Algemene gegevens / General Information

Programma / Programme	:	**COVID-19 Programma**
Subsidieronde / Subsidy round	:	**Bottom-up ronde COVID-19 aandachtsgebied 1**
Projecttitel / Project title	:	**COntinuation Versus Interruption of Immunomodulating Drugs in case of an Infectious disease in IMID patients (COVID I2 study), with special attention for COVID-19: a pragmatic, explorative randomized controlled trial.**
Projecttaal / Project language	:	**Engels / English**
Geplande startdatum / Planned start date	:	**13-07-2020**
Geplande duur / Planned duration	:	**24 maanden / months**
Datum indienen / Date of application	:	**13-05-2020**
Projecttype / Project type	:	**Toegepast onderzoek**
Vervolg eerder ZonMw-project / Continuation previously funded project ZonMw	:	**Nee / No**

Projectleden / Project members

Dr. (10)(2e) **MD PhD (Main applicant)**
Functie / Position: reumatoloog - epidemioloog | *Opleiding / Education:*
Studierichting / Subject:
T: (10)(2e) | *F:* | *E:* (10)(2e)@maartenskliniek.nl

Sint Maartenskliniek
Reumacentrum
Postbus 9011
6500 GM NIJMEGEN

M.Sc. (10)(2e) **PhD (Projectleader and secretary)**
Functie / Position: postdoc onderzoeker | *Opleiding / Education:*
Studierichting / Subject:
T: (10)(2e) | *F:* | *E:* (10)(2e)@maartenskliniek.nl

Sint Maartenskliniek
Reumacentrum
Postbus 9011
6500 GM NIJMEGEN

Prof. dr. (10)(2e) **MD PhD (Administrative responsibility)**
Functie / Position: bestuurlijk verantwoordelijke | *Opleiding / Education:*
Studierichting / Subject:
T: (10)(2e) | *F:* | *E:* (10)(2e)n@maartenskliniek.nl

Sint Maartenskliniek
Reumacentrum
Postbus 9011
6500 GM NIJMEGEN

Prof. dr. R. van Crevel MD PhD (Co-Applicant)
Functie / Position: infectioloog-onderzoeker | *Opleiding / Education:*
Studierichting / Subject:
T: (10)(2e) *F:* | *E:* (10)(2e)@radboudumc.nl

Radboudumc
Radboud Center for Infectious diseases
Department of Internal Medicine (463)
Postbus 9101
6500 HB Nijmegen

M.Sc. (10)(2e) **(Co-Applicant)**
Functie / Position: methodoloog | *Opleiding / Education:*
Studierichting / Subject:
T: (10)(2e) *F:* | *E:* (10)(2e)@maartenskliniek.nl

Sint Maartenskliniek
Reumacentrum
Postbus 9011
6500 GM NIJMEGEN

Dr. (10)(2e) **(Co-Applicant)**
Functie / Position: Maagdarmleverarts - onderzoeker | *Opleiding / Education:*
Studierichting / Subject:
T: (10)(2e) | *F:* | *E:* (10)(2e)@radboudumc.nl

Radboudumc
Maag-, Darm- en Leverziekten
Postbus 9101
6500 HB NIJMEGEN

Prof. dr. E. de Jong MD PhD (Co-Applicant)
Functie / Position: dermatoloog- onderzoeker | *Opleiding / Education:*
Studierichting / Subject:
T: (10)(2e) | *F:* | *E:* (10)(2e)@radboudumc.nl

