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WHITE PAPER

Alopecia Areata

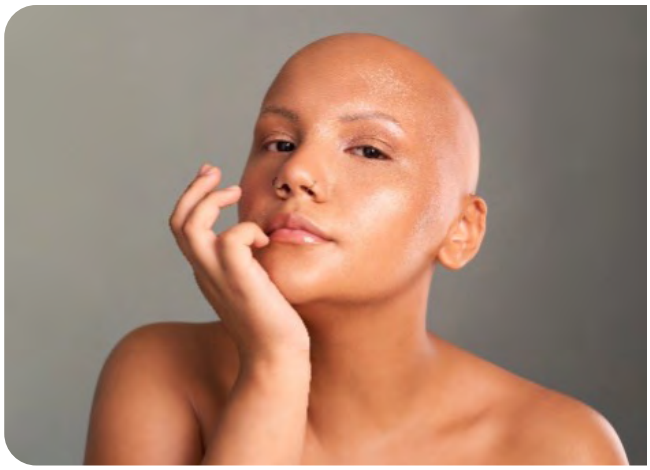
How Clinical Research is Growing Hope

Introduction:

Scientific advances have rapidly transformed both the clinical research landscape and the treatment of Alopecia Areata (AA), an autoimmune disease that causes hair loss. Despite newly approved treatments, there is still significant unmet need in AA, reflected by the growing number of clinical trials, patient registries, and biobanks. The incorporation of genetic studies, biomarkers, and new research methods and technologies have resulted in rapid expansion of knowledge and potential therapies. Developments in AA research are representative of larger trends in dermatologic clinical research, which has become increasingly complex. AA is an interesting case study in how several developing research concepts and technologies are shaping innovation in medical science, and giving patients new opportunities for hope.

Growing Understanding: What is Alopecia Areata?

Alopecia areata (AA) is an autoimmune form of hair loss with a global incidence of approximately 2%.[1] AA commonly presents as one or more round patches of hair loss on the scalp, but AA can cause extensive hair loss that may affect any hair-bearing area, including eyebrows, eyelashes, beard, and body hair.



Alopecia Totalis (AT) is the loss of all the hair on the scalp, and Alopecia Universalis (AU) refers to the loss of all hair on the body. Ophiasis is an AA subtype that causes hair loss in a band along the lower portion of the scalp and sparing the top of the head.

AA can develop at any time, but younger people are more likely to be affected; the majority of patients develop AA before age 40.[1]

Unlike most other inflammatory skin conditions, AA does not generally cause symptoms like pain, itch, or redness. Despite this, **many patients with AA experience profound disruption of their quality of life** because of the emotional and social effects of hair loss,[2] including increased rates of depression and anxiety compared with the general population.[3,4] Often patients report experiencing stigma and bullying.[2] Patients with severe AA can also experience physical side effects from widespread hair loss like cold sensitivity and increased risk of sunburn. Eyebrow and eyelash loss can result in more trouble with seasonal allergens, foreign bodies, and sweat in the eyes.

Common Comorbidities in Alopecia Areata

Immune Disorders: Vitiligo • Atopic Dermatitis • Psoriasis
Systemic Lupus Erythematosus • Autoimmune Thyrold Disease

Psychiatric Disorders: Anxiety • Depression • Panic Disorder • Sleep Disorder

Several medical conditions are more common among people with AA than the general population, including atopic dermatitis, autoimmune thyroid disease, Vitamin D deficiency, and other allergic and autoimmune diseases.[1]

Growing Possibilities: New Treatments in Alopecia Areata

The treatments options available to patients with AA have expanded significantly. Until recently, there were no approved systemic therapies for alopecia areata. The choice of treatments was limited to topical and injected steroids, immunotherapy applied to the scalp, and off-label systemic immunosuppressive medications. Available therapies had limited efficacy for people with extensive hair loss and significant side effects, including pain from dozens of injections into the scalp, skin irritation, broad immunosuppression, and risk of organ damage. A serendipitous finding of hair regrowth in a patient with AA from Janus kinase inhibitor (JAK) treatment for another condition[5], ultimately led to several clinical trial programs. In 2022, JAK inhibitor Baricitinib (Eli Lilly & Co.) was the first approved systemic treatment for AA, followed by Ritlecitinib (Pfizer Inc.) in 2023, and Deuruxolitinib (Sun Pharmaceuticals) in 2024. Primary endpoints were assessed at different times, so the results cannot be compared, but between one-fifth and one-third of patients treated with these drugs will have significant regrowth of hair, defined as at least 80% scalp coverage.[6-8]

