



FINAL ACTIVITY REPORT

Grant Agreement number: 305495

Project acronym: DESSCIPHER

Project title: To decipher the optimal management of systemic sclerosis
Funding Scheme: Small or medium-scale focused research project
Period covered: from 01/12/2012 to 30/11/2015

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I. EXECUTIVE SUMMARY

In rare diseases, up to 90% of drug treatment is off-label, due to lack of adequate clinical research data. This is particularly true for the rare autoimmune rheumatic disease systemic sclerosis (SSc). Due to the severity of SSc, several immunomodulating drugs such as cyclophosphamide, methotrexate, azathioprine etc. are used off-label in this disease but their use is mostly based on case reports or small trials, which do not meet the usual standards of controlled clinical trials, as is frequently the problem in rare diseases. Thus, it has only been possible to establish preliminary guidelines for the management of SSc so far. The DeSSciphper projects aimed at improving clinical practice in the management of SSc. The primary objective was to compare the outcomes of different preventive measures and treatments with respect to efficacy and safety of currently used off-label drugs from the early to the advanced phases of the SSc-associated organ system involvements.

This approach is based on five observational trials (OTs), which were designed to analyse and evaluate current real-life treatment strategies for digital ulcers (OT1) and hand arthritis (OT2) to the morbidity and mortality-driving manifestations such as interstitial lung disease (OT3), pulmonary hypertension (OT4) and severe heart disease (OT5). Based on more than 2,000 prospectively enrolled and well-characterised people with SSc from SSc expert centres across Europe, the DeSSciphper project aimed to compare the course of the disease under the different currently used off-label treatment regimens with respect to their efficacy and safety in the prevention or treatment of the organ manifestations under investigation. In addition, DeSSciphper aimed to define and validate appropriate outcome measures. Achievement of these objectives was based on utilization of the unique pan-European EUSTAR network (EULAR Scleroderma Trials And Research group, established and operating under the auspices of the European League Against Rheumatism (EULAR)), which in total comprises more than 190 expert centres from all European countries. In cooperation with the juvenile SSc Working Group (jSSc-WG) of the Pediatric Rheumatology European Society (PRES), not only adult but also juvenile people with SSc were observed.

The DeSSciphper project started in December 2012. After completion of preparative tasks (obtaining ethics approvals, training of staff at recruiting centres and set-up of the research database), enrolment of people with SSc into the five OTs commenced in April 2013. By the end of November 2015, a total of 2,433 individuals had been screened and 2,162 had been enrolled into at least one of the five OTs. As one person could simultaneously participate in multiple OTs, overall 4,686 datasets of people with SSc were followed prospectively in OT1-5 by the end of project month M36.

With the exception of the OT on hand arthritis, which can not be finalized as outlined below,, all DeSSciphper partner and contributing EUSTAR centres have been prepared to and agreed to continue the follow-up of the remaining four OTs beyond the DeSSciphper project period under the auspices of the EUSTAR network and World Scleroderma Foundation (WSF) up to November 2017 in order to facilitate the successful completion of the OTs. After completion of the OTs, the prospectively acquired data of the DeSSciphper project will be merged with the retrospective data of the EUSTAR cohort to become the currently largest available clinical database of SSc worldwide.

After finalization of the follow-up period and data analysis of the four ongoing OTs, the DeSSciphper project will not only be the largest multinational prospective observational research project ever performed in SSc but also become a template for how to manage such an approach including all predictable and unpredictable pitfalls prior to and during trials in rare diseases such as SSc. Its main achievement will be to provide scientific evidence for key clinical questions and problems and will facilitate to advance from off-label use of treatments to their official approval for everyday clinical use. Moreover, the findings of the DeSSciphper OTs will contribute to the development of novel treatment recommendations to improve the management of SSc and its related morbidity and mortality.



II. PROJECT CONTEXT AND OBJECTIVES

DeSScipher aims at improving clinical practice in the management of the rare autoimmune rheumatic disease systemic sclerosis (SSc) for which no orphan drug but only off-label treatments are available.

SSc is a prototypic disease characterized by a complex interaction of autoimmunity, fibrosis and vasculopathy. It is one of the most disabling and disfiguring diseases among the systemic diseases and compared to other rheumatic diseases, SSc is associated with the highest loss of life expectancy resulting in more than 30 years in female patients and 16 years in male patients. With a prevalence of approximately 1 in 2,000 of the general population, SSc is an orphan, multi-organ disease affecting the connective tissue of the skin and all internal organs, driven by alterations of both the immune system and the microvasculature. Among the different immune-mediated rheumatic diseases, SSc is one of the most incapacitating and life-threatening diseases for the affected patients. Aside from the clinically prominent thickening of the skin and the development of digital ulcers (DU), the progressive deterioration of the structure and function of internal organs, particularly the lungs, heart, kidneys and gastrointestinal tract, as well as the frequently underestimated polyarthritis result in a high morbidity and mortality ranging up to 30% over 5 years. The juvenile onset form is rarer than the adult onset form and approximately 5 - 10% of SSc patients develop the disease in childhood, usually around the age of 9 years. In contrast to the majority of other rheumatic and immunologic diseases, validated therapeutic options for SSc patients are much more limited, and neither approved disease-modifying drugs nor orphan drugs are available at present.

Over a three-year period, building upon the expertise of an established, large, multidisciplinary and experienced consortium combining physicians, biostatisticians and biologists with long-standing experience in the field of SSc, DeSScipher was designed as a systemic, integrated approach to the disease. This approach was based on observational trials (OT), which will address different crucial dimensions of this systemic disease: (i) early detection/prevention and treatment of disease manifestations, (ii) functional impairment and severe complications, (iii) affection of different organ systems (skin, joints, lungs and heart), (iv) juvenile and adult individuals.

The project aimed to compare the outcomes of different preventive measures and treatments with respect to efficacy and safety of currently used off-label drugs from the early to the advanced phases of the SSc-associated organ system involvements. For this purpose, DeSScipher also aimed to define and validate appropriate outcome measures. Based on the findings of DeSScipher, novel clinical guidelines were to be developed and validated using a Delphi approach. In addition, by involving a broad community (the European umbrella group of patient associations from 18 countries, different stakeholders, multiple international recruitment centres and renowned experts in the field) the DeSScipher project was positioned to disseminate the novel clinical guidelines rapidly and widely at the international level.