Radboudumc
Dermatologie
Postbus 9101
6500 HB Nijmegen

Projectgegevens / Project information

Aandachtsgebieden / Focus

1.1 Thema's aandachtsgebied 1
- Behandeling
- Risicoanalyse en prognostiek

1.3 Setting
- Ziekenhuiszorg

Samenvatting / Summary

Immunomodulatory Agents (IA, like methotrexate, TNF blocking agents, JAK inhibitors) are widely used for the treatment of the 200,000 patients in the Netherlands with immune-mediated inflammatory diseases (IMIDs), including rheumatoid arthritis, psoriatic arthritis, axial spondylarthritis, psoriasis and inflammatory bowel disease.
There are concerns that infection risk is increased in these patients, especially regarding COVID-19. However, data ars scarce on this matter. More importantly, it is unclear whether in case of infection (COVID-19 or other) it is better to interrupt or continue the IA treatment.
The overarching idea of temporary interruption is that this will lead to a reduced immunosuppressive effect and possibly prevention of further escalation of the infection. However, stopping IA in case of infection might not be the best approach. Firstly, the lower serum concentration might be reached too late to have any impact on course of the infection Also, stopping the IA might evoke a disease flare with subsequent negative effects. Indeed, some clinical data suggest that continuation of IA might be the preferred treatment strategy, at least in some contexts (MTX continuation and reduced surgery related infection, TNFi and reduced sepsis mortality). In case of COVID-19 infection, there are also data – although mostly circumstantial and/or preclinical - that suggest that treatment with specific IA leads to better infection outcomes, including for IL6R blockers, JAK inhibitors, IL-1 blockers, ciclosporin and HCQ.
Therefore, the objectives of the COVID I2 study are:
- to explore the effect of temporary interruption versus continuation of various IA in case of infection (COVID-19, and other infections) on risk for (progression to) serious infection.
- to study risk factors for COVID infection in IMID patients using IA

Trefwoorden / Keywords

COVID-19, inflammatory diseases, Immunomodulatory agents, treatmet interruption, randomised controlled trial

Samenwerking / Collaboration

Samenwerking tussen onderzoek en praktijk / Cooperation between research and practice:

Nee / No

Inhoud / Content

Disciplines / Disciplines

- Infecties, parasitologie, virologie / Infections, parasitology, virology
- Epidemiologie / Epidemiology
- Immunologie, serologie / Immunology, serology
- Reumatologie / Rheumatology

Financiële gegevens / Financial data

ZonMw budget

	Jaar / Year								
Kostenpost	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	**Totaal / Total**
Personeel	(10)(1c)								
Materieel									
Implementatie									
Apparatuur									
Overig									
Totaal / Total									

Co-financiering / Cofinancing

Naam co-financier / Name of cofinancier	Bedrag / Amount	Status
Radboudumc	(10)(1c)	Aangevraagd
Sint Maartenskliniek		Toegekend
Sint Maartenskliniek		Toegekend

Bijzondere gegevens / Additional information

Vergunningen / Permits

	Verklaring nodig / Statement required?		Status verklaring / Statement status		
	Ja / Yes	Nee / No	Verkregen / Acquired	Aangevraagd / Applied	Nog niet aangevraagd / Not applied yet
METC	X			X	
DEC		X			
WBO		X			

Onderschrijvingen / Assents

	Ja / Yes	Nee / No	N.v.t. / N.A.
Code biosecurity / Code Biosecurity		X	
Code openheid dierproeven / Code Transparency of Animal Testing		X	

Andere vergunningen / Other permits

geen

AANVRAAGFORMULIER PROJECTIDEE – BOTTOM-UP RONDE

COVID 19 programma

Deadline voor indiening: 14 mei 2020 (14:00 u)

LEES ALSTUBLIEFT ALLE INSTRUCTIES IN BIJLAGE "TOELICHTING INDIENING PROJECTIDEE" VAN DE OPROEPTEKST ZORGVULDIG!

Wanneer u het formulier heeft ingevuld:

1. **Zet het formulier om naar een PDF file en controleer de details**
2. **Upload het complete formulier als een bijlage bij uw indiening in Projectnet (Let op: dit zijn twee verschillende links, gebruik maar 1 van de 2!)**

ProjectNet: Aandachtsgebied 1 (voorspellende diagnostiek en behandeling)
ProjectNet: Aandachtsgebied 2 (zorg en preventie)

BASISGEGEVENS (voorpagina)

NAAM VAN DE HOOFDAANVRAGER:

Dr. (10)(2e)

ORGANISATIE:

Sint Maartenskliniek

PROJECTTITEL:

COntinuation **V**ersus **I**nterruption of **I**mmunomodulating **D**rugs in case of an **I**nfectious disease in IMID patients (**COVID I2 study**), with special attention for COVID-19: a pragmatic, explorative randomized controlled trial.

DATASTEWARD:

Wie is de datasteward die de open science en FAIR data planning in uw project ondersteunt? Zie de webinars op de ZonMw website om de datastewards te informeren en ondersteunen.

