1. ABSTRACT

Protocol No.: RWJ800077ICS4001

Sponsor's Responsible Medical Officer: Subusola Vaughan, MD, MS, DCH

Keywords: pigmentary maculopathy, pigmentary retinopathy, pentosan polysulfate sodium, ELMIRON®

EU PAS Register Number: Study Not Registered

Marketing Authorization Holder(s): Janssen Research & Development, LLC

Names and Affiliations of Principal Investigator(s): Durga Borkar MD, MMCi;
Subusola Vaughan, MD, MS, DCH

Publication (Reference): None

Study Period: 01 January 2015 to 01 March 2021

1.1. Title

Post-authorization safety study and real-world evaluation of the use of pentosan polysulfate sodium and the development of pigmentary maculopathy and pigmentary retinopathy

1.2. Background and Rationale

Interstitial cystitis (IC) is a urological syndrome characterized by symptoms of urinary urgency, urinary frequency, nocturia, bladder pain or discomfort. ELMIRON®, or pentosan polysulfate sodium (PPS) (first approved by the United States (US) Food and Drug Administration (FDA) in 1996) is the only approved oral therapy for the relief of bladder pain or discomfort associated with IC. The safety of long-term PPS use in IC was evaluated in seven studies (al-Zahrani 2011; Fritjofsson 1987; Hanno 2010; Holm-Bentzen 1987; Jepsen 1998; Nickel 2008; Parsons 1987) which showed long-term use of PPS to have good tolerability with few or no reported serious adverse events due to PPS. In 2018, an article published by Pearce et al. suggested that pigmentary maculopathy (PM)/pigmentary retinopathy (PR) might be a potential new safety finding. This study was a retrospective review of electronic medical records that identified 38 subjects (six of whom previously had been evaluated for an unidentified PM) between 2015 and 2017, who reported chronic use of PPS for a diagnosis of IC.

Subsequent case series studies and retrospective epidemiologic studies have also suggested an association between PM/PR and chronic treatment exposure to PPS, although a direct causal relationship has not been established based on a recent comprehensive review article by the FDA (Lardieri 2021). In addition, previous epidemiological studies have not described the incidence of PM/PR in patients with IC but who do not have exposure to PPS.

1.3. Research Question and Objectives

The first primary objective included estimating the incidence proportion, incidence rate, prevalence rate of study endpoints (PM/PR/Any, PM/PR/PPS, PM/PR/non-PPS) among PPS-exposed patients and assessing VA changes in relation to the study endpoint. The second primary objective consisted of estimating the incidence rate of PM/PR/Any and VA changes in relation to the study endpoint within an IC PPS Non-exposed Group while the third primary objective

assessed VA changes between an IC PPS Non-exposed Group matched to an IC PPS-exposed Group.

Secondary objectives included: describing the baseline demographics, clinical characteristics, and provider characteristics of all study participants; comparing the distribution of International Classification of Diseases (ICD)-9/10 codes before and on or after 22 May 2018 among patients exposed to PPS; and understanding a patient's journey to PPS therapy, specifically the sequence of medications and other interventions the patient received before and after receiving PPS.

Two exploratory objectives were planned, which consisted of evaluating risk factors associated with the occurrence of PM/PR/PPS and examining the involvement of retina specialists in the diagnosis of PM/PR/PPS.

1.4. Study Design

The study was a non-interventional retrospective epidemiological study of IC and PPS patients using data from the following: 1) American Academy of Ophthalmology Intelligent Research in Sight (IRIS)® Registry; 2) American Urological Association (AUA) Quality (AQUA) Registry; and 3) Komodo Health database. The study period went from 01 January 2015 to 01 March 2021.

1.5. Setting

Patient healthcare visits with ophthalmologists/optometrists or urologists within the US contributing data to the IRIS Registry or AQUA Registry, respectively. The IRIS Registry includes 70 million unique patients from over 3,100 practices, while the AQUA Registry includes 6 million unique patients, contributed by 1,800 providers. Additional data came from the Komodo Health database which collects data from aggregated, adjudicated claims curated by one of the largest pharmacy benefits managers (PBMs) in the US and maintains proprietary partnerships with more than 150 key national payers (representing over 150 million payer-complete lives) and consortiums.

