# Comparing the effect of tacrolimus (0.1%) ointment and betamethasone valerate (0.1%) cream on the epidermal barrier: a twice-weekly maintenance dose

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## INTRODUCTION

Atopic dermatitis (AD) is a multifactorial disease arising from a primary epidermal barrier defect, immunological dysregulation and negative environmental insults.[1] AD is considered a lifelong condition, the natural progression of which alternates between periods of active disease and remission.[2] The AD remission phase is characterised by a subclinical epidermal barrier defect accompanied by the presence of subclinical inflammation.[3,4] The proactive use of topical anti-inflammatory therapy is an effective method of addressing the subclinical inflammation associated with the remission phase of atopic dermatitis. Both topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) have comparable efficacy when used in this manner,[5] although to date, the interaction of a proactive treatment dose with the subclinical epidermal barrier defect in AD is yet to be determined. Here a novel study design was employed using subjects with quiescent AD that are flare-free, allowing the interaction of the treatments with the subclinical epidermal barrier defect to be determined independently from their primary anti-inflammatory properties.

### AIM

1) To perform a randomised, observer-blind functional mechanistic study (FMS) to assess the effect of proactive TCS or TCI treatment on the biophysical and biological properties of the epidermal barrier in subjects with quiescent AD.

## METHODS

### Subjects and Treatment

23 volunteers with a self-reported, recent history of AD (no symptoms in the last 6 months) were recruited. Basic exclusion criteria included pregnancy, breast feeding and being under the age of 18. Informed consent was obtained prior to participation. Volunteers applied 2FTU (finger-tip units) of betamethasone valerate (0.1%) cream (BMVc) to one forearm and 2FTU of tacrolimus (0.1%) ointment (TACo) to the opposing forearm twice-per-week for 8 weeks. 17 volunteers successfully completed the study.

### Biophysical measurements

Skin barrier function, integrity and cohesion were determined by measuring transepidermal water loss in a climate controlled room (21 ± 2°C, 38-50% RH) with an AquaFlux TEWL machine (Biox, UK)[6], tape-stripping[7] and IR densitometry.[8] Volunteers were acclimatised to the room conditions for 20 minutes prior to the assessments being made. All measurements were performed by the same, suitably trained technician.

Skin surface pH and stratum corneum (SC) hydration were determined using a Skin-pH-meter and Corneometer (C&K, Germany).[9,10]

### Biological assessments

Specific caseinolytic, chymotrypsin-like and trypsin-like protease activity was determined by *ex-vivo* analysis through adaptation of a previously published assay.[11]

### Regimen

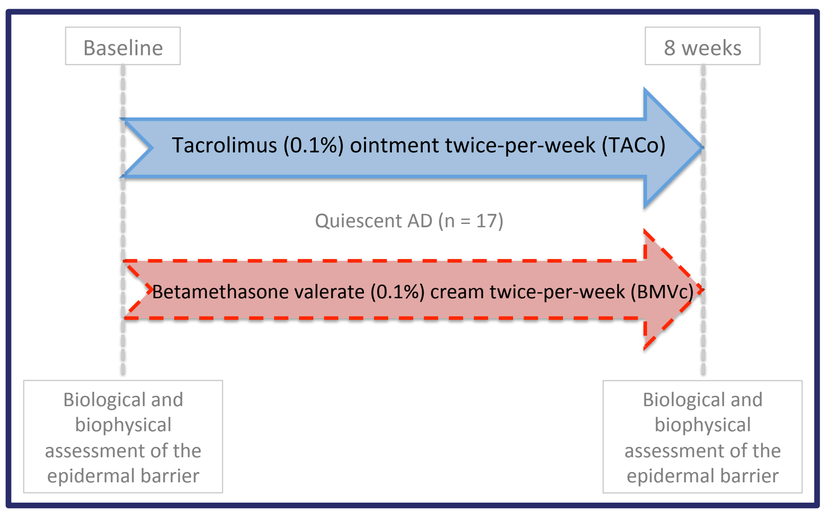



**Figure 1:** Overview of the treatment regimen designed to mimic a proactive therapy strategy once induction of flare remission has been achieved.

