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Abstract

Depression is a common side-effect of interferon (IFN)-alpha treatment of hepatitis C virus (HCV) infection and melanoma. Disturbances of tryptophan (TRP) metabolism might contribute to development of IFN-alpha–associated depression due to IFN-alpha-induced activation of indoleamine 2,3-dioxygenase (IDO), a rate-limiting enzyme of TRP–kynurenine (KYN) metabolism. The increased frequency of high producer (T) allele of IFN-gamma (IFNG) (+874) gene, that encodes IFNG production, in depressed patients suggested that increased IDO activity might be a risk factor for depression. The present study assessed KYN/TRP ratio (KTR) as a marker of IDO activity in American Caucasian HCV patients awaiting IFN-alpha treatment. KTR did not differ between 43 patients who did and 37 patients who did not develop depression. TRP concentrations were higher in patients who experienced depression. Odds of development of depression increased with elevation of serum TRP levels from 33% (TRP levels <12000 pmol/ml) to 68% (TRP levels > SPRO PO (OHYDWHG VHUXP 753 PD\ UHÀHFW WKH LPSDLUPHQW RI 753 FRQYH VXJJHVWHG OLQN EHWZHHQ VHURWRQLQ GH¿FLHQF\ DQG GHSUHVVLRQ 8S UHJXO of IFN-alpha– associated depression. Future studies shall explore the causes of elevated serum TRP in relation to IFN-alpha–associated depression.

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43 patients who did and 37 patients who did not experience IFN-alpha–associated depression (Table1).

Odds of development of depression increased as TRP levels elevated from 33% (TRP levels <12000 pmol/ml) to 68% (TRP levels>16000 pmol/ml, p<0.03) (Table 2).

Discussion

e main nding of our study was an observation that odds of thedevelopment of IFN-alpha – associated depression were increased with elevated concentrations of serum TRP. e present results suggest that high serum TRP level might be a risk factor for the development of IFN-alpha – associated depression. Recent prospective study did not nd di erences in TRP serum levels between depressed (Beck Depression Inventory, BDI scores >10) and non-depressed (BDI<10) HCV patients at each time point (baseline, one and six months) during IFN-alpha treatment and 3 months post-treatment [12]. Authors did not compare baseline TRP levels in patients who develop and

depression. e presence of high (T) producer allele of IFNG(+874) gene that encodes the production of IFNG, the strongest IDO inducer, might augment the risk of IFN-alpha – associated depression, especially in patients with de cient serotonin formation of TRP, by additional decrease of TRP availability as a substrate for serotonin biosynthesis.

Con ict of Interest Disclosure

Paul Summergrad is a non-promotional speaker for CME out tters, Inc., and consultant and non-promotional speaker for Pri-med, Inc. All other authors declare no proprietary interest regarding this study.

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References

1. Vignau J, Costisella O, Canva V, Imbenotte M, Duhamel A, et al. (2009) Impact of interferon alpha immunotherapy on tryptophan metabolism in patients with chronic hepatitis C. Results of a pilot studies on ten patients. Encephale 35: 477-483.
2. Capuron L, Miller AH (2011) Immune system to brain signaling: neuropsychopharmacological implications. PharmacolTher 130: 226-238.
3. Taylor MW, Feng GS (1991) Relationship between interferon-gamma, indoleamine 2,3-dioxygenase, and tryptophan catabolism. FASEB J 5: 2516-2522.
4. Oxenkrug G (2013) Serotonin-kynurenine hypothesis of depression: historical overview and recent developments. Curr Drug Targets 14: 514-521.
5. /DSLQ 2 (HQUXJ *) , QWHQVL¿FDWLRQ RI WKH FHQWUDO VHURWRQLQHUJLF processes as a possible determinant of the thymoleptic effect. Lancet 1: 132-136.
6. Lapin IP (1973) Kynurenines as probable participants of depression. PharmakopsychiatrNeuropsychopharmakol 6: 273-279.
7. Wichers MC, Koek GH, Robaeys G, Verkerk R, Scharpé S, et al. (2005) IDO and interferon-alpha-induced depressive symptoms: a shift in hypothesis from tryptophan depletion to neurotoxicity. Mol Psychiatry 10: 538-544.
8. Pravica V,