Schizophrenia Research 132 (2011) 35–41

Contents lists available at ScienceDirect

Schizophrenia Research

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

Long acting injection versus oral risperidone in first-episode schizophrenia: Differential impact on white matter myelination trajectory

George Bartzokis [a,b,c,*], Po H. Lu [d], Chetan P. Amar [a,c], Erika P. Raven [a], Nicole R. Detore [a], Lori L. Altshuler [a], Jim Mintz [e], Joseph Ventura [a], Laurie R. Casaus [a], John S. Luo [a], Kenneth L. Subotnik [a], Keith H. Nuechterlein [a,f]

[a] Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, The David Geffen School of Medicine at UCLA, Los Angeles, California, United States
[b] Laboratory of Neuroimaging, Department of Neurology, Division of Brain Mapping, The David Geffen School of Medicine at UCLA, Los Angeles, California, United States
[c] Greater Los Angeles VA Healthcare System, West Los Angeles, California, United States
[d] Department of Neurology, The David Geffen School of Medicine at UCLA, Los Angeles, California, United States
[e] Department of Epidemiology and Biostatistics, University of Texas Health Science Center at San Antonio, San Antonio, Texas, United States
[f] Department of Psychology, UCLA, Los Angeles, California, United States

ARTICLE INFO

Article history:
Received 29 March 2011
Received in revised form 23 June 2011
Accepted 27 June 2011
Available online 20 July 2011

Keywords:
Antipsychotic
Medication
Dopamine
Second generation
Atypical
Myelin
White matter
Gray matter
Oligodendrocyte
Development
Aging

ABSTRACT

Context: Imaging and post-mortem studies provide converging evidence that subjects with schizophrenia (SZ) have a dysregulated trajectory of frontal lobe myelination. Prior MRI studies suggested that early in treatment of SZ, antipsychotic medications initially increase frontal lobe white matter (WM) volume, which subsequently declines prematurely in chronic stages of the disease. Insofar as the trajectory of WM decline associated with chronic disease may be due to medication non-adherence, it may be modifiable by long acting injection (LAI) formulations.
Objectives: Examine the impact of antipsychotic formulation on the myelination trajectory during a randomized six-month trial of LAI risperidone (RLAI) versus oral risperidone (RisO) in first-episode SZ subjects.
Design: Two groups of SZ subjects (RLAI, N = 11; and RisO, N = 13) that were matched in pre-randomization oral medication exposure and 14 healthy controls (HCs) were prospectively examined. Frontal lobe WM volume was estimated using inversion recovery (IR) MRI images. A brief neuropsychological battery that focused on reaction times was performed at the end of the study.
Main outcome measure: WM volume change scores.
Results: WM volume remained stable in the RLAI and decreased significantly in the RisO groups resulting in a significant differential treatment effect, while the HC had a WM change intermediate and not significantly different from the two SZ groups. WM increase was associated with faster reaction times in tests involving frontal lobe function.
Conclusions: The results suggest that RLAI may improve the trajectory of myelination in first-episode patients and have a beneficial impact on cognitive performance. Better adherence provided by LAI may underlie the modified trajectory of myelin development. In vivo MRI biomarkers of myelination can help clarify mechanisms of action of treatment interventions.

Published by Elsevier B.V.

1. Introduction

Many patients treated in their first-episode of schizophrenia (SZ) respond very well to antipsychotics and can achieve high levels of symptom remission within the first year, ranging from 70 to 87% (Lieberman et al., 1993; Robinson et al., 1999; Robinson et al., 2004; Nuechterlein et al., 2006; Emsley et al., 2007; Boter et al., 2009; Saravanan et al., 2010). Over subsequent years, recurrent episodes, often brought on by poor adherence or insufficient treatment, often lead to substantial chronic deterioration (Lieberman, 2006) and reduced responsiveness to antipsychotics or "treatment resistance" (Kane et al., 1988; Lieberman et al., 2001a; Lieberman et al., 2001b). The use of long-acting injection (LAI) formulations of antipsychotics results in improved outcomes, suggesting that worse outcomes with oral medications may be due to reduced adherence (reviewed in Keith, 2009).

The mechanism through which LAI medications may improve outcomes remains unknown. It has been proposed that the biological

* Corresponding author at: 300 UCLA Medical Plaza, Suite 2200, Los Angeles, CA 90095-6968, United States. Tel.: +1 310 206 3207; fax: +1 310 794 9915.
E-mail address: gbar@ucla.edu (G. Bartzokis).

0920-9964/$ – see front matter. Published by Elsevier B.V.
doi:10.1016/j.schres.2011.06.029

underpinnings of functional deterioration and "treatment resistance" observed in chronic SZ may involve deficient myelination (Bartzokis and Altshuler, 2003; Bartzokis and Altshuler, 2005; Bartzokis et al., 2011) and that dysregulation of the myelination trajectory may contribute to the etiology of schizophrenia (Bartzokis, 2002). A deficiency in the myelination trajectory was initially observed in cross sectional imaging and postmortem studies (Bartzokis, 2002; Bartzokis et al., 2003; Uranova et al., 2004) and confirmed in prospective imaging studies of SZ and healthy control cohorts followed over several years (Ho et al., 2003; Whitford et al., 2007; Cocchi et al., 2009). We suggested that antipsychotic medications promote WM development and specifically promote myelination of the lower layers of cortex as one of their mechanisms of action (Bartzokis, 2002; Bartzokis et al., 2009; Bartzokis, 2011). In a prior cross-sectional study we observed that, very early in treatment, both typical and atypical antipsychotics increased WM volume above that of healthy controls (Bartzokis et al., 2007) primarily due to increased myelin in the lower cortical layers (Bartzokis et al., 2009). The current prospective study examined whether improved medication adherence made possible by LAI could influence this myelination process in patients with first-episode SZ.

In healthy individuals, the developmental trajectory of brain myelination continues well into middle age, when WM makes up approximately half the brain volume, with approximately half the WM volume consisting of myelin (Fig. 1) (Kemper, 1994; Bartzokis et al., 2001) (reviewed in Bartzokis and Lu, 2009). Myelin is a highly specialized lipid membrane wrapping of axons that has the highest cholesterol content of any brain tissue and increases action potential transmission speed over 100 fold (O'Brien and Sampson, 1965; Rouser et al., 1972; Saher et al., 2005). Inversion-recovery (IR) MRI images are optimal for quantifying myelination (Valk and van der Knaap, 1989; van der Knaap and Valk, 1990; Barkovich et al., 1992) because they are most sensitive to the high cholesterol concentrations in myelin (Koenig, 1991). There is an excellent agreement between the lifetime myelination trajectory of normal individuals observed in vivo with IR sequences and published post-mortem data (Bartzokis et al., 2001; Bartzokis and Lu, 2009). In the frontal lobe, peak myelination is reached at age 45 as measured by both in vivo MRI and post-mortem myelin stain data (Kemper, 1994; Bartzokis et al., 2001) (Fig. 1). This close agreement with post-mortem data validates in vivo IR volume measures and suggests that IR sequences likely track what may be better referred to as "myelinated WM volume" that includes the heavily myelinated lower layers of cortex (Bartzokis et al., 2001; Bartzokis et al., 2003; Bartzokis et al., 2007) (Fig. 1). For simplicity this IR-based measure will herein be referred to as WM.

Long-acting injectable (LAI) delivery of typical antipsychotic medications has been available for several decades. However, an atypical (also referred to as second generation) LAI antipsychotic medication, Risperdal® CONSTA® (RLAI) has only been available recently. Treatment with RLAI has been associated with substantially improved clinical outcomes, decreased hospitalizations, and significant healthcare cost savings (Lindenmayer et al., 2009; Olivares et al., 2009b; Velligan et al., 2009; Willis et al., 2010) (reviewed in Keith, 2009). In a recent study, greater improvements in clinical parameters such as number and duration of hospitalizations were observed in RLAI-treated patients who were *recently* diagnosed with schizophrenia than for those with chronic schizophrenia (Olivares et al., 2009a) suggesting that improving adherence may be particularly important early in the disease.

