Optimising adalimumab treatment in psoriasis with concomitant methotrexate.

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Primary: *To assess if combination therapy of adalimumab and MTX significantly improves the drug survival at one year compared to adalimumab monotherapy in patients with moderate-to-severe psoriasis.Secondary: *To assess if combination therapy of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Epidermal and dermal conditions
Study type	Interventional

Summary

ID

NL-OMON45239

Source
ToetsingOnline

Brief title
OPTIMAP study

Condition

- Epidermal and dermal conditions

Synonym
psoriasis

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: De studie wordt nagenoeg zonder budget uitgevoerd. Enkele onontkomelijke kosten worden betaald door het Trialteam AMC.

Intervention

Keyword: adalimumab, drug survival, methotrexate, psoriasis

Outcome measures

Primary outcome

*The drug survival at one year. (drug survival by efficacy and drug survival by adverse events)

Secondary outcome

*Efficacy expressed as the proportion of patients achieving PASI 75 and 90 at week 13, 25, 37, 49, 61, 73, 85, 97, 109, 121, 133 en 145 and reduction of absolute PASI at these timepoints;

*Change in PGA (patient global assessment) and IGA (investigator global assessment);

*Average adalimumab serum trough concentrations and ADA titers;

*Change in impact on Quality of life (Skindex 29 and DLQI);

*Occurrence of (serious) adverse events;

*Patient characteristics (age, gender, ethnicity, BMI, PsA, smoking, alcohol use, disease duration, disease severity by PASI, concomitant medication, naïve for biologics versus non-naïve (perhaps specified per biologic), trial medication and potential other co-variates (e.g. genetic polymorphisms).

Study description

Background summary

Psoriasis is a chronic, inflammatory skin disease affecting 2*3% of the Caucasian population in Western countries. It is associated with several

comorbidities, psychosocial impairment and markedly reduced quality of life1. Psoriasis is an immune-mediated inflammatory disorder involving Tcell activation, epidermal hyperplasia and cytokine production. Biologics, like adalimumab, are used for the treatment of psoriasis when traditional treatments such as topical agents, phototherapy and systemic agents (methotrexate, cyclosporine e.g.) have failed or are contra-indicated.

Adalimumab is a fully human monoclonal antibody, which binds to free circulating TNF*, preventing it from activating TNF receptors. It has been proven effective for the treatment of psoriasis 2;3. However in some patients with moderate to severe plaque psoriasis, the efficacy of adalimumab monotherapy is insufficient or declines over time and median drug survival is about 2-2.5 years4;5.
In rheumatoid arthritis (RA) and inflammatory bowel disease a clear relationship has been established between biologic drug serum trough concentrations, the presence of antidrug antibodies (ADA), and efficacy. In psoriasis, one relatively small study has investigated and confirmed the relationship between serum trough concentrations of adalimumab, neutralizing antibodies and effectiveness6. In this study, 45% of patients developed ADA within 12 weeks of starting treatment, and many of these patients had no or an insufficient improvement of psoriasis disease activity. This percentage appears to be higher than in other immune mediated inflammatory disorders, possibly due to the use of a biologic without concomitant methotrexate. In contrast, additional immunosuppressive agents such as methothrexate (MTX) are commonly used in rheumatoid arthritis on biologic therapy. MTX is a systemic therapy that has demonstrated clinical efficacy as monotherapy in patients with psoriasis 3 7;8.

Adding MTX to treatment adalimumab treatment in patients with RA has shown to have a synergistic effect. Efficacy increased and immunogenicity decreased without loss of tolerability in several studies in patients with RA 9-16. At this moment, addition of MTX to adalimumab treatment is standard of care in patients with RA according to the European guidelines. 17
In psoriasis, only two clinical trials investigating a biologic (etanercept) in combination with MTX have been conducted on short term (12 to 24 weeks). For adalimumab in combination with MTX several clinical trials no RCT evidence is available, evidence is based on small observational cohort studies and case reports. The clinical trials, observational studies and case series reports that have been conducted demonstrated an increased clinical efficacy for the combination therapy of TNF* inhibitors plus MTX. Short term adverse events were not different from what would have been expected when using monotherapy. Long term efficacy and safety data are not available although the majority of patients that start on TNF* inhibitors continue treatment for several years.4 Therefore, in order to guide usage of biologic combination treatment in clinical practice it is important to gain long-term efficacy and safety data for TNF* inhibitors plus MTX versus TNF* inhibitor monotherapy. 18-22 With these data guidance and recommendations for treatment with a combination of

adalimumab and MTX could be initiated in future clinical guidelines. 23

Adalimumab has a large inter-individual variability in plasma concentrations (trough concentration range 0-150 mg/l), particularly due to the development of ADA6;20;21;24;25. Some patients initially do not respond well to a specific biologic drug (primary non-responders), or lose response during maintenance treatment (secondary non-responders)6;25-30. Both primary and secondary non-response may be due to pathophysiological, pharmacokinetic (PK) and pharmacodynamic (PD) variability between patients.6;25-30. The most important factor causing inter-individual variability in response to adalimumab appears to be immunogenicity, resulting in ADA, which bind to adalimumab forming small immune complexes, in this way neutralizing the drug. These immune complexes are thought to clear slowly. 31
According to rheumatology data, the early combination of adalimumab and MTX could prevent the decline in efficacy by reducing ADA formation. Therefore, combination therapy could be a valuable strategy to optimize adalimumab treatment of severe or recalcitrant psoriasis. Randomised studies on the use of combination therapies in moderate to severe chronic plaque psoriasis with longer follow-up and larger patient populations are needed24;26;27.

