

## Evidence-based dermatology: treatment of melasma

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Evidence-based medicine (EBM) has become increasingly important in recent years. EBM can be defined as the 'conscientious, explicit and judicious use of current best evidence about the care of individual patients' [1]. Within this context, 'conscientious' implies an active process requiring learning, doing and reflection; 'implicit' that we can describe the process used to practice EBM, and 'best' implies that we should seek the most reliable evidence source to drive medical practice.

EBM is therefore a way of thinking and working, with the improved health of patients as its central aim. Evidence-based dermatology (EBD) may be defined as integrating one's clinical expertise with the best external evidence from systematic research, with the patient making an informed choice.

Therapy guidelines are not the same as EBM, although many dermatology guidelines now incorporate a grading system that describes the quality of evidence used to make recommendations and the evidence-based strength of those recommendations.

For example, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group classifies the quality of medical evidence as class A (high quality) through to class D or E (very low quality) [2].

Under the GRADE system, class A evidence is based on data from high-quality studies with consistent results or, in special cases, from one large multicentre trial, with further research being highly unlikely to change confidence in it; class B (moderate) evidence is derived from one high-quality study or from several studies with some limitations, in which case further research is likely to have an important impact on confidence in it; class C (low) evidence is from one or more studies with severe limitations, which further research is also likely to change; whereas class D or E (very low) evidence is based on uncertain evidence, such as expert opinion or from one or more studies with severe limitations, with any estimate of effect being very uncertain. The GRADE system can be very well illustrated with reference to the evidence for the various treatments for melasma.

### Melasma

Melasma, a skin condition characterized by areas of dark facial skin discolouration, is particularly common in women,

especially those who are pregnant or are taking hormone-based contraceptives or hormone replacement therapy, due to stimulation of melanocytes by oestrogen and progesterone.

Evidence for melasma therapies ranges from class A for the depigmenting cream Tri-Luma<sup>®</sup> (a triple combination of hydroquinone [HQ] plus the low potency steroid, fluocinolone acetonide and tretinoin), class B for topical treatments including HQ and retinoids, for example tretinoin; down to class C–D for laser ablation-based therapies, and class E evidence only for the efficacy of laser dermabrasion in melasma treatment.

The class A evidence for the safety and efficacy of Tri-Luma<sup>®</sup> cream comes from large multicentre, randomized, controlled Phase III clinical trials such as those by Taylor et al of the efficacy and safety of Tri-Luma<sup>®</sup> cream in the treatment of patients with facial melasma [3].

These were two 8-week studies of Tri-Luma<sup>®</sup> cream versus tretinoin plus HQ, tretinoin plus fluocinolone acetonide, or HQ plus fluocinolone acetonide in 641 patients with moderate to severe melasma (phototype I–IV) treated at 13 study centres. The majority of patients (97%) were women with ages ranging from 21 to 75 years. Ethnicities included Caucasian (66%), Hispanic (26%), Asian (5%) and Negroid (3%).

At week 8, 77% of Tri-Luma<sup>®</sup> cream recipients had achieved completely clear or almost clear facial melasma, compared with 47% with tretinoin plus HQ, 27% with tretinoin plus fluocinolone acetonide, and 42% of patients treated with HQ plus fluocinolone acetonide ( $P < 0.001$  versus other treatment groups) (Figure 1).

The most frequently encountered adverse events seen in the tretinoin alone group included erythema (50% at week 4), burning (37% at week 4), desquamation (25% at week 2), and telangiectasias (15% at week 8). While there were more complaints of these skin conditions at weeks 4 and 6, this was not statistically significant and no differences were seen between the groups at week 8.

Similar class A findings to those of Taylor et al were reported from an 8-week, multicentre, randomized, controlled, investigator-blinded study by Chan et al, who compared the clinical efficacy and safety of Tri-Luma<sup>®</sup> cream versus HQ 4% in 244 Asian subjects with moderate to severe melasma [4].

Statistically significant greater improvements in the mean percentage change from baseline in the melasma area

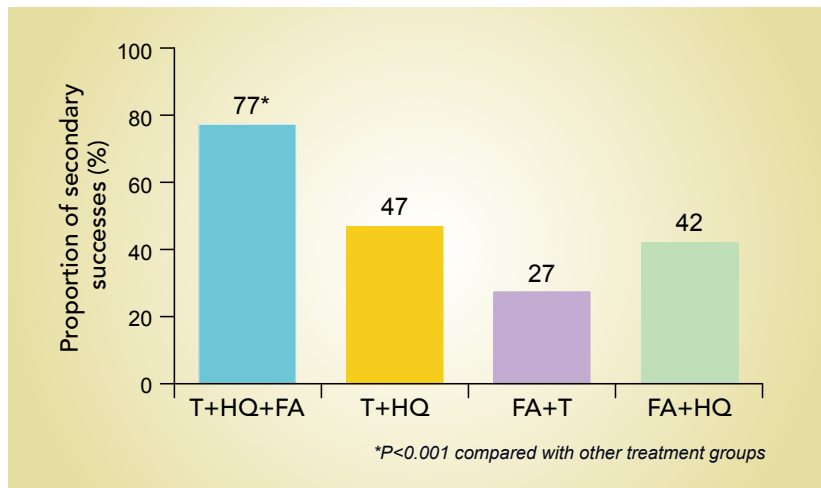


Figure 1. Efficacy of Tri-Luma<sup>®</sup> cream in the treatment of facial melasma: week 8 [3].

and severity index (MASI) score were seen with Tri-Luma<sup>®</sup> cream versus HQ 4% at weeks 4 and 8 ( $P<0.001$ ) (Figure 2).

