Unexpected benefits of topical dapsone or clindamycin/benzoyl peroxide in combination with a retinoid in treatment of comedonal acne

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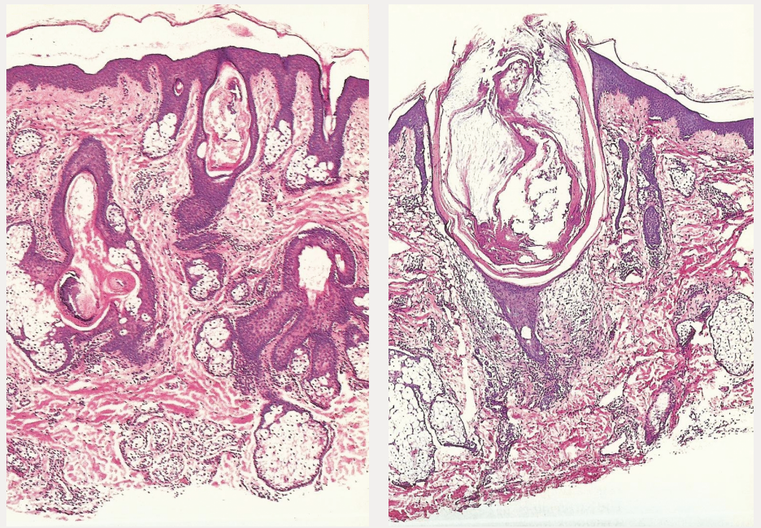
BACKGROUND

- The current dogma regarding acne pathogenesis holds that:[1,2]
  - Microcomedones develop from hyperkeratinization, abnormal epithelial desquamation, and sebaceous gland hyperplasia.
  - Comedones ("noninflammatory" acne) form with the continued accumulation of keratins and sebum.
  - Inflammatory acne forms when the immune system responds to the proliferation of *Propionibacterium acnes.*
- A growing body of histological and biochemical evidence suggests that inflammation occurs within normal-appearing acne skin, as well as open and closed comedones, and that the classification of comedonal lesions as "noninflammatory" may be a misnomer.
  - Inflammation is present in and around the sebaceous gland in histological samples of open and closed comedones[3] (Figure 1).
  - A study of normal-appearing skin from acne patients demonstrated the increased presence of $CD3^+$ and $CD4^+$ T cells and macrophages in the perifollicular and papillary dermis.[4]
  - Neutrophils have been found localized to microcomedones and comedones.[5]
  - The proinflammatory cytokine tumor necrosis factor (TNF)-α has been found in open comedones.[6]
  - The proinflammatory cytokine IL-1 has been shown to be upregulated perifollicularly in the uninvolved skin of acne patients.[4]
  - IL-1α can induce comedonal formation in vivo and in vitro.[4,7]

Figure 1: Inflammation in normal facial skin from a patient with acne (left); open comedo (right)



- Current consensus treatment guidelines recommend topical retinoids (monotherapy) for comedonal acne treatment.[8]
- Dapsone is an anti-inflammatory agent approved for the topical treatment of acne.
  - Dapsone has been found to be well tolerated and effective when used as monotherapy[9] or in combination with adapalene gel[10] to treat acne vulgaris.
- Agents with anti-inflammatory properties, including dapsone, clindamycin, and benzoyl peroxide (BPO) have been found effective at reducing comedonal acne.[9,11,12]

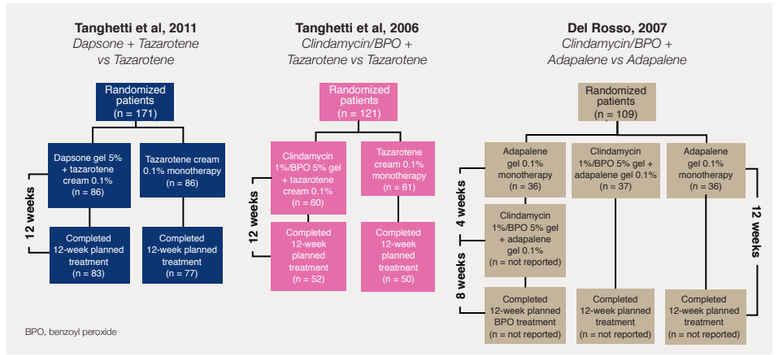
PURPOSE

- To evaluate the response of comedonal acne to combination treatment with topical retinoids plus topical agents having anti-inflammatory properties, by examining data from 3 separate clinical trials.[11-13]

STUDY DESIGNS

- Study design and patient demographics were similar for all 3 studies (Figure 2).
- Details can be found in the primary publications.[13-15]

