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The ideal management of Crohn's disease: top-down versus step-up strategies - a prospective controlled trial in the Benelux

Submission date 19/12/2005	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol
Registration date 19/12/2005	**Overall study status** Completed	[_] Statistical analysis plan [_] Results
Last Edited 03/11/2008	**Condition category** Digestive System	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
NTR379

Study information

Scientific Title

Study objectives
Newly diagnosed Crohn's disease patients will benefit more from a 'top-down' approach where they receive the most potent therapy available, than from the current 'step-up' strategy where they start with the least potent treatment and build up to the most potent therapy if necessary.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Received from the local medical ethics committee

Study design
Multicentre, randomised, active controlled, parallel group trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Crohn's disease

Interventions
Randomisation strategy 1: top-down -
Start infliximab 5 mg/kg three infusions at weeks 0, 2 and 6, and azathioprine 2 - 2.5 mg/kg day from day 0 onwards.
1. If patients improve and tolerate both drugs then continue azathioprine, repeat infliximab 1 infusion 5 mg/kg if relapse
2. If patients respond (decrease of CDAI greater than 50 if CDAI 200 - 250 at start, or greater than 75 if CDAI 250 - 350 at start, or greater than 100 if CDAI at start greater than 350) but do not tolerate azathioprine, even when given as split dose, with meals or as an evening dose, or in case of pancreatitis then stop azathioprine, start methotrexate (MTX) im 25 mg/week for 12 weeks, then taper to 15 mg/week intramuscular (im) together with folic acid 2 mg/day orally (po)
3. If symptoms flare in spite of MTX/azathioprine, repeat infliximab 1 infusion 5 mg/kg
4. If patients do not improve on the above mentioned strategy then cross over to prednisone 40 mg/day or methylprednisolone 32 mg/day at least 4 weeks after the last infliximab infusion, and continue azathioprine (or MTX)
Taper as outlined below.

Randomisation strategy 2: step-up -
First line treatment:
1. Budesonide (Entocort® CIR/Budenofalk® 9 mg per day im for ileal or ileocolonic involvement, or methylprednisone (medrol) 32 mg/prednisone 40 mg per day for colonic involvement alone or in case of severe extraintestinal manifestations (EIM), poor general well-being or fever
2. Antibiotics (Flagyl S® or quinolones) to be added at the discretion of the investigator
3. Initial therapy with intravenous (iv) methylprednisolone for up to 14 days allowed. Total parenteral nutrition (TPN)/enteral nutrition allowed as adjunctive therapy.
If improvement: tapering following guidelines.

Second line treatment:
1. If symptoms flare (increase of CDAI greater than 50 and CDAI greater than 200) during corticosteroid tapering, go back to starting dose and try to taper again. Exclude complications such as abscesses or strictures.
2. If relapse during second attempt to taper, add azathioprine 2 - 2.5 mg/kg/day po
3. If relapse within 4 months after steroid withdrawal, start steroids again, this time in combination with azathioprine
4. If refractory to corticosteroids after 4 weeks, increase the dose to 80 mg of prednisone (64 mg methylprednisolone) and add azathioprine
Adding azathiopine: start 2 - 2.5 mg/kg/day, together full dose of corticosteroids. Try to taper the steroids again according to guidelines.

Third line treatment:
1. Patients with severe adverse events on azathioprine: stop azathioprine, start MTX 25 mg /week. After three injections, start tapering corticosteroids again.
2. Patients who cannot be withdrawn from steroids in spite of azathioprine for at least 4 months in optimal dose: continue azathioprine, start infliximab 5 mg/kg at weeks 0, 2 and 6 without increasing the steroids. Continue to taper steroids after 3 infliximab infusions.

Fourth line treatment:
Patients with severe relapse in spite of MTX or intolerant to azathioprine and MTX: start infliximab 5 mg/kg at weeks 0, 2 and 6. One single 5 mg/kg infusion to be repeated upon relapse of symptoms. Continue MTX if tolerated.

