POST-AUTHORISATION SAFETY STUDY (PASS)

Final Study Report Synopsis

Title	Impact of EU label changes for medicinal products containing methotrexate for weekly administration: risk awareness and adherence, A survey study
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Product reference	Not Applicable
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Countries of study	France, Germany, Greece, Poland, and Sweden
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This study was conducted in accordance with all relevant regulatory requirements, including, where applicable, the Declaration of Helsinki (and its amendments), the guideline on good pharmacovigilance practices (GVP) Module VIII – post-authorisation safety studies, and the guidelines for good pharmacoepidemiology practice (GPP) (ISPE).

SYNOPSIS

Title

Impact of EU label changes for medicinal products containing methotrexate for weekly administration: risk awareness and adherence, A survey study

Keywords

Methotrexate, risk-minimisation measures, EU, autoimmune diseases

Background

Methotrexate (MTX) is a widely used medicine for various indications such as cancer, or autoimmune diseases. In 2019, a referral procedure (EMEA/H/A-31/1463; under Article 31 of Directive 2001/83/EC) concluded that further risk-minimisation measures (RMM) were required for oral and parenteral MTX-containing products to avoid inadvertent MTX overdose due to daily instead of weekly use. Measures were introduced for all oral and parenteral MTX formulations with at least one indication requiring once-weekly dosing (mainly rheumatologic/dermatological diseases or Crohn's disease).

Research question and objectives

This survey was conducted for prescribing physicians ('prescribers'), pharmacists, and patients to determine to what extent RMMs were effective in increasing awareness, knowledge, and self-declared behaviour on inadvertent use of once-weekly MTX.

The objectives were:

1. To determine the extent of prescriber awareness and knowledge of the risk of inadvertent overdose and adherence to SmPC recommendations for oral and parenteral MTX-containing medicines with at least one indication requiring once-weekly dosing, with particular focus on the following elements:
    1.1. Receipt and awareness of Direct Healthcare Professional Communication (DHPC), new or updated educational materials (EMs) for healthcare professional (HCPs) (checklist or guide) and awareness of the patient card
    1.2. Knowledge of the dosing frequency of MTX in the treatment of inflammatory diseases and the updated posology instructions and boxed warning

2. To determine the extent of pharmacist awareness and knowledge of the patient card, the visual reminder on the outer packaging and the need to mark the day of intake, and adherence to marking the day of intake on the outer packaging
3. To determine the extent of patient awareness and knowledge of the following elements:
    3.1. Receipt and awareness of the patient card, and knowledge of symptoms of MTX overdose and the purpose of the patient card
    3.2. Knowledge of the once-weekly dosing frequency of MTX
    3.3. Awareness and knowledge of the visual reminder on the packaging of oral and parenteral MTX-containing products; and awareness and knowledge of the boxed warning in the package leaflet

Study Design

This was a cross-sectional, multi-country, and multichannel web-based survey conducted among prescribers, pharmacists, and patients in 5 European countries - France, Greece, Germany, Poland, and Sweden. Prescribers were identified and recruited via OneKey lists (IQVIA). Pharmacists were identified and recruited via IQVIA's vendor M3 Global Research. Patients were identified and recruited via IQVIA's vendors M3 Global Research and GLocalMind. Data collection took place from 25 February 2022 - 11 April 2022.

Setting

This was a web-based survey. Questionnaires per target population i.e. prescriber, pharmacist and patient were developed.

Participants and study size

The study aimed to enrol 150 prescribers, 150 pharmacists and 150 patients from 5 countries over a 12-week time period.

Inclusion Criteria

Prescribers who prescribed MTX, pharmacists who dispensed MTX, and patients who were treated with MTX, within the past 3 months. The use of MTX was limited to a single low dose given once weekly for indications that require weekly dosing.

Exclusion Criteria

Prescribers, pharmacists, and patients who reported being currently employed by any regulatory bodies (e.g., EMA, national competent authorities etc.) or pharmaceutical company or who actively refused consent for participation in the survey.

Variables and data sources

In this survey, the primary data collection was conducted through a web-administered questionnaire.

The following variables were collected:

- Prescribers: demographic information, experience with MTX, variables related to the three outcomes (awareness, knowledge and self-declared behaviour)
- Pharmacists: demographic information, experience with MTX, variables related to the three outcomes (awareness, knowledge and self-declared behaviour)
- Patients: demographic information, details of prior and current MTX treatment including prescriber details, variables related to the two outcomes (awareness and knowledge)

To be successful, every respondent needed to provide desirable responses to all questions on awareness and self-declared behaviour and correct responses to ≥80% of questions on knowledge. Success per target population for the outcome was defined by ≥80% of respondents achieving it. The effectiveness of the RMMs was then defined per target population by being successful on all of the (two or three) outcomes.