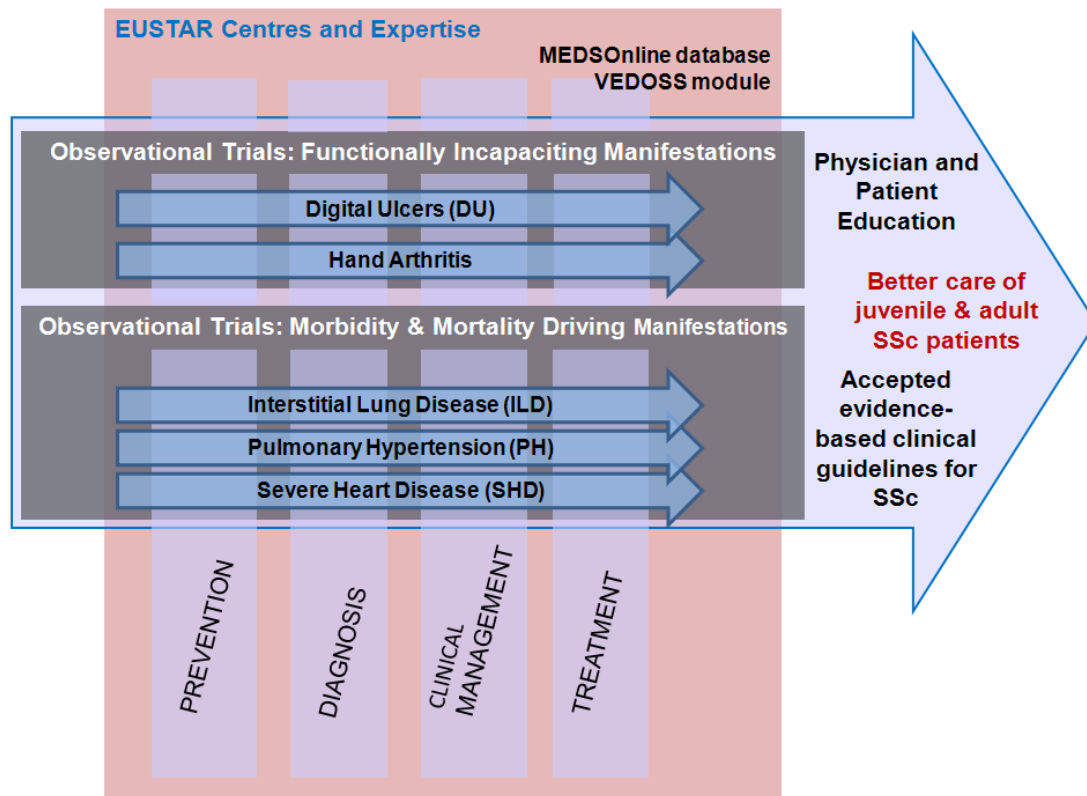
Achievement of these objectives was based on utilization of the unique pan-European EUSTAR network (Scleroderma Trials And Research group, established and operating under the auspices of the European League Against Rheumatism (EULAR)), which in total comprises more than 190 expert centres from all European countries and a network of pediatric rheumatologists. Within the established EUSTAR network, before the start of the DeSScipher project approximately 10,500 adult and 100 juvenile well-controlled and well-documented people with SSc have been taken care of regularly and followed prospectively. Thus, the DeSScipher project received the momentum of the EUSTAR cohort, the largest SSc cohort worldwide, which provided a significant number of datasets to the DeSScipher OTs.

In addition, the concept of the DeSScipher project was perfectly in line with the objectives of the International Rare Disease Research Consortium (IRDiRC), the aims of which are to deliver 200 new therapies for rare diseases and diagnostic tools for the main entities within the 7,000 rare diseases by 2020.

Furthermore, through a collaborative approach, DeSSciphier addressed the crucial challenges which have been identified by the IRDiRC for the purpose of reaching these aims by 2020:

- (i) to establish and provide access to harmonized patient data and samples;
- (ii) to perform the molecular and clinical characterization of rare diseases;
- (iii) to boost translational, preclinical and clinical research.

The DeSSciphier project was designed to provide scientific evidence for advancing from off-label use of treatments to their official approval for everyday clinical use in order to improve the management of SSc in both adult and juvenile individuals.



The concept of DeSSciphier (cf. figure above) was to use the EUSTAR long-term databank MEDSOnline (Minimal Essential Data Set) and a novel diagnostic tool termed VEDOSS (Very Early Detection Of Systemic Sclerosis). The MEDSOnline database follows people with SSc who fulfil the American College of Rheumatology (ACR) classification criteria for SSc and has recruited approximately 9,600 individuals by the end of January 2012. In contrast, the VEDOSS subcohort of EUSTAR represents an inception cohort which prospectively follows adult people who have an increased risk of developing SSc. At present, VEDOSS has recruited 610 individuals. As soon as individuals recorded in VEDOSS fulfil the classification criteria for SSc, they are transferred to MEDSOnline. The unique MEDSOnline and VEDOSS tools were used as the basis for five OT, which were designed to cover evolution phases of the disease from early functionally relevant manifestations such as digital ulcers (OT1) and hand arthritis (OT2) to the morbidity and mortality-driving manifestations such as interstitial lung disease (OT3), pulmonary hypertension (OT4) and severe heart disease (OT5). To this end, the EUSTAR cohort facilitated (i) the comparison of different treatment strategies in a significant number of well-characterized people with SSc and (ii) the evaluation of the course of the disease under different therapeutic regimens with respect to their efficacy and safety in the prevention or treatment of the organ manifestations under investigation. In addition, juvenile individuals with SSc, who were not eligible for any of the five OTs, could be enrolled in an additional separate "juvenile SSc cohort", which was based on an amendment of an established inception cohort for juvenile SSc.



