Subcutaneous vedolizumab drug de-escalation using therapeutic drug monitoring in inflammatory bowel disease: a randomized controlled pilot study

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This study has been transitioned to CTIS with ID 2024-517502-28-01 check the CTIS register for the current data. Our explorative pilot study wants to observe whether TDM can attribute to an efficient dose de-escalation strategy of SC vedolizumab in...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON51420

Source
ToetsingOnline

Brief title
SILVER-study

Condition

- Gastrointestinal inflammatory conditions

Synonym
Crohn's disease and ulcerative colitis, inflammatory bowel diseases

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Personalized medicine, Pharmacokinetics, Subcutaneous vedolizumab, Therapeutic drug monitoring

Outcome measures

Primary outcome

To evaluate whether de-escalating subcutaneous vedolizumab using concentration

measurements will be cost-effective compared to the standard dosing regimen.

Secondary outcome

Clinical remission, biochemical remission, number of patients with

exacerbation, quality of life, CRP and faecal calprotectin, pharmacokinetic

aspects, side effect profile and safety.

Study description

Background summary

Crohn*s disease (CD) and ulcerative colitis (UC) are the two main entities of inflammatory bowel disease (IBD). IBD is a chronic inflammatory disorder of the gastrointestinal tract, characterized by a relapsing and remitting course. Because of the high risk of relapse, the majority of patients require maintenance therapy. Subcutaneous (SC) vedolizumab is proven to be an effective maintenance therapy in CD and UC. The recommended dose regimen of SC vedolizumab as a maintenance treatment is 108 mg once every 2 weeks.

Globally, IBD-related costs are increasing, driven by growing costs of expensive medication partly caused by increased use of biologics and small molecules. With the advent of biological agents, a decrease in inpatient and outpatient costs was expected. Contrary to this speculation, a recent systematic review described relatively stable extent of costs during different time periods. It is of utmost importance to reduce the costs of these expensive

biologicals, without increasing the in- and outpatient costs, to decrease the financial burden on hospitals, insurance companies and the government. Therefore, our primary aim will not only focus on the costs of vedolizumab, but also include all IBD-related in- and outpatient costs. We hypothesize that TDM-guided de-escalation will be more cost-effective in daily practice.

Recent studies observed an association between SC vedolizumab serum levels and efficacy in both CD and UC, which raises the idea of implementing therapeutic drug monitoring (TDM) for SC vedolizumab, i.e. dosing based on serum trough concentrations. As most biologics, SC vedolizumab pharmacokinetics vary widely between patients. Due to this diversity, the amount of medication required differs per patient to stay above a certain trough level. Thus, it is conceivable that TDM could be an attractive approach to rapidly extend the dose injection intervals while preserving clinical efficacy.
Our study group developed a population pharmacokinetic model, which allows for individualized SC vedolizumab treatment with a variable injection interval. The model is based on observations from 62 patients with IBD that participated in the vedolizumab IV to SC switch study and gave us the opportunity to make a TDM algorithm. Based on the pharmacokinetic data of the VISIBLE studies, both for CD as UC, we determined a therapeutic threshold for SC vedolizumab of 26 µg/mL. We hypothesize that our TDM algorithm will estimate the timing of the next injection based on vedolizumab concentrations, making personalized medicine possible and probably save costs. In the VISIBLE I trial, the median serum vedolizumab concentration was higher in patients receiving the SC agent (39.8 mg/mL; 90% CI, 20.8-75.4 mg/mL) versus IV dosing (32.2 µg/mL; 90% CI, 16.5-60.7 µg/mL) at a standard dosing regimen. Because of these favourable pharmacokinetics, i.e. higher trough levels, we speculate that the intervals can be safely extended using our algorithm.
Immunogenicity, i.e. the formation of anti-drug antibodies, is uncommon with both SC and IV vedolizumab. However, neutralizing antibodies may arise in patients with sub therapeutic trough levels and are related with reduced treatment efficacy. Therefore, the development of immunogenicity must be prevented. Since we use a TDM algorithm that can prevent sub therapeutic dosing, the risk of immunogenicity and thus loss of response will be minimized.