Results

A total of 5,366 prescribers were targeted in the study. Among the prescribers contacted, 191 (3.6%) agreed to participate and 151 completed the questionnaire. The response rate for prescribers was 2.8% and refusal rate was 96.4% ranging from 88.4% in France to 97.8% in Greece.

A total of 1,127 pharmacists were targeted in the study. Among the pharmacists contacted, 204 (18.1%) agreed to participate and 150 completed the questionnaire. The response rate for pharmacists was 13.3% and refusal rate was 81.9% ranging 82.2% in France to 52.1% in Greece.

A total of 1,568 patients were targeted in the study. Among the patients contacted, 641 (40.9%) agreed to participate and 150 completed the questionnaire (substantial drop-out since we could not target users of MTX). Among patients the response rate was 9.6% and refusal rate was 59.1% ranging from 85.5% in France to 27.1% in Poland.

Overall success

The overall success for the effectiveness of RMMs related to MTX was not attained by any target population (prescribers, pharmacists, and patients). Only few individuals per target population (weighted sample for prescribers and pharmacists and unweighted sample for patients) were successful with regards to risk minimisation for all 3 outcomes (or 2 outcomes for patients): only 7.3% of prescribers responded successfully, compared to 0.7% of pharmacists and 0.7% of patients. Success according to the predefined thresholds was also not achieved when evaluated separately for awareness, knowledge, or self-declared behaviour. Key results included the following:

Prescribers

The success rates among prescribers were; 56.3% (95% CI 48.0 - 64.3%) on awareness, 42.4% (95% CI 34.4% - 50.7%) on knowledge, and 31.1% (95% CI 23.8 - 39.2%) on self-declared behaviour. Overall, >75% of prescribers desirably responded that they received DHPC (75.5%, 114/151), HCP checklist (75.0%, 45/60), and they were aware of patient card (79.5%, 120/151), and 54.5% (66/121) prescribers responded that they received HCP guide. When considered individually, the respective proportions of successful prescribers who read the DHPC and HCP checklist were 62.3% (n=94) and 36.4% (n=44). Nearly, all prescribers understood the risks related to MTX therapy (n=144, 95.4%). Knowledge related to dosing regimen and requirement of noting down the day of MTX intake on the prescription for once-weekly MTX was high (~80%) among prescribers. However, the knowledge that whether once-daily MTX can cause an overdose when prescribed for inflammatory conditions, and if MTX doses can be divided, appeared to be lower (ranging between 6.0-23.8%). Regarding success of self-declared behaviour among prescribers, the practice of noting down the complete details on the prescription was desirable (n=108, 71.5%). Less than half of prescribers desirably provided dosing instructions and information about overdose symptoms (n=62, 41.1%).

Pharmacists

The success rates among pharmacists were; 18.7% (95% CI 12.8-25.8%) on awareness, 7.3% (95% CI 4.6-15.6%) on knowledge, and 50.0% (95% CI 41.7-58.3%) on self-declared behaviour. Awareness of the visual reminder on the outer packaging was adequate (n=103, 68.7%) among the surveyed pharmacists. Only one-fourth of pharmacists were aware of the existence of the patient card and where it was located (n=40, 26.7%). Most pharmacists understood the need to note down the day of MTX intake on the outer packaging (n=83, 80.6%) and they had knowledge about the safety measures available on outer packaging of MTX (n=94, 91.3%). The knowledge of pharmacists related to dosing regimen information included in patient card was high (n=66, 75.0%). Regarding success of self-declared behaviour among pharmacists, half the pharmacists declared that they either always or frequently note down the day of the week to take MTX on its outer packaging (n=75, 50.0%).

Patients

The success rates among patients were; 28.7% (95% CI 21.6-36.6%) on awareness, and 3.3% (95% CI 1.1-7.6%) on knowledge. It was reported that around 60% of the patients were aware of the boxed warning on the MTX package leaflet (n=88, 57.3%) as well as the visual reminder (n=95, 63.3%) and ~40% patients received patients card. The patients who were reportedly aware of the patient card, most of them understood that it contained a reminder on when to take MTX (n=67, 79.8%) and in case of changing doctors or hospital etc., the patient card need to be shown to new healthcare provider to alert him/her about the once-weekly dosing schedule. Most patients understood the need to note down the day of MTX intake on the outer packaging (n=73, 76.8%). Knowledge related to overdose symptoms was low and less than half of the patients knew that in case of overdose symptoms the patient card needs to be checked (n=72, 48.0%).

