# Pravastatin Reverses Established Radiation-Induced Cutaneous and Subcutaneous Fibrosis in Patients With Head and Neck Cancer: Results of the Biology-Driven Phase 2 Clinical Trial Pravacur

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# PRAVASTATIN REVERSES ESTABLISHED RADIATION-INDUCED CUTANEOUS AND SUBCUTANEOUS FIBROSIS IN PATIENTS WITH HEAD AND NECK CANCER: RESULTS OF THE BIOLOGY-DRIVEN PHASE II CLINICAL TRIAL PRAVACUR

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**Running title:** Statins mitigator radioinduced fibrosis

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**Keywords:** curative anti-fibrotic treatment, radio-induced fibrosis, statins

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## ABSTRACT

**Purpose:** The "xxx" phase II trial (NCTxxx) assessed the efficacy of pravastatin as anti-fibrotic agent in patients with established cutaneous and subcutaneous radiation-induced fibrosis (RIF) after head and neck squamous cell carcinoma (HNSCC) radiotherapy and/or radio-chemotherapy.

**Methods and Materials:** The main inclusion criteria were: patients with HNSCC in remission, with grade ≥2 cutaneous and subcutaneous neck RIF (NCI-CTCAE v4.0); no current treatment with statins or fibrates. Patients received 40 mg pravastatin/day for 12 months. The primary endpoint was reduction of RIF thickness by more than 30% at 12 months measured by cutaneous high-frequency ultrasonography (HF-US). Secondary endpoints included RIF severity reduction, pravastatin tolerance, and quality of life.

**Results:** 60 patients with grade 2 (n=37), grade 3 (n=22) or grade 4 (n=1) RIF were enrolled from February 2011 to April 2016. The mean interval between RIF diagnosis and pravastatin initiation was 17.1 months. Pravastatin was stopped before 11 months of treatment in 18 patients [due to grade ≥2 adverse events related to pravastatin in eight (13%) patients]. Among the 40 patients in whom pravastatin efficacy was assessed by HF-US at baseline and at 12 months of treatment, a reduction of RIF thickness ≥30% was observed in 15 (35.7% of 42, 95% confidence interval (CI): 21.6% - 52.0%). At the 12-month clinical evaluation, RIF severity was decreased in 50% of patients (21/42) (95%CI: 34.2% - 65.8%), and the patients' self-perception, mood state and social functioning were significantly improved. Pravastatin was well-tolerated with very low occurrence of grade 3 toxicities (myalgia, n=1) and grade 2 toxicities (myalgia/arthralgia or esophagitis, n=3).

**Conclusions:** This phase II prospective study supports the notion of radio-induced fibrosis reversibility. It showed that pravastatin (40mg/day for 12 months) is an efficient anti-fibrotic

agent in patients with grade ≥2 cutaneous and subcutaneous fibrosis after HNSCC radiotherapy.

## INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) can develop in four main locations: oral cavity, oropharynx, larynx and hypopharynx. In 2015, 932,614 new cases were reported worldwide, and HNSCC was the 7$^{th}$ most common cancer and cause of death (1). The standard of care is a multimodal treatment approach with surgery followed by adjuvant radiotherapy (RT), or RT as definitive treatment. The control of locally advanced HNSCC, which is common in patients with history of smoking and alcohol consumption, has been significantly improved by the combination of RT and chemotherapy (RCT), and by RT altered fractionation. However, this population still displays poor outcome (2). Conversely, Human Papilloma Virus-positive and non-smoking related HNSCCs have a better prognosis (3).

Treatment intensification in HNSCC is associated with increased frequency and severity of radiation-induced toxicities, particularly radiation-induced fibrosis (RIF). Neck RIF is a substantial late toxicity. Indeed, at 3 years post-treatment, the risk of grade ≥2 RIF is 56% and 28% in patients who received RT after or not neck surgery, respectively; and 34% after RCT alone (4). The use of modern RT modalities, such as intensity-modulated radiation therapy (IMRT), has significantly reduced the incidence of acute and late toxicities (5). However, grade ≥2 RIF occurrence is still high even with IMRT. In a recent study, Nevens and colleagues observed grade ≥2 RIF in 29.2% of patients at 6 months with an increased occurrence in the case of upfront neck dissection (70.6% versus 18.1%) (6). RIF functional consequences can lead to a decreased patients' quality of life (QoL) as well as to dysphagia, trismus, lymphedema and limited cervical range of motion (7).

RIF usually occurs at least 4 months after RT completion and progresses over the years. The main manifestations of cutaneous and subcutaneous RIF are skin induration and

thickening. RIF severity is graded using the Common Terminology Criteria for Adverse Events (CTCAE) scale. As this rating scale may be subjective, other tools have been developed, such as ultrasonography (US) quantification using a high-frequency transducer. Changes in tissue echogenicity (mild, moderate and severe) are observed in function of RIF severity (8). Older studies showed that measuring tissue deformation in response to an applied force assessed using an ultrasound probe is a quantitative method to monitor RIF, and correlates with symptoms and neck rotation restriction (9).

