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CASE REPORT

Acne vulgaris in a 22-year-old cystic fibrosis patient treated with Elexacaftor-Tezacaftor-Ivacaftor and good clinical response to isotretinoin—A case report

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Abstract

Cystic fibrosis (CF) is a rare autosomal recessive genetic disorder that is now commonly treated with cystic fibrosis transmembrane conductance regulator (CFTR) modulators. Typical adverse events comprise new onset (drug-induced) acneiform eruption as well as worsening of pre-existing acne vulgaris. We present a case report of a young adult with rapid CFTR-modulator-induced worsening of pre-existing acne vulgaris refractory to minocycline treatment, which resolved within 8 months of low dose isotretinoin therapy. Monthly laboratory monitoring of liver function, lipid levels and blood count were unremarkable in this case. The optimal treatment of acne vulgaris in CF-patients and the management of drug-induced acne remain a challenge. The latter may jeopardize drug adherence. CFTR-modulators might be capable to induce acneiform skin lesions by altering electrolyte concentrations and sweat production with subsequential changes of the microbiome and follicular inflammatory response. The exact mechanism remains elusive at this point and warrants further investigation.

KEYWORDS
acne vulgaris, acneiform eruption, adverse reaction, cystic fibrosis, isotretinoin

INTRODUCTION

Acne vulgaris is one of the most prevalent inflammatory dermatoses, affecting individuals of various age groups; male adolescents and young men are prone to more severe trajectories. Cystic fibrosis (CF) is a rare autosomal recessive genetic disorder. Gene mutations (e.g. Delta F508) within the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene are causative and result in a dysfunctional transmembrane channel involved in the transport of chloride ions. Body fluids of affected individuals are unusually thick, which may negatively affect multiple organ systems. CF patients often experience recurrent bacterial infections of the lung that require antibiotic treatments. More recently, the combination of three CFTR modulators/potentiators (Elexacaftor-Tezacaftor-Ivacaftor/ELX-TEZ-IVA) was licensed for the majority of CF patients older than 6 years in Europe and the United States. CFTR modulation may

normalize the transmembranous electrolyte and water flow to correct the concentration and composition of body fluids resulting in improved organ function.[1] Typical adverse events include cough, headache, diarrhea and within the dermatological spectrum rash. More recently, new onset (drug-induced) acneiform eruption as well as worsening of pre-existing acne vulgaris was described as common side effects. The latter specifically compromise drug adherence and may require systemic treatment in moderate to severe cases. However, there are coherent concerns that retinoids might lead to worsening of CF symptoms, particularly pulmonic and hepatic function. Moreover, CFTR modulators are substrates of CYP3A4. Finally, use of antibiotics such as tetracyclines or macrolides to tackle acne is problematic due to the risk of promoting resistant bacterial strains.

CASE REPORT

In September 2017, a 16-year-old male patient with a genetically confirmed diagnosis of CF presented in a dermatological office with multiple papules and pustules on the face. Diagnosis of moderate acne vulgaris was established. The patient described psychological distress due to the skin condition worsening the burden of CF. Psychiatric disorders including depression were excluded. Considering frequent respiratory infections, he was treated repetitively with azithromycin per os and he continuously inhaled colistimethate sodium.

Topical therapy with clindamycin and benzoyl peroxide once daily and adjunct measures (antiseptic cleansers) were established. The results were unsatisfying, treatment was changed to topical erythromycin and adapalene gel 3 months later. In absence of relevant clinical improvement, an antibiotic therapy with minocycline 100 mg per os once daily in combination with topical clindamycin and benzoyl peroxide was started 6 weeks later. At that time, the patient received either ciprofloxacin or azithromycin approximately four times per year due to respiratory infections. In the following two and a half years, minocycline interval treatment (up to 6 months) was necessary four times due to relapses of acne with a high disease burden.

