Effect of a single dose of the interleukin-6 receptor antagonist tocilizumab on inflammation and troponin T release in patients with non-ST-elevation myocardial infarction: a double-blind, randomized, placebo-controlled phase 2 trial[†]

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Aims	Interleukin-6 (IL-6) contributes to atherosclerotic plaque destabilization and is involved in myocardial injury during ischaemia−reperfusion. Interleukin-6 is therefore a potential therapeutic target in myocardial infarction (MI). We hypothesized that the IL-6 receptor antagonist tocilizumab would attenuate inflammation, and secondarily reduce troponin T (TnT) release in non-ST-elevation MI (NSTEMI).
Methods and results	In a two-centre, double-blind, placebo-controlled trial, 117 patients with NSTEMI were randomized at a median of 2 days after symptom onset to receive placebo ($n = 59$) or tocilizumab ($n = 58$), administered as a single dose prior to coronary angiography. High sensitivity (hs) C-reactive protein and hsTnT were measured at seven consecutive time-points between Days 1 and 3. The area under the curve (AUC) for high-sensitivity C-reactive protein was the primary endpoint. The median AUC for high-sensitivity C-reactive protein during hospitalization was 2.1 times higher in the placebo than in the tocilizumab group (4.2 vs. 2.0 mg/L/h, $P < 0.001$). Also, the median AUC for hsTnT during hospitalization was 1.5 times higher in the placebo group compared with the tocilizumab group (234 vs. 159 ng/L/h, $P = 0.007$). The differences between the two treatment groups were observed mainly in (i) patients included ≤ 2 days from symptom onset and (ii) patients treated with percutaneous coronary intervention (PCI). No safety issues in the tocilizumab group were detected during 6 months of follow-up.
Conclusion	Tocilizumab attenuated the inflammatory response and primarily PCI-related TnT release in NSTEMI patients.
Keywords	Myocardial infarction • Interleukin-6 • Tocilizumab • Inflammation • Acute coronary syndromes

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Introduction

Inflammation is pivotal in all stages of coronary artery disease (CAD),[1] and an increased inflammatory response is associated with worse prognosis in acute coronary syndromes (ACS).[2]

Interleukin-6 (IL-6) is a multifunctional cytokine produced by a spectrum of cells, including cells in the cardiovascular system.[3] In IL-6 signalling, binding of IL-6 to the membrane-bound form of the IL-6 receptor (IL-6R) induces homodimerization of the receptor subunit glycoprotein 130 (gp130), forming a high-affinity functional receptor complex of IL-6, IL-6R, and gp130.[3] In inflammation, IL-6 serves as a secondary downstream mediator of apical cytokines such as IL-1.[4] IL-6 contributes to atherosclerotic plaque development and destabilization,[5] and seems to have a causal role in CAD.[6] IL-6 is also involved in ischaemia−reperfusion (I/R) myocardial injury,[7] and is associated with increased myocardial injury and mortality in ACS patients.[2] In addition, IL-6 is a major inducer of C-reactive protein,[8] and the ability of C-reactive protein to predict unfavourable outcomes in ACS[2] may reflect its ability to mirror upstream activation of IL-6 pathways. Experimental evidence suggests that disrupting IL-6 signalling could exert anti-atherogenic effects.[9] However, no studies have addressed the effects of IL-6 inhibition in human atherosclerotic disease, including ACS and I/R injury following revascularization in these patients.

Tocilizumab is a humanized anti-IL-6R antibody that binds to both membrane-bound and soluble (s) IL-6R.[10] It is effective and generally well tolerated in patients with autoimmune disorders.[11] In this randomized, controlled trial, we investigated the effect of short-time inhibition of IL-6 signalling with tocilizumab in patients with non-ST-elevation myocardial infarction (NSTEMI). We hypothesized that tocilizumab would attenuate the acute inflammatory response, and secondarily reduce troponin T (TnT) release.

Methods

The blood sampling protocol, methods for biochemical analyses and echocardiography protocol are available in the Supplementary material online.

