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Efficacy and Cost Analysis for Acitretin for Basal and Squamous Cell Carcinoma Prophylaxis in Renal Transplant Recipients

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Keywords

chemoprevention; acitretin; keratinocyte carcinoma; basal cell carcinoma; squamous cell carcinoma; retinoids; skin cancer prevention

Introduction

The treatment and prevention of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), collectively known as keratinocyte carcinomas (KC), present a challenge for renal transplant recipients (RTRs) who develop multiple KCs annually. Patients with multiple SCCs have an increased risk of local recurrence and nodal metastasis, in addition to experiencing a significant adverse impact on their quality of life.

Several studies have evaluated the efficacy of retinoids for chemoprevention of skin cancer. Large randomized controlled trials (RCT) evaluating isotretinoin failed to show a reduction in skin cancer formation whereas data on acitretin is inconsistent. Etretinate was utilized up until the late 1990's before being replaced by acitretin. A few small published studies showed that Etretinate had a prophylactic effect on patients with xeroderma pigmentosum and basal nevoid syndrome. Although there is a qualitative systematic review on acitretin for chemoprevention in renal transplant recipients (RTRs), it did not evaluate the pooled reduction in KCs. The present study sought to review all published literature on acitretin for KC chemoprevention, pool outcome data, and evaluate treatment costs in RTRs.

Methods/Literature Search

The Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines was followed. The review protocol was registered with PROSPERO (registration number:

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CRD42019129703). MEDLINE (www.nlm.nih.gov), EMBASE (www.embase.com), and CENTRAL (https://www.cochranelibrary.com/central) databases were searched on December 1, 2018 for English language studies published before the search date using the relevant terms. Articles were independently screened for eligibility by two authors (OB and ER). Eligible studies included 5 or more subjects. Studies were excluded if they did not report the number of BCCs and SCCs pre- and post-acitretin therapy, duration of follow up, or any original data. The following data were extracted: number of subjects, duration, dosing, number of BCCs and SCCs, and side-effects. The pre-treatment and post-treatment durations were formatted in years. The number of tumors and follow-up time were pooled. The annual rate of tumor development during the pre- and post-treatment periods were calculated using the period duration, number of tumors, and number of subjects. Though the source data delineated the number of BCCs and SCCs, we included the pool variable KCs to determine acitretin's efficacy across diagnoses and to simply the cost analysis as both BCCs and SCCs are treated with same modalities.

Cost data was obtained from the National Average Drug Acquisition Cost (NADAC) data and the Massachusetts All-Payer Claims Database (APCD) Council data.[4–5] Laboratory monitoring information and Mohs practice patterns were obtained from published resources. The repair costs for MMS and excision were estimated using a weighted average of each type of repair and the relative frequency of each repair in the claims data.

Chi-squared tests were used to compare the percent reduction in KC formation pre- and post-acitretin treatment. All analyses were conducted using Stata, version 12.0 (StataCorp, College Station, TX).

Results

The database search identified 1,748 articles. There were 1,720 articles excluded as they did not relate to the study topic or were duplicates. The remaining 28 articles were reviewed in detail. Additional articles were excluded for the following reason: lack of information (3) and case series with fewer than 5 subjects (21).

During the mean 2.05-year pre-treatment period, 103 patients developed 37 BCCs and 232 SCCs. During the mean 1.38-year post-treatment period (range 0.5 to 3.17 years), there were 8 BCCs and 71 SCCs. This corresponded to a 73% reduction in BCC (mean: 0.10 per patient per year), 54% reduction in SCC (mean: 0.57 per patient per year), and 56% reduction in KC (mean: 0.68 per patient per year) (Table 2). There was no statistical difference in the reduction by tumor subtype ($p>0.05$). Nearly all patients experienced some mucocutaneous xerosis, 14 (14%) discontinued therapy, and 1 (1%) took a drug holiday.

The average cost of a 25mg pill of acitretin in May 2018 was $15.02.[10] Based on a daily dosing regimen, the annual prescription cost for acitretin is $5482.20 and when including $503.52 in monitoring fees the total annual cost per year was $5985.72.[4–5] The average number of Mohs stages was 1.74, based on data from the APCD data. By comparison, the cost of Mohs micrographic surgery (MMS) with repair, excision of malignant lesion with repair, and ED&C is $949.36, $359.02, and $102.77, respectively (Table 3).[4–5] The financial

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breakeven point for use of acitretin occurs when patients develop 11, 30 and 103 KC's per year compared to only treating the tumors with MMS, excision and ED&C, respectively. This analysis does not factor other important factors such as the morbidity associated with surgery, patient preferences, and indirect costs (e.g. opportunity costs).

