Three-month and six-month outcomes of patients with COVID-19 associated hyperinflammation treated with short-term immunosuppressive therapy: follow-up of the CHIC study

Marlou THF Janssen,1 Sofia Ramiro,2,3 Rémy LM Mostard,1 Cesar Magro-Checa,3 Robert BM Landewé1

ABSTRACT

Objectives To prospectively investigate differences in medium-term patient-reported outcome measures and objective functional outcome measures, between patients receiving and those not receiving intensive short-term immunosuppressive therapy for coronavirus disease 19 (COVID-19)-associated hyperinflammation.

Methods Patients previously included in the COVID-19 High-intensity Immunosuppression in Cytokine storm syndrome (CHIC) study who received immunosuppressive treatment versus standard of care for COVID-19-associated hyperinflammation were invited for follow-up at 3 and 6 months after hospitalisation. At both visits, patients were assessed by a pulmonologist, completed quality of life (QoL) questionnaires and performed pulmonary and exercise function tests. At 3 months, patients additionally completed questionnaires on dyspnoea, anxiety, depression and trauma. Outcomes were compared between patients receiving and those not receiving intensive short-term immunosuppressive therapy for COVID-19-associated hyperinflammation.

Results 131 (66.5%) patients survived hospitalisation due to COVID-19-associated hyperinflammation and 118 (90.1%) were included. QoL questionnaires, pulmonary- and exercise function tests showed improvement between 3 and 6 months after discharge, which was similar in both groups. Assessed patients reached levels that were close to levels predicted from the normal population. In contrast, diffusing capacity of the lungs 3 until 6 months after the acute phase of the illness was disturbed in both groups: 69.6% and 68.1% in the control group and treated group, respectively.

Conclusions No differences in medium-term outcomes are demonstrated in survivors of COVID-19-associated hyperinflammation treated or not treated with methylprednisolone with or without tocilizumab during the acute phase. Short-term benefits of this therapy, as showed in the baseline CHIC study analysis, are thus not hampered by medium-term adverse events.

INTRODUCTION

While the coronavirus disease 19 (COVID-19) pandemic is still ongoing, more questions arise about the medium-term and long-term effects of COVID-19.

The pathophysiology, clinical characteristics and the course of the acute phase of the
disease have been extensively described. A proportion of patients with COVID-19 develop a hyperinflammatory state, which leads to an increased risk of respiratory insufficiency and thromboembolic events, and therefore to a higher mortality. Systemic glucocorticoids are now widely used to prevent the occurrence of immunemediated damage in COVID-19 and several trials proved their efficacy in lowering mortality. Furthermore, the use of tocilizumab alone has been shown to improve survival in patients with COVID-19 receiving organ support in the intensive care unit. Hence, glucocorticoids as well as tocilizumab are proven effective in the acute phase of COVID-19-associated hyperinflammation and the WHO recommends their use. However, it remains unknown whether the use of these therapies affects medium-term and long-term outcomes of these patients.

The first 6-month follow-up studies of patients with COVID-19 have been published, showing persisting symptoms of dyspnoea, anxiety and fatigue and, in particular, an impaired diffusion capacity of the lungs until 6 months after the infection. Nonetheless, none of these studies focused on patients with COVID-19-associated hyperinflammation or compared outcomes between patients treated with or without immunosuppression during the acute phase of the disease. In the COVID-19 High-intensity Immunosuppression in Cytokine storm syndrome (CHIC) study, patients with COVID-19-associated hyperinflammation were treated with short-term immunosuppression (high dose methylprednisolone with or without tocilizumab) on-top-of standard of care and outcomes were compared with patients who received standard of care only. The CHIC study was one of the first studies that proved the efficacy of a short but intensive course of immunosuppression in these patients. The homogeneous population of this study, including only patients with COVID-19-associated hyperinflammation, makes it an excellent setting for studying medium-term and long-term outcomes of these patients.

The aim of this study was to compare medium-term patient-reported outcome measures (PROMs) and functional outcomes assessed by pulmonary and exercise function tests in patients receiving and those not receiving intensive short-term immunosuppressive therapy for COVID-19-associated hyperinflammation. Additionally, we aimed at comparing the changes in PROMs and functional outcomes between 3 and 6 months between the two treatment groups.

