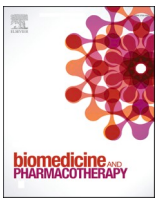
Biomedicine & Pharmacotherapy 157 (2023) 114003

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha



Letter to the editor

"Pharmacogenetics of siponimod: A systematic review" by Díaz-Villamarín et al. – Information is power

On August 12, 2022, Biomedicine and Pharmacotherpy published a systematic review on the pharmacogenetics of siponimod by Díaz-Villamarín et al. [1] We would like to acknowledge the work done by the authors, as siponimod is a drug that may occupy a priority place in the management of secondarily progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity. Therefore, we believe that research aimed at clarifying the impact of genetic variants on the effectiveness and safety of this drug is needed; therefore, we applaud the authors' efforts with this systematic review.

We consider that there are several inconsistencies in the therapeutic recommendations contained in the siponimod drug label and in those issued by the two most relevant international associations in pharmacogenetics: the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG). These are described below:

1. Current consensus on clinical pharmacogenetics recommends using the pharmacogenetic phenotype as the clinically implementable variable. Not only are CPIC and DPWG guidelines published in this line, but also recent consensus guidelines involving the European Society for Pharmacogenomics and Personalized Therapy (ESPT), the Pharmacogenomics Knowledgebase and the American Association of Molecular Pathology (AMP) [2,3]. In contrast, the American Food and Drug Administration (FDA) and the European Medicines Agency (EMA) drug labels include dosing recommendations based on diplotypes (e.g., CYP2C9**1/*3* for siponimod therapy) [4,5].
2. Abundant evidence supports the inference of CYP2C9 phenotype based on several reduced function and no function alleles [6,7]. However, FDA and EMA drug labels for siponimod only consider **2* and **3* alleles [4,5]. Any reduced function and no function allele (defined as such by CPIC and/or the Pharmacogene Variation Consortium, PharmVAR [8]) should be considered to infer CYP2C9 phenotype.
3. Abundant evidence supports the inference of a CYP2C9 intermediate metabolizer (IM) phenotype with an activity score (AS) of 1 for patients with two reduced-function alleles (e.g., **2/*2*) or one normal function allele plus one no function allele (e.g., **1/*3*) [6,7]. Hence, the dosing recommendation may be the same for CYP2C9**2/*2* and **1/*3* patients.

Pharmacogenetics is a discipline in full expansion, however, despite numerous agencies working on the drafting of clinical guidelines, it seems there is no international consensus on methodology, analytical interpretation, and therapeutic recommendations; or the existing consensus does not go parallel with the advancement of the discipline at the regulatory level.

Concerning the first and second inconsistencies, we consider it is very positive that the siponimod drug labels were published with pharmacogenetic information, but we consider it was a missed opportunity to do so in a non-standardized manner. We consider, in line with CPIC, DPWG, AMP, ESPT, etc., that the therapeutic recommendations should be issued based on pharmacogenetic phenotypes, while alleles with a previously known function should be considered for phenotype inference. It is, therefore, not necessary to demonstrate the clinical impact of each CYP2C9 allele on the safety of siponimod to recommend their genotyping and issue a clinical recommendation. Ignoring alleles only because they have not been analyzed in the study that justifies the recommendations is, in our opinion, inappropriate and far from the current consensus methodology in pharmacogenetics. We believe that our opinion is aligned with that of Díaz-Villamarín et al. in this regard because they state that *"other genetic variants resulting in* CYP2C9 *IM/PM status"* may be considered.

Considering the third inconsistency, Díaz-Villamarín et al. state that "CYP2C9**2 might be excluded from PGx testing recommendation before treatment starts with siponimod since it is not translated into a therapeutic recommendation"*. Here, we disagree with Díaz-Villamarín et al. because, as mentioned earlier, a huge body of literature supports that any IM with an AS of 1 shows a similar metabolic activity despite the diplotype inferring such phenotype (i.e., two reduced-function alleles - **2/*2* - or one normal function allele plus one no function allele - **1/*3*). The fact that there are no recommendations in the siponimod drug label for CYP2C9**2/*2* individuals does not mean that these patients are not at risk for adverse drug reactions (ADRs). It simply highlights the methodological limitations in the procedures carried out by the FDA and EMA to publish these drug labels.

Furthermore, therapeutic recommendations included in siponimod drug labels are based on a study with 24 healthy volunteers, where no **2/*2* individuals were included. In contrast, the study performed by Jin et al. [9] showed how siponimod area under the concentration-time curve for CYP2C9**2/*2, *2/*3* and **3/*6* is 2.7-, 3.0- and 4.5-fold higher compared to the CYP2C9**1/*1* genotype, respectively. This confirms that CYP2C9**2/*2* individuals may indeed be at risk for ADRs, and a dose reduction would be warranted for them.