1.6. Patients and Study Size

There was no *a priori* hypothesis testing for this study, therefore, no prespecified sample sizes were required.

Patients eligible for any of the 3 main cohorts were as follows:

1. **PPS Clean Cohort:** Patients who had their first documented exposure to PPS between 22 May 2018 to 01 March 2021;
2. **PPS Overall Cohort:** Patients who had their first documented exposure to PPS between 01 January 2015 to 01 March 2021; and
3. **Non-PPS-exposed IC Cohort:** Patients who had at least 1 IC diagnosis and had no documented exposure to PPS between 01 January 2015 through 01 March 2021.

Additionally, a group receiving PPS (Matched IC PPS-exposed Group) was created and matched (1:1) by age, sex, and baseline VA category to IC patients not receiving PPS (Matched IC PPS Non-exposed Group).

1.7. Variables and Data Sources

All variables and data were sourced from the following databases:

- The IRIS Registry supplied ophthalmologic ICD diagnoses to ascertain the key study endpoints (PM/PR/Any, PM/PR/PPS, and PM/PR/Non-PPS) and VA outcomes.
- The Komodo Health database supplied PPS dispensing data (exposure history) through National Drug Codes (NDC), patient baseline characteristics, medication use, and the diagnosis of IC.
- The AQUA Registry served as a supplemental data source to evaluate IC patients' treatment journey before and after receiving PPS.

The endpoints of interest (PM/PR/Any, PM/PR/PPS, and PM/PR/Non-PPS) were derived from structured ICD-9/10 codes, structured current procedural terminology (CPT) codes for presence of imaging procedures, and clinician notes.

- PM/PR/Any was defined as the medical conditions described by Ludwig et al. (2019) and included the following clinical conditions:
  - Toxic maculopathy
  - Hereditary retinal dystrophies (including hereditary maculopathy)
  - Secondary pigmentary degeneration
  - Retinal dystrophy in other systemic disorders and syndromes
  - Drusen
  - Nonexudative age-related macular degeneration
  - Exudative age-related macular degeneration
- PM/PR/PPS was primarily defined as a patient meeting the PM/PR/Any definition with:
  - Mention of key phrases potentially related to PPS associated PM/PR in clinical notes within 30 days of a PM/PR/Any diagnosis date
  - Presence of a fundus autofluorescence (FAF) or an ocular coherence tomography (OCT) on or before PM/PR/Any diagnosis date
- PM/PR/non-PPS was defined as a patient meeting the PM/PR/Any definition but did not meet the study endpoint definition of PM/PR/PPS on or after 22 May 2018.

VA progression analyses required all patients to have at least 2 VA measurements in the IRIS Registry. VA endpoints were presented as best-corrected VA. Because correction is not needed in patients with 20/20 vision (or better), patients whose VA was 20/20 (or better) at a specific visit but whose VA was not specified as best-corrected had their VA treated as if it was best corrected. VA conversion methods, including conversion of Snellen VA to logMAR units and letters, followed previous literature (Ninel 2010; Schulze-Bonsel 2006).

For all cohorts, study outcomes that were observed on and prior to the index date were considered a prevalent case, while diagnoses observed after the index date were considered an incident case, unless the same type of prevalent event was observed in the same eye.

1.8. Statistical Methods

For descriptive statistics, continuous variables were summarized using mean (± standard deviation [SD]) and median. Counts and proportions were used to summarize categorical variables.

For the first primary objective, the prevalence rate, incidence proportion, and incidence rate of the study endpoints (PM/PR/Any, PM/PR/PPS, PM/PR/non-PPS) were calculated for the PPS Clean Cohort and PPS Overall Cohort.

For the incidence rate calculation, time-at-risk was calculated in 2 ways:

- On-treatment time-at-risk was defined as the total duration of persistent therapeutic time from the index date (first date of PPS dispensing) to the earliest of: occurrence of study endpoint; end of inferred persistent exposure; the last day of observation in the IRIS Registry or end of eligibility in the claims database; or end of study period.
- Intent-to-treat (ITT) time-at-risk was defined as the total duration of follow-up time from the index date (first date of PPS dispensing) to the earliest of: occurrence of study endpoint, last day of observation in the IRIS Registry or end of eligibility in the claims database, or end of study period.

