ExploriNg DUrable Remission with Rituximab in ANCA-associatEd vasculitis (ENDURRANCE trial): protocol for a randomised controlled trial

Ebru Dirikgil, Jolijn R van Leeuwen, Laura S van Dam, Obbo W Bredewold, Argho Ray, Jacqueline T Jonker, Darius Soonawala, Hilde H F Remmelts, Bastiaan van Dam, Willem Jan Bos, Cees van Kooten, Joris Rotmans, Ton Rabelink, Y K Onno Teng

ABSTRACT

Introduction Both rituximab (RTX) and cyclophosphamide (CYC) are effectively used in combination with steroids as remission induction therapy for patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Several studies have shown that the effect on achieving (clinical) remission, frequency and severity of relapses is equivalent for both therapies, but there is accumulating data that the long-term safety profile of RTX might outperform CYC. Combination of RTX with low-dose CYC (LD-CYC) has been investigated in only a few uncontrolled cohort studies, in which clinical remission and a favourable immunological state with low relapse rates was quickly achieved. In this randomised controlled trial, we aim to investigate whether the combination treatment (RTX+LD CYC) is superior in comparison to standard care with RTX only.

Methods and analysis This study is an open-label, multicentre, 1:1 randomised, prospective study for patients with AAV with generalised disease, defined as involvement of major organs, that is, kidneys, lungs, heart and nervous system. In total, 100 patients will be randomised 1:1 to receive either remission induction therapy with standard of care (RTX) or combination treatment (RTX+LD CYC) in addition to steroids and both arms are followed by maintenance with RTX retreatments (tailored to B-cell and ANCA status). Our primary outcome is the number of relapses needed to maintain clinical remission over 2 years. Secondary outcomes are relevant clinical endpoints, safety, quality of life and immunological responses.

Ethics and dissemination This study has received approval of the Medical Ethics Committee of the Leiden University Medical Center (P18.216, NL67515.058.18, date: 7 March 2019). The results of this trial (positive and negative) will be submitted for publication in relevant peer-reviewed publications and the key findings presented at national and international conferences.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A strength of this study is the open-label study design and the use of well-known, approved study medications (rituximab (RTX) and cyclophosphamide (CYC)) which makes the study easily implementable and operational close to real-life clinical practice.

⇒ Another strength of this study is the predefined per-protocol analysis intended to assess the differential impact of combination therapy RTX+low-dose CYC compared with RTX only.

⇒ A study limitation is the use of a tailored RTX strategy as maintenance therapy, which is not standard practice.

Trial registration number NCT03942887.

INTRODUCTION

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic autoimmune disease characterised by capillaritis or small-vessel vasculitis and the most severe manifestations are kidney failure, lung haemorrhage and cerebritis. Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) are two entities of AAV. Current (inter-)national guidelines recommend, in addition to steroid therapy, to use either cyclophosphamide (CYC) or rituximab (RTX) as remission induction therapy and RTX or azathioprine as maintenance therapy. A previous randomised controlled study on remission induction therapy compared RTX followed by placebo with high-dose oral CYC followed by azathioprine maintenance treatment. Both treatment strategies were equivalent with respect to duration of complete remission, frequency of relapses.
and severity of relapses. The pathophysiology of AAV is closely associated with levels of ANCAAs against proteinase-3 (PR3) or myeloperoxidase (MPO). As such, B-cell depletion with RTX is successfully applied as induction and maintenance treatment in patients with AAV and is increasingly used as induction treatment in the Netherlands. Even in a cohort of patients with relapsing GPA who received dialysis or plasma exchange 12 weeks before treatment started to this multicentre study with a clinical endpoint (negative ANCA status after 24 weeks). It changed to this multicentre study with a clinical endpoint during 2021 as a result of advancing insights and considerable interest from other hospitals in immunomonitoring and the clinical outcomes of this study.

### METHODS AND DESIGN

#### Study design

The study is an open-label, multicentre (university and non-university hospitals), 1:1, prospective study in which 100 patients are randomised to either RTX+LD CYC or RTX alone. The duration of the study is 104 weeks in which patients with AAV will be evaluated for the number of RTX retreatments needed to maintain clinical remission over 2 years, tailored by B-cell and ANCA status and clinical status. Recruitment started in April 2019 and the estimated final completion date is April 2025.