RIF is the results of a dysregulation of the wound-healing process and is characterized by trans-differentiation of fibroblasts into myofibroblasts and by excessive accumulation of extracellular matrix. Tissue injury, inflammation, and repair play a role in RIF development and progression. The first strategies to reduce or treat cutaneous and subcutaneous RIF were based on top–down approaches, such as the use of superoxide dismutase (SOD) (10) or of pentoxifylline combined with α-tocopherol (vitamin E) (11,12). A better understanding of RIF molecular mechanisms allowed defining potential therapeutic targets, such as transforming growth factor beta (TGF-β) that is activated by RT and is a fibrosis driver (13). Galunisertib, a TGF-β receptor type I kinase inhibitor, combined with a platelet-derived growth factor receptor inhibitor significantly decreased lung RIF in mice models (14). The safety of an anti-TGF-β antibody (GC1008) is currently assessed in early clinical trials in patients with idiopathic pulmonary fibrosis (NCT00125385). Besides TGF-β targeting, we and others reported that the Rho/ROCK/CTGF signaling pathway also is involved in RIF development and maintenance (15,16). Pharmacological modulation of this pathway using statins (i.e., HMG-CoA reductase inhibitors) limits and reduces RIF *in vitro, ex vivo* and *in vivo* in various preclinical models of normal tissue radiation-induced toxicity (17-20).

Based on these promising preclinical results, we designed a biology-driven phase II clinical trial to assess pravastatin efficacy in patients with delayed cutaneous and subcutaneous grade ≥2 RIF after HNSCC RT (NCT xxx).

## METHODS

The protocol was approved by all local institutional review boards and was accepted by the ethics committee of xxx (file number 10-001).

### *Patients*

This bicentric phase II clinical trial enrolled 61 patients with cutaneous and subcutaneous RIF (grade ≥ 2, NCI-CTCAE v4.0) diagnosed at least 6 months but less than 24 months after HNSCC treatment (i.e., adjuvant or exclusive RT, combined or not with concomitant chemotherapy). Patients were in complete remission at inclusion.

Additional inclusion criteria were adequate kidney function (serum creatinine ≤130µM/L) and hepatic function (aspartate aminotransferase and alanine aminotransferase levels at least 2 times lower than the laboratory upper normal limit; bilirubin level 1.5 times lower or more than the laboratory upper normal limit).

Exclusion criteria were long-term steroid therapy, or current treatment with statins, fibrates or cyclosporine; history of severe heart failure; history of muscle toxicity during previous treatments with fibrates or statins; history of hereditary muscle diseases; and baseline muscle creatine kinase (MM-CK) levels 3 times higher than the laboratory upper normal limit.

At baseline, all patients underwent head and neck computed tomography (CT) to confirm HNSCC remission and high-frequency US (HF-US; at least 16-MHz linear transducer) to assess RIF thickness (in mm) compared with neighboring normal skin (upper part of the chest wall). The radiologists who performed the HF-US assessments (image collection and interpretation) were HF-US experts. As RIF is a dynamic process due to permanent extracellular matrix remodeling, RIF thickness was measured at its thickest point at baseline and at all the study time points.

Before inclusion, a written informed consent was obtained from all patients. Then, investigators from the two centers sent by fax the data required for the patient's registration to the xxx. After eligibility check and registration, a unique identification number was assigned to each patient and provided by fax to the investigator and to the pharmacist. Thus, patient registration was done independently from the study investigators. Pravastatin was given to the patients by the hospital pharmacist only after registration.

***Treatment***

Treatment (40 mg pravastatin/day per os for 12 months) began at inclusion. Dose adjustment was not permitted. Premature drug discontinuation was planned in the case of pravastatin-related toxicity (renal, hepatic or muscle problems), cancer progression, consent withdrawal, or major protocol violation. Patients who discontinued pravastatin were followed like all the other patients enrolled in the trial. Neck motion exercises or scar manipulation were not performed during the study because at that time they were not part of the standard of care for HNSCC in xxx.

***Endpoints***

The primary endpoint was RIF thickness reduction of at least 30% (compared with baseline) measured by cutaneous HF-US at 12 months.

The secondary efficacy endpoints were reduction of RIF severity (according to the CTCAE v.4.0) evaluated by clinical examination, and QoL changes using the self-administered VQ-Dermato questionnaire (21). The VQ-Dermato questionnaire is a valid and reliable dermatology-specific QoL instrument for chronic skin diseases, particularly for assessing the effect on QoL of therapeutic strategies (21). It includes seven dimensions (self-perception, daily living activity, mood state, social functioning, leisure activity, treatment-induced limitations, and physical discomfort) explored by 28 items.

Pravastatin tolerance and compliance were evaluated. Pravastatin-related toxicities were assessed by clinical examination and by blood testing (cholesterol and MM-CK level variations).

***Follow-up***

Follow-up visits with the investigator were planned each month during the first three months and then at 6, 12, 18 and 24 months after inclusion. RIF was evaluated clinically and by HF-US every 6 months after treatment start. Patients were asked to fill in the VQ-Dermato questionnaire at baseline and at 6, 12, 18 and 24 months after treatment start. Pravastatin-related toxicities were assessed monthly during the first 3 months, and then at 6 and 12 months.

