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Evaluating Topical Therapies for the Management of Confluent and Reticulated Papillomatosis

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Abstract

Confluent and reticulated papillomatosis (CARP) is a chronic dermatologic condition marked by hyperpigmented, verrucous papules and plaques that merge into a characteristic net-like, reticulated pattern, most frequently localized to the upper trunk, axillae, and shoulders. Although the pathogenesis of CARP remains poorly understood, abnormalities in keratinization and bacterial overgrowth, particularly *Corynebacterium* species, have been implicated. Historically, oral antibiotics, particularly minocycline, have been the mainstay of treatment due to their dual antimicrobial and anti-inflammatory properties. However, concerns over long-term antibiotic use—including risks of gastrointestinal disturbances, photosensitivity, cutaneous side effects, and the growing global issue of antibiotic resistance—have provoked interest in alternative or adjunctive therapies. This comprehensive review examines topical treatment modalities, such as topical minocycline, which minimizes systemic absorption while retaining local efficacy, as well as the use of retinoids like adapalene to regulate keratinization, and keratolytic agents, including salicylic acid and ammonium lactate, which enhance epidermal turnover. By evaluating clinical outcomes, safety profiles, and recurrence rates associated with these topical agents, this review aims to determine their viability as standalone therapies or as adjuncts to oral antibiotics, offering a more targeted, safer approach to managing CARP without the systemic risks tied to prolonged an-

tibiotic use.

Keywords

Confluent and Reticulated Papillomatosis (CARP), Topical Treatments for CARP, Topical Keratolytic Agents for CARP, Topical Minocycline for CARP, Topical Treatment for Resistant CARP, Topical Drug Administration versus Oral Drug Administration, Antibiotic Resistance, Side-Effects of Prolonged Antibiotic Usage

1. Introduction

Confluent and reticulated papillomatosis (CARP) is a complex dermatologic condition that presents significant challenges for both patients and healthcare providers. CARP is characterized by hyperpigmented papules which can coalesce into plaques, forming a distinctive net-like pattern. CARP predominantly affects the upper trunk, axillae, and shoulders in young teens and adults [1]. The papules and plaques associated with CARP are typically found in areas that are subject to friction and moisture, presenting as mostly asymptomatic but occasionally pruritic eruptions. The lesions appear hyperpigmented in individuals with lighter skin tones and hypopigmented in those with darker skin tones, providing a potential for misdiagnosis, often being mistaken for conditions such as tinea versicolor, acanthosis nigricans or Dowling-Degos disease [2]. While the pathogenesis of CARP was initially thought to be associated with the fungus *Malassezia furfur*, this was later refuted when studies demonstrated that individuals with CARP are not consistently colonized by the fungus [3]. The pathogenesis of CARP is now primarily understood to involve abnormalities in keratinization, which is the defining feature of this disease, with potential infectious etiologies, including *Dietzia papillomatosis*, an aerobic gram-positive actinomycete [4]. However, significant gaps remain in understanding the exact mechanisms behind the condition, with current research suggesting a complex interplay between the aforementioned infectious agent and genetic and environmental factors. Significant gaps remain in understanding the true pathogenesis of CARP such that definitive treatment may vary depending on individual etiologies. The reliance on oral antibiotics to treat this pathology prompts concerns about whether this approach may do more harm than good, especially in cases of recurrence.

Traditional treatment approaches for CARP typically involve oral antibiotics, with minocycline being the most widely used due to its demonstrated efficacy. The anti-inflammatory and antimicrobial properties of minocycline make it highly effective in managing the condition and targeting the underlying pathophysiology of CARP [1]. However, the success rates with oral antibiotics vary, and oftentimes, the condition recurs after treatment is discontinued. Oral medications are often prescribed for extended periods beyond initial expectations, presenting challenges for prescribers. Additionally, oral antibiotics pose issues with treat-

ment adherence, particularly among younger patient populations, due to factors such as forgetfulness, busy schedules, or a lack of understanding about the importance of completing the full course of medication. These limitations beg the exploration of alternative options, such as topical agents, which offer a more sustainable and effective treatment approach when compared to the oral counterparts. This raises the question of whether topical treatments for CARP could serve as a more advantageous first-line option compared to oral antibiotics, considering their overall compliance, efficacy in clearing the pathology, and favorable safety profile.