The combined efforts of the well-connected EUSTAR network under the guidance of the DeSScipher consortium provided the scientific basis for the development of novel clinical guidelines in SSc. Rapid dissemination and uptake of the DeSScipher results for a better care of adult and juvenile individuals afflicted by this severe disease was provided for by a close collaboration of the DeSScipher consortium with the EUSTAR network, the juvenile SSc Working Groups (jSScWG) of the Pediatric Rheumatology European Society (PRES) and the pan-European patient organisation FESCA.

In summary, the specific objectives of the DeSScipher project were:

- To improve clinical practice in the management of SSc for both adult and juvenile individuals
- To facilitate an earlier detection and prevention of SSc and its organ manifestations and subsequently initiate disease- or organ-specific treatment
- To improve both quality of life and morbidity/mortality in SSc by addressing functional impairments caused by digital ulcers and hand arthritis as well as life-threatening organ complications due to interstitial lung disease, pulmonary hypertension and severe heart disease
- To develop and validate a reliable algorithm for detecting organ manifestations of SSc at an early stage in adult and juvenile individuals at risk using novel tools such as the VEDOSS tool
- To compare outcomes of prevention and treatment regimens in SSc to define appropriate outcome measures for SSc trials with an aim of defining at least 5 outcome measures
- To evaluate the efficacy and safety of off-label treatments currently used to target the main disabling and life-threatening organ manifestations of SSc
- To contribute actively to the development and rapid dissemination of national, European and international guidelines for the diagnosis and management of adult and juvenile SSc using the EUSTAR and PRES international network with an aim of disseminating to at least all European countries involved in the project.



III. DESCRIPTION OF MAIN S&T RESULTS/FOREGROUND

III.1. Database and data analysis (WP1)

WP1 was lead by the University of Basel (UNIBAS) in close cooperation with the company NEW WIN. The main task of WP1 comprised (i) creation of the data model, and (ii) database programming and testing for the five OTs of DeSScIPHER (task 1.1). Further tasks addressed (i) data monitoring, (ii) source data verification, (iii) plausibility checks and (iv) monitoring of patient recruitment for OT1-5 (task 1.2). Based on these tasks, two scientific deliverables had been defined for WP1: (i) the analysis of risk factors associated with a lower quality of life (task 1.3 by UNIBAS) and (ii) the analysis of disease characteristics in juvenile SSc patients (task 1.4 by Ivan Foeldvari).

III.1.1. Creation of the datamodel and database programming and testing

The pivotal tool for achieving the goals of Task 1.1 was the existing browser-based EUSTAR MEDSOnline database the central server of which is physically hosted within the secure network of NEW WIN in Switzerland and is run behind a firewall. The data model of the MEDSOnline database was extended by the addition of specific data items for the purpose of the five OTs of the DeSScIPHER project. This was done in a step-wise procedure. In a first step, additional items necessary to answer the research questions of the DeSScIPHER OTs were identified by each of the OT-leaders for their respective OTs. Subsequently, these additional items were merged into the existing MEDSOnline data model and combined where appropriate. In a second step, the newly added items were weighted according to importance and feasibility by the OT-leaders to reduce the number of data items to the essential ones. Afterwards the remaining data items were merged if possible. For each data item the type of data entry field was decided on, namely, (i) radiobutton – only one answer possible, (ii) checkbox – various answers possible simultaneously, (iii) pull-down – only one answer possible, (iv) date fields and (v) number fields. An 'unknown' option was added to the data items where applicable. Tool-tips i.e. pop-up texts providing definitions, explanations and assistance, were added to data entry fields where it was appropriate. Moreover, plausible value ranges for data entry of continuous data were specified. Inclusion and exclusion criteria for each OT were implemented. Following this procedure, the team of NEW WIN started to transfer the theoretical data model into a functional internet application with a special focus on an intuitive and easy-to-use web interface as well as the accessibility of the database via different standard web browsers. The DeSScIPHER data model was structured into different sections namely 'patient details', 'history', 'therapy', 'physical examination', 'laboratory', 'tests/functions' and 'nailfold capillaroscopy', with various questions in each section. Printable visit forms of the electronic database have been developed for the entire data set and additionally specific forms for each OT were designed and required patient questionnaires, i.e. the HAQ, the CHFS and the three VAS, were prepared in the centre-specific languages, i.e. English, German, French, Italian and Hungarian, and programmed into an electronically accessible version.

Only EUSTAR centres which had obtained ethical approval for the DeSScIPHER project have been granted access to the DeSScIPHER database module within the EUSTAR MEDSOnline database. The eligibility of a patient for enrolment into one or more of the OTs was evaluated automatically by the system, and only if the inclusion and exclusion criteria of the patient for a specific OT were fulfilled, the user was allowed to enrol the patient into this OT.



III.1.2. Data monitoring, source data verification and plausibility checks and monitoring of patient recruitment for OT1-5

Data monitoring was performed by means of automated online algorithms, for example to identify duplicate entries or missing data. Furthermore, where appropriate, plausibility checks were programmed to increase data quality and plausible value ranges for data entry of continuous data were defined. Besides the automated algorithms, most data entry fields featured a pop-up window providing assistance. Completeness checks were implemented displaying whether each data entry field was filled out or not without the user needing to go through all data entry fields manually. Automated reminders have been e-mailed to the centres on a monthly basis to remind the centres to schedule follow-up visits of patients if medically necessary. Furthermore, detailed database instructions have been developed and the data entry clerks of recruiting study sites have been supported and instructed on a regular basis, as necessary. Data entry fields featured a full audit trail which enabled the study monitoring team to track which items have been changed, how, by whom and when. Furthermore, the progress of recruitment was monitored biweekly in cooperation with the Project Coordinator and reported to all OT leaders and recruiting study sites.

III.1.3. Analysis of risk factors associated with a lower quality of life

Since SSc can greatly impact the patients' quality of life due to the multisystem manifestations, this task aimed to identify predictors of disability in SSc. Therefore, the Health Assessment Questionnaire (HAQ), which is one of the most commonly used measures of disability in musculoskeletal disorders, was extended to form the scleroderma HAQ (SHAQ), including 5 visual analogue scales (VAS) to cover disease-specific disability aspects.

