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The Protective Role of NSAIDs in the Treatment of Nonmelanoma Skin Cancer: A comprehensive review on animal and human trial studies

Venkat A.*[1], Chaitanya P.[2] Neelima T.[1]
[1]Sri Krupa Institute Of Pharmaceutical Sciences, AP, India., [2]Lalitha College of Pharmacy, RR Dist, India

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ABSTRACT

Non-melanoma skin cancer (NMSC), consisting of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), is the most commonly occurring cancer in humans. Preclinical studies indicate that the enzyme cyclooxygenase-2 plays an important role in ultraviolet-induced skin cancers. In this review we gathered the information from various studies that have evaluated the efficacy and safety of celecoxib and other non steroidal anti-inflammatory drugs (NSAIDs), as chemo preventive agent for actinic keratosis, the premalignant precursor of nonmelanoma skin cancers, and for nonmelanoma skin cancers, including cutaneous and squamous cell carcinomas (SCCs) and basal cell carcinomas (BCCs). Experimental studies have consistently proved a protective effect of nonsteroidal anti-inflammatory drugs (NSAIDs) against nonmelanoma skin cancers (NMSC). However, minimal human epidemiological research has been done in this regard till date. In this review we used data from various sources to understand the chemo protective role of various NSAIDs on NMSC. This article also discusses the problem of associated cardiovascular effects with celecoxib and other NSAIDs and existence of correlation of results in animal models to that of efficacy in humans. Based on epidemiologic studies and its cardiovascular (CV) profile, aspirin seems to be the most promising NSAID for preventing skin cancer, even though the animal data for aspirin are less clear. A comprehensive understanding of the results of coxibs and other NSAIDs in animal studies may help inform and shape human trials of these commonly employed, relatively inexpensive, and highly effective compounds.

Keywords: *NMSC, SCC, NSAIDs, Coxibs.*

INTRODUCTION

Cutaneous squamous cell carcinomas (SCCs) and basal cell carcinomas (BCCs) classified together as nonmelanoma skin cancers (NMSC), are the most common malignancies in the United States [1]. As per the National Cancer Research Institute records the approximate number of new nonmelanoma skin cancer cases were reported more than two million and deaths were reported more than 1000 in 2012 [2]. However it is uncommon for these cancers to metastasize, they are responsible for considerable morbidity and represent a substantial economic burden to the health care system. The estimated direct cost of treatment for nonmelanoma skin cancers in the United States has been estimated to exceed $2 billion annually [3]. A significant proportion of NMSC is already invasive at the time of initial clinical presentation and will require definitive surgical intervention.

Several studies are in progress to study the efficacy of Non-Steroidal anti-inflammatory Drugs (NSAIDs) in treatment of superficial forms of NMSC. In an effort to explain the proper use and indications for the nonsurgical modalities including topical actinic keratosis (AK) and NMSC therapies which include popular Fluorouracil, Diclofenac Sodium and topical photodynamic therapy (PDT) with 5- aminolevulinic acid (ALA).

Pathology/epidemiology background of NMSC:

Precancerous lesions known as actinic keratosis (AK) are evolving cutaneous neoplasms comprising atypical keratinocytes. It has been proposed that AK are more accurately classified according to a grading system that would emphasize their progressive evolution towards squamous cell carcinoma (SCC) [4]. Generally it has been accepted that anywhere from 0.25 to 1% of AK convert to SCC every year. In a recent year review, it was confirmed that 82% of SCC arose from or were in close proximity to AK [5]. Studies suggest that the presence of AK is more strongly associated with developing SCC than any other factor such as age, skin and genotype [6].

***Corresponding author:**
Venkat A.
Sri Krupa Institute Of Pharmaceutical Sciences,
Medak Dist, A.P., India.
**E-Mail: venkey.anmula@gmail.com*

Clinically AKs are characterized as scaly, crusted, keratotic papules and plaques occurring on sun exposed areas such as the face and upper extremities. Sometimes they may also associate with epidermal atrophy and other signs of photo damage. Many variants of AK exist including a proliferative type that exhibits more aggressive behavior [7]. However, the correct diagnosis is critical for the effective treatment since, without histologic evolution, AK can be difficult to distinguish clinically from SCC.

