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Published in:
Annals of the Rheumatic Diseases

DOI:
[10.1136/ard.2010.131235](https://doi.org/10.1136/ard.2010.131235)

[Link to publication](#)

Citation for published version (APA):

van Kuijk, A. W. R., Vergunst, C. E., Gerlag, D. M., Bresnihan, B., Gomez-Reino, J. J., Regine, R., ... Tak, P. P. (2010). CCR5 blockade in rheumatoid arthritis: a randomised, double-blind, placebo-controlled clinical trial. *Annals of the Rheumatic Diseases*, 69(11), 2013-2016. <https://doi.org/10.1136/ard.2010.131235>

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CCR5 blockade in rheumatoid arthritis: a randomised, double-blind, placebo-controlled clinical trial

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► Additional supplementary data are published online only. To view these files please visit the journal online (<http://ard.bmj.com>).

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Accepted 25 June 2010

ABSTRACT

Objective C-C chemokine receptor type 5 (CCR5), a chemokine receptor expressed on T cells and macrophages, and its ligands are found in inflamed synovial tissue (ST) of patients with rheumatoid arthritis (RA). The rationale for testing CCR5 blockade in patients with RA was supported by the effects of a CCR5 antagonist in collagen-induced arthritis in rhesus monkeys. The effects of CCR5 blockade in patients with active RA were explored.

Methods In this phase Ib randomised, placebo-controlled trial, treatment with an oral CCR5 inhibitor (SCH351125) in patients with active RA was evaluated. Clinical efficacy was assessed using European League Against Rheumatism and American College of Rheumatology response criteria. ST biopsies were taken before and after 28 days of treatment, and analysed for CCR5+ cells. In a subset of patients, MRIs of an inflamed joint were obtained before and after treatment.

Results In all, 32 patients were included; 20 received SCH351125 and 12 placebo. Three patients who received SCH351125 did not complete the study due to adverse events; none of these were serious. No improvement was observed in the active treatment group compared to placebo. Results were consistent for clinical evaluation, ST analysis and MRI.

Conclusion This proof of concept study does not support the use of CCR5 blockade as a therapeutic strategy in patients with active RA.

INTRODUCTION

The inflamed synovial membrane in rheumatoid arthritis (RA) is infiltrated with inflammatory cells.¹ Chronic synovitis is believed to be a dynamic process; continuous influx of leucocytes is required to maintain the inflammatory infiltrate. Leucocyte traffic is largely regulated by chemokines.²⁻³ C-C chemokine receptor type 5 (CCR5)+ T cells and macrophages are found in the synovial fluid and synovial tissue (ST), together with the known ligands for CCR5: macrophage inflammatory protein α (MIP-1 α), MIP-1 β and chemokine (C-C motif) ligand 5 (CCL5, also known as RANTES for 'regulated upon activation, normal T cell expressed and secreted').⁴⁻⁶ Supportive evidence for the relevance of CCR5 in RA is found in the suggestion that the CCR5 δ 32 polymorphism plays a protective role in RA.⁷⁻⁸ Treatment with a CCR5 antagonist ameliorated collagen-induced arthritis in rhesus monkeys.⁹ These data suggest that CCR5 may be one of the crucial factors involved in the recruitment of monocytes/macrophages and T cells to the joint,

and that blocking CCR5 might be of therapeutic benefit in patients with RA.

This study was performed to explore the safety and clinical effects of SCH351125, an oral CCR5 receptor antagonist, in patients with active RA. In addition, we performed ST biopsy and MRI before and after treatment.

PATIENTS AND METHODS

Patients

A total of 32 patients with active RA were included in this phase Ib clinical trial, all fulfilling the American College of Rheumatology (ACR) classification criteria for RA.¹⁰ Patients had ≥ 3 tender and ≥ 3 swollen joints. Additionally, they had an elevated erythrocyte sedimentation rate (ESR) of ≥ 28 mm/h, or C reactive protein (CRP) ≥ 10 mg/litre, or morning stiffness ≥ 45 min. Concomitant treatment with a stable dose of methotrexate and/or prednisolone ≤ 10 mg/day was allowed. A washout period was required for other disease-modifying antirheumatic drugs or biologicals.