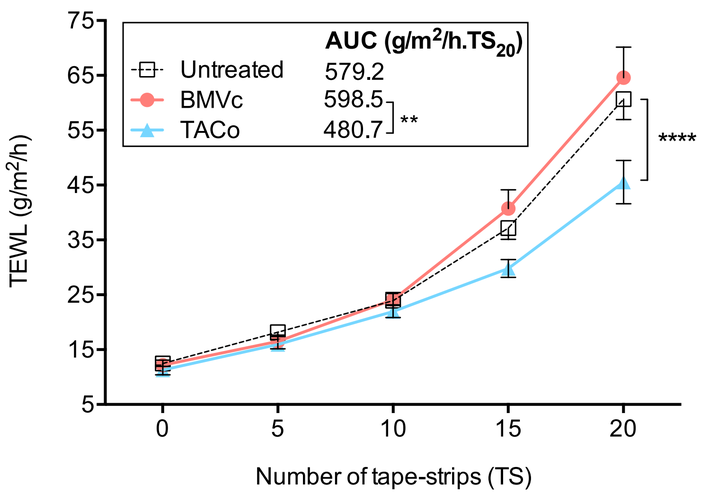
### Ethics

This study was approved by the NHS trent multicentre research ethics committee (MREC) under the project reference 04/MREC/70

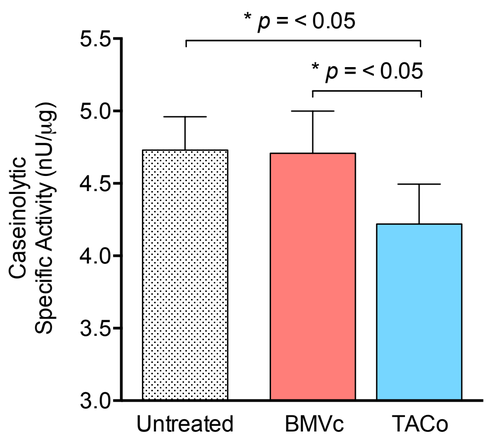
## RESULTS

### Differential effect of TACo and BMVc on the biophysical and biological properties of the epidermal barrier

**a** TACo improves SC integrity determined by tape strip TEWL




**c** TACo significantly suppresses Caseinolytic and Trypsin-like protease activity

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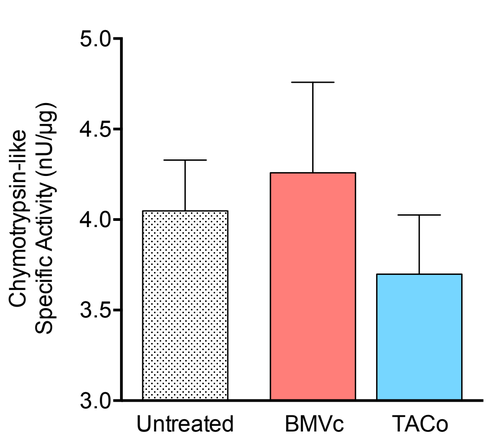


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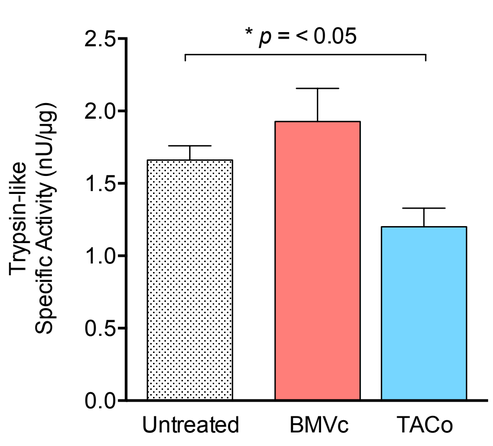
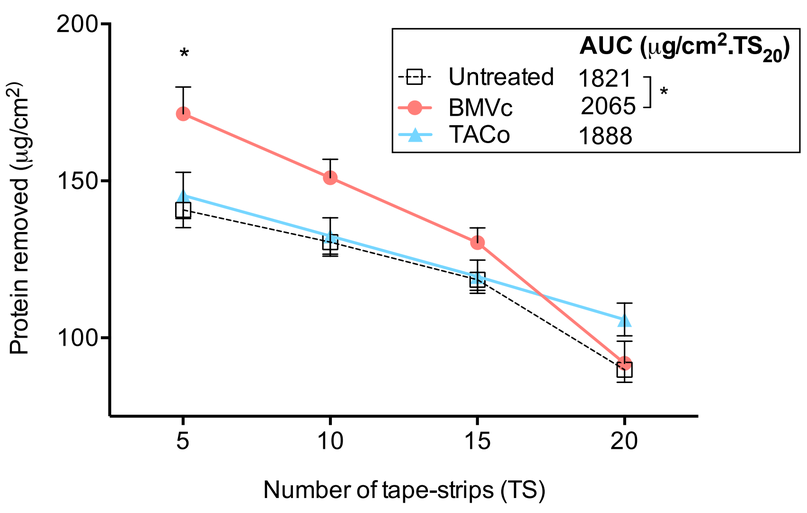
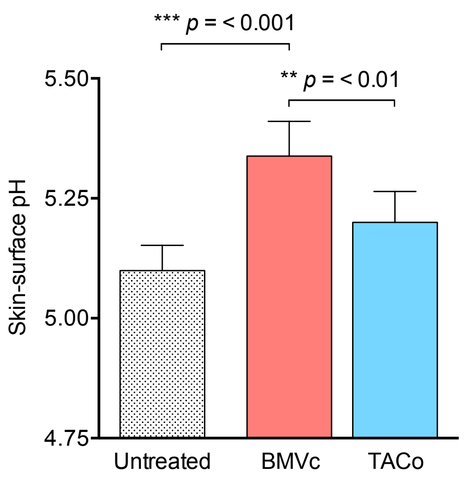


