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LETTER TO THE EDITOR

Significant reduction in bilirubin levels in a patient with Gilbert's Syndrome under isotretinoin treatment for acne vulgaris: A new area of use for isotretinoin?

Dear Editor,

Oral isotretinoin is an FDA-approved retinoic acid isomer used for the treatment of severe acne for many years (Zaenglein, 2016). One of the most common side effects in patients receiving isotretinoin treatment is the increase of serum liver enzyme levels, which is observed in approximately 2% of patients (Vallerand, 2018). Retinoids are metabolized in the liver and mostly excreted with bile. Thus, patients with hepatic dysfunction are expected to show increased sensitivity to this group of medications (Wang, 1995).

Gilbert's syndrome is a genetic disease characterized by non-conjugated hyperbilirubinemia and it affects 3–10% of the general population (Radoi, 2017). Owing to hepatic dysfunction, patients with Gilbert syndrome are expected to show increased sensitivity to isotretinoin, metabolized by hepatic oxidation and bile excretion (Fernández-Crehuet, 2014). Contrary to this expectation, a few studies in the literature reported paradoxical decrease in the bilirubin levels in patients with Gilbert syndrome receiving isotretinoin treatment for acne (Fernández-Crehuet, 2014; Wang, 1995).

A 23-year-old male patient with Gilbert syndrome was admitted to our clinic with mild papulopustular acne and folliculitis on the face and back. Oral doxycycline at a dose of 100 mg/day and topical benzoyl peroxide-clindamycin phosphate treatment was started. Due to the lack of response at the second month of treatment, low-dose isotretinoin treatment was planned. Pretreatment laboratory parameters revealed significant elevations in direct bilirubin (0.62 mg/dl; reference range: 0–0.2 mg/dl), indirect bilirubin (3.62 mg/dl; reference range: 0.1–0.9 mg/dl), and total bilirubin (4.24 mg/dl; reference range: 0.22–1.3 mg/dl) levels. The liver enzymes, alanine aminotransferase, and aspartate aminotransferase, were 12 and 19 U/L, respectively, and both were within the normal reference ranges. The patient was started on isotretinoin (20 mg/day) and after 4 weeks his biochemical tests surprisingly showed that direct bilirubin was at 0.51 mg/dl, indirect bilirubin at 2.29 mg/dl, and total bilirubin at 2.8 mg/dl levels; which were reduced respectively to 18, 37, and 33% of baseline values. Liver transaminases were within the normal reference range.

Gilbert's syndrome is a disease that is more frequently defined in males and is caused by a disruption of bilirubin excretion from the liver. Theoretically, hepatotoxic drugs, such as isotretinoin, are expected to increase bilirubin and liver enzyme levels in patients with hereditary hepatic disorders such as Gilbert syndrome. The literature encompasses scant number of cases with Gilbert's syndrome, showing reduction in bilirubin levels under isotretinoin therapy. Some hypotheses have been proposed about this unexpected finding. In a few studies, similar to the mechanism of some drugs such as phenobarbital and corticosteroids, inhibition of microsomal enzymes such as uridine diphosphate glucanosyltransferase (UDP-GT), and the inducing effects of reducing bilirubin conjugation by isotretinoin treatment are claimed (Fernández-Crehuet, 2014; Rademaker, 1991; Shah, 1993). Another study suggests that isotretinoin decreases serum testosterone levels that increase the activity of UDP-GT, or it induces hepatocytes to produce carrier proteins that eliminate bilirubin (Bruno, 1984; Goodman, 1984).

In our patient with Gilbert syndrome, isotretinoin could be continued safely without unexpected hepatic adverse effects. Furthermore, we had the chance to observe reduction in bilirubin levels during isotretinoin therapy. However, large-scale, prospective, randomized, and blinded future studies or larger case-series are required before it can be concluded that isotretinoin decreases bilirubin levels in all patients receiving isotretinoin, or at least in those affected with Gilbert syndrome. The exact mechanism(s) should also be unraveled. If confirmed, isotretinoin may find a new indication to itself in the arena of Gastroenterology and Hepatology.

CONFLICT OF INTEREST

No conflict of interest.

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REFERENCES

Bruno, N. P. (1984). Adverse effects of isotretinoin therapy. *Cutis*, *33*, 484–486.

Fernández-Crehuet, P. (2014). Hepatotoxicity of isotretinoin in patients with acne and Gilbert's syndrome: A comparative study. *BMJ Open*, *4* (3), e004441.

Goodman, D. S. (1984). Vitamin A and retinoids in health and disease. *New England Journal of Medicine*, *310*, 1023–1031.

Rademaker, M. (1991). Isotretinoin treatment alters steroid metabolism in women with acne. *The British Journal of Dermatology*, *124*, 361–364.

Radoi, V. E. (2017). Frequency of the UGT1A1* 28 polymorphism in a Romanian cohort of Gilbert syndrome individuals. *Journal of Gastrointestinal and Liver Diseases: JGLD*, *26*, 25.

Shah, A. I. (1993). The effects of retinoids and terbinafine on the human hepatic microsomal metabolism of cyclosporin. *British Journal of Dermatology*, *129*, 395–398.

Vallerand, I. A. (2018). Efficacy and adverse events of oral isotretinoin for acne: A systematic review. *The British Journal of Dermatology*, *178*, 76–85.

Wang, J. I. (1995). Isotretinoin-associated normalization of hyperbilirubinemia in patients with Gilbert's syndrome. *Journal of the American Academy of Dermatology*, *32*, 136–138.

Zaenglein, A. L. (2016). Guidelines of care for the management of acne vulgaris. *Journal of the American Academy of Dermatology*, *74*, 945–973.