METHODS

Study design and population

The CHIC study is a cohort study that included patients with COVID-19-associated hyperinflammation in the Zuyderland Medical Centre, the Netherlands, between 1 March 2020 and 17 May 2020 that has been previously described in detail. In summary, patient with COVID-19-associated hyperinflammation were included and it was defined according to a set of criteria: patients had to have an oxygen saturation at rest ≤94% (ambient air) or tachypnoea (>30/min); and patients had to meet at least two out of the following three biomarker criteria: C reactive protein >100 µg/L, serum ferritin >900 µg/L at one occasion or a twofold increase of the level at admission within 48 hours and D-dimer level >1500 µg/L. In March 2020, patients were treated with standard of care of the moment, consisting of oxygen support, antibiotics, chloroquine and anticoagulation (control group). After 1 April 2020, patients were treated according to the CHIC protocol, which was added to standard of care (treated group). This protocol included two steps: (1) intravenous methylprednisolone 250 mg on day 1, followed by methylprednisolone 80 mg intravenously on days 2–5 and an option for a 2-day extension; (2) addition of tocilizumab (single dose, 8 mg/kg body weight intravenous, maximum 800 mg) in case of lack of clinical improvement or worsening in respiratory status 48 hours after starting with methylprednisolone. One hundred ninety-seven hospitalised patients were diagnosed with COVID-19-associated hyperinflammation and were included in the CHIC study (before matching of the patients based on age and gender).

A total of 102 patients were treated with standard of care (control group) and 95 patients were treated according to the CHIC protocol (treated group). Among patients included in the last group, 56 patients received methylprednisolone and 39 patients received methylprednisolone plus tocilizumab during hospitalisation. Of all 197 patients, 47 patients in the control group and 19 patients in the treated group died during hospitalisation for COVID-19 associated hyperinflammation. Online supplemental figure S1 shows the flowchart of how many patients were included in the CHIC study. Patients who survived the hospitalisation were invited for standardised ambulatory follow-up according to the Zuyderland’s Standard of Care (SoC) post-COVID protocol. One patient in the control group and three patients in the treated group died after hospitalisation, but before the first follow-up visit. Patients were excluded if they were unable to visit the outpatient clinic. All patients provided written informed consent for the use of their data for this study.

Data collection

Patients were monitored at the outpatient clinic at 3 months and at 6 months after hospital discharge. Patients were assessed by a pulmonologist, were asked to complete questionnaires and to perform pulmonary and exercise function tests. Baseline characteristics were derived from the CHIC database of all included patients, including World Health Organisation (WHO) score at baseline and oxygen support at baseline. The WHO score consists of seven stages which are:
non-hospitalised, able to resume normal activities; (2) non-hospitalised, but unable to resume normal activities; (3) hospitalised, not requiring oxygen therapy; (4) hospitalised, requiring additional oxygen therapy; (5) hospitalised, requiring high-flow nasal oxygen therapy, non-invasive mechanical ventilation or both; (6) hospitalised, requiring extracorporeal membrane oxygenation, mechanical ventilation or both; and (7) death.

Baseline was considered the day on which patients fulfilled the criteria for COVID-19-associated hyperinflammation during hospitalisation.

**Outcomes**

**PROMs**

The modified Medical Research Council (mMRC) dyspnoea scale was used for assessing patient’s perceived functional limitations of breathlessness. The scale consists of
The questionnaire consists of 14 items with 7 items each for anxiety and depression. A higher score indicates more depression or anxiety symptoms. A score of 8 or more on the subscale anxiety or depression is abnormal.15 16

The questionnaire was used for detecting states of anxiety and depression. The questionnaire consists of 14 items with 7 items each for anxiety and depression. A higher score indicates more depression or anxiety symptoms. A score of 8 or more on the subscale anxiety or depression is abnormal.15 16

The Trauma Screening Questionnaire (TSQ) was used to screen for symptoms of post-traumatic stress disorder. The questionnaire consists of 10 questions. A higher score indicates more symptoms of post-traumatic stress. A score of 6 or more is abnormal.17 18

The EuroQol 5-dimensions 5-levels (EQ-5D-5L) questionnaire was used for measuring quality of life. The EQ-5D comprises five descriptive system questionnaires and a Visual Analogue Scale (EQ VAS). The descriptive system profile can be linked to a value set which leads to a single summary index for health status.16 A higher index and EQ VAS indicate a better QoL. Obtained EQ VAS scores and EQ-5D index scores were compared with Dutch population norms and expressed as a percentage of these norm values.19

The mMRC, HADS and TSQ were completed at the 3-month follow-up visit. The EQ-5D-5L questionnaire was completed at the 3-month and at the 6-month follow-up visit.

Pulmonary and exercise function tests

Forced vital capacity (FVC), total lung capacity (TLC) and diffusing capacity for carbon monoxide (DLCO) were tested with a pneumotachograph (Vyaire Medical, Jaeger, Würzburg, Germany) at 3 and 6 months after discharge. According to the SoC post-COVID protocol repeated DLCO measure was not obligatory in case of a normal DLCO at the first visit. DLCO was measured using the single-breath carbon monoxide uptake. These pulmonary function tests were performed according to the European Respiratory Society (ERS) and American Thoracic Society (ATS) guidelines.20 21 Values were calculated using Global Lung Function Initiative network.
Table 3  Functional outcomes at 3 and 6 months of follow-up and their difference between control (ie, standard care/no immunomodulatory therapy) and treated groups (methylprednisolone with or without tocilizumab)

<table>
<thead>
<tr>
<th>Pulmonary function tests</th>
<th>Three months after discharge</th>
<th>Six months after discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control group (N=52)</td>
<td>Treated group (N=66)</td>
</tr>
<tr>
<td>FVC % predicted</td>
<td>91.7 (15.1)</td>
<td>94.8 (17.5)</td>
</tr>
<tr>
<td>FVC &lt;80% predicted</td>
<td>20</td>
<td>17</td>
</tr>
<tr>
<td>TLC % predicted</td>
<td>89.2 (14.3)</td>
<td>92.4 (15.0)</td>
</tr>
<tr>
<td>TLC &lt;80% predicted</td>
<td>32</td>
<td>13</td>
</tr>
<tr>
<td>DLCO % predicted</td>
<td>73.8 (21.1)</td>
<td>72.7 (17.0)</td>
</tr>
<tr>
<td>DLCO &lt;80% predicted</td>
<td>58</td>
<td>61</td>
</tr>
<tr>
<td>Exercise function test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6MWT (m)</td>
<td>473.4 (124.3)</td>
<td>445.6 (126.6)</td>
</tr>
<tr>
<td>6MWT % predicted distance</td>
<td>74.6 (18.3)</td>
<td>71.4 (19.0)</td>
</tr>
<tr>
<td>6MWT &lt;82 % predicted</td>
<td>65</td>
<td>76</td>
</tr>
<tr>
<td>6MWT lowest satO2 (%)</td>
<td>91.2 (4.0)</td>
<td>90.8 (3.0)</td>
</tr>
<tr>
<td>6MWT satO2 &lt;90%</td>
<td>26</td>
<td>28</td>
</tr>
</tbody>
</table>

Data are presented as % or mean (SD). FVC measurement was performed in 51 control patients and 65 treated patients at 3 months after discharge and in 45 control patients and 52 treated patients at 6 months after discharge. TLC-values were obtained in 50 control patients and 62 treated patients at 3 months after discharge and in 30 control patients and 40 treated patients at 6 months after discharge. DLCO measurement was performed in 51 control patients and 61 treated patients at 3 months after discharge and in 30 control patients and 41 treated patients at 6 months after discharge. 6MWT was performed in 43 control patients and in 54 treated patients at 3 months and in 42 control patients and 47 treated patients at 6 months after discharge.

A 6-minute walk test (6MWT) was performed to objectively evaluate functional exercise capacity at 3 and 6 months after discharge. Saturation with pulse oximetry was continuously measured during the test. 6MWT was performed according to the ERS and ATS guidelines and values were expressed as a percentage of predicted values. A travelled distance of <82% predicted was considered abnormal.