Given the reliance on oral antibiotics for the treatment of CARP, the exploration of topical treatment modalities has become increasingly critical. While the antimicrobial and anti-inflammatory properties of minocycline are effective in managing CARP, its prolonged use raises significant concerns about long-term adverse effects. Patients and clinicians are becoming more wary of the risks associated with extended oral antibiotic therapy, including antibiotic resistance, gastrointestinal disturbances, photosensitivity and other systemic complications. As these concerns grow, the need to identify and evaluate other treatment options becomes more important. By reducing such systemic effects, topical treatments present safer and more sustainable solutions for patients that are seeking to avoid the drawbacks of long-term oral antibiotics. These alternatives offer the potential to improve patient comfort, enhance compliance, and reduce the risks linked to prolonged antibiotic use. This review aims to elucidate the benefits of topical agents for treating CARP. The focus is on highlighting the various classes of topical agents and illustrating how they can serve as substitutes for the current standard of care. Furthermore, the review underscores the advantages of these agents for patients who are concerned about side effects or prefer to avoid prolonged use of oral medications. Ultimately, it emphasizes the need for further research into the pathogenesis of CARP and the potential for topical treatments to be used as standalone therapies for this condition.

2. Discussion

2.1. Topical vs Oral Treatments for Confluent and Reticulated Papillomatosis (CARP)

Oral antibiotics, traditionally minocycline, are commonly used as the first-line therapy for CARP. In addition to oral antibiotics, topical treatments such as mupirocin, retinoids, and keratolytic treatments have also produced comparable results in patients. Gönül *et al.* reported complete resolution of lesions after one month of treatment with mupirocin 2% ointment, despite the lesions being present for three years [5]. This implies that even chronic and recalcitrant lesions of CARP can respond effectively to topical treatment. Additionally, Chong *et al.* discussed the successful use of 0.1% tacrolimus ointment in a recurrence case following the initial minocycline treatment. Furthermore, no relapse was observed following the discontinuation of the tacrolimus ointment [6]. This approach could provide an

effective alternative treatment option for managing recurrent CARP. In other words, all patients with Confluent and reticulated papillomatosis (CARP), especially children and adolescents, should begin with topical treatments and escalate to oral medications if necessary.

2.2. Safety and Systemic Effects

When comparing the safety of topical and oral treatment modalities, it is critical to assess the side effect profile, paying particular attention to systemic effects. Topical therapies tend to have reduced systemic side effects compared to oral medication. Oral minocycline effectively manages CARP but can affect multiple body systems, including nervous, gastrointestinal, respiratory, and musculoskeletal systems. Prolonged systemic use can disrupt the gut microbiome, resulting in gastrointestinal discomfort, nausea, vomiting, antibiotic resistance, and increased susceptibility to infections. In more severe cases, it may also trigger autoimmune responses [7]. Therefore, the decision to initiate oral medication should be carefully considered. Martins *et al.* reported that even a brief seven-day course of oral antibiotics can cause adverse effects for up to two years. In contrast, topical therapies offer fewer adverse events, the most common being pruritus and an upper respiratory infection [7]. These topical treatments are especially valuable for patients who cannot tolerate oral medications like tetracyclines, particularly in scenarios where systemic side effects are a concern. Garner *et al.* found severe side effects from oral minocycline including toxicity concerning single-organ dysfunctions [8]. Topical management is crucial for vulnerable populations, such as pregnant or pediatric patients. Therefore, it is important to compare and evaluate the effectiveness of oral versus topical treatment options in these cases. The high recurrence of CARP and long-term systemic use of oral antibiotics reflects the need to provide an alternative treatment. Incorporating topical treatments can provide an effective solution to recurrent CARP while minimizing severe adverse events among patients. Furthermore, topical agents should be the first line agents when treating CARP, with the potential for progression to oral medications.