***Ancillary study***

Before enrollment, an ancillary study to assess pravastatin biological efficacy was proposed to each patient. After signature of the written informed consent for the ancillary study, a skin punch biopsy in the RIF area was carried out before pravastatin treatment initiation and at 12 months. Biopsies were processed using classical histopathological procedure. Hematoxylin-Eosin (HE) staining was used for histological analysis and Sirius

Red staining for quantification of collagen infiltration, as previously described (22). Each patient was its own control.

## STATISTICAL ANALYSIS

This single-stage phase II trial tested the null hypothesis that the success rate would be lower than 10% versus the alternative hypothesis that it would be higher than 30%. This required the inclusion of 40 evaluable patients (i.e., patients who received pravastatin for at least 11 months). If there were more than eight successes among the 40 evaluable patients, pravastatin would be considered interesting in this setting. With this design, the one-sided alpha error rate was 4.2% and the power was 94.5%. According to the expected rate of early discontinuation (30%), around 55 patients were needed for the trial.

The success rate (according to the HF-US assessment and CTCAE grading) was described with the 95% confidence interval. The paired t-test was used to compare the VQ-Dermato scores at baseline and at 12 months, and to compare RIF thickness and normal skin thickness at baseline. As the sample size was small, the Wilcoxon signed rank test was used when appropriate and gave similar results as the paired t-test.

This study was registered at ClinicalTrials.gov, number xxx.

## ROLE OF THE FUNDING SOURCE

The study funder (xxx) had no role in the study design, in the data collection, analysis and interpretation, or in the report writing. The corresponding author had full access to all data and the final responsibility for the decision to submit for publication.

## RESULTS

### *Pravastatin is well tolerated and shows anti-fibrotic effect in a subset of patients*

From February 2011 to April 2016, 61 patients with grade ≥2 cutaneous and subcutaneous RIF after HNSCC were registered (Figure 1). One patient was not eligible because he was already treated with statins, and was excluded from the analyses. The patients' demographic and clinical characteristics at baseline are listed in Supplementary table 1. The total RT dose ranged from 50 to 70 Gy. Patients were mainly treated by 3D-conformal RT (61%), and the others by IMRT (37%). At baseline, 62% of patients had grade 2 RIF and 37% grade 3 RIF (Table 1). RIF was detected after a mean of 9.9 months post-RT. At baseline, skin thickness (measured by HF-US) was significantly increased in the RIF area compared with normal tissue (3.44 mm versus 1.97 mm; p=0.0004).

Eighteen patients stopped pravastatin before 11 months of treatment because of grade ≥2 pravastatin-related toxicities (n=8), consent withdrawal or patient refusal to continue treatment (n=5), or tumor relapse or death (n=5). Among the patients with pravastatin-related toxicities, six stopped treatment during the first 3 months after initiation because of: grade 2-3 myalgia (n=3; pravastatin treatment duration: 0.3 – 3 months), grade 3 arthralgia (n=1; pravastatin treatment duration: 3 months), grade 3 abdominal pain (n=1; pravastatin treatment duration: 2.8 months), and grade 3 esophagitis (n=1; pravastatin treatment duration: 1.7 months). These toxicities led to the definitive discontinuation of pravastatin. The other two patients reported hypersensitivity reaction (n=1 after 6 months of pravastatin treatment), and grade 1 diarrhea and grade 1 erectile dysfunction (n=1 after 8.7 months of pravastatin treatment). In total, 42 patients took pravastatin for at least 11.6 months. Among them, 40 patients underwent HF-US assessment both at baseline and at 12 months. In these 40 patients, the mean RIF thickness was 4.04mm at baseline and 2.24mm at 12 months (reduction by

16.9% ± 38.8%) (Figure 2). A RIF thickness decrease of 30% or more was observed in 15 patients (Table 1), corresponding to a success rate of 35.7% (95% confidence interval: 21.6% - 52.0%). Therefore, according to the hypotheses tested in this trial, the use of pravastatin as anti-fibrotic agent was successful. Besides RIF thickness decrease, pravastatin also reduced RIF severity (CTCAE) in 50% of patients (95% confidence interval = 34.2%; 65.8%). In eight patients, RIF thickness and severity were decreased at the 12-month follow-up visit. After pravastatin completion, no "rebound effect" was observed. RIF thickness, assessed by HF-US, was not significantly different at 12 months (mean=2.24 (SD=1.07); median=2.05 [range=1.00;7.60]), 18 months (mean=2.47 (SD=2.28); median=1.9 [range=1.10;15.0]) and 24 months (mean=2.92 (SD=5.96); median=1.7 [range=1.20;36.0]).

Although the VQ-Dermato questionnaire was not always fully completed by the patients, analysis of the score variations between baseline and the 12-month follow-up indicated that pravastatin treatment significantly improved the self-perception (p=0.027), mood state (p=0.010), social functioning (p=0.040) and global scores (p=0.002) (Supplementary Table 2).

Among the patients who received pravastatin for more than 11 months, compliance was excellent with a mean treatment duration of 365 days [min, max= 335 - 365] and the drug was well–tolerated (Table 2).

