Study of Immunotherapy in antibody positive psychosis: feasibility and acceptability (SINAPPS1)

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Dear editors,

Antibodies against N-Methyl D-Aspartate Receptor (NMDAR) and other neuronal cell surface targets are recognised associations of immunotherapy-responsive autoimmune encephalitis. Initially patients present with symptoms of behavioural change and psychosis, often subsequently developing seizures and cognitive impairment, rapidly progressing over a few weeks to develop a life threatening combination of autonomic instability and loss of consciousness[1]

There is in vitro and in vivo evidence that these antibodies are pathogenic and directly cause encephalitis. Although never formally demonstrated in a controlled trial, open label clinical studies show that patients receiving immunotherapy, such as intravenous immunoglobulins (IVIG) or plasma exchange (PLEX) with or without corticosteroids, have better recovery and reduced relapse rates. Therefore clinical consensus guidelines recommend immunotherapy is given as soon as possible after diagnosis[2].

Several studies have assessed the prevalence of these antibodies in purely psychiatric presentations. NMDAR antibodies are the most commonly identified; in some studies these are twice as prevalent in patients with early psychosis than in healthy controls, being seen at rates of between 4-12% of cases (OR 2.70, CI 1.11-6.56)[3] We have seen a number of such cases respond to immunotherapy in an uncontrolled study.[4] We have therefore proposed a randomised, placebo controlled trial of immunotherapy in psychosis associated with anti-neuronal antibodies, to inform clinical practice and to advance understanding of the pathogenicity of these antibodies in psychiatric illness (called “SINAPPS2”). We chose intravenous immunoglobulin as the acute treatment to induce remission because a survey revealed that it was more readily available than plasmapheresis across centres. Subsequently, rituximab aims to maintain remission for six months, meeting the operational criteria for symptomatic recovery, the primary outcome.

Concerns were raised about the safety and tolerability of people with psychosis receiving intravenous immunoglobulin within an acute hospital setting. To address this, we conducted the “SINAPPS1” trial. This was a multi-centre study of the feasibility and safety of delivering of intravenous immunoglobulin (IVIG; 2g/kg) over 2-4 days within two weeks of the decision to treat. The primary outcome was the

proportion of patients whose first infusion occurred within two weeks from the decision to treat. Importantly, we allowed investigators discretion to change the immunotherapy if they judged IVIG was unsafe, or would not be tolerated, to local standard of care (which could include plasmapheresis or steroids alone).

Participants were recruited at 5 neurology units in England. Inclusion criteria were age over 18 years, presence of psychosis symptoms for at least one week, at first episode or relapse and specified antibodies (NMDAR, VGKCC, LGI1, Caspr2, GABA(A)R in serum or cerebrospinal fluid at a threshold considered likely clinically relevant.

Exclusion criteria were current psychosis episode duration greater than 24 months, severe neurological disease, contraindications to IVIG. Concomitant treatments (i.e. antipsychotics) were not modified by the study team. Participants were assessed again within two months of the last treatment session.

The study received approval by the South Central - Oxford C Research Ethics Committee (REC reference 15/SC/0219). All participants provided written informed consent or consultee consent for those lacking capacity.

RESULTS (table 1)

10 participants were recruited in 2 sites between October 2015 and June 2017. All participants were on antipsychotics (risperidone 3, olanzapine 3, aripiprazole 2, haloperidol 2); other medications included clonazepam (3), Escitalopram (1), Lorazepam (1) and Zopiclone (1). Three centres failed to recruit any patients.

All 10 patients received immunotherapy, 9 out of 10 (90%) within 14 days of treatment allocation. Although all patients were allocated to receive IVIG, only four actually received it and six underwent plasmapheresis (with four of these also receiving steroids). All patients completed the prescribed treatments. There were no reported adverse events during treatment. One patient who had received IVIG had a subsequent pulmonary embolism. There were no concerning behaviours during the treatments.

Each patient improved with respect to their psychotic symptoms and /or functioning between baseline and follow up. (supplementary data)The mean change in total PANSS score from 92.4 (sd 37.2) to 52.7 (sd 13.9); this represents an improvement in symptom severity from being ‘markedly ill’ to being ‘mildly ill’.

