Adapalene: A New Topical Retinoid for Acne

reported by Dr. L. S. Ku

Date:	14 September, 2000
Venue:	Sheraton Hong Kong Hotel
Speaker:	Dr. D. B. Amos
Organizer:	HKSDV; Scientific Meeting

The rationale for the development of new retinoids was to attempt to maximize the beneficial effects of existing compounds such as all-trans retinoic acid (tretinoin), while minimizing side effects by targeting specific retinoid receptors in the target organs.

The first of these new synthetic retinoids to come to market was adapalene, which has now been available in the United States and Europe for 4-5 years. Adapalene has a very different structure to that of retinoic acid, with three aromatic rings and an adamantyl side chain. These differences in the molecular structure give adapalene physiochemical properties distinct from retinoic acid.

Adapalene's adamantyl side chain gives the molecule a high melting point and low solubility, resulting in low flux through the skin. This property allows high levels of the drug to remain in the skin, the target organ for the treatment of acne. These physicochemical properties of adapalene make it much easier to use, compared with the parent compound tretinoin. While it is stable in the dark, under light tretinoin degrades over time. It also degrades in the presence of oxidizing agents such as benzoyl peroxide. This destabilization process is accelerated with the combination of light and oxidizing agents. Adapalene, on the other hand, is stable in the presence of both light and oxidizing agents, due to its three aromatic rings. This property makes adapalene easy to use, as it can be applied in the morning and used together with benzoyl peroxide. Also, because it is a gel, adapalene stays in the pilo-sebaceous unit where the pathogenesis of acne occurs.

Prior to its launch, adapalene was subjected to extensive *in vitro* testing on various retinoid-sensitive human cell lines. Adapalene was shown to be equally or more effective in inducing differentiation and inhibiting growth, compared with tretinoin in these cells.

Interestingly, adapalene was also shown to possess potent anti-inflammatory properties compared with tretinoin in both *in vitro* and *in vivo* studies. In addition, it was shown to be effective in inducing comedolysis in mouse models, and it inhibited proliferation and induced differentiation in human cell models. All of these properties were greater than those of retinoic acid. The tolerability of adapalene gel 0.1% was compared with tretinoin cream 0.025% in a 4-week, randomized, investigator-masked, active controlled study in 100 patients with acne vulgaris. Adapalene performed better than tretinoin cream in most categories of side effects including desquamation, dryness, stinging and burning, and erythema.

In a controlled, randomized, cumulative irritation study, adapalene gel 0.1%, Retin-A Micro gel 0.1% (a new controlled-release formulation of tretinoin), three concentrations of tretinoin cream, and a non-medicated control substance (petroleum jelly) were compared in 26 patients with acne. The products were applied 5 times a week for 3 weeks. Adapalene had a 21-day cumulative irritation score similar to that of the petroleum jelly control. Both adapalene and the control had scores significantly lower than those of the tretinoin preparations, including Retin-A Micro gel 0.1%.

Adapalene gel 0.1% has also been compared with Retin-A Micro gel 0.1% with regard to tolerability and patient preference. In a randomized, investigator-blinded, reference-controlled, bilateral study involving 40 patients the two acne drugs were applied once daily for 4 weeks on either side of the face. In this study, the number of patients experiencing skin irritation was significantly less in the adapalene group than in the Retin-A Micro group at all time points. Adapalene was also preferred to Retin-A Micro by more patients. While these data are subjective, this is an important finding, since if a patient does not like the medication they will not use it. This preference was expressed in terms of easier spread, more rapid absorption, better smell, and a better feel with less residue. Reduced residue and ease

of spread are especially important in female patients, since they can apply cosmetics over the adapalene in the morning more easily than with tretinoin cream formulations. Because acne is not normally treated with monotherapy, adapalene gel has also been assessed in healthy volunteers in terms of skin tolerance in combination with other topical anti-acne treatments, including benzoyl peroxide 10%, clindamycin phosphate 1% lotion, and erythromycin 4% solution. Adapalene alone or in combination with these agents caused no significant increase in irritation.

In summary, the potential clinical advantages of adapalene are that it can be used in the morning, allowing twice-daily application if desired. Adapalene may also be applied with benzoyl peroxide. Finally, adapalene is less irritating than retinoids such as tretinoin, probably due to the molecule's inherent anti-inflammatory properties.

Unique binding properties

In 1980, before the advent of synthetic retinoids, the International Union of Pure and Applied Chemistry defined retinoids as "Those diterpenoids derived from a monocyclic parent compound containing five carbon-carbon double bonds and a functional group at the terminus of the acyclic portion". Various vitamins and hormones are known to have a pronounced action on the skin, including vitamin A, glucocorticoids, vitamin D, thyroid hormone, and estrogen. These all belong to the same set of nuclear receptors known as the steroid receptor superfamily. This steroid receptor superfamily includes α, β and γ isoforms of the retinoic acid receptor (RAR). There is also an RAR called RXR because the actual ligand was unknown when the receptor was discovered. This receptor also has three isoforms: RXR α, β and γ. RXR is now known to bind to 9-cis-RA, the natural metabolite of tretinoin that plays a key role in alteration in gene activity. The steroid receptor superfamily also includes estrogen, vitamin D and thyroid hormone receptors.

RARs are all found in the cell nucleus and have almost identical sequences, apart from the ligand binding region. In the skin, 90% of the RAR is the γ isoform, with RAR α comprising 10%; there is no detectable RAR β in the skin. RXRs that bind 9-cis-RA are found at a five-fold higher concentration than RAR, with 90% being RXR γ. Compared with tretinoin, adapalene is highly RAR selective. Adapalene does not bind to all RARs indiscriminately in the same way as tretinoin, but binds very tightly with the most common RAR in the epidermis, RAR γ. By not binding to RAR α or the RXR isoforms, adapalene turns on different genes, unlike tretinoin which binds indiscriminantly with all the RAR isoforms. Importantly, unlike tretinoin, adapalene does not bind to the cystolic retinoic acid binding protein (CRABP), which is thought to control the concentration of retinoic acid that reaches the nucleus. This property allows constant levels of adapalene to reach the nucleus of the keratinocyte target cells throughout the course of treatment.

Conclusion

Adapalene has a unique binding profile that may allow constant levels to reach the cell nucleus throughout the course of treatment. The anti-inflammatory properties of adapalene make it better tolerated than tretinoin preparations and its biophysical properties allow it to be used in the morning and as a part of combination therapy. Finally, adapalene has been demonstrated to be as efficacious as tretinoin at all time points during treatment.

Learning points:

Adapalene, when compared with tretinoin, is more stable, less irritative and can be used together with other acne preparations.