A cross-sectional analysis of 719 SSc patients (median age 59 years, 85% female) was carried out which revealed that dyspnoea, pain, weakness and gastrointestinal symptoms are perceived as the main factors driving the level of patient disability. Interestingly, the predictors of the HAQ and the SHAQ have been almost identical. Moreover, patients and physicians emphasized different aspects in the evaluation of their disease manifestations. These findings will be essential for further management and counseling of SSc patients especially regarding the patients' life quality also in further studies.

The results of this analysis have been presented at the World Scleroderma Congress in Lisbon, Portugal, in February 2016 and are available on the DeSScipher project webpage. A full-text paper is currently in preparation.

III.1.4. Analysis of disease characteristics in juvenile SSc patients

The analysis of disease characteristics of juvenile SSc (jSSc) patients turned out to be a very challenging task within the DeSScipher project. Originally, it was planned to collect the data of up to 120 jSSc patients. However, the low incidence of the disease, in particular in juvenile patients, and difficulties in bringing together jSSc expert centres from all over the world have been major hurdles that had to be overcome. By intensive efforts by Ivan Foeldvari it has been possible to collect the data of 30 jSSc patients from 10 international centres. However, due to difficulties of the contributing centres in fulfilling all ethical requirements, the majority of data was, unfortunately, not available for analysis and had to be removed from the DeSScipher database. In consequence, the number of five remaining jSSc patients was too small for statistical evaluation and robust clinical conclusions.



III.2. Prevention and treatment of functionally incapacitating manifestations (WP2)

WP2 was lead by the Università degli studi di Firenze (UNIFI) in cooperation with the UNIVERSITY OF LEEDS (LEEDS) and PECSI TUDOMANYEGYETEM - UNIVERSITY OF PECS (PECS) and was dedicated to investigate different approaches to prevent and treat the most important functionally incapacitating manifestations in the hands of people with SSc, in particular prevention of new digital ulcers (DU), healing of current DU as well as predictors and treatment options for hand arthritis.

To achieve this goal, three OTs have been designed to specifically address these frequent problems in people with SSc, namely:

- OT1.1 Prospective observational trial assessing the efficacy and safety of currently off-label drugs for the prevention of DU development (UNIFI)
- OT1.2 Prospective observational trial assessing the efficacy and safety of various drugs for the healing of manifest DU (LEEDS)
- OT2 Observational trial on the improvement of hand dysfunction by arthritis (PECS)

Once ethical approvals by the competent legal local/national ethics boards/bodies/administrations of all DeSScipher partners had been obtained, baseline recruitment for all OTs of WP2 was performed between April 2013 the end of November 2015.

While the follow-up of enrolled patients will be continued under the umbrella of the EUSTAR group and World scleroderma foundation (WSF) for two years with regard to OT1.1 and OT1.2, OT2 was not continued. However, the interim analysis of all OTs already provided the first interesting and important results. The progress and main outcome of each of the OTs achieved within the DeSScipher project period is described in detail below.



III.2.1. OT1.1: Prospective observational trial assessing the efficacy and safety of currently off-label drugs for the prevention of DU development

Background

DU are a heavy clinical burden in SSc, therefore their prevention is highly warranted. The objective of this OT was to determine the relative effectiveness and safety of the current off-label use of (i) sildenafil, (ii) bosentan, and (iii) the combination of sildenafil and bosentan compared to intravenous (i.v.) application of iloprost and conventional treatment with vasodilating agents such as calcium channel blockers (CCBs) or ACE inhibitors (ACEi) for the prevention of new DU in SSc patients.

Methods

This OT (study ID HEALTH-F5-2012-305495-OT1) comprised two treatment arms, a prevention arm and a healing arm. The study protocol of the prevention arm has been published at ClinicalTrials.gov, identifier: NCT01836263.

Preliminary Results

A total of 1,394 patients were available for preliminary analysis and 1,210 of them were included in the prevention substudy. A history of DU was a significant risk factor for developing new DU (OR=3.146; 95%CI:1.19-8.31, $p=0.021$), therefore interim analysis was focused on secondary prevention (prevention of new DU in patients with a history of DU). 473 out of 1,210 patients had a history of DU and 268 of them had available follow-up data (58.2% limited and 41.8% diffuse SSc subset). 47 out of the 268 patients (17.5%) were on bosentan, 33 (12.3%) on sildenafil, 40 (14.9%) on iloprost, 31 (11.6%) on sildenafil and bosentan in combination and 117 (43.7%) on CCB/ACEi alone. In patients with a history of DU in the last 24 weeks, the treatment with CCB/ACEi when given alone was associated with a 7-fold increased risk of developing new DU compared to all other treatment arms (OR=7.313, 95%CI: 1.248-42.85, $p=0.027$).

Preliminary Conclusion

A history of DU in the past 24 weeks should trigger an active prevention strategy. In this group, treatment with CCB/ACEi alone is associated with a 7-fold increased risk of developing new DU compared to all other treatment arms.

Outlook

The patients who have been enrolled into the prevention substudy of OT1 until November 2015 will be followed up for 2 years until November 2017 as a EUSTAR clinical project under the auspices of EUSTAR and WSF. After completion of the OT1 prevention substudy, OT1 will facilitate the development of validated Delphi-guidelines regarding the optimal treatment for the prevention of DU in SSc patients.

Publications so far:

Oral and poster presentation at the 4th World Scleroderma Congress (WSC) 2016 entitled "The DeSScIPHER project in systemic sclerosis: observational data on digital ulcers prevention from the EUSTAR group".

Publication plan:

An interim analysis based on the one-year follow-up results is planned in December 2016. The final analysis will be performed after completion of the 24-month follow-up and thus is planned for December 2017. One full-text paper, working title "Best treatment for prevention of digital ulcers in SSc: a report of observational trial 1 of the DeSScIPHER project of the EUSTAR group" is planned to be published in The Journal of Investigative Dermatology (the official journal of the Society for Investigative Dermatology and The European Society for Dermatological Research).



III.2.2. OT1.2: Prospective observational trial assessing the efficacy and safety of various drugs for the healing of manifest DU

Background

The objective of this OT was to determine the relative effectiveness and safety of the current off-label use of (i) sildenafil, (ii) bosentan, and (iii) the combination of sildenafil and bosentan compared to i.v. iloprost and conventional treatment with vasodilating agents such as calcium channel blockers (CCBs) or ACE inhibitors (ACEi) for the healing of DU in SSc patients.

