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RESEARCH PAPER

Use of atorvastatin as an anti-inflammatory treatment in Crohn's disease

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Background and purpose: Experimental and clinical investigations have revealed that statins can downregulate both acute and chronic inflammatory processes. Whether statins express anti-inflammatory activities in the treatment of Crohn's disease is unknown.
Experimental approach: Ten patients were given 80 mg atorvastatin once daily for 13 weeks and then followed up for 8 weeks after the treatment. The anti-inflammatory effects of statin were assessed by measuring levels of plasma C-reactive protein (CRP), soluble (s) CD14, tumour necrosis factor (TNF)-α, sTNFRI and II, CCL2 and 8 and the mucosal inflammation by faecal calprotectin. Circulating monocytes were subgrouped and their chemokine receptor expression of CCR2 and CX_3CR1 were analysed.
Key results: In 8 of 10 patients, atorvastatin treatment reduced CRP ($P = 0.008$) and sTNFRII ($P = 0.064$). A slight decrease in plasma levels of sCD14, TNF-α and sTNFRI was observed in 7/10 patients and faecal calprotectin was reduced in 8/10 patients. We also observed that the treatment diminished expression of CCR2 and CX_3CR1 on monocyte populations ($P = 0.014$). At the follow-up visit, 8 weeks after the atorvastatin treatment was terminated, CRP levels had returned to those seen before the treatment.
Conclusions and implications: Our findings imply that atorvastatin therapy reduces inflammation in patients with Crohn's disease and, therefore, encourage further investigations of statin-mediated protective effects in inflammatory bowel diseases.
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Keywords: immunopharmacology; atorvastatin; Crohn's disease; biomarkers

Abbreviations: APC, allophycocyanin; CDAI, Crohn's disease activity index; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; FITC, fluorescein isothiocyanate; IQR, interquartile ranges; PBS, phosphate-buffered saline; PE, phycoerythrin; PerCP, peridin chlorophyll protein; RFI, relative fluorescence intensity; TNF, tumour necrosis factor

Introduction

Crohn's disease (CD) is a chronic inflammatory condition characterised by local and systemic inflammation, which is thought to result from an inappropriate response of a defective mucosal immune system to the indigenous flora and other luminal antigens. There is no specific therapy for the disease, and medical treatment is directed towards suppressing the immune system. A number of potent drugs are used in the treatment but most of these have severe side effects and a risk of affecting the immune response towards commensal microorganisms. Thus, it is of interest to find immune-modulating therapy that is well tolerated.

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Hydroxymethylglutaryl coenzyme A reductase inhibitors (statins), in addition to their cholesterol-lowering activity, have pleiotropic effects, including immunomodulatory and anti-inflammatory effects (Kwak *et al.*, 2000). Studies in animal models provide evidence that statins inhibit both acute and chronic inflammation in a cholesterol-independent manner and that they exert their anti-inflammatory effects, at least in part, by interfering with endothelial adhesion and transendothelial migration of leukocytes to sites of inflammation (Diomede *et al.*, 2001). There is increasing evidence to suggest that these medications have potent anti-inflammatory effects that contribute to their beneficial effects in patients with atherosclerosis, multiple sclerosis, rheumatoid arthritis and cardiovascular disease and sepsis (McCarey *et al.*, 2004; Vollmer *et al.*, 2004; Jain and Ridker, 2005; Hackam *et al.*, 2006).

Findings from peripheral monocyte cell cultures taken from patients with active CD and animal models of acute colitis have shown that statins have the potential to ameliorate the inflammatory response (Sasaki *et al*., 2003; Grip *et al*., 2004; Jahovic *et al*., 2006; Lee *et al*., 2007). However, statins have never been tested in the treatment of CD.

We undertook a small clinical trail to assess whether atorvastatin can reduce inflammatory processes in patients with CD. To evaluate the inflammatory status, a number of markers known to be increased during active inflammation was measured—high-sensitive CRP, soluble (s) CD14, TNF-α, sTNFRI and II, CCL2 and 8 and faecal calprotectin (Tibble *et al*., 2000; Martinez-Borra *et al*., 2002; Banks *et al*., 2003; Solem *et al*., 2005; Pastor Rojo *et al*., 2007; Spoettl *et al*., 2007). Moreover, we measured the expression of two chemokine receptors, CX_3CR1 and CCR2, linked to certain monocyte subsets in patients with active CD (Grip *et al*., 2007).