The future hope of NSAIDs treatment for the NMSC:

Recent studies confirmed the role of NSAIDS/COX-2 inhibitors in the chemoprevention of cancer in humans.

Role of NSAIDS in cancer prevention:

Prostaglandins (PG) are the most abundant members of the eicosanoid family of arachidonic acid derived autacoids. Arachidonic acid is normally stored esterified to the glycerol backbone of membrane phospholipids. As such in phospholipid form they cannot be metabolized to PGs. Hydrolysis by phospholipase-A2 is the rate limiting steps for the PG synthesis, arachidonic acid is available as a substrate for enzymatic oxidation by several different enzyme systems including COXs, lipoxygenases and Cytochrome p450s. PG synthesis is thus regulated at several levels including substrate abundance and availability, the level of COX expression, and also the level of expression of PG synthesis [8]. Surprisingly, COX-1 is expressed constitutively, whereas COX-2 which is nearly undetectable in most epithelial tissues under normal conditions and is regulated by variants of physical irritants, growth factors and cytokines [9].

Selective COX-inhibiting drugs like Aspirin, inhibits three major PG products of COX-1, COX-2 namely PGE2, PGF2$_\alpha$ and PGD2 and also inhibits PG synthesis [10]. Other non-selective COX inhibitors drugs like Indomethacin that inhibits PG synthesis were subsequently developed and named as NSAIDs.

The NSAIDS are heterogeneous group of compounds and exhibits side effects like gastrointestinal (GI) complications. The prostaglandins (PGs) derived from COX-1 are responsible for homeostatic maintenance of the GI mucosa and smooth muscle contraction. COX-2 is induced during the inflammation and is over expressed in many epithelial tumors. Selective COX-2 inhibitors are referred to as coxibs, which reduced inflammation with a decreased propensity of GI complications [11]. On the basis of observed up

regulation of COX-2 in many cancers the chemo preventive activity of coxibs was examined in animal models for their safety and efficacy.

Animal studies on nonmelanoma skin cancer with NSAIDs:

Previous research works are established nonmelanoma skin cancer (NMSC) in mice with either the classical-2 stage irritation promotion protocol or by repetitive exposure to UV light. Both these models induce a marked inflammatory response.

This earliest observation triggered the study on the ability of NSAIDs to prevent NMSC which is topical indomethacin reduced skin tumor development by approximately 30% in the initiation-promotion model [12]. In more recent studies it was found that, the mice fed 150/500 ppm Celecoxib showed a dose –dependent reduction (60% and 89% respectively) in tumor multiplicity in the UV carcinogenesis model [13]. As per the previous research studies, Indomethacin (4ppm) reduced tumor multiplicity by 78%, confirming Celecoxib is markedly more effective. Interestingly it was also found that Celecoxib was relatively effective in causing the regression of preexisting UV –induced skin cancer.

It was also shown that the NSAIDs and Celecoxib that are effective in preventing NMSC also inhibit PGE2 production in UV-exposed epidermis [14]. Therefore, there is a strong correlation between short term inhibition of PGE_2 and long term efficacy in preventing NMSC. In the genetical approach studies it was confirmed that the loss of allele of COX-1 had no effect on skin tumor development, the loss of only 1 allele of COX-2 significantly reduced tumor development in response to UV exposure [15]. FDA approved topical diclofenac is the NSAID with selectivity for COX-2 inhibition, is efficacious in treating acinic keratoses. A recent clinical study on human beings showed that Celecoxib significantly reduced the development of NMSC in individuals with actinic keratosis [16]. All these studies strongly confirm that the COX-2 is critical target for preventing NMSC in human beings as well as animals.

Table No. 1: Discusses about the Relative Efficacy of the NSAIDs in animal studies

Model	Species	NSAID(ppm)	Relative Efficacy (%decreased)	HED
UV skin	Mice	Celecoxib (500ppm)	70%	533 mg
UV skin	Mice	Celecoxib (150ppm)	60%	160 mg
UV skin	Mice	Indomethacin (4 ppm)	70%	4.3 mg
UV skin	Mice	Naproxen (400 ppm)	70%	427 mg

NOTE: The calculations below are standard scaling factors that would be used for the FDA. They do not take into account specific pharmacokinetics of individual agents which can only properly be done after gavage dosing.

