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Final Study Report

Impact of EU label changes and revised pregnancy prevention programme for oral retinoid-containing medicinal products: acitretin, alitretinoin and isotretinoin

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Summary information

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Research question and objectives	<p>This report describes a pharmaco-epidemiological study using longitudinal data collected in six electronic health care databases from 4 European Union (EU) countries to investigate the use of oral retinoid-containing medicinal products authorised in the EU before and after implementation of the 2018 revised measures for pregnancy prevention in clinical practice, and effectiveness of the 2018 intervention. The research objectives were:</p> <p>Objective 1: To determine drug utilisation and prescription patterns of oral retinoid-containing medicinal products in females of childbearing potential, and to investigate whether significant changes in prescribing patterns occurred (pre-/post-intervention).</p> <p>Objective 2: To determine prescribers' compliance with the recommendations in the SmPC for oral retinoid-containing medicinal products, by indication (i.e., dermatological conditions including acne, psoriasis and eczema), by age group, by duration of use, and by database.</p> <p>Objective 3: To determine, in so far as is possible, patients' use of effective contraception in compliance with recommendations in the SmPC for oral retinoid-containing medicinal products, by indication (i.e., dermatological conditions including acne, psoriasis and eczema), by age group, by method of contraception and by database.</p> <p>Objective 4: To determine drug utilisation and prescription patterns over time for alternative medicines prescribed in females of childbearing potential and females becoming pregnant where oral retinoid-containing medicinal products had previously been prescribed or discontinued, by indication, by age group and by database.</p>

	Objective 5: Based on the results of the above, to estimate the effectiveness of the 2018 risk minimisation measures for oral retinoids.
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1. Abstract

Title

Impact of 2018 EU label changes and revised pregnancy prevention programme for oral retinoid-containing medicinal products (acitretin, alitretinoin and isotretinoin): utilisation and prescribing trends.

Keywords

Oral retinoids, acitretin, alitretinoin, isotretinoin, congenital abnormalities, contraceptive agents, dermatologic conditions, acne, eczema and psoriasis, pregnancy.

Rationale and background

In March 2018, the European pregnancy prevention program (PPP) for oral retinoids was updated. Despite a reduction in number, pregnant women exposed to retinoids have continued to occur, raising concerns about compliance and effectiveness of PPPs in clinical practice. In this context, a pharmaco-epidemiological study was conducted using longitudinal data collected in 6 electronic health care databases from 4 EU countries (Spain, Italy, Netherlands, Denmark) to describe the use of oral retinoid-containing medicinal products authorised in the EU before and after implementation of the 2018 revised measures for pregnancy prevention in clinical practice, and to measure the impact of the 2018 intervention by carrying out an interrupted time series analysis.

1.1 Objective 1

Aim: To determine drug utilisation and prescription patterns of oral retinoid-containing medicinal products in females of childbearing potential, and to investigate whether significant changes in utilisation and prescribing patterns after the 2018 European Pregnancy Prevention Programme occurred, using longitudinal data collected from six electronic health care databases from different EU countries.

Methods: An observational times series study consisting of females of childbearing age (aged 12 and 55 years) derived from electronic health record data sources in the Netherlands (PHARMO database network), Spain (Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria (BIFAP); Valencia health system integrated database (VID), Italy (ARS Tuscany), Caserta Record Linkage Database (CASERTA), and Denmark (Danish National Registers (DNR)). We estimated the incidence, prevalence and rate of discontinuation of use of oral retinoid-containing medicinal products per month, in each data source. An interrupted time series analysis was performed to assess changes after the implementation of the 2018 PRAC intervention the date could vary by country.

Results: In the study population comprising 11,570,047 women of childbearing age (12-55 years), 88,992 persons used an oral retinoid at any point during the 11 years of the study period. Most persons were below 31 years of age at start of follow-up. The most frequently used retinoid was isotretinoin (95.6%) of all users, followed by acitretin and alitretinoin. Monthly incidence and prevalence rates showed that retinoid prescriptions have a strong seasonal pattern, with decreasing incidence in the summer months, especially in southern countries. This seasonal pattern is aligned with the clinical practice recommendations to be careful with use with sunlight due to potential photosensitivity (Ferguson et al 1989), and potentially different disease severity across seasons. The pre-intervention monthly retinoid discontinuation rate in PHARMO (NL) was 7.0% and the post-intervention one was 7.5%. ARS (IT) showed a pre-intervention average discontinuation rate of 16.2% and 15.9% in the post-intervention period. In Caserta (IT), pre-intervention monthly retinoid discontinuation rate reached 16.5% and the post-intervention rate was 15.3%. Pre- and post-intervention discontinuation percentages for VID (ES) were 10.6% and 12.1% per month, respectively. In BIFAP (ES), monthly discontinuation rates were 25.1% in the pre-intervention period and 18.5% in the post-intervention time.

