thus leading to hair loss. JAKis, such as tofacitinib, ruxolitinib, and Baricitinib, have the potential for this inflammatory cascade, thus reversing hair loss in affected individuals. The complete picture of how JAKis exert their action in AA remains uncertain. [36]

In our review, one meta-analysis showed that 72.4% of patients responded favorably to JAK inhibitor therapy, with 45.7% classified as good responders and 21.4% as partial responders.[9] Another clinical trial focusing on pediatric patients reported an even higher response rate of 81.9%, with 68.5% being good responders and 7.7% as partial responders.[14]

For severe cases of AA, our investigation found that both ruxolitinib and tofacitinib induced significant hair regrowth, with no statistically significant difference between them. Ruxolitinib demonstrated a shorter duration for initial hair regrowth compared to tofacitinib and baricitinib.[15,16] A comparison study indicated that oral tofacitinib was more effective than diphenylcyclopropenone immunotherapy and conventional oral treatment for refractory cases of alopecia totalis and universalis. Another study showed a dramatic response to tofacitinib in six patients with alopecia universalis. Baricitinib was also found to be a safe and effective medication for treating AA, even in severe cases.[25-28]

The improvements with all JAKis typically occur within 12-14 weeks of continuous treatment. It is recommended to continue treatment for a minimum duration of 12 months, and maintenance therapy after complete

regrowth has proven effective in preventing hair loss recurrence. However, in a large retrospective study involving patients with alopecia totalis or universalis, approximately 77% achieved a clinical response over a treatment period of 4 to 18 months. In another clinical trial, there were no significant differences between the three drugs regarding hair regrowth during the 6-month treatment period and relapse rate at the end of the 3-month follow-up. Recurrence of AA was observed within three months after treatment discontinuation in two clinical trials.[29]

In terms of safety, the most common adverse events associated with all JAKis were generally mild and rare, including infections and laboratory abnormalities. Patients on treatment for more than six months had a higher frequency of adverse events compared to those on shorter treatment durations. The risk of major adverse cardiovascular events (MACE) and venous thromboembolism (VTE) associated with JAKis depends on the duration of exposure.[31,32]

For baricitinib, the most frequent adverse events observed in adults receiving continuous therapy for over 52 weeks included upper respiratory tract infection, headache, nasopharyngitis, acne, urinary tract infection, creatine phosphokinase elevation, and COVID-19 infection.[29] However, two randomized clinical trials involving adults reported no new safety concerns over a median of 532 days of exposure with 1868 patients, with a low incidence rate of serious infections, malignancies, and major adverse cardiovascular events.[18]

Concerning the route of administration, a 2% tofacitinib ointment and 1% ruxolitinib ointment led to partial hair regrowth in eleven patients. However, the best responses were with oral JAKis; several studies found that oral treatment outperformed the placebo and proved more effective in achieving complete response rates than placebo as well as safer than conventional steroid treatment. [29]

None of the clinical trials reviewed investigated combination treatment; all the evidence on JAKis is that while being monotherapy, combining these drugs with other treatments for AA has not been rigorously investigated, and further studies are needed. More randomized trials with identical inclusion criteria, dose, and duration of treatment are required to confirm all these findings.[38]

The limitations of this review should be considered. None of the included clinical trials investigated the combination of JAK inhibitors with other treatments, which could potentially enhance efficacy. Some trials had small sample sizes, limiting the generalizability of the findings. There is a need for further research to confirm the results of this investigation through larger randomized trials with standardized inclusion criteria, dosages, and treatment durations to provide more robust evidence.

CONCLUSION

The authors conclude that JAK inhibitors such as tofacitinib, ruxolitinib, and baricitinib are safe and effective treatments for AA, even in pediatric patients. Meta-analyses and clinical trials have demonstrated favorable responses to these drugs, with a significant percentage of patients regaining hair. All drugs have induced substantial hair regrowth with comparable efficacy, even in severe cases.

Oral treatment has proven to be better than topical treatment, with mild and rare adverse events, the most frequent being infections and laboratory abnormalities. However, cardiovascular events risk needs to be monitored when using these medications, keeping in mind that the risk depends on the duration of exposure.

In our review, there were variations in recommended treatment duration for JAKis among different clinical trials. Some trials suggested a minimum treatment duration of three months, while others recommended at least 12 months, especially for severe cases of AA. It was found that maintenance therapy after achieving complete regrowth was necessary to prevent recurrence, and discontinuing treatment could lead to recurrence within 3 months.

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