Unravelling the mechanism of action of low-dose glucocorticoids: a study of oral versus parenteral glucocorticoids.

No registrations found.

Ethical review	Not applicable
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON26487

Source
Nationaal Trial Register

Brief title
GC-first-pass

Health condition

Reumatoid arthritis, polymyalgia rheumatica, psoriatic arthritis

Sponsors and support

Primary sponsor: VUmc
Source(s) of monetary or material Support: VUmc

Intervention

Outcome measures

Primary outcome

ESR

Secondary outcome

C-reactive protein (CRP), cortisol, adrenocorticotropic hormone (ACTH) and disease activity (based on Rapid3 questionnaire). Stored serum samples may be used for further analysis of inflammatory cytokines as exploratory endpoints.

Study description

Background summary

The mechanism of action of low doses of oral prednis(o)l)one (i.e. ≤7.5 mg) is not clear. Since this dose roughly corresponds to the daily physiological production of glucocorticoids (GCs) by the adrenal gland, a systemic immunosuppressive effect of ≤7.5mg predni(so)lone by virtue of supraphysiological systemic GC concentrations seems very unlikely. We here hypothesise that this immunosuppressive effect is explained by hepatic first-pass effects of oral GC, exposing only the liver to supraphysiological concentrations via the portal circulation. A study addressing this hypothesis is clinically important, as it can provide insight into the mechanism of action of this commonly used GC drug regime, but may also open a new paradigm for anti-inflammatory treatments ('hepatic first-pass targeting') of other sorts. Although it is difficult to directly test this hypothesis in humans, there is an indirect way of doing so: if indeed low dose GCs exert their effect by virtue of a hepatic first pass effect, oral administration should be more effective than systemic administration. We therefore propose to perform a proof-of-concept study in GC treatment-naïve patients with polymyalgia rheumatica (PMR), rheumatoid arthritis (RA) or psoriatic arthritis (PsA). These patients will be randomized to initiate a 4-day course of low dose GC therapy either via the oral or the parenteral route, and then cross over to 4 days via the other route. Before starting this proof-of-concept study, we will first perform a dose-finding study to examine which dose of prednisolone (5, 7.5 or 10 mg) renders a clearly identifiable decrease in Erythrocyte Sedimentation Rate (ESR) within 4 days.

Study objective

The hypothesis is that low dose GC therapy exerts its anti-inflammatory effect by virtue of a first-pass effect through the liver. It is difficult to directly address the hypothesis, but there is an indirect way of doing so: if indeed low dose GCs exert their effect mainly by virtue of a hepatic first pass effect, oral administration should be more effective than systemic administration.

Study design

Measurements will take place at baseline, day 5 and day 9 in the main study.
Measurements will take place at baseline and day 5 in dose-finding study (pilot study).

Intervention

Patients will be randomized to initiate a 4-day course of low dose GC therapy either via the

oral or the parenteral route, and then cross over to 4 days via the other route. Before starting this proof-of-concept study, we will first perform a dose-finding study to examine which dose of prednisolone (5, 7.5 or 10 mg) renders a clearly identifiable decrease in Erythrocyte Sedimentation Rate (ESR) within 4 days.

Contacts

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Eligibility criteria

Inclusion criteria

-Reumatoid arthritis, polymyalgia rheumatica or psoriatic arthritis according to the treating physician
-Elevated ESR (≥30 mm/h)

Exclusion criteria

Difficult to measure a decreased ESR
-Current or recent (<4 weeks previously) on any form of GC therapy
-For reumatoid arthritis and psoriatic arthritis patients, change of antirheumatic medication (DMARDs, biologics) in the 4 weeks before the assessment
-Known with other health conditions that can cause elevated ESR (e.g. hematologic disorders, infections, multiple myeloma, monoclonal gammopathy etc.)

Risk of harm
-Active disease necessitating (change of) treatment within weeks, according to treating physician
-Unstable medical condition causing contra-indication for GC, according to treating physician. For example active infection, unstable diabetes, malignant hypertension, etc.

-Signs or symptoms of temporal arteritis (according to the treating physician)

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-12-2019
Enrollment:	35
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Not applicable

Application type:	Not applicable

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
NTR-new	NL7984
Other	METC VUmc : 71236

Study results