Conclusion: Prescription/dispensing rates increased slightly over time, but comparison of the incidence or prevalence rates and trends before and after the intervention (excluding COVID-19 years) and discontinuation rates showed no significant change after the RMM implementation in any of the data sources.

1.2 Objective 2

Aim: To determine prescribers' compliance with the recommendations in the SmPC (sections 4.4, 4.6) for oral retinoid-containing medicinal products, by age group and by database, using longitudinal data collected from six electronic health care databases from different EU countries.

Methods: An observational times series study consisting of females of childbearing age (aged 12 and 55 years) derived from electronic health record datasources in the Netherlands (PHARMO database network), Spain (Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria (BIFAP); Valencia health system integrated database (VID), Italy (ARS Tuscany), Caserta Record Linkage Database (CASERTA), and Denmark (Danish National Registers (DNR)), who used an oral retinoid during the study period (2010-2020). First, we estimated the number and proportion of oral retinoid users with a record of a pregnancy test within the 90 days i) before and ii) after the date of retinoid prescribing or dispensing per month. Second, we estimated the number and proportion of retinoid users with a record indicating concomitant use of contraception per month. We estimated the change in level and trend for pregnancy test and contraception proportions after the implementation of the 2018 PRAC intervention through an interrupted time series analysis.

Results: A total of 88,992 women of childbearing age who used an oral retinoid were included in the study-population for these objectives. Danish registries, ARS and Caserta were not able to capture pregnancy tests as these are claims data sources and not medical records.

Only few or no records of pregnancy tests were detected before and after the initiation of a retinoid, except in VID. The low level of recording did not allow for trend analyses nor a proper interpretation of the impact of risk minimization. Contraceptive use could not be measured in ARS and was very low in Caserta, in PHARMO, recorded contraceptive use in retinoid users was far below 100%, in VID and BIFAP, recorded contraceptive use increased over time. In BIFAP there was a significant increase in recorded contraceptive use after 2018 RMM, but still far below 100%.

Conclusion: Pregnancy tests are not recorded in the electronic health databases, neither in medical record data sources. Contraception use at start or during a retinoid treatment, was recorded very differently across databases since several non-user/non-permanent contraceptive measures are not recorded because of lack of reimbursement or OTC status. In the Netherlands and Spain, we could investigate trends of contraceptive coverage, only in BIFAP we could observe a significant increase after 2018 RMM.

1.3 Objective 3

Aim: To determine, in so far as is possible, patients' use of effective contraception in compliance with recommendations in the SmPC for oral retinoid-containing medicinal products, by indication (i.e., acne, psoriasis and eczema), by age group, by method of contraception and by database.

Methods: An observational times series study consisting of females of childbearing age (aged 12 and 55 years) derived from electronic health record data sources in the Netherlands (PHARMO database network), Spain (Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria (BIFAP); Valencia health system integrated database (VID), and Italy (ARS Tuscany), Caserta Record Linkage Database (CASERTA)), who used an oral retinoid during the study period (2010-2020). To measure effective use of contraception during retinoids, we estimated the monthly occurrence of pregnancies during and within one month after stopping retinoids using the ConcePTION pregnancy algorithm and utilizing only pregnancies with high level of certainty. Newly occurring pregnancies were aggregated pre and post intervention, and expressed as number of pregnancies per 1000 users. Pregnancies were classified by quality in the following colour code: green (high reliability, with recorded start and end date of pregnancy in the data banks), colour yellow (when the end date is recorded and start date is estimated, blue when the pregnancy start date is recorded and the end date is imputed and red with imputed start and end of pregnancy). Validation of pregnancies was conducted.

Results: In PHARMO, 41 pregnancies started during a retinoid treatment, and 20 persons started a new retinoid treatment episode during an ongoing pregnancy. Most of those occurred prior to the 2018 RMM. In the post intervention period 3 pregnancies started during the course of a retinoid treatment and 2 registered the initiation of a new retinoid treatment episode while being pregnant. In both categories of analysis, rates per 1000 retinoid users lower after the 2018 RMM.

In ARS, 19 pregnancies (8 green and 11 yellow) started during retinoid treatment, and in 9 pregnancies (1 green and 8 yellow) an oral retinoid was started while being pregnant. In both instances, rates per 1000 retinoid users decreased after the implementation of the RMM in August 2018.

In Caserta (IT), 6 pregnancies started during retinoid treatment and in 7 pregnancies the retinoid was started during pregnancy. All of those pregnancies occurred prior to the 2018 RMM.

In VID (ES), 96 pregnancies (44 green and 52 yellow) started during a period of retinoid treatment and in 100 pregnancies (22 green and 78 yellow), the retinoid was started during pregnancy. Rates in both scenarios are lower after intervention. Rate per 1000 retinoid users during pregnancy lower from 0.72 in the pre-intervention time to 0.42 in the post-intervention period; the last remains the highest rate among all DAPs. Rate per 1000 retinoid users that started a pregnancy while taking an oral retinoid decreased from 0.70 to 0.39.