Approvals

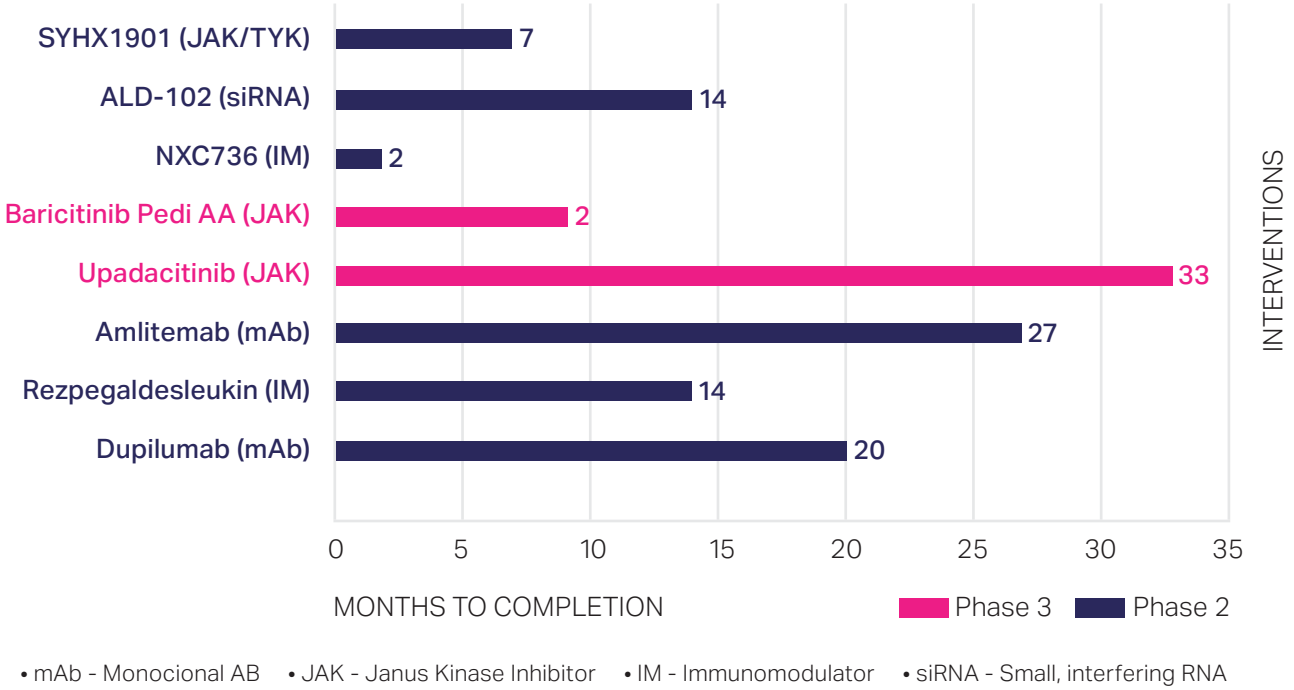
- Bariticinib 2022
- Ritlecitinib 2023
- Deuruxolitinib 2024

Recent Studies

- Bempikibart ph2
- Ivarmacitinib ph3
- IMG-007 ph 2a
- EQ-101 ph2
- Etrasimod ph2
- STS-01 ph2

In addition to the three approved JAK inhibitors, JAK inhibitors for other indications are sometimes used off-label in AA. Off-label oral minoxidil treatment for hair loss has also become mainstream, although it is generally used as an adjuvant rather than monotherapy when treating AA. Since the approval of Baricitinib, the number of clinical trial programs for both new molecules and label expansions has also increased.
New molecules being tested include additional JAK inhibitors, oral and topical, as well as monoclonal antibodies and small molecules, many with novel mechanisms of action (MOA).

Current Ph2/Ph3 Trials in Alopecia Areata - April 2025



• mAb - Monocional AB • JAK - Janus Kinase Inhibitor • IM - Immunomodulator • siRNA - Small, interfering RNA

Room for Growth: Unmet Need In AA

Despite the treatment advances in AA, there is still significant unmet need in this indication.

Children and adolescents comprise a large portion of the AA patient population, and of the three JAK inhibitors, only Ritlecitinib is currently approved for patients as young as 12. Ritlecitinib and Baricitinib are currently being evaluated in children as young as 6 with results from both trials expected by the end of 2025, possibly followed by label expansions. Safety concerns about JAK inhibitors may take on additional significance when treating children and adolescents, since both early age of initiation and potentially life-long treatment could confer additional risk of side effects.

