Transcript Details

This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/medical-industry-feature/targeting-neutrophilic-inflammation-in-bronchiectasis-an-emerging-approach/33184/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Targeting Neutrophilic Inflammation in Bronchiectasis: An Emerging Approach

Voiceover:

BRINSUPRI® (brensocatib) is indicated for the treatment of non-cystic fibrosis bronchiectasis (NCFB) in adult and pediatric patients 12 years of age and older. Please see end of video for important safety information.

Non-cystic fibrosis bronchiectasis is a chronic, progressive inflammatory disease that presents with chronic cough, sputum production, recurrent exacerbations,...[1,2]

...and abnormal dilation of the bronchi.[2]

Its pathogenesis is complex, driven by a "vicious vortex" of four key interconnected components...[3]

...including chronic neutrophilic airway inflammation.[3]

BRINSUPRI® (brensocatib) has a first-in-class mechanism of action that specifically targets neutrophilic inflammation.[2,4]

It is an oral, competitive, and reversible inhibitor of dipeptidyl peptidase 1, or DPP1.[2,5]

During neutrophil maturation, DPP1 activates proinflammatory neutrophil serine proteases, or NSPs.[5]

NSPs are key drivers of neutrophilic inflammation, and are implicated in pathogenesis and exacerbations of bronchiectasis.[4]

BRINSUPRI targets uncontrolled neutrophilic inflammation by inhibition of DPP1, blocking the activation of NSPs.[2,4,5]

Typically, neutrophils are mediators of the initial innate immune response to a stimulus, such as microbial infection.[6,7]

As neutrophils mature, DPP1 activates NSPs...[5]

...including neutrophil elastase, proteinase 3, and cathepsin G,...[4]

...which are packaged into granules in the cell.[8]

Upon an immune response to a stimulus such as microbial infection, neutrophils are directed through blood vessels towards inflammatory signals and chemokines.[4,6,7]

Following recognition of the microbe, they activate a range of cellular pathways.[7]

Through the action of NSPs and other processes, neutrophils can directly mediate microbial clearance by both intracellular and extracellular mechanisms.[4,6]

This includes intracellular NSPs to aid in phagocytosis...[4]

...the extracellular release of NSPs by degranulation...[7]

...and the release of web-like neutrophil extracellular traps, or NETs, which physically trap microbes.[4,7]

Normally, after successful destruction of the invading pathogen, feedback mechanisms initiate neutrophil cell death...[6]

...and subsequent clearance by macrophages.[6] This process is important for the resolution of inflammation...[9]

...ensuring that the neutrophil response and NSP activity does not go unchecked, preventing unnecessary damage to the host tissue.[6,9]

In chronic inflammatory conditions, such as bronchiectasis, the neutrophil response remains uncontrolled, leading to increased numbers of tissue-resident neutrophils with increased survival and excessive release of NSPs.[4,10,11]

This uncontrolled neutrophil response and release of NSPs can impair defense against bacterial infection and mucociliary clearance.[10,12] It can also promote mucus hypersecretion and proteolytic degradation of elastin and other extracellular matrix components...[10,12]

...contributing to permanent lung destruction and disease progression.[10,12]

In bronchiectasis, excessive NSP levels have been associated with increased airway bacterial load, and disease progression, with a risk of exacerbation and lung function decline.[13]

The oral DPP1 inhibitor, BRINSUPRI...[2,5]

...binds to DPP1 in neutrophils, inhibiting its enzymatic activity...[2,5]

...which can thereby reduce active NSPs stored in mature neutrophils.[2,5]

This has been shown in cell-based assays to reduce the activity of proinflammatory NSPs.[5]

By blocking activation of NSPs, BRINSUPRI presents a first-in-class mechanism for treatment of non-cystic fibrosis bronchiectasis, targeting neutrophilic inflammation.[2,4,5]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Dermatologic Adverse Reactions

Treatment with BRINSUPRI is associated with an increase in dermatologic adverse reactions, including rash, dry skin, and hyperkeratosis. Monitor patients for development of new rashes or skin conditions and refer patients to a dermatologist for evaluation of new dermatologic findings.

