ELMIRON® (pentosan polysulfate sodium)
Adverse Event of ELMIRON – Pigmentary Retinopathy or Maculopathy

SUMMARY

- Several retrospective studies and case series have reported maculopathy in patients who received long-term ELMIRON.[1-7] One retrospective study in patients with interstitial cystitis (IC) found no significant relationship between the development of any maculopathy and prior long-term ELMIRON exposure. In the same study, a time-dependent ELMIRON exposure model showed an increased risk of hereditary dystrophy following at least 4 years of exposure to ELMIRON.[7]
- Prior long-term studies did not report ocular adverse events.[8, 9]
- The mechanism and the etiology of maculopathy reported in ELMIRON-treated patients is unknown[5], however cumulative exposure to ELMIRON may be a risk factor.[7, 10] In a retrospective case-series, patients with a cumulative exposure of > 1500 g of ELMIRON were more likely to develop toxicity compared with those who received 500 g to 999 g.[10]
- Visual symptoms reported include difficulty with near vision or reading, blurred vision, general dimming of vision, and slow adjustment to darkness.[1, 11]
- Pigmentary maculopathy upon eye examination has been described as a symmetric, confluent pattern of hyper- and hypo-autofluorescent spots that involve the fovea. Clinical presentation includes hyperpigmented macular spots with interspersed pale-yellow deposits in eyes without retinal pigment epithelial (RPE) atrophy upon fundus examination. Optical coherence tomography may reveal foci or RPE elevation or thickening associated with hyperreflectance on near-infrared reflectance imaging.[11]
- A Dear Healthcare Provider Letter regarding retinal pigmentary changes was issued by Janssen, July 2020.[12]

RETROSPECTIVE STUDIES AND CASE SERIES

Ludwig et al (2019)[7] conducted a retrospective study evaluating the association between exposure to ELMIRON and maculopathy (defined as any diagnosis of drusen, nonexudative age-related macular degeneration [AMD], toxic maculopathy, or hereditary dystrophy).

- 49,899 patients with IC were analyzed from Truven Health MarketScan Commercial Claims and Encounters Database(2007 - 2016, Truven Health Analytics, San Jose, CA),of which 44,820 (89.8%) were female and most patients had a diagnosis of IC between the ages of 50 and 60 (24.6%), followed by a diagnosis between the ages of 40-50 (22.0%). Seventeen percent of patients had a diagnosis of diabetes mellitus.
- Of those who a filled an ELMIRON prescription (23%), the average patient filled prescriptions for 1230 days total.
- Of all patients with an index diagnosis of IC, 2.7% (n=1335) were diagnosed with maculopathy. The most common diagnoses were 1.5% (n=760) exudative AMD, 0.8% (n=396) drusen, 0.3% (n=145) nonexudative AMD, 0.1% (n=34) toxic maculopathy, and 0.04% (n=20) hereditary dystrophy. In an unadjusted analysis, the percentage of patients diagnosed with maculopathy who had filled an ELMIRON prescription was similar to those who had not filled a prescription (2.37% [n=227] vs. 2.77% [n=1058], respectively.
- Survival models estimating 5-year risk of maculopathy after a patient's index diagnosis of IC and any ELMIRON exposure showed no significant relationship between exposure and any of the maculopathies of interest after controlling for age, gender and diagnosis of diabetes mellitus.
- In models that utilized a time-dependent categorical variable to determine a relationship between ELMIRON exposure and a possible dose-response relationship, ELMIRON was associated with an increased risk of hereditary dystrophy at an exposure >4 years (HR 8.78, 95% [CI], 1.12-68.81; p=0.039). No association was found for patients exposed <1 year and not enough data were available for any other length of time. Length of

exposure did not affect the development of any maculopathy or other maculopathy types.

- A separate sensitivity analysis, excluding all patients with a diagnosis of diabetes, re-estimated both models in the primary analysis. There was an increased risk of any diagnosis of maculopathy (HR 1.24, 95% [CI], 1.05-1.47; *p*=0.011) and an increased risk of exudative AMD (HR 1.35, 95% [CI], 1.07-1.69; *p*=0.011) in patients exposed to ELMIRON. In the time-dependent categorical model, patients exposed to ELMIRON for at least 4 years were at an increased risk of hereditary dystrophy (HR 14.41, 95% [CI], 1.73-119.92; *p*=0.014).