Study protocol

The study protocol was approved by the Ethics Committees of all participating centres. Patients gave their written informed consent before enrolment. Physical examination, routine laboratory testing, chest x-ray and electrocardiogram were performed. Disease activity was evaluated by a blinded assessor at baseline, day 15 and 28. This included a tender joint count, swollen joint count (SJC), doctor's and patient's global health assessment, ESR and CRP. Clinical efficacy was assessed using ACR and European League Against Rheumatism (EULAR) response, using the Disease Activity Score in 28 joints (DAS28).¹¹⁻¹² Monitoring for adverse events continued until 2 months after the last administration of study medication.

Study drug

Patients were randomised in a double-blind fashion to receive SCH351125 50 mg tablets twice a day or matched placebo (2:1 ratio) for 28 days.

ST biopsy and analysis

If possible, an arthroscopy of an inflamed index joint (knee, ankle or wrist) was performed in patients at baseline and day 28, to obtain ST biopsies. In one centre, blinded needle biopsy was performed.¹³ Biopsies were snap-frozen immediately; tissue sampling and storage have been described previously.¹⁴⁻¹⁶

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The number of CCR5+ T cells and macrophages was assessed by immunofluorescent double staining. Biopsy sections were incubated overnight at 4°C with primary fluorescein isothiocyanate (FITC)-labelled monoclonal antibody against CCR5, washed and incubated with FITC-labelled markers for CD3, CD4, CD8 and CD68 as previously described.⁶ Sections were analysed using a fluorescent photomicroscope with confocal scanning. Coexpression of cellular markers with CCR5 was determined using computer-assisted digital image analysis.¹⁷

MRI

If possible, an MRI scan of a clinically inflamed wrist or knee joint was obtained before and after 28 days of treatment, according to protocol (see supplementary material), and evaluated by a blinded reader (MM).

Statistical analysis

Student's t test and Wilcoxon signed rank test were used where appropriate for comparison of both treatment groups. The ACR20/50/70 and EULAR response rates were compared using the Fisher's exact test.

RESULTS

A total of 32 patients (13 men, 19 women) were enrolled into the study and randomised between SCH351125 (n=20) and placebo (n=12) (table 1). Both groups were comparable with regard to demographic data and clinical disease activity, although the mean SJC was higher in the SCH351125 group (11.4 vs 7.7, p=0.026).

SCH351125 was generally well tolerated. In all, 8 patients (67%) in the placebo group and 15 patients (75%) in the SCH351125 group reported at least 1 adverse event. None of these were serious adverse events. One patient in the placebo group discontinued because of non-compliance with the protocol (deviation of visit schedule), and three patients in the SCH351125 group discontinued due to adverse events.

Clinical efficacy

DAS28 slightly improved in patients receiving SCH351125 from 5.72±1.33 (median±SD) to 5.09±1.53 (p=0.022). DAS28 also

decreased in the patients treated with placebo from 5.31±0.81 (median±SD) to 4.80±0.98 (p=0.051) (figure 1). In total, 13 patients met the EULAR response criteria (1 good and 12 moderate responders), 8 patients fulfilled the ACR20 response criteria. The response rates were similar between patients treated with placebo and SCH351125 (table 2). No significant differences between the groups were detected in the individual disease parameters, including CRP and ESR.

ST analysis

Paired ST samples were available from 13 patients (n=8 in the SCH351125 group, n=5 in the placebo group). No significant reduction in numbers of CCR5+ T cells or macrophages was observed after SCH351125 treatment compared to placebo (table 2). We did find a significant decrease in the number of CD8 T cells after CCR5 blockade (p<0.05). It is unclear whether this represents a true biological effect. There was no decrease in the number of CD68 macrophages after active treatment.

MRI

Paired MRIs were available from nine patients (six wrists and three knees; SCH351125 n=6, placebo n=3). All patients treated with placebo showed worsening of the MRI score after 28 days. The MRI score of the patients treated with SCH351125 worsened in three cases, was unchanged in two and improved in one after 28 days. These data are consistent with clinical and histological data, showing no clear improvement after CCR5 blockade.