RESULTS

A total of 118 patients were included in this follow-up, having their follow-up at 3 months (66 treated and 52 control patients) and 99 of them had the 6-month follow-up visit (54 treated and 45 control patients). Two patients died before this second follow-up visit: one patient of the treatment group died because of sudden cardiac death (age 66) and one patient of the control group died of an unknown cause (age 84). Online supplemental figure S1 shows the flowchart of patient inclusion.

Table 1 presents the baseline characteristics of the 118 included patients. The mean age was 63 (SD 10) years in the control group and 65 (SD 13) years in the treated group. Patients were men in 83% of the control group and in 79% of the treated group. Body mass index was higher in the control group and diabetes mellitus was more common in the control group. Hypertension was in both groups the most common comorbidity. At the moment of fulfilment of the criteria for hyperinflammation, 44% of the patients in the control group needed an OxyMask/non-rebreathing mask, high flow oxygen or mechanical ventilation during hospitalisation, versus 43% in the treated group, though more patients in the control group were mechanically ventilated (15% vs 2%).

Statistical analysis

Descriptive statistics, namely mean and median values, were used for all outcomes. Differences in outcomes between 3 and 6 months after hospital discharge were computed for each patient and mean values were described. Differences between treatment groups were analysed with the independent samples t-test or Mann-Whitney U test for continuous variables, as appropriate, and with the $\chi^2$ test for categorical variables. Data were analysed with the statistical package SPSS Statistics V.26. A p value ≤0.05 was considered statistically significant.
Differences in PROMs between treated and control groups

Table 2 shows the results of the PROMs. The mMRC was higher in the treated group. The absence of dyspnoea after 3 months, reflected in an mMRC of 0, was reported in 43% of the control patients and 35% of the treated patients (p=0.240). The HADS anxiety and depression scores, as well as the TSQ and the EQ-5D, did not differ between the groups.

In both groups, the EQ VAS was more than 80% of the population norm at 3 months after discharge. At 6 months after discharge, the EQ VAS was 90% and 91% of the population norm in the control and the treated groups, respectively. The EQ-5D index was numerically, but not statistically significantly, higher in the treated group compared with the control group at 3 and 6 months after discharge (p=0.141 and p=0.228, respectively). In both groups the EQ-5D index was more than 85% of the population norm at both 3 months and 6 months after discharge.

Differences in pulmonary and exercise function tests between treated and control groups

Table 3 shows the results of the pulmonary and the exercise function tests. Mean values of the FVC % predicted and the TLC % predicted at 3 and 6 months after discharge were within a normal range and did not differ between the two groups. Mean DLCO % predicted was abnormal both at 3 months and 6 months after discharge in both the treated group (72.7% (SD 17.0) and 73.5% (SD 16.5)) predicted) and the control group (73.8% (SD 21.1) and 69.6% (SD 16.2) predicted). Results of the DLCO % predicted did not differ significantly between the two groups.

Results of the 6MWT did not differ between the two groups neither at 3 months nor at 6 months after discharge. At 6 months after discharge, 21% of the control patients and 19% of the treated patients still had a saturation below 90% during the 6MWT. DLCO % predicted was 61.0 (SD 14.8) and 73.0 (SD 15.9) in the group with and without desaturation during 6MWT, respectively.

Differences in Pulmonary and functional outcomes between 3 months and 6 months between the treated and control groups

Table 4 shows a comparison in the change in QoL, pulmonary function and 6MWT between 3 and 6 months between the two groups. QoL, pulmonary function and 6MWT improved in both groups in the time interval between the two consecutive outpatient visits. Improvement did not differ between the control and the treated groups.

