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An overview of benvitimod for the treatment of psoriasis: a narrative review

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Key words: efficacy, safety, psoriasis, benvitimod, nonsteroidal, adherence, management

Abstract:

Introduction: The most frequently prescribed first-line treatment for limited (mild-to-moderate) psoriasis is topical corticosteroids, which are associated with a number of adverse effects with long term use. Benvitimod is an aryl hydrocarbon receptor immunomodulator that is both efficacious and tolerable for use in patients with mild to severe psoriasis with a body surface area (BSA) range of 1-20%.

Areas covered: In this review, the authors conducted a PubMed and Google Scholar search of key words and a review of clinical trials. They discuss the targeted mechanism of action for psoriasis, efficacy and safety profile of topical benvitimod, and its indications. Benvitimod affects key regulators of psoriasis, including proinflammatory markers and skin barrier proteins. Benvitimod is well-tolerated in patients with mild to severe plaque psoriasis. Treatment-emergent adverse events (TEAEs) include pruritus, contact dermatitis, and folliculitis; however,
the majority of TEAEs were mild to moderate in severity, and most resolved without further treatment. A limitation of this study includes a small number of trials due to the novelty of the drug.

Expert opinion: Benvitimod may serve as a good alternative for psoriatic patients who desire a nonsteroidal topical option. The usefulness of benvitimod may be limited by prior authorizations that discourage health care providers from prescribing the medication and poor outcomes.

Article Highlights:

- Benvitimod is an aryl hydrocarbon receptor immunomodulator that is both efficacious and tolerable for use in patients with mild to severe psoriasis with a body surface area (BSA) range of 1-20%.
- Benvitimod leads to improvements in Physician Global Assessment (PGA) and Psoriasis Area and Severity Index (PASI) scores compared to vehicle, placebo, and positive controls.\(^8\text{-10,12,15}\)
- Benvitimod is well tolerated in clinical trials for patients with psoriasis.
- Benvitimod may face similar struggles as its competitors when it reaches the market due to limitations from prior authorization, particularly medication adherence issues with patients who meet criteria.
- Some methods to increase medication adherence in this population include increasing follow up visits, strengthening the doctor-patient relationship, providing customized physician training sessions, and addressing unresolved medication concerns or beliefs about alternative forms of medicine.
1. Introduction:

Psoriasis is a chronic dermatologic condition that has a great impact on the lives of patients and caregivers. Topical agents, such as corticosteroids, vitamin D₃ analogs, tazarotene, and calcineurin inhibitors, are the current standard of care for patients with limited psoriasis with mild to moderate severity, with topical corticosteroids (TCS) prescribed most frequently.¹ TCS-related adverse effects can be local, such as dermal atrophy and cutaneous infection or systemic, such as hypothalamic-pituitary-adrenal (HPA) axis suppression.²,³ Well-tolerated, nonsteroidal, topical therapies are needed for long-term use.

Benvitimod is a novel topical therapy for psoriasis. The bacteria *Photorhabdus luminescens* produces the metabolite 3,5-dihydroxy-4-isopropylstilbene (benvitimod) in the *Heterorhabditis* genus nematode. Benvitimod is an aryl hydrocarbon receptor (AhR) modulating agent.⁴ AhR is a ligand-dependent transcription factor that modulates the body’s inflammatory and immune responses in psoriasis. Benvitimod downregulates pro-inflammatory cytokines IL-17A and IL-22, inhibiting keratinocyte hyperproliferation.⁵,⁶ Benvitimod also possesses antioxidant capabilities. The drug may scavenge reactive oxygen species via both intrinsic characteristics, as well as through partial activation of the Nrf2 pathway, which maintains homeostasis.⁶

Furthermore, benvitimod induces epidermal differentiation. In a study treating primary human keratinocytes with either dimethyl sulfoxide (DMSO) or 0.1 and 1.0 µM of benvitimod, benvitimod stimulated transcription of the genes of filaggrin, hornerin, and involucrin proteins in keratinocytes, promoting the skin’s water-tight barrier (Figure 1).⁶ Benvitimod is theorized to possess antimicrobial abilities against gram-positive bacteria and fungi. The drug alters the skin’s microbiome and improves the skin’s condition.⁷ In this review, we discuss the targeted
mechanism of action for psoriasis, efficacy, and safety of topical benvitimod, as well as its indications.