HEDs were calculated as follows, using 100 ppm (100mg/g diet) as an example. Rats, which eat 15 g food daily, would consume 1.5 mg drug; for a 250 g rat, the daily weight-based dose would be 6 mg drug/kg body weight. Dividing by the rat-to-human scaling factor of 6, the HED is 1 mg/kg body weight; for an 80 kg human this is 80 mg. Mice, which eat 4 g food daily, would consume 0.4 mg drug; for a 25 g mouse, the daily weight-based dose would be 16 mg drug/kg body weight. Dividing by the mouse-to-human scaling factor of 12, the HED is 1.33 mg/kg body weight; for an 80 kg human this is 106 mg.

Abbreviations: HED: human equivalent dose. (8), Susan M. Fischer, Ernst et.al, 20121:

Role of NSAIDS in chemoprevention of Non melanoma skin cancer:

Preclinical studies indicated that the enzyme cyclooxygenase-2 plays an important role in UV-induced skin cancers. Many previous clinical studies on human beings evaluated the efficacy and safety of NSAIDs as a chemo preventive agent for actinic keratoses, the premalignant precursor of nonmelanoma skin cancers and for melanoma cancer including cutaneous squamous cell carcinomas (SCCs) and basal cell carcinomas (BCCs) [17].

Preclinical and epidemiological data suggests that COX-2 is involved in the pathogenesis of NMSCs. In previous animal studies, treatment with Celecoxib inhibits the development of UV-induced premalignant skin papillomas which are thought to correspond to actinic keratoses. Previous clinical studies in which, a randomized, placebo-controlled, double blind trail was studied to evaluate the efficacy and safety of Celecoxib, a COX-2 inhibitor as a chemo protective agent for actinic keratosis in patients with extensive actinic keratoses. In the study there was no difference observed in the incidence of new actinic keratoses between the two groups this was considered as primary end point. Compared with placebo, Celecoxib administered was highly effective in preventing non-melanoma skin cancers in subjects who had large members of actinic keratoses. The key implications of this human study were, celecoxib was not effective in preventing new actinic keratoses, but the study results raised the new hypothesis that, it may prevent some nonmelanoma skin cancers, in patients who had actinic keratoses and thus they are at high risk for the NMSC. There were major limitations including, the development of nonmelanoma skin cancers was not a primary or secondary end point of this study. All the subjects experienced extensive actinic damage. This human study could not reveal, if celecoxib would have the same effect in subjects with less or no actinic damage.

The below table discusses the Adverse Events (AEs) in participants who received Celecoxib/placebo.

(Adverse events in participants who received celecoxib or placebo)

Table No. 2: *Two sided x^2 test[17]

Type of AE	Celecoxib	Placebo	P*
Any AE No. of participants (%)			
0	19 (16)	18 (15)	.95
≥1	103 (84)	100 (85)	
Serious Adverse Events (SAEs) No. of participants (%)			
NO	113 (93)	111 (94)	.65
YES	9 (7)	7 (6)	
Cardiovascular (CVS) Adverse events, No of participants (%)			
NO	115 (94)	113 (96)	.59
YES	7 (6)	5 (4)	

At the end of this clinical study, 84% celecoxib treated subjects reported at least one adverse event (AE) compared with 85% of control subjects (P= .95). The most common AEs were infections and infestations, followed by gastrointestinal, musculoskeletal skin disorders and hypertension. The COX-2 inhibitors have been reported to increase the risk of serious cardiovascular events (i.e. myocardial infarction, stroke, congestive heart failure (CHF), and cardiovascular deaths). However, the number of subjects in the two treatment arms who experienced a cardiovascular event was not statistically significant in difference.

Recently an another clinical study, evaluated the effect of NSAIDs on the recurrence of NMSC. In this clinical study, the association of NSAID use and with the risk of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). In this study, subjects were randomized into two different groups to either placebo or 50 mg of daily beta-carotene. Confirmed lesions were considered as the endpoints for this study [18].

