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JAAD: One-year safety and efficacy of tapinarof cream for the treatment of plaque psoriasis: Results from the PSOARING 3 trial

- *What is the general condition, procedure or disease under study?*
  - The use of topinarof 1% cream QD in the treatment of mild to severe plaque psoriasis
    - MOA: topinarof binds and activates aryl hydrocarbon receptor (AhR), a transcription factor that downregulates IL17A & F, modulates filaggrin and loracrin expression, and increases antioxidant activity
    - In two phase 3 trials, topinarof demonstrated a significant decrease in physician global assessment (PGA) over 12 weeks when compared to vehicle (response rate 35.4% and 40.2%, respectively).
    - A phase 2 study demonstrated that efficacy was maintained for 4 weeks following 12 week treatment.

- *What were the research question(s)?*
  - Does topinarof 1% cream daily continue to be effective, safe and maintain a remission effect post 12 weeks of usage?
    - Design: Patients (18-75 yo) with mild, moderate or severe psoriasis (excluding scalp, fingernails palms, soles, toenails) had completed 12 weeks of previous trials.
    - %BSA affected was between 3% and 20%
    - Patients entering with PGA >=1 applied cream once daily until PGA=0, then discontinued
    - Patients entering with PGA=0 discontinued treatments unless worsening at q4 week follow ups.

- *Was the question answered to your satisfaction - validity? Do you trust the conclusions and recommendations?*
  - Yes, the study demonstrated that tapinarof cream 1% QD had continued improvement in efficacy beyond 12 weeks and was well tolerated with long-term use of up to 52 weeks
  - 40.9% of participants (312/763) achieved complete disease clearance (PGA = 0) at least once during the trial
    - 58.2% (302/519) of patients with PGA>2 at the beginning of the study achieved PGA = 0 or 1 at least once – indicating that the original trials may have not been long enough to truly assess efficacy.
  - For patients entering with PGA = 0 (n = 79), the total duration of the remission effect was 188.3 (92.8) days

        - For anybody who reached PGA = 0 at any time during the trial (n = 312), the total duration of remission effect off therapy was around 4 months
    - AEs included folliculitis (22.7%), contact dermatitis (5.5%), and upper respiratory tract infection (4.7%) which was consistent with previous trails
    - I do trust the recommendations by the authors. Results demonstrated that efficacy with longer treatment periods increases without affecting the rates of adverse events.
    - Notably, no tachyphylaxis was reported with up to 52 weeks of observation

- *Were these good questions? (impact, importance, interest and novelty). Does this article or research change your treatment or concept of this condition?*
    - I do believe these were good questions because our options for topical therapy are limited. For our patients with hesitation or contraindications to biologics, we oftentimes find ourselves in the this constant chase of acute flares with potent topical steroids which comes with significant risk (atrophy, telangiectasias, hypopigmentation, etc). Having a medication that is efficacious, tolerable and allows for significant remission without tachyphylaxis is extremely important for patients with mild to moderate psoriasis.

- *Does this study prompt or inspire a different and better study?*
    - This trial used a "forced withdrawal" design which may have underestimated how many patients would have achieved full clearance at the end of the study period since participants were asked to stop therapy once achieving PGA=0 to assess remission effect. This warrants a similar study that continues therapy until 40 weeks despite PGA score with a control arm (lacking in this study) to better elucidate long term effects.
    - Furthermore, a study that assesses more difficult to treat areas including palm, soles and scalp is warranted.
    - With its unique long remission effect, it would be interesting to see the efficacy of topinarof used as a maintenance topical following therapy with steroids and calcineurin inhibitors for acute flares.

JAMA DERM: Real-time Analysis of Skin Biopsy Specimens With 2-Photon Fluorescence Microscopy

- *What is the general condition, procedure or disease under study?*
    - The use of two-photon fluorescence microscopy in the evaluation of non-melanoma skin cancers.

- *What were the research question(s)?*
    - Does two-photon fluorescence microscopy (TPFM) have the same diagnostic potential (on the basis of sensitivity, specificity and accuracy) for identifying non-melanoma skin cancers (NMSC) as conventional paraffin histologic analysis?

