Title: Omega-3 Fatty Acids Mitigating Isotretinoin-Induced Cheilitis

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Whilst isotretinoin is an effective treatment for severe acne vulgaris, isotretinoin induced cheilitis is one of the most troubling side effects of the treatment. [1] In their excellent review, which briefly covers the treatments for isotretinoin induced cheilitis, the authors have overlooked the utility of Omega-3 Fatty Acids (O3FA). O3FA, a cluster of long-chain and very-long-chain polyunsaturated fatty acids that the human body cannot synthesise intrinsically, have demonstrated efficacy in improving specific conditions characterised by inflammation, dryness, and moisture loss. [2] There are three main types of O3FA: α-linolenic acid (ALA; found in nuts, seeds, and vegetable oils), eicosapentaenoic acid (EPA; found in fish), and docosahexaenoic acid (DHA; found in fish). [3] Evidence suggested that the consumption of O3FA may abrogate some of the mucocutaneous adverse effects of oral isotretinoin in individuals with acne with few adverse effects. [2] Although the mechanism is unclear, it may be due to anti-inflammatory properties as these fatty acids can modify cell membrane composition, inhibit pro-inflammatory transcription factors like nuclear factor κB, and activate anti-inflammatory factors such as peroxisome proliferator-activated receptor γ, leading to a reduction in the expression of inflammatory genes and, in animal models, reduce transepidermal water loss. [3] A 16-week case-controlled study [2] (n = 104; 64.4% females; mean age 22.8 years) suggested that patients with moderate-severe acne who take O3FA soft gel capsules (1 g/day) alongside isotretinoin (0.5 mg/kg) compared to isotretinoin of same dose alone had significantly reduced dry nose and dry skin (Week 0-16, $p < 0.05$), dry lips (Week 0-12, $p < 0.05$; statistically insignificant reduction in Week 12-16), and dry eyes (Week 0-4, $p < 0.05$; statistically insignificant reduction in Week 4-16). A separate randomised controlled trial [4] on acne (n = 60; 66.7% female; mean age 26.1 years) recommended that O3FA (1 mg/kg) taken with isotretinoin (0.5 mg/kg) compared to isotretinoin monotherapy significantly reduces xerosis (p <0.001) and dry lips (p = 0.013). No adverse effects of O3FA have been reported with either trial. Side effects of systematic isotretinoin such as dryness of the skin and mucosal surfaces can lead to non-concordance and discontinuation of medication. [2] Even though using a lower dose of isotretinoin may ameliorate some of these symptoms, this requires a longer course of isotretinoin, necessitating more follow-up appointments and a longer need to maintain pregnancy prevention measures and monitor psychosexual guidelines. Whilst the above studies are small in number and both efficacy and potential side effects need substantiation in larger trials, we would encourage dermatologists to consider suggesting the

use of this seemingly non-toxic nutraceutical adjunct to patients taking isotretinoin, as part of the holistic care of acne patients.

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