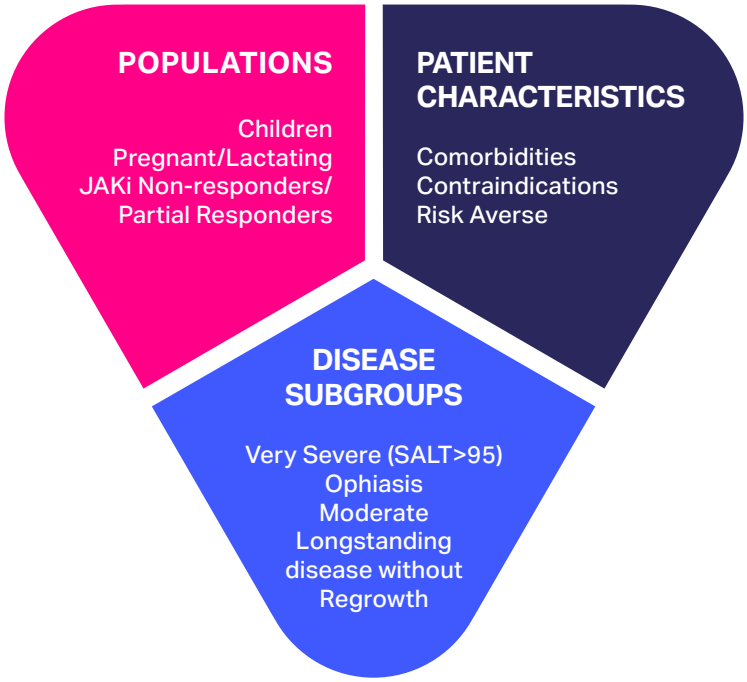
AA is slightly more common in women and because it generally affects younger patients,[1] **there will be many women of childbearing potential who will be faced with managing treatment during conception and pregnancy.**

JAK inhibitors are contraindicated during pregnancy, and one would anticipate that patients desiring pregnancy would welcome a treatment option that would not require discontinuing therapy and risking disease flare with resulting hair loss. **Effective treatments with fewer safety concerns would likely be attractive to these patient populations and the physicians who treat them.**

Many patients are either partial responders or do not respond to available treatments, and additional therapeutic options are still needed. In all of the phase 3 JAK inhibitor trials, many more patients in the treatment cohort achieved meaningful regrowth compared to placebo, but the majority of treated patients did not achieve the endpoint of SALT20 (≤20% hair loss).[6-8] **Patients with the most severe disease (approximately SALT 95-100) are less likely to respond to JAK inhibitors, as are those patients with longer disease duration (more than 3-4 years).**[10]

Ophiasis is also more treatment resistant than patchy AA. These patient populations will potentially benefit from additional therapies, including therapies with different mechanisms of action.