Gingival and Periodontal Adverse Reactions

Treatment with BRINSUPRI is associated with an increase in gingival and periodontal adverse reactions. Refer patients to dental care services for regular dental checkups while taking BRINSUPRI. Advise patients to perform routine dental hygiene.

Live Attenuated Vaccines

It is unknown whether administration of live attenuated vaccines during BRINSUPRI treatment will affect the safety or effectiveness of these vaccines. The use of live attenuated vaccines should be avoided in patients receiving BRINSUPRI.

ADVERSE REACTIONS

The most common adverse reactions ≥2% in the ASPEN trial included upper respiratory tract infection, headache, rash, dry skin, hyperkeratosis, and hypertension. The safety profile for adult patients with NCFB in WILLOW was generally similar to ASPEN, except for a higher incidence of gingival and periodontal adverse reactions.

Less Common Adverse Reactions

Liver Function Test Elevations

In ASPEN, there was an increase from baseline in average ALT, AST, and alkaline phosphatase levels at all time points from Week 4 through Week 56 in both BRINSUPRI 10 mg and 25 mg arms compared to placebo. The incidence of ALT >3X upper limit of normal (ULN) was 0%, 1.2%, and 0.9%; the incidence of AST >3X ULN was 0.2%, 0.3%, and 0.5%; and the incidence of alkaline phosphatase >1.5X ULN was 2.5%, 4.1%, and 4.0% in patients treated with placebo and BRINSUPRI 10 mg and 25 mg, respectively.

Skin Cancers

In ASPEN, the incidence of skin cancers among patients treated with BRINSUPRI 10 mg and 25 mg was 0.5% and 1.9%, respectively, compared to 1.1% in placebo-treated patients.

Alopecia
In ASPEN, the incidence of alopecia among patients treated with BRINSUPRI 10 mg and 25 mg was 1.5% and 1.6% respectively, compared to 0.4% in placebo-treated patients.

USE IN SPECIFIC POPULATIONS
Pregnancy: There are no clinical data on the use of BRINSUPRI in pregnant women.

Lactation: There is no information regarding the presence of BRINSUPRI and/or its metabolite(s) in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BRINSUPRI and any potential adverse effects on the breastfed child from BRINSUPRI or from the underlying maternal condition.

Pediatric use: The safety and effectiveness of BRINSUPRI for the treatment of NCFB have been established in pediatric patients aged 12 years and older. Common adverse reactions in pediatric patients aged 12 years and older enrolled in ASPEN were consistent with those in adults. The safety and effectiveness of BRINSUPRI have not been established in pediatric patients younger than 12 years of age.

INDICATION
BRINSUPRI is indicated for the treatment of non-cystic fibrosis bronchiectasis (NCFB) in adult and pediatric patients 12 years of age and older.

Please see full Prescribing Information.

References:

1. Chalmers JD, et al. *Nat Rev Dis Primers.* 2018;4(1):45.
2. Chalmers JD, et al. *N Engl J Med.* 2020;383(22):2127-2137.
3. Flume PA, et al. *Lancet.* 2018;392(10150):880-890.
4. Chalmers JD, et al. *Front Immunol.* 2023;14:1239151.
5. Cipolla D, et al. *Respir Res.* 2023;24(1):133.
6. Bekkering S, et al. *World J Hematol.* 2013;2(2):44-58.
7. Burn GL, et al. *Immunity.* 2021;54(7):1377-1391.
8. Cowland JB, et al. *Immunol Rev.* 2016;273(1):11-28.
9. Amulic B, et al. *Annu Rev Immunol.* 2012;30:459-489.
10. Dente FL, et al. *Mediators Inflamm.* 2015;2015:642503.
11. Bedi P, et al. *Am J Respir Crit Care Med.* 2018;198(7):880-890.
12. Gramegna A, et al. *Respir Res.* 2017;18(1):211.
13. Chalmers JD, et al. *Am J Respir Crit Care Med.* 2017;195(10):1384-1393.