Narrowband ultraviolet B phototherapy is associated with a reduction in topical corticosteroid and clinical improvement in atopic dermatitis: a historical inception cohort study

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Summary

Background. Despite decades of use, the magnitude of efficacy of narrowband ultraviolet B (NB-UVB) phototherapy for atopic dermatitis (AD) beyond industry-sponsored trials remains unclear.

Aim. To evaluate the clinical efficacy of NB-UVB in AD under real-world conditions.

Methods. We conducted a historical inception cohort study using automated recording of dispensed drugs to provide an objective treatment outcome in a large population catchment of 420 000 people over 15 years. We analysed clinical treatment outcomes, recorded multicentre and prospectively over 15 years, of a large AD treatment cohort (n = 844), along with the drugs dispensed to this cohort.

Results. The majority (70%) of patients with AD received significantly fewer topical corticosteroids (TCS) during the 12-month window after finishing NB-UVB compared with the 12-month window before starting the treatment (median reduction from 37.5 to 19.7 g/month). The number of patients dispensed with oral corticosteroids and antihistamines also dropped significantly (from 20% to 10% and from 69% to 31%, respectively), while all AD-unrelated drugs dispensed remained unchanged. Clinically, NB-UVB treatment achieved a ‘clear’ or ‘almost clear’ status in 48.7% of patients, while 20.4% achieved ‘moderate clearance’. Treatment outcomes scores were validated by a strong correlation with reduction in AD-specific drug treatment.

Conclusion. Our data confirm the significant efficacy of NB-UVB for AD under conditions of routine care.

Introduction

Narrowband ultraviolet B (NB-UVB) has been in use for atopic dermatitis (AD) for decades, and its efficacy has been confirmed in randomized controlled trials.¹,² However, data on efficacy beyond formal studies are limited to small studies or case series,¹-⁴ some focused only on children,⁵-⁹ and a lack of information on efficacy under real-world conditions is well recognized.¹⁰ The assessment of efficacy beyond controlled interventional studies is limited by a number of issues, including (i) lack of prospective data collection, (ii) patient selection bias and (iii) recording bias due to incomplete data return. The population in Tayside in Scotland receives near-complete provision of healthcare organized by a single provider (the National Health Service) that offers resources addressing these limitations, including automated capture of all prescription drugs, prospectively collected NB-UVB treatment outcomes, electronic recording of specialist-validated diagnoses and review status for all patients referred for treatment from primary care in a
population catchment of 420 000. Using these resources, we previously reported on the clinical characteristics of patients with AD not controlled in primary care, along with the amounts of topical corticosteroids (TCS) and emollients dispensed to these patients.11

Randomized controlled trials commonly report outcomes for AD treatments, using instruments such as the Eczema Area and Severity Index (EASI) and SCORing Atopic Dermatitis (SCORAD), in a blinded manner. By contrast, in routine clinical care, outcome monitoring is aimed at establishing if a perceived benefit would justify potential future repeat treatment for a given patient. Therefore, clinical outcomes are openly recorded on a categorical scale with respect to change from baseline. Notably, despite the lack of blinding, we previously observed that the clinically assigned outcomes recorded for NB-UVB correlate with prospectively and assessor-blinded effects on consumption of TCS in psoriasis.12 We therefore sought to explore whether clinical outcome scoring could also provide a valid measure of efficacy in AD.

A general limitation in real-world AD studies is that the severity of disease at baseline is not strictly quantified in routine clinical care. Therefore, patient populations are more heterogeneous than those studied in interventional trials. In this regard, we previously detailed the clinical severity profile of all patients with AD referred to dermatology departments from primary care in Tayside/North-East Fife.11 We report the efficacy of NB-UVB in AD under conditions of routine clinical care.

Methods

Owing to space constraints, the ethics and STROBE statements, along with a detailed Methods section have been placed into Data S1 except for the following brief summary on study design.

