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## INTRA-ARTICULAR SOMATOSTATIN 14 REDUCES SYNOVIAL THICKNESS IN RHEUMATOID ARTHRITIS: AN ULTRASONOGRAPHIC STUDY

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**Summary:** Sixteen patients with RA (3 males, 13 females), diagnosed according to RA revised criteria, were selected and entered the study. They underwent six intra-articular injections of 750 mcg of SST14 at 15-day intervals. The thickness of the synovial membrane (SM) was measured with a 5-MHz linear sound with longitudinal and transversal scanning carried out on the upper patellar cavity. The contralateral knee was also assessed together with the injected knee in order to ascertain any systemic effect of the drug. A significant reduction of SM thickness was observed already at the first control (T3) in 14 out of 16 patients. At the 5th and 6th injections (T5 and T6) the reduction was still significant but to a lower extent. In 8 out of 16 cases a reduction of SM thickness was observed in the contralateral knee. Analysis of these data clearly shows that the intra-articular injection of SST14 is able to reduce the thickness of SM in patients with RA, and indicates that SST14 may directly reduce synovitis. This particularity has been detected in our work with a non-invasive technique such as the joint ultra-sound (US). In conclusion, our work confirms the efficacy of SST14 in the control of RA synovial hypertrophy and the reliability of US technique in the measurement of SM thickness.

### Introduction

Somatostatin 14 (SST14) is the tetradecapeptide which has been shown to be effective in the treatment of psoriatic arthritis (1) and rheumatoid arthritis (RA) (2). The analgesic effect of SST14 (3) in the management of painful joints cannot explain the long-standing anti-inflammatory effect of the drug leading to a marked reduction of synovitis (4). SST14 has been demonstrated to interfere with the

generation of neurogenic inflammation by inhibiting the release from sensory terminals of substance P (5), a neuropeptide which significantly increases in the synovial fluid of RA patients (6,8).

Ultra-sound (US) joint examination is a non-invasive tool for the examination of the periarticular tissue, synovial membrane (SM) and cartilage. The technique allows the highlighting of the morphological modifications of SM, by detecting the presence of hypertrophic tissue (villi) as well as measuring the changes in thickness (9,13).

The aim of our study was to verify whether the intra-articular anti-inflammatory activity of SST14 on RA synovitis is characterized by a reduction in SM thickness.

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**Materials and methods**

Sixteen patients with RA (3 males, 13 females, mean age 47.5 years), diagnosed according to RA revised criteria (14), were selected and entered the study. The fundamental criteria of choice was the disease activity characterized by evident knee joint synovitis. They underwent six intra-articular injections of 750mcg of SST14 (Stilamin, Serono) (2) at 15-day intervals. The thickness of SM was measured with a 5-MHz linear sound with longitudinal and transversal scanning carried out on the upper patellar cavity.

Measurement of SM thickness in the selected knee joint was carried out at basal time (T0) and subsequently after the 3rd injection (T3), the 5th

injection (T5) and 15 days after the last intra-articular injection (T6). The contralateral knee was also assessed, together with the injected knee in order to ascertain any systemic effect of the drug. The joint cartilage was not especially investigated, because of the brief duration of the study. Statistical evaluation was performed with a paired Student's *t* test.

**Results**

A significant reduction of SM thickness was observed already at the first control (T3) in 14 out of 16 patients. At T5 and T6 the reduction was still significant but to a lower extent.

