Received: 12 July 2023 | Accepted: 19 July 2023

DOI: 10.1111/srt.13425

LETTER

WILEY

Combination of baricitinib and conventional immunomodulating therapy for alopecia totalis

Dear Editor,

Alopecia totalis (AT) is a severe form of alopecia areata (AA) that affects the entire scalp. AA treatment depends on patient age, disease phase, and disease severity, and AT usually requires aggressive systemic treatment.[1] For treatment of AT, immunomodulating agents, such as steroids and cyclosporine, have been used as off-label treatments. Recently, the oral selective JAK 1/2 inhibitor baricitinib has received Food and Drug Administration approval for AA, but in two previous randomized controlled trials, 19.3%–19.4% of participants had Severity of Alopecia Tool (SALT) scores of ≤20 after 16 weeks of treatment with 4 mg of baricitinib, followed by 35.9%–38.8% achieving the threshold after 36 weeks, reflecting suboptimal outcomes.[2]

A 26-year-old man presented with AT that had persisted for 15 years (Figure 1). There was a history of atopic dermatitis, asthma, and allergic rhinitis. He had received herbal medicine, oral methotrexate, intralesional corticosteroid injections, and diphenylcyclopropenone contact therapy, but the waxing and waning persisted. Improvement was seen when he took oral tofacitinib for 1 year, but tofacitinib was discontinued due to cardiovascular risk.[3] For rapid improvement, baricitinib (4 mg) with methylprednisolone pulse and tapering therapy were prescribed for 16 weeks, and a good response, equivalent to SALT 0, was achieved. Low-dose oral cyclosporine (50–25 mg/day) maintenance was added to minimize the rebound caused by steroid discontinuation. Hair regrowth was maintained after 12 weeks of cyclosporine replacement (Figure 2).

For this patient, we aimed to treat AT more effectively by using a combination of drugs that have immunomodulating effects through different mechanisms.

In hair follicles of AA, interferon-γ (IFN-γ) secretion increases because of reduced immunotolerance. This is associated with Janus kinase-transducer and activator of transcription protein (JAK-STAT) activation in follicular epithelial cells, as well as interleukin (IL)-15 and major histocompatibility complex (MHC) activation, among others, leading to inflammatory responses by CD8+ NKG2D+ T cells, and IFN-γ is secreted again, repeating the inflammatory cycle.[4] Baricitinib blocks this cycle by selectively inhibiting JAK 1/2, suppressing inflammation and causing hair regrowth.

Steroids act on glucocorticoid receptor complexes in cell nuclei, participate in gene transcription, and regulate pro-inflammatory cytokines—such as IL-1, IL-2, IL-6, IFN-γ, and tumor necrosis factor alpha (TNF-α)—thereby facilitating anti-inflammatory and immune-regulation effects. Cyclosporine forms a complex with cyclophilin and inhibits the activity of calcineurin phosphatase to block downstream signaling pathways inside CD4+ T cells. It suppresses IL-2 secretion, which stimulates cytokines, such as IFN-γ and granulocyte-macrophage colony-stimulating factors. It depletes CD8+ T cells, which play a major role in AA.[5]

However, the combination of cyclosporine and baricitinib is not recommended owing to the risk of severe infection and lymphomam without any clinical evidence. In our case, cyclosporine dose was lower than usual dose, and no side effects or hair loss were reported after 5 months of combined treatment with cyclosporine and baricitinib. The side effects of cyclosporine are dose dependent, so it is presumed to be safe at low doses.[5]

Additionally, black dots, broken hairs, short vellus hairs, and tapering hairs were identified during trichoscopy, and these observations showed improvement after treatment. These findings align with

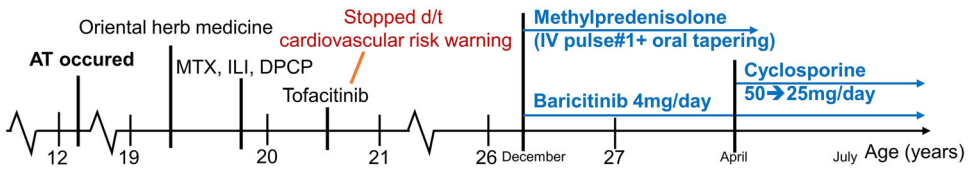

FIGURE 1 Timeline of patient's medical history and treatment. AT, alopecia totalis; DPCP, diphenylcyclopropenone; ILI, intralesional corticosteroid injection; MTX, methotrexate.