Regarding CF, in August 2020, treatment with the newly licensed CFTR-modulator combination (ELX-TEZ-IVA 100 mg/50 mg/75 mg) was started. Within 1 month, the patient reported a significant worsening of acne vulgaris. Another treatment interval with minocycline was given, which lead to insufficient clinical improvement. Furthermore, concerns regarding the repetitive use of minocycline outweighed the benefit. Given moderate severity of acne, therapy with isotretinoin 10 mg per os once daily (patient weight: 50 kg) was introduced in February 2023. Monthly laboratory monitoring of liver function, lipid levels and blood count was unremarkable. In the subsequent months, the patient showed a steady clinical improvement, with a marked decrease in the number of inflammatory lesions (papules and pustules) and comedones. Besides mild cheilitis and dry skin, the patient did not report any side effects; CF treatment was continued and well tolerated. Isotretinoin was administered for a total of 8 months, and the patient achieved a complete resolution of acneiform lesions (Figure 1). The patient remained in full remission until now (8 months later).

DISCUSSION

Overall, retinoid treatment of acne vulgaris in CF patients appears to be safe although the obligatory side effect of exsiccation is suggestive of potentially aggravating CF-symptoms. The tolerability is comparable to acne patients without CF, although the clinical experience is very limited and a literature review revealed only 13 published case reports until 2016.[2] Abnormal laboratory findings were transient in retrospective analyses.[3,4] Worsening of lung function and raised frequency of pulmonal infections during isotretinoin administration were not reported.[2] Now there is an emerging number of CF-patients with either new onset or worsening of acneiform lesions within weeks to months of initiation of ELX-TEZ-IVA. One hypothesis is that ELX-TEZ-IVA might modulate the skin microbiome composition in the course of altered electrolyte concentrations and sweat production. Another explanation might be an inflammatory response in turn to the rapid decrease of chloride in the sweat. This is supported by the histological finding of necrotizing folliculitis in a fourth of patients in a recent French case series of 16 patients.[5] The cohort was composed predominantly of females (68.7%) with a median age of 27, the median onset of symptoms was 45 days with a range spanning from 15 to 150 days. In our patient, worsening of acne vulgaris was reported within 1 month of drug initiation comparable to 20% of patients in another case series of 19 patients.[6] This might point towards a drug-associated inflammatory mechanism rather than worsening of follicular occlusion or altered epidermal differentiation. However, the time of onset is subject to patient recall and larger studies are warranted to shed light on the pathophysiological mechanism, which is still unclear at this point. 63% of the patients of the latter cohort were female with an age range of 21–38

