VITAMIN A DERIVATIVES USE IN THE TREATMENT OF SKIN CONDITIONS

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ABSTRACT

Retinoids are used to treat various skin diseases. They add valuable impact of when used early in the treatment of dermatological conditions. Overall, vitamin A derivatives are underused, with isotretinoin is the most used. This paper aims to develop prescribers’ knowledge about their benefits, to improve their usability and aids in alleviating patient concerns to improve therapeutic outcomes in dermatological conditions. In acne vulgaris, adapalene gel and tretinoin cream showed equal efficacy. In psoriasis the combination of acitretin and PUVA was superior to PUVA alone.

INTRODUCTION

Vitamin A has both natural and synthetic derivatives, collectively known as retinoids. Retinoids play an important role in embryogenesis (including both cell growth and differentiation) and in cellular inflammation. They exert their actions through binding to different retinoid-binding proteins and to retinoid nuclear receptors. Retinoids are widely used to treat a range of dermatological conditions due to their effects on the proliferation of keratinocytes and epidermal differentiation [1]. The retinoids used to treat various skin diseases are divided into three generations. ‘First generation’ are the naturally occurring non-aromatic retinoids which include: Vitamin A (all-trans retinol), tretinoin (all-trans retinoic acid), isotretinoin (13-cis retinoic acid) and alitretinoin (9-cis retinoic acid). ‘Second-generation’ are the monoaromatic derivatives, which include: etretinate and its biologically active metabolite acitretin. ‘Third generation’ are the polyaromatic derivatives which include: adapalene, bexarotene and tazarotene [1].

Purpose of the review

This review aims to highlight the positive impact of the use and/or early use of vitamin A derivatives, both natural and synthetic, in the treatment of dermatological conditions. In the authors’ local areas, during the past 3 y, Vitamin A derivatives were underused (table 1), with only isotretinoin been used. This paper aims to develop prescribers’ knowledge about their benefits to improve their usability and aids in patients scares reductions as one of the main goals of dermatological conditions therapeutics outcomes.

Table 1: Cost of Isotretinoin provided by one CCG in west midlands with a population of 210,319

| Costs                        | 2017      | 2018       | 2019       | 2020      | TOTAL     |
|------------------------------|-----------|------------|------------|-----------|-----------|
| Isotretinoin 0.05%/Erythromycin 2% gel | £452.16   | £557.83    | £514.16    | £41.74    | £1,565.89 |
| Total                        | £452.16   | £557.83    | £514.16    | £41.74    | £1,565.89 |
| Items                        | 2017      | 2018       | 2019       | 2020      | TOTAL     |
| Isotretinoin 5 mg capsules   | £53       | £57        | £56        | 5         | £171.00   |
| Total                        | £53       | £57        | £56        | 5         | £171.00   |

Mode of action

Retinoids exert their effects by binding to retinoid-binding proteins, or activating, the nuclear retinoic acid receptors (RAR) and retinoid X receptors (RXR). Each of these receptors are composed of 3 isotypes: α, β and γ. Both types of receptors exist together as a dimer. The retinoids exhibit different binding affinities and characteristics to both types of receptors [2].

Side effects

The side effects of systemic retinoids are dose-dependent and resemble those seen in hypervitaminosis A. The most common are mucocutaneous, with chelitis being the earliest and most frequently observed side effect [3]. Other mucocutaneous effects include dryness in the oral and nasal mucosa (which might lead to epistaxis), dryness of the eyes, hair loss and nail fragility. Musculoskeletal effects include bone pain, arthralgias and myalgia. Hyperlipidaemia is caused by increased cholesterol and triglyceride levels and a reduction in HDL levels. Teratogenicity remains the most concerning side effect caused by retinoids. The FDA considers oral retinoids to be category X as they may cause foetal malformation by their effects on the developing central nervous system, heart, ear and thymus. Transient elevation in transaminase levels has been reported in 20% of patients, especially those treated with acitretin, and less
frequently those treated with isotretinoin and be Roxotene [4]. In
terms of psychiatric effects, opposing opinions exist between
dermatologists and psychiatrists on the effect of isotretinoin in the
occurrence of mood disorders especially depression and this topic
has been heavily debated. Bremner et al. (2012) have demonstrated a
difference between isotretinoin and depression [5]. They provided
evidence from case reports in the literature, temporal association,
challenge-re-challenge studies, dose-response, biological plausibility
and class effect. On the other hand many dermatological studies have
suggested that the presence of acne itself causes depression
and treating acne with isotretinoin is one way to treat depression,
since there will be improved self-image and an overall more positive
behaviour by the affected person [6]. Neurological effects are rare
although symptoms of pseudotumor cerebi may occasionally occur.