Methods

Patients

Patients with a confirmed diagnosis of CD and elevated levels of plasma CRP ($>2.0\,mg\,L^{-1}$) were included in the study. The patients lacked clinical signs of infection or intestinal perforation, and the results of examinations of stools for pathogens and *Clostridium difficile* toxin were negative. The patients excluded were those with a CDAI (Best *et al*., 1976) >450; inability to give informed consent; ongoing lipid-lowering treatment; previous side effects to statin treatment; prednisolone dosage above $15\,mg\,day^{-1}$ or change in dosage within the 4 weeks before the first visit; change in dosage of immunosuppressive drugs within the 12 weeks before the first visit; clinically significant kidney disease or aspartate aminotranspherase, alanine aminotranspherase, or kreatinine kinas more than twice the upper reference level; and pregnancy, breastfeeding or planned pregnancy.

Study design

The study was designed as an open, single centre, exploratory study in which the patients were offered 80 mg atorvastatin once daily as a supplementary treatment for 13 weeks. Baseline drugs were kept unchanged. Patients were followed up for weeks 0, 2 (initiation of treatment), 6, 15 (end of treatment) and 23. The study was approved by the Medical Products Agency, the Regional Ethical Review Board and monitored according to the Good Clinical Practice. The study was registered at ClinicalTrials.gov: NCT00454545.

Inflammatory markers in plasma

Plasma levels of high-sensitive CRP were measured by an automated immonoturbidimetric assay system (IMMAGE immunochemistry system) at Malmö University Hospitals' clinical routine laboratory at the Department of Clinical Chemistry with a minimum detectable dose of $0.2\,mg\,L^{-1}$. The method is validated by participation in Equalis (external quality assurance in laboratory medicine in Sweden) and the accredited coefficient of variation is 6% at the level of $15\,mg\,L^{-1}$. The other inflammatory substances were assessed by a quantitative, sandwich, ELISA. These parameters were analysed all at the same time at the end of the study, and plasma was stored during the study at −20 °C. ELISA kits were processed according to the manufacturer's instructions. The mean minimum detectable dose was: for TNF-α, $0.106\,pg\,mL^{-1}$, for sTNFRI, $0.77\,pg\,mL^{-1}$, for sTNFRII, $0.6\,pg\,mL^{-1}$, for sCD14 $<125\,pg\,mL^{-1}$ and for CCL2, $<5.0\,pg\,mL^{-1}$.

Mucosal inflammation

To determine the mucosal inflammation, the neutrophil marker protein calprotectin was measured in faeces by an ELISA with a polyclonal capture antibody, PhiCal test, according to the manufacture's instruction with a minimum detectable dose of $20\,mg\,kg^{-1}$.

Flow cytometry analysis

Blood samples for flow cytometry were collected in Vacutainer tubes containing 3.2% sodium citrate solution as anticoagulant. Samples were stained according to a whole blood technique using a protocol described previously (Stewart and Stewart, 2001). Briefly, 50 μL of whole blood, contained in Falcon tubes, were stained in the dark for 15 min at 4 °C with the appropriate amount of FITC-conjugated anti-CX_3CR1, APC-conjugated anti-CD56, PE-conjugated anti-CD16 and Alexa Fluor 647 anti-CCR2 and PerCP-conjugated anti-CD14. Fluorochrome-conjugated isotype-matched control antibodies against rat IgG_{2b} as well as mouse IgG_1 and IgG_{2b} were used to check the non-specific reactivity. Erythrocytes were lysed and leukocytes fixated for 10 min with BD FACS lysing solution before being washed twice with PBS and centrifuged for 3 min at 1500 *g*. Flow cytometry was performed on a fluorescence-activated cell sorting calibur four colour flow cytometer, and data were acquired from at least 7000 monocytes, gated morphologically (bivariate plot of forward vs side scatter) with CellQuest software, before analysis using WinList software. Relative flourescence intensity (RFI) was displayed as the ratio of the linearized positive median to the linearized isotype control median.

