Topical retinoids for acne vulgaris (Protocol)

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[Intervention Protocol]

Topical retinoids for acne vulgaris

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of topical retinoids in the treatment of acne .

BACKGROUND

Description of the condition

Acne vulgaris (which we refer to as acne for the purpose of this review) is a common skin disease of the pilosebaceous gland, which produces oil to keep the skin lubricated. Acne typically begins in puberty, affecting about 80% of adolescents and young adults, but may also arise in adulthood, affecting 8% of those aged 25 to 34 and 3% of those aged 35 to 44 (White 1998). It is estimated that approximately 3.5 million people with acne consult their family doctor annually in the UK (Purdy 2006) and in the US, about 40 to 50 million people are affected by some form of acne (White 1998). Acne lesions are most likely to occur on the face, neck, upper trunk (chest and back) and upper arms where there is a high density of pilosebaceous glands producing sebum. Acne lesions can often leave permanent marks, hyper-pigmentation, less frequently hypertrophic scars, keloids and pitted scars (Longshore 2003).

Impact

Although acne is not a life-threatening condition, it can cause substantial morbidity. Acne and resulting scarring can have a psychological impact including lowered self-image and self-esteem, social impairment and anger (Koo 1995). Even those with minimal acne experience psychological effects and for those people, the psychosocial burden may be the most significant problem with this disease. (Koo 1995) It has been shown that even clinically mild to moderate acne can be associated with higher rates of depression and suicidal thoughts than other chronic and disfiguring skin diseases (Gupta 1998). Adolescents, who are developing their self-identity and are undergoing rapid sexual maturation, are often hormonally and emotionally unstable, so are particularly vulnerable to the psychological impact. Another group at risk of psychological effects due to acne is women, aged 25 to 40, who face such issues as motherhood, adult sexuality and career demands. Acne can add an enormous burden to this group (Richard 2006). Furthermore, it has been shown that there is more unemployment among adults with acne in the UK (Cunliffe 1986). In summary, acne is an important condition and appropriate intervention is essential to prevent complications such as acne scarring, psychological impacts and secondary impaired social function

Causes

It is not fully understood what causes acne. The acne lesion begins with the micro-comedo, a microscopic precursor of all the acne lesions. A therapeutic goal therefore is to stop these lesions from forming (microcomedogenesis.) (Cunliffe 2003) It is believed that the interaction of the following four factors contributes to the development of acne:

a) excess build-up of keratin in the pilosebaceous follicles;

b) excessive sebum production;

c) hypercolonization of the pilosebaceous duct by the bacteria *Propionibacterium acnes (P.acnes);*

d) direct or indirect inflammation due to the release of pro inflammatory mediators from P.acnes resulting in an immune response (Millikan 2003).

As well as these primary factors, some other factors such as genetic factors, stress, diet, smoking, sex (male) and age (youth) have been suggested to affect the acne condition (Haider 2004; Krautheim 2004), however their relationships with acne have not been proven so far. It has been suggested that acne treatment should be directed at these pathogenetic factors, and preferably be combined in order to target as many factors as possible (Gollnick 2003).

Conventional treatments

Conventional acne treatments work by either preventing the pilosebaceous duct from becoming blocked at its follicular opening, reducing the numbers of acne bacteria or controlling excess sebum production (Goulden 2003). Most treatments work on a combination of these factors. Many anti-acne drugs also have an anti-inflammatory effect.

However, a drawback of conventional treatments is that they are mostly palliative, in that they control the symptoms, rather than cure the condition. In fact, acne usually resolves as people grow older, rather than because of treatment. Widely used conventional treatments include retinoids, antibiotics and benzoyl peroxide. Oral contraceptives, which contain an estrogen and a progesterone, may also be helpful in women (Arowojolu 2004). Oral isotretinoin is the only acne treatment available that might be considered curative, it is used in severe acne when standard treatment has failed, but still a proportion of people do not respond, and a substantial number of people relapse and require further treatment (Layton 1992; Leyden 1997). Oral isotretinoin also can very rarely have psychiatric effects such as depression leading to suicide (Charakida 2004).

Currently, there is an emerging interest in light therapies for acne. Many of these use the healing properties of light of different wavelengths and treatments include lamps and lasers as well as photodynamic therapy (Ross 2005; Rotunda 2004). Some researchers propose diverse light therapies as a new treatment, however, there have been few randomised trials of the effects of these treatments and outcomes of existing trials are contradictory (Mariwalla 2005). Although there may be some grounds to be cautiously optimistic about the role of light, lasers and radio frequency devices in acne management, establishing further evidence is critical.