☐ Ik betrek een datasteward bij mijn project:
Naam: Klik of tik om tekst in te voeren.
Instituut: Klik of tik om tekst in te voeren.
E-mail: Klik of tik om tekst in te voeren.
Was aanwezig bij de webinar: ☐ Ja ☐ Nee

☒ Ik heb nog geen datasteward.

ONDERZOEKSVOORSTEL max 3 pagina's A4 (inclusief literatuurreferenties)	(voorpagina met basisgegevens niet meegerekend - font type Arial 10 pts)

1. PROBLEEMSTELLING EN DOELSTELLING(EN):

Immunomodulatory Agents (IA) are widely used for the treatment of patients with immune-mediated inflammatory diseases (IMIDs) including rheumatoid arthritis (RA), psoriatic arthritis (PsA), axial spondylarthritis (axSpA), psoriasis (PsO) and inflammatory bowel disease (IBD). Examples of IA are classic agents such as methotrexate and hydroxychloroquine, biologicals such as the TNF-inhibitors and targeted small molecules like JAK-inhibitors. However, IA use is sometimes associated with a (somewhat) increased risk for infectious disease, and this notion has gained much urgency in light of the recent COVID-19 pandemic. In clinical practice, two important questions especially arise.

1) What are risk factors for infectious disease in general, and especially COVID-19, in IMID patients using IA?
2) Should IA treatment be interrupted or continued when an infection occurs?

With regard to the first question it has been shown that general background infection risk is already somewhat higher in some IMID diseases such as RA. Patients characteristics like age and comorbidities further contribute to a higher risk of infection, and specifically COVID-19. Concerning use of IA, the incident infection risks vary a bit between drug and dosing, but increase in risks are generally low to absent. Some IA seem even associated with decreased specific infection risk by virtue of their antibiotic origins, such as sulfasalazine and hydroxychloroquine (HCQ). The first observational data concerning COVID-19 risk in IMID patients using IA seems cautiously reassuring (1).

The second question, and perhaps even more practically important, is whether the IA should be stopped or not in case infection. In clinical practice, both strategies are used, although generally it is advised (and included in SMPC texts) to interrupt IA treatment in case of (serious) infection. The overarching idea of temporary interruption is that this will lead to a reduced immunosuppressive effect and possibly prevention of further escalation of the infection. However, there are some arguments that stopping IA in case of infection might not be the best approach. Firstly, the lower serum concentration might be reached too late to have any impact on course of the infection Also, stopping the IA might evoke a disease flare with subsequent negative effects. Lastly, some clinical data suggest that continuation of IA might be the preferred treatment strategy, at least in some contexts (MTX and surgery related infection, TNFi and sepsis mortality) (2,3). In case of COVID-19 infection, there are also data – although mostly circumstantial and/or preclinical - that suggest that treatment with specific IA leads to better infection outcomes, including for IL6R blockers, JAK inhibitors, IL-1 blockers, ciclosporin and HCQ (4).

In conclusion, IA of some type and in specific dosages may increase the risk for infection, but estimates for this risk in IMID patients currently being treated with IA, and interaction between risk factors have not been adequately studied. Data on COVID-19 infection risk in IMID patients using IA are scarce but not alarming thus far. Furthermore, it can be concluded that there is equipoise whether temporarily interruption or continuation of IA in case of infection might be the best treatment option.

Therefore, the objectives of the COVID I2 study are:

- to explore the effect of temporary interruption versus continuation of various IA in case of infection (including COVID-19) on risk for (progression to) serious infection.
- to study risk factors for infection (with special interest in COVID-19) in IMID patients using IA

The results of this study will improve outcomes by making informed decision on management of IA in IMID patients, thus resulting in less severe infection, and associated sequelae including hospital admissions, death, loss of quality of life, and costs.

2. PLAN VAN AANPAK:

Design

The COVID I2 study is a multicentre, explorative, open-label randomized controlled trial in the Netherlands among patients with IMIDs using (one or multiple) IA at any dose and without current infection. Participants are (at baseline) randomized 1:1 to a strategy of drug continuation (intervention) or temporary interruption (control) in case of an infection. Patients are followed-up for 12 months from baseline.