Therapeutic recommendations should follow the logical AS system, which is the consensus methodology reached for some genes, including CYP2C9. If patients with AS of 1.0 require a dose reduction of 50 % (i.e., a maintenance dose of 1 mg instead of 2 mg), then poor metabolizers (PMs) with an AS 0.5 may require a dose adjustment of 75 %. (i.e., a maintenance dose of 0.5 mg). In contrast, siponimod drug label only considers a 50 % dose reduction for IMs with AS of 1 (i.e., **1/*3*) and PMs with an AS of 0.5. This does not seem consistent, especially when

https://doi.org/10.1016/j.biopha.2022.114003
Received 28 September 2022; Received in revised form 8 November 2022; Accepted 9 November 2022
Available online 11 November 2022

Table 1
Prescribing recommendations for siponimod. a) Current recommendations issued in siponimod drug label based on CYP2C9 genotypes; b) Potential recommendations based on CYP2C9 phenotype, complying with current pharmacogenetic analytical and methodological consensus.

a) Current recommendations issued in siponimod drug label

Genotype^	Phenotype	AS	Maintenance dose
**1/*1*	NM	2	2 mg
**1/*2*	IM	1.5	2 mg
**2/*2*[#]	IM	1	2 mg
**1/*3*[#]	IM	1	50 % reduction (1.0 mg)[$]
**2/*3*	PM	0.5	50 % reduction (1.0 mg)[$]
**3/*3*	PM	0	Siponimod contraindicated

b) Potential recommendations based on CYP2C9 phenotype

Phenotype[@]	Genotype (examples)^	AS	Potential adjustments*
NM	**1/*1, *9/*9*	2	2 mg
IM	**1/*2, *4/*9*	1.5	25 % dose reduction (1.5 mg)[!]
IM	**2/*2, *1/*3*	1	50 % reduction (1.0 mg)
PM	**2/*3, *5/*6*	0.5	75 % reduction (0.5 mg)[!]
PM	**3/*3, *13/*13*	0	Siponimod contraindicated

*The information contained in part b) of the table should be interpreted with caution and is shown for information purposes only, based on the author's judgement. The authors disclaim any liability.
Inconsistencies observed in siponimod drug label: [#]two different groups of intermediate metabolizers (IM) with the same activity score (AS) are related to different prescribing recommendations; [$]two different phenotype groups are related to the same prescribing recommendation; ^ only CYP2C9*2 and *3 alleles are acknowledged; according to the authors' criteria, any allele with a known clinical function (as per the Pharmacogene Variation Consortium (PharmVAR) [8] and Clinical Pharmacogenetics Implementation Consortium (CPIC)) may be consider to infer CYP2C9 phenotype.
^@ The pharmacogenetic phenotype, rather than individual genotypes, should be used as the clinically implementable variable in pharmacogenetics.
[!] Additional research is required to confirm the appropriateness of these dose adjustments.

formulations on the market that allow a finer adjustment are available. Additional research should be conducted to clarify if IMs with AS of 1.5 require a 25 % dose reduction to avoid ADRs and if a 75 % dose reduction for PMs with an AS of 0.5 is appropriate (Table 1).

Finally, we cannot advise non-compliance with the recommendations contained in siponimod drug labels, as these are legally binding documents. However, we believe that genotyping of the CYP2C9*2 allele and other reduced function alleles is essential to identify patients at increased risk for ADR development. It should be the clinician's judgment that guides dosing in *2/*2 patients. In our opinion, these patients should be treated in the same way as *1/*3 individuals, because both are IMs with AS of 1, or, at least, caution and special care should be advised. We do not consider advisable to ignore this information because it may be clinically relevant; it is best to inform the prescribing physician and let them decide. Nonetheless, the aim of this letter was not to recommend modification of the CYP2C9-based dose adjustments of siponimod as indicated in its drug label. Further population-based data on response, safety, and pharmacokinetics of siponimod should continue to be collected to determine the ideal dosing adjustments and validate them clinically. What we certainly recommend is to continue genotyping CYP2C9*2 and to closely monitor CYP2C9*2/*2 individuals as they could potentially be subject to an increased risk of ADRs. This statement is consistent with current pharmacogenetic knowledge and in no way contradicts the siponimod drug label.

In the Monty Hall problem, derived from the television "Let's make a deal", when the presenter opens the first door containing a goat and not the Ferrari, the contestant then intuitively changes their door because the probability of choosing the Ferrari has increased to 67 % [10]. In this context, the likelihood of ADRs is reduced if CYP2C9*2/*2 patients are identified and this information is provided to the physician. Although regulatory agencies do not provide a therapeutic recommendation for CYP2C9*2/*2 individuals, the history and track record in clinical pharmacogenetics teaches us that these patients may indeed be overexposed to siponimod and present a higher risk for ADRs. After all, information is power, and it is very likely that many patients will benefit from *2 (and other reduced function alleles) genotyping and the correct interpretation of these results.

Funding

P. Zubiaur is financed by Universidad Autónoma de Madrid, Margarita Salas contract, grants for the requalification of the Spanish university system.

CRediT authorship contribution statement

Pablo Zubiaur, Miriam Saiz-Rodríguez and Francisco Abad-Santos have contributed equally for this letter.

Declaration of Interest

Francisco Abad-Santos has been consultant or investigator in clinical trials sponsored by the following pharmaceutical companies: Abbott, Alter, Chemo, Cinfa, FAES Farma, Farmalíder, Ferrer, GlaxoSmithKline, Galenicum, Gilead, Italfarmaco, Janssen-Cilag, Kern Pharma, Normon, Novartis, Servier, Silverpharma, Teva and Zambon. The remaining authors declare no conflicts of interest.

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