        - Paraffin sectioning is a multiple day process that requires fixation and staining to develop the slide. Frozen sections, while quick are subject to inter-user variability and disruptions artifacts. With TPFM, images are generated via properties of tissues (refraction, absorption, etc) and can be viewed in vivo with direct fluorescent staining of nuclei and stroma to resemble conventional histology (without the use of H&E).
        - Design: Comparative effectiveness pilot study. 29 excised biopsies were examined via TPFM and conventional histology. Specimen were first stained with DNA label acridine orange and the eosin-analogue sulforhodamine 101. The 1040 nm laser would excite florescence from these chromophores and be picked up by channels and viewed on a monitor. The specimens then underwent conventional processing (stains are completely removed during paraffin processing by xylene). Of the image pairs, 12 were used for a training set and 15 were randomly masked for evaluation by a dermatopathologist (DP) with no experience with TPFM.
            - For each pair, the DP was randomly shown either TPFM or permanent section and asked to comment on dx (benign, BCC, SCC, other). After a 2-week washout, the second half of the set was evaluated the same.
- *Was the question answered to your satisfaction - validity? Do you trust the conclusions and recommendations?*
    - For overall NMSC diagnosis, TPFM had a 93% sensitivity, 100% specificity and 93% accuracy
    - For BCC, TPFM had 100% specificity, sensitivity and accuracy
    - For SCC, TPFM had 89% sensitivity, 100% specificity and 93% accuracy
    - While these numbers sound promising, the cohort size was very small. There was no mention of NMSC subtypes (especially for tumors that may exhibit characteristics of both BCC and SCC). The diagnoses were subject to selection bias as it was in a multiple choice format.
    - Furthermore, these biopsy specimens are superficial (can only penetrate 100 microns). The authors suggest that this technique may be useful for Mohs Surgery where rapid point of care (POC) processing is warranted, but this would require bi-sectioning and breadloafing for complete margin evaluation which defeats the purpose of its “rapid” interpretation.

- *Were these good questions? (impact, importance, interest and novelty). Does this article or research change your treatment or concept of this condition?*
    - I think this is an interesting concept as the images appear to mimic conventional H&E staining with more efficient processing. As the authors mention, 70% of patients with a diagnosis of NMSC prefer to have same-day biopsy and treatment to avoid incurred additional costs or inconvenience. Oftentimes, we treat patients with suspicious lesions and a history of recurrent NMSCs with ED&C in anticipation of the biopsy result. Theoretically, it would be great to have

an accurate histological tool that could be used in real time to help mitigate these decisions.

- *Does this study prompt or inspire a different and better study?*
    - Further studies with a larger sample size, including multiple variations of NMSC is warranted. Furthermore, having multiple double-blinded dermatopathologists without multiple choice selections for diagnosis would reduce inter-rater and selection bias.

FIXING THE CONCEPT OF THE NEUTROPHILIC FIXED DRUG ERUPTION

By Warren R. Heymann, MD, FAAD
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Can anyone other than your mother recognize you from your baby photograph? The concept that lesions have lives is nothing new — clinical and histopathological changes vary from lesional inception to involution. Despite this truism, confusion about nosology for many dermatoses, based on the timing of assessment, is replete in the medical literature. This commentary will focus on the neutrophilic fixed drug eruption (nFDE).
In 1987, Van Voorhees and Stenn detailed the case of a 79-year old man with a urinary tract infection who developed a trimethoprim/sulfamethoxazole-induced FDE. Histological studies were performed on days 1 and 5 after the drug exposure. The 1-day-old lesion showed a hypersensitivity response suggestive of Sweet's syndrome: diffuse spongiosis, dermal edema and hemorrhage, eosinophils, and neutrophilic polymorphonuclear leukocyte abscess formations. At 5 days the histological changes were characteristic of a FDE. The authors underscored the dynamic changes that occur in the evolving FDE lesions, with neutrophilic infiltration appearing early. (1)

The term nFDE was coined by Agnew and Oliver when discussing the case of a 49-year-old Samoan man who developed a bullous FDE due to amoxicillin-clavulanic acid at the same site of a prior eruption 5 years earlier when antibiotics (presumably the same) were administered for furunculosis. A biopsy was performed on the new lesion 16 hours after the onset of the eruption. Histopathology revealed an intact epidermis with intraepidermal collections of neutrophils, serum and eosinophils. Within the dermis, a marked perivascular and interstitial mixed inflammatory infiltrate with a predominance

of intact neutrophils was appreciated. Importantly, no interface changes were seen. The authors favored this lesion being a FDE rather than drug-induced Sweet's syndrome because of its fixed location and the absence of systemic symptoms. (2)