Study objective

This study has been transitioned to CTIS with ID 2024-517502-28-01 check the CTIS register for the current data.

Our explorative pilot study wants to observe whether TDM can attribute to an efficient dose de-escalation strategy of SC vedolizumab in patients with IBD in order to reduce costs. In this study we will compare costs and clinical efficiency of TDM-guided de-escalation using vedolizumab concentrations versus standard dosing. We expect that overall costs, medical and societal, will be lower in the *TDM-guided de-escalation* strategy. Overexposed patients can de-escalate SC vedolizumab timely, whilst being sufficient to control the

disease with an adequate drug serum levels to maintain remission.

Study design

This study is a single-centre, randomized controlled (1:1), open label pilot study with a duration of 48 weeks. At screening, the following data will be collected: age, gender, diagnosis and classification according to Montreal (age of onset, disease location and behaviour/extent), disease duration, prior medical and surgical history including prior biologic treatment, concomitant medical treatment, body weight and height, smoking status, vedolizumab trough level measurements, anti-drug antibodies against vedolizumab, HBI or SCCAI, FCP, CRP and routine laboratory tests. When patients have undergone one or more of the following screening procedures within 12 weeks before signing the informed consent form in the context of standard care, it is allowed to use these data as screening procedures: routine laboratory tests, vedolizumab serum concentration, anti-drug antibodies against vedolizumab and FCP.

Patients will be randomized 1:1 to either the intervention group (TDM-guided de-escalation strategy) or the control group (standard of care: SC vedolizumab 108 mg every other week).

Patients in the intervention group will reduce SC vedolizumab dose by prolonging the dose-interval using a TDM-algorithm if possible. The SC vedolizumab injection interval will be extended based on vedolizumab concentrations, we maintain a threshold of 26 µg/mL. At baseline, a serum vedolizumab concentration will be measured for all patients. Patients randomized to the intervention group will be de-escalated using TDM algorithm if possible.
The patient draws blood by a finger prick test and sends it to Sanquin for examination of capillary vedolizumab concentration at week 8, 14, 24, 30 and 40. Samples taken at week 8, 24 and 40 are obtained only to verify that the vedolizumab concentration is not decreasing too rapidly. In that case, an adjustment of the interval can be made based on the algorithm to prevent from significant decrease. Samples drawn at week 0, 14 and 30 will be used to adjust the dosing interval of the SC vedolizumab. In the following week, the result will be completed and the study doctor will determine the adjustment of the injection interval. Changes in the injection interval will be made in whole weeks and will not be extended longer than once every 4 weeks.

At 8, 14, 24, 30 and 40 weeks after inclusion, all participating patients will be interviewed via telephone to assess for symptoms and potential disease activity. All questionnaires (SIBDQ, EQ-5D-5L, HBI or SCCAI, cost-questionnaire) will be completed by the patient during or prior to these interviews. All questionnaires will be performed at the outpatient clinic at screening and end of study (after 48 weeks).

Intervention

Based on concentration measurements, the injection interval will be adjusted to every 2, 3 or 4 weeks. During screening, a serum concentration measurement will be performed in all patients, followed by a finger prick in patients in the intervention group after 8, 14, 24, 30 and 40 weeks. There are 3 moments in the study where the injection interval can be adjusted, and extra control moments to prevent the concentration from falling too far.

Study burden and risks

There is a risk of disease flare if the injection interval is prolonged.
However, patients will be closely monitored for clinical and biochemal signs of disease activity and pharmacokinetics to minimize the risk of a disease flare.

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

patients with inflammatory bowel diseases in remission on a stable dose of subcutaneous vedolizumab

Exclusion criteria

presence of anti-drug antibodies against vedolizumab, usage of glucocorticosteroid, active draining peri-anal fistula or imminent need for IBD-related surgery

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	09-02-2023
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Entyvio

Generic name:	vedolizumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	29-09-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-12-2022
Application type:	First submission
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	05-07-2024
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
EU-CTR	CTIS2024-517502-28-01
EudraCT	EUCTR2022-000837-17-NL
CCMO	NL80854.018.22