Unmet Needs in Alopecia Areata



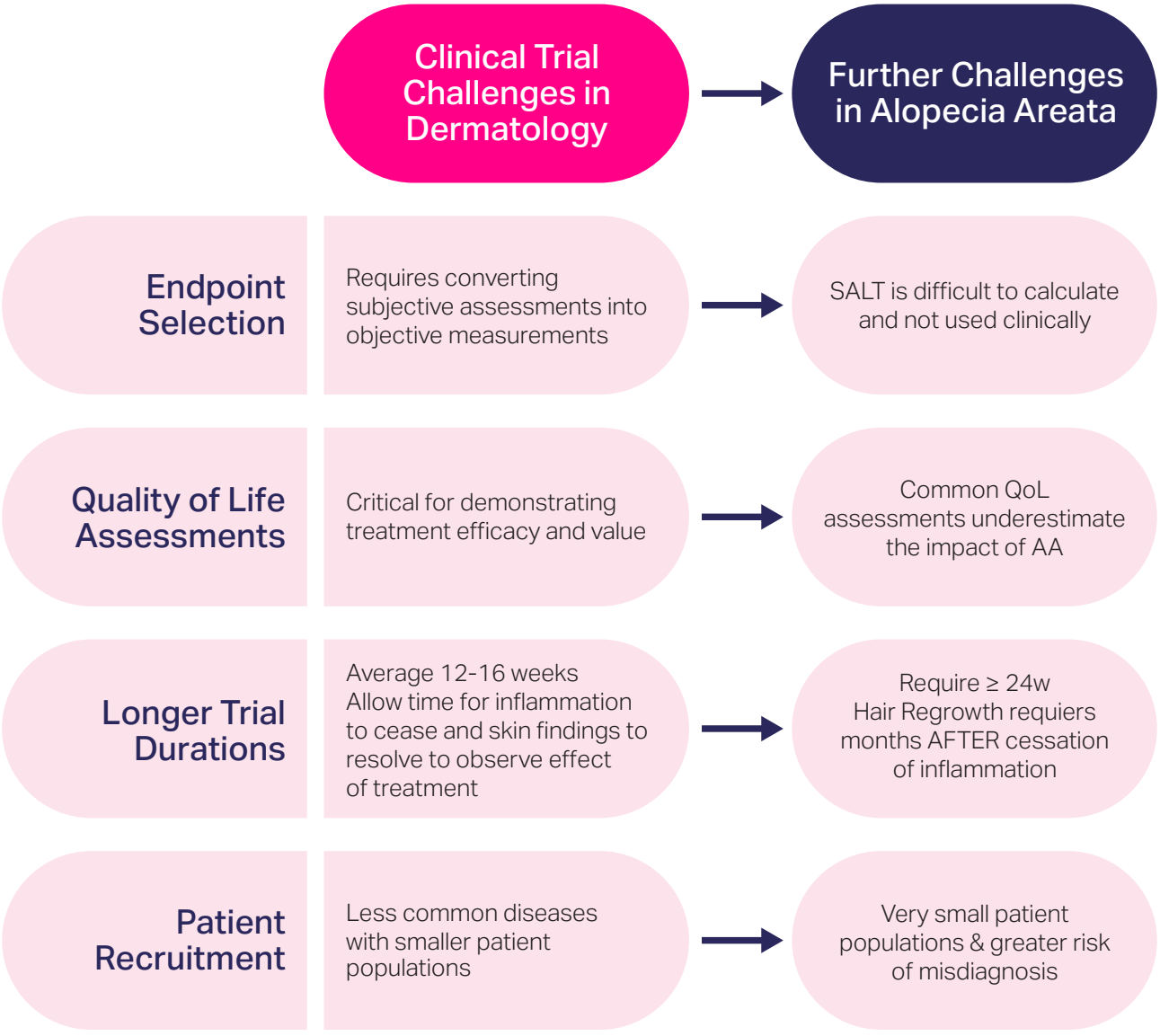
Comorbid conditions, when present, may affect the treatment options available for patients and influence medication prescribed by physicians. Currently only the JAK inhibitor class is approved for AA, but patients may have comorbidities or other indications that preclude treatment with JAKs, creating a need for drugs with other MOAs. **Alternatively, comorbidities with similar underlying pathophysiology may be treated with the same medication,** for instance there is a current trial of Dupixent in AA in patients with a history of atopy. The need to treat alopecia areata in the context of other conditions is shaping both research priorities and treatment decisions.

A less obvious unmet need is treatments for patients with moderate AA. All currently approved systemic therapies are indicated for severe and very severe alopecia areata (defined in clinical trials as at least 50% hair loss). Consequently, there aren't published data on the response of moderate disease to these agents from randomized, placebo-controlled trials. Many payers use the SALT 50 threshold to determine coverage for JAK inhibitors. As a result, patients with significant hair loss that is below the SALT 50 threshold may not be able to access JAK therapy, even if they have failed other topical and systemic treatments. Although there is expert support for upgrading the severity classification if the patient is treatment resistant or is experiencing significant emotional/social distress,[11] it is unclear whether this has affected payer criteria for coverage. In addition, patients and physicians may be reluctant to treat mild or moderate AA with a systemic therapy, but existing localized treatments may not be effective. Pain from intralesional steroids can be an impediment to treatment particularly for multifocal disease. Additional therapeutic options are needed for this patient cohort.

Pursuing new indications in dermatology, like AA, requires deep disease state expertise as well as sharp strategic insights about the needs of patients and the physicians who care for them.

Growing Pains: Challenges in Alopecia Areata Clinical Trials

Clinical trials in AA share challenges commonly faced in dermatology research, but there are additional complexities that can affect trial outcomes and market impact in AA.



The subjective nature of dermatology complicates endpoint selection. Clinical trial endpoints are often based on visual analog scales or investigator global assessments. These assessments are indication-specific, and many dermatologic conditions have multiple validated trial assessments. Strategic selection of endpoints requires knowledge of strengths and weaknesses of available endpoints within the contexts of the disease and its market.