Jain et al (2019)[5] conducted a retrospective, matched-cohort study to determine an association between ELMIRON and macular disease using claims data from Clinformatics Data Mart Database (OptumInsight, Eden Prairie, Minneapolis, USA) from 2002 to 2016.

- Patients were excluded if they had any previous diagnosis of retinal toxicity, hereditary retinal degeneration, AMD or drusen.
- The primary outcome was 1) atypical maculopathy outcome: any new diagnosis of a hereditary or secondary pigmentary retinopathy and 2) atypical maculopathy + AMD: any new diagnosis of dry age-related macular degeneration (AMD) or drusen, plus atypical maculopathy.
- A total of 3012 and 1604 ELMIRON users were compared with 15,060 and 8017 matched controls at 5 and 7 years, respectively.
- At the 5- and 7-year follow-up, 9 (0.3%) and 10 (0.6%) ELMIRON users had an atypical maculopathy outcome, compared with 32 (0.2%) and 328 (4.1%) controls, respectively.
- At the 5- and 7-year follow-up, 103 (3.4%) and 87 (5.4%) ELMIRON users had the atypical maculopathy + AMD outcome, compared with 440 (2.9%) and 328 (4.1%) controls, respectively.
- At 5 years, multivariate analysis showed no significant association ($p > 0.13$). At 7 years, ELMIRON users had increased risk of atypical maculopathy + AMD outcome (Odds Ratio [OR] 1.41, 95% CI 1.09 to 1.83, $p = 0.009$).

Shah et al (2019)[3] conducted a retrospective, cross-sectional analysis of patients diagnosed with IC at the Emory Eye Center between 2014 and 2018. Use of ELMIRON and features of suspected maculopathy on ophthalmic imaging were compared in those with and those without exposure to ELMIRON. Images were classified according to their resemblance to characteristic maculopathy as: 1 (Affected), 2 (Possibly affected), 3 (Unaffected), and 4 (Insufficient imaging).

- Of 216 patients with IC 89 had documented exposure to ELMIRON and 127 did not have exposure to ELMIRON. The mean age for the ELMIRON group was 58.8 compared to 63.0 years in the non-ELMIRON group (*P*=0.0429). In the ELMIRON group, 82 were female compared with 110 in the non-ELMIRON group (*P*=0.204).
- In the ELMIRON group, 14 (15.7%), 7 (7.9%), 25 (28.1%), and 43 (48.3%) patients received grades 1, 2, 3, and 4, respectively. In the non-ELMIRON group, 0, 4 (3.1%), 23 (18.1%), and 100 (78.7%) patients received grades 1, 2, 3, and 4, respectively.
- Because no patients were graded 1 in the non-ELMIRON group, grades 1 and 2 were consolidated into one group of "unspecified pigmentary maculopathy" with an odds ratio of 9.50 (95% [CI], 3.13-28.80; *P*=0.0001).

EVALUATION OF RISK FACTORS

Vora et al (2020)[10] evaluated the prevalence and risk factors for the development of maculopathy in patients with IC and long-term exposure to ELMIRON at Kaiser Permanente Northern California health system.

- Of the 1120 patients identified with IC on their active problem list, 475 (42%) were taking ELMIRON at the time of the study. Optical coherence tomography and fundus photography was conducted in 117 of 138 patients who had been dispensed at least 500g of ELMIRON during the prior 20-year period.
- Two retina specialists, masked to total medication use, independently reviewed all retinal imaging studies and scored each patient for either the presence of definite or no definite signs of ELMIRON maculopathy.
- Univariate analysis of several risk factors was compared between those presenting with maculopathy and those without. Potential risk factors included female sex, race (white), cumulative dose tertile (500-999g, 1000-1500g, & >1500g), and mean age, weight, body mass index, duration of therapy, daily dose, and cumulative dose.
- Of those screened, 27 (23.1%) had definite signs of maculopathy and 90 (76.9%) did not. Patients with maculopathy had been dispensed a mean of 1350g of ELMIRON compared to 1040g in those without maculopathy (P<0.01). Toxicity increased from 12.7% in those who consumed 500 to 999 g to 41.7% to those who were exposed to >1500 g of ELMIRON (P=0.01; OR 2.95, 95% [CI], 1.01-8.65; P=0.05). Compared to those in the 500 to 999 g exposure group, those with >1500g were more likely to develop toxicity (OR 4.91, 95% [CI], 1.64-14.7; P=0.01).

