RetinoidRiskAware

Impact of EU label changes and revised pregnancy prevention programme for medicinal products containing oral retinoids: risk awareness and adherence

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Summary

RetinoidRiskAware - Impact of EU label changes and pregnancy prevention programme for medicinal products containing oral retinoids: risk awareness and adherence

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Keywords

Teratogenicity; retinoids; risk minimization; risk awareness; pregnancy prevention programme; European Union; online survey; interviews; patients; pharmacists; prescribers

Rationale and background

Oral retinoids (acitretin, isotretinoin, alitretinoin and tretinoin) are licensed as medicinal products for dermatological conditions, including (severe) acne, eczema and psoriasis. Other oral retinoids are used to treat skin manifestations of T-cell lymphoma (bexarotene) and acute promyelocytic leukaemia (tretinoin). The teratogenic risk, congenital malformations and neurodevelopmental disorders associated with the use of retinoids by pregnant women are well established.

A pregnancy prevention programme (PPP) launched in 2003 for isotretinoin has since been extended to other oral retinoids treating dermatological conditions: acitretin and alitretinoin.. The effectiveness of the PPP has been closely reviewed and despite a reduction in the number of pregnancies exposed to retinoids, cases of pregnancy exposure continued to occur, raising concerns about compliance with the PPP.

On 22 March 2018, the European Medicines Agency (EMA) Committee for Medicinal Products for Human use (CHMP), advised by the Pharmacovigilance Risk Assessment Committee (PRAC) concluded that an update of measures for pregnancy prevention was needed. In 2018, the PRAC established a new pregnancy prevention programme (PPP) to ensure that patients are made fully aware of the risks and the need to avoid pregnancy and revised the educational materials. These include a patient reminder card, a physician checklist and risk acknowledgement form, and a pharmacist checklist.

Research question and objectives

The research question of the study presented in this report was:
"To what extent are patients and healthcare professionals in the European Union aware of the risk of teratogenic effects of oral retinoids and of the PPP for oral retinoid containing medicinal products?"

The main objectives of the research were:

1. To assess the influence of the PPP on patients', prescribers', pharmacists' and midwives' awareness about the teratogenic risks of oral retinoids use during pregnancy, and on their knowledge, attitudes and practices.
2. To evaluate health care professionals' (prescribers, pharmacists, midwives) knowledge and adherence to the PPP and risk minimisation measures in relation to the use of medicinal products containing oral retinoids and their influence on retinoid exposure during pregnancy.
3. To assess patient knowledge and adherence to the PPP and risk minimisation measures.

Study design

The study was of mixed nature and involved collection and analysis of both quantitative and qualitative components. A cross sectional, web-based survey was developed and conducted among physicians, pharmacists and patients across eight European Union member states to provide insight into the key determinants of awareness and use of pregnancy prevention measures among patients and healthcare professionals.

Semi-structured telephone interviews with patients using oral retinoids shed light on the rationale for decision-making regarding treatment by healthcare professionals and patients.

Setting

The multi-country study was conducted in eight member states of the European Union: Belgium (only Flanders), Denmark, Greece, Latvia, Portugal, the Netherlands, Slovenia and Spain. We conducted telephone interviews with patients in Portugal and the Netherlands.

Subjects and study size

For the web-based survey, the patients included (n=298) were all women of childbearing age (aged 15-50) who were using or had used oral retinoids. The pharmacists included (n=660) had previously provided advice or dispensed oral retinoids to at least one woman in the childbearing age. The prescribers included(n=560) were either general practitioners or specialists, who previously consulted or prescribed oral retinoids to at least one woman in the childbearing age. In Spain and in the Netherlands, midwives have consulting functions. In these two member states, midwives, who had a consultation with at least one woman in childbearing age treated with oral retinoids, were included (n= 57).

Recruiting patients for the semi-structured telephone interviews during the COVID-19 crisis revealed to be a difficult mission. We aimed to hold telephone interviews with 6-8 patients from a convenience sample, both in Portugal and the Netherlands. In Portugal, six women agreed to be interviewed. In the Netherlands, only one patient could be interviewed.

Variables and data sources

In the web-based survey, patients were asked about:

- Characteristics (gender, age, type of retinoid used and education level)
- Awareness of risks of oral retinoids
- Source of information that created awareness
- Familiarity with the educational materials (patient brochure; patient reminder card; risk acknowledgement form; warning symbol; Patient Information Leaflet; QR code)
- Discussion on contraceptive measures with healthcare professionals
- Change of medication because of pregnancy
- Pregnancy testing before, after and during treatment with oral retinoids
- Pregnancies and treatment when using oral retinoids, before and after 2018
- Contraception methods and perceptions
- Change in retinoid use after 2018

Pharmacists were asked about:

- Characteristics (gender, age, type of pharmacist, work experience, frequency of dispensing oral retinoids, ever seen or suspected malformations caused by retinoids, perception of ‘women in fertile age’)
- Knowledge about the teratogenicity of oral retinoids and the sources of this knowledge

- Procedure at most recent dispensing of an oral retinoid
    - Current use of educational materials and likely future use
    - Counselling of female patients about contraception and treatment during pregnancy
    - Counselling of female patients at repeat prescriptions
    - Behaviour change since 2018
    - Awareness about/Use of measures from the prevention programme and influence on daily practice

Prescribers were asked about:

- Characteristics (gender, age, type of prescriber, work experience, counselling frequency, ever seen malformations caused by oral retinoids, perception of 'women in fertile age')
- Knowledge about the teratogenicity of oral retinoids and the sources of this knowledge
- Procedure at most recent prescribing of an oral retinoid
    - Current use of educational materials and likely future use
    - Prescribing habits
    - Monthly appointments
    - Pregnancy test implementation
    - Discussing effective contraception
    - Behaviour change since 2018
    - Awareness about/Use of measures from the prevention programme and influence on daily clinical practice

The midwives in Spain and the Netherlands were asked about:

- Characteristics (gender, age, work experience, attending frequency, counselling frequency, ever seen malformations caused by oral retinoids, perception of 'women in fertile age')
- Knowledge about the teratogenicity of oral retinoids and the sources of this knowledge
- Procedure at most recent consultation with a woman of childbearing age taking an oral retinoid
    - Current use of educational materials and likely future use
    - Counselling of women, also at repeat prescriptions
    - Behaviour change since 2018
    - Measures from the prevention programme influencing their daily clinical practice
    - Change in provided information
    - Difficulties in implementation and or use of prevention measures established in 2018

Results

The results of the web-based surveys show that there is a very high awareness of the teratogenic risks of oral retinoids among patients and healthcare professionals. However, although there seems to be medium awareness about the measures established by the EMA in 2018, both the implementation of and the adherence to these measures vary across member states. Despite being aware of the teratogenic risks, women do not always adhere to recommendations regarding the use of contraceptives and pregnancy testing. This could be related to their relatively young age. Less than half (48%) of women discussed the use of contraceptives with a health care provider and 53% applied contraceptive measures. A minority of women performed pregnancy testing either before (27%), during (22%) and after (5%) the use of oral retinoids.

Patients had to a very limited extent come across information materials, including the patient brochure, the reminder card and the risk acknowledgement form as their sources of information about teratogenic risks. The awareness was mainly raised through verbal communication from health care professionals (mainly prescribers) as well as from the internet. Patients also indicated both on the survey and during interviews that the information they received from their prescriber was very important.

The warning symbol on the package was noticed by almost half of the patients (49%). The risk acknowledgement form was the other most frequently recognized material by patients among the dedicated information materials introduced by EMA in 2018. Approximately one out of five patients (21%) had signed the risk acknowledgement form. The reminder card, the patient brochure and the QR-code were only familiar to a limited number of patients respectively 4%, 7% and 6%. On the other hand, an overwhelming majority (95%) of the patients had read the patient information leaflet (PIL).

The pharmacists considered the warning symbol on the package to be very helpful both currently and towards the future, when informing patients about risks and as a reminder to verbally alert to the risks around pregnancy and medication use. They also indicated that patients are reluctant to repeatedly listen to the same information.

Healthcare professionals participating in this study had, to a large extent, gained their knowledge and awareness about the teratogenicity of retinoids during their academic training or post graduate education, rather than through the Pregnancy Prevention Programmes.

Prescribers considered the patient brochure and the risk acknowledgement form to be the most valuable risk management measures. Yet other tools such as educational materials from other sources, were also frequently reported as useful in their daily clinical practice.

Only a small proportion of health care providers and patients adhered to all aspects of the pregnancy prevention program.

Discussion

This study has shown that there is very high awareness of the teratogenic risks of oral retinoids among patients, prescribers and pharmacists. In Spain and the Netherlands, where midwifes hold consulting functions, their awareness was substantially lower than that of pharmacists and prescribers. Thus efforts to increase awareness among midwives are urgently needed as they may play an important role in periconception advice.

The awareness about the risk minimization measures and educational materials was moderate. However, their implementation, i.e. translation of evidence into healthcare practice, is a very challenging process and often not as straight forward as expected. Risk minimization measures that require significant time from healthcare professionals in clinical practice, such as the review and signature of the risk acknowledgement form, are less likely to be implemented. Furthermore, implementation of measures depends heavily on the healthcare system in each member state. Nevertheless, the measures contribute somewhat to the repetition of the teratogenic risk message, which is considered essential by patients when trying to prevent exposure to oral retinoids during pregnancy. While adherence to individual measures was far from ideal, women's awareness of the teratogenic risks of retinoids was very high.

Visual measures, such as the warning symbol were perceived as helpful by patients and pharmacists as reminders to pay attention to treatment risks. The PIL remains an important information source for patients. Almost all patients reported to have read it.

Healthcare professionals had gained their knowledge and awareness about the teratogenicity of oral retinoids during their academic training or post graduate education. Most health care providers reported to be aware of the teratogenic risks of retinoids for longer than 5 years. Additional postgraduate training in communication about teratogenic risks may help to further optimise the PPPs. Specific issues, such as the use of the educational materials, the interpretation of the fertile age, the tasks of different healthcare providers when counselling patients and inter-disciplinary cooperation are topics to be further discussed and explored. Furthermore, professionals should have easy access to educational materials. Embedment of information from regulatory sources into the prescribing and dispensing systems would facilitate the uptake of all information and measures.

Conclusion

Despite a strikingly high awareness about the teratogenic risks of oral retinoids among patients and healthcare professionals, the use of risk minimization measures and educational materials remained low across the participating countries. Use of oral retinoids during pregnancy seems to still occur, although there is a high awareness about its risks. Since a baseline measurement is lacking, we cannot ascertain the extent to which an eventual use during pregnancy has been affected since the implementation of the 2018 measures.

Patients and pharmacists consider the repetition of the message about teratogenic risks to be essential and recognize visual measures such as the use of the warning symbol in the outer packaging as a helpful reminder. Ongoing patient counselling would be highly facilitated if the educational materials and information were easily accessible in prescribing and dispensing software systems.