The Severity of Alopecia Tool (SALT) is a well-established trial assessment in AA, however SALT is time-consuming and complex to calculate, and it doesn't translate well to clinical practice. The currently-approved JAK inhibitors in AA and Upadacitinib all used the same primary endpoint, "Percentage of patients achieving SALT ≤20" in their phase 3 trials. The selection of SALT 20 is based on an expert consensus statement that incorporated patient feedback[12] and FDA input. A recent trend in phase II AA trials has been a pivot to using "change from baseline SALT" (either raw score or percentage change). Although demonstrating efficacy compared to placebo may be easier using this endpoint, there is some risk in choosing a less rigorous endpoint than will be used in phase III. Additionally, this endpoint is less clinically relevant than SALT 20, since it may indicate any regrowth, rather than meaningful regrowth.

Since most dermatologic conditions worsen life rather than shorten it, much of the value of any treatment is in its ability to improve quality of life (QoL) for affected people. QoL assessments are standard in dermatology clinical trials, but there are many different assessments that may be used. Which assessment best captures an intervention's effects on QoL varies by patient population and indication. QoL assessments like Skindex or DLQI are standard in dermatology trials. Since these general dermatology QoL assessments include several questions about physical symptoms, they may underestimate the impact of AA on QoL and the improvement in QoL following successful treatment.[13] To mitigate this limitation in AA clinical trials, Skindex and DLQI are often paired with more specific AA questionnaires and the Hospital Anxiety and Depression Scale (HADS), but their use increases the time and complexity of patient study visits. App-based Patient Reported Outcomes (PROs) and Computerized Adaptive Testing (CAT) may decrease the burden for trial participants, but these tools must be built and validated, resulting in added cost and potential delays.

Study duration is a potential pitfall in AA, requiring a balance between cost and opportunity. A longer duration can increase the number of patients that meet the endpoint, particularly in AA. **The intervention must have enough time to decrease inflammation, and then the hair must regrow enough to be clinically evident,** generally resulting in longer phase III trials than for other indications. However, allowing enough time for an adequate response requires greater financial investment and increased patient burden with additional study visits and assessments. Prior phase III trials in AA have ranged from 24 weeks to 36 weeks, compared with AD and Psoriasis trials that are generally 12-16 weeks.

Patient recruitment is often difficult in clinical research, and recruitment in AA can face additional challenges, even compared with other dermatologic conditions. AA is a relatively rare disease; a 2023 study based upon US claims data reported that the prevalence of AA in the previous 12 months was approximately 0.2%.[14] Of this small patient population, many patients will have mild and/or self-limited disease (lasting less than a year). The most severe subtypes of AA, AT and AU, only comprise about 5-10% of AA cases. Trial inclusion criteria usually specify patients with at least SALT 50, and they generally select for disease of at least 6 months' duration, attempting to eliminate patients whose disease is likely to resolve without treatment. Of this small potential pool of trial participants, not all will be willing, able, and eligible to participate in a given trial. Screening failure due to incorrect diagnosis is an additional barrier to patient recruitment for AA studies. Patients that are referred for a trial may have other forms of alopecia like male pattern baldness, inflammatory alopecia, or multifactorial hair loss, particularly among Black patients. Mesinkovska, et al. noted 8 of 14 Black patients were screen failures due to misdiagnosis, with the authors commenting, "incorrect diagnosis highlights the need for improved evaluation of hair loss conditions among patients of color".[15]