Noteworthy, this study started as a single centre study with a target of 47 patients and a primary immunological endpoint (negative ANCA status after 24 weeks). It is guided by B-cell levels, which is a read-out for detecting a potentially more profound immunological and clinical remission of RTX+LD CYC than RTX alone.

#### Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

#### Study population

Detailed inclusion and exclusion criteria are listed in table 1. Briefly, patients must be adults (≥18 years) with an anti-PR3 or anti-MPO positive GPA and MPA, who required remission induction treatment because of generalised disease. We defined generalised disease as involvement of one of the following major organs: kidneys, lungs, heart or nervous system. Excluded are patients with an unacceptable medical risk and patients who received dialysis or plasma exchange 12 weeks before or during screening or >3000 mg of methylprednisolone 4 weeks before screening.
Study treatments

Patients will be randomised to receive the standard of care with or without LD-CYC infusions (figure 1).

Standard of care

Standard care consists of RTX, pulse steroids and oral steroids. RTX remission induction therapy consists of 1000 mg RTX (or biosimilar) within the first week and a second dosage of 1000 mg 14 days later. Before every infusion of RTX patients will receive intravenous methylprednisolone 100 mg (unless simultaneously administered with pulse steroids) together with oral acetaminophen 1000 mg and intravenous clemastine 2 mg. Pulse steroids consist of one to three pulses of 500 mg methylprednisolone, up to a maximum cumulative dose of 3000 mg, taking into account the 12 weeks before screening. After pulse steroids, oral prednisolone will be given. The recommended tapering is shown in table 2.

Intervention

In addition to the standard care, patients in the intervention arm will receive a total of six infusions of LD-CYC 500 mg intravenously with 2-week intervals. Before every infusion, granisetron will be administered to prevent nausea.

Maintenance therapy

Patients in both treatment arms will receive a tailored regimen for intravenous RTX 500 mg retreatment when one of the following criteria is met after remission induction treatment (ie, 12 weeks and onwards) and clinical remission is achieved: CD19+ counts >5×10⁶ cells/L, ANCA reappearance (eg, conversion from negative to positive) or ANCA-ELISA units doubled from previous nadir. After the study tailored treatment with RTX can be continued or patients can be switched to another immunosuppressive regimen. This decision is left to the discretion of the treating physician.

Rescue therapy

Subjects randomised to the RTX treatment have the option to receive LD-CYC infusions according to the study protocol if the treatment fails. Treatment failure is defined as a relapse, refractory disease or no ability

### Table 1 Inclusion and exclusion criteria of the ENDURRANCE trial

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥18 years of age.</td>
<td>Pregnant or breast feeding.</td>
</tr>
<tr>
<td>Clinical diagnosis GPA or MPA consistent with Chapel-Hill Consensus Conference definitions.</td>
<td>Active infection not compatible with start of remission-induction therapy.</td>
</tr>
<tr>
<td>Newly-diagnosed or relapsed AAV with generalised disease requiring induction treatment with cyclophosphamide or rituximab.</td>
<td>Positive HIV antibody test or positive serology for hepatitis B or C.</td>
</tr>
<tr>
<td>Positive test for anti-PR3 or anti-MPO (current of historic).</td>
<td>Significant infection history that would make the candidate unsuitable for the study.</td>
</tr>
<tr>
<td>Willing and able to give written informed consent.</td>
<td>History of a primary immunodeficiency.</td>
</tr>
<tr>
<td>IgG&lt;4.0 g/L or IgA&lt;0.1 g/L.</td>
<td>Neutrophils&lt;1.5×10⁹/L.</td>
</tr>
<tr>
<td>AST, ALT, alkaline phosphatase or bilirubin &gt;3 times the upper limit of normal.</td>
<td>History of a primary immunodeficiency.</td>
</tr>
<tr>
<td>Other clinically significant abnormal laboratory value.</td>
<td>Dialysis or plasma exchange within 12 weeks prior to screening.</td>
</tr>
<tr>
<td>Immunisation with a live vaccine 1 month before screening.</td>
<td>&gt;3000 mg of methylprednisolone equivalent, within 4 weeks prior to screening.</td>
</tr>
<tr>
<td>Any medical condition or disease which causes an unacceptable risk for study participation.</td>
<td>Immunisation with a live vaccine 1 month before screening.</td>
</tr>
<tr>
<td>History of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies.</td>
<td>Any medical condition or disease which causes an unacceptable risk for study participation.</td>
</tr>
<tr>
<td>History of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies.</td>
<td>Any medical condition or disease which causes an unacceptable risk for study participation.</td>
</tr>
</tbody>
</table>