Intervention Type
Drug

Phase
Not Specified

Drug/device/biological/vaccine name(s)
Infliximab, azathioprine, methotrexate (MTX), folic acid, prednisone, methylprednisolone (Medrol), budesonide (Entocort®, Budenofalk®)

Primary outcome(s)
Remission (CDAI less than 150) at 6 months starting at randomisation. The treatment phase of the study will last two years, but follow-up will be extended as long as feasible.

Key secondary outcome(s))
1. Remission (CDAI less than 150) at 9, 12, 15, 18, 21 and 24 months following randomisation
2. Inflammatory Bowel Disease Questionnaire (IBDQ) and European Quality of LIfe instrument (EUROQoL) measured every three months
3. Number of draining fistulas at any point of evaluation
4. Serious adverse events caused by medication with causality assessment (World Health Organization [WHO] criteria)
5. Prednisone/budesonide/prednisolone free days
6. Number of days absent from work, school or normal daily activities due to disease related problems (should also be assessed for the month prior to randomisation)
7. Number and type of surgeries for Crohn's disease or related problems

8. Number of days in the hospital for Crohn's related problems and for any other problems
9. Total cost of medication, surgeries and hospitalisation during the 2 year period and possibly beyond (pharmaco-economic evaluation) and visits to specialist/general practitioner

Completion date
01/02/2006

Eligibility

Key inclusion criteria
1. Men and women aged 16 - 75 years
2. New diagnosis of Crohn's disease (CD), endoscopically and histologically or radiologically (in the case of small bowel disease) proven or diagnosis of Crohn's disease in the previous 4 years but never treated with corticosteroids/budesonide or immunomodulators (azathioprine/6-mercaptopurine/methotrexate/cyclosporin/tacrolimus [FK 506]/mycophenolate mofetil) or biologics (Remicade® or any other investigational drugs)
3. Clinical Disease Activity Index (CDAI) greater than 200 for more than four weeks (to exclude self-limited problems) in new patients or greater than 200 for more than two weeks for patients with known CD
4. Symptoms do not improve with 5-aminosalicylic acid (5-ASA) therapy in appropriate doses (Pentasa® 4 g per day for 6 weeks) or are considered too serious to be treated with 5-ASA alone. Antibiotics can be given at the discretion of the investigator.
5. Willing to sign the informed consent form
6. Ability to comply with study visits and other protocol requirements
7. Women of childbearing potential must be willing to use adequate birth control measures in the 6 month period following each infliximab infusion. If pregnant, they will be excluded from further infliximab infusions.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Key exclusion criteria
1. Need for surgery at diagnosis or in the immediate future: complications such as abdominal abscess or stricture with obstruction
2. Current signs or symptoms of severe, uncontrolled or progressive renal, hepatic, haematologic, endocrine, pulmonary, cardiac, neurologic or cerebral disease
3. Serious infections such as viral hepatitis, pneumonia, pyelonephritis in the last 3 months
4. Recent or ongoing tuberculosis (less than 2 years) or treatment for tuberculosis
5. Less serious infections should be treated appropriately, after which the patient can be included upon the discretion of the investigator
6. Use of biologics, corticosteroids or immunemodulators for other diseases
7. Documented human immunodeficiency virus (HIV) infection

8. Any currently known malignancy or premalignant lesion or any history of malignancy in the last 5 years
Active pregnancy or immediate pregnancy wish; pregnancy should be deferred until at least 6 months after the last infliximab infusion
9. Patient on azathioprine have to continue this medication should they become pregnant during the study
10. Allergy to murine proteins
11. Known recent substance abuse (drugs or alcohol)
12. Symptomatic stenosis or ileal/colonic strictures with prestenotic dilatation
13. Positive stool culture for enteric pathogens

Date of first enrolment
01/05/2001

Date of final enrolment
01/02/2006

Locations

Countries of recruitment
Belgium

Luxembourg

Netherlands

Study participating centre
Academic Medical Centre
Amsterdam
Netherlands
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Sponsor information

Organisation
Academic Medical Centre (AMC) (The Netherlands)

ROR
https://ror.org/03t4gr691

Funder(s)

Funder type
Not defined

Funder Name
Not provided at time of registration

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration