Appendix I: Background information

Solar exposure has a therapeutic effect on AE. It is dependent of the ultraviolet (UV) dose whereas it seems independent of the solar spectrum at ground level.[42] Both radiation with relative higher UVA content (altitude below sea level, e.g. Dead Sea),[42] as well as radiation with relative higher UVB content (high mountains, e.g. Davos) were found effective.[43]

Photobiology of AE treatments

Both UVA and UVB are effective in the treatment of AE, although photochemical and photobiological activities are different. At molecular level, UVB effects are mainly mediated by anaerobic direct damage to DNA whereas UVA acts mainly through oxidative damage to DNA, proteins and lipids. The depth of penetration into the skin affects the target cell populations; UVB penetrates only the epidermis, whereas UVA also penetrates the dermis.

Despite these biological differences, both wavebands have beneficial effects on reducing inflammation, restoring barrier function, rebalancing bacterial colonization and relieving itch.

In AE lesions, NB-UVB phototherapy causes depletion of T cells, suppresses the Th2, Th22, and Th1 axes and removes inflammatory leukocytes.[44] It inhibits keratinocyte ICAM-1 upregulation thus preventing the maintenance of the inflammatory infiltrate.[45] Unlike UVA, UVB increases TNF-alpha concentration in suction blister fluid.[46]

The expression of terminal differentiation proteins loricrin (LOR), filaggrin (FLG), and involucrin (IVL) in keratinocytes is normalized, mainly through the activation of the vitamin D system, leading to restoring of epidermal differentiation and functionality of the skin barrier.[44, 47]

BB-UVB restores the natural antimicrobial function of the skin increasing the synthesis of antimicrobial peptide (AMP), beta-defensin (mBD)-2, mBD3 and cathelin-related antimicrobial peptide (CRAMP) in mouse skin.[47]

NB-UVB was found to increase cathelicidin in human AE skin.[48] Further, it increases the microbial diversity of lesional skin and reduces the proportion of Staphylococcus aureus.[49] NB-UVB increases serum vitamin D level in AE patients but effects on circulating blood cell populations or serum cytokines seem low, if any.[50]

UVA1 induces apoptosis of T helper cells in the dermal compartment of AE skin,[51] and depletion and loss of function of antigen-presenting cells, including Langerhans cells, within the epidermis and dermis. In AE skin, mRNA expression of Th2-associated cytokines IL-5, IL-13 and IL-31[52] and

levels of ICAM-1[45] are reduced whereas the mRNA expression of anti-inflammatory IL-10 is increased.[53] In addition, UVA1 suppresses proinflammatory cytokines such as IFN-γ,[45] TNF-α and IL-12, which activate antibody-dependent cell-mediated cytotoxicity (ADCC) and inflammatory leukocytes such as eosinophils.[46] UVA1, unlike UVB, induces both early and late apoptosis of human Th2 cells cloned from lesional AE skin.[51]

Both UVA and UVB target cutaneous sensory nerves, neuropeptides, neurotrophins and certain nerve-related receptors, improving itch and modulating immune responses.[54]

Artificial light sources and current treatment regimens for AE

Lights with different emission spectra in the UV range have been used successfully for phototherapy in AE. Examples are UVB (incl. broadband (BB, 280-315nm) and narrowband (NB, 311-313nm)), UVA (incl. UVA1 (340-400nm), psoralens and UVA (PUVA)), and UVAB (280-400nm). A recent survey among 238 dermatologists from 30 European countries showed that photo(chemo)therapy is the first line therapy of choice in this population, prescribed by 41.5% of dermatologists,[33] in particular NBUVB (80.9%).[33] Currently, the mainstay phototherapy modalities used for AE in Europe are NB-UVB and UVA1, increasingly replacing BB-UVB and UVAB.

The use of other light therapies has been explored recently. Non-erythemogenic short-wave visible light (> 380 nm) ('blue light') had some effects in an uncontrolled pilot study,[55] and in an RCT enrolling a small number of patients.[56] 308nm monochromatic excimer laser and pulsed-dye laser have also demonstrated some effectiveness,[57, 58] but due to the small irradiation field they are suitable only for patients with localized AE that is resistant to topical treatments.

For all treatments with UVB in the emission spectrum, initial light doses are set on the basis of the individual minimal erythemal dose (MED) or the skin phototype, and the dose is adjusted at each session (usually 2-3 per week) with 5-20% dose increments. Because of the low erythemogenicity, UVA1 is delivered with fixed doses and 2-3 weekly exposures to high (70-130 J/cm^2), medium (40-60 J/cm^2) and low doses (10-30 J/cm^2).

PUVA photochemotherapy is based on the oral or topical exposure to psoralen followed by increasing doses of BB-UVA (320-400 nm). It was widely used from 1970s to 1990s but it is now

considered a second-line treatment because of the long-term risks of skin cancer, in particular noted in psoriasis cohorts.[38, 39] Extracorporeal PUVA (photopheresis) was used for the treatment of patients with severe AE that is refractory to all other treatments.[59]

Practical aspects of AE treatment

In clinical practice, the choice for a certain UV treatment is limited by the availability of the phototherapy equipment. NB-UVB is found in the large majority of dermatology departments but only few centers have other equipments, such as UVA1 machines. Difficulties for the patient are the limited access to in-office treatment, difficulty adhering to twice- or thrice-weekly treatment schedules, and flaring from excessive heat. Preliminary data indicate that home phototherapy can increase treatment adherence without a decrease of overall effectiveness.[60] Further, UV light does not effectively treat hairy areas and major skin folds. At the beginning of phototherapy, the concomitant use of topical corticosteroids and emollients should be considered to prevent a possible flare-up. UV therapy has to comply with special requirements with regard to personnel, documentation, UV protection especially of the eyes, contraindications and technical aspects.

