Add-on clinical effects of simvastatin and ondansetron in patients with schizophrenia stabilized on antipsychotic treatment: pilot study

Imran B. Chaudhry, Nusrat Husain, Richard Drake, Graham Dunn, M. Omair Husain, Ajmal Kazmi, Munir M. Hamirani, Raza Rahman, John Stirling and William Deakin

Abstract

Objectives: There is some evidence that anti-inflammatory treatment may have beneficial effects in schizophrenia and major depression. Statins are cholesterol-lowering agents but have been found to be anti-inflammatory and also decrease C-reactive protein (CRP). Ondansetron is a serotonin (5-HT₃) receptor antagonist widely used to prevent nausea and vomiting in patients receiving chemotherapy for cancer. Small studies have suggested that adjunctive ondansetron is efficacious against schizophrenia symptoms. We carried out a feasibility study in schizophrenia patients (within 5 years of first diagnosis) to explore the adjunctive use of simvastatin and ondansetron on positive, negative and general psychopathology.

Methods: This was a 12-week rater-blind placebo-controlled study. A total of 36 patients with DSM-IV diagnosis of schizophrenia were recruited, 12 in each arm. Patients were assessed at baseline and at 12 weeks using Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression (CGI) scale, Global Assessment of Functioning (GAF) and Abnormal Involuntary Movement Scale (AIMS).

Results: Both simvastatin and ondansetron provide some evidence of a reduction in symptoms compared with treatment as usual (TAU) on PANSS total score, although this was not statistically significant. In the secondary analyses, no significant differences were seen on CGI, GAF and AIMS.

Conclusions: Anti-inflammatory treatments have been shown to have some beneficial effects in schizophrenia. Both simvastatin and ondansetron provide some evidence of a reduction in symptoms compared with TAU. This study has led to a larger Stanley Medical Research Institute (SMRI)-funded, double-blind, randomized control trial.

Keywords: Psychosis, schizophrenia, anti-inflammatory, simvastatin, ondansetron

Background

Schizophrenia is a chronic and disabling disease with poor long-term outcomes. The current antipsychotic medications, both first and second generation, are efficacious in alleviating the positive symptoms. However, the evidence for acceptable outcomes on negative symptoms and cognitive decline, which have a marked impact on social integration of patients with schizophrenia, is still limited.

There is some evidence that anti-inflammatory treatment may have beneficial effects in schizophrenia and major depression. Cox-2 inhibitors and aspirin have been tested in preliminary clinical trials for schizophrenia and depression, showing favourable effects compared with placebo [Müller and Schwarz, 2008; Laan *et al.* 2010].

Statins are widely used in schizophrenia sufferers, particularly those taking second-generation

Ther Adv Psychopharmacol

2014, Vol. 4(3) 110–116

DOI: 10.1177/

2045125313511487

© The Author(s), 2013.

Reprints and permissions:

[http://www.sagepub.co.uk/](http://www.sagepub.co.uk/journalsPermissions.nav)

[journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

Correspondence to:

M. Omair Husain

Southwest London and

St George's NHS Trust,

London, UK

so_moo@hotmail.com

Imran B. Chaudhry, MD

Nusrat Husain, MD

Richard Drake, PhD

Graham Dunn, PhD

John Stirling, PhD

William Deakin, PhD

University of Manchester,

Manchester, UK

Ajmal Kazmi, DPM

Pakistan Institute of

Learning & Living,

Karachi, Pakistan

Munir M. Hamirani, FCPS

Abbassi Shaheed Hospital

Karachi, Karachi, Pakistan

Raza Rahman, FCPS

Dow University of Health

Sciences, Karachi,

Pakistan

antipsychotics, to treat hypercholesterolemia. Statins were introduced as cholesterol-lowering agents but have found much wider usage. They are anti-inflammatory agents and thus similar to the Cox-2 inhibitors, which have shown some ability as adjuncts to improve the symptoms of schizophrenia in preliminary studies. The statins are also known to decrease C-reactive protein (CRP), which has been shown to be elevated in a study of individuals with schizophrenia. Fan and colleagues demonstrated in a small study in patients with schizophrenia that higher than normal levels of CRP (0.5 mg/dl) were associated with marked negative symptoms and higher total Positive and Negative Syndrome Scale (PANSS) scores [Fan *et al.* 2007].