Regarding safety, 49% of subjects had treatment-related dermatological adverse events, including erythema, irritation, exfoliation, discomfort and pruritis, which patients should be told to expect before treatment. However, just 4% had a moderate adverse event and no severe adverse events were seen.

In contrast to the class A evidence for the safety and efficacy of Tri-Luma<sup>®</sup> cream in melasma therapy, the class B evidence for tretinoin comes from smaller studies such as that by Griffiths et al, in which 38 women were treated with topical 0.1% tretinoin cream or placebo once daily for 40 weeks, after which 68% of tretinoin recipients were improved versus 5% with placebo ( $P=0.00$ ), while colorimetry showed a 0.9-unit lightening with tretinoin versus 0.3-unit darkening with placebo ( $P=0.01$ ) [5].

The class B–C evidence for the safety and efficacy of intense pulsed light (IPL) is from an uncontrolled,

non-comparative, open-label study in 89 Chinese women with melasma. Sixty-nine (77.5%) of the patients obtained 51–100% improvement according to dermatologists, with 71% of patients considering they had >50% improvement, while mean MASI scores decreased substantially from 15.2 to 4.5 [6]. However, study limitations included no control or comparative treatment group.

More class B–C evidence is from a small Taiwan study of IPL in the treatment of refractory melasma in 17 patients versus 16 controls. Those in the IPL group did better than controls, with 35% versus 14% having >50% improvement [7].

Finally, an example of very low class D–E evidence is derived from just two case reports of improvement following treatment of refractory dermal melasma with the MedLite C6 Q-switched Nd:YAG laser.

In conclusion, EBM is based on the concept of an evidential hierarchy ranging from no evidence at all to case reports and expert opinion, case series, non-randomized clinical trials, randomized controlled trials, to systematic reviews, with each step of the hierarchy becoming less biased. Evidence is derived from electronic bibliographic databases and, for clinical trial data, the Cochrane central register of controlled clinical trials.

## References

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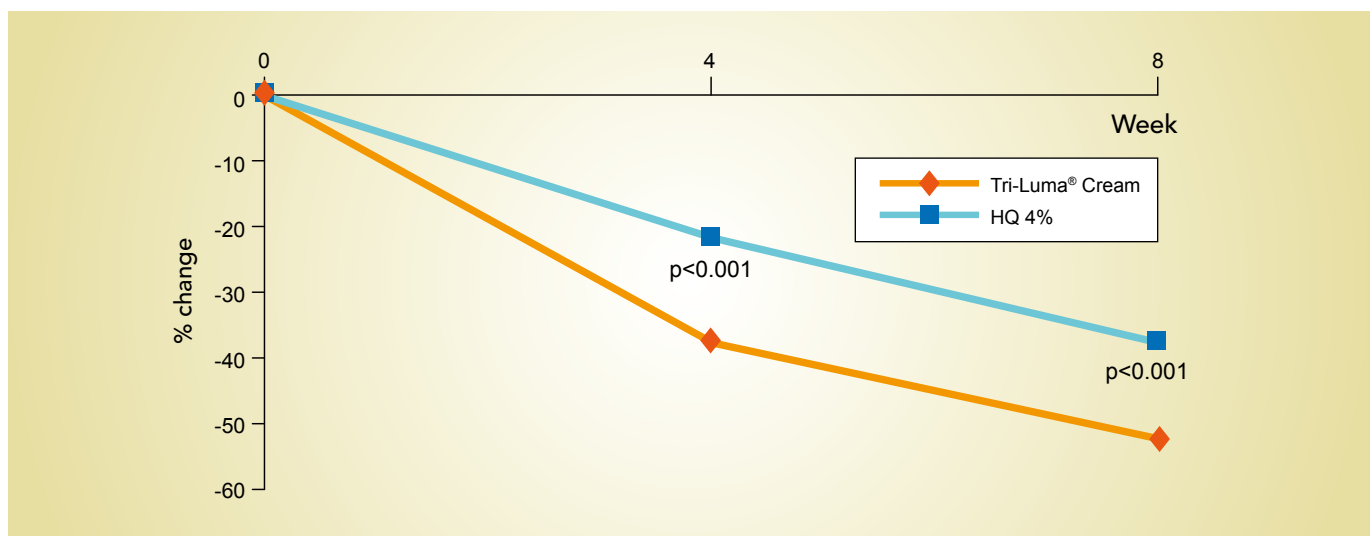


Figure 2. Mean percent change from baseline in the MASI score: Tri-Luma<sup>®</sup> cream versus HQ 4% [4].