Drugs and materials. Atorvastatin was obtained from Pfizer (Sollentuna, Sweden); the IMMAGE immunochemistry system from Beckman Coulter (Bromma, Sweden); ELISA, R&D Systems (Abingdon, UK); PhiCal test, CALPRO AS (Lysaker, Norway); Vacutainer tubes, BD Diagnostics (Stockholm, Sweden). FITC-conjugated anti-CX_3CR1 was from MBL International (Woburn, MA, USA); APC-conjugated anti-CD56 from MACS (Miltenyi Biotec, Bergisch Gladbach, Germany); PE-conjugated anti-CD16, Alexa Fluor 647 anti-CCR2, PerCP-conjugated anti-CD14, mouse IgG_1 and IgG_{2b} and BD FACS lysing solution were all obtained from BD Pharmingen (Stockholm, Sweden); Fluorochrome-conjugated isotype-matched control antibodies against rat IgG_{2b}, eBioscience (San Diego, CA, USA); fluorescence-activated cell sorting Calibur and CellQuest, BD Biosciences (Stockholm, Sweden); WinList, Verity Software House Inc. (Topsham, ME, USA).

Statistical analysis
Results are expressed as medians with IQR (q1–q3). Differences were analysed by the Friedman repeated measures ANOVA on ranks followed by Student–Newman–Keuls method and the Wilcoxon signed-rank test using SigmaStat 3.1 (Systat Software Gmbh, Germany) software. A P-value <0.05 was regarded as significant. Comparisons were made between baseline (week 0) vs after 13-week treatment (week 15) and between weeks 15 and 8 after treatment stopped (week 23).

Results

Study population
Of the 17 patients screened for the study, 13 were included. However, three patients withdraw before the study treatment ended because of side effects—flatulence and dyspepsia ($n=1$), itching ($n=1$) and muscle fatigue ($n=1$). Table 1 presents the characteristics of 10 patients who completed the treatment. During the follow-up period for two patients, the disease was exacerbated, and therefore immunosuppressive treatment was initiated. One patient experienced impotence during the treatment, which was reversed when atorvastatin intake was terminated. All patients treated had a pronounced reduction in their plasma total cholesterol levels, from a median of 4.8 (4.2–5.3) to 2.8 (2.5–3.1) mmol L^{-1}, $P=0{,}002$, a reduction of triglycerids from 1.2 (0.9–1.8) to 0.8 (0.6–0.9) mmol L^{-1}, $P=0.004$, a reduction of apolipoprotein B from 0.9 (0.8–1.0) to 0.5 (0.4–0.6) g L^{-1}, $P=0.002$, and a slight, non-significant increase in their high-density lipoprotein levels, from a median of 1.1 to 1.2 mmol L^{-1}, $P=0.652$, during treatment. Aspartate aminotranspherase remained unchanged during treatment at 0.4 μkat L^{-1}, whereas a slight non-significant increase was seen of alanine aminotranspherase from 0.3 to 0.6 μkat L^{-1}, $P=0.064$. Median levels of kreatinine kinas were unaffected during treatment, 1.3 vs 1.2 μkat L^{-1}, $P=0.557$. Total monocyte counts in plasma remained unchanged during the treatment, 0.6 vs 0.6×10^{9} L^{-1}. The patients who were at low risk for atherosclerotic disease, as all were normotensive, had no ischaemic heart or cerebrovascular disease and none were taking aspirin.

Inflammatory markers in plasma
Thirteen weeks of atorvastatin therapy induced a reduction in the levels of all measured inflammatory markers, except for CCL2; Table 2. Of note, in 8/10 patients treated, CRP levels decreased, and among all patients treated, a median reduction of CRP by 44% was found, that is, before treatment 8.8 (5.7–14.4) vs during treatment 4.9 (3.3–6.2) mg L^{-1}, $P=0.008$, Figure 1. In two patients, CRP levels did not change, $< \pm 0.5$ mg L^{-1}. Eight weeks after withdrawal of the atorvastatin therapy, the concentrations of inflammatory markers were reanalysed. At the follow-up visit, seven patients whose CRP levels had decreased during the treatment showed higher CRP levels, which were comparable with those measured at baseline, before the study treatment. The median increase between the cessation of the study drug to the follow-up visit was 49%, $P=0.039$. Owing to an initiation of immunosuppressive therapy before the follow-up visit, CRP was not measured in one patient.

A similar trend was also observed for the other variables analysed (Table 2). Although these responses were non-significant, the most pronounced effect was observed for sCD14 and sTNFRII. Detectable levels of CCL8 were found only in three patients at baseline and in 2 at the follow-up visit.