Methods

This OT (study ID HEALTH-F5-2012-305495-OT1) comprised two treatment arms, a prevention arm and a healing arm. The study protocol of the prevention arm has been published at ClinicalTrials.gov, identifier: NCT01836263.

Preliminary Results

Thus far, longitudinal data for 156 out of 265 patients with DU could be collected. 57% of patients were on vasodilators (sildenafil, i.v. iloprost and CCB, alone or in combination), 5.8% were on a single vasoactive drug (bosentan) and 37.2% patients were on combination therapy. The mean number of DU per patient at the inclusion visit was comparable among the three treatment arms. At 12 and 24 months, the mean number of healed DU per patient was 1.5 and 1.8 fold higher in the vasodilator group compared to the vasoactive and combination groups ($p < 0.013$ and $p < 0.018$), respectively. No significant difference in the mean number of healed DU per patient was observed at 6 months. Initial exploratory analysis also suggested that the estimated mean time to healing of at least one DU was 9.71 ± 2.2 months in the vasoactive arm, 8.7 ± 0.5 months in the vasodilator arm and 7.9 ± 0.6 in patients on combination therapy. Furthermore, when considered separately, patients on sildenafil ($\pm$ CCB) showed the highest healing rate at 6 months follow-up, compared to other drug combinations.

Preliminary Conclusion

The combination treatment appears to result in a shorter time to healing. However, a longer follow-up extension and a correction for concurrent treatment and confounding factors are still in progress.

Outlook

The patients who have been enrolled into the healing substudy of OT1 until November 2015 will be followed up for 2 years until November 2017 as a EUSTAR clinical project under the auspices of EUSTAR and WSF. After completion of the OT1 healing substudy, OT1 will facilitate the development of validated Delphi-guidelines regarding the optimal treatment for the healing of DU in SSc patients.

Publications so far

Poster presentation at the 4th WSC 2016 entitled "Healing of digital ulcers in systemic sclerosis: real life data from the DeSSciphier observational study of the EUSTAR group".

Publication plan

An abstract entitled "The efficacy of vasoactive and vasodilating drugs on digital ulcers healing in systemic sclerosis: data from the DeSSciphier observational study of EUSTAR group" has been submitted to the EULAR 2016 congress to be held in London, UK, in June 2016.

The final analysis will be performed after completion of the 24-month patient follow-up in November 2017. One full-text paper, working title "Best treatment for healing of digital ulcers in SSc: a report of observational trial 1 of the DeSSciphier project of the EUSTAR group" is planned to be published in The Journal of Investigative Dermatology (the official journal of the Society for Investigative Dermatology and The European Society for Dermatological Research).



III.2.3. Retrospective subtask prior to start of OT2: the effect of different treatment options on joint involvement in SSc

Background

Hands are commonly affected in SSc patients evolving into significant disability. In particular, arthralgia, arthritis, joint contractures and tendon friction rubs are contributors to impairment of hand function. Therefore, the objective of this retrospective study was to investigate the effects of different treatments on joint involvement – defined as arthritis, joint contractures and/or tendon friction rubs – in SSc patients. We intended to examine the effectiveness of currently used therapeutic approaches in the management of patients with joint involvement in a retrospective analysis of the EUSTAR SSc cohort.

Methods

The data of the EUSTAR MEDSonline database from June 2004 up to April 2012 have been analyzed. Patients fulfilling the ACR classification criteria of SSc have been included if they received one of the following drugs or combinations of drugs on at least 2 visits 12 ± 1 months apart from one another:

1. methotrexate (MTX) with or without low-dose corticosteroids, without biologic therapy (study group 1)
2. azathioprine with or without low-dose corticosteroids, without biologic therapy (study group 2)
3. mycophenolate with or without low-dose corticosteroids, without biologic therapy (study group 3)
4. low-dose corticosteroids without DMARDs, without biologic therapy (study group 4)
5. rituximab with or without DMARDs, with or without corticosteroids (study group 5)
6. imatinib with or without DMARDs, with or without corticosteroids (study group 6)
7. TNF-alpha antagonist with or without DMARDs, with or without corticosteroids (study group 7)
8. no DMARD, biologic or corticosteroid treatment (control group) (study group 8)

Preliminary Results

From the pre-planned 8 study-groups we could only analyse five groups, because there were not enough patients with follow-up within 12 ± 1 months in study groups 5, 6 and 7 ($n=24$, 4 and 16, respectively). With regard to the remaining study groups, a decrease in the prevalence of joint synovitis over the time could be observed in all treatment groups including the control group. The decrease was most prominent in study group 1. However, the decrease was found to be statistically significant only in the control group ($p=0.014$). The lowest prevalence of synovitis could be observed in study groups 2 and 3. In contrast, as expected, the prevalence of joint contractures did not decrease over time in most treatment arms. However, in study group 3 the prevalence of contractures decreased by 13%, although this was not statistically significant. Another interesting tendency was that the number of contractures did not increase in the control group in contrast to study groups 1, 2, and 4. With regard to tendon friction rubs, a reduction could be observed in study groups 1, 4 and the control group; however, this was only statistically significant in study group 4 ($p=0.022$).

Preliminary Conclusion

In many groups it was not possible to draw any conclusion because of the lack of reliable, well-defined data. Corticosteroid treatment seemed to show some efficacy with regard to the improvement of tendon friction rubs. Although no statistical difference was demonstrated, methotrexate (and maybe some other immunomodulating drugs as well) may have some effect on the treatment of synovitis. These findings need to be interpreted with caution due to the limitation of the retrospective nature of this analysis. In particular, the definitions of synovitis, joint contractures and tendon friction rubs have not been clearly specified, and different groups used different criteria for these particular items causing a patient reporting bias. However, the available data indicate that certain drugs may be efficient in the treatment of synovitis and tendon friction rubs. Therefore, it was reasonable to perform OT 2 as planned in the DeSSciph project.



III.2.4. OT2: Prospective observational trial on the improvement of hand dysfunction by arthritis

Background

The objective of this particular prospective trial was to investigate the effects of different treatments on joint involvement in SSc patients. The CDAI along with the HAQ-DI and CHSF have been used to analyse and compare the efficacy of the off-label DMARDs MTX, leflunomide, azathioprine, mycophenolate mofetil and low-dose corticosteroids.