***Skin structure is improved and collagen infiltration decreased after 12-month treatment with pravastatin (ancillary study)***

HE staining of skin punch biopsies collected before and after pravastatin treatment (n=19 patients) showed that after 12 months of treatment, the skin histopathological structure was improved in 14 patients, as indicated by the decreased infiltration of immune cells and

normalization of the epidermis thickness (Figure 3A). In the other five patients, no modification was observed. Moreover, collagen infiltration (Sirius Red staining quantification) was decreased in 8/14 patients after pravastatin treatment (Figure 3B and C).

## DISCUSSION

This phase II clinical trial confirmed previous preclinical data on pravastatin anti-fibrotic potential. To the best of our knowledge, this is the first study combining objective and subjective criteria (RIF thickness and severity, respectively) to provide evidence of pravastatin anti-fibrotic efficacy in patients. Although IMRT has significantly reduced the incidence of acute and late toxicities, grade ≥2 RIF still occurs and pravastatin could be proposed to such patients. Pravastatin was well-tolerated and only six patients (10%) experienced discomfort (arthralgia, myalgia) that led to treatment withdrawal during the first 3 months of the trial. This suggests that pravastatin could be better tolerated than the current anti-fibrotic treatment based on pentoxifylline/vitamin E that caused discomfort (hot flushes, nausea, epigastralgia, severe asthenia, headache, or vertigo) in 45% of patients (11), and definitive treatment discontinuation in 11% of patients (n=3/27) because of myalgia, diarrhea or nausea during the first 4 months of treatment (23).

Tissue injury induced by RT can be managed by administering prophylactic agents (or radioprotectors) before RT or mitigators after RT completion, and by curative interventions, after the appearance of radiation-induced toxicities. Here, pravastatin was assessed as a curative approach (i.e., several months after RT completion and in the presence of established ≥ grade 2 fibrosis). This strategy presents several advantages, including the absence of interference with the anti-cancer treatments and its administration only to the patients who really need it. Curative treatment after RIF appearance are based on the idea that fibrotic tissue can be mobilized and the fibrogenic process reversed by normalizing tissue

homeostasis. The biological basis of fibrosis reversion has been reviewed elsewhere (24-26), and several pharmacological strategies have been proposed to achieve this (reviewed by (26)).

As the objective evaluation of fibrosis regression is a critical issue in clinical trials, we chose HF-US to assess pravastatin efficacy and to obtain quantitative measurement of RIF thickness. Delanian and colleagues measured the variation in length and width of the cutaneous fibrotic surface to monitor the efficacy of the pentoxifylline–vitamin E combination (12). However, this measure is operator-dependent and consists in the palpation of the fibrotic block edges. Recently, a systematic review by Shaw and colleagues on objective tools including CT (densitometry and perfusion), Cutometer and US found that US is a better objective measurement than palpation (9). Moreover, 84.9% agreement of inter-rater reliability regarding RIF grade was reported when physical examination was associated with US (8); however, the value of US-based assessment of RIF modulation after anti-fibrotic treatment has never been evaluated. In our study, the decrease of both RIF thickness and severity was observed only in 8 patients. Our findings in normal tissue and RIF areas are in agreement with those of a pilot-study using HF-US for RIF assessment presented at the ESTRO 35 meeting (27). Nevertheless, additional investigations are needed to confirm HF-US value for RIF assessment during anti-fibrotic treatment.

One of the major secondary outcomes of the present phase II clinical trial is that pravastatin efficiently reduced RIF severity and improved QoL. Specifically, 50% of patients displayed a RIF severity decrease of at least one point in the CTCAE grading system, resulting in a quality of life improvement, particularly self-perception, mood and social functioning. No other clinical trial assessing anti-fibrotic agents has focused on these secondary endpoints. Here, we found that pravastatin significantly improved three dimensions of the VQ-Dermato questionnaire (self-perception, mood state and social functioning) and consequently also the global score. Conversely, Gothard and colleagues did not observe any

QoL improvement after 6 months of pentoxifylline– vitamin E treatment for breast RIF (28). Our results are consistent with those reported by Delanian and colleagues (pentoxifylline–vitamin E for at least 6 months), with a mean decrease of the SOMA score by 35% (±20%) and by 48% (±21%) at 6 months and 1 year, respectively (29).

Many preclinical studies assessed different anti-fibrotic agents that target TGF-β 1, inhibit collagen production, or deplete macrophages. Some clinical trials and pilot studies showed RIF reduction after low-dose interferon-gamma therapy (n=4) (30), and higher range of motion after treatment with pirfenidone (n=6) (31). Ongoing clinical trials are assessing different curative strategies: the Tocovid SupraBio-pentoxifylline combination in bowel radiation-induced disease after pelvic RT (NCT02230800); topical superoxide dismutase in skin RIF in patients after HNCC (NCT01771991). A phase I trial evaluates the efficacy of umbilical cord mesenchymal stem cells in established lung fibrosis (NCT02277145). Other clinical trials are assessing mitigation strategies, particularly for the prevention of lung fibrosis by administration of enalapril (NCT01754909), captopril (NCT00077064), or nicorandil (NCT02809456). To date, none of them has reported results comparable with those obtained here using a compound selected on the basis of its biological efficacy (18,20,32). Finally, the results of our ancillary study are consistent with the clinical data, although performed in a limited number of patients. They showed that pravastatin treatment induced structural improvement of the skin in 14 of the 19 patients, suggesting that increasing the treatment duration could lead to further improvement. Moreover, collagen infiltration was reduced in 8/14 patients. In these eight patients, RIF thickness also was reduced by more than 30% (by HF-US), or RIF severity grade was decreased. A specific evaluation of the Rho/ROCK/CTGF pathway would have been interesting, but was difficult to perform in skin punch biopsies due to their small size. These molecular analyses are more accurate in

preclinical and experimental models in which more mechanistic studies can be conducted using both pharmacologic and genetic approaches.

