

SHORT COMMUNICATION

Topical Calcineurin Inhibitors, Topical Glucocorticoids and Cancer in Children: A Nationwide Study

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Systemic immunosuppression is significantly associated with the development of non-melanoma skin cancer (NMSC) and lymphoma in adults (1). The introduction of topical calcineurin inhibitors (TCI) tacrolimus and pimecrolimus for treatment of atopic dermatitis (AD) led the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to issue a “black box warning” that the compounds could, in theory, be considered “cancerogenic” (2). This has led to a dramatic reduction in the prescription of these compounds and increased anxiety among patients, parents and doctors.

However, many and large studies have not been able to confirm an increased risk of cancer in children using TCI (3–5). One study showed that the development of skin tumours was increased by application of 3% tacrolimus on guinea pig skin, together with either DMBA (7,12-dimethylbenz(alpha)anthracene) and/or TPA (12-O-tetradecanoylphorbol-13-acetate) painting, which are strong inducers of benign papillomas and, in a minor group (8.5%), squamous cell carcinoma (6). A study in mice using ultraviolet light induction of skin cancer could not show that 3 times weekly application of TCI augmented the occurrence of skin carcinomas (7). A database study has suggested that, among 953,064 persons using TCI, cutaneous T-cell lymphoma (CTCL) was increased (8).

TCI were introduced in Denmark in 2002. Children who had been exposed to TCI or topical glucocorticoids (TGC) between 2002 and 2009 were evaluated for the incidence of melanoma, NMSC, lymphoma and leukaemia during the period 2004 to 2011 through the Danish Cancer Registry (DCR).

MATERIAL AND METHODS

A total of 1,131,628 children were included in the current study. As control group, 20% of the background population (BGP) in DCR was used. The TCI group was children who had at least one prescription of TCI. There was no confirmation of the doctor’s diagnosis, but we assumed that close to 100% must be AD as the compounds are registered only for the use in patients with AD over the age of 2 years. Among children in this group most have also received TGC. The TGC group were children for whom TGC was prescribed, but not TCI. Here a significant subgroup had had AD, but any inflammatory TGC-treated skin condition was included. The third group was 20% of the BGP excluding persons in the TCI and TGC groups. All groups were then compared with the DCR.

In Denmark any prescription by a doctor is registered in a database (Register of Medicinal Product

Statistics), which includes how much of the drug has been prescribed over time for each individual, e.g. has it been prescribed only once or several times. Thus, we could estimate the use of the compound for each child.

Statistical analyses were performed using OpenEpi: Source Epidemiologic Statistics for Public Health (www.OpenEpi.com). A *p*-value <0.05 was regarded as statistically significant. Fischer’s exact test was used to calculate significance (see Table I).

RESULTS

A total of 34,921 children were exposed to TCIs, 444,600 to TGC and 652,107 were exposed to neither TCI nor TGC. In these groups of children 3, 60 and 121, respectively, had melanoma, and 0, 46 and 65 NMSC. Finally, leukaemia/lymphoma were diagnosed in 21, 207 and 268 cases, respectively.

When comparing the incidence of cancer in the different groups there was no significant increase in incidence of melanoma between the TCI group and the TGC group (odds ratio (OR) 0.64; 0.2–2.03), nor an increase in lymphoma/leukaemias (OR 1.29; 0.82–2.02). This was also the case when comparing the TCI group with the BGP on melanoma (OR 0.46; 0.15–1.46) and leukaemia/lymphoma (OR 1.46; 0.94–2.28) (Table I).

There was no significant difference in the mean amount of TCI or TGC used in any of the groups, or in the number of days treated when looking at cancers in the groups. The median time for use of TCI was 814 days.

Taken together, we found no increased risk of cancer among children treated with TCI compared with children treated with TGC and the control group (BGP).

DISCUSSION

Is AD associated with an increased risk of cancer? We and others have not been able to document this, except

Table I. Statistical analysis comparing cancer incidence after using topical calcineurin inhibitors (TCI) or topical glucocorticoids (TGC) compared to the background population (BGP)

Cancer type	Frequency (10 ⁻⁵)			Odds ratio (95% limits)	
	TCI	TGC	BGP	TCI/TGC	TCI/BGP
Melanoma	8.6	13.5	18.6	0.64 (0.20–2.03)	0.46 (0.15–1.46)
Non-melanoma skin cancer	0	10.4	10.0	Not applicable	Not applicable
Lymphoma or leukaemia	60.1	46.5	41.1	1.29 (0.82–2.02)	1.46 (0.94–2.28)

No statistical difference could be detected using Fisher’s exact test.

for an increase in non-melanoma cancer among adults (9, 10). Arellano et al. (11), using a nested-case control study of 3,500,194 individuals in the THIN UK database, observed that there was an increased incidence of lymphoma associated with the use of potent TGC, whereas no lymphoma cases were observed in TCI users. The authors considered the number of TCI users too low for optimal comparison. However, in users of systemic glucocorticoids, a Danish study showed a marginal increase in basal cell carcinomas, but not other cancers related to systemic steroid immunosuppression (12). A recent study of the literature indicates that severe AD and use of both TCI and TGC is associated with an increased risk of lymphoma (13).

TCI were introduced as a non-glucocorticoid remedy in the treatment and long-term control of AD. The drugs are large molecules and can hardly be absorbed systemically. Thus, in 85% of pimecrolimus-treated children (14), no drug was present in the blood and there was no accumulation of the drug; i.e. TCI will not act as systemic immunosuppressants. Hence we cannot support the FDA and EMA concerns that TCI, on theoretical grounds, are a risk for cancer development, at least not in children.

The reasons for not including the adult group in our study were: (i) AD is mainly a disease of children; only 20–25% continue to have AD after the age of 18 years and at 40 years of age the disease has resolved in all but 2% of cases (15). (ii) Although Hui et al. (8) observed, in a retrospective database study of 953,064 subjects that TCI users had a significant increase in CTCL, only 27.5% of subjects had AD (the remainder had “eczema”) and only 25% were children. (iii) Adult CTCL patients, who do not improve on treatment with normal topical remedies, have a skin inflammation for which patients will try “everything”, including TCI, as the disease is progressive.

In conclusion, there seems to be no increased risk for the development of cancer in children using TCI.

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