Ondansetron is a serotonin (5-HT₃) receptor antagonist that is generic and widely used to prevent nausea and vomiting in patients receiving chemotherapy for cancer. GSK undertook a small study on it as an antipsychotic in the 1980s. Since then, several small studies have suggested that it is effective as an adjunct drug in improving the symptoms of schizophrenia [Akhondzadeh *et al.* 2009]. In an open-labelled study Sirota and colleagues demonstrated that while ameliorating symptoms of schizophrenia, ondansetron also significantly improved features of tardive dyskinesia in this group of patients [Sirota *et al.* 2001].

We carried out a feasibility study in patients with chronic schizophrenia to explore the adjunct use of simvastatin and ondansetron on positive, negative and general psychopathology.

Methods

This was a randomized 12-week rater-blinded study conducted in two psychiatric units, Karwan e Hayat Hospital and the Department of Psychiatry, Civil Hospital Karachi.

Subjects

A total of 36 patients aged between 18 and 65 years who met Diagnostic and Statistical Manual-IV (DSM-IV) diagnosis of schizophrenia, schizoaffective disorder, psychosis not otherwise specified or schizophreniform disorder were included in the study.

Inclusion criteria. Included patients were competent and willing to give informed consent to participate in the study and had to be stable on

medication 4 weeks prior to baseline assessments. Patients had to be able to take oral medication and complete the required evaluations. Female participants of child-bearing age were asked to use adequate contraceptives for the duration of the study, to have a pregnancy test pretreatment and at 10-weekly intervals while on study medication.

Exclusion criteria. Patients with relevant medical illness (renal, hepatic, cardiac, serious dermatological disorders such as exfoliative dermatitis, systemic lupus erythematosus) in the opinion of the investigators, on concomitant penicillin and anticoagulant therapy, presence of a seizure disorder (not including clozapine-induced seizures), presently taking valproic acid, any change of psychotropic medications within the previous 4 weeks, with a diagnosis of substance abuse (except nicotine or caffeine) or dependence within the last 3 months according to DSM-IV criteria, pregnant or breast-feeding females were all excluded.

Conduct

Institutional Review Board approval was obtained for the study. All patients signed written informed consent. After consenting to take part in the study patients' clinical symptoms, cognitive, neurological and general level of function were assessed. The patients were then randomized to one of the three treatment arms: (1) treatment as usual (TAU); (2) TAU + simvastatin; or (3) TAU + ondansetron.

Drug preparation

The study pharmacist carried out study drug randomization procedures and also dispensed the drugs and counted returned drugs in order to assess compliance. Simvastatin was started at 20 mg once daily, this was increased to 40 mg after 4 weeks. Ondansetron was administered in an 8 mg dose.

Assessments

Patients were clinically assessed at baseline and at 12 weeks. Primary outcomes were assessed using PANSS scores, a 30-item tool which is widely used to assess positive and negative symptoms of schizophrenia [Kay *et al.* 1997], particularly a negative subscale derived according to well-established criteria [White *et al.* 1997].

Secondary outcomes were the Clinical Global Impression (CGI) scale [Guy, 1976], Global Assessment of Functioning (GAF) (DSM-IV-TR) and Abnormal Involuntary Movement Scale (AIMS) [Guy, 1976]. CGI is a clinical assessment tool that evaluates the severity of psychopathology and change from the initiation of treatment on seven-point rating scales. GAF is a scale that looks at the level of social, occupational and psychological function. The scale ranges from 0 to 100 and is displayed in the DSM-IV-TR. AIMS is a 12-item clinician-rated scale that establishes the severity of dyskinesia in patients taking neuroleptic medication.

