Prednisolone addition for patients with recent onset psychotic disorder: the role of immune-modulating strategies in the treatment of psychosis.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Central nervous system infections and inflammations
Study type	Interventional

Summary

ID

NL-OMON46871

Source
ToetsingOnline

Brief title
Prednisolone addition for patients with recent onset psychotic disorder.

Condition

- Central nervous system infections and inflammations
- Schizophrenia and other psychotic disorders

Synonym
psychotic disorder, schizophrenia

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Het Amerikaanse 'Stanley Medical Research Institute'.

Intervention

Keyword: Immune-modulatig treatment, Prednisolone, Psychotic disorder

Outcome measures

Primary outcome

Change in 'Positive and Negative Symptom Scale (PANSS)' total score compared to

baseline.

Secondary outcome

Secundary objectives concern the comparison of the 2 groups with regards to

changes in:

- Positive and Negative Symptom Scale (PANSS) subscales

- Cognitive performance (tested by the 'Brief assessment in cognition', BACS)

- General functioning (tested by Global Assessment of Functioning, GAF)

- Depressive symptoms (tested by Calgary Depression Scale for Schizophrenia)

- Safety data will be evaluated by comparing incidences (number and % of

subjects with at least one occurrence) of key SAEs and SUSARs (e.g.

hospitalisations).

- Changes in immune profile, measured by blood markers.

Study description

Background summary

Schizophrenia is a severe mental disorder with a worldwide prevalence of around 1%, placing significant burnden on global health. Although the introduction of antipsychotic medications in the 1950s has substantially improved clinical symptoms of schizophrenia, the disease is still causing considerable morbidity and mortality. Also patients are affected by substantial impairment in multiple domains of life. Therefore the need for better treatment paradigms is hampered by insufficient knowledge on the underlying disease mechanisms. The pathogenesis of schizophrenia is still far from elucidated. Different lines of evidence now suggest that low grade inflammation in the central nervous system is involved in the pathogenesis of schizophrenia. Such inflammation could cause increased gray matter loss and consequently contribute to more severe negative and cognitive symptoms.

Study objective

We propose to investigate the effect of administering a broad-acting, potent immune suppressive agent early in the course of the disease as this may prevent neuronal damage caused by low-grade inflammatory processes in the brain. It is expected that symptom severity will be improved. Prednisolone predominantly has glucocorticoid capacities and only slight mineralcorticoid potency. It interferes with almost all primary and secondary immune cells, inculding monocytes, microglia cells, T-cells and granulocytes. Furthermore prednisolone can easily pass the blood-brain-barrier, which is a prerequisite to induce immune modulation in the brain. Finally, there is ample clinical experience with prednisolone and its side-effects and safety profiles are well known. Therefore, we propose to investigate the effects of administering the corticosteroid prednisolone versus placebo on psychotic symptoms in addition to standard antipsychotic medication in patients with early stage schizophrenia or related disorders.

Study design

In the current 'proof of concept' study, we aim to investigate the effect of additional treatment with prednisolone on cognition, symptomatic improvement, global functioning and on immunological parameters in patients with early-stage psychotic disorder, applying a randomized double-blind placebo-controlled design. A placebo-controlled design was chosen in order to differentiate between clinical effects of prednisolone and effects associated with experimental treatment, such as induced expectations of participants. Randomization is applied to minimize bias. All 90 patients will be randomized 1:1 to either prednisolone or placebo daily for 6 weeks. During the treatment period, patients will be seen at weekly intervals to assess symptom severity, depressive mood and suicidal ideation, global functioning and side effects. After 6 weeks of treatment, 2 follow-up assessments take place at 4, 6 and 12 months after a patient entered the study.