CLINICAL PRESENTATION AND VISUAL SYMPTOMS

Hanif et al (2019)[11] conducted a multi-institutional, retrospective, case-series of patients who exhibited characteristic maculopathy in the setting of prior ELMIRON exposure from 2012 to 2018 (N=35, 70 eyes). The objective was to characterize exposure characteristics and clinical manifestations of ELMIRON-associated maculopathy.

- Electronic health records at Emory Eye center, Emory University School of Medicine (n=16), Casey Eye Institute, Oregon Health and Science University (n=6), University of Michigan Kellogg Eye Center (n=11), Northern California Retina Vitreous Associates (n=2) were searched for patients with ELMIRON exposure.
- Expert reviewers at each institution assessed retinal imaging for characteristic features of pigmentary maculopathy. Expert graders masked to exposure histories reviewed images to confirm inclusion to the case series. Image analysis of the affected eyes were evaluated for various features.
- Thirty-five patients were identified with active ELMIRON use. Thirty-four of the 35 patients were female (97%), the median age at the time of diagnosis was 60 (37-79) years, and 33 patients were white (94%). The most common presenting diagnosis was macular or pattern dystrophy (N=15) and age-related macular degeneration (N=10). Patients reported a median interstitial cystitis symptom duration of 19 (6-44) years. Median duration of ELMIRON intake was 15 (3-22) years, with a median daily dose of ELMIRON prescribed of 300 mg (150-592 mg) or a cumulative exposure per unit of body mass index of 24.7 mg/kg (9.83-61.9 mg/kg).
- The most commonly reported symptoms were blurred vision (n=17), prolonged dark adaptation (n=17), and metamorphopsia (n=4). Most eyes (86%) had a logMAR best-corrected visual acuity (BCVA) of 0.30 (Snellen equivalent, 20/40) or better. Visual field testing, except in the presence of RPE atrophy, demonstrated generally normal responses.
- Fundus autofluorescence imaging of the affected eyes in all patients revealed bilateral involvement, centered on and involving the fovea. Disease presentation typically revealed a confluent, densely packed pattern of hyperautofluorescent and hypoautofluorescent spots and reticular changes, occasionally extending into the periphery (36%).
- Eyes with atrophy of the RPE exceeding one-third of disc diameter in size was noted in 26 of 66 eyes. Eyes with atrophy were less likely to have hyperpigmented clumps than those without atrophy (23% (6 of 26 eyes) vs. 74% (28 of 38 eyes), P<0.001).

- Optical coherence tomography demonstrated pigmented macular spots consisted of focal elevation or thickening of the RPE.

CLINICAL EVALUATION AFTER DISCONTINUATION OF ELMIRON

There is limited data about the continued progression of maculopathy following the discontinuation of ELMIRON. **Huckfeldt et al (2019)**[4] report a case of a 62-year-old woman with suspected progressive maculopathy following discontinuation of ELMIRON who was retrospectively identified as having maculopathy consistent with ELMIRON-exposure following the publication of Pearce et al.[1] This patient did not have any known predispositions for inherited retinal degenerations. Following an ophthalmic visit at the age of 62, the patient complained of blurry vision in her left eye and difficulty seeing at night the prior year. There was no history of retino-toxic exposure in the patient's medical history. Following discontinuation of ELMIRON, the patient had continuing worsening vision in both of her eyes over 6 years until the age of 67. At the age of 69, the patient experienced worsening central vision in her left eye. The total patient-reported cumulative dose exposure was about 200mg per day throughout her treatment period of ~18 years (3.5mg/kg).

LITERATURE SEARCH

A literature search of MEDLINE® (and/or other resources, including internal/external databases) pertaining to this topic was conducted on August 26, 2022. Additional case reports identified are not detailed in this summary. [1, 6, 13]

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