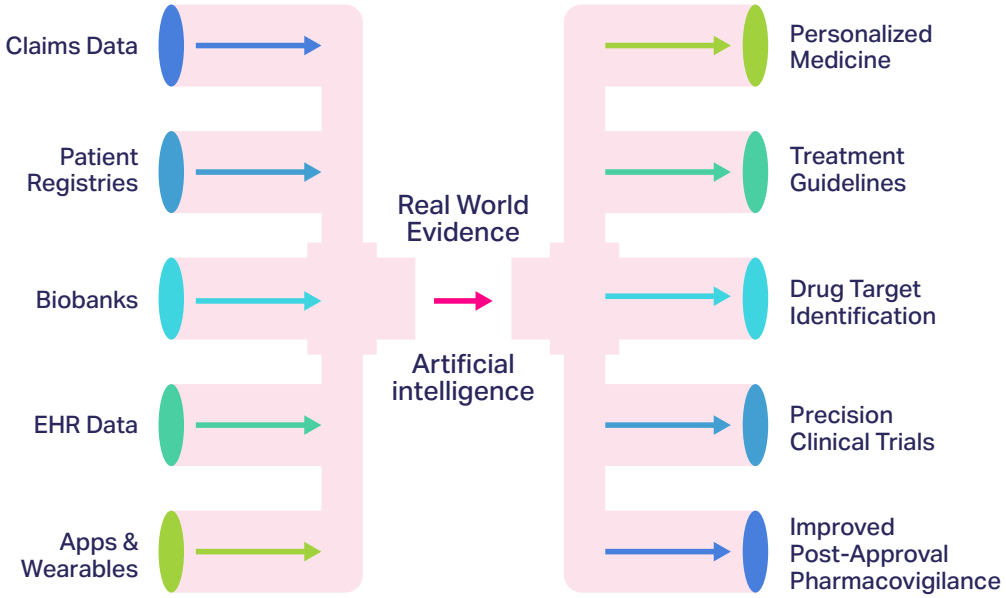
Trial site selection in AA often focuses on Hair Centers of Excellence or dermatologists with additional expertise in hair loss. Although these sites have larger numbers of potential subjects, patients may be traveling from farther away to receive care from a hair expert. Significant distance to the trial site can pose an additional barrier to recruitment compared with large numbers of geographically diverse sites. The barrier posed by distance may be somewhat overcome by the ability incorporate technology like remote visits or wearable devices as well as the trend toward decentralized trials. The largest AA advocacy group, National AA Foundation (NAAF), encourages participation in research, and can serve as a partner to help raise awareness about clinical trials currently recruiting.

There are many decisions in clinical trial design that can determine a study's success or failure. Expert guidance can help inform key choices such as selecting appropriate endpoints, assessments, patient populations, and trial sites. Creative solutions to recruitment challenges often involve leveraging technology, partnering with advocacy groups, and tapping into networks of experts and thought leaders. Recognizing that patient experience is essential to recruitment and retention, the focus is on conducting efficient, well-managed trials that serve both sponsors and participants effectively.

Growing Innovation:

Leveraging Technology in Alopecia Areata Outcomes Research

The demand for real world evidence (RWE) continues to grow as stakeholders recognize its value in drug development, payer negotiations, and patient care.
RWE provides a wealth of information to augment clinical trial data. A larger and more diverse pool of patients yields valuable safety and efficacy data. For physicians, RWE can yield additional clinical data that can improve patient care, including identifying risk factors for side effects, patient characteristics that affect drug response, and the effects of drug holidays and dose changes. Real world data can be useful in developing evidence-based clinical guidelines. Demonstrating that a therapy decreases total healthcare expenditures or significantly improves QoL for patients can influence payer coverage and formulary tiering decisions. Innovative use of emerging technologies like Machine Learning (AI) and personal devices is rapidly expanding the ability to capture and utilize health outcomes data that was previously inaccessible at scale.



Currently, the majority of health outcomes studies analyze RWE derived from patient claims data, **but it is difficult to capture relevant and granular RWE from insurance claims data in many dermatologic conditions.** For instance, ICD-10 codes in AA only differentiate between AT, AU, ophiasis, and other AA. These codes do not define the percentage of hair loss more specifically than any hair loss (AA or ophiasis) or total hair loss (AT/AU). The inability to characterize the severity of AA from ICD-10 code prevents accurate analysis of treatment patterns, prognosis, or comorbid conditions from claims data alone. Claims data are also unable to capture change; fifty percent hair regrowth at a follow-up office visit will not be evident in the claims data.

In response to the need for more detailed information, patient registries have emerged to fill the gap. These registries offer a range of patient populations, including specific conditions and subgroups, as well as types of data available. The registries of hospital systems or academic centers generally rely on data-mining electronic health records (EHRs), while other registries enroll patient volunteers. The National Alopecia Areata Foundation (NAAF) patient registry with biobank began in 2000, and it has made a significant contribution to both patient impact measurement as well as genetic studies in AA. As a result of the Genome Wide Association Study performed using NAAF's biobank samples, JAK inhibitors were identified as a potential therapy for AA.[16] Target RWE and Corevitas are national entities that launched AA registries in 2021 and 2023, respectively. In partnerships with AA experts, these commercial registries were proactively designed to capture additional data relevant to industry like patient and physician reported outcomes (PROs), QoL measures, and potentially accompanying biomarkers and genetic studies.