In BIFAP (ES), 11 pregnancies started (yellow) during a retinoid treatment and in 12 (yellow) the retinoid was started during pregnancy. The rate of retinoid prescriptions during the course of a pregnancy decreased from 0.17/1000 users before the 2018 RMM to 0.11/1000 users after the 2018 RMM. Rate of pregnancies started while taking a retinoid doubled from 0.12/1000 users in the pre-intervention period to 0.22/1000 users in the post-intervention one.

Conclusion: Based on currently available data we observe pregnancies occurring during use of oral retinoids before and also after 2018 RMM. Verification of pregnancies confirm that pregnancies happened during retinoids, or that retinoids were started during pregnancy. Since we focused on pregnancies where a registry entry or an end date was available, we will underestimate pregnancies at the end of the follow-up period leading to a potential beneficial effect that would require to be confirmed with more follow-up time.

1.4 Objective 4

Aim: To determine drug utilisation and prescription patterns over time for alternative medicines prescribed in females of childbearing potential and female becoming pregnant where oral retinoid-containing medicinal products had previously been prescribed or discontinued, by indication, age group and database, using longitudinal data collected from six electronic health care databases from different EU countries.

Methods: An observational times series study comprising females of childbearing age (aged 12 and 55 years) from the corresponding databases in the Netherlands (PHARMO), Spain (VID and BIFAP), Italy (ARS and Caserta), and Denmark (DNR), who had a recorded prescription or dispensing of an oral retinoid-containing medicinal product between 01 January 2010 and 31 December 2020. We estimated the incidence rates of alternative medication use (prescriptions/dispensing) for eczema, psoriasis and acne among oral retinoid users and the rate of switching from oral retinoid to an alternative medicine per month. We estimated the change in level and trend of switches from retinoids to alternative medications after the implementation of the 2018 PRAC intervention through an interrupted time series analysis.

Results: We found a steady trend of alternative medicines use for acne, except in the Danish registers where we observed a gradual decrease, and in VID, where alternative medicines use decreased after the last trimester of 2019 (COVID-19 pandemic period). Alternative medication use for eczema showed an increasing trend for the Danish registers and PHARMO, but a steady use through the study period for the other databases. For psoriasis, more heterogenous patterns are found, with an increasing trend for Danish registers, PHARMO and ARS, while after 2019 it increased in Caserta and decreased in VID. The ITS analysis of switching rates from retinoids to alternative medicines before versus after the 2018 RMMs revealed that there was a non-statistically significant change in level nor trend for PHARMO, and ARS. For Caserta, VID and BIFAP, a statistically significant decrease in slope trend of switchers was observed. However, this change disappears when excluding the COVID-19 pandemic period from the model. For the Danish register, it was not possible to model the ITS analysis because there were not enough time points after the 2018 RMMs.

Conclusion: A seasonal pattern of alternative medication consumption was seen for acne especially in ARS and VID, and for psoriasis in DNR. When comparing retinoid switching to alternative medications before and after the 2018 RMM, no significant changes were seen for any of the countries involved.

1.5 Abstract Objective 5

Aim: To draw conclusions on the effectiveness of the 2018 EU RMMs for retinoids.

Methods: Evidence generated from Objectives 1-4, weighed by the strengths and limitations of the analyses, was used to draw conclusions on the effectiveness of the RMMs, per country and across European countries included in the study. Pregnancies were classified by quality of the underlying information to estimate the start and end date in green (recorded end and start date), yellow (recorded end date and imputed start date), blue (recorded start date imputed end date) and red (both start and end date imputed).

Results: We found no change in oral retinoid use after the 2018 RMMs in any of the data sources (Objective 1), and only a slight increasing trend in recorded contraceptive measures in BIFAP and VID (Objective 2). In each of the data sources pregnancies occurred during retinoid treatment before and after the RMM, there is a delay in detection of pregnancies, as often they need to finish before being recorded, which may artificially lower the post-intervention rates. Furthermore, we observed no change in switching rates from retinoids to alternative medications (Objective 4). Noteworthy, these findings should be interpreted in context of the limitations that we faced, such as an inability to investigate some objectives due to limited data availability on pregnancy test or over-the-counter use of some contraceptives, and the occurrence of COVID-19 pandemic, which has shortened and impacted our post-intervention period and limited our ability to run ITS analyses for some objectives and some databases.

Conclusion: Based on the above findings on various objectives in this study, we can conclude that there was very limited measurable impact of the 2018 RMM on oral retinoid use and the pregnancy prevention measures among women of childbearing age in our included databases. Moreover, pregnancies still seem to happen during oral retinoid treatment after the implementation and with the focus on pregnancies with certainty of happening (yellow/green), that were also validated.