An in vitro model of drug-induced Stevens-Johnson syndrome/ toxic epidermal necrolysis (SJS/TEN)

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Introduction

Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) is a serious disorder usually caused by an adverse drug reaction. The anti-TNF therapeutic, Etanercept, is an effective treatment of SJS/TEN. Epidermal high mobility group box 1 (HMGB1) expression has been shown to be an early marker of epidermal injury in SJS/TEN. In this study the aim was to develop and validate an in vitro model of SJS/TEN using TNF-α-meditation and investigate etanercept modulation.

The mechanism of TEN is thought to be related to the production of cytotoxic proteins and pro-inflammatory cytokines by localised, activated T-cells which cause widespread keratinocyte death and modulate degradation of intracellular adhesion molecules

Results

Patients on immune checkpoint inhibitors for advanced melanoma were recruited upon initial presentation of SJS/TEN or maculopapular exanthem. Serum samples (10 ml) were collected at the time of diagnosis. Healthy skin biopsies exposed to TNFα (10 ng/mL), SJS/TEN (10% and 100% dilution), rash or healthy control sera (10% and 100% dilution), were cultured in the absence/presence of Etanercept (1µg/mL). A negative control (skin in media only) (Figure 1) and positive control (Anakinra (10µg/mL) (Figure 2) were used in all assays. Skin was incubated with or without sera and with or without etanercept for 3 days and then graded for histopathological damage (grades I-IV) using criteria similar to those used clinically. Grade II and grade III were positive responses. Skin sections were reported for necrosis or intra-epidermal damage.

Skin cultured with TNFα showed grade II responses with vacuolisation of the epidermis in absence of Etanercept with reduced necrosis in the presence of Etanercept (Figure 3, A, B). A grade III positive response was observed in response to SJS/TEN sera at 10x dilution with intra-epidermal damage and severe necrosis (Figure 4) and reduced to a grade II response in the presence of Etanercept (Figure 3. C, D) At 100x dilution of SJS/TEN sera, the skin damage showed a grade II response with necrosis and some intra-epidermal damage in the absence and reduced necrosis in the presence of Etanercept (data not shown). Rash sera at 10x and 100x dilution also showed a grade II response in the absence of Etanercept and reduced necrosis in the presence of Etanercept (data not shown).

Intra-epidermal damage observed shows damage typical of blister formation in Toxic Epidermal Necrolysis (TEN) caused by a severe drug-induced reaction. Results show typical TEN characteristics with epidermis destruction and blister formation.

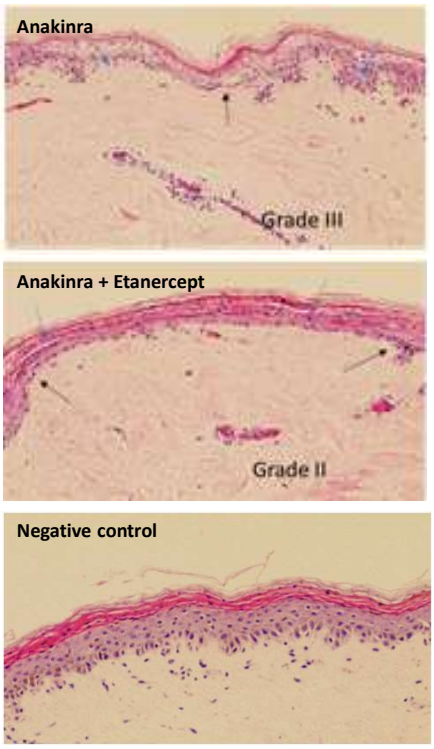

Figure 1: TEN lesions in the presence of Anakinra (Grade III) and down regulated with reduced necrosis to grade II by Etanercept.

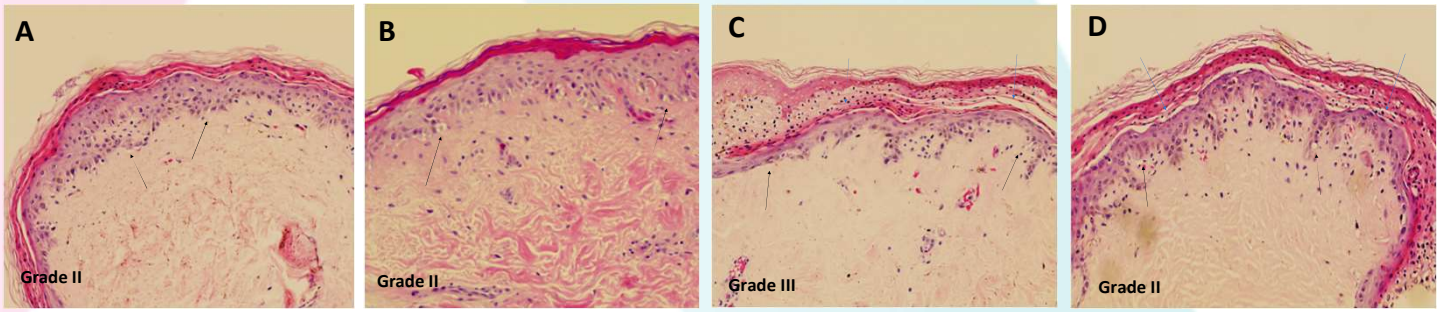

Figure 3. TNFα (10 ng/mL) in the absence (A) and presence (B) of Etanercept. SJS/TEN sera (10x) in the absence (C) and presence (D) of Etanercept. Grade III reaction reduced to grade II

Conclusions

The study demonstrate exposure to TNFα, SJS/TEN sera and rash sera can induce the histopathological features of SJS/TEN which in return can inhibited by etanercept. The study describes an ex vivo model of SJS/TEN with the potential to be utilised as a nonclinical safety screen and as a tool for investigating mechanisms of SJS/TEN pathogenesis.

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Collaborators

DSTC Drug Safety Testing Center