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CORRESPONDENCE

Comment on "New anti-hyperglycaemic agents for type 2 diabetes and their effects on diabetic retinopathy"

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To the Editor:

In the recent review "New anti-hyperglycaemic agents for type 2 diabetes and their effects on diabetic retinopathy," experimental and clinical data suggested GLP-1 agonists had beneficial effects on diabetic retinopathy [1]. However, semaglutide was an exception since secondary analysis in the SUSTAIN-6 clinical trial showed a statistically significant association with worsening diabetic retinopathy [2].

Prior analyses of adverse effects (AEs) of GLP-1 agonists reported to the Food and Drug Administration Adverse Event Reporting System (FAERS) suggested no association between this class of drugs and diabetic retinopathy [3]. We sought to tabulate the ocular AEs of GLP-1 agonists reported in FAERS until June 30, 2020, including semaglutide, using previously described methods [4].

Among 4822 AEs associated with semaglutide since its FDA approval in December 2017, 335 were ocular AEs, with 24 cases of diabetic retinopathy and 3 cases of macular oedema. The number of cases of diabetic retinopathy, as a percentage of all ocular AEs and all AEs, was higher for semaglutide (7.16 and 0.50%) compared to other GLP-1 agonists like albiglutide (4.35 and 0.05%), dulaglutide (1.95 and 0.05%), liraglutide (3.35 and 0.07%), and exenatide (2.35 and 0.07%) (Table 1). In addition, the proportion of all AEs that affected the eye was higher for semaglutide compared to other GLP-1 agonists.

Since the FAERS collected post-approval AEs, a reporting bias following SUSTAIN-6 could have contributed to more reports of semaglutide associated with diabetic retinopathy and other ocular AEs, compared to other GLP-1 agonists. The FAERS did not have detailed clinical histories, precluding further analysis, so this surveillance mechanism may be inadequate to detect increased retinopathy progression. It would be unusual to attribute this purported effect to semaglutide's mechanism of action, when this was not noted in other GLP-1 agonists. The worsening of diabetic retinopathy observed with rapid glycemic correction with semaglutide hearkens to the "early

Table 1 FDA Adverse Event Reports for GLP-1 Receptor Agonists.

GLP-1 receptor agonist	Year of FDA approval	Reported DR	Reported DMO	Reported adverse ocular events	Reported total adverse events
Semaglutide	2017	24	3	335	4822
Albiglutide	2014	4	0	92	8633
Dulaglutide	2014	16	4	819	29,393
Liraglutide	2010	23	9	687	32,208
Exenatide	2005	49	20	2084	70,558

DR diabetic retinopathy, *DMO* diabetic macular oedema, *FDA* food and drug administration, *GLP-1* glucagon-like peptide-1.

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worsening of diabetic retinopathy" noted with strict glycemic control in the DCCT [5]. Although a similar mechanism may be present in this case, further longitudinal studies are necessary to confirm diabetic retinopathy progression with semaglutide and whether additional screening on top of regular examinations is indicated for these patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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