In conclusion, this biology-driven phase II clinical trial shows a curative efficacy and good tolerance of pravastatin in patients with established cutaneous and subcutaneous grade ≥2 RIF in the neck after RT for HNSCC. These results need to be confirmed in a phase 3 randomized trial. However, as very few anti-fibrotic strategies can be proposed to patients in the clinical practice, statins could be already used as secondary treatment in patients with severe cutaneous RIF. More studies are required to investigate the biological differences between responders and non-responders to better target the patients who will benefit from this strategy.

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## FIGURES LEGENDS

**Figure 1.** Study flow chart

**Figure 2:** Relative change in RIF thickness between baseline and 12 months of pravastatin treatment. Negative values indicate a reduction in RIF thickness between baseline and the 12-month follow-up visit; positive values indicate an increase in RIF thickness between these time-points. In the y axis change into: Relative change (%) in RIF thickness between baseline and 12 months.

**Figure 3**: Histological analysis of a skin punch biopsy from a patient with RIF who responded to pravastatin treatment. Punch skin biopsies in the RIF area were performed before pravastatin initiation and at 12 months. (A) Representative images of HE-stained skin sections before (left) and at 12 months of pravastatin treatment (right) showing decreased immune cell infiltration (asterisks) and normalization of the epidermis thickness (arrow); magnification X40. (B) Representative images of Sirius Red-stained sections before and at 12 months of pravastatin treatment showing the reduction of collagen deposition; magnification X40. (C) Densitometric analysis of collagen deposition before treatment and at 12 months of pravastatin treatment.

