Topical Clindamycin For Acne Vulgaris: Pharmacovigilance Safety Review and Retrospective Analysis of Gastrointestinal Events

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SYNOPSIS

- Clindamycin, a lincosamide antibiotic, was the 125th most prescribed medicine in the US in 2020[1,2]
- Topical formulations of clindamycin combined with topical benzoyl peroxide (BPO) or a retinoid are used for acne vulgaris (AV) treatment[3,4]
- Oral clindamycin carries warnings and contraindications regarding the development of gastrointestinal (GI) adverse events (AEs) including *Clostridioides difficile* (*C. difficile*) colitis[5]
- While topical formulations have similar warnings and contraindications,[6-8] the real-world incidence of these AEs has not been studied

OBJECTIVE

- To summarize available safety data on topical clindamycin when used for AV treatment

METHODS

- Safety data from published literature, previously unpublished pharmacovigilance data, and two unpublished retrospective cohort studies were reviewed, with a focus on gastrointestinal AEs following topical administration of clindamycin monotherapy or combination therapy for AV

RESULTS

Case Reports

METHODS: Case reports were identified through literature search on GI AEs associated with topical clindamycin use for AV treatment

RESULTS: Only 4 case reports of topical clindamycin-associated GI AEs have been published; none were recent (1981 to 1997)

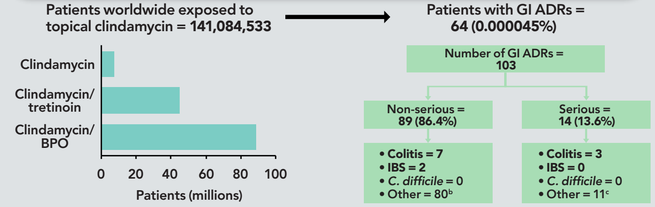
- ***C. difficile* pseudomembranous colitis**[9]
  Clindamycin phosphate (dose unknown) bid
- ***C. difficile* pseudomembranous colitis**[10]
  Clindamycin HCl 1% and BPO 5% (separate formulations) bid
- **Diarrhea**[11]
  Clindamycin 1% bid
- **Severe abdominal cramping + diarrhea**[12]
  Clindamycin phosphate 1% (dosage unknown)

AE, adverse event; AV, acne vulgaris; bid, twice daily; BPO, benzoyl peroxide; *C. difficile, Clostridioides difficile*; GI, gastrointestinal; HCl, hydrochloride.

Pharmacovigilance Data

METHODS: Worldwide pharmacovigilance data were analyzed from Jan 1, 1900–Dec 31, 2022 for topical clindamycin monotherapy or combination therapy with BPO or tretinoin and GI ADRs[a]

RESULTS: Of the **hundreds of millions patients** exposed to topical clindamycin, **<0.0001% of patients** reported GI ADRs, including colitis or IBS; over 85% of events were non-serious



[a]ADRs from spontaneous individual case safety reports, including reports from healthcare professionals, consumers, scientific literature, competent authorities worldwide, and serious ADRs from solicited non-interventional studies.
[b]Diarrhea (37 events); abdominal (21); vomiting (7); nausea (5); constipation, dyspepsia, flatulence (2 each); anal fissure, frequent bowel movements, hematochezia, mucous in stools (1 each).
[c]Abdominal (5 events); constipation, diarrhea, hematochezia, nausea, proctalgia, vomiting (1 each).
Limitations: delays between drug use and related ADR detection, ADR underreporting, and missing or duplicated reports.
ADR, adverse drug reaction; BPO, benzoyl peroxide; *C. difficile, Clostridioides difficile*; GI, gastrointestinal; IBS, irritable bowel syndrome.

Retrospective Analyses

Published Data

- In a retrospective study of patients receiving antibiotic prescriptions from 1977–1980, there were 0 colitis reports from any of the 1,124 patients estimated to have received topical clindamycin[13]
  - It was not noted if the prescriptions were for AV

Unpublished Studies

- As there is little published retrospective data on this topic, we carried out 2 retrospective cohort studies using the IBM Explorys database

METHODS: Electronic medical records from 53 million US patients (from >40 healthcare delivery networks) were retrospectively examined in patients aged ≥10 years with a first AV diagnosis linked to a dermatology encounter between Jan 1, 2011 and either Jan 31, 2019 (study 1) or July 1, 2019 (study 2)

STUDY 1: Examined frequency of topical clindamycin prescriptions in patients:

- With an AV diagnosis in the past year
- With or without a history of inflammatory bowel disease (IBD; Crohn's disease or ulcerative colitis)
- Without any prior clindamycin treatment

STUDY 2: Determined incidence of pseudomembranous colitis diagnoses in patients:

- With an initial topical clindamycin prescription for AV within 30 days
- Without a prior diagnosis of colitis

RESULTS:
- **Rates of colitis/pseudomembranous colitis are low** in patients with AV prescribed topical clindamycin
- Physicians prescribe clindamycin for AV treatment equally to patients with or without IBD history

STUDY 1: AV patients with or without IBD prescribed topical clindamycin within 1 year of first AV diagnosis (n=70,666)

IBD History	Total Patients	Patients Prescribed Topical Clindamycin, n (%)
None	70,151	14,495 (20.7%)
IBD[a]	515	98 (19.0%)
Crohn's disease	301	55 (18.3%)
Ulcerative colitis	262	52 (19.8%)

