

Assessing Clinically Meaningful End Points for the Management of Actinic Keratosis with Diclofenac 3% Gel

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Sir,

Actinic keratosis (AK) is an early stage of evolving skin cancer and may be classified as a squamous cell carcinoma (SCC) *in situ*, which originates from keratinocytes and appears on areas of skin exposed to sunlight, such as the face and arms. It is a common condition in the general population, with prevalence increasing with age and cumulative sun exposure. The American Academy of Dermatology estimates that 60% of predisposed individuals aged 40 years and over have at least one AK lesion (1). The ultimate treatment goal is to prevent progression to SCC (2).

Recent insights into the relationship between cyclo-oxygenase-2 (COX-2) and carcinogenesis have provided a rationale for the topical use of non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of AK. The most studied of these, diclofenac 3% gel (Solaraze™ 3% gel; Shire Pharmaceuticals Contract Ltd, Basingstoke, UK), is thought to have an effect on AK via selective COX-2 inhibition (3) and regulation of cell proliferation and apoptosis, although the exact mechanisms of action remains to be determined. The hyaluronic acid vehicle is a key component in this topical treatment. It has been shown to be capable of delivering twice as much diclofenac to the epidermis over a 24-h period than an aqueous control or sodium carboxymethyl, and to enhance the localization and retention of diclofenac in areas of inflammation within the epidermis (4, 5).

A series of clinical studies have provided evidence for the use of topical diclofenac 3% gel for the treatment of AK (6–10). Two randomized, double-blind, parallel group, multicenter studies (Study A (7) and Study B (8)) have compared the effect of 0.5g bid diclofenac 3% gel vs. placebo (hyaluronic acid gel alone) for up to 90 days in patients with AK. The primary efficacy variables were the proportion of patients achieving a target lesion number score (TLNS) or a cumulative lesion number score (CLNS) equal to zero, where TLNS refers to the number of lesions identified at baseline, and CLNS refers to any new lesions appearing during the treatment phase plus remaining target lesions. In Study A, 50% of patients receiving diclofenac 3% gel achieved complete resolution of all target lesions (TLNS=0), compared with 20% in the placebo group ($p < 0.001$), at the 30-day follow-up visit after the end of the 90-day treatment period (7). A similar difference was observed for CLNS (CLNS = 0) between the active and placebo groups (47% and 19%,

respectively, $p < 0.001$). In Study B, 33% of patients treated with diclofenac 3% gel for 60 days achieved complete clearance (TLNS = 0), compared with 10% of placebo patients ($p < 0.05$) (8).

Complete lesion clearance, however, is an extremely rigorous study end-point that can underestimate the clinical benefits of a treatment as a patient who experiences a resolution of 9 out of 10 lesions would be classed as a failure, and frequently patients experience an increase in lesion count during treatment due to the appearance of subclinical lesions. Partial clearance ($\geq 75\%$), therefore, has been proposed as a more clinically meaningful end-point and has been used in other clinical trials investigating treatments for AK (11–13). A recent open-label study, evaluating the efficacy of diclofenac 3% gel, showed that 78% of patients had at least a 75% clearance after 90 days of treatment, rising to 85% at the post-treatment follow up on day 120 (9).

Based on this rationale, we re-analyzed the TLNS and CLNS data from the two randomized, double-blind, placebo-controlled, multicenter studies (Study A (7) and Study B (8)) in order to establish the proportion of patients achieving a lesion clearance rate of $\geq 75\%$.

MATERIAL AND METHODS

The two studies were re-analyzed individually; no pooling of data across studies was made. The re-analysis comprised all patients who had post-baseline lesion count data. Statistical analysis was made by Fisher's exact test.

RESULTS

In Study A (90 treatment days), at the 30-day follow-up visit, the proportion of patients achieving a clearance rate of $\geq 75\%$ with diclofenac 3% gel was approximately 71% (TLNS) and 69% (CLNS), compared with approximately 48% and 44%, respectively, in placebo-treated patients ($p=0.014$ and $p=0.009$, respectively; Table I). At the 30-day follow-up visit in Study B (60 treatment days), approximately 56% (TLNS) and 52% (CLNS) of patients treated with diclofenac 3% gel had achieved a clearance rate of $\geq 75\%$, compared with approximately 22% and 20%, respectively, in the placebo group (Table I). More patients in the 90-day study achieved $\geq 75\%$ clearance than in the 60-day study, indicating a correlation between the duration of treatment and the rate of treatment success. In both studies, a better clinical

Table I. Proportion of patients achieving $\geq 75\%$ clearance rate of target lesion number score (TLNS) and cumulative lesion number score (CLNS) following 90 days treatment in Study A (7) and 60 days treatment in Study B (8)

	TLNS		<i>p</i> -value	CLNS		<i>p</i> -value
	Diclofenac 3% gel <i>n</i> (%)	Placebo <i>n</i> (%)		Diclofenac 3% gel <i>n</i> (%)	Placebo <i>n</i> (%)	
<i>Study A</i>						
End of treatment	34 (58.6)	27 (45.8)	NS	32 (55.2)	27 (45.8)	NS
30-day follow-up	41 (70.7)	28 (47.5)	0.0144	40 (69.0)	26 (44.1)	0.0090
<i>Study B</i>						
End of treatment	17 (35.4)	11 (22.4)	NS	15 (31.3)	10 (20.4)	NS
30-day follow-up	27 (56.3)	11 (22.4)	0.0008	25 (52.1)	10 (20.4)	0.0015

NS: not significant

response was observed 30 days after the completion of treatment with 3% diclofenac in 2.5% hyaluronic acid, i.e. at follow-up. The safety and tolerability profile of diclofenac 3% gel was comparable to that of placebo, and any adverse events were mild to moderate in nature and mostly skin related. The most frequently reported events were pruritus, application site reactions and dry skin.