Poor adherence to medications may be a modifiable risk factor for suboptimal outcomes in SZ antipsychotic treatment (reviewed in Keith, 2009). We examined treatment with risperidone, which is available in both RLAI as well as oral risperidone (RisO) formulations. We performed a randomized clinical trial comparing these two formulations in first-episode subjects to test the hypothesis that improved adherence can positively impact frontal lobe myelination and cognitive functions dependent on the frontal lobe.

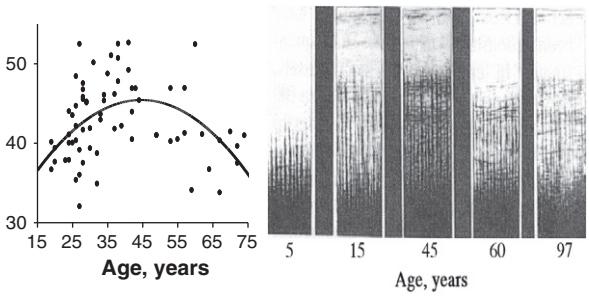

Fig. 1. Quadratic (inverted U) trajectories of human brain myelination over the lifespan. Myelination (Y axis) versus age (X axis) in frontal lobes of normal individuals. Left panel is in vivo data from Bartzokis et al. (2001). Right panel shows post-mortem *intracortical* myelin (ICM) stain data from Kaes (1907) adapted and reproduced in Kemper (1994) depicting the heavy myelination of the lower cortical layers. Used with permission. The data were acquired 100 years apart yet the two samples of normal individuals show remarkably similar frontal lobe myelination trajectories, both reaching a peak in the middle of the fifth decade.

2. Methods

2.1. Subjects

Schizophrenic subjects were recruited from the fourth cohort of the Developmental Processes in Schizophrenia Disorders Project, conducted at the UCLA Aftercare Research Program (Nuechterlein et al., 1992; Nuechterlein et al., 2008). The first psychotic episode for the SZ subjects (18 males and 6 females, aged from 18 to 33 years old) began within the last 2 years (median duration since onset of first episode was 6 months (SD = 5.9)) and a DSM-IV diagnosis of schizophrenia or schizoaffective (depressed type) disorder was established using the Structured Clinical Interview for DSM-IV by diagnosticians with demonstrated inter-rater reliability (Nuechterlein et al., 2008). Patients with significant substance abuse or history of neurological disorders or significant head trauma were excluded (Nuechterlein et al., 2008).

All subjects received written and oral information about the study and signed written informed consents approved by the local Institutional Review Board prior to study participation. Selection criteria were as follows: no evidence of significant current or past psychiatric diagnosis or substance dependence based on DSM-IV criteria; no significant use of drugs or alcohol in the past year (amount of use did not meet DSM-IV criteria for alcohol/substance dependence or abuse); no history or gross evidence of central nervous system impairment or any history of neurological disorder, including head trauma with loss of consciousness for greater than 15 min; no history of chronic medical conditions that are likely to result in structural brain abnormalities (i.e., stroke, transient ischemic attack, seizure disorder, etc.).

Forty-five patients were recruited for this MRI study component and entered the randomized trial in the Developmental Processes in Schizophrenia Disorders Project. All subjects were taking oral antipsychotic medications prior to randomization: risperidone 52%, olanzapine 24%, quetiapine 20%, and ziprasidone 4%. To establish a common baseline assessment point, the 48% of subjects whose antipsychotic medication was not already RisO were cross-tapered from their initial antipsychotic medication to RisO. All subjects were on RisO as the sole antipsychotic medication for a minimum of 10 weeks prior to baseline MRI assessment. When participants reached the randomization point, treatment arm assignment was done using a random number table. All treatment were open-label and not blinded. The RisO or RisC dose was optimized by the treating psychiatrists based on the clinical response of each patient. This resulted in a mean dose of 2.9 mg (SD = 1.8, range 1 to 7.5 mg) for the