1.0 Abstract

Title

Linaclotide Safety Study for the Assessment of Diarrhoea Complications and Associated Risk Factors in Selected European Populations with IBS-C

Keywords

Linaclotide, Irritable Bowel Syndrome, Diarrhoea, Constipation

Rationale and Background

Irritable bowel syndrome (IBS) is a chronic, relapsing gastrointestinal condition characterised by abdominal pain, bloating and changes in bowel habits. Irritable bowel syndrome with predominant constipation (IBS-C) is a subtype of IBS, which occurs in about 30% of IBS cases. Linaclotide (Constella®) is the first medicine authorised in the European Union (EU) for the treatment of adult patients with moderate-to-severe IBS-C. This study assessed the safety of linaclotide in terms of the risk of severe complications of diarrhoea (SCD) during treatment among patients with IBS-C in the three selected European countries: the UK, Sweden and Spain.

Research Question and Objectives

The study addressed the following research questions:

1. What is the estimated risk of SCD among patients with IBS-C prescribed linaclotide?
2. What are the risk factors associated with SCD in patients with IBS-C, specifically linaclotide prescription vs no linaclotide prescription?

Both research questions were assessed in three different countries: the UK, Sweden and Spain.

The research objectives of the overall study were as follows:

1. Describe the crude incidence of diarrhoea among patients with IBS-C
2. Investigate the potential risk factors associated with SCD in patients with IBS-C
3. Estimate the risk of SCD among patients with IBS-C who received linaclotide prescription vs those who did not, controlling for other potential SCD risk factors
4. If a cohort study design is feasible, based on the results of the SCD cases and controls validation:
    - Describe the crude incidence of SCD among patients with IBS-C prescribed linaclotide (first-time users)
    - Describe the crude incidence of SCD among patients with IBS-C prescribed linaclotide (first-time users) who were at increased risk of SCD:
        - Patients ≥65 years old
        - Patients with hypertension, diabetes or cardiovascular disease diagnostic codes

Study Design

This was an observational study, designed as a case-control study nested within a cohort of patients with IBS-C, where patients with SCD were identified as cases and patients without SCD as controls. Cases were matched with up to four controls based on year of birth, IBS-C status, years of active history in the database, observation time for assessing SCD event and geographic region. A pseudo-SCD event date was assigned to the matched control, based on the control's IBS-C cohort entry date and the time between the matched case's cohort entry date and the case's SCD event date.

Setting

This study used observational data from three different countries: the UK, Spain and Sweden.

Subjects and Study Size, Including Dropouts

Study size in each country is shown in the table below.

Country	IBS-C cohort	Case-control analysis sample, based on algorithm-identified SCD cases*
UK	272,588	10,716 algorithm-identified cases; 42,821 matched controls
Spain	15,736	126 algorithm-identified cases; 480 matched controls
Sweden	33,675	786 algorithm-identified cases; 3,144 matched controls

IBS-C = Irritable Bowel Syndrome with Predominant Constipation; SCD = Severe Complications of Diarrhoea; UK = United Kingdom

* Each case was matched to up to four controls; in the UK, four algorithm-identified SCD cases were dropped from the sample after the matching, due to inability to find a suitable matched control.

Variables and Data Sources

IBS-C diagnosis: A combination of IBS diagnosis codes, IBS symptom codes and laxative prescriptions, in addition to the IBS-C-specific codes, were used to identify patients with IBS-C.

Outcome: SCD was identified using a predefined algorithm; identified cases in the UK and in Spain and, in Spain, also a sample of controls, were validated. Validation was not possible in Sweden due to the lack of access to free-text medical notes and the inability to reach out to treating physicians to confirm SCD events.

Exposure: Exposures to linaclotide and laxatives were categorised as current user (i.e., exposure in the 90 days before the [pseudo] SCD event date), past user (i.e., exposure more than 90 days before the [pseudo] SCD date) and non-user based on prescription or dispensation data.

Other variables collected in this study included: patient demographic characteristics (e.g., age, gender, body mass index [BMI], socioeconomic status, and pregnancy and breast-feeding); comorbidities (e.g., obesity, cardiovascular disorder [CVD], psychiatric disorder); comedications (e.g., laxatives, antibiotics, proton pump inhibitors); other clinical characteristics (e.g., history of cholecystectomy).