Prior to entering the study all patients went through a physical examination and physical assessments including blood pressure, pulse, height, waist, weight and body mass index (BMI), and these assessments were repeated at 12 weeks. Haematological investigations included complete blood count, erythrocyte sedimentation rate, liver function tests, urea and creatinine, electrolytes and CRP.

There was no formal measurement tool used for the monitoring of side effects. Research assistants would ask about tolerance to medication by enquiring about a list of side effects from the British National Formulary [BNF, 2012].

Statistical analysis

Analyses were undertaken in Stata (version 10) after completion of endpoint assessments; primary analysis was by intention-to-treat. Treatment effects were estimated using analysis of covariance (ANCOVA), allowing for the baseline (prerandomization) measurement of the relevant outcome scale as a covariate. Results were presented as 95% confidence intervals, and not significance tests, following the usual recommendations for pilot/feasibility studies [Lancaster *et al.* 2004].

Results

From the 2 centres, 44 patients between the ages of 18 and 35 years were assessed for eligibility, 36 patients were randomized and 34 patients completed 12 weeks (Figure 1). The three treatment groups appear to be well balanced in terms of mean baseline scores. Both simvastatin and ondansetron provide some evidence of a reduction in symptoms compared with TAU. Summary statistics for the clinical outcome measures are

provided in Table 1. Treatment effect estimates and their confidence intervals are provided in Table 2. The total PANSS scores indicate a greater improvement in simvastatin and ondansetron groups, although 95% confidence intervals include no difference; however, there appears to be little effect on negative symptoms. Differences in CGI between the three groups were negligible; however, there was greater improvement in functioning on the GAF in the simvastatin group in comparison with the ondansetron and TAU groups. Both ondansetron and simvastatin appear to be well tolerated, with little difference between the three groups on AIMS.

Discussion

Schizophrenia is a devastating disorder affecting approximately 1 in a 100 people worldwide at some time [Akhondzadeh *et al.* 2006]. Although, current antipsychotic medications are effective in treating positive symptoms, impact on negative symptoms and cognitive decline is still limited. Our study aimed to explore the adjunct use of simvastatin and ondansetron on positive, negative and general psychopathology in comparison with TAU over a 12-week period in patients with chronic schizophrenia.

A total of 36 patients enrolled in this pilot study with 2 eventually withdrawing, 1 of these providing partial information. Reduction in total symptoms in both simvastatin and ondansetron exceeded the reduction in TAU, although both confidence intervals included 0. On further investigation, it appeared that for both agents this effect was largely as a result of a reduction in positive and general symptoms, rather than negative symptoms.

Anti-inflammatory treatments have been shown to have beneficial effects in schizophrenia. In preliminary clinical trials for schizophrenia Cox-2 inhibitors have shown favourable effects [Muller and Schwartz, 2008]. Statins are primarily HMG-CoA reductase inhibitors commonly used as cholesterol-lowering drugs and have been shown to reduce the incidence of coronary heart disease in clinical trials [Castilla *et al.* 2008; Nassief and Marsh, 2008]. During the past decade, however, evidence has begun to emerge that statins have neuroprotective effects [van der Most *et al.* 2009]. Immune response modulation has been implicated as a neuroprotective mechanism amongst actions such as improvement of blood flow and

Figure 1. Consort flowchart.

reduction in oxidative damage [van der Most *et al.* 2009]. As with Cox-2 inhibitors, the anti-inflammatory properties of statins have shown potential to improve symptoms of schizophrenia.