AAV, ANCA-associated vasculitis; ALT, alanine transaminase; ANCA, antineutrophil cytoplasmic antibody; AST, aspartate aminotransferase; ENDURRANCE, Exploring Durable Remission with Rituximab in ANCA-associated vasculitis; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase-3.
to complete RTX administration of 1000 mg two times. Relapse is defined as worsening of disease, after having previously achieved remission (Birmingham Vasculitis Activity Score (BVAS)=0), requiring reinduction therapy that involves: (1) One or more major items in BVAS or (2) Three or more minor items in BVAS or (3) One or two minor items in BVAS recorded at two consecutive study visits. Refractory disease is defined as (1) unchanged or increased BVAS within 4 weeks after start of therapy or (2) less than 50% reduction of BVAS within 6 weeks after start of therapy or (3) chronic, persisting disease activity within 12 weeks after the start of therapy or (4) insufficient treatment response requiring a switch in medication according to the treating physician.

Concomitant medications
At start of treatment all immunosuppressive treatments, other than the study regimen, must be withdrawn prior to receiving RTX or LD-CYC intravenously. During the study all concomitant immunosuppressants are prohibited except for oral and intravenous steroids and intra-articular injections. Also, the use of live vaccines and investigational agents are prohibited during the study. Adequate prophylactic therapy is strongly recommended during the study, including pneumocystis jirovecii prophylaxis, osteoporosis prophylaxis, nausea prophylaxis and gastroprotection. Antiproteinuric agents, statins and non-steroidal anti-inflammatory drugs are allowed. If a female patient is of childbearing potential, appropriate use of effective contraception is recommended.

<table>
<thead>
<tr>
<th>Table 2 Prednisolone taper scheme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone dosage</td>
</tr>
<tr>
<td>Prednisolone 1×60 mg</td>
</tr>
<tr>
<td>Prednisolone 1×40 mg</td>
</tr>
<tr>
<td>Prednisolone 1×30 mg</td>
</tr>
<tr>
<td>Prednisolone 1×20 mg</td>
</tr>
<tr>
<td>Prednisolone 1×15 mg</td>
</tr>
<tr>
<td>Prednisolone 1×12.5 mg</td>
</tr>
<tr>
<td>Prednisolone 1×10 mg</td>
</tr>
<tr>
<td>Prednisolone 1×7.5 mg</td>
</tr>
<tr>
<td>Prednisolone 1×5 mg</td>
</tr>
<tr>
<td>Prednisolone alternating dosage 5 mg and 2.5 mg*</td>
</tr>
<tr>
<td>Prednisolone 1×2.5 mg during*</td>
</tr>
<tr>
<td>Prednisolone alternating dosage 2.5 mg and 0 mg*</td>
</tr>
<tr>
<td>Hereafter prednisolone is stopped*</td>
</tr>
</tbody>
</table>

*Can be personalised to the tolerance of outpatient patients.

<table>
<thead>
<tr>
<th>Table 3 Response criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term</td>
</tr>
<tr>
<td>Clinical remission</td>
</tr>
<tr>
<td>Disease remission</td>
</tr>
<tr>
<td>Sustained disease remission</td>
</tr>
<tr>
<td>Relapse</td>
</tr>
</tbody>
</table>

BVAS, Birmingham Vasculitis Activity Score.

Study endpoints
The study’s primary endpoint is the number of RTX retreatments needed to maintain clinical remission over 2 years, based on CD19+B-cell status and ANCA status, in both arms.