Discussion

The analysis presented found a reduction in BCCs (73%) in addition to SCCs (54%). These findings support most of the smaller published studies regarding SCC and also demonstrate efficacy for BCC reduction.

Despite the efficacy demonstrated herein of acitretin for KC chemoprevention, the medication is likely underutilized for a few reasons. The first is the direct cost of the medication and associated monitoring. Based on a 25mg daily dosing regimen, the annual cost is $5985.72 in the United States (U.S.), which increased 157.5% from 2000–2008 and continued to increase until 2013.[3] Based on the same 25mg daily dosing regimen, the annual prescription cost in Canada is $547.50 and the total annual cost with monitoring is $1051.02, which is almost 600% lower than in the U.S. There are other factors that impede acitretin utilization such as the need for frequent lab studies, bothersome side effects, and rebound after cessation of efficacious therapy.

Conclusion

Although this study is subject to limitations due to variability in study characteristics (i.e. follow-up time, and variable dosing), generalizability (i.e. non-RTRs), and cost data (i.e. indirect costs and cost saving due to a reduction in metastasis and actinic keratoses), the data shows that acitretin is efficacious for chemoprevention of both BCC and SCC. Although the cost of acitretin has been decreasing since 2013, it is still 4 to 10 times higher than in other countries and is a barrier to providing appropriate care to patients most in need of skin cancer chemoprevention.

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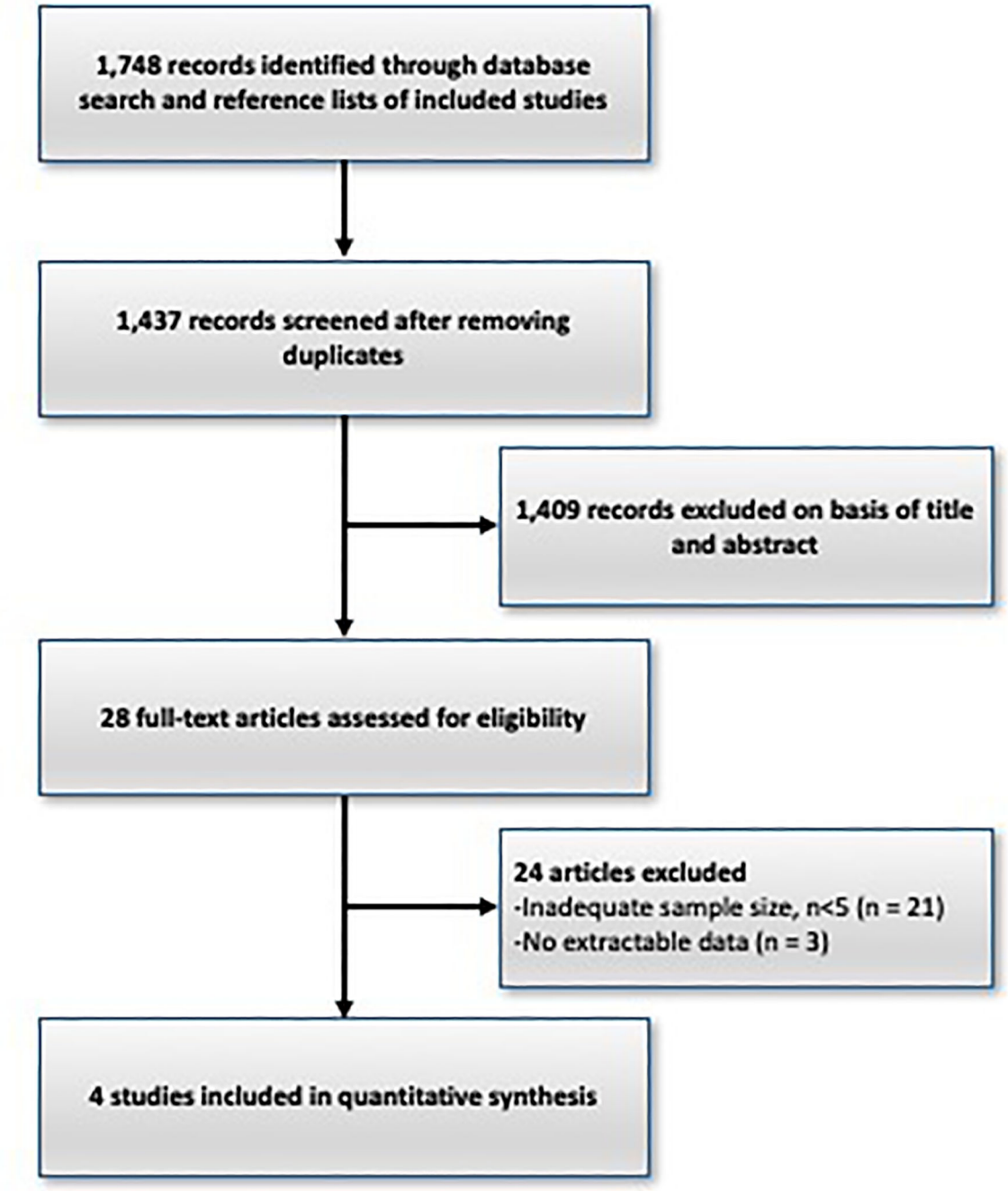

Figure 1.