Appendix II: Search strategy

We carried out an update of the search strategy from Garritsen et al. in CENTRAL on 03 July 2020. This search was limited to publication date 26 October 2012 onwards as shown below. The search strategy retrieved a total of 235 hits. All records from Embase (n=104) and PubMed (n=79) were included, after deduplication 185 records remained. All records underwent title and abstract screening by one reviewer. Records from clinical trial registries were excluded (n=52).

#	Search term	Hits
1	MeSH descriptor: [Eczema] explode all trees	1039
2	MeSH descriptor: [Dermatitis, Atopic] explode all trees	1760
3	MeSH descriptor: [Neurodermatitis] explode all trees	68
4	MeSH descriptor: [Dermatitis] explode all trees	4026
5	eczema or dermatitis or neurodermatitis:ti,ab,kw	10196
6	besnier$ prurigo:ti,ab,kw	7
7	#1 or #2 or #3 or #4 or #5 or #6	10789
8	MeSH descriptor: [Phototherapy] explode all trees	3109
9	MeSH descriptor: [Ultraviolet Therapy] explode all trees	597
10	MeSH descriptor: [Photochemotherapy] explode all trees	846
11	MeSH descriptor: [PUVA Therapy] explode all trees	233
12	MeSH descriptor: [Ultraviolet Rays] explode all trees	651
13	MeSH descriptor: [Lasers] explode all trees	2096
14	(photodynamic therap*):ti,ab,kw or (phototherap*):ti,ab,kw or (photochemotherap*):ti,ab,kw or (puva):ti,ab,kw or (ultraviolet):ti,ab,kw	8060
15	(light therap*):ti,ab,kw or (photoradiation therap*):ti,ab,kw or (BBUVB):ti,ab,kw or (NBUVB):ti,ab,kw or (BB-UVB or NV-UVB):ti,ab,kw	9541
16	(broad band uvb):ti,ab,kw or (broad band ultraviolet b):ti,ab,kw or (narrow band uvb):ti,ab,kw or (narrow band ultraviolet b):ti,ab,kw	262
17	(psoralen ultraviolet a):ti,ab,kw or (psoralen uva):ti,ab,kw	236
18	(balneophototherapy):ti,ab,kw or (balneo-phototherapy):ti,ab,kw	20
19	MeSH descriptor: [Furocoumarins] explode all trees	194
20	MeSH descriptor: [Heliotherapy] explode all trees	22
21	MeSH descriptor: [Climatotherapy] explode all trees	8
22	(LLLT or LILT or LPLT):ti,ab,kw	805
23	(psoralen*):ti,ab,kw or (furocoumarin*):ti,ab,kw or (furanocoumarin*):ti,ab,kw or (ficusin):ti,ab,kw or (khellin):ti,ab,kw or (visammin):ti,ab,kw or (deltasoralen):ti,ab,kw or (ammoidin):ti,ab,kw or (meladinin*):ti,ab,kw or (meloxine):ti,ab,kw or (methoxa*):ti,ab,kw or (methoxsa*):ti,ab,kw or (oxsoralen):ti,ab,kw or (ultramop):ti,ab,kw or (xanthotoxin):ti,ab,kw or (dermox):ti,ab,kw or (puvalen):ti,ab,kw or (methoxypsoralen):ti,ab,kw or (geroxalen):ti,ab,kw (8?mop):ti,ab,kw or (8mop):ti,ab,kw or (trioxsalen):ti,ab,kw or (trioxysale*):ti,ab,kw or (nsc?71047):ti,ab,kw or (nsc71047):ti,ab,kw or (trimethylpsoralen):ti,ab,kw or (trisoralen):ti,ab,kw	648
24	(heliother*):ti,ab,kw or (helio?ther*):ti,ab,kw or (heliothalasso*):ti,ab,kw or (helio?thalas*) or (balneophoto*):ti,ab,kw or (balneo?photo*):ti,ab,kw or (balneoclimat*):ti,ab,kw or (balneo?climat*):ti,ab,kw or (climatother*):ti,ab,kw or (climat* NEXT therap*):ti,ab,kw or (mountain* NEXT therap*):ti,ab,kw or (altitude NEXT therap*):ti,ab,kw or (Alpine NEXT therap*):ti,ab,kw or (klima* NEXT therap*):ti,ab,kw or (climat* NEXT treat*):ti,ab,kw or (mountain* NEXT	100

	treat*):ti,ab,kw or (altitude NEXT treat*):ti,ab,kw or (Alpine NEXT treat*):ti,ab,kw or (klima* NEXT treat*):ti,ab,kw	
25	#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24	17516
26	#7 and #25	436 (Trials 395, Reviews, 38, Protocols 3)
	Data added to CENTRAL trials database from 26/10/2012 until 30/06/2020	235 hits (Embase = 104, PubMed = 79, CT = 32 and ICTRP = 20) Duplicates removed = 52