**Figure 1**

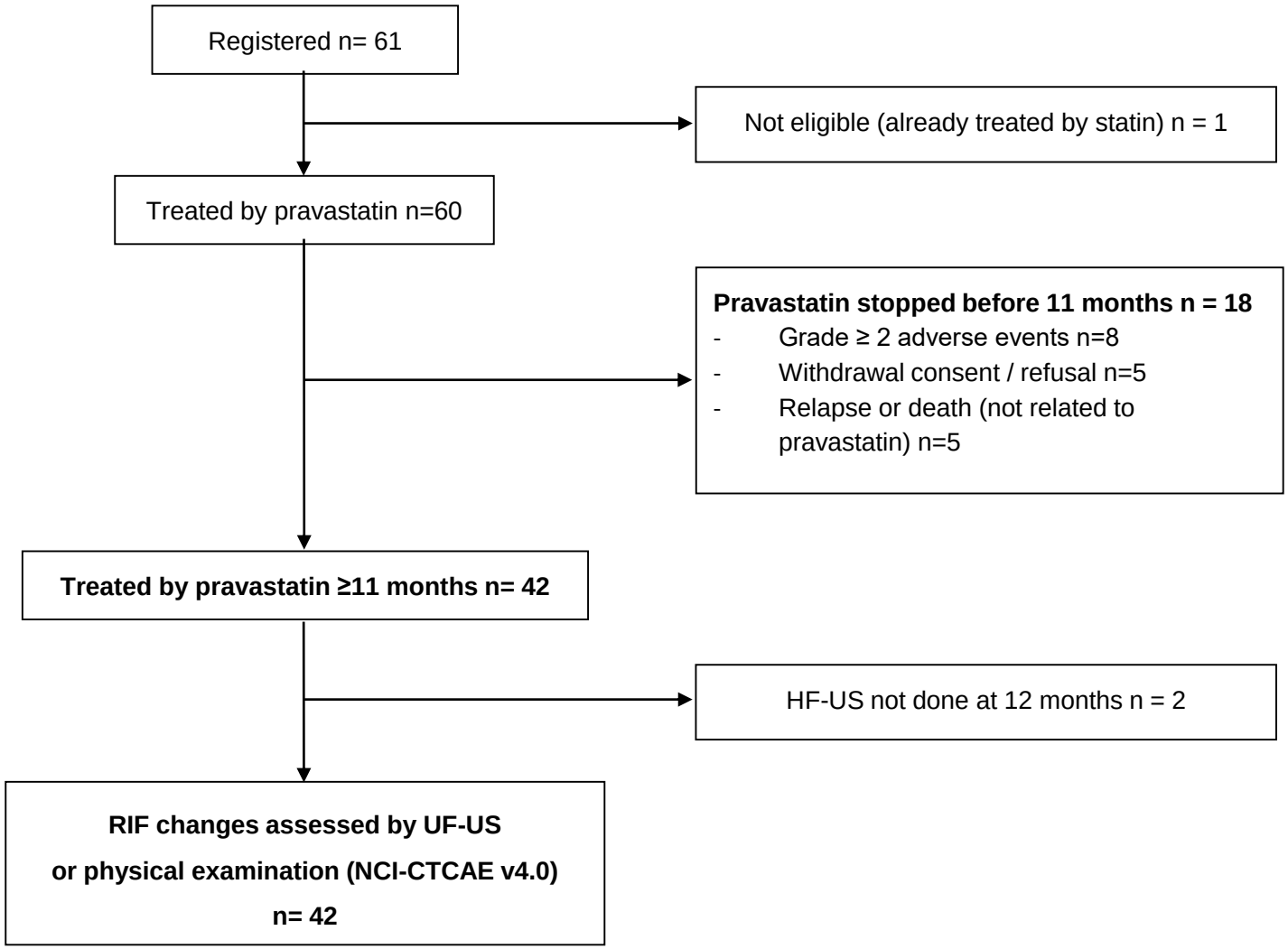

Registered n= 61
Not eligible (already treated by statin) n = 1
Treated by pravastatin n=60
Pravastatin stopped before 11 months n = 18
- Grade ≥ 2 adverse events n=8
- Withdrawal consent / refusal n=5