Intervention

The main investigational product used in this trail is prednisolone, which is approved for systemic treatment of disorders in rheumatology, pulmonology, gastroenterology, endocrinology, hematology, oncology, neurology, dermatology and ophtalmology. Also it is used topically in dermatology and rheumatology. Furthermore, it is used as an immunosuppressant in organ transplantation. In the current study, prednisolone will be administered for six weeks; during the first week patients will use 40mg for 3 days and 30mg for 4 days. In each following week, the dose will be decreased with 5 mg, so patients will use 5mg per day in week 6. In the last 4 days of week 6 they will use 5 mg every other day ((0 mg * 5 mg * 0 mg * 5 mg). After this week they can stop using prednisolone. Additionally, a placebo product is used consisting of an inactive substance (filler), which is visually identical to the prednisolone tablet.

Study burden and risks

The total burden and risks for the patients is based on the following factors:
1. Time investment: the complete study involves 10 visits, with a total time investment of 11 hours. A detailed overview of all protocol procedures and questionnaires can be found in Table 1 of the protocol.
2. Risks due to protocol procedures: these risks are limited to the known risks for venapunction.
3. Side effects of prednisolone. Despite the fact that not all patients will experience side effects, the nature of prednisolones side effects shoudl not be underestimated. All side effects are listed in the SPC as well as an appendix to the Informed Consent Document.

Risks are minimized through:
- Elaborate in- and exclusion criteria
- Implementation of appropriate, pro-active safety measures (e.g. strict monitoring of onset and course of specific side effects)
- Applying specific 'stopping rules', which means that in case patients seem to develop specific side effects, they will be dropped out of the study, after which appropriate follow-up take splace as well as treatment if necessary.
- Prednisolone use is limited to 6 weeks. Of these 6 weeks, the maximum dosage will be given for 1 week. Patients will take 40 mg/daily during 3 days and 30 mg/daily during 4 days.
- Annual review of patient safety and study progress information by the independent Data Safety Monitoring Board.

A complete consideration of risks and burden on the one hand and benefits on the other is provided in section 13.2 'Synthesis' of the structured risk analysis of the protocol.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. DSM-IV-R diagnosis of 295.x (schizophrenia, schizophreniform or schizoaffective disorder) or 298.9 (psychosis NOS).;2. Start of first psychosis no longer than 7 years ago.;3. Age 18-70 years.;4. Patients use a stable dosis of antipsychotic medication for at least 3 weeks.;5. Written informed consent is obtained.;6. Female patients of childbearing potential need to utilize a proper method of contraception in case of sexual intercourse during the study.

Exclusion criteria

1. Presence of any of the contra-indications of prednisolone as reported in the SPC.;2. Presence of diabetes mellitus or random (non-fasting) glucose levels exceeding 11 mmol/L at screening, severe heart failure, severe osteoporosis or systemic fungal infections.;3. Body

Mass Index (BMI) of >30.0;4. Current or chronic use of systemic glucocorticosteroids (temporary use is permitted, if stopped 1 month before start of treatment trial);5. Chronic use of non-steroidal anti-inflammatory drugs (2 months or more of continuous use) ;6. Pregnancy or breast-feeding. ;7. Concurrent use of carbamazepine, riphampicine, primidone, barbiturates and phenytoine ;8. Concurrent use of HAART medication (both HIV protease inhibitors and (non)-nucleoside reverse transcriptase inhibitors), especially efavirenz, ritonavir and lopinavir;9. Current use of telaprevir and boceprevir in treatment of Hepatitis C.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-04-2015
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Prednisolon Mylan
Generic name:	Prednisolone
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	10-07-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	31-07-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	19-03-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	08-01-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	08-02-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	06-10-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	10-10-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	19-10-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	16-11-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO	

Date:	05-01-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	26-01-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	14-03-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
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Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	01-08-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	31-10-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	11-01-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
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Approved WMO Date:	15-05-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-000520-14-NL
CCMO	NL46653.041.14
Other	submissie bij www.clinicaltrial.gov is geinitieerd

Study results

Results posted: 23-03-2021

Actual enrolment: 30

First publication
01-01-1900