STUDY 2: Incidence of pseudomembranous colitis within 30 days of initial prescription for AV treatment (n=28,422)

	Patients, n	IBD History, n (%)	Pseudomembranous Colitis Diagnosis, n (%)
Total	28,422	254 (0.9)	3 (0.01)[b]
Topical clindamycin treatment			
Clindamycin	5,977	66 (1.1)	0[b]
Clindamycin + (tretinoin or BPO)	12,001	94 (0.78)	2 (0.02)[b]
Clindamycin + (oral clindamycin)	34	0	1 (2.9)[b]
Other treatment[c]	10,410	94 (0.9)	0

[a]Some patients had diagnoses for both Crohn's disease and ulcerative colitis.
[b]Patients had no history of IBD.
[c]Tretinoin monotherapy (n=10,307), oral clindamycin monotherapy (n=84), or oral clindamycin + topical tretinoin (n=19).
Limitations: limited generalizability of the data, underreporting of AEs, lack of information regarding whether prescriptions were filled and how much was used, and no control for other prescriptions known to be associated with GI AEs (eg, non-clindamycin oral antibiotics).
AE, adverse event; AV, acne vulgaris; BPO, benzoyl peroxide; GI, gastrointestinal; IBD, inflammatory bowel disease.

Clinical Trials

METHODS: Safety data for GI AEs were gathered from published articles indexed on PubMed® or from US FDA New Drug Applications[3] of pivotal clinical studies of topical clindamycin for AV

RESULTS: GI AE rates in 8 phase 3[a] pivotal clinical trials of clindamycin-containing topicals for AV **were low (up to 1.4%) and comparable to tretinoin, BPO, and vehicle**[14-18]

2,672 participants (safety populations) with AV treated with:
- Clindamycin phosphate 1% or 1.2%
- Clindamycin phosphate 1.2%/BPO 2.5%–5%
- Clindamycin phosphate 1.2%/tretinoin 0.025%
- Clindamycin phosphate 1.2%/adapalene 0.15%/BPO 3.1%

→ **GI-related AE rate[b] up to 1.4% (38/2,672)**

1,621 participants (safety populations) with AV treated with:
- Tretinoin 0.025%
- BPO 5%
- Vehicle

→ **GI-related AE rate[b] Tretinoin: up to 2.4% (11/464) BPO: up to 0.96% (2/208) Vehicle: up to 1.1% (10/949)**

[a]One phase 2 study was included as the data had been pooled with those from the phase 3 study.[17]
[b]Rates are maximal calculated values, assuming reported AEs occurred in different individuals and are mutually exclusive (eg, multiple GI AEs or GI infection-related AEs did not occur in the same individual); as such, the actual percentage of participants who reported AEs may be lower than calculated.
Limitations: see footnote b.
AE, adverse event; AV, acne vulgaris; BPO, benzoyl peroxide; FDA, Food and Drug Administration; GI, gastrointestinal.

CONCLUSIONS

- A review of published case reports, worldwide pharmacovigilance data, retrospective US prescription data, and clinical trials safety data demonstrate that the incidence of colitis or pseudomembranous colitis in patients with or without IBD exposed to topical clindamycin is extremely low
  - Global incidence of GI-related AEs (via pharmacovigilance) is estimated at 0.000045%
  - Rates of pseudomembranous colitis within 30 days of initial topical clindamycin prescription for AV (without concurrent oral clindamycin prescription) are <0.02%
  - Rates of GI AEs in pivotal clinical trials were similar for topical clindamycin (monotherapy or combination) versus tretinoin, BPO, or vehicle

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AUTHOR DISCLOSURES

Natalia M. Pelet del Toro and Andrew Strunk have no conflicts of interest. Jashin Wu has served as an investigator, consultant, or speaker for AbbVie, Almirall, Amgen, Arcutis, Bausch Health US, Boehringer Ingelheim, Bristol-Myers Squibb, Dermavant, Dr. Reddy's Laboratories, Eli Lilly, Galderma, Janssen, LEO Pharma, Novartis, Regeneron, Sanofi Genzyme, Sun Pharma, and UCB. Linda Stein Gold has served as investigator/consultant or speaker for Ortho Dermatologics, LEO Pharma, Dermavant, Incyte, Novartis, AbbVie, Pfizer, Sun Pharma, UCB, Arcutis, and Lilly. James Q. Del Rosso has served as a consultant, investigator, and/or speaker for Ortho Dermatologics, Abbvie, Amgen, Arcutis, Dermavant, EPI Heath, Galderma, Incyte, LEO Pharma, Lilly, MC2 Therapeutics, Pfizer, Sun Pharma, and UCB. Robert T. Brodell has served as an investigator for Novartis and Corevitas; owns stock in Veradermics, Inc; and has received educational grants from Pfizer. George Han is or has been an investigator, consultant/advisor, or speaker for AbbVie, Athenex, Boehringer Ingelheim, Bond Avillion, Bristol-Myers Squibb, Celgene, Eli Lilly, Novartis, Janssen, LEO Pharma, MC2, Ortho Dermatologics, PellePharm, Pfizer, Regeneron, Sanofi Genzyme, Sun Pharma, and UCB.

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