Study design and patients

This two-centre, randomized, double-blind, placebo-controlled trial was designed to evaluate the effect of a single dose of the anti-IL-6R antibody tocilizumab in patients with NSTEMI scheduled for coronary angiography (ClinicalTrials.gov, NCT01491074). The study was performed at Oslo University Hospital Rikshospitalet, Oslo, and St Olavs Hospital, Trondheim, Norway. The study was approved by the Regional Committee for Medical and Health Research Ethics of South-Eastern Norway and the Norwegian Medicines Agency, and conducted according to the Helsinki Declaration. All participants provided written, informed consent.

Patients were included on the day of scheduled coronary angiography. Patients between 18 and 80 years of age with NSTEMI presumed to be due to CAD were eligible for inclusion. Major exclusion criteria were clinically significant cardiac disease other than CAD, clinical instability, diseases or medication affecting inflammation, contraindications to tocilizumab, and any condition that could interfere with protocol adherence.

Baseline blood samples were obtained at inclusion. The patients were then randomized to receive a single intravenous infusion of tocilizumab 280 mg or matching placebo prior to coronary angiography. Patients remained in the study ward for 50 ± 1 h for post-treatment blood sampling (Day 1: evening; Day 2: morning, afternoon, evening; Day 3; morning, afternoon), echocardiography, and safety assessment. Follow-up with blood sampling, safety assessment, and echocardiography (only 6 months) was performed at 3 and 6 months (Supplementary material online, *Table S1*).

Endpoints

The primary endpoint was the between-group difference in the area under the curve (AUC) for high-sensitivity C-reactive protein during hospitalization (days 1−3). The between-group difference in AUC for high-sensitivity TnT (hsTnT) was pre-defined as the most important secondary endpoint. We also analysed within-group differences in absolute values, and between-group differences in changes from baseline at separate timepoints during hospitalization. Other pre-defined secondary endpoints were IL-6-related parameters, N-terminal pro-brain natriuretic peptide (NT-proBNP), routine clinical biochemistry (safety analyses), echocardiographic left-ventricular (LV) ejection fraction (EF) and dimensions, and serious adverse events.

Randomization and treatment allocation

The randomization list was generated using a computerized procedure. Patients were allocated in a 1 : 1 ratio to either tocilizumab or placebo. Descriptions of randomization and masking are available in the Supplementary material online.

Drug dose and administration

A standardized dose of 280 mg tocilizumab was prepared by replacing 14 mL 0.9% NaCl from a 100 mL infusion bag with 14 mL tocilizumab (20 mg/mL). The placebo infusion consisted of 100 mL 0.9% NaCl. The infusions were administered intravenously over 1 h. Pharmacokinetics and pharmacodynamics are described in the Supplementary material online.

Statistics

The primary endpoint was the between-group difference in AUC for high-sensitivity C-reactive protein during hospitalization. Our estimations are based on data from a similar population where C-reactive protein (AUC ≤2 months post ACS) was collected less frequently, but over a longer period.[12] To observe a 50% reduction in the AUC for high-sensitivity C-reactive protein on active treatment when compared with placebo, with an α of 5% and a power of 80%, we needed a total of 98 patients (49 per group). To allow for drop-outs and analyses of secondary endpoints, we aimed to enrol 120 patients.

Detailed description of statistical methods is available in the Supplementary material online.

Results

Baseline characteristics

A total of 121 patients with NSTEMI were enrolled between August 2011 and November 2013. Of these, 117 patients were included in the final analyses (Supplementary material online, *Figure S1*). Follow-up ended in April 2014. Details regarding study drop-outs (n = 6, three in the tocilizumab and three in the placebo group) are provided in Supplementary material online, *Table S2*.

The majority of patients (75%) were initially admitted to their local hospital and subsequently transferred to the trial centres for

scheduled coronary angiography within 72 h. The groups were well matched with regard to baseline characteristics (*Table 1*). Time from symptom onset to study inclusion was similar, and myocardial damage prior to inclusion was modest in both treatment groups. Pharmacological treatment was provided in adherence to prevailing guidelines.[13] We performed coronary angiography in all patients. Percutaneous coronary intervention (PCI) was performed in 47 patients (80%) allocated to placebo and 41 patients (71%) allocated to tocilizumab. In no patients coronary artery bypass grafting was performed during the first 3 days following inclusion.