Overall study design

This was an inception cohort study combining prospective and retrospective elements as follows. At the time of administration, NB-UVB formed part of routine medical care. This study included all consecutive treatment courses meeting the inclusion criteria (failure of topical treatment and suitability for phototherapy, see Data S1 for Methods). The primary outcome measures included the quantities of TCS dispensed in primary care for the 12 months before and 12 months after NB-UVB treatment course. These data were collected prospectively, either blinded (dispensed drugs) or open (NB-UVB therapy clinical outcome score). Data on dispensed drugs were gathered from Health Informatic Centre Tayside, while clinical outcomes of NB-UVB therapy, rated by both phototherapy nurses and patients combined, were collected using datasets derived from the Photosys database at four independent treatment sites. Data analysis and statistical testing were performed retrospectively. Patient selection, assembly of cohort, data refinement and quality checks have been described in detail previously.11 Definition of observational window, cohort refinement and validation are detailed in Data S1. The overall design was a nonplacebo-controlled before-versus-after treatment analysis as detailed in Results below.

Results

A large multicentre real-world atopic dermatitis treatment cohort

Table 1 summarizes the baseline characteristics of the patient cohort prior to receiving NB-UVB. Patients received near-universal regular TCS, and exhibited a comorbidity profile in keeping with active AD (Table 1). Approximately one-fifth of patients had received oral systemic corticosteroids prior to NB-UVB, while the cohort was largely naïve to other systemic immunosuppressive treatments. Body surface area (BSA) and EASI data had not been collected as part of routine care. Nonetheless, the availability of quantitative monthly data on TCS dispensed makes it likely that mean BSA involvement exceeded 10% at baseline across the cohort, as detailed previously.11 This inference was further supported by measurement of EASI in an explorative patient group at baseline, which yielded a mean ± SD score of 22 ± 12 (n = 6). In addition, the presence of continued active AD in this patient cohort is further supported by the fact that significant time elapsed between primary care referral and (i) initial dermatology review (range 2–10 weeks), (ii) initiation of phototherapy (2–8 weeks) and (iii) completion of the first 10 courses of treatment (range 1–89 treatments per course). The patients comprising this cohort did not default appointments or drop out early, all of which makes spontaneous substantial improvement of their condition unlikely. Taken together, despite the lack of EASI/SCORAD data, the cohort presented here probably represents a moderate to severe AD phenotype.
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**Table 1** Baseline clinical characteristics of the patients with atopic dermatitis treated with narrowband ultraviolet B.a

| Clinical characteristics | n (%) |
|--------------------------|-------|
| Age, years; mean ± SD    | 30.8 ± 16.5 |
| Male, %                  | 46.9 |
| Baseline NB-UVB, MEDb; mean ± SD | 0.17 ± 0.086 |
| Pre NB-UVB treatment status, n (%) | |
| Dispersed TCS           | 762 (94.3) |
| Oral systemic corticosteroid treatment* | 167 (19.8) |
| Other systemic treatments for AD* | 6 (0.7) |
| Atopic comorbidities, n (%) | |
| Asthma*                    | 243 (28.8) |
| Elevated IgE              | 249 (28.5) |
| Allergic rhinitis          | 93 (11) |

AD, atopic dermatitis; MED, minimal erythema dose; NB, narrowband; TCS, topical corticosteroid; UVB, ultraviolet B. aThe treatment cohort comprised all patients with AD referred for a first-ever course of NB-UVB for AD not controlled by topical treatment during the period 1 January 1986–1 September 2017. A comprehensive co-morbidity spectrum of the patient cohort has been reported previously.11 For details, see Methods. bMED to NB-UVB at 24-h reading. cValue shown represents the percentage observed (90.3%) after correction for missing data (Information Services Division Scotland reported overall completeness of data capture of 95.8% ± 1.0% for the index years 2010–2016). dAt least one course of oral systemic corticosteroids in the 12 months prior to NB-UVB. eMethotrexate, ciclosporin, azathioprine. Defined by required regular dispensing of asthma-specific British National Formulary-coded preparations prior to baseline.11

