DARWIN EU® - A multi-national network cohort and self-controlled case series study of the effect of doxycycline versus active comparators on the risk of suicidality in individuals with acne

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Background

There have been several case reports of a potential association between use of doxycycline and suicide, as well as psychiatric symptoms in observational studies.

Objective

1. To use a new-user cohort study to assess the association between doxycycline and composite suicide and suicide-related events (completed suicide, suicide ideation and suicide attempt, self-harm), depression and anxiety, compared to active comparators in individuals with acne
2. To use a self-controlled case series study to assess the association between use of doxycycline and composite non-fatal suicide-related events (including suicide ideation, suicide attempt, self-harm), depression and anxiety in individuals with acne

Methods

This drug safety study used primary care data from the UK (CPRD GOLD), the Netherlands (IPCI), Spain (SIDIAP, with hospital discharge linkage) over the period 2010-2023. Individuals were included based on new use of doxycycline, erythromycin, or isotretinoin, with a condition record of acne within 180 days prior. This was part of a larger study including other indications including lower-respiratory tract infections, chlamydia and rosacea, which are not reported here. Individuals were excluded if use of the study drugs, data source start date, or outcome fell within 365 days prior to the index date. The *CohortMethods* R package was used to perform the new-user cohort study. Propensity-score matching of patients prescribed doxycycline to the respective active comparator cohorts. Individuals were followed up until occurrence of the outcome, death, data end-date, or end of the treatment episode plus seven-days. Cox-proportional hazards regression was used to estimate hazard ratios for the association between doxycycline and composite suicide-related events (ideation, attempt, completion, self-harm), anxiety, and depression compared to erythromycin or isotretinoin. We performed a self-controlled case series (SCCS) study with the *SelfControlledCaseSeries* R package to perform conditional Poisson regression to estimate incidence rate ratios (IRR) for each outcome of interest: composite non-fatal

suicide-related events (ideation, attempt, self-harm), depression and anxiety. The IRRs were calculated for each assessment window that consisted of the baseline window (>90 days prior to the index date when non-exposed), a pre-treatment assessment window [-90,0], and the risk windows [1,90], [1,30], [31,60], [61,90], [91,inf], where day 0 is the index date.

Results

We included 31,097 individuals prescribed doxycycline, 48,473 prescribed erythromycin, and 13,948 prescribed isotretinoin. In the new-user cohort study, an association with suicide-related events was identified in individuals prescribed doxycycline compared to erythromycin in SIDIAP (HR 3.77, 95% CI [1·03-17·80]), and in CPRD GOLD there was a non-statistically significant association (HR 1.71, 95% CI [0.74-4.07]). Meta-analysed together, there was an association with suicide-related events (HR 2.11, (95% CI [1.01-4.39]). No association for suicide-related events was found in individuals using doxycycline for acne compared to individuals using isotretinoin and the full results can be seen in **Figure 1**. In IPCI, an association with anxiety in doxycycline users for acne was observed compared to isotretinoin users (HR 1.94, 95%CI [1.28-2.94]). No associations were identified between doxycycline use and anxiety compared to erythromycin in CPRD GOLD and SIDIAP (HR 1.06, 95% CI [0.84-1.32] and HR 0.96, 95% CI [0.73-1.26] respectively). There were no associations identified between doxycycline and the outcome of depression using any active comparator.

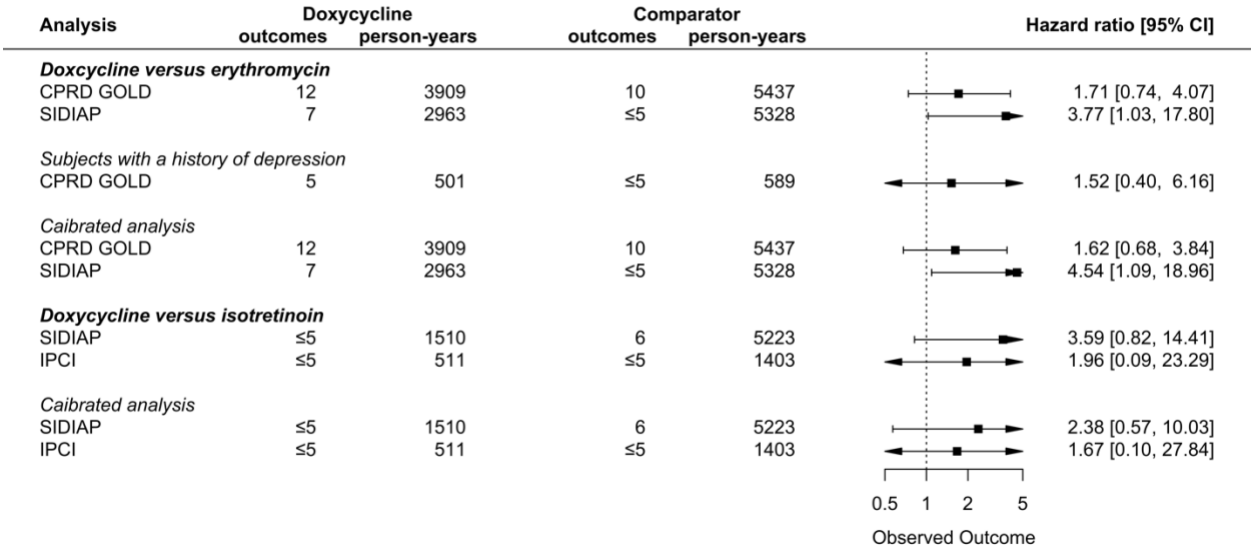

Figure 1. Cox proportional hazards results of doxycycline versus erythromycin or isotretinoin on the effect of suicide-related events in individuals with acne. Results are presented per data source CPRD GOLD (UK), SIDIAP (Spain), and IPCI (Netherlands). Additional analysis in individuals with a history of depression and calibrated by negative control outcomes are also presented.

In the SCCS study, we identified no associations between doxycycline and non-fatal suicide-related events in any time period. In CPRD GOLD the 1-30 day risk period there were no associations between doxycycline and anxiety (IRR 0.89, 95% CI [0.79-0.99]) and in the 1-90 day risk period (IRR 0.94, 95% CI

[0.88-1.00]). In IPCI there were no associations observed between doxycycline and anxiety in the 1-30 day risk period (IRR 0.82, 95% CI [0.66-1.00]) and the 1-90 day risk period (IRR 0.91, 95% CI [0.80-1.02]. In CPRD GOLD there were decreased associations between doxycycline and depression in the 1-30 day risk period (IRR 0.80, 95% CI [0.71-0.90]) and the 1-90 day risk period (IRR 0.90, 95% CI [0.84-0.97]). In IPCI, no associations were observed in the 1-30 day risk period (IRR 1.11, 95% CI [0.83-1.45]) and 1-90 day risk period (IRR 0.98, 95% CI [0.81-1.16]). In SIDIAP no estimates were unblinded for the 1-30 and 1-90 day risk periods.

Conclusions

We identified a two-fold increased risk of suicide-related events in individuals who use doxycycline compared to individuals who use erythromycin for acne in CPRD GOLD and SIDIAP in the new-user cohort study. We also identified a two-fold increased risk of anxiety with doxycycline use compared to isotretinoin use in IPCI. However, the SCCS did not support these associations. All results were included in the full regulatory assessment and no regulatory actions were taken by the European Medicines Agency for doxycycline.

Disclaimer

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