Data sources used in this study were:

- **UK:** Clinical Practice Research Datalink (CPRD) GOLD and Aurum, linked to Hospital Episode Statistics (HES) datasets and death registration data from the Office for National Statistics (ONS).
- **Spain:** Information System for the Development of Research in Primary Care (SIDIAP).
- **Sweden:** Linked National Patient Registry (NPR), Prescribed Drug Register (PDR) and Causes of Death Register (CDR).

Methods

Descriptive statistics were used to summarise patient characteristics at cohort entry and at the (pseudo) SCD date for cases and controls.

The study used a case-control design nested within an IBS-C cohort. The number and proportion of patients with algorithm-identified SCD events were reported, and the algorithm's performance in identifying SCD was evaluated using positive predictive value (PPV) and negative predictive value (NPV). Conditional logistic regression was used to assess the association between linaclotide and SCD. Both univariable and multivariable models were used, with the best model selected based on Akaike's Information Criterion (AIC). Estimated odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were reported.

Results

This study included an IBS-C population with 272,588 patients in the UK, 33,675 in Sweden and 15,736 in Spain. The incidence proportion of diarrhoea was 29.7% in the UK, 17.3% in Spain and 7.1% in Sweden. The occurrence of algorithm-identified SCD events was low: 3.9% in the UK over about a 10-year period, and 0.8% in Spain over an approximate 5-year period and 2.3% in Sweden over an approximate 5-year period. Validation results indicated that the predefined SCD algorithm had a low PPV of 32.5%

in the UK and 14.3% in Spain, with an NPV of 100% in Spain. The incidence proportion of true SCD was 1.31% in the UK and 0.11% in Spain.

In the validated case-control sample, the OR of SCD for current linaclotide use (vs no use) could not be estimated due to no exposure among cases in both the UK and Spain. Sensitivity analyses using algorithm-identified cases and their matched controls showed no evidence of an association between current linaclotide exposure and SCD, adjusting for covariates, across all three countries, with an adjusted OR of 0.66 (95% CI: 0.39 – 1.12) in the UK, 1.37 (0.30 – 6.22) in Spain and 3.31 (0.83 – 13.23) in Sweden. Comorbidities and comedications associated with increased risk of validation confirmed SCD in the UK included CVDs, psychiatric disorders and the prescription of opioids and other analgesics.

Discussion

This study provides insights into the characteristics of patients with IBS-C, the incidence proportion of SCD and associated risk factors in the UK, Spain and Sweden. The algorithm used for SCD identification had a low PPV, particularly in Spain, overclassifying a large proportion of patients as having SCD. Severe Complications of Diarrhoea was not common among the IBS-C population, with an incidence proportion of true SCD of 1.31% in the UK and 0.11% in Spain.

The proportion of patients exposed to linaclotide was low. The OR for current linaclotide use could not be estimated due to no exposure among cases in both the UK and Spain. No association was found between linaclotide use and SCD risk in sensitivity analyses using algorithm-identified cases and their matched controls. This finding is supported by patient numbers from the AbbVie Global Safety Database (GSD), indicating that the overall risk of SCD is low, given the rarity of cases reported and the estimated number of patients exposed to linaclotide over the length of time linaclotide has been on the market.

The results should be interpreted in the context of the diverse data sources utilised across countries. In the UK, comprehensive primary care data linked to hospital data were employed, while in Spain, comprehensive primary care data with limited information on

hospital discharge diagnosis were used, and in Sweden, hospital data from the whole population were combined with prescription data across primary and secondary care settings. Overall, the use of large, nationally representative datasets in the UK and Sweden, and a regionally representative dataset in Spain, enhances the understanding of the association between linaclotide use and SCD risk across countries in Europe and the generalisability of the findings to the broader populations in these countries. The incidence of SCD among patients with IBS-C is low and the current cumulative evidence does not support a significant association between linaclotide use and increased SCD risk.

Marketing Authorisation Holder(s)

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