Subpopulation analysis of circulating monocytes
We found that the size of the investigated subpopulations, $CD14^{high}CD16^{-}$, $CD14^{high}CD16^{+}$, $CD14^{low}CD16^{+}$ and $CD14^{+}CD^{56+}$, was not affected by the treatment studied. Figure 2 illustrate representative dot plots of these subpopulations.

On the basis of the chemokine expression within the subpopulations, we found that the RFI of CCR2 decreased in monocytes with a high expression of the pattern recognition receptor CD14 during treatment. In $CD14^{high}CD16^{-}$ monocytes, the RFI was reduced by 25%, 5.1 (4.2–5.7) vs 3.8 (3.6–4.4), $P=0.02$, and in $CD14^{high}CD16^{+}$ monocytes, the RFI was reduced by 12%, 4.4 (3.9–5.2) vs 3.9 (3.7–4.7), $P=0.049$ (Table 3). Although not significant, we observed a reduction in the percentage of cells expressing CCR2 during the treatment. In the $CD14^{low}CD16^{+}$ population, the number of cells expressing CCR2 was very few and we did not detect any significant change.

Table 1 Demographic data of patients

Age (years)	*Sex*	*Duration of disease (years)*	*Involvement*	*Smoking*	*CDAI*	*P-CRP (mg L^{-1})*	*F-calprotectin (mg kg^{-1})*	*IBD-related drugs*
24	F	1	Ileocolonic	Yes	194	37.7	1233	Bud
25	F	12	Ileocecal	No	128	14.4	90	AZA
31	F	1	Ileocolonic	No	62	10.2	973	5-ASA
42	F	8	Ileocolonic	No	192	2.7	30	Pred/5-ASA
44	F	1	Oesophagus to rectum	Yes	317	5.6	1303	
23	M	0.5	Ileal and rectal	No	356	16.6	1705	Bud
27	M	0.5	Ileocolonic	Yes	115	7.5	251	
33	M	15	Ileocolonic	No	326	6.8	1180	
35	M	1	Ileal	No	22	5.7	494	Bud
40	M	8	Ileal	Yes	49	10.1	266	

Abbreviations: 5-ASA, 5-aminosalicylate; AZA, azathioprine; Bud, budesonide; CDAI, Crohn's disease activity index; CRP, C-reactive protein; IBD, inflammatory bowel disease; Pred, prednisolone.

Table 2 Inflammatory markers in plasma

	Median baseline levels (q1–q3) (pg mL^{-1})	*Median level after 13-week treatment*	*Number of patients with a positive response after the 13-week treatment*	*Median level at 8 weeks after treatment stopped (pg mL^{-1})*	P
sCD14	1270 (905–1450)	1030 (884–1140)	7/10	1280 (993–1440)	NS
TNF-α	1.45 (1.25–1.9)	1.35 (1.20–1.8)	7/10	1.25 (1.00–1.85)	NS
sTNFRI	716 (694–864)	685 (640–814)	7/10	768 (716–857)	NS
sTNFRII	1513 (1214–1853)	1304 (1130–1626)	8/10	1268 (1020–1549)	NS
CCL2	152 (134–175)	158 (131–178)	5/10	148 (122–164)	NS
CCL8	373 (143–377)	312 (106–345)	3/3	—	NS

Abbreviations: NS, not significant; s, soluble; TNF, tumour necrosis factor.