High-sensitivity C-reactive protein

The median AUC for high-sensitivity C-reactive protein during hospitalization was 2.1 times higher in the placebo than in the tocilizumab group (4.2 vs. 2.0 mg/L/h, $P < 0.001$). The levels of high-sensitivity C-reactive protein increased in the placebo arm, and decreased in the tocilizumab arm during hospitalization (*Figure 1A*). Although the dose of tocilizumab was 280 mg in all patients regardless of weight, the percentage change in high-sensitivity C-reactive protein during hospitalization did not correlate significantly with weight in either the tocilizumab ($r = -0.20$, $P = 0.14$) or the placebo group ($r = -0.03$, $P = 0.80$). The serum levels of high-sensitivity C-reactive protein had returned to normal, and there were no significant between-group differences at 3 and 6 months (Supplementary material online, *Table S3*).

High-sensitivity troponin T

The median AUC for hsTnT during hospitalization was 1.5 times higher in the placebo arm than in the tocilizumab arm (234 vs. 159 ng/L/h, $P = 0.007$). hsTnT increased significantly in the placebo group during the first 24 h, but not in the tocilizumab group (*Figure 1B*). At 3 and 6 months, levels of hsTnT had returned to normal, and there were no significant between-group differences (Supplementary material online, *Table S3*).

The effect of coronary intervention and time from symptom onset

The tocilizumab-induced reduction in high-sensitivity C-reactive protein was more pronounced in patients treated with PCI (*Figure 2A*). The effect of tocilizumab on hsTnT, occurred in these patients only (*Figure 2B*).
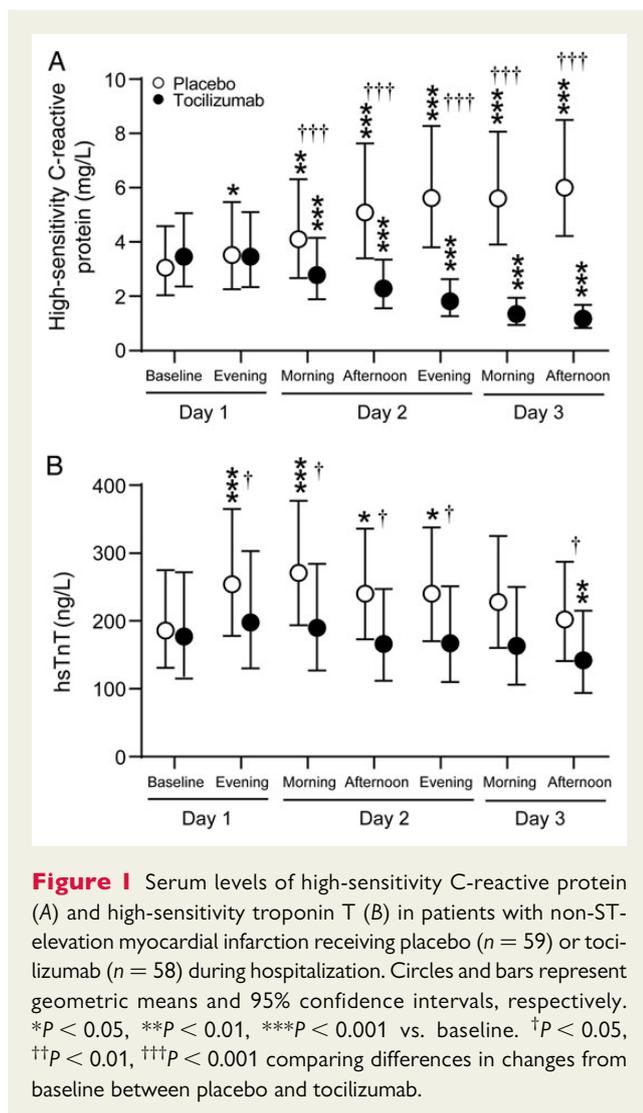
The effect of tocilizumab on high-sensitivity C-reactive protein remained the same regardless of whether time to inclusion was ≤ 2 or > 2 days after symptom onset (*Figure 2C*). However, while there were significant between-group differences in changes from baseline for hsTnT favouring tocilizumab for patients included ≤ 2 days after symptom onset, no difference was observed for patients included > 2 days after symptom onset (*Figure 2D*).