It has been reported that increased levels of inflammation have been found in many individuals with schizophrenia, leading to the view that immune mechanisms are important components in the pathogenesis of schizophrenia [Dickerson *et al.* 2007]. Fan and colleagues examined CRP levels in 26 inpatients with schizophrenia or schizoaffective disorder and found that higher levels are associated with marked severity in negative symptoms and general psychopathology scales of

PANSS [Fan *et al.* 2007]. Dickerson and colleagues conducted a similar study with a larger sample of 413 patients with schizophrenia [Dickerson *et al.* 2007]. They found that elevated serum levels of CRP in schizophrenia were associated with the severity of cognitive but not psychiatric symptoms. In a recent study, Plenge and colleagues investigated simvastatin's anti-inflammatory effect in a randomized, controlled, double-blind trial [Plenge *et al.* 2002]. They reported that simvastatin lowers highly specific CRP independent of its effect on LDL cholesterol. This finding has also been reported in some earlier studies [Ridker *et al.* 1998; Freeman *et al.* 2001]. To the best of the authors' knowledge, however,

Table 1. Summary statistics.

Baseline scores									
	Simvastatin			Ondansetron			TAU		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
PANSS positive	12	19.08	5.28	12	17.67	4.44	12	20.67	5.63
PANSS negative	12	19.67	4.31	12	21.75	4.54	12	19.92	5.48
PANSS general	12	42.25	13.55	12	41.33	8.80	12	41.58	9.61
PANSS total	12	81.00	22.28	12	80.75	13.89	12	82.17	17.16
CGI	12	4.33	0.98	12	4.42	0.67	12	4.58	1.00
GAF	12	55.80	11.60	12	55.00	9.00	12	52.50	08.70
AIMS	12	0.92	0.90	12	0.83	1.03	12	0.83	0.83
Follow-up scores									
	Simvastatin			Ondansetron			TAU		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
PANSS positive	11	15.45	3.56	11	15.36	4.88	12	18.5	4.10
PANSS negative	11	16.91	4.39	11	16.82	3.16	12	16.92	3.23
PANSS general	11	32.27	6.15	11	32.36	6.14	12	35.83	6.51
PANSS total	11	64.64	11.30	11	64.55	12.00	12	71.25	12.76
CGI	11	4.18	0.75	11	4.18	0.40	12	4.25	0.62
GAF	11	69.10	8.30	11	51.80	4.00	12	53.30	6.50
AIMS	11	0.27	0.47	11	1.09	0.94	12	0.92	1.44
TAU, treatment as usual; SD, standard deviation; PANSS, Positive and Negative Syndrome Scale; CGI, Clinical Global Impression scale; GAF, Global Assessment of Functioning; AIMS, Abnormal Involuntary Movement Scale.									

Table 2. Estimated treatment effects: differences in mean score between treatment and treatment as usual groups at follow up, adjusted for baseline score, for the intention-to-treat sample.

	Simvastatin			Ondansetron		
	Estimate	SE	95% confidence interval	Estimate	SE	95% confidence interval
PANSS positive	-2.69	1.68	-6.12 to +0.73	-2.17	1.73	-5.70 to +1.36
PANSS negative	-0.01	1.53	-3.12 to +3.11	+0.10	1.55	-3.07 to +3.27
PANSS general	-3.63	2.66	-9.05 to 1.80	-3.45	2.65	-8.87 to +1.97
PANSS total	-6.62	5.11	-17.05 to +3.81	-6.63	5.11	-17.07 to +3.81
CGI	-0.04	0.24	-0.54 to +0.46	-0.06	0.24	-0.56 to +0.44
GAF	-0.49	0.28	-1.05 to +0.08	-0.20	0.28	-0.77 to +0.36
AIMS	-0.64	0.45	-1.55 to +0.27	+0.17	0.44	-0.73 to +1.08
SE, standard error; PANSS, Positive and Negative Syndrome Scale; CGI, Clinical Global Impression scale; GAF, Global Assessment of Functioning; AIMS, Abnormal Involuntary Movement Scale.						

there has been no study that has used statins as anti-inflammatory agents in the treatment of schizophrenia.