Therapeutic uses
Acne vulgaris
The US Food and Drug Administration (FDA) approved the medical
use of isotretinoin in 1982. The European Directive for prescribing
systemic isotretinoin for acne vulgaris stated in 2006, that
isotretinoin should only be used to treat severe acne (nodular,
conglobata) that has not responded or is not responding to
appropriate antibiotics and topical therapy [7]. Isotretinoin (13-cis
retinoic acid) has anti-inflammatory properties, decreases
hyperkeratinisation which will reduce comedone formation, reduces
production of sebum and reduces colonization of the pilosebaceous
duct with Propionibacterium acnes [8]. P. acnes induce the immune
production of sebum and reduces colonization of the pilosebaceous
duct with Propionibacterium acnes [8]. P. acnes induce the immune
response in affected patients, which results in the inflammatory
response of acne [9]. Isotretinoin reduces Toll-like receptor-2 (TLR-
2) expression in monocytes which will result in decreasing
inflammatory cytokine production in response to P. acnes. It was
found to have greater efficacy and comparable tolerability to tretinoin in
three patients treated with adapalene, but there was no improvement
in the scores of erythema or telangiectasia in the same group. The
results showed a reduction of lesions in the 0.3 mg/kg isotretinoin group while the
dosages, doxycycline or placebo. The results showed a 90%
reduction of lesions in the 0.3 mg/kg isotretinoin group while the
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Psoriasis
The only systemic retinoid that has been approved by the FDA for
psoriasis is acitretin. Acitretin exerts its effects by binding to all
subtypes (α, β and γ) of RAR and RXR receptors, which result in
reduction of the proliferation of epidermal keratinocytes. This leads to
a decrease in erythema, desquamation and thickness of the lesion
[15]. Acitretin is indicated in the treatment of pustular psoriasis,
erythrodermic psoriasis and severe psoriasis that cannot be
managed by topical treatment or phototherapy [16]. It was found in
a randomized, double-blind, placebo-controlled study that the
combination of acitretin and PUVA in treating severe psoriasis was
superior to PUVA alone, achieving a 75% decrease in Psoriasis
Severity Index and resulting in complete remission [17]. Tosti et al.
(2009) evaluated the efficacy of acitretin in treating isolated nail
psoriasis over a period of 6 mo. Their results showed a reduction of
41% in the Nail Psoriasis Severity Index (NAPSI) score and they
concluded that the reduction in NAPSI score achieved with low dose
acitretin treatment is comparable to that achieved with the biologics
[18]. In a study conducted on 10 patients with severe psoriasis
receiving acitretin treatment daily, four patients had plasma
etretinate (the teratogenic ethyl ester of acitretin) in teratogenic
levels, this was linked to alcohol consumption which leads to re-
esterification of acitretin to etretinate. For this reason, any female of
childbearing age receiving acitretin should be advised to continue
using contraception for a period of 3 y, since etretinate was found to
accumulate in the adipose tissue for a period of 18 mo post cessation
of the treatment [19, 20].

Tazorotene is the only topical retinoid approved for the treatment of
psoriasis. In the UK tazarotene is indicated for treating mild to
moderate plaque psoriasis affecting up to 10% of the surface area of
the body, while in the US it is indicated in treating stable plaque
psoriasis affecting up to 20% of the surface area of the body [16].
Tazarotene is metabolised to tazarotenic acid its active metabolite by
estrases in the skin. It is thought that tazarotene modulates
proliferation and differentiation of keratinocytes and also regulates
inflammation [21]. Mason et al. conducted a meta-analysis of topical
preparations for the treatment of psoriasis, which reported tazarotene
to have clinical efficacy similar to potent steroids and cikaptopril [22].

Chronic hand eczema
Alitretinoin was approved in the UK in 2008 for treating chronic
hand eczema that is refractory to topical steroid treatment in
patients who are>18 y old. It exerts its effects by binding to both
RAR and RXR receptors. In a randomized controlled study of
patients receiving oral alitretinoin once daily for up to 24 w, there
was almost 50% improvement in patients with chronic hand eczema
that was refractory to standard therapy [23, 24].