2. Methods:

A PubMed search included the key words psoriasis, safety, tolerability, topical corticosteroids, side effects, treatment, long term effects, ahr receptor, dioxin, ahr agonist, aryl hydrocarbon, benvitimod, medication adherence tapinarof, anchoring and psoriasis, framing and psoriasis, follow up and adherence, patient beliefs and medication adherence, workshops and adherence for psoriasis, and adherence in psoriasis and communication. A Google Scholar search included the key words benvitimod, tapinarof, pediatric, and psoriasis.

3. Results:

Benvitimod is a revolutionary nonsteroidal topical treatment option for patients with mild to severe psoriasis. Clinical trials and pre-clinical data assessing the efficacy and common adverse effects of this new medication, as well as its placement in the treatment paradigm, will be discussed.

3.1 Pre-Clinical and Clinical Efficacy of Benvitimod

This new medication is effective in adults with mild to severe psoriasis. Benvitimod leads to improvements in Physician Global Assessment (PGA) and Psoriasis Area and Severity Index (PASI) scores compared to vehicle, placebo, and positive controls, which correlate with better symptomatic control (Table 1). In two identical randomized, double-blind, vehicle-controlled studies of 510 and 515 patients with mild to severe plaque psoriasis, participants who used benvitimod cream 1% once daily (QD) for 12 weeks had improvements in both their PGA score and PASI compared to participants who used a control vehicle (P < 0.0001).
After a 12 week randomized, phase 2 clinical trial of 175 participants, those treated with benvitimod had lower PGA and higher PASI75 response rates compared to those using a vehicle (P < 0.05). These results were seen as early as week two and were maintained four weeks following cessation of the study treatment at week 16 (P < 0.05), suggesting its utility for short and potential long-term treatment.

Benvitimod inhibits both inflammatory cytokine expression and T cell activation. The potency of benvitimod was analyzed in vitro through its half maximal inhibitory concentration (IC\textsubscript{50}) value of 7.92. However, a limitation of this study was its inability to evaluate the drug’s efficacy in vivo.

3.2 Safety Profile of Benvitimod

Benvitimod is well tolerated in clinical trials for patients with psoriasis. The most frequent adverse effects include folliculitis, contact dermatitis, and pruritus. The majority of adverse effects were mild to moderate in severity, and few discontinued the study due to treatment-emergent adverse events (Table 2). In a randomized clinical trial of 36 patients with mild to moderate psoriasis, the majority of side effects were mild, local, and relieved without further treatment. The majority of benvitimod-associated folliculitis cases were mild, local reactions that rarely resulted in study discontinuation and were not related to acne-prone areas.

The leading theory for the most prevalent adverse effect, benvitimod-induced folliculitis, is related to the drug’s ability to effectively modulate the AhR pathway. Patients who are acne-prone or are exposed to other factors that give rise to the AhR pathway activation may be at greater risk for this adverse effect.

AhR can be activated and inhibited by a variety of ligands that possess diverse conformations, which may be possible due to each ligand’s unique binding site on the receptor (Table 3). 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is a well-studied halogenated aromatic
hydrocarbon with a high affinity for the aryl hydrocarbon receptor. After binding to the receptor, TCDD produces numerous negative effects, including immunotoxicity, cardiotoxicity, hepatotoxicity, teratogenesis, and dermal toxicity.\textsuperscript{37} AhR activation is not necessarily toxic, as gene expression is differently modulated depending on where the ligand binds, regulatory factors, and the signaling pathway induced.\textsuperscript{20,37}

3.3 Indications for the Use of Benvitimod

Benvitimod has certain benefits compared to other nonsteroidal, topical treatments on the market, but its effects on certain populations as well as its long term effects are not well studied.\textsuperscript{21} Benvitimod improves inflammatory skin lesions as soon as week two and up to week 16, four weeks after stopping treatment.\textsuperscript{15} For patients who present with recurrence of disease after treatment with benvitimod, 73.3\% receive a sPGA score of zero or one at week 52 after retreatment.\textsuperscript{16}