DISCUSSION

Re-analysis using a $\geq 75\%$ lesion clearance rate demonstrated that diclofenac 3% gel is an effective treatment for the management of AK. A significant number of patients achieved $\geq 75\%$ lesion clearance. In addition, this clinical reduction in lesions is comparable to other topical treatment options for AK, such as 5-fluorouracil and imiquimod 5% cream (14, 15). Therefore, assessing lesion clearance rates of $\geq 75\%$ may be a more clinically meaningful end-point for the management of mild-to-moderate, multiple, diffuse non-hyperkeratotic AK using diclofenac 3% gel.

Conflict of interest: Dr Rivers has served as a consultant and speaker for Shire Pharmaceuticals Ltd.

REFERENCES

1. Drake LA, Ceilley RI, Cornelison RL, Dobes WL, Dorner W, Goltz RW, et al. Guidelines of care for actinic keratoses. *J Am Acad Dermatol* 1995; 32: 95–98.
2. Cohn BA. From sunlight to actinic keratosis to squamous cell carcinoma. *J Am Acad Dermatol* 2000; 42: 143–144.
3. Riendeau D, Percival MD, Brideau C, Charleson S, Dube D, Ethier D, et al. Etoricoxib (MK-0663): preclinical profile and comparison with other agents that selectively inhibit cyclooxygenase-2. *J Pharmacol Exp Ther* 2001; 296: 558–566.
4. Freemantle C, Alam CAS, Brown JR, Seed MP, Willoughby DA. The modulation of granulomatous tissue and tumour angiogenesis by diclofenac in combination with hyaluronan (HYAL EX-0001). *Int J Tiss Reac* 1995; 17: 157–166.
5. Brown MP, Hanpanitcharoen M, Martin GP. An in vitro investigation into the effect of glycosaminoglycans on the skin partitioning and deposition of NSAIDs. *Int J Pharm* 2001; 225: 113–121.
6. Rivers JK, McLean DI. An open study to assess the efficacy and safety of topical 3% diclofenac in a 2.5% hyaluronic acid gel for the treatment of actinic keratoses. *Arch Dermatol* 1997; 133: 1239–1242.
7. Wolf JE Jr, Taylor JR, Tschen E, Kang S. Topical 3.0% diclofenac in 2.5% hyaluronan gel in the treatment of actinic keratoses. *Int J Dermatol* 2001; 40: 709–713.
8. Rivers JK, Arlette J, Shear N, Guenther L, Carey W, Poulin Y. Topical treatment of actinic keratoses with 3.0% diclofenac in 2.5% hyaluronan gel. *Br J Dermatol* 2002; 146: 94–100.
9. Nelson C, Rigel D, Smith S, Swanson N, Wolf J. Phase IV, open-label assessment of the treatment of actinic keratosis with 3.0% diclofenac sodium topical gel (Solaraze™). *J Drugs Dermatol* 2004; 3: 401–407.
10. Gebauer K, Brown P, Varigos G. Topical diclofenac in hyaluronan gel for the treatment of solar keratoses. *Australasian J Derm* 2003; 44: 40–45.
11. Korman N, Moy R, Ling M, Matheson R, Smith S, McKane S, et al. Dosing with 5% imiquimod cream 3 times per week for the treatment of actinic keratosis: results of two phase 3, randomized, double-blind, parallel-group, vehicle-controlled trials. *Arch Dermatol* 2005; 141: 467–473.
12. Szeimies RM, Gerritsen MJ, Gupta G, Ortonne JP, Serresi S, Bichel J, et al. Imiquimod 5% cream for the treatment of actinic keratosis: results from a phase III, randomized, double-blind, vehicle-controlled, clinical trial with histology. *J Am Acad Dermatol* 2004; 51: 547–555.
13. Lebwohl M, Dinehart S, Whiting D, Lee PK, Tawfik N, Jorizzo J, et al. Imiquimod 5% cream for the treatment of actinic keratosis: results from two phase III, randomized, double-blind, parallel group, vehicle-controlled trials. *J Am Acad Dermatol* 2004; 50: 714–721.
14. Loven K, Stein L, Furst K, Levy S. Evaluation of the efficacy and tolerability of 0.5% fluorouracil cream and 5% fluorouracil cream applied to each side of the face in patients with actinic keratosis. *Clin Ther* 2002; 24: 990–1000.
15. 5-fluorouracil SmPC. 2005 November 7. Available from: URL: www.medsafe.govt.nz/Profs/datasheet/e/Efudixcr1.htm [last accessed 9 Jan 2007]