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Study objective

Primary:
*To assess if combination therapy of adalimumab and MTX significantly improves the drug survival at one year compared to adalimumab monotherapy in patients with moderate-to-severe psoriasis.

Secondary:
*To assess if combination therapy of adalimumab and MTX improves the efficacy at 13, 25, 37, 49, 61, 73, 85, 97, 109, 121, 133 en 145 weeks compared to adalimumab monotherapy;
*To assess if combination therapy of adalimumab and MTX leads to a higher average adalimumab trough concentration and lower ADA titers compared with adalimumab monotherapy at 13, 25, 37, 49, 61, 73, 85, 97, 109, 121, 133 en 145 weeks;
*To compare Quality of Life between the combination (adalimumab and MTX) and the monotherapy (adalimumab) group at 13, 25, 37, 49, 61, 73, 85, 97, 109, 121, 133 en 145 weeks;
*To assess the tolerability and safety of the combination therapy compared to the monotherapy group;
*To determine the correlation of certain patient characteristics like age, gender, ethnicity, BMI, PsA, smoking, alcohol use, disease duration, disease severity by PASI, concomitant medication, naïve for biologics versus non-naïve (perhaps specified per biologic), trial medication and potential other co-variates (e.g. genetic polymorphisms) with other endpoints.

Study design

A prospective randomised open label outcome assessor blinded multicentre study.

Intervention

Patients will be randomised 1:1 to adalimumab (per label) with concomitant MTX 10 mg/week and folic acid 5 mg/week (combination therapy group) or adalimumab

per label (monotherapy group).

Study burden and risks

All patients randomised in this study are patients in whom adalimumab therapy is being initiated. They will be randomised in treatment with adalimumab either with or without MTX, Therefore, patients must be eligible for adalimumab and MTX treatment at the time of inclusion. If randomised for the combination treatment group they will receive adalimumab (per label) and concomitant MTX 10 mg/week and folic acid 5 mg/week. MTX therapy will be initiated 2 weeks prior to adalimumab therapy. At each visit the PASI score and IGA will be assessed and patients will be asked for side-effects. The questionnaires PGA, Skindex 29, DLQI need to be filled in and this will require 15 minutes extra time for the patients. At each visit two (extra) blood sample need to be collected for determining antidrug antibodies and drug serum level. At the start of the study, one extra sample will be obtained for pharmacogenetic sampling.
If the patient participates in the extension study (week 49-145) MTX dosing can be adjusted for efficacy or safety reasons. Adalimumab is provided in a standard dose that will not be adjusted throughout the entire study.
The burden and risk of use of MTX is associated with potential side-effects like ulcerative stomatitis, low white blood cell count (and thus predisposition to infection), nausea, abdominal pain, fatigue, fever and dizziness. Potential benefits are that the combination therapy group may achieve a better clinical efficacy and drug survival, resulting in a longer period of optimal response to adalimumab. Based on the reassuring experience with combined MTX and biologic treatment in patients with rheumatoid arthritis it is not expected that safety problems will be an issue during this study.

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

In order to be eligible to participate in this study, a subject must meet all of the following criteria:;*Have a diagnosis of moderate to severe plaque psoriasis (PASI*8 at time of screening);
*Is a candidate for the treatment with biologic drugs according to the pertaining guidelines (NVDV 2011);
*Willing and able to use adequate contraceptives during the study (all men and pre-menopausal women);
*Adalimumab therapy will be started for the treatment of psoriasis
*Signed informed consent.

Exclusion criteria

*History of significant MTX or adalimumab toxicity, intolerability or contraindication
*Prior treatment with adalimumab
*Age < 18 years;
*Pregnant and nursing women.
*other immunosuppressive medication (prednisone, mycofenolaatmofetyl (Cellcept e.g.), ciclosporine (Neoral e.g.), sirolimus (Rapamune), systemic tacrolimus (Prograft e.g.) e.g.)

Study design

Design

Study phase: 4

Study type:	Interventional
Intervention model:	Other
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	31-03-2014
Enrollment:	100
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	folonic acid
Generic name:	folonic acid
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Methotrexate
Generic name:	methotrexate
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	12-12-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-02-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-02-2014

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-02-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-05-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-11-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-04-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
Other	2013-004918-18
EudraCT	EUCTR2013-004918-18-NL
CCMO	NL47129.018.13