Ondansetron is a selective 5-HT₃ antagonist used commonly as an anti-emetic in patients with

cancer [Marty *et al.* 1990]. A study conducted by Sirota and colleagues looked at the use of ondansetron in the treatment of neuroleptic-induced tardive dyskinesia [Sirota *et al.* 2000]. They found that ondansetron is beneficial in treating tardive dyskinesia alongside psychotic symptoms in

patients with schizophrenia. Zoldan and colleagues investigated the use of ondansetron in treating psychosis in advanced Parkinson's disease and found it beneficial in control of psychotic symptoms [Zoldan *et al.* 1995]. Small studies, including some randomized clinical trials have shown that as an adjuvant ondansetron can improve negative symptoms and memory in patients suffering from schizophrenia [Ankhonzadeh *et al.* 2009; Levkovitz *et al.* 2005; Zhang *et al.* 2006]. Ankhonzadeh and colleagues recently conducted a 12-week, double-blind study of parallel groups of patients with stable chronic schizophrenia [Ankhonzadeh *et al.* 2009]: 30 patients were recruited from inpatients and outpatients departments. The study found that patients receiving ondansetron as an adjuvant had greater improvement in negative symptoms, general psychopathological symptoms and PANNS scores. Our study results were not inconsistent with their improvements in general psychopathological symptoms and PANSS scores. However, negative symptoms did not appear to improve. Ankhonzadeh and coworkers also found that administration of ondansetron improved visual memory based on improvement in visual reproduction, visual paired associate and figural memory subtests of Wechsler Memory Scale but we did not assess cognition. We found that the drug was very well tolerated and caused no major side effects. Sirota's group speculated that 5-HT₃ antagonists can restore and maintain dopamine function in patients with schizophrenia and may produce an antipsychotic effect without inducing sedation or extrapyramidal symptoms [Sirota *et al.* 2000].

Negative symptoms and cognitive deficits are features of schizophrenia which have a major impact on social functioning and quality of life. Standard drug treatments have little impact on either and arguably no impact on primary negative symptoms. Social dysfunction has a major economic consequence in both the developed and developing world. Further research is required to explore the effects that anti-inflammatory drugs such as simvastatin and selective 5-HT₃ drugs such as ondansetron have in the treatment of schizophrenia.

A major limitation of this study is a small sample size we are now carrying out an appropriately powered study funded by the Stanley Medical Research Institute. This is a double-blind, randomized controlled trial of simvastatin and ondansetron with a factorial design.

Funding

This study was funded by the Pakistan Institute of Learning and Living and the Neuro-Psychiatry Unit at the University of Manchester.

Conflict of interest statement

The author declares that there is no conflict of interest.

References

- Akhondzadeh, S., Mohammadi, N., Noroozian, M., Karamghadiri, N., Ghoreishi, A., Jamshidi, A.H. *et al.* (2009) Added ondansetron for stable schizophrenia: a double blind, placebo controlled trial. *Schizophr Res* 107: 206–212.
- Akhondzadeh, S., Rezaei, F., Larijani, B., Nejatisafa, A., Kashani, L. and Abbasi, S. (2006) Correlation between testosterone, gonadotropins and prolactin and severity of negative symptoms in male patients with chronic schizophrenia. *Schizophr Res* 84: 405–410.
- British National Formulary (BNF) (2012). British Medical Association, Royal Pharmaceutical Society of Great Britain, Edited by Joint Formulary Committee.
- Castilla, G., Del Carmen Fernandez, M., Lopez Chozas, J. and Jimenez, H. (2008) Statins in stroke prevention: what an internist should know. *Eur J Intern Med* 19: 8–14.
- Dickerson, F., Stallings, C., Origoni, A., Boronow, J. and Yolken, R. (2007) C-reactive protein is associated with the severity of cognitive impairment but not of psychiatric symptoms in individuals with schizophrenia. *Schizophr Res* 93: 261–265.
- Fan, X., Pristach, C., Liu, E., Freudenreich, O., Henderson, D. and Goff, D. (2007) Elevated serum levels of C-reactive protein are associated with more severe psychopathology in a subgroup of patients with schizophrenia. *Psychiatry Res* 149: 267–271.
- Freeman, D., Norrie, J., Sattar, N., Neely, R.D., Cobbe, S.M., Ford I. *et al.* (2001) Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. *Circulation* 103: 357–362.
- Guy, W. (1976) *ECDEU Assessment Manual for Psychopharmacology: Revised* (DHEW publication number ADM 76-338). Rockville, MD: US Department of Health, Education and Welfare, Public Health Service, Alcohol, Drug Abuse and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs, pp. 534–537.