Table 1 Participant demographics, investigations and clinical ratings (n=10)

Variable	N (%) Mean (sd)	Median (IQR)
Age, in years	26 (13.8)	22 (20.7, 24)
Gender, female	5 (50%)	
Ethnicity White Black Asian Mixed	 6 (60%) 2 (20%) 1 (10%) 1 (10%)	
Duration of current psychosis episode, in months	13.1 (17.8)	8.5 (1.7, 14.2)
Antibody type and titre threshold: NMDAR 1:100 VGKCC 400pmol/l[1] GABA(A)R 1:50	 5 (50%) 4 (40%) 1 (10%)	
Investigations done/abnormal: EEG Lumbar puncture MRI head	 7(70%)/4(57%)[2] 7(70%)/1(14%)[3] 4(40%)/0 (0%)	
Baseline PANSS[4] Positive symptoms subscale	16.8 (7.9)	16 (11.2, 22.5)
Baseline PANSS[4] Negative symptoms subscale	29.8 (13.8)	31(13.8,41.8)
Baseline PANSS[4] General symptoms subscale	46.9 (18.9)	47.5(32,50)
Baseline GAF score	33.4 (17.2)	32.5 (25.7, 49)
Number of days between last treatment visit to follow-up	46.6 (26.3)	41 (22.5, 71)
Follow-up PANSS Positive scale total score (n=9)	10.3(3.2)	9 (8, 14)
Follow up PANSS Negative symptoms (n=8)	17.4 (5.4)	16.5(14,19)
Follow up PANSS General symptoms (n=8)	23.6(7.2)	23.5(19.8, 24.5)

Follow-up GAF score	61.3 (13.3)	60 (52, 70)

1. Samples were negative for LGI1 and CASPR2 antibodies
2. Excess slow waves(2), diffuse theta delta activity (2)
3. NMDAR antibodies in CSF at 1:10 dilution. No raised WCC or oligoclonal bands

4. Positive and Negative Syndrome Scale (PANSS), a researcher/clinician rating scale for assessment of severity of psychopathology in individuals diagnosed with schizophrenia. Thirty items are rated from 1 (Absent) to 7 (Extreme) based on patient self-report and their family and care workers' reports over the previous two weeks.

5. Global Assessment of Functioning scale (GAF), a researcher/clinician-rated scale for assessment of impairment in functioning by a single rating between 1 (severe life threatening state) and 100 (superior functioning).

The main finding of the SINAPPS1 study is that immunotherapy can be delivered rapidly and safely to people with acute psychosis within an acute hospital setting. The treatments were tolerated and there were no cases of worsening of psychotic symptoms, even with the use of corticosteroids. At one month after presentation, all patients had improved, although an uncontrolled study of this size cannot determine causality; that is the aim of the on-going randomised placebo-controlled SINAPPS2 trial, whose design was influenced by the current trial.

All patients with NMDAR antibodies showed a dramatic improvement, if not complete resolution of psychotic symptoms following treatment. Improvement was less marked for patients with VGKCC or GABA(A)R antibodies; they showed moderate improvement in their psychosis. One explanation for this difference may be that

some of the patients with serum VGKCC antibodies had antibodies that we now know to be clinically irrelevant: against intracellular targets or against the dendrotoxin used in the radioimmunoassay to detect the antibodies[5]. Perhaps this is the case for these two patients, whose moderate improvement reflected the response to antipsychotics only. We no longer screen for VGKCC antibodies, instead testing directly for LGI1 and CASPR2 antibodies in cell-based assays.

This study revealed two striking logistical issues. Firstly, 3/5 sites were unable recruit any patients, because of a lack of screening and identification of patients in surrounding psychiatric services, a lack of availability of either treatment option, a lack of appropriate facilities to provide mental health input into neurological treatment centres, or neurologists choosing not to offer the treatments to patients. This emphasises the importance of having integrated psychiatric and neurological practice to deliver immunotherapy to patients with acute psychosis. Secondly, at the two treating centres there was a predilection of some neurologists to use plasmapheresis over the allocated treatment of IVIG, despite the lack of evidence for differential efficacy. Inadvertently this led to the bias that all patients with NMDAR antibodies were treated with PLEX rather than IVIG, and 3 also receiving a course of steroids.

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REFERENCES

1. Dalmau J, Tüzün E, Wu HY, Masjuan J, Rossi JE, Voloschin A, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol. 2007 Jan;61(1):25-36.

2. Graus F, Titulaer MJ, Balu R, Benseler S, Bien CG, Cellucci T, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 2016;15(4):391–404

3 T. A. Pollak, K. Beck, S. R. Irani, O. D. Howes, A. S. David, P. K. McGuire Autoantibodies to central nervous system neuronal surface antigens: psychiatric symptoms and psychopharmacological implications Psychopharmacology (Berl) 2016; 233: 1605–1621

4 Zandi MS, Deakin JB, Morris K, Buckley C, Jacobson L, Scoriels L, et al. Immunotherapy for patients with acute psychosis and serum N-Methyl D-Aspartate receptor (NMDAR) antibodies: a description of a treated case series. Schizophr Res. 2014 Dec;160(1-3):193-5.

5. Lang B, Makuch M, Moloney T et al Intracellular and non-neuronal targets of voltage-gated potassium channel complex antibodies J Neurol Neurosurg Psychiatry 2016;0:1–9.