**Table 2** Monthly dispensed topical corticosteroid to patients with atopic dermatitis during the 12 months before and after narrowband ultraviolet B.a

| TCS dispensed, g/month | Before | After |
|------------------------|--------|-------|
| Patients | Mean | CI | Median | Mean | CI | Median |
| All patients | 50.6 | 46–54 | 37.5 | 41.0 | 35–46 | 19.7* |
| Age range, years |   |      |       |   |      |       |
| 0–15 | 70.0 | 50–89 | 54.6 | 55.3 | 39–71 | 32.5 |
| (n = 49) |       |       |       |       |       |       |
| 16–25 | 43.5 | 39–47 | 34.8 | 32.8 | 27–38 | 16.6* |
| (n = 314) |       |       |       |       |       |       |
| > 25 | 54.0 | 47–60 | 35.8 | 46.0 | 36–55 | 21.6* |
| (n = 373) |       |       |       |       |       |       |

TCS, topical corticosteroid. aData shown include patients with atopic dermatitis not receiving TCS (approximately 5%). The corresponding data, excluding any patients not receiving any TCS treatment are shown in Table S7. bP < 0.001 for before vs. after narrowband ultraviolet B (Wilcoxon matched-pairs signed-rank test).

Significant reduction of topical corticosteroids dispensed after narrowband ultraviolet B treatment

The data for dispensed TCS are electronically captured for all patients (see Methods). Observers are blinded to this quantity. Hence, the TCS dispensed before vs. after NB-UVB treatment provides a prospectively collected, objective clinical endpoint. To minimize seasonal fluctuations impacting on the dispensed TCS data, we analysed the mean dispensed TCS or the 12 months before and 12 months after NB-UVB treatment. The mean number of NB-UVB treatments per course received was 27 (interquartile range 17). Data were analysed for the entire cohort, as well as for three age-range subgroups (< 16, 16–25, > 25 years), respectively.11 with the cutoff between these groups chosen as the best fit to the age distribution observed within this cohort.

As shown in Table 2, we observed an overall reduction of median TCS dispensed from 37.5 to 19.7 g/month following NB-UVB (P < 0.001), mirroring a marked increase in the number of patients not requiring any TCS at all among the adult cohorts (Fig. 1a). We also noted a slight decrease in the dispensed emollients, reaching borderline significance in male patients (Fig. S1). Approximately 70% of patients exhibited a decrease in TCS dispensed (Fig. 1b). Despite the overall mean reduction in dispensed TCS, there was individual patient variability, with some patients showing only a slight decrease and some showing an increase in the amount of TCS received. This variability might partly be explained by greater use of milder TCS products, although we did not analyse dispensed TCS by potency. When analysed by sex, changes were more pronounced in female patients (Fig. 1c). As expected, the reduction in dispensed TCS was even greater within the first 3 months immediately after NB-UVB (Fig. S2). Furthermore, the number of patients who were started on systemic immunosuppressive treatment during the 12 months after NB-UVB treatment remained small at 1.1% (n = 10), particularly in the context of there being six patients who had received immunosuppressive treatment prior to phototherapy, suggesting that the observed 12-month data probably represent a continued prolonged effect of the phototherapy treatment.

Changes in drug treatment after narrowband ultraviolet B are specific to atopic dermatitis-targeted treatments

We also observed a significant reduction in the number of patients dispensed antihistamines or oral systemic corticosteroids after NB-UVB (Fig. S3). By
contrast, there were no changes in any of a large number of treatments unrelated to AD (Table S1).