In this study to evaluate the effect of NSAIDs on there are two different types of approaches were used. In the first, the relation between NSAID use and the number of cancers diagnosed during the trail for BCC. A baseline NSAID use conferred a significant reduction of risk in the whole analysis. In the second approach, the association between NSAID use during the first two years of the study and the average number of NMSC diagnosed in the subsequent three years.

In relation to the skin, the effect of NSAIDs, particularly aspirin, on carcinogenesis has been investigated in invtro and invivo [19]. Many human studies have reported a decrease in the number of new skin tumors or regression of existing tumors with the use of topical/oral

NSAIDs. Surprisingly, there were some epidemiological studies explored the risk of various cancers including NMSC, in relation to use of NSAIDs [20].

However, a randomized trial has provided good evidence of therapeutic properties of NSAIDs showed the efficacy of topical diclofenac against actinic keratoses, proliferative lesions that are thought to be the precursors of SCC. Previous single arm open-label study of topical diclofenac and actinic keratosis reached similar positive conclusions [21].

Underlined protective mechanism of NSAIDS on NMSC:

The well-known mechanism of action of NSAIDs is the inhibition of COX-2, the inducible isoform of the cyclooxygenase enzyme, implicated in inflammation and promotion of neoplastic tumors. In the skin, experimental studies have shown that acute UV-light exposure can cause COX-2 over expression in murine and human skin and high levels of the enzyme are present in neoplastic lesions following UV irradiation. Many animal studies provide strong evidence for a role of COX-2 as an endogenous promoter of skin neoplasia.

Limitations of the clinical study:

In these studies, the effect of observed NSAIDs use was too short to have affected the occurrence of NMSC. For any other cancer like colorectal cancer, at least 10 years of consistent use may require for a protective effect. These types of clinical studies also use less number of SCCs subjects, and hence have limited statistical power to detect significant associations for this endpoint. Inaccuracies in the assessment of NSAID use, and frequency of dosage, duration and other measurement errors could have biased the study findings. Finally any other confounding factor may show impact on the clinical study.

Controversies and conclusions:

There are some controversies that have arisen in the field and some previous studies offered some speculation based on preclinical studies of NSAIDs in carcinogenesis. One of the controversies raised is whether Celecoxib has some unique prevention efficacy as compared with most NSAIDS. However, the first study achieved a 95% reduction in colon cancer in contrast to traditional NSAIDs [22]. A subsequent study a similar dose achieved roughly an 85% effect similar to traditional NSAIDs [23]. A lower dose of Celecoxib is somewhat effective in skin cancer models, but no more effective than a wide variety of NSAIDs at their own human equivalent doses. As per the previous research work in humans, Celecoxib at 400 mg twice daily was more effective at polyp prevention than Aspirin, but less effective than the combination of Sulindac and DFMO [24]. The comparisons between Celecoxib and NSAIDS needs to also take into consideration than there are variabilities in outcome between the studies.

Substantial off-target effects of NSAIDS:

Celecoxib was observed to inhibit Akt activation and this COX-2 independent activity is associated with its apoptotic activity in some cell types. There are some off-target effects of aspirin seems to be cell type dependent. Aspirin induces apoptosis in cervical cancer cells through reduction of ErbB2 expression [25]. In a different scenario, where Sulindac produces a major metabolite (Sulindac sulfone) with substantially different properties and targets (it does not inhibit COX-2). In the other case of Sulindac, Sulindac sulfone is not a COX-2 inhibitor where the other major metabolite sulindac sulfone is aCOX-2 inhibitor. Recently studied UV-induced skin model showed the local inhibition of COX-2 induced PGE_2 is predictive of preventive efficacy is similarly compatible with a COX-2 target, then a non-specific NSAID that would inhibit PG production by COX-1 and COX-2 should be effective because most tumors do express COX-1 and COX-2 is well.