Methods

The study protocol of this OT (study ID HEALTH-F5-2012-305495-OT2) has been published at ClinicalTrials.gov, identifier: NCT01834157.

Preliminary Results

Out of 199 SSc patients with hand arthritis who have been enrolled into OT2, the baseline HAQ-DI was recorded for 131 patients (65.8%). Out of these, 1-year follow-up data were available for 72 SSc patients but baseline and follow-up data were available only for 39 SSc patients, and further 14 patients had to be excluded for other reasons. The preliminary analysis of the remaining 25 patients showed variable HAQ-DI scores between 1.3 and 1.9 with the highest score in patients treated with MTX $\pm$ corticosteroids. Over time, a tendency towards decrease of HAQ-DI scores was observed in all treatment arms. However, the low number of patients did not allow any statistical analysis of the primary endpoint.

Preliminary Conclusion

While OT2 has recruited a high number of SSc patients with arthritis, measurements such as the HAQ-DI or CHSF turned out to be rarely used in routine clinical practice. Therefore, no conclusions on the treatment effect of different DMARDs on hand arthritis in SSc could be drawn. However, OT2 delivered important new information about the pattern of joint involvement as well as real-life treatment of arthritis in SSc, including data on the safety of off-label treatment. In particular, an unexpectedly frequent off-label use of biologics deserves publication and also is of importance for further planned studies.

Outlook

OT2 was discontinued by January 2016.

Publication plan

No publications so far. A full-text paper, working title "Joint involvement and hand dysfunction in systemic sclerosis: a cross-sectional descriptive analysis of the multicentre prospective observational trial 2 of the DeSSciphper project of the EUSTAR group" is planned to be published in Annals of the Rheumatic Diseases (the official journal of the EULAR). Furthermore, a full-text paper on "Real-life treatment patterns of arthritis in systemic sclerosis" and a manuscript about the safety data of off-label use of DMARDs in SSc patients with hand arthritis are planned to be published.



III.2.5. Subtask of OT2: Validation of the articular disease activity indices DAS28, DAS28(CRP), SDAI and CDAI in SSc patients

Background

Aim of this subtask was to validate the Disease Activity Score of 28 Joints using ESR (DAS28-ESR) and CRP (DAS28-CRP), the Simplified Disease Activity Index (SDAI), and the Clinical Disease Activity Index (CDAI) used in rheumatoid arthritis (RA) for SSc patients.

Method

Seventy-seven SSc patients, 40 RA patients, 20 patients with primary Raynaud's syndrome (PR), and 28 healthy volunteers were assessed. Besides the DAIs, the European Scleroderma Study Group Activity Index (EScSG-AI), the HAQ-DI, the Cochin Hand Function Scale (CHFS) and the Short Form Health Survey (SF36) were evaluated. The validation procedure included the assessment for truth, discrimination and feasibility.

Results

DAS28-ESR, DAS28-CRP, SDAI and CDAI showed significant correlation with EScSG-AI, HAQ-DI, CHFS, and the physical component of SF36 ($p < 0.001$). All four indices discriminated patients with SSc from RA, PR and healthy controls, respectively ($p < 0.01$). With the exception of DAS28-CRP, the other three indices also discriminated between subgroups of SSc based on value of EScSG-AI (≤ 3 and > 3) ($p < 0.05$). All four DAIs showed a good inter- and intraobserver reliability based on repeated measures of two independent investigators ($p < 0.001$).

Conclusion

All four disease activity composite indices were found to be valid measures for assessing arthritis in SSc. DAS28-ESR showed the best performance regarding reliability and construct validity.

Publications so far

Poster presentation at the EULAR congress 2015 entitled "Validation of disease activity indices using the 28 joint count assessment in systemic sclerosis".

Publication plan

A full-text paper has been submitted to Rheumatology and is currently under revision.



III.3. Prevention and treatment of severe vital organ manifestations (WP3)

WP3 was lead by the Seconda Università degli studi di Napoli (UNINA2) and conducted in cooperation with the teams of the Charité – Universitätsmedizin Berlin (CHARITE), University College London (UCL), Université Paris Descartes (UPD) and was dedicated to investigate different approaches to prevent and treat severe vital organ manifestations in people with SSc, in particular interstitial lung disease (ILD), pulmonary hypertension (PH) and severe heart disease (SHD).

To achieve this goal, three OTs have been designed to specifically address the abovementioned severe, mortality-driving manifestations in people with SSc, namely:

- OT3 Observational trial on the prevention and treatment of ILD (CHARITE & UCL)
- OT4 Observational trial on the development and prevention of PH (UPD)
- OT5 Observational trial on the development and prevention of SHD (UNINA2)

Moreover, several subtasks of each OT have been designed to address different further aspects of these disease manifestations.

Subtask of OT3

- Retrospective analysis to identify the current standard of therapy for ILD in adult and juvenile patients from the EUSTAR and jSScWG cohorts

Subtask of OT4

- Retrospective analysis of the epidemiology and off-label drug treatment of PH in adult and juvenile patients from the EUSTAR and jSScWG cohorts and identification of predictors for the development of SSc-related PH including validation of the Cochin risk prediction score based on data from the EUSTAR database

Subtasks of OT5

- Retrospective analysis of the epidemiology and off-label drug treatment of SHD in the EUSTAR cohort
- Prospective identification of predictors for the development SHD in asymptomatic patients

Once ethical approvals by the competent legal local/national ethics boards/bodies/administrations of all DeSSciphер partners had been obtained, baseline recruitment for all OTs of WP3 was performed between April 2013 the end of November 2015. While the follow-up of enrolled patients will be continued under the umbrella of the EUSTAR group and WSF for at least one year for OT3 and OT5, the patients enrolled into OT4 will be followed for up to two years.

The progress and main outcomes of each of the retrospective subtasks as well as the prospective OTs achieved within the DeSSciphер project period are described in detail below.



III.3.1. Retrospective analysis to identify the current standard of therapy in SSc-ILD

Background

ILD represents one of the most frequent causes of death in SSc patients. Yet, there are no approved drugs for the treatment of SSc-ILD, consensus of management is difficult, and robust scientific evidence facilitating a treatment algorithm for everyday practice is lacking.