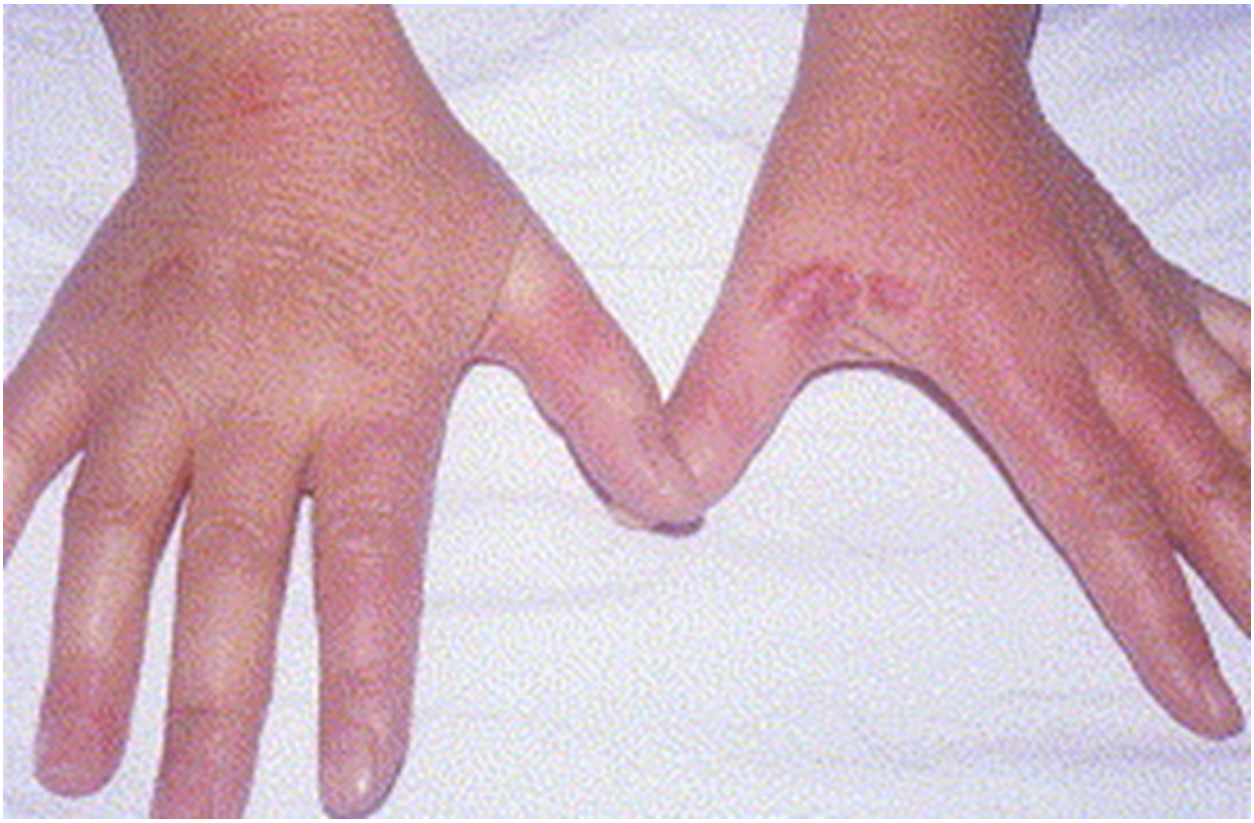

Image from reference 3.Similar cases have been reported subsequently. A 51-year-old woman developed nFDE to naproxen. Histologically this case was similar to the original report in that there was no mention of interface changes. The timing of the biopsy relative to the onset of the rash was not reported. The authors questioned if nFDE is a distinct entity or just the earliest presentation of a FDE. (3) In other cases of nFDE, however, interface changes including necrotic keratinocytes have been reported with dermal neutrophilic infiltration (4,5) that may be accompanied by eosinophils. (5) Neither case reported systemic symptoms.

Acar et al reported the case of a 65-year-old woman who developed nFDE twice in response to gabapentin, with both episodes accompanied by fever and neutrophilic leukocytosis. A biopsy performed on day 7 of the initial eruption displayed a neutrophil-rich infiltrate without attendant vacuolar alteration or necrotic keratinocytes. The authors opined that their patient had nFDE rather than drug-induced Sweet's syndrome because the lesions had the same distribution in both episodes and the neutrophilic infiltration was not as intense as usually observed in Sweet's syndrome. (6)

