

CORRESPONDENCE

Systemic treatment with isotretinoin suppresses itraconazole blood level in chronic granulomatous disease

DOI:10.1111/pai.12181

To the Editor,

Acne vulgaris affects about 3–9% of the population. Common treatment options include the topical application of benzoyl peroxide and salicylic acid. If refractory, nodular lesions and scarring justify the use of systemic isotretinoin, which is increasingly used also for the treatment of moderate acne vulgaris (1). Chronic granulomatous disease (CGD) is an immunodeficiency that is caused by an inborn defect of the oxygen burst reaction in phagocytes. As patients with CGD are at increased risk for invasive bacterial and fungal infections, conservative therapy is based on the lifelong prophylactic use of cotrimoxazole and itraconazole. The latter substantially lowers the incidence of invasive aspergillosis and thus significantly improved long-term outcome in CGD in terms of morbidity and mortality (2). However, multiple drug interactions of itraconazole must be considered as itraconazole raises levels of calcineurin inhibitors (tacrolimus, cyclosporine A), while rifampicin lowers levels of itraconazole (3). We here report on a 21-yr-old patient with X-linked CGD who received at the same time systemic isotretinoin for the treatment of acne vulgaris and itraconazole for the prevention of invasive aspergillosis in CGD.

The patient was diagnosed with CGD at the age of 2 months, due to a BCG lymphadenitis that developed after vaccination and was treated successfully with antimycobacterial chemotherapy. Despite prophylaxis with cotrimoxazole and itraconazole, he developed further episodes of pneumonia, recurrent lymphadenitis, perianal abscesses, and colitis. Intermittent escalation of anti-infectious therapy could always control these complications. However, the basic principle of the therapy remained the prophylactic use of cotrimoxazole and itraconazole. The patient had been followed up in our institution for over 20 yr. When the patient was not treated in hospital for complications, he was seen in regular intervals. Prior to the aspergillosis upon outpatient visits, blood trough levels of itraconazole are documented (in 2010) over a period of 5 yr (Table 1). At the age of 19 yr, the dosage of itraconazole was raised as trough levels were not detectable on two occasions. At the age of 20 yr, the patient was started on systemic isotretinoin for moderate acne. Two weeks after the initiation of treatment, itraconazole was not measurable in plasma and the patient presented (in 2011) with dry cough accompanied by lowered endurance. Computed tomography revealed a new pulmonary lesion in the upper left lobe with possible invasion into the pericard as seen in magnetic resonance imaging (Fig. 1). The suspicion of invasive aspergillosis was further supported by a significant increase in aspergillus-specific antibodies from 1:160 to 1:640. No fungi could be detected by bronchoalveolar lavage and transbronchial biopsy. Suspecting a failure of itraconazole prophylaxis due to comedication with isotretinoin, we stopped isotretinoin

Table 1 depicts the blood trough levels of itraconazole and its major metabolite hydroxyitraconazole. The therapeutic range for itraconazole is 0.25–1.6 µg/ml, and the therapeutic range for hydroxyitraconazole is 0.5–4 µg/ml. Abnormal values are shown in bold characters.

Date	Itraconazole	Hydroxyitraconazole
11.07.2006	0.34 µg/ml	0.5 µg/ml
04.07.2007	0.37 µg/ml	0.099 µg/ml
29.01.2008	0.58 µg/ml	1.31 µg/ml
14.05.2008	1.63 µg/ml	0.63 µg/ml
04.03.2009	0.7 µg/ml	0.3 µg/ml
24.06.2009	0.31 µg/ml	0.14 µg/ml
23.09.2009	0.28 µg/ml	0.70 µg/ml
06.01.2010	0.10 µg/ml	0.26 µg/ml
21.04.2010	Non-detectable	Non-detectable
14.07.2010	Non-detectable	Non-detectable
20.10.2010	0.63 µg/ml	0.60 µg/ml
19.01.2011	0.20 µg/ml	0.66 µg/ml
11.05.2011	Non-detectable	Non-detectable

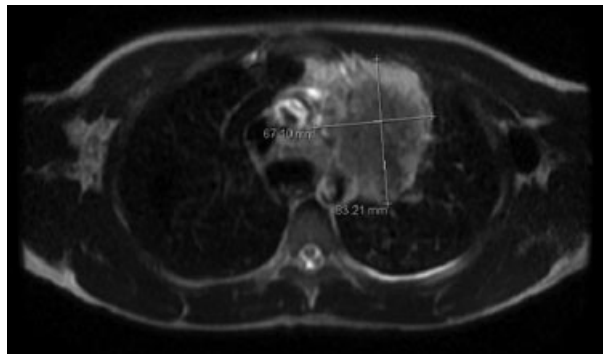


Figure 1 MRI scan. Pulmonary lesion in the upper left lobe with possible invasion into the pericardium.

and replaced antifungal prophylaxis with itraconazole to a long-term intravenous therapy with voriconazole for 9 months. This therapy has led to the control of the aspergillosis, yet not to a complete resolution as seen on a follow-up computed tomography (Fig. 2).