Flow chart of studies included in the systematic review.

This figure summarizes the literature search methodology based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria.

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Table 1.

Summary of studies included in the systematic review.

Reference	Publication Year	Study Design	Quality of Evidence‡	Inclusion criteria	Medium FU (Range), Months	No. of Cases	Dose	Patient Population
Bavinck et al.4	1995	RCT	1	10+ keratotic lesions	6	38 (n=19 in each arm)	30mg QD	Renal Transplant
McKenna et al.5	1999	Prospective	4	2+ KC	38	16	0.3mg/kg/day	Renal Transplant
George el al.[6]	2002	Randomized cross over trial	1	3+ KC or 10 actinic keratoses	24	23	25mg QD or QOD	Renal Transplant
de Sevaux et al.[7]	2003	RCT using 2 different doses	1	1+ KC with 10+ actinic keratoses	12	26	0.4mg/kg/d (n=14) or 0.4 × 3 months -> 0.2mg/kg/d × 9 months (n=12)	Renal Transplant

Abbreviations: FU: follow up; RCT: randomized controlled trial; KC: keratinocyte carcinoma; No.: number; d: day; QD: one a day; QOD: one every other day; Wk: week

‡Quality of evidence assessed using the Quality Rating Scheme for Studies and Other Evidence[14]: 1) Properly powered and conducted randomized clinical trial or systematic review with meta-analysis; 2) Well-designed controlled trial without randomization or prospective comparative cohort trial; 3) Case-control studies or retrospective cohort study; 4) Case series with or without intervention or cross-sectional study; and 5) Opinion of respected authorities or case reports.

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Table 2.

citretin SCC, BCC, and KC.

	SCC							BCC							KC						
	Pre-Treatment		Post-Treatment		Reduction (annual)			Pre-Treatment		Post-Treatment		Reduction (annual)			Pre-Treatment		Post-Treatment		Reduction (annual)		
	Total reported	Annually	Total reported	Annually	Abs.	Mean (per patient)	%	Total reported	Annually	Total reported	Annually	Abs.	Mean (per patient)	%	Total reported	Annually	Total reported	Annually	Abs.	Mean (per patient)	%
	16	32	2	4	28	0.74	88	2	4	0	0	4	0.1	100	18	36	2	4	32	0.84	89
	100	31.5	18	5.68	25.87	1.62	82	11	3.5	3	0.95	2.52	0.16	73	111	35	21	6.62	28.39	1.78	81
	88	17.6	21	10.5	7.1	0.31	40	21	4.2	4	2	2.2	0.1	52	109	21.8	25	12.5	9.3	0.4	42
	28	28	30	30	−2	−.08	−7	3	3	1	1	2	0.08	67	31	31	31	31	0	0	0
	232	109.1	71	50.18	58.97	0.57	**54**	37	14.7	8	3.95	10.72	0.10	**73**	269	123.8	79	54.12	69.69	0.68	**56**

arcinoma; BCC, basal cell carcinoma; KC, keratinocyte carcinoma

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Table 3.

Summary of Acitretin and surgical costs.

Reference	Description	Cost
Acitretin Related Costs		
APCD [2]	E/M	$58.20
APCD [2]	CBC	$10.03
APCD [2]	LFT	$26.97
APCD [2]	Lipid panel	$20.14
APCD [2]	BMP	$9.09
NADAC [1]	Acitretin 25mg pill (U.S. as of May 2018)	$15.02
Canadarxconnection.com	Acitretin 25mg pill (International as of May 2018)	$1.50–$4.00
Surgical Costs		
APCD [2]	Average Mohs micrographic surgery (MMS) first stage	$392.33
APCD [2]	Average Mohs micrographic surgery (MMS) additional stage	$338.32
APCD [2]	Average excision of malignant lesion	$156.16
APCD [2]	Average intermediate/complex repair	$202.86
APCD [2]	Average flap/graft repair	$634.75
APCD [2]	Electrodessication and curettage (ED&C)	$102.77

Abbreviations: APCD, All-Payer Claims Database; E/M, evaluation and management; CBC, complete blood count; LFT, liver function test; BMP, basic metabolic panel

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