- Relapse or death (not related to pravastatin) n=5
Treated by pravastatin ≥11 months n= 42
HF-US not done at 12 months n = 2
RIF changes assessed by UF-US
or physical examination (NCI-CTCAE v4.0)
n= 42

**Figure 2**

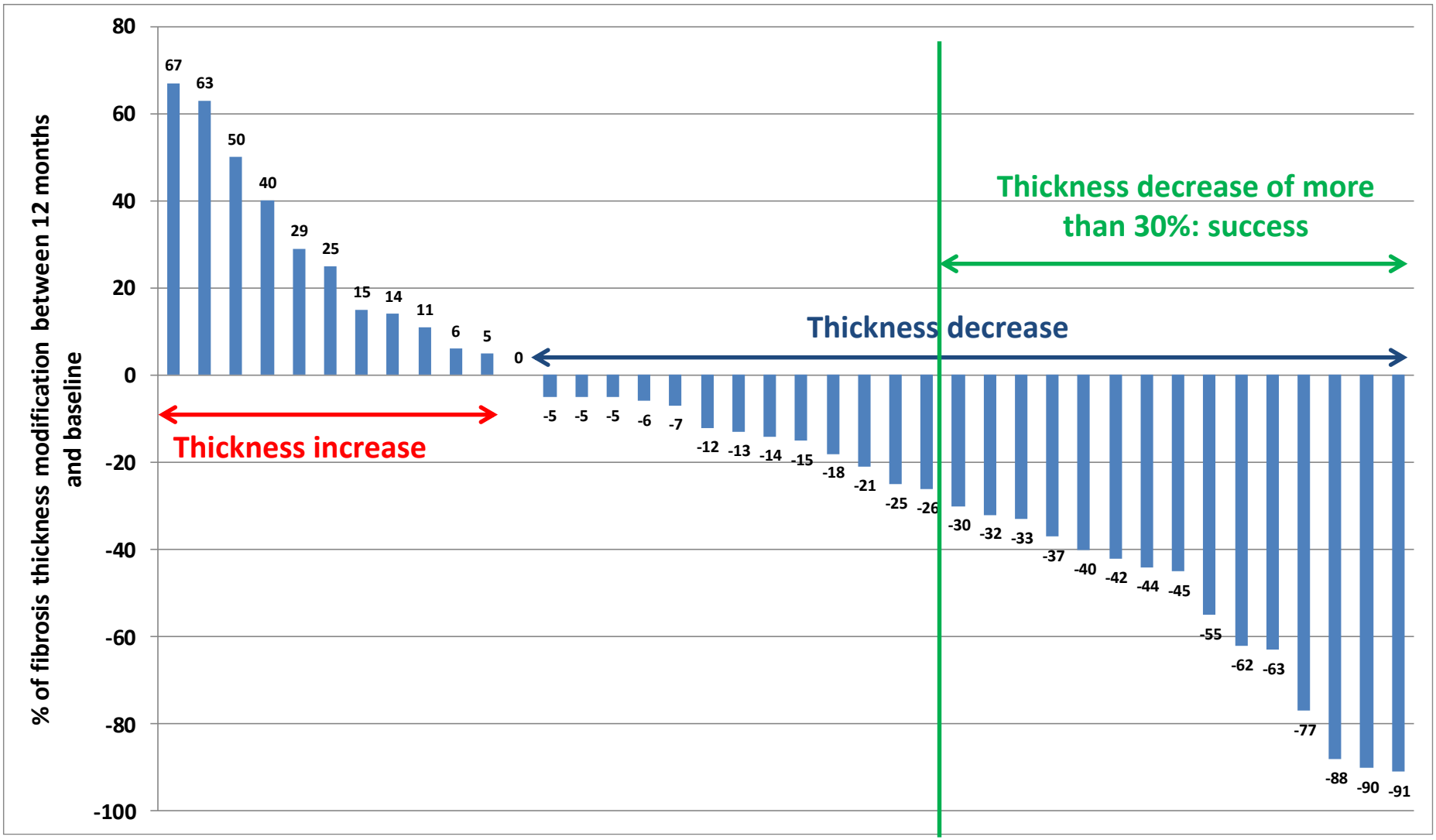
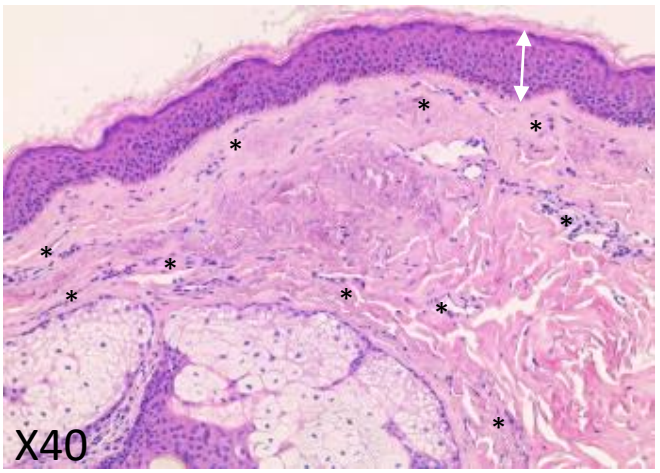