Significantly improved clinical outcome in almost half of patients did not differ significantly across four independent treatment sites

We next analysed the recorded clinical outcomes of NB-UVB based on nurse assessor combined with patient’s opinion, using a categorical scale (Fig. S4a). As clinical outcomes are assigned without blinding, we initially performed a systematic analysis of bias. Recorded outcomes did not significantly differ between four independent treatment sites staffed by different raters (Fig. S4b). They also remained remarkably stable across >2 decades (Fig. S4c), indicating resilience to ‘scoring drift’ over time. Overall, a clinical outcome of ‘significant improvement’, which included the outcomes of ‘clear’ or ‘almost clear’, was assigned to 48.7% of patients with AD, whereas ‘moderate clearance’ was assigned to 20.4% of patients with AD (including patients lacking recorded outcome, who were conservatively scored as ‘not improved’).

Clinical outcome scores are independently validated by the impact of narrowband ultraviolet B on dispensed topical corticosteroids

We next asked whether the clinically recorded outcomes correlate with the measured reduction in dispensed TCS. As shown in Fig. 2a, the reduction in dispensed TCS after finishing treatment was greatest in patients recorded as significantly improved and smallest in those without clinically recorded improvement, both in terms of the actual quantity of dispensed TCS (Fig. 2a) and the number of prescriptions filled per patient (Table 3). Importantly, these results did not change after exclusion of patients with minimal UVB exposure (Table S2). Equally, the results did not change after exclusion of patients with concurrent potentially confounding diagnoses (psoriasis, discoid eczema, urticaria: Fig. S5). Furthermore, the number of patients exhibiting a substantial reduction in dispensed TCS (defined as ≥25%) was also significantly associated with clinical outcome groups (Fig. 2b). Taken together, clinical outcome, assessed at the conclusion of treatment, strongly correlated with reduction of dispensed TCS during the subsequent 12 months.
Patients with good clinical outcome after narrowband ultraviolet B exhibit greater reduction in antihistamines and oral systemic corticosteroids dispensed

We next analysed all other treatments before vs. after NB-UVB in the three clinical outcome subgroups. As shown in Fig. 3, patients with substantial clinical improvement also showed a significantly greater reduction in treatment with oral systemic corticosteroids and in antihistamines, but not in any non-AD-related drug treatment. These data further support the validity of the clinical recorded outcomes.

Discussion

NB-UVB is widely used as a treatment for moderate to severe AD. However, the lack of objective clinical outcome measures available in routine clinical care has prevented reliable assessment of efficacy under real-world conditions. In this study, we analysed the efficacy of NB-UVB using automated prescription capture as an objective outcome measure in a large real-world cohort. Collected at the point of drug dispensing, these data allow quantification of the actual AD medications issued to patients. Overall, NB-UVB caused a significant reduction in median dispensed TCS, which was sustained for at least a year after treatment and is of clinical relevance. There were also reductions in dispensed antihistamines (reflecting the antipruritic activity of NB-UVB) and oral systemic corticosteroids, but none in AD-unrelated treatments.

In addition to objective recording of dispensed drugs, we analysed in detail the validity and overall result of clinical outcome recording. Despite the lack of blinding, the assignment of clinical outcomes did not differ significantly across different raters in four independent treatment sites or across different years. This may be due to the fact that scores are not recorded to confirm efficacy but rather as a management guide to inform decisions on future repeat treatment. The validity of the assigned clinical scores is further supported by the significant overlap between these scores and the reduction in dispensed TCS, antihistamines and oral systemic corticosteroids. Future studies are needed to assess the effect of NB-UVB on quality of life (QoL).

In terms of prediction of treatment outcome, none of the potential predictors available at baseline, including dispensed TCS or antihistamines, minimal erythema UVB dose, age or sex was associated with clinical outcome. Genetic association studies, e.g. using the population-based recruitment strategies previously used for psoriasis, might uncover predictive markers allowing prospective identification of patients likely to benefit from treatment.