First described in 1979, systemic isotretinoin has become a popular, if not the most popular treatment of moderate to severe acne vulgaris. However, systemic isotretinoin is usually administered for 3–6 months, to assure success (1). As already 2 wk after initiation of isotretinoin, we could not measure itraconazole in the patient systemic isotretinoin probably caused the complete and immediate suppression of itraconazole levels. Although we cannot exclude a lack of



Figure 2 HRCT of the lung. Significant improvement, yet not complete remission of pulmonary aspergillosis after 9 months of intravenous voriconazole.

adherence to itraconazole medication that coincided with the start of isotretinoin medication with complete certainty, this possibility seems very unlikely as adherence to itraconazole medication has been well documented on most previous follow-up visits over a period of 5 yr (Table 1). Our observation is in sharp contrast to previous reports on the successful treatment of acne vulgaris with low-dose systemic isotretinoin in patients with CGD (4–6). The first report describes the successful treatment of acne vulgaris in a 14-yr-old patient who was treated with isotretinoin for 3 months (4). The second report describes the successful treatment of acne vulgaris in a 30-yr-old patient who was treated with isotretinoin for 3 months (5). The third report describes the successful

treatment of acne vulgaris in a 13-yr-old patient who was treated with isotretinoin for 5 months (6). In none of the reports, the authors provide information on the concentration of itraconazole in blood of their patients while on comedication with isotretinoin, so we suspect that the life-threatening suppression of itraconazole by isotretinoin in the previously reported patients was most likely simply not noticed by the treating physicians (4–6). So their recommendation to use isotretinoin in patients with CGD must be carefully revisited (4–6). We here highlight the need to at least closely monitor levels of itraconazole when given together with systemic isotretinoin, if not the necessity to refrain from isotretinoin for treatment of acne vulgaris if cotreatment with itraconazole is mandatory as in CGD. The increased metabolism of itraconazole by systemic isotretinoin leading to induction of cytochrome P450 is highlighted in the pharmaceutical information on isotretinoin and is probably well known to the dermatologist.

However to our knowledge, our report for the first time explicitly shows that comedication of itraconazole with systemic isotretinoin may cause dangerously low levels of itraconazole in CGD. The potentially life-threatening suppression of itraconazole by isotretinoin must be considered when using isotretinoin for a common and non-life-threatening condition like acne vulgaris in patients with CGD.

Horst von Bernuth^{1,2} & Volker Wahn¹

¹Department of Pediatric Pneumology and Immunology, Charité Hospital – Humboldt University, Berlin, Germany; ²Fachbereich Immunologie, Labor Berlin Charité Vivantes GmbH, Berlin, Germany

E-mail: Volker.wahn@charite.de

References

1. Simpson RC, Grindlay DJ, Williams HC. What's new in acne? An analysis of systematic reviews and clinically significant trials published in 2010–11. *Clin Exp Dermatol* 2011; **36**: 840–3.
2. Seger RA. Advances in the diagnosis and treatment of chronic granulomatous disease. *Curr Opin Hematol* 2011; **18**: 36–41.
3. Bruggemann RJ, Alffenaar JW, Blijlevens NM, et al. Clinical relevance of the pharmacokinetic interactions of azole antifungal drugs with other coadministered agents. *Clin Infect Dis* 2009; **48**: 1441–58.
4. Spillane AP, Hivnor CM. Isotretinoin use in a case of chronic granulomatous disease. *Pediatr Dermatol* 2009; **26**: 756–8.
5. Barbi E, Berti I, Minute M, Zennaro F. Successful treatment of acne with isotretinoin in chronic granulomatous disease. *Eur J Dermatol* 2011; **21**: 111–2.
6. Alonso-de-Celada RM, de-Lucas Laguna R. Safe and successful treatment of acne vulgaris with isotretinoin in a patient with chronic granulomatous disease. *Pediatr Dermatol* 2012; **29**: 662–3.