% of fibrosis thickness modification between 12 months and baseline
80
60
40
20
0
-20
-40
-60
-80
-100
67
63
50
40
29
25
15
14
11
6
5
0
-5
-5
-5
-6
-7
-12
-13
-14
-15
-18
-21
-25
-26
-30
-32
-33
-37
-40
-42
-44
-45
-55
-62
-63
-77
-88
-90
-91
Thickness increase
Thickness decrease
Thickness decrease of more than 30%: success

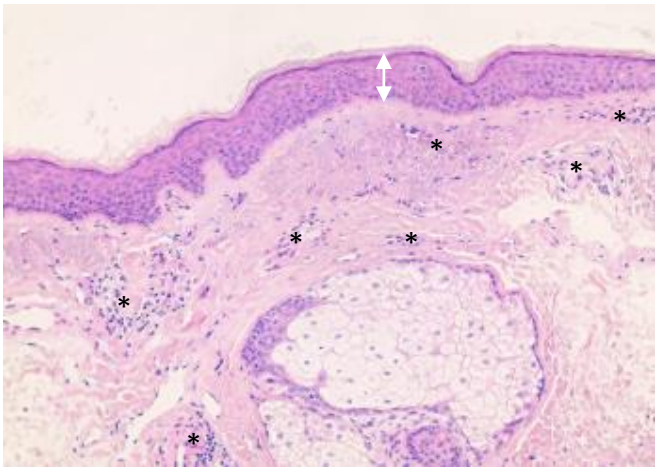
Figure 3

A

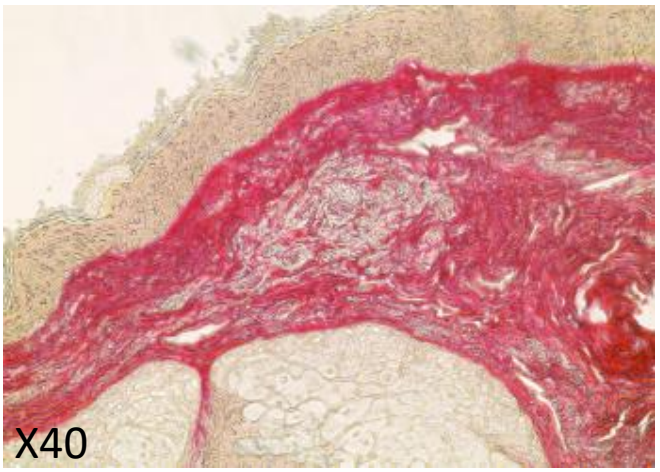
Before Pravastatin treatment

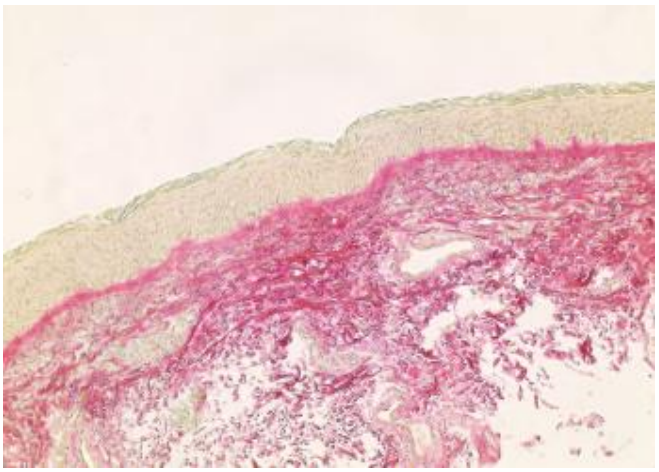
After 12 mo of Pravastatin treatment



B



C

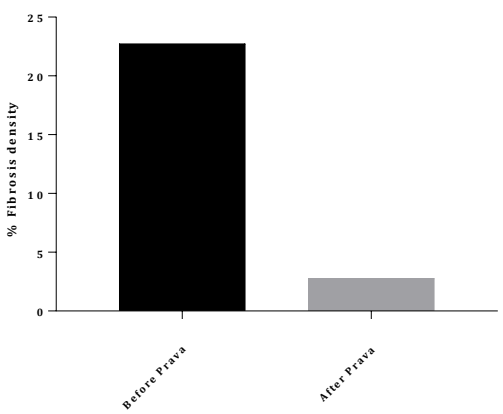


**Table 1:** Evaluation of fibrosis at baseline

| | **Pravastatin for <11 months (N=18)** | **Pravastatin for ≥11 months (N=42)** | **Total N=60** |
|---|---|---|---|
| **TIMING OF RIF APPEARANCE (after RT completion, in months)** | | | |
| Mean (SD)] | 10.7 (8.5) | 9.6 (9.8) | 9.9 (9.4) |
| **TIMING OF PRAVASTATIN INITIATION AFTER RIF ONSET (in months)** | | | |
| Mean (SD) | 17.7 (14.1) | 16.9 (10.5)] | 17.1 (11.6) |
| **BASELINE RIF SEVERITY GRADE (clinical assessment according to the CTCAE v.4.0)** | | | |
| 2 | 11 (61%) | 26 (62%) | 37(62%) |
| 3 | 7 (39%) | 15 (36%) | 22 (37%) |
| 4 | 0 | 1 (2%) | 1 (2%) |
| **BASELINE RIF AND HEALTHY SKIN THICKNESS (in mm, by HF-US)** | | | |
| RIF thickness (Mean (SD); median [range]) | 2.30 (0.96)<br>2.45 [0.70 – 4.40] | 3.92 (4.42)<br>2.40 [0.70 – 20] | 3.44 (3.80)<br>2.45 [0.70 – 20] |
| Healthy skin thickness (Mean (SD); median [range]) | 1.47 (0.52)*<br>1.60 [0.40 – 2.40] | 2.17 (3.53)*<br>1.60 [0.70 – 24] | 1.97 (2.99)**<br>1.60 [0.40 – 24] |
| Thickness difference between RIF and healthy skin (Mean (SD); median [range]) | 0.71 (0.86)*<br>0.70 [-1.4 ; 2.0] | 1.38 (2.78)*<br>0.70 [-4.0 ; 15.4] | 1.18 (2.39)**<br>0.70 [-4.0 ; 15.4] |
| **PRIMARY ENDPOINT – RIF THICKNESS DECREASE (between baseline and the 12-month assessment)** | | | |
| Success (i.e., thickness decrease of 30% or more compared with baseline) [95% confidence interval] | **0 (0%)**<br>**[0% - 18.5%]** | **15 (35.7%)**<br>**[21.6% - 52.0%]** | - |
| Failure (i.e., thickness decrease lower than 30% compared with baseline) | 4 (22.2%) | 25 (59.5%) | - |

| | | | |
|---|---|---|---|
| Unknown – HF-US not done | 14 (77.8%) | 2 (4.8%) | - |
| **SECONDARY ENDPOINT – RIF CTCAE GRADING MODIFICATION (12-month assessment compared with baseline)** | | | |
| Decrease of severity (-2 points) | 0 (0%) | 2 (5%) | - |
| Decrease of severity (-1 point) | 3 (16.7%) | 19 (45%) | - |
| Stable (same score) | 5 (27.8%) | 17 (40%) | - |
| Increase of severity (+1 point) | 0 (0%) | 3 (7%) | - |
| No clinical evaluation at 12 months | 10 (55.6%) | 1 (2%) | - |
| **Success (grade decrease)**<br>[95% confidence interval] | **3*** (16.7%)**<br>**[3.6% - 41.4%]** | **21 (50.0%)**<br>**[34.2% - 65.8%]** | **-** |
| **RIF AND HEALTHY SKIN THICKNESS AT 12 MONTHS (in mm, by HF-US)** | | | |
| RIF thickness (Mean (SD);<br>median [range]) | | 2.24 (1.07)<br>2.05 [1.00 – 7.60] | |
| Healthy skin thickness (Mean (SD);<br>median [range]) | | 1.33 (0.42) $<br>1.40 [0.50 – 2.00] | |

* data missing for one patient;

** data missing for two patients;

*** two patients received pravastatin for 1.7 months and one patient for 8.7 months

$ No significant difference in healthy skin thickness between baseline and 12 months

**Table 2:** Pravastatin tolerance in the 42 patients who received pravastatin for more than 11 months

| **ARTHRALGIA** | **N (%)** |
|---|---|
| None | 39 (93%) |
| Grade 1 | 1 (2%) |
| **Grade 2** | **2 (5%)** |
| **MYALGIA** | |
| None | 32 (76%) |
| Grade 1 | 8 (19%) |
| **Grade 2** | **1 (2%)** |
| **Grade 3** | **1 (2%)** |
| **CRAMPS** | |
| None | 34 (81%) |
| Grade 1 | 8 (19%) |
| **FATIGUE** | |
| None | 39 (93%) |
| Grade 1 | 3 (7%) |
| **DYSPHAGIA – ESOPHAGITIS** | |
| None | 39 (93%) |
| Grade 1 | 1 (2%) |
| **Grade 2** | **2 (5%)** |