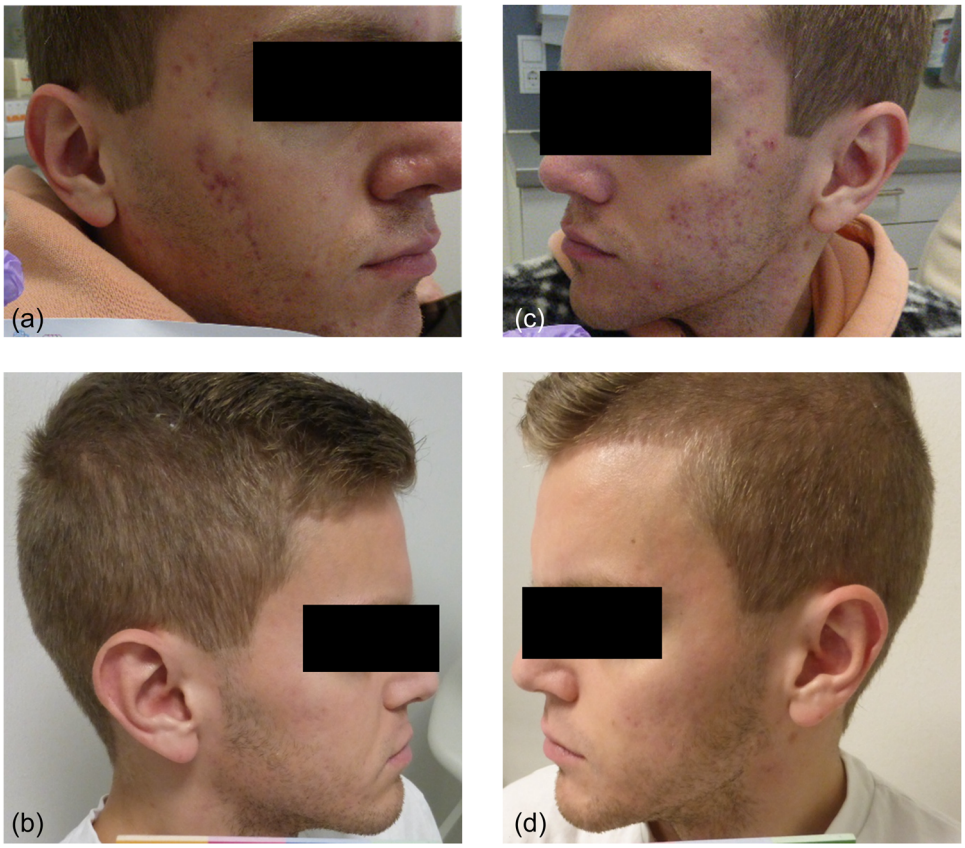

FIGURE 1 Clinical picture of the patient before (a, c) and after 8 months of treatment (b, d) with isotretinoin 10 mg p.o. once daily.

years, 47% reported pre-existing acne. Notably, acne was not reported as typical adverse event in the pivotal phase 3 clinical trials, which described moderate 'rash' to occur in 4% [7] and 11.9% [1] of participants older than 12 years over the course of 4 weeks treatment, respectively. Interestingly, females were affected more often by rash and an association with oral contraceptives was proposed. During 144 weeks of an open-label extension study, acne again was not mentioned. However, 16.2% of participants experienced 'rash events,' with a female predominance of 60%.[8] From a dermatological perspective, acne vulgaris per definition includes follicular hyperkeratosis and presence of comedones whereas acneiform rash comprises different inflammatory skin lesions such as papules and pustules in an acneiform distribution affecting the face, neck and chest. A more precise distinction would be useful in reporting dermatological adverse events in clinical trials to draw meaningful conclusions.

Hepatic side effects are a main concern of isotretinoin use in CF patients as more than 10% of the patients treated with either isotretinoin or ELX-TEZ-IVA experience asymptomatic elevation of liver enzymes.[1,9] The exact effect of liver damage with isotretinoin use is unknown, yet it might represent direct toxicity rather than hypersensitivity. Therefore, low doses are favorable in combinatorial treatments with other potentially hepatotoxic drugs. We opted for a dose of 0.2 mg/kg body weight in our patient, which proved to be sufficient. Notably, ELX-TEZ-IVA is not recommended in high-grade liver dysfunction (CHILD-B/C), while no dose adjustment is necessary for low-grade liver dysfunction (CHILD-A). Monthly laboratory follow-up is necessary; elevation of transaminases greater than five-fold and bilirubin elevation greater than two-fold requires hold of therapy.

In summary, isotretinoin proved to be a highly efficacious and well-tolerated therapeutic option for moderate acne vulgaris during CFTR-modulator treatment after failure of multiple cycles of tetracycline-based antibiotic therapy in this case. Further studies and long-term follow-up are essential to delve into the issue of CFTR-modulator-associated acne vulgaris and acneiform eruptions.

AUTHOR CONTRIBUTIONS

Isabelle Pfeiffer: Data collection; analysis and interpretation of results; writing—original draft. **Mark Berneburg**: Data collection. **Zeljka Hopfner**: Data collection. **Dennis Niebel**: Data collection; analysis and interpretation of results; writing—original draft. All authors reviewed the results and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

Dennis Niebel has been an advisor and/or received speakers' honoraria or travel expense reimbursements and/or received grants and/or participated in clinical trials of the following companies: Abbvie, Almirall, Astra-Zeneca, Boehringer Ingelheim, Bristol-Myers-Squib, GlaxoSmithKline, Incyte, Janssen-Cilag, Kyowa Kirin, LEO Pharma, Lilly, L'Oreal/Cerave, MSD, Novartis, Pfizer, Regeneron and UCB Pharma. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The patient in this manuscript have given written informed consent for participation in the study and the use of their deidentified, anonymized, aggregated data and their case details (including photographs) for publication. Ethical Approval: not applicable.

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