The following categories of VA changes were defined and calculated as a proportion (%) for the 3 main cohorts:

- no change (refers to <1 line of worsening or improvement considered not clinically meaningful);
- 1 to <3 lines of worsening;
- ≥3 lines of worsening;
- 1 to <3 lines of improvement; and
- ≥3 lines of improvement.

In addition to the overall estimate, the analyses were also performed for patients with cataract or glaucoma surgery on or prior to their index VA date or if patients met cumulative days of exposure threshold for potential VA-impacting medications.

The analyses for Primary Objective #2 are conducted similarly to those for Primary Objective #1 but on the Non-PPS-exposed IC Cohort.

The matched analysis for Primary Objective #3 between IC PPS-exposed and Non-exposed Groups assessed VA changes based on age, sex, and time between the first and last VA measurements. This was conducted using eyes as units, unless otherwise specified.

1.9. Results

Baseline Characteristics

The demographic characteristics were similar between the PPS Overall and PPS Clean Cohorts, with mean age of 56 years and approximately 87% to 88% being female. Per the study design, longer follow-up was observed in the PPS Overall Cohort (40.8 months) as compared with the PPS Clean Cohort (17.3 months). The PPS Overall Cohort also had a longer on-treatment time (26.41 months) as compared with the PPS Clean Cohort (14.3 months). For IC patients not exposed to PPS, the mean age was 57 years of age and 90% were females, with an average follow-up time of 35.5 months.

Rates of PM/PR/Any and PM/PR/PPS in PPS Clean Cohort

In the PPS Clean Cohort (N 3,632), 306 prevalent cases met the criteria for PM/PR/Any for a prevalence rate of 8.43% (95% CI: 7.52%, 9.33%). There were 102 incident cases yielding an incidence rate (per 100 person-years) of 2.07 (95% CI: 1.67, 2.47) for the on-treatment analysis and 2.13 (95% CI: 1.72, 2.55) for the ITT analysis. While no prevalent cases met the criteria for PM/PR/PPS, seven incident cases did. The incidence rate of PM/PR/PPS (per 100 person-years) was 0.09 (95% CI: 0.00, 0.18) for the on-treatment analysis and 0.13 (95% CI: 0.03, 0.23) for the ITT analysis.

Because PM/PR/PPS accounted for only a small fraction of PM/PR/Any cases, the incidence rates of PM/PR/non-PPS were similar to the results of PM/PR/Any in both cohorts.

Rates of PM/PR/Any and PM/PR/PPS in PPS Overall Cohort

In the PPS Overall Cohort (N 14,053), 584 prevalent cases met the criteria for PM/PR/Any for a prevalence rate of 4.16% [95% CI: 3.83%, 4.49%]. There were 1,288 incident cases yielding an incidence rate (per 100 person-years) of 2.83 (95% CI: 2.67, 2.98) for the on-treatment analysis and 2.81 (95% CI: 2.66, 2.96) for the ITT analysis.

Two patients met the prevalence criteria for PM/PR/PPS while 76 incident cases were identified. The incidence rate of PM/PR/PPS (per 100 person-years) was 0.11 (95% CI: 0.09, 0.15) for the on-treatment analysis and 0.15 (95% CI: 0.12, 0.19) for the ITT analysis.

Because PM/PR/PPS accounted for only a small fraction of PM/PR/Any cases, the incidence rates of PM/PR/non-PPS were similar to the results of PM/PR/Any in both cohorts.

Rate of PM/PR/Any in the Non-PPS-exposed IC Cohort

In the Non-PPS-exposed IC Cohort, the incidence rate (per 100 person-years) of PM/PR/Any was 2.38 (95% CI: 2.30, 2.46).

Changes in Visual Acuity

In each of the 3 main cohorts (PPS Clean and PPS Overall Cohorts, and Non-PPS-exposed IC Cohort), approximately 50% of patients without PM/PR/Any had no line change between their baseline and last VA measurements during the study follow-up period, while approximately 5% lost 3 or more lines of vision. Among patients with PM/PR/Any, approximately 12% of patients in the PPS Overall Cohort and 9% in the PPS Clean Cohort lost more than 3 lines of vision during the follow-up period. Similarly, in the Non-PPS-exposed IC Cohort, approximately 10% of patients with PM/PR/Any lost more than 3 lines of vision.

