Photosafety of the Antidiabetic Drug Sitagliptin

To the Editor,

Sitagliptin (SIT) is a dipeptidyl-peptidase inhibitor, used as an oral hypoglycaemic drug. It is often combined with metformin (MET), for the treatment of type 2 diabetes mellitus (T2DM), which is a chronic disease of high prevalence.¹ The European Medicines Agency (EMA)² reported, in 2007, several side effects related to SIT (Januvia®); however photosensitivity was not included as part of its adverse reactions.

The chemical structures of SIT and MET (Fig. 1A) do not suggest the possible appearance of a photosensitization reaction, since they should not absorb in the UVB-UVA region of the solar spectrum. Nonetheless, two clinical cases concerning the photosensitivity of SIT have been reported^{3,4}. On the one hand, in the clinical case studied by Stricklin and co-workers³ eruptions occur in areas exposed to sunlight, concluding that it is a photosensitivity reaction related to SIT. This photosensitivity has been attributed to the drug absorption at *ca.* 400 nm (SIT UV spectrum was not shown in the publication). On the other hand, Nakatani *et al.*⁴ assign the observed generalized skin eruption to a possible photosensitization reaction induced by SIT, relying on the reasons previously exposed by the above-mentioned authors.

Recently, a 56-year-old man with Type 2 diabetes mellitus treated with SIT in combination with MET (Janumet®) for 1 year, attended the Dermatology Unit at Hospital La Fe in Valencia due to a skin eruption (Fig. 1B) in sunlight exposed areas (facial region, neckline and arms). The patient denied the use of other medications apart from Janumet® like analgesics, anti-inflammatory drugs and herbal products. The physical examination showed subacute eczematous plaques, being very striking the almost exclusive distribution of them in the photoexposed areas, which could be compatible with contact eczema, photoallergic eczema, polymorphic light eruption, subacute cutaneous lupus, chronic actinic dermatitis and pellagra. Moreover, the histological features of skin biopsy were characteristic of subacute spongiotic dermatitis compatible with eczema. In order to make an accurate diagnosis, blood tests, including antinuclear antibodies (ANA), extractable nuclear antigen (ENA), anti-Histones, complement, tryptophan, and urine porphyrins tests were performed and all of them resulted normal. With this background, the goal of this work is to investigate the feasibility of a photosensitivity reaction induced by SIT. For this purpose, clinical studies (patient's phenotyping and photopatch test) were combined with absorption spectral measurement of SIT and *in vitro* phototoxicity test (3T3 NRU, Neutral Red Uptake).

Phototesting was carried out to the patient in order to assess the skin's sensitivity to UV radiation by determining the minimal erythema dose (MED) and the anomalous responses to UVB, UVA and visible radiations. Irradiations were performed using a Medisun Gigatest-1-MED® lamp for UVB and UVA range and a slide projector for visible range. The MED value resulted to be normal for his skin phototype, indicating that the patient was not objectively photosensitive. To discard a photoallergic reaction to SIT, photopatches using the Spanish standard battery, the photobiology battery (GEIDAC)⁵, SIT and patient's own cosmetics products (Heliocare® 360 airtel and Nivea® body milk) were performed with a Hapro summer Glow® lamp. No significant positivity was detected in the photopatch test.

The absorption spectrum of SIT was recorded using ultrapure water and methanol as solvents at different concentrations. As expected from the chemical structure, this only showed two absorption peaks with maxima at 200 and 267 nm. As it is shown in Fig. 1C, there is no evidence for an absorption band above 290 nm, even at high drug concentrations, as was indicated by Stricklin *et al.* The appearance of that band could be attributed to an artefact or a sample impurity. Therefore, SIT does not absorb in the UVB-UVA-visible sunlight region. Drug-induced photosensitivity reactions are predominantly triggered by UVA radiation⁶⁻⁸ although occasionally a peak of absorption within the UVB range can be related to secondary photochemical reactions.⁹ The absorption spectrum of SIT only shows two absorption peaks within the UVC spectrum; thus, taking into account that the UVC irradiation does not reach the surface of the earth, it can be concluded that this compound should not be involved in photosensitization reactions.