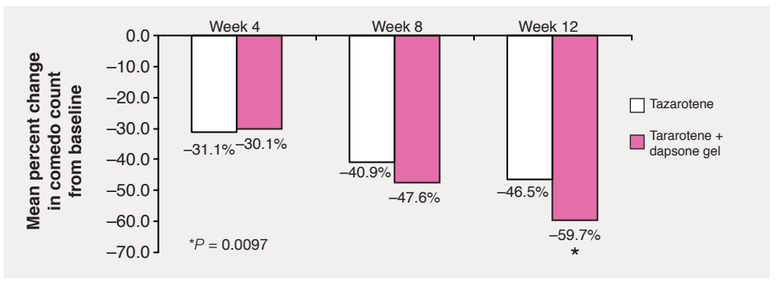
Figure 2: Study designs



RESULTS

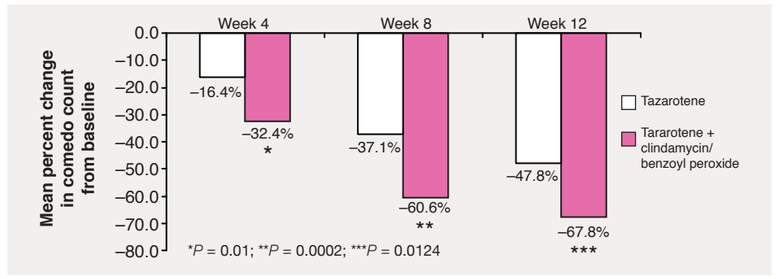
- Tanghetti et al, 2011
  - Significant decreases from baseline comedonal lesion counts were seen with both tazarotene 0.1% cream monotherapy and tazarotene 0.1% cream plus dapsone 5% gel combination therapy at 12 weeks (Figure 3).
  - Tazarotene 0.1% cream plus dapsone 5% gel combination therapy resulted in significantly greater reductions in comedonal lesion counts from baseline than tazarotene 0.1% cream monotherapy at week 12 ($P = 0.0097$).

Figure 3: Mean percent change in comedo count from baseline (Tanghetti et al, 2011)



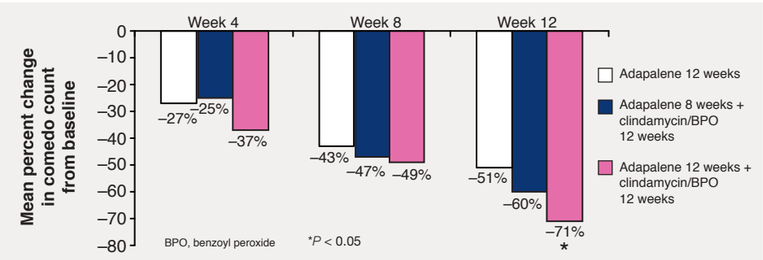
- Tanghetti et al, 2006
  - Significant decreases in comedonal lesion counts from baseline were achieved with both tazarotene 0.1% cream monotherapy and tazarotene cream 0.1% plus clindamycin 1%/BPO 5% combination therapy at 12 weeks (Figure 4).
  - Tazarotene 0.1% cream plus clindamycin 1%/BPO 5% combination treatment produced significantly greater reductions in comedonal lesion counts from baseline than tazarotene 0.1% cream monotherapy at weeks 4 ($P = 0.01$), 8 ($P = 0.0002$), and 12 ($P = 0.0124$).

Figure 4: Mean percent change in comedo count from baseline (Tanghetti et al, 2006)



- Del Rosso, 2007
  - Significant decreases from baseline comedonal lesion counts occurred in all 3 treatment groups at week 12 (Figure 5).
  - Combination treatment with adapalene 0.1% gel (12 weeks) plus clindamycin 1%/BPO 5% gel (12 weeks) resulted in significantly greater reductions in lesion counts than with adapalene 0.1% gel alone at week 12 ($P = 0.05$).
  - All other differences were not statistically significant.

Figure 5: Mean percent change in comedo count from baseline (Del Rosso, 2007)



SUMMARY

- Combining a retinoid with an anti-inflammatory or antibacterial agent can effectively treat comedonal acne.
- Concurrent use of an anti-inflammatory or antibacterial agent with a retinoid enhances the efficacy against comedonal acne relative to the use of a retinoid alone.

CONCLUSIONS

- Based on the histologic, biochemical, and functional (ie, therapeutic responsiveness) evidence, inflammation appears to be present at all stages of acne, including early comedonal acne. These data suggest that the term "noninflammatory" is inaccurate as a descriptor of these acne lesions. It would be more accurate to refer to this type of acne as comedonal, to include microcomedones, and open and closed comedones.
- The combination of an anti-inflammatory agent, such as dapsone, or an antibacterial agent, such as clindamycin, with a retinoid is effective, and potentially more effective than a retinoid alone, for the treatment of comedonal acne.
- Dapsone is an anti-inflammatory agent that has not shown activity against *P acnes*. Although clindamycin has both antibacterial and anti-inflammatory properties, its effects on comedonal lesions observed in these studies may have been due to its anti-inflammatory actions.
- These data challenge existing treatment guidelines, which stipulate the use of a retinoid alone to treat comedonal acne.

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