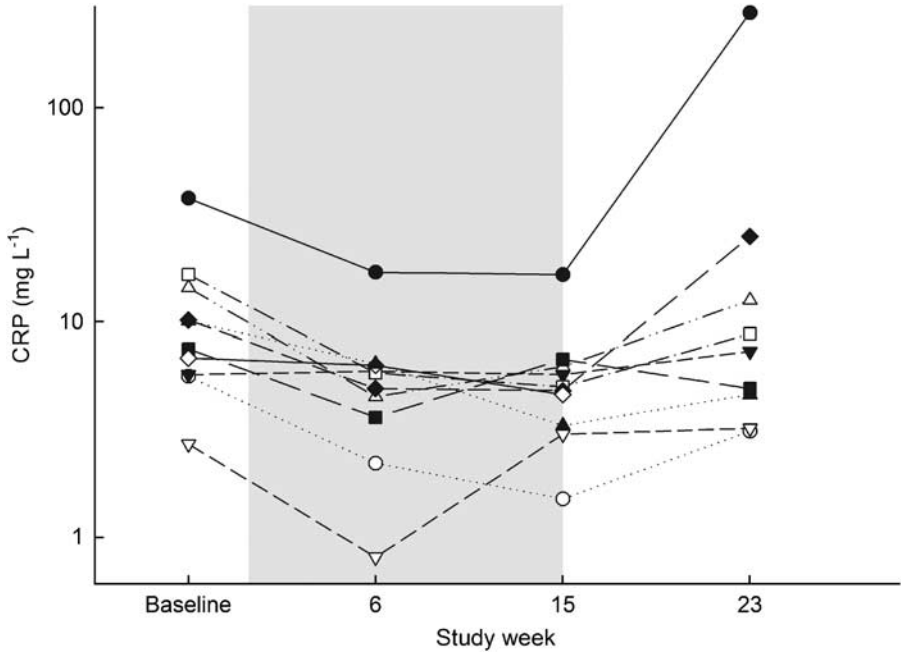

Figure 1 C-reactive protein (CRP) levels of 10 patients receiving 80 mg atorvastatin once daily for 13 weeks (grey area) and then followed up 8 weeks after the termination of treatment.

Analysis of CX_3CR1 in $CD14^{high}CD16^+$ monocytes showed a decrease in RFI by 29%, 5.3 (4.9–5.7) vs 3.8 (3.0–4.4), $P=0.049$. In $CD14^{high}CD16^-$, $CD14^{low}CD16^+$ and in $CD14^+CD56^+$ monocytes, we observed a non-significant decrease. In $CD14^{high}CD16^-$, the percentage of monocytes expressing CX_3CR1 was reduced by 31%, 57.3 (52.7–73.7) vs 39.5 (7.6–47.9), $P=0.049$, and in $CD14^{high}CD16^+$, a 24% reduction was observed, 86.7 (76.0–88.7) vs 66.1 (43.3–82.3), $P=0.014$. In the $CD14^{low}CD16^+$ and in the $CD14^+CD^{56+}$ populations, we observed a non-significant reduction.

Mucosal inflammation

Faecal calprotectin was reduced in 8/10 patients during the treatment, and among all those treated, a reduction was seen by 48%, that is, before treatment 734 (251–1233) and during treatment 384 (151–958) mg kg^{-1}, $P=0.232$. In two patients, calprotectin increased during the treatment. However, 8 weeks after the termination of treatment, the calprotectin levels increased again in 5/6 patients. It should be noted that faecal samples were not analysed in two patients at the follow-up visit because of a prior initiation of immunosuppressive therapy.

Clinical response

We found that CDAI dropped in 7/10 patients during the treatment and returned to higher levels in 4/6 patients 8 weeks after the termination of treatment. Although not significant, the median change was a reduction of CDAI by 82 points from 160 (62–317) to 78 (48–180), $P=0.105$ during the treatment. The CDAI remained unchanged in two patients, $< \pm 20$ points, during the study, and in one patient, it increased by 63 points (Figure 3).

Discussion

In this exploratory study, we show that in patients with CD, the use of atorvastatin for 13 weeks (80 mg daily), combined with existing anti-inflammatory therapy, reduced the levels of inflammatory markers in plasma and faeces, and also