Also in patients included ≤ 2 days from symptom onset, PCI was a major determinant of the between-group difference in hsTnT. Nonetheless, hsTnT was reduced in the active treatment arm also

Table 1 Baseline characteristics according to treatment group

	Placebo (*n* = 59)	Tocilizumab (*n* = 58)	*P*-value
Age, years, mean (SD)	60.1 (9.9)	59.8 (7.7)	0.859
Female, *n* (%)	5 (8.5)	9 (15.5)	0.364
Body mass index, kg/m^2, mean (SD)	27.4 (4.4)	28.8 (3.3)	0.055
Blood pressure, systolic, mmHg, mean (SD)	136.8 (18.0)	139.7 (18.1)	0.389
Blood pressure, diastolic, mmHg, mean (SD)	80.5 (12.1)	82.9 (12.0)	0.273
Hypertension, *n* (%)	17 (28.8)	26 (44.8)	0.109
Diabetes mellitus, *n* (%)	10 (16.9)	11 (19.0)	0.966
Current smoking, *n* (%)	17 (28.8)	15 (26.3)	0.926
Previous myocardial infarction, *n* (%)	7 (11.9)	9 (15.5)	0.760
GRACE score, mean (SD)	90.3 (20.2)	86.3 (19.1)	0.272
Symptom onset to inclusion, days, median (25th, 75th percentiles)	2 (1, 3)	2 (1, 3.5)	0.197
Maximum TnT before baseline, ng/L, *n* = 85, geometric mean (CI)	310 (214–449)	334 (217–514)	0.789
Maximum TnI before baseline, ng/L, *n* = 31, geometric mean (CI)	1571 (517–4773)	2221 (826–5976)	0.626
Aspirin, *n* (%)	59 (100)	57 (98.3)	0.496
Clopidogrel, *n* (%)	32 (54.2)	32 (55.2)	1.0
Ticagrelor, *n* (%)	27 (45.8)	26 (44.8)	1.0
Low molecular weight heparin, *n* (%)	54 (91.5)	51 (89.5)	0.952
Statin, *n* (%)	53 (89.8)	53 (91.4)	1.0
Beta-blocker, *n* (%)	45 (76.3)	45 (77.6)	1.0
PCI, *n* (%)	47 (79.7)	41 (70.7)	0.367
Stents per PCI-treated patient, mean (SD)	1.85 (1.28)	1.85 (1.15)	0.982
CABG, *n* (%)	7 (11.9)	6 (10.3)	1.0
Medical treatment, *n* (%)	5 (8.5)	11 (19.0)	0.167
SYNTAX score, median (25th, 75th percentiles)	8.0 (5, 14)	8.0 (4, 18)	0.629

TnT, troponin T; TnI, troponin I; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

Figure 1 Serum levels of high-sensitivity C-reactive protein (*A*) and high-sensitivity troponin T (*B*) in patients with non-ST-elevation myocardial infarction receiving placebo (*n* = 59) or tocilizumab (*n* = 58) during hospitalization. Circles and bars represent geometric means and 95% confidence intervals, respectively. *P < 0.05, **P < 0.01, ***P < 0.001 vs. baseline. †P < 0.05, ††P < 0.01, †††P < 0.001 comparing differences in changes from baseline between placebo and tocilizumab.

in patients included ≤2 days after symptom onset who were not treated with PCI. However, the number of patients in this subset of patients was small (*n* = 9 tocilizumab, *n* = 5 placebo) (Supplementary material online, *Table S4*).

The effect of GRACE and SYNTAX scores

Disease severity as quantified by GRACE or SYNTAX scores did not confound the effect of tocilizumab on levels of high-sensitivity C-reactive protein. However, for hsTnT there were significant between-group differences in changes from baseline in favour of tocilizumab at a few timepoints in patients with low GRACE and low SYNTAX scores, but not in patients with high scores (Supplementary material online, *Tables S5* and *S6*).

Mediators in the IL-6 system during follow-up

In the placebo group, there was a modest but significant increase in IL-6 levels. In the tocilizumab group, however, there was a pronounced increase in IL-6 that persisted during hospitalization. The between-group differences in changes from baseline were significant

throughout hospitalization (Supplementary material online, *Figure S2A*). Whereas IL-6R did not change in the placebo group, there was a substantial, gradual increase in IL-6R in patients allocated to tocilizumab. Again, the between-group differences in changes from baseline were significant throughout hospitalization (Supplementary material online, *Figure S2B*). In contrast, the groups did not differ with regard to changes in sgp130 during hospitalization (Supplementary material online, *Figure S2C*).