Discussion

This study provides insights about the awareness, knowledge, and behaviour of prescribers, pharmacists, and patients regarding RMMs for once-weekly MTX throughout Europe. The overall success for the effectiveness of RMMs related to MTX was not attained by any target population (prescribers, pharmacists, and patients) for any study outcome. At the outcome level, the highest proportion of successful respondents was achieved by prescribers for awareness (56.3%) and knowledge (42.4%) outcomes. Regarding awareness, 28.7% of

patients and 18.7% of pharmacists were successful. For knowledge, pharmacists (9.0%) performed better than patients (3.3%). For self-declared behaviour, 31.1% of prescribers and 50.0% of pharmacists achieved success.

Key limitations of this online survey study include:

- Due to online design of survey, the results were restricted to a specific population. We lacked basic demographic details of the invited persons who did not participate and could therefore not quantify potential differences with the included participants.

- The outcomes of the current study could not be compared to a baseline situation before implementation of the RMM, as an alternative method to evaluate the effectiveness of the RMMs.

- Participation rate was low. It was especially low for prescribers, compared to pharmacists and patients, while their overall performance seemed better. Possibly, self-selection of more aware and knowledgeable respondents, specifically prescribers, may have even overestimated our results. Participation rate was low. It was especially low for prescribers, compared to pharmacists and patients, while their overall performance seemed better. Possibly, self-selection of more aware and knowledgeable respondents, specifically prescribers, may have even overestimated our results.

- The approval and distribution of the EMs (2019-2021) in all countries largely coincided with the coronavirus disease-2019 (COVID-19) pandemic. This could have had a negative impact on the actual distribution rates of these EMs, and in turn affected the outcomes.

In this study, an a priori threshold of 80% of successful participants for the outcomes of awareness, knowledge, and self-declared behaviour were considered appropriate for assessing the effectiveness of EMs/RMMs. Please note thresholds were relatively stringent. The thresholds were set to define the overall success and success at the outcome and individual level. These were not based on any prior literature or regulatory requirements and were purely arbitrary.

For prescribers, there was a slight preference for DHPC over the other EMs. Knowledge on splitting a once-weekly dose and changing the once-weekly dose according to the clinical response showed most room for improvement. Incorrect responses received for questions on the division of MTX doses could have been driven by earlier recommendations that allowed dividing doses. For pharmacists, awareness was relatively lacking,

and especially awareness of both the existence and location of the patient card. However, among pharmacists who were aware of only the existence of the patient card, performance on knowledge of the patient card related to the once-weekly dosing regimen of MTX was high. For patients, the awareness of the patients card was low. Although patients were aware of boxed warning and visual reminder on MTX outer packaging. The proportions of correct answers for patients on MTX overdose symptoms were low, the high proportions of patients answering, "I don't know". Moreover, patients seemed to rely on phone alarms for reminders instead of MTX packaging or patient cards, suggesting that digitalising informational materials might be a more efficient way of disseminating knowledge on avoiding harm among patients.

The countries participating in the survey were selected based on their representativeness in terms of the target population size, European region and regulatory feasibility. Overall, they represented geographies in which MTX had sufficient market penetration in Europe. The sampling for prescribers was done using high coverage database (OneKey), pharmacists and patients were sampled through similarly robust and trusted vendor panels. Weighting per country increased the fit of the results to the target populations. Both unweighted and weighted results, where relevant, are reported in this report. The predefined sample size was met.

In conclusion, this survey study showed that prescribers, pharmacists and patients throughout Europe did not attain prespecified levels of successful performance (≥80%) on awareness of, knowledge on, and self-declared behaviour for RMMs to avoid inadvertent dosing for once-weekly MTX. Nevertheless, performance on several aspects of these outcomes was fair to good. Almost all prescribers understood the risks related to MTX therapy. Most prescribers (~80%) and pharmacists (80.6%) understood the need to note down the day of MTX intake on the outer packaging and 91.3% of pharmacists had knowledge about the safety measures available on outer packaging of MTX. Patients who were aware of the patient card mostly understood its content. Findings also suggest several areas for improvement, e.g., pharmacist awareness and knowledge were relatively low.

Marketing authorisation holder (MAH)

Not applicable

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