Controversies regarding to Aspirin:

Recent physician's health study confirmed that, alternate day use of low-dose aspirin was reported to be ineffective in reducing the risk of cancer. Also, a recent compilation of data, however showed that doses as low as 75 mg/day are effective in reducing cancer risk after extended dosing. The long duration of Aspirin use required to prevent cancer, may reflect the tie required for cancer to develop from precursor lesions. Animal studies reflected that high doses of aspirin are required for efficacy; of course which may be based on inter species differences in metabolism [26]. However, the recent finding showed that Celecoxib was equally effective in inhibiting adenoma formation in individuals taking low doses of Aspirin. Recent studies confirmed that in skin and bladder cancers, the NSAIDs and coxibs are effective even when tumors are present. The greater efficacy at later stages is consistent with the finding in various adenoma studies that NSAIDs seem more effective in prevention of advanced adenomas compared with later. In addition, recent data in skin shows that although Celecoxib was ineffective in blocking the formation of early stage actinic keratosis, it reduced the formation of NMSC by 50%.

Prediction of NSAIDs efficacy in human studies:

Multiple clinical efficacy trails employing NSAIDs/Coxibs for blocking the development of adenomas have shown these agents are effective, with aspirin showing more limited activity than celecoxib or sulindac plus. Recent clinical trial of oral celecoxib showed that this agent could inhibit the formation of squamous and basal cell skin cancers by roughly 60%. Further clinical data showed that topical application of diclofenac is partially effective in preventing actinic keratosis and may be more effective in blocking SCCs of the skin, Thus, clinical results seem to be in the same line with the high efficacy of late intervention observed in animal models.

Toxicity of NSAIDs:

Previous animal data, significant epidemiologic data and clinical trials particularly in skin cancers, the identification of an NSAID/Coxib that can be used safely in prevention setting is a high concern. The primary concern with regard to NASIDs was ulcers and severe bleeding. Although the incidence of these events are probably less than 1 in10,000 for most NSAID users.

It was recorded that, COX-2 inhibitors are associated with significantly less upper GI toxicity [27]. However, Rofecoxib and Valdecoxib seem to increase cardiovascular events. Celecoxib at the standard dose alone does not significantly increase cardiovascular events, the higher doses used in adenoma prevention trials did. Further examination of NASAIDs and agents such as diclofenac clearly increased cardiovascular events and has led to a black box warning. Naproxen is the NSAID, which consistently proven with minimal cardiovascular effects and cardio protective, although the data from Alzheimer's disease and anti-inflammatory prevention trail is suggestive of increased cardiovascular risk. As previously discussed, low dose of Aspirin is cardio protective and good chemo preventive when taken over an extended duration [28].

These clinical studies raised few questions with reference to NSAIDs toxicity, they are (i) Low dose celecoxib probably has low GI toxicity and less cardiovascular effect but for which prevention data was unclear so far. (ii) However, aspirin seems to be cardio protective with extended duration of use, but effective dose remained unclear. (iii) Naproxen, proven with greater cardio protective nature and potential proton pump inhibitor, which decreases GI events. From the most recent research works it was confirmed that Aspirin would seem to be the choice based most epidemiological data [29].

As with all prevention studies, the real question is the risk to benefit ratio and, concomitantly, whether one can identify predictive markers of greater benefit and lesser potential harm from particular NSAIDs and whether one can define a high –risky group who has more gain than lose through interventions of this nature.

CONCLUSION

Dermatologists will continue to face the NMSC epidemic heads on. At present there are several well accepted therapeutics for treating AK. From the various animal and human studies it is now unambiguously recognized that the increased risk associated with the administration of COX-2 inhibitors is a class effect. Many studies were confirmed the chemo preventive role of NSAIDs on NMSC. The main limitation of some human studies is that the effect of celecoxib on nonmelanoma skin cancer was not primary or secondary end point. Therefore additional studies will need to be conducted in which the effect of cyclooxygenase inhibitors on nonmelanoma skin cancer development is the primary endpoint to confirm the chemo preventive observation.

In conclusion, these studies demonstrate that the cyclooxygenase-2 inhibitors drugs are effective chemo preventive agents for NMSC in patients who are at high risk for the disease. It may be possible that a combination of medications that includes sunscreens as well as cyclooxygenase inhibitors and chemo preventive agents could be taken on a regular basis by individuals at risk for development of NMSC to reduce the incidence of this exceptionally common malignancy.

Recent studies may strengthen the research outcomes to confirm the efficacy and safety of NSAIDs selectively COX-2 inhibitors in NMSC chemoprevention.

The future of coxibs may be an example of personalized medicine, with greater efficacy with least adverse effects in NMSC patients.

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