There were no between-group differences in IL-6 parameters at 3 and 6 months (Supplementary material online, *Table S3*).

The effect of tocilizumab in relation to baseline interleukin-6 levels

Using univariate regression with log high-sensitivity C-reactive protein AUC as the dependent variable and tocilizumab, log baseline levels of high-sensitivity C-reactive protein and IL-6 and the interaction log IL-6 baseline × tocilizumab as independent variables; we detected a trend ($P = 0.049$) towards an interaction between IL-6 and tocilizumab on high-sensitivity C-reactive protein. The difference between the treatment arms was more pronounced in the patients with the highest levels of IL-6 at baseline (Tertile 3, median high-sensitivity C-reactive protein AUC: 25.7 vs. 2.6 mg/L/h, $P = 0.03$ for placebo vs. tocilizumab; Tertile 1, median high-sensitivity C-reactive protein AUC: 2.2 vs. 1.1 mg/L/h, $P = 0.12$). There was no interaction between IL-6 and tocilizumab regarding hsTnT ($P = 0.74$).

Interleukin-1β

Evidence suggests that IL-1β is an up-stream inducer of IL-6 in MI.[14] Overall, IL-1β levels decreased significantly in both groups from baseline, and there were no between-group differences in changes from baseline during hospitalization (Supplementary material online, *Table S7*).

Associations between changes in key biomarkers during hospitalization

In both treatment arms, changes in hsTnT were significantly associated with changes in high-sensitivity C-reactive protein levels, but not with changes in IL-6 and sIL-6R. Changes in high-sensitivity C-reactive protein did not correlate with changes in IL-6 and sIL-6R in the placebo group, but correlated inversely with changes in IL-6 in the tocilizumab group (Supplementary material online, *Table S8*).

Biochemical parameters

Total leucocyte counts increased in the placebo group but decreased in the tocilizumab group, resulting in significant between-group differences in changes from baseline (*Table 2*). This difference was predominantly driven by a decrease in neutrophils in patients allocated to tocilizumab. However, levels returned to normal during long-term follow-up (Supplementary material online, *Table S3*). There were modest between-group differences in changes from baseline in alanine aminotransferase and total cholesterol during hospitalization (*Table 2*), but there were no between-group differences at follow-up (Supplementary material online, *Table S3*).
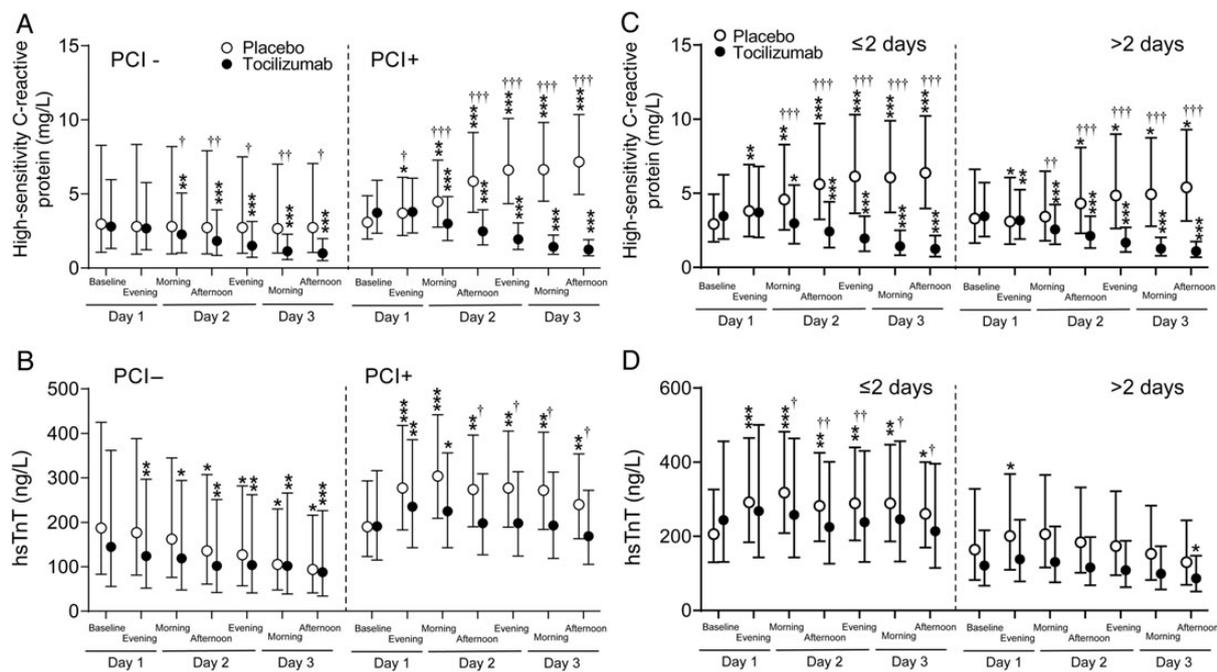
Figure 2 Serum levels of high-sensitivity C-reactive protein (*A* and *B*) and high-sensitivity troponin T (*C* and *D*) in patients with non-ST-elevation myocardial infarction receiving placebo (*n* = 59) and tocilizumab (*n* = 58) during hospitalization divided into two groups according to percutaneous coronary intervention (47 placebo and 41 tocilizumab) or not (12 placebo and 17 tocilizumab) (left panels), and divided into two groups according to inclusion ≤2 days (36 placebo and 30 tocilizumab) or >2 days (23 placebo and 28 tocilizumab) from symptom onset (right panels). Circles and bars represent geometric means and 95% confidence intervals, respectively. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ vs. baseline. †$P < 0.05$, ††$P < 0.01$, †††$P < 0.001$ comparing differences in changes from baseline between placebo and tocilizumab.