Secondary objectives are assessing safety, quality of life, clinical responses and immunological responses. Safety is assessed by recording adverse events according to WHO toxicity criteria, infectious events, serious hypersensitivity or infusion reactions and malignancies. In accordance to Good Clinical Practice guidelines, serious adverse events and Suspected Unexpected Serious Adverse Reaction (SUSARs) will be reported to the Medical Ethics committee Leiden The Hague Delft (METC-LDD). Quality of life will be assessed by the AAV-PRO (AAV patient-reported outcome) questionnaire and the SNOT-22 (sino-nasal outcome test) questionnaire.

The clinical endpoints for disease activity will be assessed by BVAS scores, Vasculitis Damage Index (VDI) scores and physician global assessment scores. In addition, concomitant immunosuppressants, remission and relapse rates and clinical biomarkers including kidney function will be recorded and assessed. Criteria used for remission and relapse are listed in table 3. Durable immunological response will be assessed by recording of time to an ANCA negative test as measured by a high quality ELISA, recording of time to ANCA return (defined as seroconversion to positive on at least two consecutive visits or doubling of ANCA serum levels compared with a previously achieved nadir) and recording of duration of B-cell depletion defined as time taken to detect a repopulation of B-cells above the detection limit of standard flow cytometry.

Statistical analyses
To estimate the sample size for the study, we have extracted the number of RTX retreatments from two large, representative studies for each study arm. We used the RTX retreatments from the MAINRITSAN-2 trial for the control arm and data of ANCA negativity and B-cell depletion of the CycLowVas study for the invention arm. RTX+LD-CYC is estimated at an average number of retreatments at 1.86 in 2 years while RTX is estimated
at 3.06 retreatments. With an estimated SD of 2.13, the study requires to randomise 100 patients with AAV in a 1:1 ratio in each treatment arm to achieve a power of 80% with a significance alpha of 0.05. To further corroborate our target study population size, we confirmed that also when a Poisson-regression analysis was used that a study population size of 100 patients had an adequately high power of more than 90% to detect a difference between treatment arms.

Data on demographic and baseline characteristics will be summarised for continuous variables, in case of normal distribution by mean and SD, and in case of non-normal distribution by median and IQR. For discrete variables (eg, race and sex) data will be summarised by proportions (percentages). In general, for continuous data unpaired Student’s t-test will be used to calculate differences between groups for normally distributed data or Mann-Whitney U test for non-normally distributed data. The $\chi^2$ test will be used to compare dichotomized outcomes between the groups. Kaplan-Meier curves will be plotted for time to events analyses (eg, time to ANCA negativity, time to ANCA reappearance).

ETHICS AND DISSEMINATION

The trial will be conducted according to the International Conference on Harmonisation, Good Clinical Practice Guidelines and all other applicable regulatory requirements and adheres to the ethical principles that have their origin in the Declaration of Helsinki.

This study has received approval of the Medical Ethics Committee of the Leiden University Medical Center and all protocol amendments will be noted to this committee. Monitoring and auditing will take place two times a year and a data monitoring committee was not necessary based on the risk factors. A clinical trial insurance is available for patients who suffer harm from trial participation.

Written informed consent will be obtained from all patients and all patients will have the right to withdraw from the study at any time during the trial. Confidentiality of data and biomaterials will be protected by a coding protocol where each participant will receive a specific number. All medical information, blood and urine samples will be coded before collection, usage, storage and publication.

Study information will be publicly available at www.clinicaltrials.gov, and the results of this trial (positive and negative) will be submitted for publication in relevant peer-reviewed publications and the key findings presented at national and international conferences. This paper complies with the Standard Protocol Items: Recommendations for Interventional Trials recommendations for protocol reporting.

DISCUSSION

This study aims to demonstrate a more durable immunological remission after the combination treatment of RTX+LD CYC than after RTX alone. RTX induction treatment was chosen as standard of care because it is recommended in multiple guidelines and even showed a high efficacy in patients with relapsing AAV. There is a strong immunological rationale to study the combination of RTX and CYC because of their differential effect across the B-cell lineage. This favourable immunological state was also demonstrated in three uncontrolled trials. If our study confirms the hypothesis of a more durable immunological remission, the combination treatment will lead to a reduced number of tailored RTX retreatments to remain in clinical remission. Then, this will prove that the combination of RTX+LD CYC is at least equivalent to RTX alone in efficacy in inducing remission and preventing relapses while fewer RTX retreatments over time. As a result, this study will contribute to optimise the treatment strategy for patients with AAV and potentially make treatment cost-effective. However, it is clear that cost-effectiveness is dependent on local health-care organisation to determine if the potential reduction in RTX infusions will outweigh the initial costs of add-on CYC infusions. Moreover, this study will also contribute to insights into the impact of RTX maintenance after RTX-based remission induction therapy. Presently, superior efficacy of RTX as maintenance treatment is only demonstrated after remission was achieved with CYC and several studies are investigating the efficacy of RTX maintenance after remission is achieved with RTX.

