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HEALTH TECHNOLOGY BRIEFING
JUNE 2021

Baricitinib for treatment of severe alopecia areata in adults

NIHRIO ID	25500	**NICE ID**	10598
Developer/Company	Eli Lilly and Company Ltd	**UKPS ID**	660097

Licensing and market availability plans	Currently in phase III trials.

SUMMARY

Baricitinib is in clinical development for the treatment of adults with alopecia areata (AA). AA is a disease that develops when the body attacks its own hair follicles (where the hair grows from), which can cause hair loss as small round patches of baldness anywhere on the body. Most commonly, this occurs on the scalp and has high rates of recurrence. There are also psychological implications such as increased levels of anxiety and depression in people with AA.

Baricitinib is an inhibitor of janus kinases (JAKs). JAKs play a major role in signalling for hair follicle growth, specifically JAK inhibitors impede the immune system (the body's defence against germs), including pathways involved in antiviral immunity (i.e., type I and type II prominent interferon (IFN)), which appear to be active in AA. Additionally, as baricitinib can be taken orally it may increase adherence. If licensed, baricitinib would offer an additional treatment option for those with AA.

PROPOSED INDICATION

Treatment of patients 18 years and older with severe alopecia areata, including alopecia totalis and alopecia universalis.[a]

TECHNOLOGY

DESCRIPTION

Baricitinib (Olumiant, LY3009104) is a selective and reversible inhibitor of the janus- kinase (JAK) acitivity. JAKs enzymes are involved in haematopoiesis, inflammation and immune function. Baricitinib specifically inhibits the activities of JAK1, JAK2, Tyrosine Kinase 2, and JAK3 thereby reducing the phosphorylation and activation of signal transducers and activators of transcription (STATs).[1,2]

Barcitinib is currently in phase II/III clinical development for treatment of adults (⩾18 years old) with AA (NCT03570749; BRAVE-AA1, NCT03899259; BRAVE-AA2). During the trials patients are provided with either a low (2mg) or high dose (4mg).[b3,4]

INNOVATION AND/OR ADVANTAGES

Barcitinib may have a couple of possible advantages over other types of treatment. Firstly, it can be taken orally, making it more attractive to patients and possibly increasing adherence. Secondly, JAK inhibitors inhibit multiple pathogenic pathways simultaneously, including both type I and type II prominent interferon (IFN) receptor pathways, which appear to be active in AA.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Baricitinib is currently licenced in the UK for the treatment of:[1,2]

- Moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs. It may be used as a monotherapy or in combination with methotrexate.
- Moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy.

Based on integrated data across both rheumatoid arthritis and atopic dermatitis indications Very common adverse events (occurs in ⩾ 1 in 10 patients) of baricitinib are upper respiratory tract infections and hypercholesterolaemia.[1,2]

Baricitinib is in phase III clinical development for juvenile idiopathic arthritis, atopic dermatitis, systemic lupus erythematosus, rheumatoid arthritis, and COVID-19 pneumonia. It is also in phase II clinical development for relapsing giant cell arteritis, Aicardi Goutieres syndrome, idiopathic inflammatory myopathies, polymyalgia rheumatic, Nakajo-Mishimura syndrome, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome, STING-associated vasculopathy with onset in infancy, and chronic graft vs host disease (after allogeneic hematopoietic stem cell transplantation).[6]

[a] Information provided by Eli Lilly and Company Ltd on UK PharmaScan
[b] Information provided by Eli Lilly and Company Ltd

PATIENT GROUP

DISEASE BACKGROUND

AA is a complex genetic, immune mediated disease that target anagen hair follicles, although the hair follicle does not usually sustain permanent damage and maintains its potential to regrow hair.[7] This polygenic autoimmune disease causes hair loss that can range from circular patches on the scalp to complete hair loss.[5] As with other autoimmune diseases, AA is a chronically relapsing inflammatory disorder, which suggests a cyclic recurrence of disease-promoting events.[8] Due to the chronic relapsing-remitting nature and pathophysiology of AA, it is notoriously difficult to manage and study in clinical trials.[9]

The general concept of the pathophysiology of AA is thought to be due to immune privilege loss of the hair follicle. The target antigen is still not clearly defined, however, melanocytes are often targeted by the immune system and are involved during the active pigment production phase of the anagen phase of the hair cycle. It is suggested that downregulation of major histocompatibility complex (MHC) class I expression in anagen hair bulbs sequesters autoantigens from being presented to CD8+ T cells. Additionally, local production of immunosuppressant molecules such as transforming growth factor (TGF)-β1, interleukin (IL)-10, and α-melanocyte-stimulating hormone (MSH) are thought to contribute to this immune privilege.[5,8,9]

Triggers such as stress/trauma to the skin can cause increased intrafollicular secretion of interferon (IFN)-γ, which induces T helper (Th)1 chemokines CXC motif ligand 10 MHC class I expression leading to cytotoxic T (Tc)1 and Th1 cells accumulating around hair bulbs. This leads to immune privilege loss and the autoimmune attack of anagen follicles results in prematurely entering into the catagen phase. Furthermore, animal models show that the production of IFN-γ signals, via JAK1 and JAK2, to stimulate production of IL-15 in the hair follicle. IL-15 binds to CD8+ T cells, further stimulating JAK1 and JAK3 to produce IFN-γ. Human studies show an overexpression of IFN-γ, JAK1, JAK2, and to a greater extent JAK3.[9]

One of the major concerns with AA patients is the increased likelihood of higher anxiety and depression levels, combined with lower self-esteem, poorer quality of life, and poorer body image.[10]

Currently, there is no cure and whilst complete regrowth can occur within a year without treatment, further episodes of hair loss can occur in the future. Additionally, if there is extensive hair loss from the start, the chances of it regrowing are not as good. For example, those with more than half of their hair lost at the start of the condition or with complete hair loss at any stage have an approximate 1 in 10 chance of full recovery. The chances of regrowth are also smaller in young children and those with the condition affecting the hairline at the front, back or side.[11]

CLINICAL NEED AND BURDEN OF DISEASE

AA affects up to 2% of the general population.[9] In the UK it is estimated to affect approximately 15 in 10,000 people.[12] There is no known age, race, or ethnic preponderance.[7]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

NICE suggests for management purposes that the natural history of the condition and treatment options be discussed. Discuss whether treatment is required based on regrowth or lack thereof. If treatment is an option, this may be done on a 3-month trial basis. Additionally, cosmetic options for

camouflaging hair loss should be discussed (e.g. wigs). Referral to a dermatologist should be arranged if hair loss does not respond to treatment in primary care or if treatment is declined, the diagnosis is uncertain, or a child, pregnant or breastfeeding woman is affected.[13]

Common treatment pathways include the use of local steroid injections, which can be used on the scalp and brows (most effective on small patches of hair loss). Injections can be repeated every four to six weeks and are stopped once regrowth is achieved. Special care must be taken around the eyes as injecting too much may cause glaucoma. Steroid tablets, large doses may result in hair regrowth. However, when the treatment stops AA often recurs. There are many possible side effects including raised blood pressure, diabetes, stomach ulcers, cataracts and osteoporosis. Contact sensitisation treatment where a patient is made allergic to a substance (usually diphencyprone) and this is then applied in very weak strengths to the bald patches, commonly once a week. Depigmentation can occur and it must be used with caution in those with dark skin. This treatment is only available in specialised centres. Ultraviolet light treatment (PUVA) could be utilised, which involves taking a tablet or applying cream that makes the skin sensitive to light, then exposing the bald patches to ultraviolet (UV) light (two or three times a week). Relapse of AA is common when treatment is stopped and there is a possible long-term risk of skin cancers.[11]

CURRENT TREATMENT OPTIONS

For AA treatment the British Association of Dermatologists (BAD) and Alopecia UK recommend the following:[11,14]

- Topical corticosteroids (creams and scalp applications), applied to the bald patches (usually twice a day for a limited time).
- Intralesional corticosteroids (local steroid injections); such as hydrocortisone acetate and triamcinolone acetonide.
- Systemic corticosteroids (steroid tablets or injection into the muscle); such as oral prednisolone or intramuscular triamcinolone acetonide (Kenalog).
- Dithranol (anthralin) cream may stimulate some hair growth, although the evidence is weak.
- Contact immunotherapy (sensitisation treatment); such exposure to diphenylcyclopropenone (DPCP) to cause a local allergic reaction and stimulate hair growth.
- Minoxidil lotion, which is available over the counter, can be applied to bald patches and may help some people but the hair is often fine.
- Immunosuppressant tablets, including sulfasalazine, methotrexate, ciclosporin, and azathioprine. They suppress the immune system and are occasionally used to treat severe AA which is unresponsive to other treatments. Evidence is limited and severe side effects can occur.
- Prostaglandin analogs, including eye drops, latanoprost and bimatoprost (which may cause hair growth on the eyelids), further studies are needed to confirm its effect on scalp AA.

PLACE OF TECHNOLOGY

If licensed, baricitinib would offer an alternative treatment option for adults with AA.