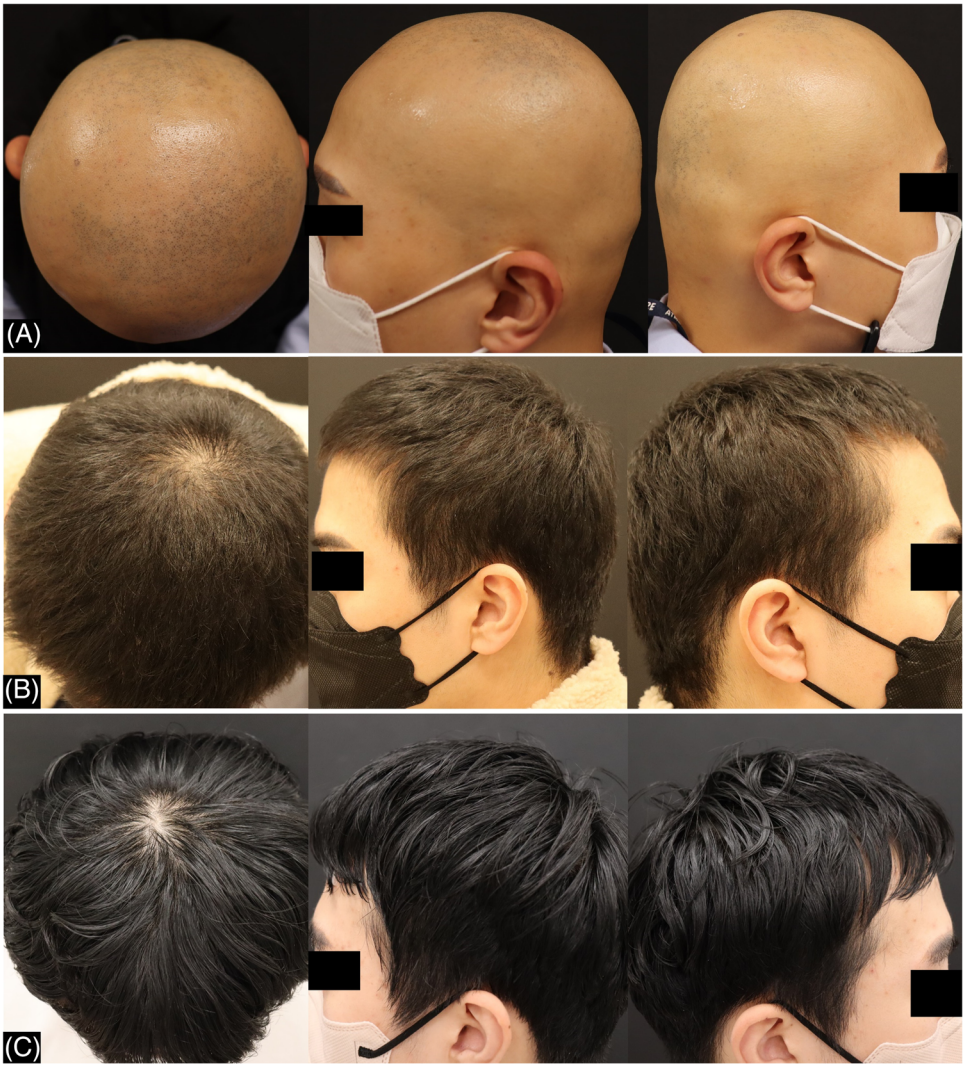

FIGURE 2 Clinical presentation of a 26-year-old man with alopecia totalis. (A) Multiple bald patches easily seen on the scalp before treatment. (B) Marked hair regrowth observed after 16 weeks of treatment with baricitinib and methylprednisolone tapering. (C) Hair regrowth was well maintained after 12 weeks of replacing methylprednisolone with cyclosporine.

the results of Al-Dhubaibi et al.'s meta-analysis, suggesting that incorporating trichoscopy as an active tool in AA treatment could be advantageous for monitoring progress.[6]

In conclusion, the combination of baricitinib with appropriate use of conventional immunomodulating therapy may be effective and safe for treating AA, including AT.

CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

FUNDING INFORMATION

The authors received no specific funding for this work.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article, as no new data were created or analyzed in this study.

INFORMED CONSENT

The patient in this manuscript provided written informed consent to publish his case details and clinical pictures.

Young Gue Koh[1]
Hye Sung Han[2]
Joon Seok[1]
Sun Young Choi[2]
Kapsok Li[1]
Beom Joon Kim[1]
Kwang Ho Yoo[2]

[1]*Department of Dermatology, Chung-Ang University College of Medicine, Seoul, Republic of Korea*
[2]*Department of Dermatology, Chung-Ang University Gwangmyeong Hospital, Chung-Ang University College of Medicine, Gwangmyeong-si, Gyeonggi-do, Republic of Korea*

Correspondence
Kwang Ho Yoo, Chung-Ang University Gwangmyeong Hospital, Chung-Ang University College of Medicine, Gwangmyeong-si, Gyeonggi-do, Republic of Korea.
Email: psyfan9077@naver.com

ORCID

Young Gue Koh https://orcid.org/0000-0002-6376-0328
Beom Joon Kim https://orcid.org/0000-0003-2320-7621
Kwang Ho Yoo https://orcid.org/0000-0002-0137-6849

REFERENCES

1. Fukuyama M, Ito T, Ohyama M. Alopecia areata: current understanding of the pathophysiology and update on therapeutic approaches, featuring the Japanese Dermatological Association guidelines. *J Dermatol*. 2022;49(1):19-36. doi:10.1111/1346-8138.16207
2. King B, Ohyama M, Kwon O, et al. Two phase 3 trials of baricitinib for alopecia areata. *N Engl J Med*. 2022;386(18):1687-1699. doi:10.1056/nejmoa2110343
3. Kawalec P, Śladowska K, Malinowska-Lipień I, Brzostek T, Kózka M. European perspective on the management of rheumatoid arthritis: clinical utility of tofacitinib. *Ther Clin Risk Manag*. 2018;14:15-29. doi:10.2147/TCRM.S138677
4. Pratt CH, King LE, Messenger AG, Christiano AM, Sundberg JP. Alopecia areata. *Nat Rev Dis Primers*. 2017;3:17011. doi:10.1038/nrdp.2017.11
5. Ryan C, Amor KT, Menter A. The use of cyclosporine in dermatology: Part II. *J Am Acad Dermatol*. 2010;63(6):949-972.
6. Al-Dhubaibi MS, Alsenaid A, Alhetheli G, Abd Elneam AI. Trichoscopy pattern in alopecia areata: a systematic review and meta-analysis. *Skin Res Technol*. 2023;29(6):e13378. doi:10.1111/srt.13378