At present, this is the first randomised controlled trial comparing remission induction therapy with RTX+LD CYC combined to RTX only. Until now, this combination has been studied in three uncontrolled cohorts. Due to the absence of control groups and randomisation it is not possible to compare the outcomes to any standard of care treatment. However, these trials did demonstrate a favourable immunological state and indicate that the combination is safe. To clearly demonstrate the effect of adding LD-CYC infusions to RTX remission induction therapy, the intervention treatment is completely the same as the standard of care treatment. A dosage of 500 mg of CYC six times was chosen to conform the dosage used in the CycLowVas trial. This is lower than the usual cumulative dosages of 6–16 g of CYC as remission induction therapy (given without addition of RTX), which reduces the risk of long-term toxicity associated with higher cumulative doses. The induction treatment is combined with a relative fast tapering of steroids, because it was substantiated in two cohorts that it is possible to use a reduced cumulative dose of prednisolone when combining RTX+CYC. Steroid dosage and tapering can be adjusted according to the discretion of the treating physician and the cumulative doses will be analysed as one of the secondary outcomes.

In the previous uncontrolled studies the maintenance therapy after RTX+CYC remission induction was not defined and most patients received azathioprine or mycophenolate mofetil as maintenance therapy. In this trial, remission induction therapy will be followed by a tailored
RTX regimen combined with prednisolone tapering. The RTX retreatments will be given tailored on basis of ANCA titres and B-cell count. Although ANCA titres and B-cell counts are not established biomarkers and the predictive value of these parameters is still evolving, they can be safely used for tailoring of RTX as demonstrated in the MAINRITSAN-2 trial. Furthermore, for patients who reached remission after RTX induction treatment, the absence of ANCA titres and B-cell counts was demonstrated to have a high negative predictive value for relapses preventing the potential under-treatment or failure to prevent relapse of patients. Of note, in contrast to the MAINRITSAN-2 trial, no fixed RTX infusion will be given at 6 months because our induction therapy with RTX will already induce B-cell depletion. During this study we will monitor the ANCA titres and B-cell count every 8 weeks, which is more frequent than in the MAINRITSAN-2 trial.

The total number of RTX retreatments to remain in remission will be the primary endpoint of this present study. The rationale underpinning this study is the hypothesis that combination therapy RTX+LD CYC will result in an improved, faster and more durable induction of remission with ‘deeper’ immunological remission. If this null-hypothesis is true this will be expressed in a remission state with longer depletion of B-cells and longer regression of ANCA titres. As the retreatments are protocollar based on these immunological parameters, the number of retreatments will be an objective outcome to test this hypothesis. The incidence of major flares during 2 years of follow-up is expected to be low and therefore an unsuitable primary endpoint to prove superior durable immunological remission. Of course, the clinical status, including flares, will be recorded as secondary outcomes and is frequently assessed during the first months of treatment.

With respect to the sample size calculation aimed to substantiate superiority of RTX+LD CYC, we based our calculations on data of tailored RTX retreatments from the MAINRITSAN-2 trial and reported data of B-cell counts and ANCA titres from the CycLowVas trial. Given that as yet no large, controlled studies have been published on RTX maintenance treatment after remission was induced with an RTX-based regimen, several assumptions had to be made. For the control arm, it needs to be highlighted that MAINRITSAN-2 induced remission with CYC and patients were not B-cell depleted at start of maintenance treatment which instigated a design to initiate maintenance treatment with an RTX infusion. Because patients in the ENDURRANCE study are expected to be B-cell depleted when remission is achieved, maintenance treatment is not automatically initiated with an RTX infusion but tailored according to study protocol. For sample size calculation, it would be unfair to simply subtract one infusion for each patient because it will impact immunological parameters of the primary endpoint and, hence, the frequency of the following RTX infusions.