DISCUSSION

This prospective comparative cohort study shows that in survivors of hospitalisation due to COVID-19-associated hyperinflammation, patients treated with standard treatment only and patients treated with short-term immunosuppression on top of standard treatment, did similarly well with regard to medium-term subjective and functional outcomes. The beneficial treatment effects of immunosuppression, as described in the baseline data of the CHIC study, are therefore mainly limited to the first weeks after administration. We did not show differences in prognosis in treated and not treated patients after hospital discharge. Importantly, the short-term beneficial

<table>
<thead>
<tr>
<th>Quality of life</th>
<th>Mean absolute difference between 3 and 6 months in control group*</th>
<th>Mean absolute difference between 3 and 6 months in treated group*</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>EQ VAS</td>
<td>+7.61 (10.1)</td>
<td>+2.24 (12.9)</td>
<td>0.077</td>
</tr>
<tr>
<td>EQ-5D Index</td>
<td>+0.04 (0.1)</td>
<td>+0.06 (0.2)</td>
<td>0.664</td>
</tr>
</tbody>
</table>

Pulmonary function tests

<table>
<thead>
<tr>
<th>FVC % predicted</th>
<th>Mean absolute difference between 3 and 6 months in control group*</th>
<th>Mean absolute difference between 3 and 6 months in treated group*</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>+4.91 (7.5)</td>
<td>+5.19 (6.8)</td>
<td>0.848</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TLC % predicted</th>
<th>Mean absolute difference between 3 and 6 months in control group*</th>
<th>Mean absolute difference between 3 and 6 months in treated group*</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>+2.17 (10.2)</td>
<td>+2.20 (6.9)</td>
<td>0.989</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DLCO % predicted</th>
<th>Mean absolute difference between 3 and 6 months in control group*</th>
<th>Mean absolute difference between 3 and 6 months in treated group*</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>+4.23 (7.7)</td>
<td>+4.05 (5.5)</td>
<td>0.906</td>
<td></td>
</tr>
</tbody>
</table>

Exercise function test

<table>
<thead>
<tr>
<th>6MWT (m)</th>
<th>Mean absolute difference between 3 and 6 months in control group*</th>
<th>Mean absolute difference between 3 and 6 months in treated group*</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>+19.03 (61.9)</td>
<td>+22.40 (74.1)</td>
<td>0.824</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6MWT % predicted distance</th>
<th>Mean absolute difference between 3 and 6 months in control group*</th>
<th>Mean absolute difference between 3 and 6 months in treated group*</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>+4.43 (11.0)</td>
<td>+3.51 (11.0)</td>
<td>0.703</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6MWT lowest satO2</th>
<th>Mean absolute difference between 3 and 6 months in control group*</th>
<th>Mean absolute difference between 3 and 6 months in treated group*</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>+0.03 (3.0)</td>
<td>+0.98 (3.3)</td>
<td>0.181</td>
<td></td>
</tr>
</tbody>
</table>
effects of immunosuppression had not been erased by medium-term adverse events.

In the CHIC study, hospital mortality in the control group was higher compared with the treatment group and therefore survivors of the control group in that study were probably less seriously ill. Nevertheless, the current study demonstrated that 6 months after discharge, patients in the treated group and the control group had the same performance in terms of functional and QoL outcomes.

To our knowledge, this is the first study that assesses medium-term outcomes in patients hospitalised for COVID-19-associated hyperinflammation. This is also the first study that assesses medium-term outcome differences between patients who were treated and not treated with high doses of intravenous glucocorticoids and if needed tocilizumab for this hyperinflammatory state during hospitalisation. Recently, our group already demonstrated that antibody response did not differ between these two groups 3 months after hospitalisation.24

In comparison to the baseline population of the CHIC study, this study contains younger patients and fewer active smokers. This is likely an example of channelling, due to higher mortality in older patients and in active smokers during hospitalisation in the CHIC study population. Older age and smoking are known risk factors for COVID-19-related mortality.25

Main other findings of the study were the considerable proportion of patients with an abnormal DLCO at 3 and 6 months after hospitalisation and the substantial proportion of patients with a desaturation below 90% during the 6MWT. Results of other studies also showed that reduced DLCO was also the most prominent finding 3 to 6 months after hospitalisation for COVID-19.11-13 26 Results of the 6MWT in the current study were compatible with a multicentre prospective cohort study with 113 patients with COVID-19.11 SARS-CoV-2 mainly affects the pulmonary alveoli and the surrounding vascular components.1 The impaired diffusing capacity and the desaturation during 6MWT may be the result of incomplete resolution of this damage. Another possible explanation is that patients had pre-existing diffusion capacity abnormalities, as we did not have baseline pulmonary function tests data.