2.3. Appropriate Therapies

Choosing the appropriate therapy that aligns with the patient's preference can increase treatment adherence. Oral antibiotics are associated with adverse events, and alternative effective topical therapies have decreased reliance on oral medication [9]. Patients and parents may be reluctant to start long courses of oral antibiotics and instead prefer to manage the condition with topical treatments. Younger children are also associated with worse adherence to oral medication compared to adolescents [10]. Non-compliance may be attributed to younger children having difficulty tolerating severe side effects or challenges integrating a more complex medication regimen. This could be due to younger children being unable to take oral medication. Hester *et al.* also reported that the use of topical therapies was significantly higher among those who filled prescriptions [10]. Topical treatments

may be beneficial in enhancing medication adherence and addressing patient challenges. For a pathology such as CARP, which typically presents in young adults, some of whom may struggle ingesting pills, a topical strategy for treatment allows for enhanced compliance and patient satisfaction.

2.4. Advantages of Topical Therapies

Topical therapies offer several advantages, including high drug concentrations at localized sites, smaller doses needed for effectiveness, and a reduced risk of antibiotic resistance [7] [11]. This indicates that topical therapies could be an effective standalone option for managing recurrent CARP. Additionally, oral antibiotic use is shortened when a topical agent is employed as part of the treatment plan in acne patients [12]. Consequently, a combination of topical and oral therapies should be considered for managing CARP, as this may help reduce the duration of oral antibiotic use and the risk of adverse events. Future initiatives should continue to explore the effectiveness of combined topical and oral therapies with long-term management of CARP, as such research could better inform medication management.

3. Topical Alternatives

3.1. Topical Antibiotics

For the management of dermatologic conditions, topical treatments are commonly prescribed due to their ease of use and ability to target the affected area directly. The choice of treatment depends largely on the severity of the condition. For instance, mild acne is typically managed with topical retinoids or common treatments like salicylic acid [13]. Topical antibiotics are particularly effective in managing acne by targeting *C. acnes* bacteria, reducing bacterial load on the skin and alleviating inflammation in acne lesions [13]. Minocycline, a primarily bacteriostatic antibiotic, functions by binding to the 30S subunit of the bacterial ribosome [7]. This binding interferes with the attachment of aminoacyl-tRNA, a molecule necessary for adding new amino acids to growing protein chains, thereby halting the bacterial growth and reproduction. In certain cases, alternative long-term treatment options with a favorable safety profile and proven efficacy, such as topical minocycline, must be considered for specific dermatologic conditions. New evidence suggests that topical minocycline may also be beneficial for confluent and reticulated papillomatosis (CARP), demonstrating its potential as an effective, safer option for managing this condition long-term.

Minocycline, a second-generation tetracycline derivative, offers enhanced pharmacodynamic properties and antimicrobial activity [7]. In the US, systemic minocycline is available in oral tablets, capsules, subgingival microspheres, and intravenous forms and is primarily used to treat acne vulgaris and rosacea. In October 2019, the FDA approved the first topical minocycline as a 4% foam formulation [7]. Phase III studies demonstrated its efficacy, with 52.1% and 49.1% of participants achieving an Investigator's Global Assessment (IGA) score of "clear"

or "almost clear" by week 12, compared to 43% and 39% with the vehicle in the treatment of rosacea [14]. Inflammatory lesion reduction was also superior, with pruritus as the most common mild adverse event [14]. Current topical minocycline formulations include Amzeeq (4% foam) and Zilxi (1.5% foam). The manufacturer, BiopharmX, is also conducting late-stage clinical trials for BPX-01 and BPX-04, which are 1% and 2% gels, respectively [7]. These formulations use an anhydrous hydrophilic gel to fully dissolve minocycline hydrochloride for rapid skin absorption. Hovione has developed 1% and 3% anhydrous gels using a hydrocarbon-based gelling agent to retain moisture and improve skin barrier function. Moreover, Hovione's gel stabilizes a new crystalline form of minocycline, the free-base form, which is less acidic than other products, reducing skin irritation and making it gentler for sensitive or compromised skin [7]. These advances in topical minocycline formulations improve both efficacy and tolerability in treating inflammatory skin conditions like rosacea and acne, with potential for broader dermatologic use.

Topical minocycline (**Table 1**) is emerging as a promising treatment option for various dermatological conditions, including confluent and reticulated papillomatosis (CARP), with evidence from case studies and clinical trials highlighting its potential. Martins *et al.* conducted a phase IIb clinical trial evaluating its use for papulopustular rosacea (PPR), which demonstrated the efficacy of topical minocycline, finding the 3% gel formulation superior to the 1% version [7]. Although two different diseases, PPR and CARP share several similarities that begs the question if they can share treatment modalities as well. In one case reported by Lateef *et al.*, a patient with CARP achieved complete clearance of plaques after just one month of daily application of 4% minocycline foam, demonstrating rapid and significant improvement [15]. Current evidence, such as the above case study for the treatment of (CARP) shows promising results, with significant improvement and resolution of lesions after one month of continuous use. However, while individual case reports and smaller studies demonstrate the potential of topical minocycline, larger and more rigorous clinical trials are needed to verify its efficacy for CARP.