A few limitations exist with the drug’s effects on specific populations. Benvitimod has not been studied in the pediatric population, although approximately 25\% of psoriasis cases appear before the age of 18.\textsuperscript{22} More studies are necessary to analyze the safety of benvitimod in pregnant patients.\textsuperscript{23}

4. Conclusion:

Psoriasis is an inflammatory dermatologic condition caused by an abnormal immune response that has a substantial impact on the lives of patients and their caregivers. The treatment for psoriasis is multifactorial, and topical agents including TCS are first line treatment.\textsuperscript{26} There have been few new nonsteroidal topical therapies approved for psoriasis over the past decade.\textsuperscript{8} Benvitimod activates the AhR, downregulating proinflammatory cytokines, scavenging reactive
Benvitimod appears to be well tolerated and efficacious for mild to severe plaque psoriasis. Patients treated with benvitimod have improvements in PGA, PASI, and BSA.\textsuperscript{6–12,27} Benvitimod users also have greater improvements in Investigator’s Global Assessment (IGA) scores compared to vehicle users at both short and long term endpoints.\textsuperscript{28} Common adverse effects of benvitimod include headache, folliculitis, and contact dermatitis.\textsuperscript{28,29} A limitation of our review involves the small number of published trials including benvitimod, as well as the lack of real life experiences using the drug. However, the promising outcomes from phase 2b clinical trials have led to progression to phase 3 clinical trials, which will provide us with further evidence of the efficacy and safety profile of this medication.\textsuperscript{4} Future reviews will help deduce the drug’s application for use in plaque psoriasis.

5. Expert Opinion:

While the efficacy and safety of benvitimod observed in clinical trials were very promising, practical issues associated with prior authorization may limit the drug in clinical practice. With other nonsteroidal topical treatments, such as the calcineurin inhibitors topical tacrolimus and pimecrolimus, insurance companies covered these medications only after their patients failed TCS treatment. The hassles of prior authorization and the addition of black box warnings may have contributed to a sudden drop in the use of topical calcineurin inhibitors. The topical PDE4 inhibitor crisaborole, another non-steroidal topical anti-inflammatory that appeared promising in clinical trials, did not have a black box warning like the topical calcineurin inhibitors had, yet it, too, was disappointing in real life practice suggesting that the hassles of prior authorization (and not the black box warning) contributed to limited use in clinical practice.

Prior authorization for a new topical non-steroidal medication typically requires patients to fail TCS (and possibly generic non-steroidal topical anti-inflammatory medication) before
insurance would cover the new drug. The most common reason for failing a TCS for inflammatory skin disease is poor adherence. Thus, the prior authorization process, when health care providers do take the time to get prior authorization for a topical treatment, may select for patients who are non-adherent to topical treatment.

When benvitimod comes to market, it could face the same struggles as crisaborole, requiring patients to fail multiple first line treatments, including TCS, before being prescribed the medication (Figure 2). The patients who will meet prior authorization requirements for new, topical, nonsteroidal psoriasis drugs like benvitimod may be much less adherent to their treatment than were patients in the clinical trials.

Another factor that will limit adherence and outcomes in clinical practice compared to clinical trials is the paucity of visits in clinical practice as compared to clinical trials. Clinical trials generally involve follow-up visits at weeks one, two, four, six, eight, etc., which encourages better adherence; in clinical practice, patients are often told to use the medication and return in 8-12 weeks. Similar to students who increase their practice time before their piano lessons or people who floss more before a visit to the dentist, patients are more adherent to treatment before their appointments with their physician, a phenomenon termed “white coat adherence.” In a population where nonadherent patients are already selected (due to prior authorization requirements that they failed multiple topical treatments in the past), these new psoriasis drugs will likely not be as effective in practice as they were in trials (Figure 2).