There were some limitations to this study. It was a noncomparative study. We used drugs dispensed to patients or drugs received by patients as a proxy for drug use in the interpretation. Data on the strength of the TCS received by the patients were not available, therefore, changes in TCS potency such as an increased amount of milder TCS or a reduced amount of more potent TCS dispensed to patients after NB-UVB therapy were not captured. The results reported here may not transfer to populations exhibiting a different genetic background. Other limitations include the relatively low number of patients in both the young and older population segments, the lack of access to direct quantitative data on pretreatment disease severity, and...
other pertinent clinical features such as body mass index or measures of QoL.17

Conclusion
NB-UVB leads to reported clearance and near-clearance in roughly half of patients with moderate to severe AD under real-world conditions, and 70% of patients exhibit significantly reduced dispensed TCS. Measurement of dispensed drugs may afford an important clinical endpoint that will be useful to define the impact of emerging systemic treatments.

Acknowledgement
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What’s already known about this topic?

- NB-UVB has shown efficacy in AD in small clinical trials.

What does this study add?

- In this study, 70% of patients with AD showed a significant reduction in dispensed TCS during the 12-month period after finishing NB-UVB, compared with before starting NB-UVB.
- This reduction lasted for at least a year after treatment.
- NB-UVB treatment achieved a ‘clear’ or ‘almost clear’ status in 48.7% of patients.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

File S1. Contains the additional material described in brief below.
Table S1. The number of prescriptions of atopic dermatitis-unrelated drugs received by patients before and after narrowband ultraviolet B.
Table S2. Atopic dermatitis-related prescriptions for patients before and after at least 10 treatments per course of narrowband ultraviolet B.
Table S3. The observational windows for atopic dermatitis-related and atopic dermatitis-unrelated drug prescriptions and quantity of drug dispensed, respectively.
Table S4. Monthly topical corticosteroids dispensed before vs. after exclusion of patients with concurrent chronic inflammatory confounding diagnoses.
Table S5. Monthly topical corticosteroids dispensed before vs. after exclusion of patients with 2nd treatment commenced within 12 months after first course of narrowband ultraviolet B.

Table S6. Monthly topical corticosteroids dispensed between patients with and without second treatment commenced within 12 months after first course of narrowband ultraviolet B, respectively.

Table S7. Monthly topical corticosteroids dispensed limited to atopic dermatitis patients receiving topical corticosteroids prescriptions before and after narrowband ultraviolet B, respectively.

Figure S1. Daily amount of emollient (in grams) dispensed to patients during 12 months before narrowband ultraviolet B (grey) and 12 months after narrowband ultraviolet B (white), respectively, broken down by sex.

Figure S2. The monthly amount of topical corticosteroids (in grams) dispensed to patients with atopic dermatitis during the first 3 months after narrowband ultraviolet B (grey), as well as the entire 12-month interval after narrowband ultraviolet B (white), respectively, broken down by sex and age range.

Figure S3. The number of patients with atopic dermatitis (%) who received topical corticosteroid, antihistamine and systemic corticosteroid respectively, 12 months before (grey) and 12 months after (white) narrowband ultraviolet B, respectively.

Figure S4. The overall clinical outcome of narrowband ultraviolet B treatment for atopic dermatitis under real-world conditions in NHS Tayside.

Figure S5. Monthly topical corticosteroids (in grams) dispensed to atopic dermatitis patients during 12 months before (grey) and 12 months after (white) narrowband ultraviolet B, respectively, after exclusion of patients with concurrent chronic inflammatory confounding diagnoses.

Figure S6. Ultraviolet B analysis for clinical vs. technical efficacy of narrowband ultraviolet B.

Figure S7. The distribution of patients (in %) with their respective number of treatments per course of narrowband ultraviolet B, broken down by the three main clinical outcomes.

Figure S8. The distribution of clinical outcomes (in %) between subgroups of patients with and without second ultraviolet B treatment commenced within 12 months of post narrowband ultraviolet B period, including only patients with minimal exposure (at least 10 treatments per course) in the first exposure of narrowband ultraviolet B in both subgroups.