Cardiac function and heart failure

There were no cases of overt heart failure during follow-up in either treatment arm (Supplementary material online, *Table S9*). Left-ventricular EFs and dimensions were normal during hospitalization, and were not affected by treatment assignment (Supplementary material online, *Table S10*). Levels of NT-proBNP were modestly elevated at baseline. There were no between-group differences in changes from baseline during hospitalization (*Table 2*). Levels of NT-proBNP had returned to normal and there were no between-group differences at follow-up (Supplementary material online, *Table S3*).

Serious adverse events

We recorded 27 serious adverse events (SAE) in 17 patients allocated to placebo and 16 SAE in 12 patients allocated to tocilizumab during 6 months of follow-up (Supplementary material online, *Table S9*). There were six major adverse cardiovascular events (MACE) in the placebo group and three in the tocilizumab group. Overall, there were no significant between-group differences in SAE during follow-up.

Discussion

This trial is the first to assess the effect of IL-6 inhibition in ACS. We show that treatment with tocilizumab significantly attenuates inflammation and primarily PCI-related TnT release in patients with NSTEMI. There were no major safety concerns.

Elevated levels of C-reactive protein and IL-6 are associated with a poor prognosis in ACS.[2] Certain drugs used in the treatment of ACS (e.g. gpIIb/IIIa-inhibitors) attenuate IL-6 levels,[15] but IL-6 appears to be suboptimally suppressed with current treatment. Statins attenuate inflammation in ACS,[16] and reduce periprocedural myocardial injury during PCI.[17] However, in the MIRACL study, while suppressing C-reactive protein, atorvastatin failed to reduce IL-6 levels.[16] In our trial, where the majority of patients were treated with statins, a single dose of tocilizumab induced a sustained decrease in high-sensitivity C-reactive protein. This suppressive effect of tocilizumab was paralleled by a significant decrease in hsTnT, significantly correlated to the changes in high-sensitivity C-reactive protein, suggesting a link between inflammation and myocardial injury in these patients. However, the TnT release was modest, and the clinical significance of the tocilizumab-induced attenuation of TnT release is not clear.