Thus, the usefulness of benvitimod may be limited by prior authorizations that discourage health care providers from prescribing the medication and poor outcomes (due to poor adherence) in the patients who are prescribed the drug. New drugs like benvitimod may be more effective in a clinical setting if they address the limitations of poor adherence, for example if they require less frequent dosing or are administered in clinic. Fortunately, benvitimod requires
only once daily dosing which could be beneficial in this regard. Being a non-steroidal medication, benvitimod also has the potential advantage of overcoming the hurdle of steroid phobia.\textsuperscript{35,36} If patients have access to benvitimod and are adherent to the treatment, it may provide symptomatic improvement in psoriasis patients with even otherwise refractory disease.

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**Declaration of Interest:**

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**Reviewer Disclosures:**

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.
References:


This article discussed benvitimod’s early onset effectiveness, as well as its ability to maintain its effects 4 weeks following cessation of treatment.


The authors of this article utilized a phase III clinical trial to test the benvitimod’s safety and efficacy in psoriasis. Importantly, they included a positive control (calcipotriol) that is one of the current standard of care drugs used for psoriasis.
25. van den Bogaard EH, Esser C, Perdew GH. The aryl hydrocarbon receptor at the forefront of host-microbe interactions in the skin: A perspective on current knowledge gaps and directions for future research and therapeutic applications. Experimental Dermatology. 2021;
This article stresses the importance of addressing medication adherence in the workup of patients with refractory disease. Once steps are taken to increase medication adherence, patients are able to see better symptomatic improvement with a similar regimen.

This article highlights the importance of early and frequent follow ups, especially when starting a new medication, to ensure good adherence. It also explains why physicians may not be conditioned to follow up as frequently due to the usual timing of clinical trials.
### Table 1: Clinical Efficacy of Benvitimod

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Number of Participants</th>
<th>Severity of Psoriasis</th>
<th>Length of Time</th>
<th>Methods</th>
<th>Results of Clinical Trials</th>
</tr>
</thead>
</table>
| 2 identical RCT, DB, VC | 510, 515 | Mild – severe | 12 weeks | Patients were randomized 2:1 for benvitimod cream 1% QD or vehicle QD | • PGA responses were 35.4% and 40.2% for benvitimod 1% QD  
• PASI75 response rates were 36.1% and 47.6% |
| RCT, DB, VC | 175 | Mild – severe | 12 weeks with 4 week f/u | Patients were randomized 1:1:1:1:1 for benvitimod 1% BID, 1% QD, 0.5% BID, 0.5% QD, vehicle BID, or vehicle QD | • PGA responses, PASI50 scores, and PASI90 scores improved in a dose dependent manner (P < 0.001)  
  - PGA score improvements: -1.8 for 1% BID, -1.7 for 1% QD, -1.7 0.5% BID, and -1.3 for 0.5% QD vs -0.5 for vehicle BID and -0.4 for vehicle QD  
  - PASI50 responses through week 16: 83% (1% BID), 77% (1% QD), 62% (0.5% BID), and 71% (0.5% QD) vs 26% (vehicle BID) and 16% (vehicle QD)  
  - PASI90 responses through week 16: 38% (1% BID), 42% (1% QD), 27% (0.5% BID), and 18% (0.5% QD) vs 0% (vehicle BID) and 0% (vehicle QD) |
| RCT, DB, PC, PoC | 686 | Mild – moderate | 12 weeks | Patients were randomized | • 50.4% of 1% benvitimod cream users had a PASI75 |
Table 2: Safety Profile of Benvitimod

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Number of Participants</th>
<th>Most Common Adverse Effects</th>
<th>Severity of Majority of Adverse Effect</th>
<th>Study Discontinuation due to TEAE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 identical RCT, DB, VC</td>
<td>510, 515</td>
<td>Folliculitis, contact dermatitis, headache, pruritus,</td>
<td>Mild to moderate</td>
<td>5.6%, 5.8%</td>
</tr>
</tbody>
</table>