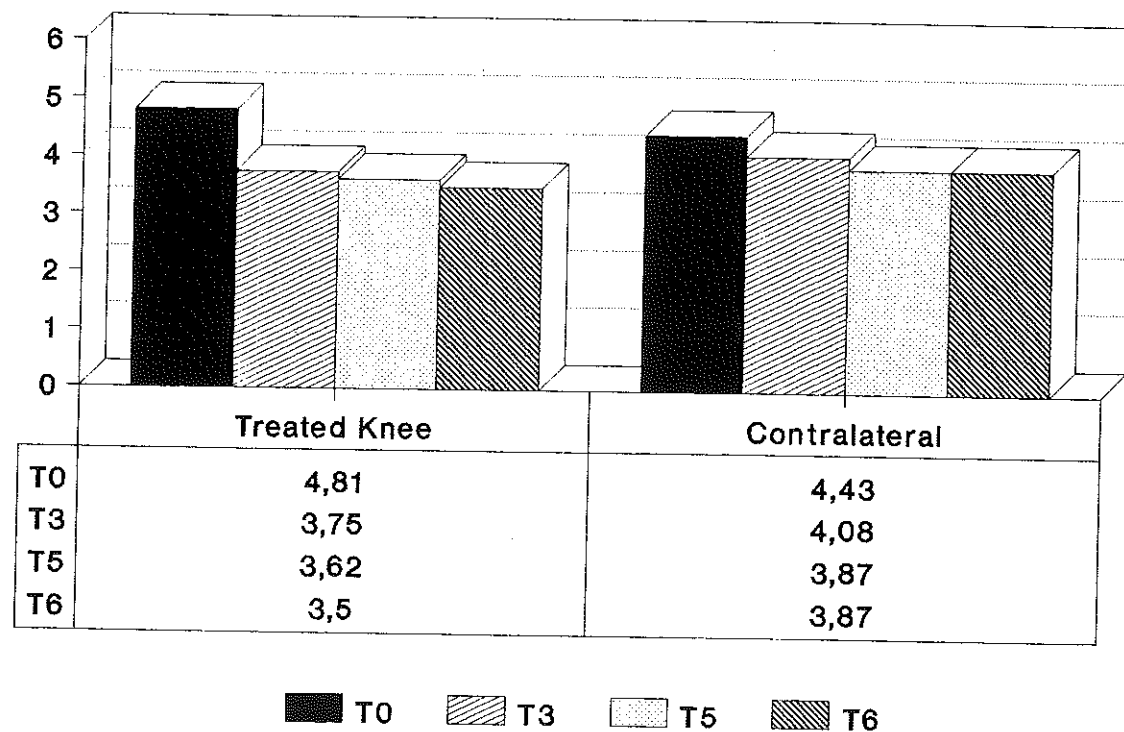


Fig. 1 Thickness of the synovial membrane in treated and contralateral knees.

The average thickness of SM in all patients is shown in Fig. 1; it is noteworthy that in healthy subjects the SM thickness usually ranges from 3.0 to 3.5 mm.

In our cases we started at T0 with 4.81 mm and then was followed by a reduction to 3.75 mm at T3, and further reductions at T5 and T6 to 3.62 mm and 3.5 respectively. When expressed in % versus T0, the reductions obtained were 22% at T3, 24% at T5 and 27.2% at T6 (Fig. 2). Statistical analysis confirms that the best results are obtained after the last time-point: we could affirm that the injection of 750mcg of SST14 has a rapid effect of the SM thickness (as early as the 3rd injection T3) which is still improved after the 5th injection (T5) and also

15 days after the last intra-articular injection (T6) (Table I).

In the contralateral knee, a reduction of SM thickness was observed in 8 out of 16 cases; the thickness tapered from 4.43 mm at T0 down to 4.06 mm at T3 and 3.87 mm at T5 and T6 (Fig. 1). Variations of 8.3% at T4, 12.6% at T5 and T6 were found (Fig. 2), but these are absolutely not significant as compared to the change obtained in the treated knee.

Fig. 3 (a,b,c) shows the reduction of SM thickness in an SST14-treated patient. Starting from a thickness of 8 mm at basal time (Fig. 3a), it tapered to 4 mm at T3 (Fig. 3b) and 3 mm at T6 (Fig. 3c).