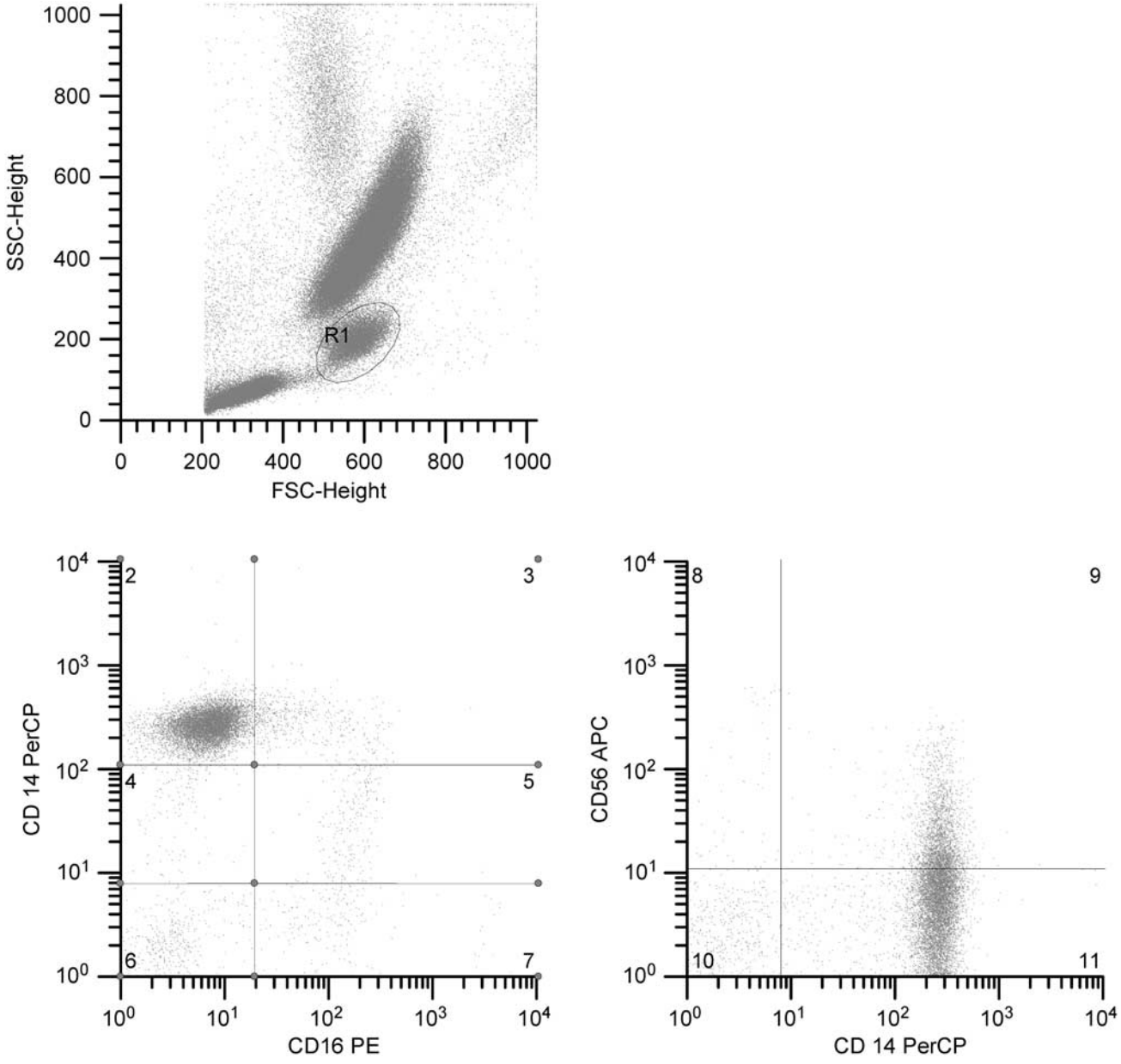

Figure 2 Peripheral monocytes analysed by flow cytometry. Leukocytes initially separated in bivariate plot of forward scatter (FSC) vs side scatter (SSC) to identify monocytes and ellipse gated in R1. Then gated monocytes were subdivided by expression of CD14, CD16 and CD56. Subpopulations are defined as $CD14^{high}CD16^{-}$, region 2; $CD14^{high}CD16^{+}$, region 3; $CD14^{low}CD16^{+}$, region 5 and $CD14^{+}CD56^{+}$, region 9.

reduced clinical disease activity. In addition to the lowering of cholesterol levels, atorvastatin led to significant decreases of CRP. CRP is an objective marker of inflammation and, in gastrointestinal diseases such as CD, its levels correlate with clinical disease activity. Therefore, CRP is useful as a laboratory marker to predict prognosis and relapse in patients with CD. (Solem *et al*., 2005) Hence, it has been shown that strong anti-inflammatory agents work particularly well in patients with active gut inflammation and elevated levels of CRP (Vermeire *et al*., 2006). Our findings support the contention that a significant lowering of CRP levels by statin therapy may inhibit inflammation in patients with CD.