The incorporation of AI will dramatically expand the capabilities of health outcomes research. RWE studies that combine AI with patient registries and biobanks will increase the breadth and precision of information compared to claims data alone. AI Large Language Models (LLMs) enable faster and more detailed data analysis from free-text sections of EHRs that generally contain information about disease severity, previous treatments, disease duration, and response to therapy. Registry/biobank data linking treatment outcomes or adverse events to cytokine profiles, biomarkers, clinical presentation, and genotypes coupled with AI could:

- Increase the speed with which new therapeutic candidates can be identified
- Save unnecessary exposures to investigational drugs
- Decrease risk in phase III trials for patients and sponsors

Most importantly, these techniques may eventually enable physicians to practice precision medicine, optimizing treatment for individual patients.

Apps and wearable devices offer another opportunity to collect RWE while mitigating the distance and time commitment that can become barriers to patient participation in health outcomes research. Wearable devices can facilitate more frequent data collection and improve patient compliance with questionnaires. Currently, few published RWE studies in inflammatory conditions have incorporated data from wearable devices or apps, but there are examples that illustrate what use of these technologies could offer in dermatology. Physiologic indicators of poor sleep or stress measured by wearables juxtaposed with PRO questionnaires administered via smartphone apps could better assess an intervention's QoL effect in AA. Generative AI will reduce the cost of building new apps, potentially expanding options for what kind of data are collected, such as global assessments calculated from patient photos. A truly holistic approach to RWE may become possible with the incorporation of new technologies.

Whether RWE is needed for payer dossiers, medical education, post-marketing surveillance, or indication expansion, a meaningful study begins with asking the right questions. From concept development to analysis, expertise and creativity are essential to guide effective RWE study design. A deep understanding of the specific therapeutic area is critical to harnessing and maximizing the value of available real-world data. Awareness of the strengths and limitations of RWE sources, combined with a forward-looking approach to emerging technologies, enables the full utilization of available options to best meet client needs.

References:

1. Villasante Fricke AC, Miteva M. Epidemiology and burden of alopecia areata: a systematic review. Clin Cosmet Investig Dermatol. 2015 Jul 24;8:397-403. doi: 10.2147/CCID.S53985. PMID: 26244028; PMCID: PMC4521674.

2. Mesinkovska N, Craiglow B, Ball SG, Morrow P, Smith SG, Pierce E, Shapiro J. The Invisible Impact of a Visible Disease: Psychosocial Impact of Alopecia Areata. Dermatol Ther (Heidelb). 2023 Jul;13(7):1503-1515. doi: 10.1007/s13555-023-00941-z. Epub 2023 Jun 8. PMID: 37289409; PMCID: PMC10307747.

3. Koo JY, Shellow WV, Hallman CP, Edwards JE. Alopecia areata and increased prevalence of psychiatric disorders. Int J Dermatol. 1994 Dec;33(12):849-50. doi: 10.1111/j.1365-4362.1994.tb01018.x. PMID: 7883407.

4. Lauron S, Plasse C, Vaysset M, Pereira B, D'Incan M, Rondepierre F, Jalenques I. Prevalence and Odds of Depressive and Anxiety Disorders and Symptoms in Children and Adults With Alopecia Areata: A Systematic Review and Meta-analysis. JAMA Dermatol. 2023 Mar 1;159(3):281-288. doi: 10.1001/jamadermatol.2022.6085. PMID: 36696123; PMCID: PMC9878435.

5. Craiglow BG, King BA. Killing two birds with one stone: oral tofacitinib reverses alopecia universalis in a patient with plaque psoriasis. J Invest Dermatol. 2014 Dec;134(12):2988-2990. doi: 10.1038/jid.2014.260. Epub 2014 Jun 18. PMID: 24940651.

6. King B, Ohyama M, Kwon O, Zlotogorski A, Ko J, Mesinkovska NA, Hordinsky M, Dutronc Y, Wu WS, McCollam J, Chiasserini C, Yu G, Stanley S, Holzwarth K, DeLozier AM, Sinclair R; BRAVE-AA Investigators.
Two Phase 3 Trials of Baricitinib for Alopecia Areata. N Engl J Med. 2022 May 5;386(18):1687-1699. doi: 10.1056/NEJMoa2110343. Epub 2022 Mar 26. PMID: 35334197.