We have chosen to perform an explorative randomized controlled trial due to the expected heterogeneity between diseases, types of infection and classes of IA and because of the lack of evidence for any of the subgroups precludes the design of a smaller, more homogenous trial at this time. This trial will inform on the effect between temporary interruption and continuation overall and provide clues for further research into specific subgroups. Randomization is performed to prevent confounding by indication and obtain high quality estimates. Because patients without current infection are recruited, the trial will also inform on the incidence of infection and enable us to study risk factors.

Patients
In this study we will include adult patients with at least one of the following diagnoses: RA, PsA, axSpA, PsO, IBD (ie Crohns Disease {CD} or ulcerative colitis {UC}) and using at least one IA in any dose without current infection. IA agents that are included are classic agents (e.g. methotrexate, hydroxychloroquine), biologicals/biosimilars (e.g. TNF-inhibitors, IL6R-inhitibors) and targeted small molecules (e.g. JAK-inhibitors, PDE4-inhibitors). Agents that are excluded are monotherapy with intravenous rituximab and infliximab, due to long t1/2 times, postkinetic effects (b-cell depletion), and because continuation is cumbersome logistically in a putative infection related hospital setting. Also glucocorticoids are excluded, as stopping is not feasible due to the risk of secondary hypocortisolism. Patient recruitment is inclusive and will be aimed at patients of all (adult) ages, sex, gender, and race.

Treatment strategies
Patients randomized to the control strategy will stop all IA medication as soon as possible in case an infection occurs and until the infection has resolved. This means any clinical infection that is reported by patient and/or physician, independent of location and type (pathogen) with a severity of GRADEs 2 to 4 according to the Common Toxicity Criteria for Adverse Events. We will provide detailed instruction to participants about the situation in which they should interrupt treatment and when to contact the research team. Some infections are excluded, because they are so mild that IA would normally not be stopped. Infection directly related to active IBD are also excluded, because the assumption is that continuation of IA is beneficial for the infection because it treats the underlying cause. IA will be restarted when the signs and symptoms of infection has subsided.
Patients randomized to the intervention strategy will continue the use of their IA medication in case of an infection, in the same dose and interval as before. The IA will also be aimed to be continued in case of hospital admission or intensive care admission. Participants are free to use all other types of medication as needed. As the trial is a pragmatic strategy study, all final treatment decision will be made by shared decision making between patient and health care provider. This notwithstanding, a specific advice how to use the DMARD is provided to the healthcare provider by the study team.

Study procedures
Patients will – after obtaining consent - receive a baseline questionnaire to obtain patient characteristics. At this moment, patients will also be randomised to the continuation or interruption strategy in case an infection occurs. Remaining patient- disease- and treatment characteristics will be obtained from the electronic health record. Furthermore, a monthly follow-up questionnaire about medication use, behavioural and environmental characteristics, occurrence of infections and other adverse events will be sent to participants. In case an infection occurs, an additional questionnaire is completed on the infection characteristics and additional information will be obtained from the electronic health record of the treating facility. Patients will be encouraged to contact the research study team by phone as soon as possible in case of infection and in case the infection has resolved.

Outcome measures
The primary outcome measure is the proportion of participants developing a serious infection (i.e. GRADE 3 or higher) within one year of follow-up. Secondary outcome measures are among others incidence of infection (also looking at incidence of COVID-19 specifically), infection characteristics (type, severity, duration, antibiotic treatment, hospitalization), disease flare (patient reported), other adverse events, medication use and direct costs, and associations between outcome and patient-disease and treatment characteristics.

Sample size
Although this is an explorative study, we did perform a sample size calculation to get insight into the precision of estimates we can obtain when recruiting a convenient sample (the number estimated to be feasible within the centres currently participating and considering study duration and budget limitations). When assuming 5% of patients developing a serious infection and a difference of 2.5% between control and intervention, randomization of 906 patients per group is needed (two sided alpha of 0.05, power 80%). Because of the uncertainty in both the rate of infection, and the effect size and direction thereof, we plan for interim analyses at 50% of evaluable patients. The maximum number of patients to be included in this design is 914 per group. Accounting for 20% drop out or non-adherence, based on the numbers above, the study should include at least 2*914*1.2= 2194 patients. To err on the safe side, a maximum inclusion of 2200 patients is aimed for.

