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Effect of long-term treatment with tumour necrosis factor-α inhibitors on single-dose ultraviolet-induced changes in human skin

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Dear Editor,

Tumour necrosis factor (TNF)-α is induced by ultraviolet (UV) light and is important in photoinflammation.[1] Although TNF-α inhibitors are commonly used for various inflammatory disorders like psoriasis, sometimes in combination with phototherapy, the effect of long-term TNF-α inhibitor treatment with UV exposure on skin is unclear. This study was undertaken to see if chronic TNF-α inhibition affects epidermal responses to UV, inflammatory infiltrate and collagen composition in vivo.

Among 20 included patients, 10 were on long-term TNF-α inhibitors (mean duration 32·5 months; etanercept, n = 6; adalimumab, n = 3; infliximab, n = 1). The other 10 subjects were not on TNF-α inhibitors and were receiving only topical steroids and calcipotriene. All were white, nonsmoking men, and TNF-α inhibitor-untreated and inhibitor-treated patients had similar distribution of age (65·32 ± 5·66 vs. 62·48 ± 13·18 years), Fitzpatrick skin type and median minimal erythema dose (MED; 7·36 vs. 8·15). Following individual MED measurement, nonlesional inner arm skin was irradiated with 1× MED, followed by biopsy before (baseline) and after (24 h and 48 h). The light source emits UVA1, UVA2 and UVB in a ratio similar to sunlight. The study was approved by the ethics committee at the University of Pennsylvania, and was conducted according to the Declaration of Helsinki. All

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participants gave written informed consent. Measurements at each time point were compared between the groups using the Mann–Whitney *U*-test. UV-induced chronological changes within each group were analysed by Wilcoxon signed-rank test.

UV-induced epidermal hyperplasia protects against UV-induced DNA damage by reducing UV transmission.[2] In this study, patients chronically treated with TNF-α inhibitor had thicker epidermis before irradiation {median 247·4 μm [interquartile range (IQR) 183·7–289·8] vs. 189·9 μm [IQR 152·9–227·8]; P = 0·03} (Fig. 1a, b). Consistent with increased epidermal thickness, proliferation markers keratin 6 (K6; P = 0·02) and Ki-67 (P = 0·03) were upregulated, with suppressed differentiation marker K10 (P < 0·001) at baseline in TNF-α inhibitor-treated patients (Fig. 1c–e). Long-term TNF-α inhibitor treatment suppresses the nuclear factor kappa B (NF-κB) pathway, potentially causing epidermal hyperproliferation previously described in mice with a loss-of-function NF-κB mutation or IKK2 ablation.[3,4] However, TNF-α inhibitor-treated patients showed a less pronounced epidermal response to UV. After UV exposure, epidermal K6 expression was markedly increased and K10 was reduced only in non-TNF-α inhibitor-treated patients. The lack of response in TNF-α inhibitor-treated patients could represent a ceiling effect, with the epidermal hyperplasia having already reached its maximum before UV irradiation. However, decreased UV-induced epidermal thickening in TNF-α inhibitor-treated patients may suggest a need for enhanced photoprotection.

TNF-α and UV trigger inflammatory cell infiltration.[5,6] In this study, even short-term, low-dose UV exposure induced a massive macrophage infiltrate into the skin, and UV-induced infiltration was profoundly decreased in TNF-α inhibitor-treated patients (Fig. 1f). This finding is intriguing because the lower dose used in this study is more reflective of physiological daily UV exposure, which does not induce erythema.[7] Acute low-dose 1–1·5× MED UV irradiation can still have damaging effects like sunburn cell formation and nuclear p53 accumulation.[7] However, inconsistent with previous reports,[6,8] UV and TNF-α inhibitor treatment had a negligible impact on mast cell and neutrophil infiltration (Fig. 1g, h). The discordance might be owing to the brief low-dose 1× MED used in this study vs. higher doses (2–11× MED) in previous studies.

As TNF-α inhibits type I collagen synthesis and enhances collagen degradation by increasing skin metalloproteinases,[1] we evaluated if TNF-α inhibitors affect dermal collagen by hue measurement of picrosirius red-stained sections. There was no significant difference between the two groups with regard to the percentage of mature or densely packed collagen fibres (red on imaging) and immature, or thin collagen fibres (green on imaging) at baseline (Fig. 1i, j). Short-term, low-dose UV exposure did not significantly influence dermal collagen composition, irrespective of TNF-α inhibitor treatment, despite a UV-induced trend of decreasing red collagen and increasing green collagen in TNF-α inhibitor-treated patients. This could reflect more destruction and less synthesis of mature collagen and enhanced type III collagen synthesis, implying TNF-α inhibitor-mediated mixed profibrotic and antifibrotic effects on UV-induced collagen change.

Collectively, this study demonstrates that chronic TNF-α blockade affects human skin epidermal thickening and dermal inflammatory infiltrate in response to UV. There are

potential effects on collagen, although the low dose and short duration of UV exposure in this study suggest a need for future studies with longer repetitive UV exposure to different UV wavelengths and other indications for TNF-α inhibitors to understand fully the combined effects of TNF-α inhibitors and UV. Considering the extensive use of TNF-α inhibitors, their combination with phototherapy and daily UV exposure, physicians should be aware of the potential influence on photoinflammation and educate patients about photoprotection.

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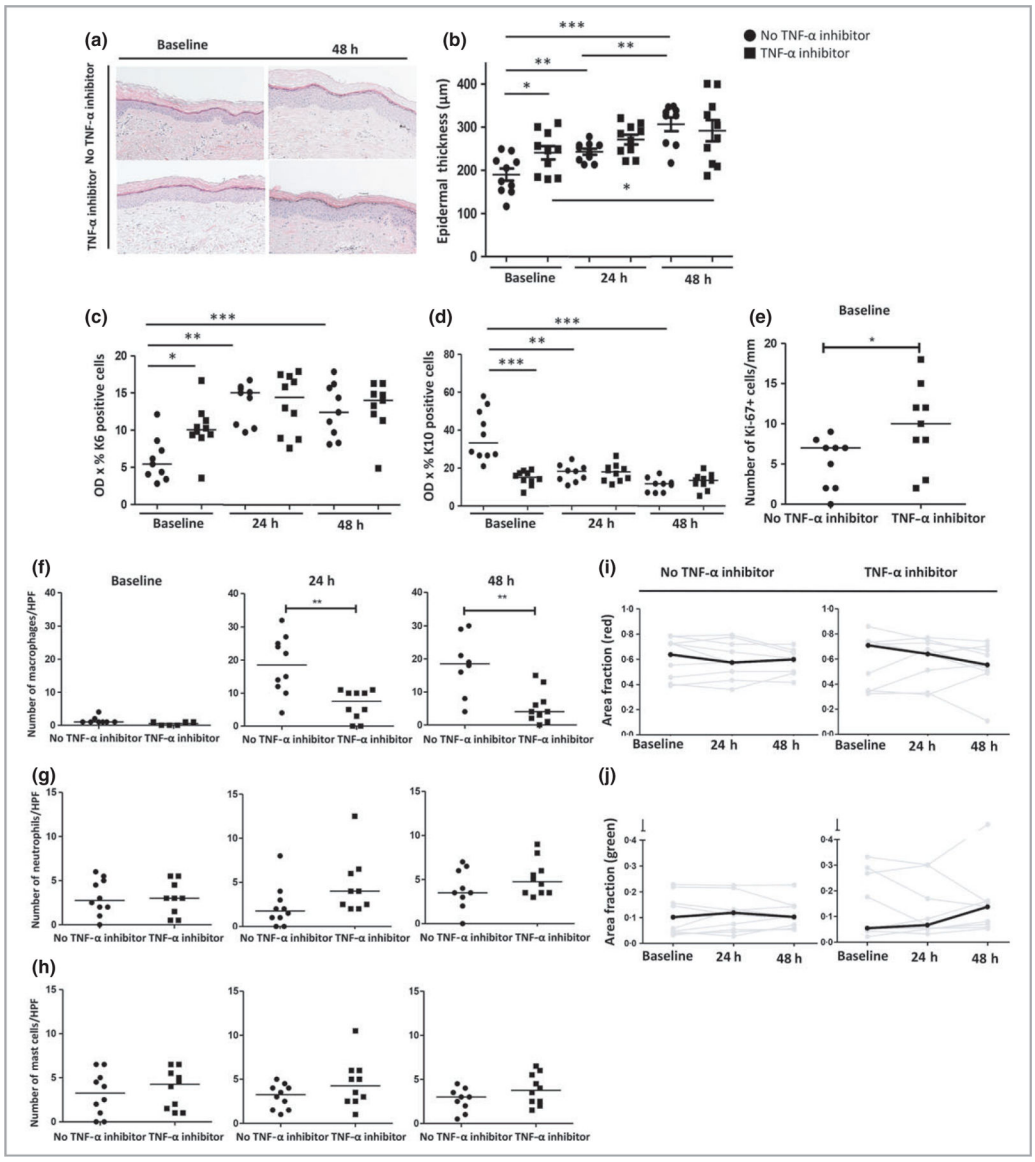

Fig 1.

(a–e) Effect of tumour necrosis factor (TNF)-α inhibitor treatment and ultraviolet (UV) irradiation on epidermal thickness. (a) Representative skin sections at baseline and 48 h. Haematoxylin and eosin (original magnification ×400). (b) Median epidermal thickness was compared between patients with and without long-term TNF-α inhibitor treatment, both at baseline and after UV exposure. (c) The expression of K6 as an epidermal proliferation marker and (d) K10 as a differentiation marker was evaluated by multiplying the staining intensity by the proportion of positive cells on immunohistochemistry. (e) The number of Ki-67-positive cells at baseline was counted and averaged over 1 mm of epidermis. (f–i) UV-induced inflammatory cell infiltrate in the skin. After immunohistochemical staining, cells were counted in five random, nonoverlapping fields of the dermis at 400× magnification. (f) The number of macrophages at different time points before and after UV exposure. (g) Neutrophil elastase-staining dermal neutrophils. (h) Metachromatically toluidine blue-

positive mast cells. (i, j) Changes in collagen composition with TNF-α inhibitor treatment and UV exposure. Picrosirius red-stained sections were visualized with circular polarized light microscopy at a total magnification of 40×. Images were cropped to exclude epidermis, and then analysed with a program designed in MATLAB® to measure hue composition. (i) Mature and densely packed collagen fibres, which were red on imaging, in TNF-α inhibitor-untreated and TNF-α inhibitor-treated patients. (j) Immature and thin fibres, which were green on imaging, in TNF-α inhibitor-untreated and TNF-α inhibitor-treated patients. The thick black lines connect the median values of mature and thin fibres in each treatment group. *$P < 0{\cdot}05$, **$P < 0{\cdot}01$, ***$P < 0{\cdot}001$. OD, optical density; HPF, high-powered field.