CLINICAL TRIAL INFORMATION

Trial	**BRAVE-AA1; NCT03570749; A multicentre, randomized, double-blind, placebo-controlled, operationally seamless, adaptive phase 2/3 study to evaluate the efficacy and safety of baricitinib in adult patients with severe or very severe alopecia areata.** **Phase II/III –** Active, not recruiting

	Location(s) – USA and other countries **Actual primary completion date –** February 2021
Trial design	Randomised, parallel assignment, double blinded.
Population	N = 725 (estimated), 18 to ≤60 years for males and ≤70 years for females, with severe or very severe AA (current episode of more than 6 months, hair loss ≥50% of the scalp), no spontaneous improvement over the past six months, and the current episode of severe/very severe AA is less than 8 years (although maybe eligible if episodes of regrowth have been observed on the affected areas over the past 8 years).
Intervention(s)	- Baricitinib 4 mg administered orally. - Baricitinib 2 mg administered orally.[c]
Comparator(s)	Placebo, administered orally.
Outcome(s)	Percentage of participants achieving severity of alopecia tool (SALT) score of ≤20. See trial record for full list of other outcomes
Results (efficacy)	Results of BRAVE-AA1 showed that at Week 36, the proportion of patients reaching 80 percent or more scalp hair coverage was achieved by 35 percent ($p \leqslant 0.001$) of patients treated with baricitinib 4-mg/day, 22 percent ($p \leqslant 0.001$) of patients treated with baricitinib 2-mg/day and five percent of patients in the placebo group, meeting the primary endpoint. The proportion of patients self-reporting at least 80 percent scalp hair coverage was significantly greater in the 2-mg and 4-mg groups compared to placebo ($p \leqslant 0.001$) by Week 36.[15]
Results (safety)	The most common treatment-emergent adverse events (TEAEs) in BRAVE-AA1 and BRAVE-AA2 included upper respiratory tract infections, headache and acne. No deaths or venous thromboembolic events (VTEs) were reported in the trials. The safety profile of baricitinib in the two studies was consistent with its known safety profile in patients with rheumatoid arthritis (RA) and atopic dermatitis (AD).[15]

Trial	**BRAVE-AA2; NCT03899259; A multicentre, randomized, double blind, placebo controlled, phase 3 study to evaluate the efficacy and safety of baricitinib in adult patients with severe or very severe alopecia areata.** **Phase III – Active, not recruiting** **Location(s) – USA and other countries** **Actual primary completion data – January 2021**
Trial design	Randomised, parallel assignment, double-blinded.
Population	N = 546 (actual),[16] 18 to ≤60 years for males and ≤70 years for females, with severe or very severe AA (current episode of more than 6 months, hair loss ≥50% of the scalp), no spontaneous improvement over the past six months, and the current episode of severe/very severe AA is less than 8 years (although maybe

[c] Information provided by Eli Lilly and Company Ltd

	eligible if episodes of regrowth have been observed on the affected areas over the past 8 years).
Intervention(s)	- Baricitinib 4 mg, administered orally. - Baricitinib 2 mg, administered orally.[d]
Comparator(s)	Placebo, administered orally.
Outcome(s)	Percentage of participants achieving severity of alopecia tool (SALT) score of ≤20. See trial record for full list of other outcomes
Results (efficacy)	BRAVE-AA2 showed that at Week 36 the proportion of patients reaching 80 percent or more scalp hair coverage was achieved by 33 percent ($p \leqslant 0.001$) of patients treated with baricitinib 4-mg/day, 17 percent ($p \leqslant 0.001$) of patients treated with baricitinib 2-mg/day and three percent of patients in the placebo group, meeting the primary endpoint. The proportion of patients self-reporting at least 80 percent scalp hair coverage was significantly greater in the 2-mg and 4-mg groups compared to placebo ($p \leqslant 0.001$) by Week 36.[15]
Results (safety)	The most common treatment-emergent adverse events (TEAEs) in BRAVE-AA1 and BRAVE-AA2 included upper respiratory tract infections, headache and acne. No deaths or venous thromboembolic events (VTEs) were reported in the trials. The safety profile of baricitinib in the two studies was consistent with its known safety profile in patients with rheumatoid arthritis (RA) and atopic dermatitis (AD).[15]

ESTIMATED COST

Baricitinib is already marketed in the UK. The NHS indicative price for a 28 pack of 2mg or 4mg tablets both costing £805.56 per pack.[17]

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant guidance identified

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

No relevant guidance identified

OTHER GUIDANCE

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[d] Information provided by Eli Lilly and Company Ltd

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ADDITIONAL INFORMATION

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NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.