Methods

The EUSTAR database was established in 2004 to collect annually data on specialized care of people with SSc. Based on this database, the DeSScipher project consisting of several OTs was initiated, of which one focuses on ILD. The EUSTAR database was analyzed with respect to immunosuppressive therapy of ILD.

Results

Out of a cohort of 11,496 SSc patients, we identified 3,778 adult patients who fulfilled the ACR or, according to available data, the new ACR-EULAR criteria and showed signs of ILD (either on plain X-ray or high resolution computed tomography) with at least one report of immunosuppressive treatment. Mean age was 55.5 ± 13.4 years, with 83.6% females and a mean SSc disease duration of 8.5 ± 7.9 years. Mean mRSS was 10.6 ± 8.7 , 44.4% had diffuse skin involvement, 46.9% the limited SSc subtype, and 7.5% sclerodactyly only.

Compared to the 2,681 (71%) patients who had at least one episode of immunosuppressive therapy the 1,097 (29%) patients without use of immunosuppressants ever (never IS) were on average 5 years older, had longer disease duration (3.2 years), more often limited skin involvement, higher DLCO and FVC values.

The immunosuppressants most frequently used were prednisolone (PRED, 58.8%), cyclophosphamide (CYC, 19.1%), azathioprine (AZA, 15.0%), methotrexate (MTX, 14.7%), and mycophenolate mofetil (MMF, 13.1%). All others were prescribed in less than 3%. With regard to highest treatment intensity ever received, similar proportions of patients got monotherapies (34.0%) and combinations of two drugs (32.4%), while triple therapy was comparably rare with 4.1%. When comparing patient characteristics at treatment start of the most frequent regimens, differences compared to the "never IS" group and between treatment arms became apparent.

Conclusion

Use of immunosuppressants is frequent in routine treatment of SSc-ILD patients showing a wide variety of single and combined substances with distinct patient patterns between treatment regimens. However, prospective studies are still necessary to define indications and outcomes. The DeSScipher project was initiated to achieve this goal.

Publications so far

Poster presentation at the EULAR congress 2015 entitled "Immunosuppressive "Routine" Treatment of SSc Patients with Interstitial Lung Disease – Results of the FP7 DeSScipher Project of the EUSTAR Group".

Publication plan

A full-text paper has been submitted to Rheumatology and is currently under revision.



III.3.2. OT3: Treatment of SSc-ILD

Background

SSc-ILD represents one of the most frequent causes of death in SSc patients and is associated with alveolitis-induced fibrosis and a decline in lung function if untreated. Treatment aims at reducing the pulmonary interstitial inflammatory processes in order to halt or even improve the development of lung function deterioration. Therefore, the aim of OT 3 was to procure a better understanding of ILD and its therapy by specifically comparing different immunomodulatory and antifibrotic treatment arms, which are currently used off-label in routine clinical practice (e.g. cyclophosphamide (CYC), azathioprine (AZA), mycophenolate mofetil (MMF) and methotrexate (MTX)).

Methods

The study protocol of OT 3 (study ID HEALTH-F5-2012-305495-OT3) has been published at ClinicalTrials.gov, identifier: NCT01858259.

Preliminary results

Despite a high number of enrolled SSc-ILD patients, the treatment arm allocation turned out to be a major challenge because of unexpected new treatment patterns, which in general were quite different from what was anticipated to be the standard of care. For the preliminary analysis, 296 patients had at least one follow-up visit and could be allocated to the four predefined treatment groups (CYC n=16, MMF n=76, methotrexate n=29, AZA n=47, no therapy n=128). For further explorative analysis, two additional treatment groups, one consisting of patients receiving CYC and/or MMF in combination with another DMARD (n=36) and patients on glucocorticoid therapy only (n=4), have been defined. When comparing CYC and MMF, no significant differences with regard to a decline of forced vital capacity could be observed. The comparison of AZA and MTX also did not reveal any differences in the decline of the observed lung function parameters. In contrast, differences between the combination of CYC and/or MMF with another DMARD versus CYC by itself with respect to a decline of forced vital capacity, and the combination therapies as well as MMF alone showed a better course than patients on CYC alone with respect to the diffusing capacity. In further analyses, the results will have to be corrected for additional potential confounders.

Preliminary conclusion

A substantial number of SSc-ILD patients receive not only immunosuppressive monotherapy but combinations of immunosuppressants or biologics. Interestingly, MMF was used three times more frequent than CYC, and CYC was the most uncommon treatment in SSc-ILD patients, even after the use of AZA or MTX. This was a surprising observation because the official EUSTAR therapy recommendation for SSc-ILD currently support only the use of CYC. Moreover, patients receiving CYC and MYC remained relatively stable with respect to their lung function although we expect a selection bias in both groups, as these therapies are usually reserved for patients with progressive and inflammatory SSc-ILD. Nevertheless, while some patients had to be excluded due to unclear treatment arm allocation and the follow-up period has not been completed so far, first important differences between immunosuppressive treatments could be elucidated.

Outlook

The patients who have been enrolled into OT3 until November 2015 will be followed up for a further year until November 2016 as a EUSTAR clinical project under the auspices of EUSTAR and WSF.

Publication plan

A full-text paper, working title "Immunosuppressive treatment of SSc related interstitial lung disease: a report of the prospective observational trial of the DeSSciph project of the EUSTAR group" is planned to be submitted to the European Respiratory Journal (the official journal of the European Respiratory Society).



III.3.3. Retrospective analysis of the epidemiology and off-label drug treatment of PH in adult SSc patients from the EUSTAR cohorts and identification of predictors for the development of SSc-related PH including validation of the Cochin risk prediction score

Background

The retrospective subproject prior to the start of OT4 was devoted to the evaluation of (i) treatments for the prevention of and (ii) potential risk factors for the development of SSc-related PH in the EUSTAR SSc cohort with a special emphasis on a risk prediction score and baseline therapies.