Changes in Visual Acuity Within Matched Analysis

In the IC group of patients exposed to PPS (N 3,209), a small letter reduction was observed through 36 months of follow-up period, which similarly occurred within the Matched IC PPS Non-exposed Group. The baseline VA was approximately 80 letters (approximate to 20/25) and across each 6-month observation period the VA decreased <5 letters (or 1 line of vision). In terms of lines of worsening, there is a similar pattern at 6, 12, 18, 24, 30, and 36 months between the Matched IC PPS-exposed and Non-exposed Groups.

Risk Factors Associated with PM/PR/PPS

Due to a very limited number of PM/PR/PPS cases, the risk factor analysis was not performed.

Involvement of Retina Specialists

Among PPS Overall Cohort patients with the PM/PR/PPS endpoint, 51 patients (65.38%) visited a retina specialist according to the IRIS Registry on their PM/PR/PPS diagnosis. There were 57 patients (73.08%) who visited a retina specialist within 1 year prior to their PM/PR/PPS diagnosis.

Limitations

Selection bias may arise from the types of practices and healthcare providers who participate in the registries, which are largely community practices. Additionally, the study requires patients having records in both Komodo and IRIS registry; therefore, there might be an over-representation of patients who had clinical visits to ophthalmologists or retinal specialists thus potentially making the study findings not be generalizable to all patients exposed to PPS from other clinical settings. The potential association of retinal pigmentary changes and PPS exposure was first described in 2018; hence, there are no specific clinical diagnoses (ie, ICD codes) documenting any changes in retinal pigment epithelium that are unique to PPS exposure. Because this is a newly described association, such clinical notes reflecting an association of PM/PR with PPS use would not be expected prior to the first publication by Pearce et al. on 22 May 2018, leading to potential underestimation of PM/PR/PPS cases prior to this date. It is worth noting that the definitions used for PM/PR/PPS were not intended to draw any causal relationship between the PM/PR diagnosis and exposure to PPS, but rather to reflect how these patients are evaluated and captured in the

databases based on clinical practice. Due to lack of access to actual ocular imaging data (eg, FAF or OCT results), it cannot be ascertained whether some of non-PPS exposed patients who had a diagnosis of PM/PR might have had similar ocular photographic presentations as the PM/PR/PPS cases did. The relatively short-term treatment duration and limited total exposure to PPS in this study, which is in part due to data availability of the databases for cross-linking, placed further constraints on evaluating any potential association between PM/PR and a long-term exposure to PPS.

1.10. Conclusions

To our knowledge, this is the first study that has used cross-linked medical records from the IRIS Registry (an ophthalmology-focused database) and Komodo claims database to primarily evaluate: 1) prevalence and incidence rates of PM and PR; and 2) changes of VA in patients exposed to PPS (ie, PPS Clean Cohort and PPS Overall Cohort) and in IC patients not exposed to PPS. Study results have demonstrated the following:

- The prevalence of PM/PR/Any was relatively common in both PPS cohorts (Clean and Overall) prior to PPS exposure.
- The crude incidence rates of PM/PR/Any varied slightly across the 3 cohorts but were in general relatively similar based on the ITT analysis.
- Based on the study definition, the incidence rate of PM/PR/PPS was relatively uncommon in both cohorts exposed to PPS, and a direct causal relationship could not be assessed.
- The relatively short-term treatment duration and the limited total exposure to PPS (based on the linked databases) constrained the interpretation of long-term use in relation to PM and PR.
- Across all 3 cohorts, the proportion of patients having no clinically meaningful changes in VA during the study period appeared higher in patients without PM/PR/Any compared with those with PM/PR/Any, whereas the proportion of patients with 3 or more lines of vision worsening appeared twice as high in patients with PM/PR/Any compared with those without PM/PR/Any. The changes in VA could not be reliably assessed in relation to PM/PR/PPS in both PPS Cohorts due to the limited number of cases.
- In the IC Cohort analyses that matched on age, sex, baseline VA severity level, and the timing of the VA measurement, a small decrease in VA was observed in both groups and the changes during the follow-up period were similar between the Matched IC PPS-exposed Group and the Matched IC PPS Non-exposed Group.

Disclaimer

Information in this posting shall not be considered to be a claim for any product, whether marketed or under development. In case of a marketed product, some of the information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.