To the Editor:
The hallmark of sarcoidosis is the formation of granulomas consisting of activated and fused macrophages and lymphocytes (1). Spontaneous remission is seen in over half of patients (2), but severe organ damage may occur to ongoing inflammation and subsequent fibrosis. Current treatment options include glucocorticoids, methotrexate, azathioprine and tumor necrosis factor $\alpha$ (TNF-$\alpha$)-blockers (3). As a result of side effects and refractory disease there is still an unmet need for new therapeutic options in patients with chronic sarcoidosis and a search for novel treatment strategies is needed.

Somatostatin (SS) is a neuropeptide with a variety of actions throughout the human body, including a regulatory role in the immune system (4). SS has five receptor subtypes (sst 1-5), of which sst2 is widely expressed in normal monocytes and macrophages as well as monocytes, macrophages and epithelioid cells of granulomatous tissues (5, 6). Somatostatin receptor scintigraphy (SRS) is a valuable tool in diagnosing sarcoidosis by imaging sst2 positive lesions (7, 8). Previously, we found in an oversimplified model for sarcoidosis that macrophage induced fibroblast proliferation, was effectively inhibited by octreotide (unpublished results). Moreover, two sarcoidosis patients treated with octreotide have been described, one patient with pulmonary and mediastinal involvement did not show a clinical response, while the other patient with refractory skin and lymph node sarcoidosis showed a decrease in SRS uptake and remission of skin lesions and lymph node size (6). Both patients had biopsies positive for sst2 and positive SRS, yet only one patient showed a clinical response to octreotide. Furthermore, a case was recently described by by Lapa et al, where targeting somatostatin receptors through peptide receptor radionuclide therapy showed a promising result in one patient with refractory sarcoidosis (9).

Sandostatin is the stable, synthetic analogue of somatostatin, with indications for acromegaly and neuroendocrine tumors (10). Two pilot trials with sandostatin reported clinical improvement in a subgroup of patients with rheumatoid arthritis (11, 12). Interestingly, sandostatin is also effective in patients with uveitic chronic macular edema (13).

We evaluated the clinical effects of sandostatin in patients with chronic sarcoidosis with SRS in a prospective Phase II study. This study was approved by the Medical Ethics Committee of the Erasmus MC, Rotterdam, The Netherlands (MEC-2014-099) and registered at www.trialregister.nl (NTR4655). This trial was financially supported by Novartis. The sponsor had no influence in design of this study, patient inclusion, data analysis and manuscript writing. Included patients provided written informed consent. Due to the limited number of enrolled patients in this study, we also report our results in therapy-refractory patients treated with octreotide outside this trial.

Sandostatin therapy in patients with chronic sarcoidosis

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Included patients had biopsy-proven, SRS positive chronic sarcoidosis for >3 years with indication for therapy with involvement of skin, joint, lymph node and/or lung (diffusion capacity between 60-75%) (Table 1). Exclusion criteria included corticosteroid use up to three months before trial, chronic renal failure, liver disease or underlying cardiac disease, indication for intensifying immunosuppressive therapy or threatening organ damage and non-responders to TNFα-blocking therapy.

Prior to start of sandostatin treatment, SRS and electrocardiography were performed and quality of life (RAND-36 questionnaire) (14, 15) and pulmonary function (forced vital capacity (FVC) and diffusing capacity (DLCO)) were assessed. Additional blood tests included CRP, ESR, full blood count, lysozyme, Angiotensin-Converting Enzyme, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, soluble interleukin-2 receptor (sIL-2R), liver enzymes, glucose and thyroid stimulating hormone. Sandostatin was administered with intramuscular injections with a duration of six months. Patients visited the outpatient clinic two weeks after first injection and every three months for evaluation of disease activity and adverse events.

The primary endpoint of this study was change in uptake per organ measured with the four point scale as previous described (8). The secondary endpoint included blood tests, RAND-36 score and pulmonary function test.

Four patients were included, but two patients discontinued before first injection; due to personal reasons and an unknown interaction with other medication. Patient 1 and 2 received sandostatin in this trial and patient 3 and 4 were treated outside this trial (Table 1). The latter two patients were refractory to previous medication including immunosuppressive medication and TNFα-blockers with threatening organ damage and were treated with sandostatin as there were no other proven treatment options available.

Uptake on SRS did not change during treatment (Table 1). In addition, no substantial or durable improvement was seen in secondary endpoints including pulmonary function and sIL-2R. Furthermore, clinical evaluation did not show a decrease in disease activity. In this respect our patients still showed symptoms in spite of sandostatin; patient 1 had evident arthritis, patient 2 experienced general systemic complaints, while patient 3 had a uveitis flare and patient’s 4 kidney function continued to decrease.

The adverse events caused by sandostatin are well known due to its extensive use in other diseases. Most common side effects of sandostatin are gastrointestinal complaints; nausea and diarrhea, and mostly show spontaneous resolution (10). All patients reported mild gastrointestinal complaints as described in literature. Patient 1 developed a significant increase in liver enzymes. Sandostatin was discontinued whereupon the enzymes quickly decreased to a stable level before the patient choose to quit the study. Furthermore, gallstones can be formed and is reported in 20-30% of patients, while in most cases this will not lead to problems as they are usually asymptomatic (10). Patient 2 developed symptomatic gallstones after 11 months leading to a

| Patient/ Age | Disease duration (y) |Trial yes/no | Indication | Initial SRS score | Initial FVC (%) | Initial DLCO (%) | Initial Eye activity | Eye SRS score | Initial sIL-2R | Initial Creatinine | Creatinine | Efficacy yes/no |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1/M/43 | 11/4 | yes | Joints | 4 | ND | 111 | 117 | 83 | ND | ND | 7300 | 6100 | ND | ND | no |
| 2/F/55 | 21/6 | yes | Pulmonary | 4 | 5 | 81 | 83 | 62 | 63 | ND | 2500 | 2100 | ND | ND | no |
| 3/F/50 | 7/11 | no | Uveitis | ND | ND | 112 | 110 | 45 | 41 | uveitis | Flare | 16900 | 10400 | ND | ND | no |
| 4/F/58 | 10/5 | no | Kidney | 6 | 6 | ND | ND | ND | ND | ND | 28900 | 38600 | 160 | 173 | no |

Results primary and secondary endpoints at baseline and during treatment with sandostatin Pulmonary functions FVC and DLCO presented in % predicted.

* Patient 3 had a flare of panuveitis of the left eye with a need of starting corticosteroid treatment.

sIL-2R in pg/mL; creatinine in μmol/L. M; Male, F; Female, y; years, m; months, SRS; somatostatin receptor scintigraphy, ND; not determined, FVC; forced vital capacity, DLCO; diffusing capacity, sIL-2R; soluble interleukin-2 receptor.
cholecystectomy. Patient 3 had significant and objective weight loss during treatment necessitating stop of treatment. Patient 4 discontinued sandostatin after 5 due to lack of effectivity.

This report presents our experience with sandostatin in patients with chronic, active sarcoidosis. We did not observe a response on SRS or any clinical parameter. Adversely, our patients did experience gastrointestinal adverse events including one serious adverse event; cholelithiasis leading to cholecystectomy. In contrast to macrophages, fibroblasts selectively express sst1 and subsequently sandostatin does not bind to fibroblasts. However, pasireotide could potentially target fibroblasts as it also binds to sst1. For future studies, the newer somatostatin analogue pasireotide could be considered a therapeutic target specifically in fibrotic sarcoidosis due to multireceptor targeting (16). In conclusion, sandostatin did not demonstrate significant clinical effects in our patients with chronic active and therapy refractory sarcoidosis.

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