- Kay, S., Fisbein, A. and Opler, L. (1997) The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull* 13: 261–276.
- Laan, W., Grobee, D., Selten, J., Heijnen, C., Kahn, R. and Burger, H. (2010) Adjuvant aspirin reduces symptoms of schizophrenia spectrum disorders: results from a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 71: 520–527.
- Lancaster, G., Dodd, S. and Williamson, P. (2004) Design and analysis of pilot studies: recommendations for good practice. *J Eval Clin Pract* 10: 307–312.
- Levkovitz, Y., Arnest, G., Mendlovic, S., Treves, I. and Fennig, S. (2005) The effect of ondansetron on memory in schizophrenic patients. *Brain Res Bull* 65: 291–295.
- Marty, M., Pouillart, P., Scholl, S., Droz, J., Azab, M., Brion, N. *et al.* (1990) Comparison of the 5-hydroxytryptamine₃ (serotonin) antagonist ondansetron (GR 38032F) with high-dose metoclopramide in the control of cisplatin-induced emesis. *N Engl J Med* 322: 816–821.
- Müller, N. and Schwarz, M. (2008) COX-2 inhibition in schizophrenia and major depression. *Curr Pharm Des* 14: 1452–1465.
- Nassief, A. and Marsh, J. (2008) Statin therapy for stroke prevention. *Stroke* 39: 1042–1048.
- Plenge, J., Hernandez, T., Weil, K., Poirier, P., Grunwald, G., Marcovina, S. *et al.* (2002) Simvastatin lowers C-reactive protein within 14 days: an effect independent of low-density lipoprotein cholesterol reduction. *Circulation* 106: 1447–1452.
- Ridker, P., Rifai, N., Pfeffer, M., Sacks, F.M., Moye, L.A., Goldman, S. *et al.* (1998) Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels: Cholesterol and Recurrent Events (CARE) Investigators. *Circulation* 98: 839–844.
- Sirota, P., Mosheva, T., Shabtay, H., Giladi, N. and Korczyn, A. (2000) Use of the selective serotonin 3 receptor antagonist ondansetron in the treatment of neuroleptic-induced tardive dyskinesia. *Am J Psychiatry* 157: 2.
- Sirota, P., Mosheva, T., Shabtai, H. and Korczyn, A. (2001) Treating tardive dyskinesia with ondansetron. *J Clin Psychopharmacol* 21: 355–356.
- van der Most, P., Dolga, A., Nijholt, I., Luiten, P. and Eisel, U. (2009) Statins: mechanisms of neuroprotection. *Prog Neurobiol* 88: 64–75.
- White, L., Harvey, P., Opler, L. and Lindenmayer, J. (1997) Empirical assessment of the factorial structure of clinical symptoms in schizophrenia: a multisite, multimodel evaluation of the factorial structure of the Positive and Negative Syndrome Scale. The PANSS Study Group. *Psychopathology* 30: 263–274.
- Zhang, Z., Kang, W., Li, Q., Wang, X.Y., Yao, S.M. and Ma, A.Q. (2006) Beneficial effects of ondansetron as an adjunct to haloperidol for chronic, treatment-resistant schizophrenia: a double-blind, randomized, placebo-controlled study. *Schizophr Res* 88: 102–110.
- Zoldan, J., Friedberg, G., Livneh, M. and Melamed, E. (1995) Psychosis in advanced Parkinson's disease: treatment with ondansetron, a 5HT₃ receptor antagonist. *Neurology* 45: 1305–1308.