Non-interventional study report

A Prospective Pediatric Longitudinal Evaluation to Assess the Long-Term Safety of Tacrolimus Ointment for the Treatment of Atopic Dermatitis (APPLES™)

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Title

APPLES™: A Prospective Pediatric Longitudinal Evaluation to assess the Long-Term Safety of Tacrolimus Ointment for the Treatment of Atopic Dermatitis

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Keywords

Tacrolimus, Atopic Dermatitis, Long-Term Safety, Cancer, Children, Topical Calcineurin Inhibitor

Rationale and background

As part of the approval process of tacrolimus ointment for the treatment of atopic dermatitis (AD) in children (Protopic® Ointment 0.03%) and in adults (Protopic® Ointment 0.03% and 0.1%), the United States Food and Drug Administration (FDA) requested a post-marketing commitment regarding the long-term safety of tacrolimus ointment in children with AD, and the European Medicines Agency (EMA) requested that the study was expanded to countries in the EU.

Research question and objectives

The research question was: Does topical treatment of children with tacrolimus ointment increase the long-term risk of malignancy?

The APPLES™ study aimed to assess the long-term safety of tacrolimus ointment 0.03% or 0.1% in the treatment of children with AD under actual use conditions, including the risk of developing cutaneous or systemic malignancies. The main endpoint of the study was the standardised incidence ratio (SIR) for all observed cancer events, with the expected number of events being derived from cancer registries covering the relevant background populations. All potential cancer events were reviewed by an independent Endpoint Review Committee.

Study design

This was a prospective, observational cohort study with primary data collection. A cohort of children and young adults treated for at least 6 weeks with topical tacrolimus with first exposure at age < 16 years were to be followed for 10 years. The calculated incidence rate for malignancy in the study was compared to the incidence rate in the background population of the same age, sex and, in the USA, also race. Enrolment criteria were very liberal, and

treatment during enrolment was unrestricted, to represent actual use conditions. No medication was supplied to study participants as part of the study setup.

Setting

In total, 8,071 subjects were enrolled in the study at 314 sites in North America and Europe, and 7,954 eligible subjects were included in the analysis. 117 subjects turned out not to be eligible. Enrolment started in 2005 and was completed in 2012. The follow-up was terminated earlier than planned, on 31 January 2019, as endorsed by the FDA on 16 July 2018 based on futility of continuation. The EMA agreed to the early termination on 7 November 2018. The study was closed in all countries with the last subject exited on 31 January 2019 and the last site closed on 6 June 2019.

Subjects and study size, including drop-outs

To be enrolled in the study subjects had to be diagnosed with AD, had to have been exposed to tacrolimus ointment before the age of 16, and the subject or guardian had to have given written informed consent and assent (when relevant) to comply with the program requirements, including annual physical examinations, biennial dermatological examinations and direct contact twice a year for questionnaire completion.

The sample size of 8,000 subjects followed for 10 years (theoretically corresponding to 80,000 person-years of observation (PYRS)) was agreed with the FDA as a compromise between feasibility and the ability to detect an increase in risk. The aim was to be able to exclude a tripling of the risk with a power of 95%, although a lower increase in risk would also be clinically relevant. An expected annual attrition rate of 10% was not brought into the sample size calculation.

Variables and data sources

Baseline data included data needed for extraction of expected cancer incidence rates, prior malignancies, prior exposure to topical calcineurin inhibitors, severity of the AD and other atopic comorbidity. During follow-up focus was on collection of serious adverse events (SAEs) from site and non-site physicians as well as directly from subjects and guardians to detect any malignancy. Tacrolimus exposure in terms of amount used since last contact was also collected during follow-up. The main events of interest were adjudicated cancer events.

Results

Of 7,954 eligible subjects enrolled in the study, 1,176 subjects (14.8%) completed the planned 10 years of follow-up, and 949 (11.9%) were censored at study termination, adding up to a total of 2,125 subjects not 'lost' during the study. Subjects who had left the study before completion of their planned follow-up duration or before study termination included: 1,454 (18.3 %) who withdrew consent to participate, and 4,368 (54.9%) either enrolled more than 10 years before 31 January 2019 who were lost to follow-up or enrolled less than 10 years before 31 January 2019 and had no contact within 6 months before this date. In addition, 7 subjects died during their study participation.

A total of 6 malignancies were observed in the study, giving a point estimate of 1.01 for the SIR with a 95% confidence interval of 0.37 to 2.20. The events were one chronic myeloid leukaemia, one alveolar rhabdomyosarcoma, one carcinoid tumour appendix, one spinal cord neoplasm, one malignant paraganglioma, and one spitzoid melanoma. There was no pattern regarding time between first exposure and cancer diagnosis. The number of malignancies was too small to study associations with level of exposure.

Discussion

The dataset comprises 44,629 PYRS after enrolment, using a lag time of 6 months after first exposure in case this reached into the enrolment period. The study was powered to exclude a 3-fold increase in all cancer incidence in a study with a 100% completion rate, i.e. based on 80,000 PYRS.

The APPLES™ study results did not show any association between treatment of AD with topical tacrolimus during childhood or adolescence, and the risk of cancer. The number of cancers observed in this cohort during the study was as expected, based on incidence rates for the sex, age, race and country of residence matched background populations. No lymphomas or non-melanoma skin cancers were observed. Sensitivity analysis showed that the results were robust to biased loss to follow-up.

The results of this study have alleviated the concern that topical tacrolimus might increase the risk of malignancy, in particular regarding skin cancer and lymphoma. Thus, the benefit/risk balance of Protopic® has changed in a favourable direction.