Pimecrolimus and Tacrolimus

Pimecrolimus and tacrolimus are used to treat atopic dermatitis, a type of eczema. The drugs are prescribed to children and adults. Pimecrolimus is applied as a cream directly to the affected skin until the condition is cleared. Tacrolimus is similarly applied as an ointment. Pimecrolimus and tacrolimus are calcineurin inhibitors, i.e., they inactivate calcineurin, thereby suppressing the immune response. They have been used since the year 2000 as alternatives to steroids for the treatment of atopic dermatitis. Tacrolimus also has long been used as a systemic drug by injection or ingestion for immunosuppression in organ transplant patients.

Pimecrolimus passed the animal data screen. Tacrolimus passed the human data screen. Each compound underwent a preliminary toxicological evaluation, and each is being brought to the Carcinogen Identification Committee for consultation. This is a compilation of the relevant studies identified on each compound during the preliminary toxicological evaluations. Pimecrolimus and tacrolimus are presented together because of their similarity in structure and biologic activity. The CIC is being asked to advise OEHHA on whether either chemical should be brought to the committee for a full evaluation of the carcinogenicity evidence at a future meeting.

Epidemiological data

**Pimecrolimus**
- Topical application
  - Retrospective cohort study
    - Possible risk of T-cell lymphoma: Hui et al. (2009)
  - Case-control study
    - No association between use and lymphoma: Arellano et al. (2007)
  - Case reports
    - Cutaneous tumors (6 cases) and lymphomas (4 cases): Reviewed by Wooltorton (2005)

**Tacrolimus**
- Injection or oral administration
  - Case-control study - 1000 liver transplant patients
    - Increased risks of oropharyngeal (oral cavity, pharynx and larynx), respiratory and skin cancers: Jain et al. (1998)
- Topical application
  - Retrospective cohort study
    - Increased risk of T-cell lymphoma: Hui et al. (2009)
Case-control study
  - No association between use and lymphoma: Arellano et al. (2007)

Case reports
  - Lymphomas (9 cases) and skin tumors (squamous cell carcinoma, cutaneous sarcoma and malignant melanoma) (10 cases): Reviewed by Wooltorton (2005)
  - Skin squamous cell carcinoma at site of application: Langeland and Engh (2005); von Felbert et al. (2010)

Animal carcinogenicity data

Pimecrolimus
  - Studies in rats
      - Increase in thyroid follicular cell adenoma in males (by pairwise comparison and trend)
      - No treatment-related thyroid tumors in females
    - Two-year gavage studies in male and female Wistar rats (study #1): FDA (2001, pp. 6-8); FDA Approved Label (2010)
      - Increase in benign thyomas in males
      - No treatment-related tumor findings in females
    - Two-year gavage studies in male and female Wistar rats (study #2): FDA (2001, pp. 6-8); FDA Approved Label (2010)
      - Increase in benign thyomas in males and females (by pairwise comparison)
  - Studies in mice
    - Gavage carcinogenicity studies in male and female mice: FDA Approved Label (2010)
      - Increase in lymphomas in males and females (by pairwise comparison)
    - Dermal carcinogenicity study in mice: FDA Approved Label (2010)
      - No treatment-related tumor findings
    - Dermal 13-week repeat dose study in mice: FDA Approved Label (2010)
      - Increase in lymphomas and other lymphoproliferative lesions
  - Study in monkeys
    - Oral 39-week toxicity study in monkeys: FDA Approved Label (2010)
- **Immunosuppressive-related lymphoproliferative disorder (IRLD) associated with lymphocryptovirus (simian analog of human Epstein Barr virus).** IRLD is a precancerous condition that can progress to lymphoma in monkeys and humans.

**Tacrolimus**

- Studies in rats
  - 104-week diet studies in male and female rats: FDA Approved Label (2006)
    - No treatment-related tumor findings in males or females

- Studies in mice
  - 80-week diet studies in male and female mice: FDA Approved Label (2006)
    - No treatment-related tumor findings in males or females
  - 104-week dermal studies in male and female mice: FDA Approved Label (2006)
    - Increase in lymphomas in males and females (by pairwise comparison)
    - Increase in skin papilloma, and papilloma and carcinoma (combined)

**Other relevant data**

- Genotoxicity

  **Pimecrolimus**
  - Review: FDA Approved Label (2010)
    - No evidence of genotoxicity in a battery of in vitro tests or in a mouse in vivo micronucleus assay

  **Tacrolimus**
    - No evidence of genotoxicity in bacteria, mammalian cells in culture, mouse in vivo clastogenicity assays, or unscheduled DNA synthesis assays in rodent hepatocytes

- Mode of action considerations
  - Like the known human carcinogen cyclosporine, pimecrolimus and tacrolimus are immunosuppressive drugs that are calcineurin inhibitors. Cyclosporine causes lymphoma, skin and other cancers.
- Dermal tacrolimus in mice decreases CD4/CD8 helper cell ratio, a risk factor for malignancy: Niwa et al. (2003)
- Tacrolimus and other immunosuppressive drugs increase the incidence of chromosomal aberrations and tumors in mice exposed to UVB radiation: Dworkin et al. (2009)
References


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1 Excerpts or the complete publication have been provided to members of the Carcinogen Identification Committee, in the order in which they are discussed in this document.