DISCUSSION

Oral administration of SCH351125, a small molecule blocking CCR5, for 28 days to patients with RA was safe and generally well tolerated. If SCH351125 treatment could induce robust improvement in RA, we would have expected improvement in clinical parameters, ST markers or inflammation on MRI, based on previous experience in small proof of principle clinical trials.¹⁸ However, no significant differences or trends were observed differentiating SCH351125 from placebo. Paired ST samples did not show clear-cut differences in CCR5+ cells after treatment. The number of CD68 synovial macrophages was not reduced after active treatment. We have previously shown that all effective antirheumatic drugs ultimately decrease this cell population in

Table 1 Demographic and clinical data of patients at baseline

	Placebo (n=12)	SCH351125 (n=20)
Sex, female/male (n)	7/5	12/8
Age in years, mean (range)	52.8 (40–71)	60.4 (35–79)
Body weight in kg, mean (range)	67.1 (54–83)	74.9 (59–94)
BMI, mean (range)	24.4 (21.1–34.6)	27.3 (18.8–33.7)
Disease duration in months, mean (range)	78 (3–240)	92 (2–420)
Rheumatoid factor positive, n (%)	9 (75%)	17 (85%)
Erosive disease, n (%)	9 (75%)	13 (65%)
SJC, mean (range)*	7.7 (3–11)	11.4 (4–19)
TJC, mean (range)	7.8 (3–14)	11.0 (3–24)
ESR mm/h, mean (range)	37.6 (6–117)	40.4 (7–106)
CRP mg/litre, mean (range)	24.3 (1.0–75.6)	16.9 (0.5–96.3)
VAS patient assessment mm, mean (range 0–100)	44.7 (12–90)	53.4 (21–95)
VAS doctor assessment mm, mean (range 0–100)	41.5 (6–70)	48.7 (20–100)
Morning stiffness min, mean (range)	79 (0–300)	175 (0–1440)
DAS28, mean (range)	5.14 (3.79–6.53)	5.68 (2.59–8.42)

*p=0.026.

BMI, body mass index; CRP, C reactive protein; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale.

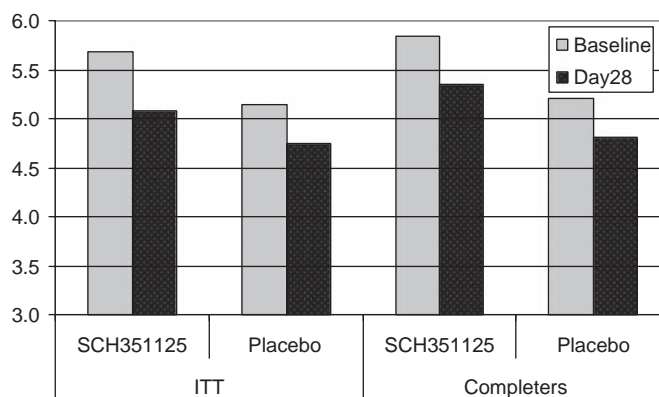


Figure 1 Median Disease Activity Score in 28 joints (DAS28) at baseline and day 28 for the patients treated with SCH351125 or placebo. Comparison of median DAS28 between SCH351125 and placebo at baseline and end of dosing (day 28) in all subjects (intention-to-treat (ITT) analysis and completers) of the 28-day dosing period.

Table 2 Distribution of clinical response after 28 days of treatment with SCH351125 (oral CCR5 blocker) or placebo (intention to treat analysis) (upper) and immunohistochemical results of synovial tissue biopsies before and after 28 days of therapy for placebo and SCH351125 (lower)

Criteria	Patients			
	Placebo (n=12)		SCH351125 (n=20)	
EULAR responder	5 (42%)		8 (40%)	
EULAR good responder	0		1 (5%)	
EULAR moderate responder	5 (42%)		7 (35%)	
ACR20 criteria	4 (33%)		4 (20%)	
ACR50 criteria	0		2 (10%)	
ACR70 criteria	0		0	
	Placebo (n=5)		SCH351125 (n=8)	
	Before	After	Before	After
CD3	37 (19)	46 (31)	23 (74)	13 (22)
CD4	41 (37)	23 (34)	27 (18)	21 (16)
CD8	5 (30)	22 (30)	40 (56)	9 (31)*
CD68	164 (148)	227 (90)	141 (90)	175 (170)
CD3CCR5	2 (1)	0 (2)	0 (2)	0 (1)
CD4CCR5	5 (4)	6 (3)	4 (3)	1 (2)
CD8CCR5	1 (5)	0 (4)	1 (4)	0 (1)
CD68CCR5	68 (38)	37 (35)	16 (22)	17 (39)

Upper panel shows the number of patients (%) fulfilling the EULAR and ACR response criteria. Differences between SCH351125 and placebo were not significant.