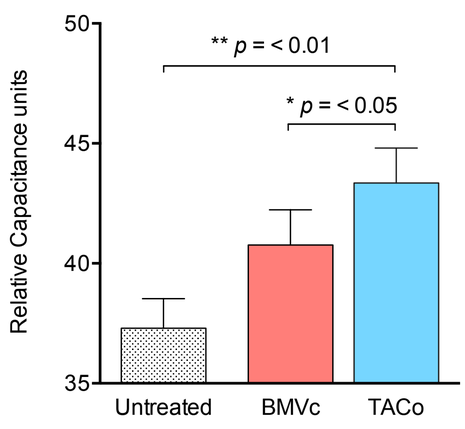

**b** BMVc elevates skin-surface pH with concomitant loss of SC cohesion




**f**




**g** TACo elevates SC hydration

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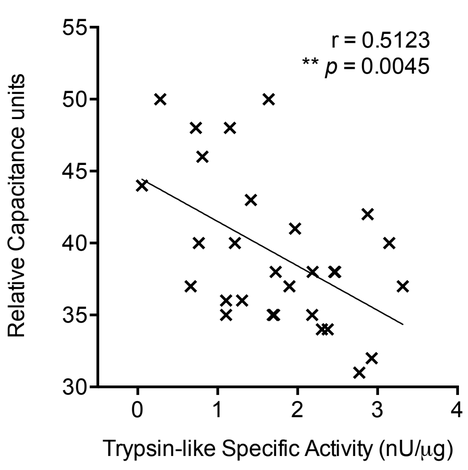


**Figure 2: (a)** Tape-stripping combined with TEWL measurements every 5 discs to quantify epidermal barrier integrity in response to the treatment interventions. A significant differential effect on epidermal barrier integrity was observed following an area under the curve (AUC) analysis (**$p$ = < 0.01). At disc 20, a 1-way analysis of variance (ANOVA) combined with Bonferroni post-test identified an improvement in epidermal barrier integrity by TACo compared to untreated skin (****$p$ = < 0.0001). **(b)** IR densitometry was employed to assay SC integrity. An AUC analysis combined with 1-way ANOVA demonstrated the damaging effect of BMVc on SC integrity (*$p$ = < 0.05). **(c)** TACo significantly suppressed Caseinolytic (*$p$ = < 0.05), **(e)** Trypsin-like (*$p$ = < 0.05), but not **(d)** Chymotrypsin-like protease activity compared to untreated skin quantified *ex-vivo* from pooled tape-strips 1-3. **(f)** BMVc significantly elevated skin-surface pH (***$p$ = < 0.001). **(g)** TACo significantly hydrated the SC compared to the BMVc treated arm (*$p$ = < 0.05) and untreated skin (**$p$ = < 0.01). **(h)** The relationship between SC hydration and trypsin-like protease activity observed at untreated sites (Pearson coefficient r = 0.51). The graphs represent the mean of 17 volunteers with error bars indicating the SEM.

## CONCLUSIONS

- A FMS using subjects with quiescent AD is a novel tool for assessing the direct action of topical anti-inflammatory therapy on the defective epidermal barrier.
- The proactive use of BMVc over 8 weeks raised skin-surface pH with a concomitant loss of SC cohesion.
- By significantly improving SC hydration and integrity, lowering caseinolytic / trypsin-like protease activity and preserving multiple components of epidermal barrier function, TACo treatment offers superior epidermal barrier safety for the proactive management of AD.
- Treatment regimens focusing on epidermal barrier repair could reduce AD severity and in the long-term be disease modifying.[12]

## REFERENCES

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## FURTHER INFORMATION

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https://www.sheffield.ac.uk/infectionandimmunity/units/dermatology

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