BID- twice daily; BSA- body surface area; CT- clinical trial; DB- double blind; f/u- follow-up; OL- open-label; PASI- psoriasis area and severity index; PASI 50- A 50% reduction in psoriasis area and severity index score; PASI 75- A 75% reduction in psoriasis area and severity index score; PC- placebo controlled; PGA- physician global assessment; PoC- positive controlled; QD- once daily; R- randomized clinical trial; TCS- topical corticosteroids; VC- vehicle controlled; WBI-1001- benvitimod
<table>
<thead>
<tr>
<th>Application-site</th>
<th>TEAE</th>
<th>Severity</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burning/stinging, pruritus</td>
<td>Mild to moderate</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Pruritus, contact dermatitis, folliculitis</td>
<td>Mild</td>
<td>8.4%</td>
<td></td>
</tr>
<tr>
<td>Folliculitis, headache</td>
<td>n/a</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>Mild</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis, application site discoloration, folliculitis</td>
<td>Mild to moderate</td>
<td>5%</td>
<td></td>
</tr>
</tbody>
</table>

CT- clinical trial; DB- double blind; OL- open-label; PC- placebo controlled; R- randomized clinical trial; TEAE- treatment-emergent adverse event; VC- vehicle controlled

Table 3: AhR Agonists

<table>
<thead>
<tr>
<th>Dioxins</th>
<th>Flavonoids</th>
<th>Tryptophan photoproducts</th>
<th>Malassezia metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,3,7,8-tetrachlorodibenzop-dioxin (TCDD)</td>
<td>quercetin, diosmin, tangeritin, tamarixetin, luteolin, myricetin, hesperidin, apigenin</td>
<td>6-formylindolo[3,2-b]carbazole (FICZ), 6,12-diformylindolo[3,2-b]carbazole (dFICZ)</td>
<td>indirubin, indolo[3,2-b]carbazole (ICZ), malassezin, tryptantrin</td>
</tr>
</tbody>
</table>
Figure 1: Ligand with affinity for the aryl hydrocarbon receptor (AhR) binds within the cell’s cytoplasm and activates the AhR to translocate into the cell’s nucleus. The ligand-activated AhR heterodimerizes with the aryl hydrocarbon receptor nuclear translocator (ARNT). This complex then binds to DNA to induce transcription of CYP1A1 and skin barrier protein genes.

Figure 2: Prior authorization guidelines from insurance companies prevent physicians from prescribing benvitimod until their patient fails multiple first line therapies, including topical corticosteroids (TCS). TCS are highly effective therapies for most psoriasis patients, so the lack of response in patients who have tried multiple first line treatments may be due to poor adherence rather than ineffective treatment. Without addressing issues with adherence, patients who meet requirements to be prescribed benvitimod will likely continue to not show any symptomatic improvement.
Title: An overview of benvitimod for the treatment of psoriasis: a drug evaluation

Abbreviations Used
• body surface area (BSA)
• treatment-emergent adverse events (TEAEs)
• topical corticosteroids (TCS)
• hypothalamic-pituitary-adrenal (HPA)
• aryl hydrocarbon receptor (AhR)
• dimethyl sulfoxide (DMSO)
• Physician Global Assessment (PGA)
• Psoriasis Area and Severity Index (PASI)
• half maximal inhibitory concentration ($IC_{50}$)
• 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)
• Phosphodiesterase-4 (PDE4)
• Investigator’s Global Assessment (IGA)
• Total Lesion Severity Score (TLSS)
• Visual Analog Scale (VAS)
• twice daily (BID)
• clinical trial (CT)
• double blind (DB)
• follow-up (f/u)
• open-label (OL)
• A 50% reduction in psoriasis area and severity index score (PASI 50)
• A 75% reduction in psoriasis area and severity index score (PASI 75)
• placebo controlled (PC)
• positive controlled (PoC)
• once daily (QD)
• randomized clinical trial (R)
• vehicle controlled (VC)
• WBI-1001- benvitimod
• 6-formylindolo[3,2-b]carbazole (FICZ)
• 6,12-diformylindolo[3,2-b]carbazole (dFICZ)
• indolo[3,2-b]carbazole (ICZ)
• aryl hydrocarbon receptor nuclear translocator (ARNT)