The increase in IL-6 levels in patients receiving tocilizumab might seem paradoxical. However, tocilizumab does not bind to IL-6 itself, but prohibits IL-6 from interacting with its receptors by blocking membrane-bound as well as soluble IL-6R. A similar rise in IL-6 levels has been observed after the administration of tocilizumab in patients with autoimmune disorders, and seems to reflect attenuated elimination of IL-6 from the circulation due to decreased IL-6R-mediated clearance caused by tocilizumab-mediated IL-6R blockade.[10]

Table 2 Clinical biochemistry during hospitalization

	Group	Baseline	Day 3
NT-proBNP (ng/L)	Placebo	283 (202−395)	204 (144−291)**
	Tocilizumab	259 (180−372)	126 (86−185)***
Hb (g/dL)	Placebo	15.2 (1.4)	14.6 (1.4)*** ††
	Tocilizumab	15.0 (1.1)	14.8 (1.1)*
Platelets (10^9/L)	Placebo	240 (54)	229 (56)**
	Tocilizumab	250 (67)	243 (60)*
Leucocytes (10^9/L)	Placebo	7.3 (6.8−7.8)	7.4 (7.0−7.8) †††
	Tocilizumab	7.7 (7.1−8.3)	4.4 (4.0−4.8)***
Neutrophils (10^9/L)	Placebo	4.52 (4.10−4.98)	4.47 (4.15−4.83) †††
	Tocilizumab	4.96 (4.45−5.53)	1.68 (1.42−1.98)***
Total cholesterol (mmol/L)	Placebo	5.1 (4.9−5.5)	4.5 (4.2−4.7)*** ††
	Tocilizumab	5.0 (4.7−5.3)	4.6 (4.3−4.8)***
LDL-C (mmol/L)	Placebo	3.29 (0.99)	2.81 (0.94)***
	Tocilizumab	3.00 (0.97)	2.79 (0.78)**
HDL-C (mmol/L)	Placebo	1.05 (0.27)	1.02 (0.23)
	Tocilizumab	1.12 (0.33)	1.06 (0.30)**
Triglycerides (mmol/L)	Placebo	1.89 (1.66−2.16)	1.45 (1.29−1.63)***
	Tocilizumab	1.89 (1.64−2.19)	1.52 (1.36−1.69)***
AST (U/L)	Placebo	41 (35−48)	46 (39−53)
	Tocilizumab	43 (35−53)	60 (52−71)**
ALT (U/L)	Placebo	30 (26−36)	45 (37−55)*** ††
	Tocilizumab	33 (28−38)	64 (53−78)***
Creatinine (μmol/L)	Placebo	78 (74−83)	82 (77−86)***
	Tocilizumab	75 (71−79)	79 (75−83)***

Data are given as mean (SD) and geometric mean (CI).
Hb, haemoglobin; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ vs. baseline.
†$P < 0.05$, ††$P < 0.01$, †††$P < 0.001$ comparing between-group differences in changes from baseline.

The increase in free IL-6 was accompanied by decreased IL-6 bioactivity as reflected by C-reactive protein levels. In fact, changes of C-reactive protein were inversely correlated with changes in IL-6 only in the tocilizumab group, underscoring that the rise in IL-6 could be a marker of tocilizumab efficiency *in vivo* rather than the opposite.

Several studies have shown that PCI itself can induce an increase in C-reactive protein and TnT.[18] This biomarker release probably reflects I/R injury. In our patients, tocilizumab significantly attenuated the increase in TnT observed after PCI. In fact, in the present study, where patients could be included at a time when the primary myocardial injury had already occurred, the main finding was that tocilizumab attenuated inflammation and TnT release following PCI, illustrating the ability of IL-6 inhibition to attenuate I/R injury following this 'second myocardial hit'. In contrast, our data do not provide compelling evidence on the ability of tocilizumab to modulate the 'first hit' or the primary myocardial injury in NSTEMI. Although we also showed a significant attenuation of TnT release when looking at early included patients (≤2 days from symptom onset), which could indicate an effect also on the primary TnT release, this

observation also seems to be primarily driven by PCI. Nevertheless, the tocilizumab-induced reduction of TnT release after PCI, on top of statin treatment, may suggest a cardioprotective potential of IL-6 inhibition in I/R injury.