In an attempt to explore the anti-inflammatory effect of atorvastatin further in patients with CD, we evaluated other inflammatory markers that are not dependent on an elevation of CRP. The disturbance of the mucosal barrier, dysregulation of intestinal immune responses as well as bacterial and other environmental factors are known to have a function in the development of CD. In this context, various protein biomarkers can be used to describe inflammation in CD. For instance, it has been shown that the levels

Table 3 Change in expression of chemokine receptors in peripheral monocytes after 13-week treatment

Monocyte population	*Percentage of relative fluorescence intensity*	*Number of patients with a positive response*	P	*Percentage of positive cells*	*Number of patients with a positive response*	P
CCR2						
$CD14^{high}CD16^{-}$	−25	9/10	0.020	−34	7/10	0.064
$CD14^{high}CD16^{+}$	−12	9/10	0.049	−23	9/10	0.064
CX_3CR1						
$CD14^{high}CD16^{-}$	−20	7/10	0.105	−31	8/10	0.049
$CD14^{high}CD16^{+}$	−29	8/10	0.049	−24	9/10	0.014
$CD14^{low}CD16^{+}$	−19	7/10	0.275	−5	7/10	0.131
$CD14^{+}CD56^{+}$	−21	8/10	0.084	−40	8/10	0.064

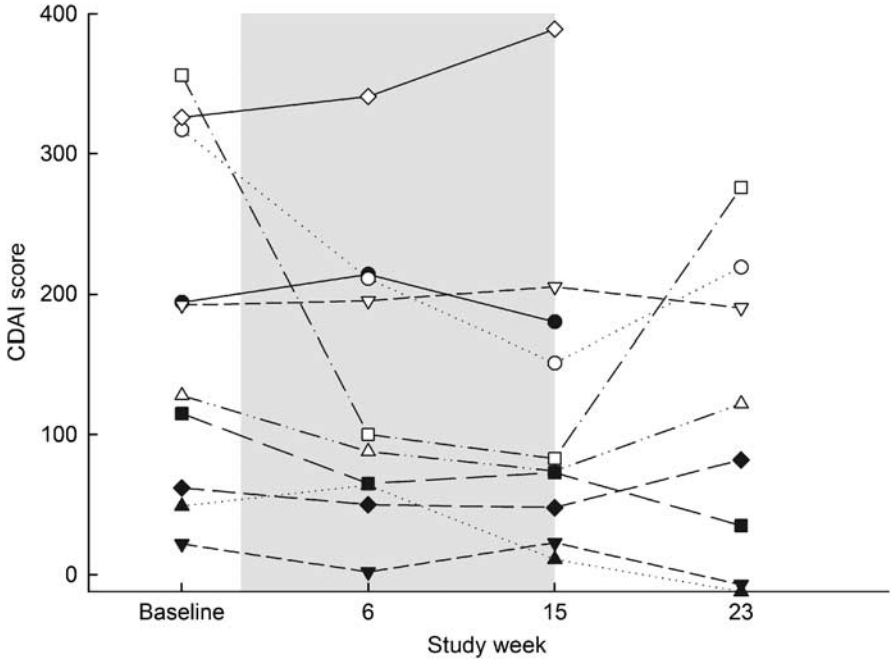

Figure 3 Crohn's disease activity index (CDAI) of 10 patients receiving 80 mg atorvastatin once daily for 13 weeks (grey area) and then followed up 8 weeks after the termination of treatment.

of sCD14, an acute-phase protein and a modulator of cell-associated and humoral immune responses (Arias *et al*., 2000; Bas *et al*., 2004), are increased during active inflammation, and in patients with inactive and/or treated CD, a persistant elevation of sCD14 has been observed despite a marked reduction of CRP (Pastor Rojo *et al*., 2007). The rise in sCD14, together with lipopolysaccharide-binding protein was suggested to reflect a passage of enteric bacterial products into the circulation. On the other hand, several studies have shown that faecal calprotectin, a marker of intestinal inflammation, is significantly increased in CD and correlates well with intestinal permeability. (Berstad *et al*., 2000; Konikoff and Denson, 2006) As a matter of fact, in our CD patients treated with atorvastatin, we observed a very small lowering of sCD14 levels and a decrease, but not a normalization, of faecal calprotectin levels in most of the patients studied. This indicates that atorvastatin effectively reduces the liver-derived, acute-phase reactant CRP, but expresses only a minor effect on markers related to local inflammatory processes.

