

DISPROPORTIONALITY ANALYSIS OF THE SKIN TOXICITY OF INGENOL MEBUTATE USING THE FDA ADVERSE EVENT REPORTING SYSTEM DATABASE



Background and importance >>

Ingenol mebutate granted a marketing authorisation from European Medicines Agency (EMA) to treat actinic keratosis. On 30 April 2020, due to an increased risk to provoke skin cancer in treated patients compared to imiquimod, EMA withdrawn it after a safety data review. The final results of the 3-year safety study (NCT01926496) in 484 patients showed that, among skin malignancies, squamous cell carcinoma (SCC) was that with higher incidence with ingenol mebutate gel compared with imiquimod (3.3% versus 0.4% of patients).

Aim and objectives >>

This study aims to evaluate the safety issue (signal) of increased occurrence of skin malignancy (e.g. squamous cell carcinoma (SCC) of skin) during therapy with ingenol mebutate by mining of the FDA Adverse Event Reporting System (FAERS) database.

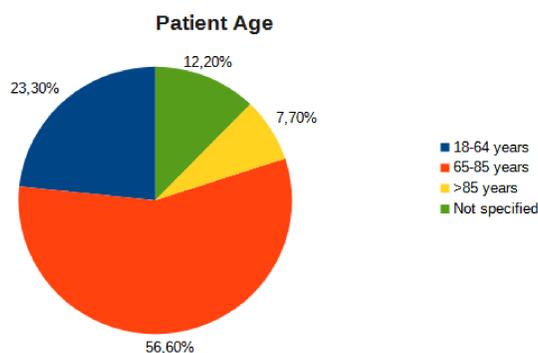
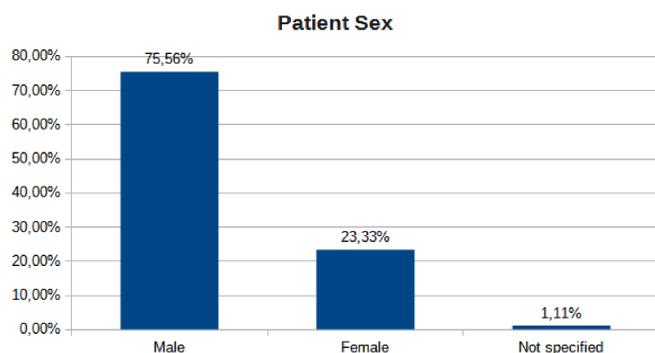
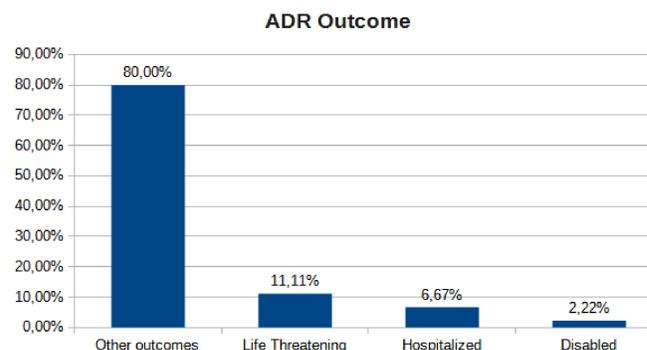
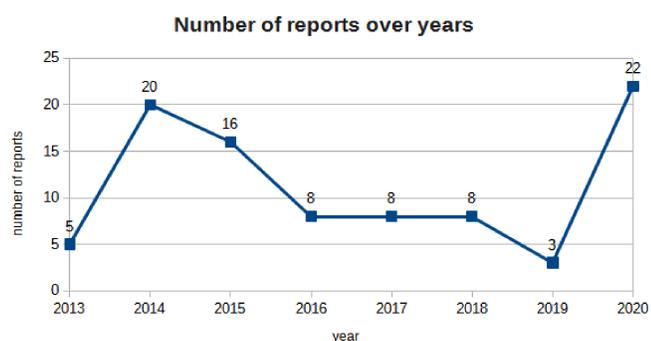
Material and methods >>

By querying FAERS, we searched for the cases of SCC associated to ingenol mebutate from 1st January 2013 to 30th June 2020 using the following MedDRA Preferred Terms (PTs) "squamous cell carcinoma of skin", "skin squamous cell carcinoma metastatic" and "skin squamous cell carcinoma recurrent". Therefore, via contingency table we computed PRR to evaluate the strength of association between SCC and ingenol mebutate.

Results >>

We found the following data of co-occurrence: ingenol mebutate/SCC (DE)=90 reports, ingenol mebutate/other ADR (De)=5.128, other drugs/SCC (dE)=2.882 and other drugs/other ADR (de)=13.899.084 from 2012 to 2020. The two by two contingency table turned out a value of PRR 44.4105 (95% CI, 33.332; 59.1711), P value < 0.001. Assessment of SCC reports revealed that all ADR were serious and resulted in different outcomes: 80% other outcomes, 11.11% life threatening, 6.6% hospitalized and 2.2% disabled. Patient affected were aged 65-85 years (56.6%), 18-64 years (23.3%), >85 years (7.7%) and not specified (12.2%); 75,6% were male and 23.3% female.

Images >>



Conclusion and relevance >>

Disproportionality analysis showed that ingenol mebutate-SCC pair is reported more often than expected. Based on this statistical association, our data confirm the safety signal evaluated by EMA that led to the withdrawn of ingenol mebutate from the EU market. In addition to this, it raises the question why FDA has not still revoked the marketing authorisation of the drug in USA.

6- References and/or acknowledgements >>

<https://clinicaltrials.gov/ct2/show/NCT01926496>

https://www.ema.europa.eu/en/documents/referral/picato-article-20-referral-risks-picato-actinic-keratosis-outweigh-benefits_en.pdf