Even though inflammation is implicated in ACS, few studies have examined the potential of anti-inflammatory interventions in these patients. Based on the role of IL-1 as a regulator of downstream cytokine responses including IL-6, targeted therapy against IL-1 in ACS has been explored. Randomized trials have shown that IL-1 receptor antagonist (IL-1Ra) attenuates C-reactive protein levels in patients with STEMI,[19] and in NSTEMI this is accompanied by reduced levels of IL-6.[14] However, in the NSTEMI study, IL-1Ra did not reduce TnT release.[14] In that study, TnT was measured less frequently than in the present study, reducing the power to detect a treatment effect on TnT release. In the STEMI trials, treatment with IL-1Ra mitigated inflammation, LV remodelling, and HF,[19−21] but did not reduce infarct size. However, IL-1Ra was often administered several hours after acute PCI, at a time when most of the myocardial damage could already have occurred. In our study, tocilizumab did not affect levels of IL-1β, suggesting that IL-1β is

up-stream to IL-6 in the cytokine cascade during NSTEMI, and not the other way around. However, although IL-1 can induce IL-6, they can still have distinct functions, and combined IL-1/IL-6 inhibition could be a potential option in forthcoming studies.

This trial was not powered to evaluate differences in clinical outcomes. On the other hand, tocilizumab seemed to have a favourable safety profile in patients with NSTEMI. Despite a significant fall in neutrophils during hospitalization, there was no increase in serious infections in patients receiving tocilizumab. In fact, neutrophils are important mediators of inflammation during plaque destabilization[22] and MI.[7] The tocilizumab-induced decrease in neutrophils may well reflect a favourable response to treatment rather than a troubling side effect in NSTEMI.

Our study has several limitations. The number of patients was modest, and the trial was not powered to evaluate effects on clinical outcomes. There was a small number of clinical events, including MACE. This may partly be explained by the limited myocardial necrosis observed, and partly by the strict exclusion criteria. There was a wide distribution in the time from symptom onset to study drug administration. A shorter time from symptom onset to tocilizumab infusion is required to fully evaluate the effect of tocilizumab on the primary myocardial injury.

This trial provides encouraging data concerning short-time inhibition of IL-6 with tocilizumab in patients with NSTEMI. We observed an attenuated inflammatory response, a reduction in PCI-related TnT release, and a favourable safety profile. We need further studies that also give priority to early inclusion after symptom onset, to assess the potential effects of IL-6 inhibition on clinical outcomes in ACS.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Authors' contributions

O.K., T.U. performed statistical analysis; L.G. and R.W. handled funding and supervision; O.K., G.K., M.B., K.B., E.H., B.H.A., and L.G. acquired the data; O.K., M.B., T.U., B.B., B.H.A., S.A., J.K.D., P.A., R.W. and L.G. conceived and designed the research; O.K., T.U., T.E., J.K.D., P.A., R.W. and L.G. drafted the manuscript; O.K., G.K., M.B., T.U., K.B., E.H., A.E.M., B.B., B.H.A., T.E., S.A., J.K.D., P.A., R.W. and L.G. made critical revision of the manuscript for key intellectual content.

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CARDIOVASCULAR FLASHLIGHT

FDG-PET reveals coronary artery inflammation proceeding to cardiac allograft vasculopathy progression

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A 48-year-old man with idiopathic dilated cardiomyopathy received heart transplantation on March 2005, who has undergone coronary angiography (CAG) and intravascular ultrasound (IVUS) to examine cardiac allograft vasculopathy (CAV) every 1−3 years. Although CAG has not shown significant stenoses or angiographic changes in coronary arteries (*Panels A1−A5*), IVUS examinations have detected gradual atheroma progression followed by the tubular structure formation in adventitia in the proximal left anterior descending (LAD) coronary artery (*Panels B1−B5*). In contrast, 18-fluoro-deoxyglucose positron emission tomography (FDG-PET) and computed tomography angiogram had already detected FDG uptake in the left main trunk to proximal LAD on May 2007 (*Panels C1 and C2*), which was continued predominantly in the left main trunk by March 2015 (*Panels C3 and C4*), suggesting the association between coronary artery inflammation and CAV progression. 18-fluoro-Deoxyglucose-positron emission tomography may be a promising modality to reveal coronary artery inflammation, which can be the very beginning of CAV after heart transplantation.

Panels A1−A5: Serial coronary angiography. *Panels B1−B5*: Intravascular ultrasound detected gradual atheroma progression followed by the tubular structure formation in adventitia in the proximal left anterior descending (LAD) coronary artery. *Panels C1−C4*: 18-fluoro-Deoxyglucose positron emission tomography and computed tomography angiogram demonstrated that FDG uptake persisted in the left main trunk to proximal LAD.