7. King B, Zhang X, Harcha WG, Szepietowski JC, Shapiro J, Lynde C, Mesinkovska NA, Zwillich SH, Napatalung L, Wajsbrot D, Fayyad R, Freyman A, Mitra D, Purohit V, Sinclair R, Wolk R. Efficacy and safety of ritlecitinib in adults and adolescents with alopecia areata: a randomised, double-blind, multicentre, phase 2b-3 trial. Lancet. 2023 May 6;401(10387):1518-1529. doi: 10.1016/S0140-6736(23)00222-2. Epub 2023 Apr 14. Erratum in: Lancet. 2023 Jun 10;401(10392):1928. doi: 10.1016/S0140-6736(23)01078-4. PMID: 37062298.

8. King B, Senna MM, Mesinkovska NA, Lynde C, Zirwas M, Maari C, Prajapati VH, Sapra S, Brzewski P, Osman L, Hanna S, Wiseman MC, Hamilton C, Cassella J. Efficacy and safety of deuruxolitinib, an oral selective Janus kinase inhibitor, in adults with alopecia areata: Results from the Phase 3 randomized, controlled trial (THRIVE-AA1). J Am Acad Dermatol. 2024 Nov;91(5):880-888. doi: 10.1016/j.jaad.2024.06.097. Epub 2024 Jul 23. PMID: 39053611.

9. Raval RS, Nohria A, Desai D, Mourtzanakis K, Buontempo M, Shapiro J, Lo Sicco K. The use of minoxidil in the treatment of alopecia areata: A systematic review. J Am Acad Dermatol. 2024 Sep;91(3):508-509. doi: 10.1016/j.jaad.2024.05.037. Epub 2024 May 23. PMID: 38796079.

10. King BA, Craiglow BG. Janus kinase inhibitors for alopecia areata. J Am Acad Dermatol. 2023 Aug;89(2S):S29-S32. doi: 10.1016/j.jaad.2023.05.049. PMID: 37591562.

11. King BA, Mesinkovska NA, Craiglow B, Kindred C, Ko J, McMichael A, Shapiro J, Goh C, Mirmirani P, Tosti A, Hordinsky M, Huang KP, Castelo-Soccio L, Bergfeld W, Paller AS, Mackay-Wiggan J, Glashofer M, Aguh C, Piliang M, Yazdan P, Lo Sicco K, Cassella JV, Koenigsberg J, Ahluwalia G, Ghorayeb E, Fakharzadeh S, Napatalung L, Gandhi K, DeLozier AM, Nunes FP, Senna MM. Development of the alopecia areata scale for clinical use: Results of an academic-industry collaborative effort. J Am Acad Dermatol. 2022 Feb;86(2):359-364. doi: 10.1016/j.jaad.2021.08.043. Epub 2021 Aug 30. PMID: 34474079.

12. Wyrwich KW, Kitchen H, Knight S, Aldhouse NVJ, Macey J, Nunes FP, Dutronc Y, Mesinkovska N, Ko JM, King BA. The Alopecia Areata Investigator Global Assessment scale: a measure for evaluating clinically meaningful success in clinical trials. Br J Dermatol. 2020 Oct;183(4):702-709. doi: 10.1111/bjd.18883. Epub 2020 Apr 3. PMID: 31970750; PMCID: PMC7586961.

13. Mendoza TR, Osei J, Duvic M. The Utility and Validity of the Alopecia Areata Symptom Impact Scale in Measuring Disease-Related Symptoms and their Effect on Functioning. J Investig Dermatol Symp Proc. 2018 Jan;19(1):S41-S46. doi: 10.1016/j.jisp.2017.10.009. PMID: 29273105.

14. Mostaghimi A, Gao W, Ray M, Bartolome L, Wang T, Carley C, Done N, Swallow E. Trends in Prevalence and Incidence of Alopecia Areata, Alopecia Totalis, and Alopecia Universalis Among Adults and Children in a US Employer-Sponsored Insured Population. JAMA Dermatol. 2023 Apr 1;159(4):411-418. doi: 10.1001/jamadermatol.2023.0002. PMID: 36857069; PMCID: PMC9979012.

15. Elsanadi R, Esse I, Phong C, Ortega AA, Yale K, Mesinkovska NA. Alopecia areata clinical trial enrollment and retention outcome factors among underrepresented ethnic and racial groups: A cross-sectional study. J Am Acad Dermatol. 2023 Dec;89(6):1253-1256. doi: 10.1016/j.jaad.2023.07.003. Epub 2023 Jul 11. PMID: 37442278.

16. Petukhova L, Christiano AM. Functional Interpretation of Genome-Wide Association Study Evidence in Alopecia Areata. J Invest Dermatol. 2016 Jan;136(1):314-317. doi: 10.1038/JID.2015.402. PMID: 26763452; PMCID: PMC4870380.

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