Several studies show that TNF levels are elevated in the serum, mucosa and stools of patients with CD, (Murch *et al*., 1993; Nicholls *et al*., 1993; Komatsu *et al*., 2001), and infusion of monoclonal anti-TNF antibody is an efficacious therapy. TNF-α has a major function in inflammatory bowel disease through two receptors, p55 (RI) and p75 (RII) expressed on many cell types, in particular neutrophils and monocytes (Hattar *et al*., 2001; Rossol *et al*., 2007). Accordingly, sRI and RII (sRI/RII) are believed to have potent anti-inflammatory actions. Interestingly, sTNFRII levels have been shown to be higher in the serum of patients with CD compared to those with ulcerative colitis (Spoettl *et al*., 2007). We therefore measured plasma TNF-α and sRI/II levels in our patient group, but found that these markers were non-significantly affected by atorvastatin treatment. We also measured CCL2 and 8 levels because in CD, a local

upregulation in tissues CCL2 and 8 is often seen and correlates with disease activity (Banks *et al*., 2003). We have previously seen, in patients with active CD, a modestly elevated level of CCL2 in plasma, and a marked increased production of this chemokine from peripheral monocytes that are suppressed by atorvastatin treatment *ex vivo* (Grip *et al*., 2004). Supporting this, in a large study, the levels of CCL2 in plasma were shown to be reduced by atorvastatin treatment in subjects at high risk of contracting cardiovascular disease (Blanco-Colio *et al*., 2007). In this study, however, we were not able to detect a reduction in plasma CCL2 levels. Taken together, our findings indicate that inflammatory markers that are generated closer to the actual site of inflammation are only slightly affected by atorvastatin, which supports the idea that the effect of statins may be more directed to the liver. On the other hand, it has also been suggested that lipid reduction *per se* may reduce the inflammatory response in specific tissues (Moriarty *et al*., 2001). As mentioned above, CD patients treated with atorvastatin showed a strong reduction of lipid levels. However, to confirm whether there is a direct link between the lipid-lowering and anti-inflammatory effects of atorvastatin in CD patients, larger studies need to be carried out.

The recruitment of inflammatory cells and consequently the abnormal function of the innate immune system in CD is suggested to be linked to a decreased bacterial clearance because of macrophage dysfunction (Tlaskalova-Hogenova *et al*., 2005; Marks *et al*., 2006). However, it is now better understood that monocytes are heterogeneous, and subpopulations have been identified on the basis of physical, functional and surface marker criteria (Grage-Griebenow *et al*., 2001). The subpopulations are distinguished by different expressions of chemokine receptors, and previously we have seen that the monocyte population, which increased in patients with active CD is the $CD14^{high}CD16^{+}$ cells that have a high expression of CCR2 and an intermediate expression of CX_3CR1 (Grip *et al*., 2007). In this study, we found no effect of statin treatment on the size of the subpopulations investigated. However, we found atorvastatin to be a potent suppressor of the expression of both CCR2 and CX_3CR1 on all monocyte subpopulations, indicating a broad effect that may even be seen on other cell types. Our findings are in agreement with an experimental study showing that statins reduce CCL2 and CCR2 expressions in both human endothelial cells and macrophages (Veillard *et al*., 2006).

There are recent studies, in accordance with our findings, that show a convincing reduction of CRP by atorvastatin, but a less pronounced effect on other inflammatory markers (Goicoechea *et al*., 2006; Konduracka *et al*., 2007; Kinlay *et al*., 2008). Nevertheless, we showed that markers known to be raised during ongoing inflammation in CD can be reduced by atorvastatin treatment, and these are reversed to baseline when the treatment is terminated. Interestingly, recently it has been found that surrogate markers of atherosclerosis are abnormal in CD patients, which implies that the atherosclerotic process is accelerated in CD, and therefore atorvastatin may also have an atheroprotective effect (van Leuven *et al*., 2007; Schinzari *et al*., 2008).

Statins are widely used and have few side effects, making them suitable candidates for maintenance therapy. Long-term, high-dose statin therapy has proved to be well tolerated in cardiovascular trials, and fewer than 1 in 20 to 1 in 50 properly selected patients have discontinued atorvastatin 80 mg therapy because of an adverse, drug-related effect (Davidson and Robinson, 2007). Although, in our study, three patients discontinued therapy because of minor side effects, we propose that randomized trials should be carried out to evaluate statin therapy in CD.

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Conflict of interest

OG gave paid lectures for Schering-Plough, MEDA and Ferring. SJ has received research grants from AstraZeneca. AB has no conflicts of interest.

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