Journal of Affective Disorders 145 (2013) 300–307

Contents lists available at SciVerse ScienceDirect

Journal of Affective Disorders

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

Research report

Might different cytokine trends in depressed patients receiving duloxetine indicate differential biological backgrounds

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ARTICLE INFO

Article history:
Received 21 June 2012
Received in revised form
2 August 2012
Accepted 2 August 2012
Available online 14 September 2012

Keywords:
Cytokines
Th1
Th2
Duloxetine
Depression

ABSTRACT

Background: Correlational studies investigating neurohormonal-cytokine modulation by antidepressants suggest, among others, variations in cytokines balances as state markers of different biological subtypes of major depressive disorder (MDD) and response predictors to specific treatments. Objective of the study was to investigate cytokines modulation by duloxetine, a relatively newer SNRI with "clean" dual serotonin/norepinephrine mechanism.

Methods: 30 MDD patients and 32 healthy controls were assessed using Hamilton Depression Scale (HAM-D) and monitored for levels of IL-1β, IL-2, IL-4, IL-10, IL-12, IFN-γ and TNF-α, at baseline, week 6 and week 12 of duloxetine treatment (60 mg/day) and at baseline, respectively.

Results: Early responders (ER: defined at week 6 by reduction >50% of baseline HAM-D score) and early non-responders (ENR) showed opposite trends in cytokine levels during duloxetine treatment: ENR were characterized by baseline Th2 shift compared to controls (lower IL-1β, IFN-γ and TNF-α) with increase in Th1 cytokines levels during treatment (increase of IL-1β, IL-12, IFN-γ, IL-1β/IL-10 and TNF-α/IL-10, decrease of IL-10), achieving clinical response at week 12; ER were characterized by baseline Th2-to-Th1 relative switch compared to ENR (higher IL-1β, IL-1β/IL-10 and TNF-α/IL-10) with reduction in Th1 cytokines levels during treatment (decrease of TNF-α and TNF-α/IL-10), achieving clinical response at week 6.

Limitations: Small sample size.

Conclusions: In accordance to early clinical response, duloxetine treatment could divide depressed patients into at least 2 subgroups characterized by clinical and laboratory differentiated behavior, suggesting different neurobiological background within depressive syndrome differentially sensitive to different drug components: pro-serotonergic effect and increase in Th1 cytokines in ENR vs. pro-noradrenergic effect and decrease in Th1 cytokines in ER.

1. Introduction

Within the past years, a growing number of investigations explored the relationship between immune and neuroendocrine systems and different psychiatric conditions, especially Mood and Anxiety disorders, with the aim of a better comprehension of their pathophysiology and a more effective therapeutic management (Hickie and Lloyd, 1995). Correlations between differential clinical response to drugs and differential biological patterns of clinically similar conditions, suggest, among others, the variations in cytokines balances as state markers of different biological subtypes of depression and response predictors to specific treatments. Physiologically, *T* lymphocytes differentiates into subsets of cells producing distinct types of cytokines (Mosmann and Coffman, 1989); Th1-like cytokines such as Interleukin (IL)-1β, IL-2, IL-12, Interferon (IFN)-γ and Tumor Necrosis Factor (TNF)-α mainly promotes cell-mediated immunity, while Th2-like cytokines such as IL-4, IL-6 and IL-10 mainly promotes humoral immunity (Elenkov, 2008). Since the synthesis and release of pro- or anti-inflammatory cytokines is modulated by levels of pro- or anti-inflammatory cytokines from different cellular sources, an immunological antagonism has been observed between Th1-like and Th2-like cytokines (Hernandez-Pando et al., 1996; Paul, 2003; Pavon et al., 2006), leading to the concept of Th1/Th2 balance: in this context, TNF-α/IL-10 ratio and IL-1β/IL-10 ratio have been used in the study of several diseases including major depression (Huang and Lee, 2007). Evidence accumulated along the last 3 decades indicates that brain neurohormonal messages modulate cytokine balance (Elenkov, 2008). Physiological doses of serotonin (5-HT) induces the secretion

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http://dx.doi.org/10.1016/j.jad.2012.08.007

of pro-inflammatory cytokines (Kubera et al., 2005), while glucocorticoids (GCs) and norepinephrine (NE) favor a establishment a Th2 profile with a down regulation of Th1 cytokine secretion (Elenkov, 2008).

From a physiological perspective, environmental stress activates NE system, hypothalamus-pituitary-adrenal (HPA) axis with cortisol release and Th2 shift, components of the neuro-endocrine-immune (NEI) stress-adaptation system (Elenkov and Chrousos, 2006); such systems, in turn, induce a compensatory response with feedback mechanisms in 5-HT system and Th1 components (Kubera et al., 2005; Lanfumey et al., 2008). Major Depressive Disorder (MDD) seems to be associated to HPA axis hyperactivity (Axelson et al., 1993; Holsboer, 2000; Pariante and Miller, 2001), which, in some cases, leads to deficit in 5-HT compensatory tone (Gonzalez et al., 2007; Lopez et al., 1998). Neuroendocrine alterations are associated with inflammation and immune activation: a recent meta-analysis shows that some cytokines, such as TNF-α and IL-6, are consistently increased in depression (Dowlati et al., 2010). Some authors have reported a polarization towards a Th2 type circulatory cytokine profile in depressed patients before treatment (Elenkov, 2004; Elenkov and Chrousos, 1999; Pavon et al., 2006). Other authors suggest the role of Th1-like compound and cell-mediated immune activation in depression (Maes, 2011). In this context, unipolar depressive disorders might represent a disorder of NEI stress-adaptation system mainly characterized by hyposerotonergic state, HPA axis hyperactivation and Th1/Th2 balance shifts.

Correlational studies showed that antidepressants (which mainly act on the 5-HT/NE balance) might reduce Th1-like cytokines and increase Th2-like cytokines, while others showed opposite effects: conflicting data may depend on pharmacodynamic issues, duration and dose of treatment, or specific substrate investigated (Martino et al., 2012). Selective Serotonin Reuptake Inhibitors (SSRIs), via chronic blockade of 5-HT transporter (5-HTT), desensitize 5-HT1A autoreceptors, in turn enhancing 5-HT and reducing NE transmissions (El Mansari et al., 2005; Hensler, 2002; Szabo et al., 2000). In a long term clinical study on depressed patients, SSRIs seem to increase Th1 cytokines and decrease Th2 cytokines and cortisol levels, showing that 5-HT effects on the immune response are dose-dependent and time-dependent (Hernandez et al., 2008). Serotonin Norepinephrine Reuptake Inhibitors (SNRIs), via chronic blockade of NE transporter (NET) (Stahl et al., 2005) (in addition to 5-HTT), also desensitize α2 receptor, in turn strengthening NE transmission (Parini et al., 2005), and enhance dopamine (DA) activity in specific areas (Linner et al., 2001). Among SNRIs, venlafaxine seems to reduce Th1 cytokines and to increase Th2 cytokines in a dose dependent manner (De Berardis et al., 2010; Kubera et al., 2004; Kubera et al., 2001), possibly in relation to its peculiar pharmacodynamic, acting as a pro-serotonergic drug at low dose, but producing a pro-noradrenergic effect at higher dose (Debonnel et al., 2007). Duloxetine, a relatively newer SNRI, in contrast to venlafaxine blocks the same extent 5-HTT and NET, enhancing 5-HT and NE transmission at standard dose (e.g., 60 mg/day or lower) (Rueter et al., 1998; Trivedi et al., 2008). To our knowledge, to date there are no clinical or preclinical data on cytokines modulation by duloxetine, except for our previous study focused on IL-6 (Fornaro et al., 2011b). Overall, it seems that the greater the NE-ergic component of antidepressant, the higher the increase in Th2 cytokines, the greater the 5-HT-ergic component, the higher the increase in Th1 cytokines, although the differential action of antidepressants on different subgroup of patients would suggest a relative, rather than absolute, modulation of Th1/Th2 balance that ideally compensate previous NEI imbalances (Martino et al., 2012). Our previous works suggested that duloxetine treatment could identify different subgroup of depressed patients on the basis of early clinical response related to differential trends in biological parameters such as cytokine (IL-6) and electroretinographic (ERG) patterns (Fornaro et al., 2011a, 2011b), coherent with each other if considered potential epiphenomena of variations in neurotransmitter balances.

Objective of the study was to extend the investigation on the effect of 60 mg/day duloxetine on plasma concentration of IL-1β, IL-2, IL-4, IL-10, IL-12, IFN-γ and TNF-α in 30 depressed outpatients and 32 healthy controls within a period of 12 weeks, with the aim of a better appreciation of the interaction between antidepressant response and cytokines balance in the context of hypothetically different biological backgrounds of depressive syndrome.

2. Methods

Thirty-eight outpatients diagnosed with MDD were screened during a period of 12 months for inclusion into a 12 weeks open-label trial investigating the effect of duloxetine 60 mg/day (q.d.) monotherapy on several cytokines levels. All diagnoses were made according to the Diagnostic and Statistical Manual for Mental Disorders-Fourth Edition (DSM-IV) criteria (A.P.A., 1994) assessed by the Structured Clinical Interview for Axis-I Disorders/Patient edition (SCID-I/P) (Ventura et al., 1998). At baseline, 30 patients were eligible to enter the study, fulfilling all the inclusion criteria, including the actual presence of a single or recurrent, drug-naïve, major depressive episode, age of 18–65 and ability to give a valid informed consent upon approval by the local Ethical Committee. Exclusion criteria included the following: Bipolar Disorder, Schizoaffective Disorder, Schizophrenia, Dementia, any Anxiety Disorder, Substance Use Disorders (substance abuse, except for nicotine, during the screening period), current suicidal and/or psychotic ideation. Additional exclusion criteria included pregnancy, breast-feeding and history of relevant medical comorbidities (i.e., autoimmune, allergic, neoplastic and endocrine diseases, surgery, vascular stroke or acute or chronic infection within the past month). Any eventual concomitant medication (including other antidepressants and non-psychotropic drugs such as NSAIDs and oral anti-contraceptives) had to be discontinued at least 15 day prior assumption of duloxetine, four weeks early in case of fluoxetine. Zolpidem 5–10 mg/day or diazepam 5–10 gtt./day have allowed, but could not assumed the night before scheduled assessments. As mandatory inclusion criterion, it has been considered also the presence of a baseline total score of the Hamilton Depression Scale (HAM-D) at 17 items ≥ 18 (Hamilton, 1960), when undergoing a physical examination, standard laboratory tests and immunological monitoring of IL-1β, IL-2, IL-4, IL-10, IL-12, IFN-γ and TNF-α levels. The whole sample was re-screened at week (W)6 using HAM-D and cytokines sampling. Early responders (ER) to duloxetine treatment (defined by reduction of HAM-D score at W6 $\geq 50\%$ vs. baseline) concluded the trial at W6, while early non-responders (ENR) continued up to W12 (end of the study) and were re-evaluated on HAM-D and cytokines sampling. The Young Mania Rating Scale (YMRS) was also administered at baseline, W6 and W12 (only for ENR) in order to assess any eventual drug-induced (hypo)manic switch, defined by total score > 13 (Young et al., 1978). At the end of the protocol, patients who completed the study underwent a 12 months follow-up. All blood samples were obtained at 08.30–10.00 am, in order to limit a potential circadian rhythm variance bias. IL-1β, IL-4, IL-12, IFN-γ, TNF-α (Bender Med Systems®) and IL-2, IL-10 (eBioscience) serum levels were measured by colorimetric enzyme-linked immunosorbent assays (ELISA) following the manufacturer's instructions. The limits of detection were 3.9 pg/ml for IL-1β, 8 pg/ml for IL-4, 3.2 pg/ml for