Heterogeneity between patients with AAV with generalised disease makes it hard to specify results for subgroups or specific patients. At the moment, there is an evidence gap concerning the efficacy of RTX in patients with severe kidney failure and patients with MPO positive AAV. In contrast to the RAVE trial, patients with eGFR below 30mL/min will be included in this study, which will provide more information into the efficacy or RTX-only for this group. Frequent study visits during induction reassure this treatment can be safely studied, with the possibility to switch to rescue therapy when necessary. Since the study is not blinded, there is a risk that physicians might be more inclined to augment the treatment of patients in the RTX-arm, but because the study protocol allows physicians to augment therapy on their own discretion and clinical decision, this is comparable to real-life practice. Patients in the RTX-arm with treatment failure have the opportunity to receive LD-CYC as rescue therapy. At the end of the study, we will perform an intention-to-treat analysis to compare the efficacy of both treatment arms and a per-protocol analysis to study the effect on immunological parameters, corrected for augmentation with LD-CYC in the standard arm. Additionally, as a result of stratification at randomisation, we will be able to compare efficacy of treatment regimens for MPO and PR3 positive patients separately. With regard to patients needing dialysis or plasmapheresis, no new information will be gathered, because these patients are excluded at screening.

During screening, selection bias can occur if physicians decide not to include the most severe patients with AAV in the study, but treat them with RTX+CYC outside of the trial, since RTX and CYC are both commonly available for the treatment of AAV. Consequently, special attention is given to a thorough identification of the source population from which study patients are selected during the recruitment for this study.

In conclusion, the ENDURRANCE study is the first randomised controlled trial to compare remission induction treatment with RTX+LD CYC to RTX only, followed by an RTX tailored regimen based on immunological parameters. If the combination therapy leads to reduced RTX retreatments this will prove RTX+LD CYC is able to induce a more durable immunological and clinical state of remission than RTX therapy only. This will lead to less RTX and CYC toxicity, less chronic damage, less patient burden and possibly reduced treatment costs.

Author affiliations
1Department of Nephrology, Leiden University Medical Center, Leiden, Zuid-Holland, The Netherlands
2Department of Nephrology, Alrijne Hospital, Leiderdorp, Zuid-Holland, The Netherlands
3Department of Nephrology, HagaZiekenhuis, Den Haag, Zuid-Holland, The Netherlands
4Department of Nephrology, Meander Medical Centre, Amersfoort, Utrecht, The Netherlands
5Department of Internal Medicine, St. Antoniusziekenhuis, Nieuwegein, Netherlands
6Department of Nephrology, Leiden University Medical Center, Leiden, Zuid-Holland, The Netherlands
7Department of Nephrology, Alrijne Hospital, Leiderdorp, Zuid-Holland, The Netherlands
8Department of Nephrology, HagaZiekenhuis, Den Haag, Zuid-Holland, The Netherlands
9Department of Internal Medicine, St. Antoniusziekenhuis, Nieuwegein, Netherlands
10Department of Nephrology, Leiden University Medical Center, Leiden, Zuid-Holland, The Netherlands
11Department of Internal Medicine, St. Antoniusziekenhuis, Nieuwegein, Netherlands
Correction notice This article has been corrected since it first published. Author ‘Laura S van Dam’ has been included in the author byline.

Twitter Ebru Dirikgil @LuvacsL and Y K Onno Teng @LuvacsL

Contributors YKOT and TR initiated and designed this study. ED, JRiL and YKOT were involved in the development of the study protocol, preparation of the manuscript and its subsequent revisions and provided final approval of the version published. OWB, AR, JTJ, DS, HHfr, BvD, WJB, CvK and JR provided critical feedback on the manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors approved the final version to be published.

Funding YKOT’s work is funded by the Netherlands Scientific Organisation and the Dutch Kidney Foundation (KJPB12.028 and 170KG04).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Ebru Dirikgil http://orcid.org/0000-0002-5619-8138
Jolijn R van Leeuwen http://orcid.org/0000-0001-9341-7566
Y K Onno Teng http://orcid.org/0000-0001-9920-2195

REFERENCES