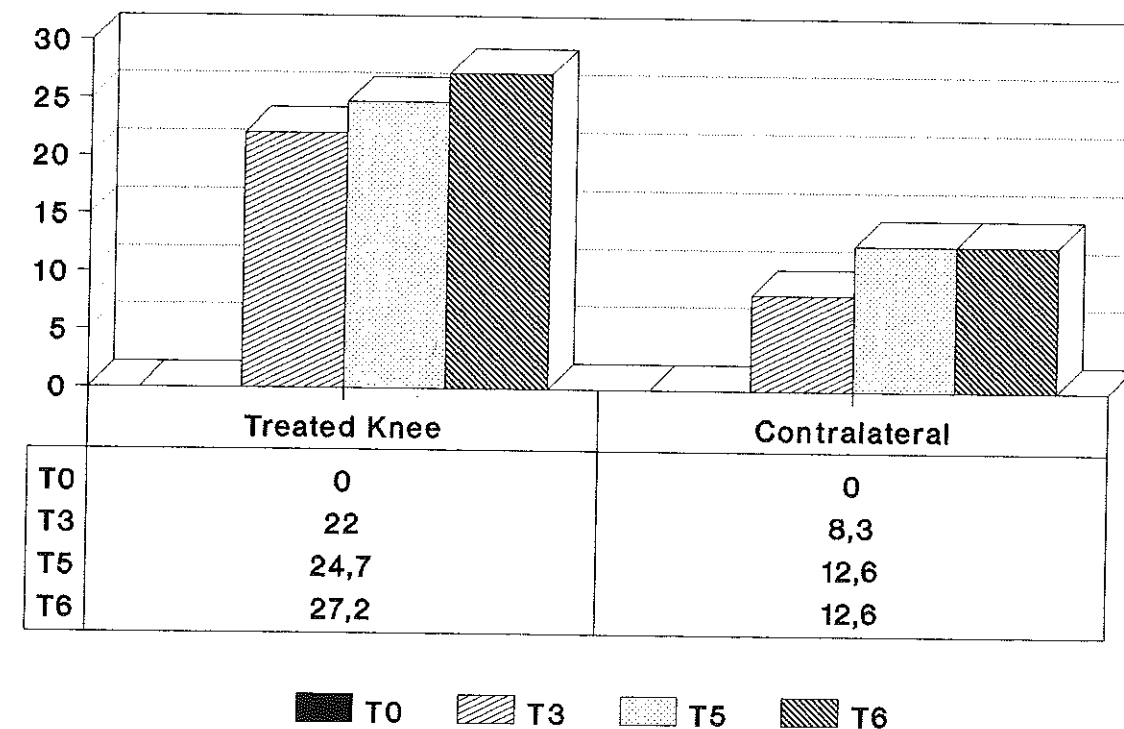


Fig. 2 Reduction in % of the thickness of the SM in treated and contralateral knees.