Complementary to the absorption spectral measurements, the *in vitro* 3T3 NRU phototoxicity assay was carried out according to the OECD Guideline 432¹⁰. Therefore, cytotoxicity profiles of BALB/c 3T3 fibroblasts treated with SIT were measured, using neutral red as vital dye, both in dark and in the presence of UVA light Chlorpromazine (CPZ) was used as positive control and sodium dodecyl sulphate (SDS) as negative control. For each compound tested, dose-response viability curves were obtained using GraphPad Prism 6 software package version (Fig. 2A-C). Then, the IC₅₀ (concentration of compound producing a 50% reduction of the neutral red uptake) in the absence and in the presence of UVA light was determined and used to calculate the Photoirritant Factor (PIF) of CPZ, SDS and SIT (Fig. 2D) following the equation:

$$PIF = \frac{IC_{50} (DARK)}{IC_{50}(UVA LIGHT)}$$

For SIT, PIF value is below 2; indicating that neither UVA radiation nor sunlight affect the toxicity of the compound, and therefore, according to the OECD Guideline¹⁰, SIT cannot be considered a phototoxic drug.

Two months after Janumet® withdrawal, the patient showed up a new outbreak of similar skin lesions in exposed areas. On this occasion, a new skin biopsy showed a perivascular and periadnexal infiltrate with an interstitial increase of the mucin. All histological changes were compatible with cutaneous lupus, despite a direct negative immunofluorescence. Accordingly, the patient was treated with hydroxychloroquine, achieving remission and control of the lesions. The probability that SIT could have triggered cutaneous lupus in the patient is low because the lesions did not resolve after SIT discontinuation and no case has been reported in the literature related to SIT-induced lupus. However, given the chronological relationship, SIT cannot be completely excluded as the initial trigger of the disease in our patient.

Due to both the clinical evaluation of our patient, and the *in vitro* and complementary tests carried out, we have reasonable evidence supporting that SIT is not capable of triggering photosensitivity reactions.

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CONFLICT OF INTEREST

None declared.

REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas. 6th ed. Brussels, Belgium: International Diabetes Federation 2013. Accessed August 28, 2018.
2. European Medicine Agency (EMA). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000722/WC500039057.pdf. Accessed July 16, 2018.
3. Stricklin S, Stoecker W, Rader R, Hood A, Litt, J, Schuman, T. Persistent edematous-plaque photosensitivity observed with sitagliptin phosphate (Januvia®). *Dermatology Online Journal* 2012;18(2). <https://escholarship.org/uc/item/0d70k7b2>. Accessed July 16, 2018.
4. Nakatani K, Kurose T, Hyo T, Watanabe K, Yabe D, Kawamoto T, Seino Y. Drug-induced generalized skin eruption in a diabetes mellitus patient receiving a dipeptidyl peptidase-4 inhibitor plus metformin. *Diabetes Ther* 2012;3:14.
5. Hervella-Garcés M, García-Gavín J, Silvestre-Salvador JF. The Spanish standard patch test series: 2016 update by the Spanish Contact Dermatitis and Skin Allergy Research Group (GEIDAC). *Actas Dermosifiliogr* 2016;107:559-566.
6. Lehmann P, Schwarz T. Photodermatoses: Diagnosis and treatment. *Deutsches Ärzteblatt International* 2011;108(9):135-141.
7. Kim W B, Shelley AJ, Novice K, Joo J, Lim HW, Glassman SJ. Drug-induced phototoxicity: A systematic review. *J. Am. Acad. Dermatol* 2018; ppi:S0190-622(18)32220-5.

8. Garcia-Lainez G, Martínez-Reig AM, Limones-Herrero D, Jiménez MC, Miranda MA, Andreu I. Photo(geno)toxicity changes associated with hydroxylation of the aromatic chromophores during diclofenac metabolism. *Toxicology and Applied Pharmacology* 2018;341:51-55.
9. Palumbo F, Garcia-Lainez G, Limones-Herrero D, Coloma MD, Escobar J, Jiménez MC, Miranda MA, Andreu I. Enhanced photo(geno)toxicity of demethylated chlorpromazine metabolites. *Toxicology and Applied Pharmacology* 2016;313:131-137.
10. Guidelines for the Testing of Chemicals Test No. 432: In Vitro 3T3 NRU Phototoxicity Test. OECD Ed. (Original Guideline, Adopted 13th April 2004).

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