Description of the intervention

Topical retinoids, which in the past were prescribed mostly for people with mainly comedonal acne, are now considered to be a first-line treatment for all types of acne including inflammatory acne due to their anti-inflammatory actions (Gollnick 2003). De-

pending on the severity of the acne, retinoids are used either alone as monotherapy or in combination with other topical and systemic drugs (Zaenglein 2006). Retinoids are also suitable for a maintenance treatment because they prevent micro-comedones, and thus new lesions from forming. (Goulden 2003; Zane 2006).

Retinoids are a class of chemical compounds derived from vitamin A (retinol). There are three generations of retinoids which have different chemical structures:

1. the non aromatics;
2. the mono aromatics;
3. the poly aromatics.

The new synthetic retinoids e.g. third generation retinoids bear little structural resemblance to retinol, but they still have the ability to bind with retinoid receptors and are thus included in this family (Sardana 2003). Several types of topical retinoids are available for acne treatment. The most common options in Europe or the US include tretinoin, isotretinoin, adapalene and tazarotene: in some countries, motretinide, retinaldehyde and beta-retinoyl glucuronide are also approved for acne treatment (Zane 2006).

How the intervention might work

Topical retinoids have several mechanisms of action and address several of the four primary factors in acne pathogenesis. Topical retinoids regulate excess build-up of keratin in the pilosebaceous follicles by increasing epithelial turnover and thus normalize the shedding of the outer layers of the skin. (Gollnick 1998; Zaenglein 2006). They do not affect sebum production as oral retinoids do. Topical retinoids reduce free fatty acid levels in the micro-comedo and prevent the formation and inflammation of the comedone. Because of the altered follicular microclimate, retinoids enhance the penetration of other topical anti-acne agents such as antibacterial drugs and antibiotics (Thielitz 2001; Zaenglein 2006). Topical retinoids have been shown to affect inflammation directly by inhibiting the release of mediators that regulate inflammation such as prostaglandins, leukotrienes and pro inflammatory cytokines and regulating the immune response (Wolf 2002; Zaenglein 2006). Although retinoids from different generations have different chemical structures, they share more or less the same mechanisms of action and target the micro-comedo.

Types of Topical Retinoids (ABPI Medicines Compendium 2008)

Tretinoin

Tretinoin and isotretinoin are first generation retinoids. One of the major and early side effects of tretinoin (all-trans retinoic acid) which limit their use is dose-related skin irritation associated with its hydroalcoholic vehicle. To address this problem, various formations and concentrations are now available as;

- 0.025%, 0.01%, 0.05%, 0.1%, and 0.4% cream;
- 0.025% gel; a 0.05%, 0.1%, and 0.2% solution;
- 0.1% lotion; a 0.05% ointment; 0.05% in compresses;
- 0.1% gel microsphere: and a 0.025% polymer cream.

Other reported problems include delayed and variable improvement, photosensitivity and exacerbation of acne after two to four weeks "pustular flare" (demonstrated by the initial hydroalcoholic formulation of tretinoin) (Krautheim 2004).

Isotretinoin

Topical isotretinoin (13-cis retinoic acid) is considered to have similar effects to tretinoin on acne lesions. It is available as a 0.05% gel and a 0.01% cream (Krautheim 2004). It has very different effects from oral isotretinoin which exerts a sebum-suppressive effect (Karlsson 2003). Topical isotretinoin does not reduce sebum secretion.

Adapalene

Adapalene, a naphthoic acid, is a third-generation retinoid. Studies have shown that it shares some of the biological characteristics of tretinoin (Cunliffe 1997; Cunliffe 2002). Some additional properties such as increased chemical and light stability, rigidity, and high lipophilicity are purported to cause reduced risk of photo-instability and local skin irritation, possibly enhancing compliance. In addition, adapalene is not very well absorbed from the skin and is partitioned into the lipid environment of the pilosebaceous duct, the target area. It is available as a 0.1% gel, solution, and cream (Krautheim 2004; Millikan 2000).

Tazarotene

This third-generation retinoid belongs to a novel family of topical receptor-selective acetylenic retinoids. It is available as a gel or cream in 0.05% or 0.1% (0.1% concentration is approved for acne treatment in the US) and has light stability (Krautheim 2004; Shalita 1999; Shalita 2004). Common local adverse events include dryness, peeling/flaking, itching, redness/erythema, burning and skin irritation (Bershad 2002).

Motretinide

Motretinide is a second-generation mono-aromatic retinoid and is available as 0.1% cream and solution (Krautheim 2004).

Retinaldehyde

Retinaldehyde (RAL) is transformed into all-trans-retinoic acid (tretinoin), and its biological activity has been found to be qualitatively identical to that of retinoic acid (RA) (Didierjean 1999; Sorg 1999). It has been demonstrated that in vitro, RAL unlike the first-generation 'parent' natural retinoids such as retinoic acid or

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