Remarkable was, despite the abnormalities in pulmonary function and 6MWT, that QoL scores came close to normal population values in both groups. In the first months of 2020, scarce evidence concerning the epidemiology and disease behaviour of COVID-19 and the strict isolation measures confronted the patients with a pronounced psychological burden. A possible explanation for the nearly normal QoL scores could be that these patients were so relieved that they survived hospitalisation, that they put less weight to other outcomes. QoL was assessed in another study with hospitalised patients with COVID-19 6 months after discharge and showed a median EQ VAS of 80, which is slightly higher than in our study. However, the median age in their study was lower and they included also patients with non-severe COVID-19 who did not need supplementary oxygen during hospitalisation.10 The subjective burden of disease seems limited and therefore, although objective abnormalities in terms of DLCO and 6MWT are still present, long-COVID-19 in terms of reduced QoL appears to be rather infrequent in this group of patients who survived severe COVID-19.

Strengths of our study are the prospective design, the homogeneous population and the combination of PROMs and objective outcomes measures. The homogeneous population is strengthened by focusing on patients with COVID-19-associated hyperinflammation and allowing us to generalise conclusions to this restricted population with serious disease. Also, in our study, patients were treated according to a standard protocol, allowing a better comparison of the outcomes between patients treated and not treated with immunosuppression. Not only addresses this study differences between patients treated and not treated for COVID-19-associated hyperinflammation, but it also gives valuable information about the sequelae of this infection in this group as a whole. Limitations of this study include the absence of baseline data regarding pulmonary and exercise function, anxiety, depression and QoL, which is due to the acute and severe nature of the studied disease. Another well appreciated limitation of this study is that not all potentially eligible patients had visited the outpatient clinic after 3 months (118/127 eligible patients) and 6 months (99/116 eligible patients), and that not all patients who had come had completed all questionnaires and performed all pulmonary and exercise function tests. Whether the missing data are derived from patients who were not able to visit the outpatient clinic because of severe impairment or from patients who were fully recovered and waived to perform the tests, is unknown. It could well be that we have presented a relatively favourable reflection of all patients with severe COVID-19. Still, and in spite of potential completers bias, this study demonstrates similar improvements in both groups, as well as a strong tendency to improve to near premorbid conditions in a significant proportion of the patients.

In conclusion, this study shows that among the survivors of hospitalisation for COVID-19-associated hyperinflammation no differences in medium-term outcomes are present in patients treated or not treated with methylprednisolone with or without tocilizumab during the acute phase. This suggests that the beneficial effects of this therapy including reduced mortality, as showed in the baseline analysis of the CHIC study,9 are mainly limited to the first 2 weeks and that these short-term benefits of this therapy are not hampered by medium-term adverse events.

Contributors All authors were fully involved in the preparation of this article. Guarantor: MTHF Janssen

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests SR reports personal fees from Abbvie, personal fees from Eli Lilly, grants and personal fees from MSD, personal fees from Novartis, personal fees from Sanofi, personal fees from UCB, outside the submitted work. RL reports fees from Sanofi, personal fees from UCB, outside the submitted work. RL reports

personal fees from AbbVie, personal fees from Eli-Lilly, personal fees from Novartis, personal fees from Roche, personal fees from UCB, personal fees from Pfizer, personal fees from Jansen, outside the submitted work. RLMM reports personal fees from Roche, personal fees from Boehringer Ingelheim, personal fees from Galapagos, outside the submitted work.

Patient consent for publication Not applicable.

Ethics approval Medical Ethical Committee (METC) and the Board of Zuyderland Medical Centre in Heerlen, the Netherlands. Number: METC202000126.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution (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 Marlou THF Janssen http://orcid.org/0000-0002-8280-9561
Robert BM Landewé http://orcid.org/0000-0002-0577-6620

REFERENCES