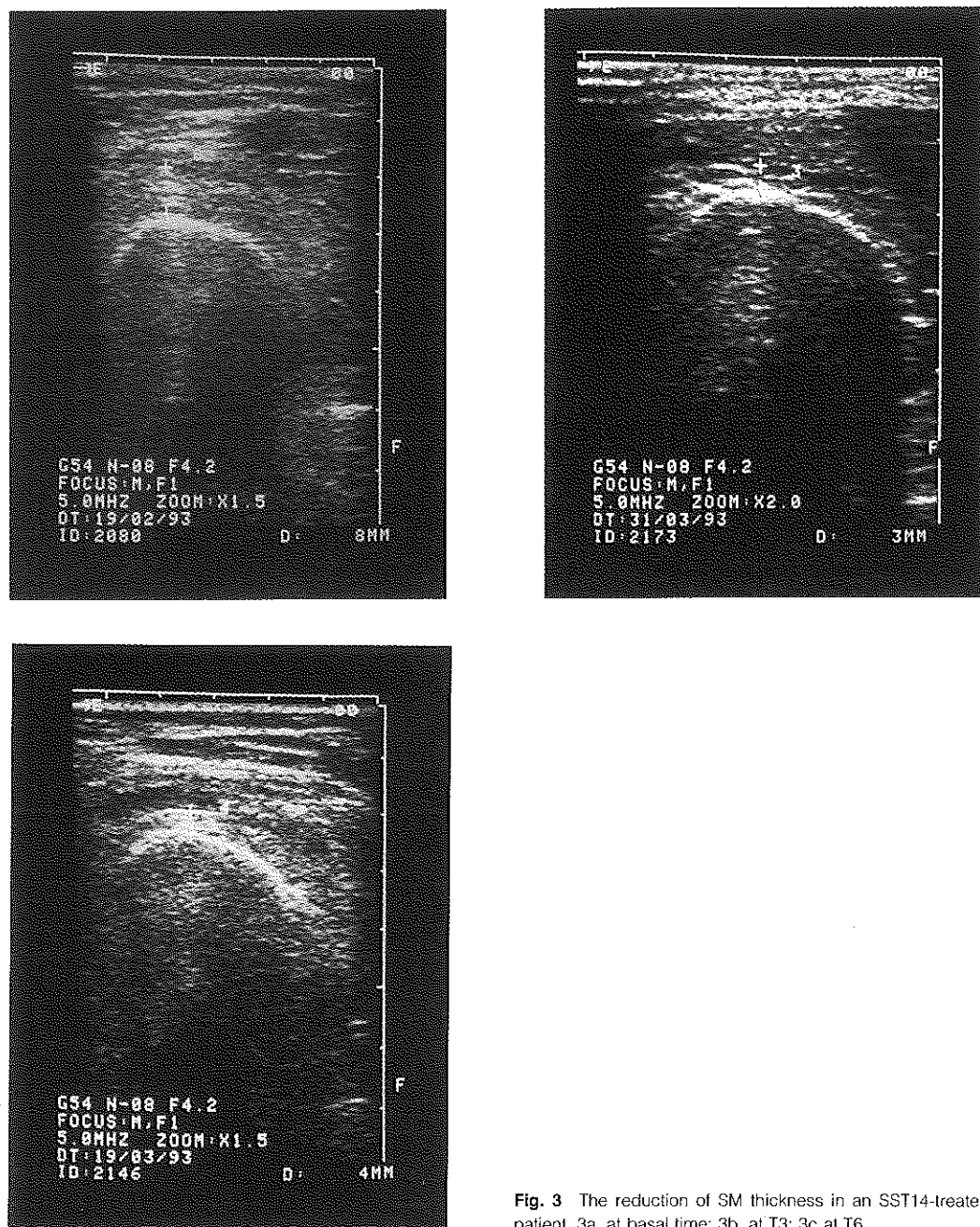


Fig. 3 The reduction of SM thickness in an SST14-treated RA patient. 3a, at basal time; 3b, at T3; 3c at T6

Table I Statistical significance between the values found for the thickness of the synovial membrane at the various examination times (Students *t* test)

	T0	T3	T5	T6
T0		p < 0.01	p < 0.005	p < 0.005
T3	p < 0.01	—	n.s.	n.s.
T5	p < 0.005	n.s.	—	n.s.
T6	p < 0.005	n.s.	n.s.	—

### Discussion

Analysis of these results clearly shows that the intra-articular injection of SST14 is able to reduce the thickness of SM in patients with RA, indicating that SST14 may directly reduce synovitis. This peculiar effect has been detected in our work with a non-invasive technique such as the joint US. The present results are in agreement with the previous reports on SST14 efficacy on human (1,3) and experimental arthritis (15,26). The reduction of SM thickness may help to explain the long-standing improvement obtained with SST14 administration by the intra-articular (2,3) and endovenous routes (1). The contralateral knee showed a slight reduction of SM thickness; this seems to indicate that the quantity of SST14 diffused by the intra-articular injection in the systemic circulation does not influence the inflammatory process of the contralateral knee.

It is clear that our work cannot explain the mechanism by which SST14 may induce the reduction of synovitis. Some authors have proposed it as an anti-chemotactic drug (17), but this view is still controversial (18). A recent investigation has shown, in a rat model of inflammation, that SST14 analogues reduce the volume and leukocyte concentration of the exudate, and reduce the levels of substance P, TNF alpha and CHR (19). Another mechanism that seems more likely to account for the anti-inflammatory activity is the ability of SST14 to reduce

neurogenic inflammation through the reduction of substance P release from sensory terminals (4).

Our results also confirm that joint ultra-sound evaluation is a non-invasive method able to measure the changes of the synovial membrane thickness, US examination is thus a reliable tool that may be used for a frequent assessment of the joint and periarticular tissues. Magnetic-resonance imaging has been also proposed as a very precise tool for measuring the SM thickness, but the problem with this technique is the high cost and the fact that it cannot be frequently repeated within a limited space of time.

In conclusion, our work confirms the efficacy of SST14 in the control of RA synovial hypertrophy and the reliability of US technique in the measurement of SM thickness.

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