Lower panel shows immunohistochemical results of synovial tissue biopsies before and after 28 days of therapy for placebo and SCH351125. Number of positive cells is presented as median (SD). There were no significant changes in the number of CCR5+ cell numbers, although there was a trend towards reduction of CD4CCR5+ cells in the SCH351125 group.

*p<0.05.

ACR, American College of Rheumatology; CCR5, C-C chemokine receptor type 5; EULAR, European League Against Rheumatism.

the synovium.^{18–20} Serial MRIs did not reveal marked improvement of synovial inflammation.

The lack of effect could be a reflection of suboptimal dosing, too short exposure to the drug, or a false negative effect related to the relatively small size of the study sample. Alternatively, CCR5 may not be a good therapeutic target in active RA. First, inadequate dosing appears unlikely, because extensive dose finding studies in healthy individuals have shown good bioavailability for the dose used (data not shown). Moreover, a lower dose of SCH351125 (25 mg every 12 h) was shown to have clear biological effects in patients with HIV1 infection, starting within 3–5 days after initiation of treatment.²¹ Second, we did not find a reduction of synovial inflammation. Previous studies have shown changes in synovial biomarkers within 2 weeks of effective treatment.^{22–25} If CCR5 were a key molecule involved in the continuous influx of monocytes into the inflamed joint in RA, 4 weeks of CCR5-blocking therapy should have resulted in a decrease in the number of synovial macrophages. A false negative result could also be due to the relatively small number of patients in this proof of principle study. However, previous studies with a similar design^{18–22} have indicated that the number of patients should be sufficient to detect relevant changes in DAS28 and synovial inflammation after effective treatment. Therefore, CCR5 may not be a good target for the treatment of active RA. This notion is supported by two studies with other CCR5 antagonists that were tested in patients with RA (Maraviroc, Pfizer, <http://clinicaltrials.gov> NCT00427934; and AZD5672, AstraZeneca).²⁶

There may be different mechanisms explaining the lack of effect of CCR5 blockade in RA. First, CCR5 is also expressed by T regulatory cells.²⁷ The lack of efficacy could perhaps be explained by inhibition of T regulatory cells. Another explanation may be redundancy of the chemokine system. Monocytes express CCR5 as well as other chemokine receptors such as CCR2 and CCR1. CCR5 blockade may be bypassed by other chemokines. Blockade of solely CCR1²⁸ or CCR2²⁹ did not

result in clinical improvement either. Combinations of different chemokine receptor blockers may be a way to get around this problem. Alternatively, homodimer and heterodimer chemokine receptors are found on the cell membrane. Binding to their ligands stabilises specific receptor conformations and activates distinct signalling cascades.³⁰ Heterodimerisation may allow for specific functions of receptors essential for receptor activity.^{31–32} Conceivably, CCR5 heterodimers are present in the inflamed synovium and not effectively blocked by SCH351125.

In conclusion, we did not find evidence of clinical efficacy of SCH351125 in patients with active RA.

Funding The clinical study was supported by Schering-Plough. DMG was supported by the Dutch Arthritis Association ('Reumafonds'). This research was also supported by the European Community's FP6 funding ('Autocure'). This publication reflects only the views of the authors; the European Community is not liable for any use that may be made of the information herein.

Competing interests MCK was employed by Schering-Plough. The study was sponsored by Schering-Plough.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the Ethics Committees of all participating centres.

Provenance and peer review Not commissioned; externally peer reviewed.

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Ann Rheum Dis 2010 69: 2013-2016 originally published online August 6, 2010

doi: 10.1136/ard.2010.131235

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