3. HAALBAARHEID VAN HET PROJECT:

TIJDSSCHEMA
May 2020 – June 2020: METC approval (already in progress)

July 2020 – Feb 2022: Patient recruitment and follow-up
March 2022 – June 2022: Analyses and reporting

MOTIVATIE HAALBAARHEID
We think this study is feasible to complete within a two year period. The involved stakeholders (Sint Maartenskliniek and Radboudumc) have access to enough potential participants for the intended study (approximately 10,000 patients). Furthermore, the project team has ample experience in executing multicentre clinical trials. We foresee no problems regarding the current COVID-19 measures as no study visits are required for this trial and these vulnerable patient groups will not have to face any additional risk by coming to the hospital for study measurements. All questionnaires can be completed digitally (or on paper, when preferred by the patient) and contact with the study team will be by telephone.
We intended to perform this study well before the COVID-19 pandemic, but have seen the urgency for answers to our research questions increase sharply in the last months. We have therefore been pro-active in setting up this study, while parallel searching for sufficient funding. At this moment, the study has been submitted to the METC. Qualitative research into the attitude and beliefs of patients and care providers concerning continuation and temporary interruption of IA treatment in case of infection has started which will provide useful insights informing us on the best communication strategy for our trial. Lastly, quick upscaling of the research team involved is possible.

4. RELEVANTIE VOOR DE PRAKTIJK:

The results of this study will guided treatment decisions for 200,000 Dutch IA using IMID patients, resulting in better outcomes of infections, especially COVID-19. As we will perform event rate based pre-planned interim analyses, results will be implementable as soon as possible.
The current context in the Netherland (COVID-19 pandemic, a large well established IA using IMID population, excellent health care infrastructure, and existing collaboration between hospitals and medical specialties), makes an ideal breeding ground for this study to be performed.
Research comparing continuation or temporary interruption of IA in case of infection has, to our knowledge, never been performed. Also there are no ongoing studies on this subject. Therefore, the Dutch Society for Rheumatology has endorsed research into this specific theme and will support this study, and the same will be asked from the dermatology and gastroenterology society. Also, this first and unique study on effects of interruption or continuation of IA in case of infection will certainly be incorporated in (inter)national guidelines on use of IA in IMID patients.
For this research, public funding is paramount, as there are no private stakeholders who have a vested interest in performing this study. Of note, cofounding has been obtained for an amount of 210,000 euro from the Sint Maartenskliniek, and by means of a crowd funding https://www.gofundme.com/f/onderzoek-reuma-medicijnen-en-coronavirus), and another funding request for 240,000 euro has reached the final round (25% success rate).

5. DEELNAME VAN DE STAKEHOLDER(S) (e.g. patiënten, zorgprofessionals, etc.):

The current proposal can only be executed within a collaboration of researchers and physicians from several medical specialties as the project concerns a gap of knowledge for health care providers in different fields all using IA for various conditions. Therefore, we have installed a project group with members from the Sint Maartenskliniek, Radboudumc and LUMC, and from departments of Rheumatology, Dermatology, Gastroenterology, Health Evidence and Infectious Diseases. Additionally, we have recruited two patient research partners and will seek collaboration with regional general practitioners.

6. LITERATUURREFERENTIES (optioneel):

(1) Clinical course of COVID-19 in a series of patients with chronic arthritis treated with immunosuppressive targeted therapies. Monti S, Balduzzi S, Delvino P, Bellis E, Quadrelli VS, Montecucco C. Ann Rheum Dis. 2020 May;79(5):667-668
(2) Methotrexate and early postoperative complications in patients with rheumatoid arthritis undergoing elective orthopaedic surgery. Grennan DM, Gray J, Loudon J, Fear S. Ann Rheum Dis. 2001 Mar;60(3):214-7.
(3) Antitumor necrosis factor therapy is associated with improved survival in clinical sepsis trials: a meta-analysis. Qiu P, Cui X, Sun J, Welsh J, Natanson C, Eichacker PQ. Crit Care Med. 2013 Oct;41(10):2419-29.
(4) Associations between immune-suppressive and stimulating drugs and novel COVID-19-a systematic review of current evidence. Russell B, Moss C, George G, Santaolalla A, Cope A, Papa S, Van Hemelrijck M. Ecancermedicalscience. 2020 Mar 27;14:1022.