Topical minocycline represents a significant advancement in the treatment of various dermatological conditions, offering targeted therapy with reduced risks compared to systemic administration. Systemic use can cause adverse effects such as skin hyperpigmentation and nail discoloration [16]. Topical minocycline, in contrast, delivers a higher concentration of the drug directly to the skin, minimizing systemic exposure. This localized application requires a much smaller amount to achieve therapeutic levels in the skin compared to oral administration [7]. Dermal safety studies of topical minocycline revealed no signs of phototoxicity or photoallergic reactions. The most frequently reported adverse events with topical minocycline foam are headaches with the 4% formulation and diarrhea with the 1.5% formulation. Additionally, patients may notice a temporary yellow tint on the skin caused by the minocycline molecule in the product. This tint is not permanent and can be easily washed off with soap and water [17]. Furthermore, sig-

nificant side effects associated with systemic minocycline are largely avoided with topical use. Overall, the benefits of topical minocycline, including targeted delivery and a better safety profile, outweigh the risks.

3.2. Keratinolytic and Exfoliating Methods

Keratinolytic and exfoliating topical agents offer distinct therapeutic advantages in managing confluent and reticulated papillomatosis (CARP). Notable examples include adapalene, a retinoid with keratolytic properties, salicylic acid, a widely recognized keratolytic agent, ammonium lactate, a hydrating exfoliant, urea, an effective keratolytic agent, and azelaic acid, which exhibits mild keratolytic properties. Since the pathogenesis of CARP is believed to be rooted in keratinization, these topical treatments may help diminish the papules and hyperpigmentation characteristic of active CARP.

Retinoids have long been utilized to address anti-aging and hyperpigmentation concerns due to their proven ability to promote keratinocyte proliferation, cellular differentiation, and anti-inflammatory effects through binding retinoic acid receptors [18]. Among these, adapalene (**Table 1**) stands out for its selective receptor-binding affinity, resulting in fewer side effects compared to other retinoids. In the treatment of confluent and reticulated papillomatosis (CARP), adapalene's ability to enhance cellular turnover helps reduce the keratin buildup that contributes to papule formation, while also lightening hyperpigmented areas. Topical vitamin A derivatives, such as tretinoin, have demonstrated effectiveness in managing similar conditions [19]. Given its comparable mechanism of action to tretinoin, yet with a more favorable side effect profile, adapalene should be considered a first-line therapeutic option for CARP [18]. By effectively addressing both keratinization and pigmentation issues while minimizing adverse effects, adapalene offers a superior treatment alternative for managing this challenging condition.

Salicylic acid (**Table 1**) works by reducing the pH of the stratum corneum, ultimately decreasing the number of intracellular cohesions [20]. This action promotes skin exfoliation, which removes excess keratin and aids in fading hyperpigmented areas, potentially smoothing the skin's texture in confluent and reticulated papillomatosis (CARP). Exfoliation through salicylic acid has been effective in reducing hyperpigmentation, stimulating circulation and collagen production, and aiding in the regulation of keratinocyte proliferation in the basal layer, which promotes increased skin renewal and removal of hyperpigmented layers [21]. These effects enhance skin renewal and facilitate the removal of hyperpigmented layers, making salicylic acid a promising treatment for improving both the appearance and texture of skin affected by CARP.

Ammonium lactate (**Table 1**) is a moisturizing topical cream composed of lactic acid derivatives, with lactic acid acting as a natural moisturizing factor within the epidermis [22]. This intense hydration can help soften and improve the appearance of rough, papular skin often seen in confluent and reticulated papillo-

matosis (CARP). Additionally, the use of oil-free moisturizers, such as ammonium lactate cream, along with sunscreen, can effectively minimize the risk of irritation and photosensitivity, providing a dual benefit for individuals with sensitive skin [23]. Given its hydrating and protective properties, ammonium lactate cream offers a promising therapeutic option for improving skin texture and minimizing symptoms associated with CARP, ultimately enhancing both skin health and patient comfort.

Urea (**Table 1**) is another topical agent that may play a beneficial role in managing CARP. Known for its ability to treat hyperkeratotic conditions, urea promotes desquamation and reduces skin thickness, helping soften the skin and dissolve excess keratin [24]. Its versatility has helped manage a variety of dermatologic conditions including atopic dermatitis, ichthyosis, xerosis, seborrheic dermatitis and psoriasis. Urea is well tolerated but may show mild skin irritation. Piquero-Casals *et al.* notes that urea has an ability to facilitate transport of molecules such as antifungals, corticosteroids and hormones [25]. Although urea alone has not been used in CARP conditions, it could be an effective addition to other topical medications to aid in their absorption and decrease duration of treatment.

Azelaic acid (**Table 1**) shows promise as a treatment for confluent and reticulated papillomatosis (CARP), though further research is needed to clarify its efficacy and therapeutic mechanisms. Azelaic acid possesses anti-inflammatory, bactericidal, and follicular keratinization inhibition properties [26]. While it has not been specifically used for CARP, its pharmacologic benefits have proven effective in treating acne and hyperpigmented disorders. Topical azelaic acid is generally well-tolerated, with only mild skin irritation reported as a side effect [27]. Given its mechanism of action in treating similar conditions, its potential for CARP treatment warrants further exploration.

Overall, these treatments focus on regulating keratinization, improving the skin barrier, and increasing cell turnover, showing potential in managing CARP. Since CARP's precise etiology remains unclear, these therapies target the disordered keratinization to allow skin renewal and restore its natural texture and appearance. Major side effects of these treatments include irritation, redness, itchiness, and possible photosensitivity. While further research needs to be conducted, anti-keratin and anti-proliferative measures of treatment show promise.

3.3. Topical Antifungals

Antifungals have been employed in cases where Malassezia furfur colonization is suspected to contribute to confluent and reticulated papillomatosis (CARP). Although this etiology is not widely accepted, there have been favorable outcomes with antifungal treatments, such as 2% ketoconazole (**Table 1**). A notable case involved a 43-year-old male with histological examination revealing subtle papillomatosis, who experienced complete resolution of CARP by day seven [28]. This case suggests a potential benefit of antifungal therapy in managing CARP. Addi-

tionally, selenium sulfide (Table 1), another topical antifungal, has demonstrated efficacy in treating CARP. Friedman & Albert reported the successful resolution of CARP in a 22-year-old male after five weeks of consistent use of 2.5% selenium sulfide lotion [29]. These cases underscore the potential value of antifungal treatments in CARP management, warranting further exploration and consideration of antifungal therapies as a viable treatment option for this challenging condition.

4. Summary

CARP remains a significant burden for patients, especially those who experience systemic side effects from oral antibiotics. This review highlights the understanding of the pathogenesis of CARP, as well as topical options for patients such as topical minocycline, retinoids, salicylic acid, ammonium lactate, urea and azelaic acid. Despite the limited studies that have been performed, there is substantial evidence that topical therapies are efficacious. As seen in Figure 1, there are numerous topical treatments that are effective in clearing CARP. As seen in Figure 1, topical treatments such as Ketoconazole had clearance within 1 week of treatment. More studies of these topical therapies should be conducted with follow up to understand the recurrence rate and success rate. The variable presentations present a diagnostic challenge that should be taken into account. Future studies should continue to investigate CARP pathogenesis, as a deeper understanding is integral to finding the most effective topical treatment for patients with the least amount of side effects. Larger studies with topical agents with anti-keratin and anti-proliferative mechanisms should be considered for CARP pathogenesis, specifically, to make a therapeutic recommendation.

5. Findings

Table 1. Case reports illustrating the potential for topical therapeutics that provide a favorable outcome for topical treatment of CARP.

Antibiotics			
Topical Treatment Name	***Mechanism of Action***	***Reference***	***Outcome***
Minocycline	Binds the 30S subunit of the bacterial ribosome to interfere with the attachment of aminoacyl-tRNA.	Martins, A. M., Marto, J. M., Johnson, J. L., & Graber, E. M. (2021). A Review of Systemic Minocycline Side Effects and Topical Minocycline as a Safer Alternative for Treating Acne and Rosacea. *Antibiotics*, *10*(7), 757. https://doi.org/10.3390/antibiotics10070757	Halts bacterial growth and reproduction.
Keratinolytic and Exfoliative Agents			
Topical Treatment Name	***Mechanism of Action***	***Reference***	***Outcome***

Continued

Adapalene	Binds retinoic acid receptors (RAR-β and RAR-γ) increasing proliferation and differentiation of keratinocytes.	Milosheska, D., & Roškar, R. (2022). Use of Retinoids in Topical Antiaging Treatments: A Focused Review of Clinical Evidence for Conventional and Nanoformulations. *Advances in therapy*, *39*(12), 5351-5375. https://doi.org/10.1007/s12325-022-02319-7	Enhances cellular turnover reducing papule formation and hyperpigmentation.
Salicylic acid	Decreases pH of the stratum corneum layer, reducing number of intracellular adhesions.	Jacobi, A., Mayer, A., & Augustin, M. (2015). Keratolytics and emollients and their role in the therapy of psoriasis: a systematic review. *Dermatology and therapy*, *5*(1), 1-18. https://doi.org/10.1007/s13555-015-0068-3	Promotes skin exfoliation, reducing pigmented areas and promoting smooth texture.
Ammonium lactate	Acts as a humectant, increasing hydration to the stratum corneum from moisture below the stratum corneum and from the atmosphere.	Kang, S. Y., Um, J. Y., Chung, B. Y., Lee, S. Y., Park, J. S., Kim, J. C., Park, C. W., & Kim, H. O. (2022). Moisturizer in Patients with Inflammatory Skin Diseases. *Medicina* (*Kaunas*, *Lithuania*), *58*(7), 888. https://doi.org/10.3390/medicina58070888	Intense hydration of the skin promotes improved appearance and texture in cases of papules.
Urea	Decreases DNA synthesis in basal cells, while increasing genetic transcription in epidermal differentiation. Breaks hydrogen bonds within keratin, and acts as a humectant increasing moisture in the stratum corneum.	Piquero-Casals, J., Morgado-Carrasco, D., Granger, C., Trullàs, C., Jesús-Silva, A., & Krutmann, J. (2021). Urea in Dermatology: A Review of its Emollient, Moisturizing, Keratolytic, Skin Barrier Enhancing and Antimicrobial Properties. *Dermatology and therapy*, *11*(6), 1905-1915. https://doi.org/10.1007/s13555-021-00611-y	Regulates keratinocyte proliferation, improves skin barrier, and provides antimicrobial defenses.
Azelaic acid	Dicarboxylic acid that reversibly inhibits tyrosinase and oxioreductases with antimicrobial and bactericidal effects.	Schulte, B. C., Wu, W., & Rosen, T. (2015). Azelaic Acid: Evidence-based Update on Mechanism of Action and Clinical Application. *Journal of drugs in dermatology*, *14*(9), 964-968.	Anti-inflammatory, antimicrobial, bactericidal, and tyrosinase inhibition improve irritation and pigmentation seen in CARP.
		Antifungals	
Topical Treatment Name	***Mechanism of Action***	***Reference***	***Outcome***
2% Ketoconazole	Inhibits the formation of ergosterol in fungal cells.	Hamaguchi, T., Nagase, M., Higuchi, R., & Takiuchi, I. (2002). A case of confluent and reticulated papillomatosis responsive to ketoconazole cream. *Nihon Ishinkin Gakkai zasshi = Japanese journal of medical mycology*, *43*(2), 95-98. https://doi.org/10.3314/jjmm.43.95	Anti-fungal treatment showed a positive improvement with seven days of treatment in CARP associated with Malassezia furfur.

Continued

2% Selenium Sulfide	A cytostatic agent that interacts with enzymes important for cellular proliferation.	Friedman, S. J., & Albert, H. L. (1986). Confluent and reticulated papillomatosis of Gougerot and Carteaud: treatment with selenium sulfide lotion. *Journal of the American Academy of Dermatology*, *14*(2 Pt 1), 280-282. https://doi.org/10.1016/s0190-9622(86)80354-1	Anti-fungal treatment showed a positive improvement of CARP with 5 weeks of consistent treatment.

