Dermatologic Adverse Events Associated With Gamma Secretase Inhibitor Nirogacestat

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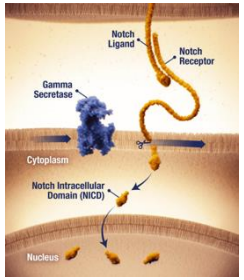
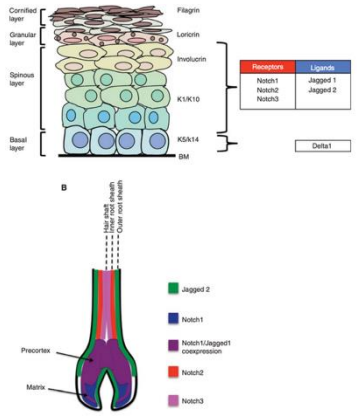
Disclosures: Connie Shi: VisualDX (Honoraria)

Background:

- Nirogacestat is a first-in-class small molecule gamma secretase inhibitor[1]
- FDA Approved Nov 2023 for desmoid tumors (1st FDA approved treatment)
  - Desmoid tumors highly express Notch[1,3]
  - Gamma secretase inhibitors block Notch signaling





- Dermatologic adverse events (dAEs) in clinical trials:[1]
  - Maculopapular rash (33%)
  - Acneiform dermatitis/folliculitis (13%)
  - Hidradenitis (9%)
- Cohort from phase-II trial:[2]
  - 9/17 patients (53%) with follicular/cystic lesions or hidradenitis suppurativa-like lesions
- Real-world data on dAEs with nirogacestat limited to case reports/case series

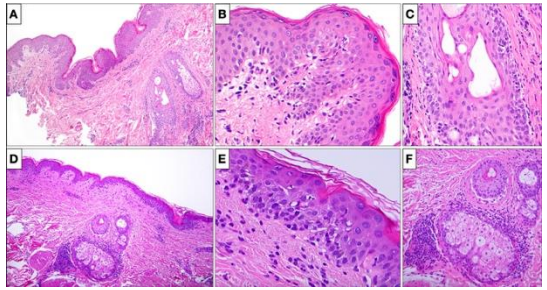
Methods:

- Retrospective analysis of patients treated with nirogacestat at two tertiary academic centers from 11/2023-11/2024
- Demographic information, details of dAEs, and impact on therapy continuation were collected
- dAE severity was graded using the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0

Results

- 13/28 patients (46.4%) experienced dAEs
  - Drug hypersensitivity eruption, 7/28 (25%)
    - Morbilliform morphology, average onset ~18 days after initiation
    - 5/7 (71.4%) Grade 2-3 eruptions
    - 3 patients (Grade 3) required temporary treatment hold. Able to resume therapy without rash recurrence.
    - No cases of severe cutaneous adverse reaction (SJS/TEN or DRESS)
    - Treatments: Topical steroids, H1 antihistamines, oral and/or IV steroids (Grade 3 eruptions)
- Follicular-based dAEs, 5/28 (17.9%)
  - Hidradenitis suppurativa, inflamed epidermal cysts, seborrheic dermatitis, keratosis pilaris, acne/folliculitis
  - All grade 1 (or Hurley Stage 1)
  - Onset months after nirogacestat initiation
    - 4/5 (80%) had no pre-existing history of such conditions
- Less common dAE's
  - Granuloma annulare (1/28)
  - Eczematous dermatitis (1/28)

Vacuolar interface changes with involvement of pilosebaceous unit



(A-C) Skin punch biopsy from left upper arm

(D-F) Skin punch biopsy from right posterior thigh

Discussion

- Main patterns of dAEs with nirogacestat are drug hypersensitivity eruptions and follicular-based dAEs
- Incidence of follicular reactions in our cohort (17.9%) was lower than the 52.9% in a prior analysis of a phase II trial cohort[2]
  - Under-recognition as a side effect of nirogacestat therapy?
- NOTCH signaling pathway is active in cell differentiation and homeostasis of hair follicles
  - Prevalence of follicular-based dAEs
  - Interface changes involving pilosebaceous units in hypersensitivity eruptions

Limitations

- Retrospective nature of the study, restriction to two tertiary centers
- Cohort size
- Further work needed to determine true association with rare dAE's such as granuloma annulare, eczematous dermatitis in this cohort

Conclusions

- Main patterns of dAEs with nirogacestat are drug hypersensitivity eruptions and follicular-based dAEs
- Drug hypersensitivity eruptions:
  - May require temporary dose hold (grade 2-3)
  - Do not recur with rechallenge
  - Do not prevent treatment continuation
- Follicular-based dAEs can include hidradenitis suppurativa, inflamed epidermal cysts, acne/folliculitis, seborrheic dermatitis, keratosis pilaris
  - These dAEs may be under-recognized in real-world practice

References

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2. O'Sullivan Coyne G, Woodring TS, Lee CCR, Chen AP, Kong HH. Hidradenitis Suppurativa-Like Lesions Associated with Pharmacologic Inhibition of Gamma-Secretase. J Invest Dermatol. 2018;138(4):979-981. doi:10.1016/j.jid.2017.09.051
3. 1. Nowell C, Radtke F. Cutaneous Notch Signaling in Health and Disease. Cold Spring Harb Perspect Med. 2013;3(12):a017772. doi:10.1101/cshperspect.a017772

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