Photaging and aging
Retinoids in clinical trials have been shown to decrease the levels of
Matrix Metalloproteinases (MMP) that are responsible for catalysing
the degradation of collagen and elastin. They have also been
demonstrated to increase the thickness of the epidermis which in
turn will reduce the appearance of fine wrinkles [25]. The chemical
structures of retinoids allow them to absorb UV radiation and trap
free radicals, enabling them to protect cellular proteins from photo-
degradation and oxidative stress. Retinoids bind to nuclear
receptors and modulate the expression of the genes involved in
cellular proliferation and differentiation. Retinoids can increase the
synthesis and decrease the degradation rate of collagen and
hyaluronate; two important components of the dermis that are
frequently altered and decreased by the process of aging [26].

Rosacea
Topical and systemic isotretinoin can be used 'off-label' (outside of
the licensed indications) in the treatment of rosacea. In a study
conducted by Altinyazar et al. (2005) to evaluate the efficacy of
topical adapalene gel (0.1%) and topical metronidazole gel (0.75%)
in the treatment of papulopustular rosacea. The study showed a
significant reduction in the total number of inflammatory lesions in
the patients treated with adapalene, but there was no improvement
in the scores of erythema or telangiectasia in the same group. The
group treated with metronidazole showed improvement in the
erythema score [27]. In a placebo-controlled, randomized clinical
study conducted over a period of 12 w for 573 patients with rosacea
subtype II and III, patients either received isotretinoin in 3 different
dosages, doxycycline or placebo. The results showed a 90%
reduction of lesions in the 0.3 mg/kg isotretinoin group while the
doxycycline group demonstrated 83% reduction in the lesions.
Complete remission was achieved in 24% of the patients treated
with 0.3 mg/kg isotretinoin compared to only 14 % achieved in the
doxycycline group. Thus, the study concluded that isotretinoin can
be used as an alternative to oral antibiotics in the treatment of
rosacea subtype II and III [28].

Lichen planus
In a review of literature on the safety and effectiveness of topical
retinoids in oral lichen planus patients. Sixteen studies were
reviewed covering a total of 280 patients diagnosed with oral lichen
planus who were treated with various classes of retinoids. The
review concluded that isotretinoin was the most frequently used retinoid. Most of the studies demonstrated clinical and histopathological efficacy of retinoids used in the treatment of oral lichen planus [29].

**Cutaneous T-cell lymphoma (CTCL)**

In 1999 the FDA approved bexarotene for the treatment of cutaneous T-cell lymphoma (CTCL) that is refractory to at least one systemic treatment. Bexarotene exerts its effects by binding to the retinoid X receptor (RXR), which leads to apoptosis of CTCL cell lines [30]. In a multi-centre study conducted by Hamada et al. (2019) to evaluate the efficacy, safety and tolerability of bexarotene over 24 w, in 10 Japanese adults with cutaneous T-cell lymphoma (CTCL), the objective response rate was 53.8% [31]. Morita et al. (2020) studied the efficacy and safety of combination therapy with photo-chemotherapy and bexarotene in 25 Japanese patients diagnosed with cutaneous T-cell lymphoma (CTCL) over 24 w. The patients were treated with bexarotene 300 mg and PUVA or narrow-band UVB. The results were reported using two different assessments: the modified Severity-Weighted Assessment Tool (mSWAT) and the Physician Global Assessment of Clinical Condition (PGA). The response was 80.0% (mSWAT) and 84.0% (PGA) [32].

**Kaposi sarcoma**

In a multicentre, randomized, double-blind, controlled study that was conducted over a period of 12 w for 268 patients with cutaneous Kaposi sarcoma to evaluate the efficacy and safety of altrettinoi 0.1% gel, or matched vehicle with no active drug as control. The study results showed altrettinoi 0.1% gel was superior to placebo in treating cutaneous Kaposi sarcoma lesions and that altrettinoi was well tolerated by the patients and safe to use [33].

**CONCLUSION**

This review demonstrates that in a wide range of dermatological conditions, retinoids can be highly effective and well-tolerated when used with an effective pregnancy prevention program. It is believed that if these outcomes are more widely understood and patient concerns are properly addressed with factual information, many more patients would benefit from the group of medications.

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**AUTHORS CONTRIBUTIONS**

All authors contributed equally to perform the review and compile the submitted manuscript.

**CONFLICT OF INTERESTS**

The authors have no conflicts of interest to declare.

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