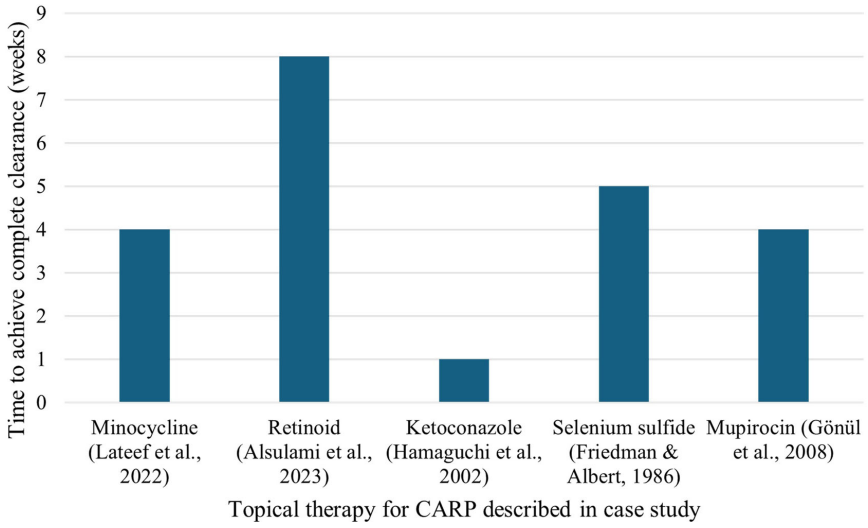

Figure 1. Duration required for CARP clearance with topical therapies based on case study insights.

6. Future Directions and Research Gaps

Future research should prioritize increasing the number of studies assessing topical treatments' effectiveness and feasibility in confluent and reticulated papillomatosis (CARP). Although current literature demonstrates the benefits of topical therapy, these findings are from individual case reports or small studies, limiting their generalizability. Current assessments of combined topical and oral therapies have primarily been studied among acne and eczema patients. The studies indicated a reduction in oral antibiotic use when combined with a topical treatment, showing no significant benefit from adding oral medication [12] [30]. However, there continues to be a lack of randomized controlled trials focusing on the potential use of topical treatments in CARP. Given the prolonged use of oral antibiotics among CARP patients and the risk of severe adverse events, it is crucial to continue investigating new formulations. Future randomized control trials could explore the benefits of combining different therapies and better inform if such combinations reduce side effects and improve patient outcomes. Such research can better inform effective care plans and standardize approaches for CARP management.

Current antibiotic delivery systems are being reevaluated to address drug resistance. There has been an increase in liposome-based treatments, emphasizing

novel metallic nanoparticles. Nanoparticle delivery systems target the delivery of antibiotics to the area of interest, minimizing systemic effects [31]. While this approach has benefits, more research is needed to understand the long-term effects of using metallic nanoparticles on antibiotic resistance. Markowicz reports that metallic nanoparticles could cause mutations that lead to the development of new antibiotic resistance [32]. Although these emerging therapies may help reduce the systemic effects of oral antibiotics, it is crucial to consider their limitations when selecting a treatment option.

The limited understanding of CARP pathogenesis is an obstacle to improving clinical outcomes and developing targeted therapies in CARP patients. Hanania *et al.* demonstrated that treatment responses were less effective in obese CARP patients than nonobese patients [33]. Future research is necessary to confirm this relationship, which could provide deeper insights into CARP pathogenesis. Furthermore, investigating this relationship can help develop targeted therapies that address the root causes of CARP. Further research in understanding CARP pathogenesis is essential to improving treatment efficacy and patient outcomes.

7. Conclusion

Topical treatments, including minocycline formulations, keratolytics, retinoids, and antifungals, offer effective alternatives or adjuncts to oral antibiotics in managing confluent and reticulated papillomatosis (CARP). These therapies address key aspects of CARP pathogenesis, such as abnormal keratinization, inflammation, and microbial overgrowth, with comparable efficacy to oral treatments while reducing the risk of systemic side effects. Topical therapies may improve patient adherence, particularly in individuals who are unable to tolerate or adhere to oral treatments, although challenges such as local irritation should be considered. Further research is needed to optimize these treatments, and clinicians should consider their use in appropriate patient populations, especially those with severe or recalcitrant CARP.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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