Histologically, the hallmarks of FDE are vacuolar alteration at the epidermal-dermal junction, individually necrotic keratinocytes, and a perivascular infiltrate of lymphocytes and eosinophils. FDEs are mediated by CD8+ memory T cells in genetically predisposed patients. According to Anderson and Lee: "Within 24 hours of ingestion of a

culprit medication, these CD8+ T cells migrate upward in the epidermis, produce cytokines such as interferon-gamma and TNF-alpha, and take on the phenotype of a natural killer cell, expressing the cell surface molecule CD56 as well as the cytotoxic molecules granzyme B and perforin… At the same time, CD4+ Foxp3+ regulatory T cells migrate into the epidermis, curbing the damage inflicted by the CD8+ T cells. The action of the CD4+ regulatory T cells, which includes the production of the anti-inflammatory cytokine IL-10, explains the self-limited nature of FDEs." (7)

In a fascinating case report of a 56-year-old man with chronic myeloid leukemia, Bergman et al reported two episodes of a neutrophilic dermatosis, with attendant flu-like symptoms, due to the multiple tyrosine kinase inhibitor dasatinib. Lesions recurred at the same sites; intriguingly, these episodes occurred 5 years apart, while on dasatinib for the duration. The authors used the descriptive term "recurrent and fixed neutrophilic dermatosis" in this case. (8)

Li and Kazlouskaya sought to determine if nFDE is a distinct entity, a rare variant, or an early stage of FDE. They retrospectively analyzed 16 cases of FDE and demonstrated that neutrophils are relatively common (11/16, 68%) and that cases with abundant neutrophils have a significantly shorter onset-to-biopsy interval (3.7 versus 16.9 days). Their findings support the concept that nFDE is an early phase of FDE rather than a disorder *sui generis.* (9)

As trite as it is, clinical-pathologic correlation is of paramount importance in deciphering neutrophilic dermatoses. On a histologic basis alone, many of the features described could be observed in Sweet's syndrome, adult-onset Still disease, autoinflammatory disorders, non-bullous bullous pemphigoid, or prurigo pigmentosa. A good clinical history and morphologic description will help guide your dermatopathologist. Conversely, if you get a report of neutrophilic involvement with or without classical features of FDE, it may be worthwhile determining if drugs are the culprit of the rash.

Point to Remember: In most circumstances, neutrophils may be observed early in fixed drug eruptions, rather than representing a distinct entity known as "neutrophilic fixed drug eruption". For patients with systemic symptoms, however, further research is required to determine if neutrophilic fixed drug eruption, drug-induced Sweet's syndrome, or recurrent and fixed neutrophilic dermatosis are part of a spectrum of disease.

Our expert's viewpoint

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The concept of a “neutrophilic FDE” is challenging to understand because: FDE is classically a lichenoid interface dermatitis, this term broadens the spectrum of histopathologic findings, and frankly because some prior descriptions of this entity actually represent a neutrophilic dermatosis, namely Sweet’s syndrome. At least two reports describe edematous plaques and variable systemic findings associated with classic histopathologic features of Sweet’s syndrome. (2, 6) Recurrence at prior sites of disease should not be used in isolation when distinguishing FDE from other dermatoses, and systemic symptoms are not always present in neutrophilic dermatoses. Other descriptions identify neutrophilic dermal infiltrates in examples of FDE with otherwise standard clinicopathologic features. (4, 5) In this scenario, this feature is noteworthy but should not prove ultimately distracting. Lastly, a few references do support the basis for considering a neutrophilic infiltrate as a manifestation of early FDE. However, prominent spongiosis and neutrophil exocytosis were described in these cases, and clinical features and distribution were more typical of FDE than Sweet’s syndrome. (1, 3) Of course, the best corroborating evidence is a later biopsy with standard features. (1) This idea is also easier to accept since I have observed cases of EM, Stevens-Johnson syndrome, and toxic epidermal necrolysis in which the first biopsy obtained at onset was primarily spongiotic with variable neutrophilic or eosinophilic spongiosis prior to the appearance of vacuolar change, keratinocyte apoptosis, and clinical evidence of necrosis. The following approach is suggested: classic histopathologic features of Sweet’s syndrome should be reported as such; otherwise standard cases of FDE with dermal neutrophils should be described as “FDE with neutrophilic infiltrate;” and a differential diagnosis should be provided for cases with clinical findings of FDE but with prominent spongiosis and neutrophil exocytosis instead of interface tissue reaction. In the last scenario, clinical follow-up and/or another biopsy should permit distinction between “the early stage of FDE” and “neutrophilic dermatosis.” Of note, this approach does not require the term “neutrophilic FDE,” which is likely to produce confusion.

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