Methods

Data from baseline and follow-up visits recorded in the EUSTAR MEDSonline database until June 2012 were analyzed. All included patients met the EULAR/ACR SSc disease classification criteria. From the total cohort we examined risk factors of precapillary PH (group 1 and group 3 of the Pulmonary Hypertension World Health Organisation clinical classification Dana Point 2008). A Cochin Risk Predictive Score (RPS) >3 was chosen as inclusion criterion to identify high risk patients.

Results

From a total of 27,632 patient evaluations in 10,305 different SSc patients, the gold standard (GS) diagnosis of PH could be adjudicated in 3,056 evaluations, corresponding to 1,997 different patients. Among the 3,056 evaluations, PH could be confirmed by right heart catheterisation (RHC) in 134. For all analyses, the GS adjudicated diagnosis of PH was confirmed by RHC with a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg together with a capillary wedge pressure (CWP) < 15 mmHg. PH was excluded by (i) mPAP < 25 mmHg, or (ii) mPAP ≥ 25 mmHg but CWP ≥ 15 mmHg (which represents postcapillary PH), or (iii) a systolic PAP < 35 mmHg measured by echocardiography together with a diffusing lung capacity for carbon oxide (DLCO) $> 75\%$ of the predicted value. For an initial cross-sectional analysis, several parameters were associated with the presence of proven PH in univariate analyses. When entered into a multivariate model analysis, all factors (except for redundancy and baseline treatment for PH) that emerged as significantly associated with the presence versus the absence of GS adjudicated diagnosis of PH in the univariate analyses, only the 2 following factors remained significantly associated factors: mRPS ($p=0.001$) and the NYHA class of dyspnea ($p=0.004$). For a longitudinal analysis, from a total of 10,253 patients who had at least two evaluations, 1,124 patients fulfilled the inclusion criteria: absence of PH at baseline and the possibility to adjudicate the presence or absence of PH during follow-up. Of these, 34 patients had PH (incident cases) whereas PH could be ruled out in 1,090 patients. Patients who developed versus did not develop PH during follow-up had mainly at baseline more severe dyspnea as estimated by the NYHA class ($p<0.001$), reduced DLCO ($p<0.001$), increased serum levels of CRP ($p=0.03$) and/or CK ($p=0.010$) as well as a higher mRPS ($p<0.001$). There were no differences between groups concerning demographic characteristics, and any other characteristics of the disease, including baseline drug regimen, except for ACE inhibitors and diuretics ($p=0.001$ each). However, in multivariate analysis, only DLCO remained associated with PAH during follow-up ($p=0.007$).

Conclusion

The EUSTAR cohort confirmed the value of RPS to identify SSc patients at high risk of development of PH. The prospective OT will be of great value to determine the outcomes of SSc patients with a high baseline RPS value. Within the limitations of this retrospective part of the project, no baseline therapy seemed to influence the occurrence of PH but a larger sample size, a more accurate and systematic assessment together with a prospective follow-up will provide more relevant results.

Publication plan

The data have not been and are not planned to be published.



III.3.4. OT4: Assessing the efficacy and safety of various drugs for the prevention of PH

Background

PH is a fatal disorder characterized by an increase in pulmonary vascular resistance, which leads to right ventricular failure and a dismal survival. Therefore, the objective of this task was to compare the outcomes of SSc patients who are at high risk of developing PH and are receiving either different vasodilator treatments or no vasodilator treatment.

Methods

The study protocol of this OT (study ID HEALTH-F5-2012-305495-OT4) has been published at ClinicalTrials.gov, identifier: NCT01840748.

Preliminary Results

By the end of August 2015, 348 patients had been enrolled into OT4, of whom 12 violated the inclusion criteria ($RPS < 3$ or PH diagnosed by RHC prior to inclusion or information missing at inclusion). Therefore, 336 cases fulfilling the inclusion criteria were enrolled. There were 2/336 patients for whom treatment arm allocation was uncertain and these 2 patients were excluded from the final analyses that thus comprised 334 patients. There were no juvenile patients eligible for OT4. By October 2015, when only patients with at least one follow-up were analysed ($n=206$), the mean $\pm$ SD follow-up was 11.6 ± 4.9 months in the CCB arm ($n=90$), 12.0 ± 5.0 in the prostanoid or PDE5/ETRA arm ($n=116$), 11.7 ± 4.6 in the no vasodilator arm. Overall, in the whole sample, the mean duration of observation of the 206 patients was 11.7 ± 4.9 months. The differences between the 3 arms were not significant regarding duration of observation. For the whole group ($n=341$) the mean $\pm$ SD duration of observation was 7 ± 6.9 and it was similar in the various arms. When only patients having at least one follow-up were analysed, the mean $\pm$ SD duration of observation was 11.6 ± 5.1 and it was similar in the various arms. During the project and among the 341 patients, 25 RHC had been performed allowing to identify 10 patients with the incidence of PAH/PH.

Preliminary Conclusion

So far, the follow-up was too short to draw conclusions. Nevertheless, it can be highlighted that the profile of the 10 incident SSc-PAH cases is the following: 10/10 female, 4 with dcSSc and 6 with lcSSc, all age >60 years, disease duration 12.4 ± 11.3 years, lung fibrosis in 6 patients, normal left heart function (mean FEVG: $58.8 \pm 9.6\%$) and mean baseline sPAP within normal range at 36.3 ± 7.7 mmHg. More incident PH events need to be collected and are going to be organized under the auspices of EUSTAR and WSF to at least record whether the patients have developed or will develop incident PAH/PH in the next months.

Outlook

The patients who have been enrolled into OT4 until November 2015 will be followed up for two years until November 2017 as a EUSTAR clinical project under the auspices of EUSTAR and WSF.

Publication plan

A full-text paper, working title "Development and prevention of pulmonary hypertension in SSc: a report of the prospective observational trial 4 of the DeSSciphper project of the EUSTAR group" is planned to be submitted to the European Respiratory Journal (The official journal of the European Respiratory Society).



III.3.5. Determination of the prevalence of SHD (CB, VA, CHF, SD) and its association with drug treatment

Background

This subtask prior to the start of OT5 assessed the prevalence of SHD, i.e. cardiac block (CB), ventricular arrhythmias (VA), congestive heart failure (CHF), and sudden death (SD) in the EUSTAR SSc cohort and aimed to identify associated epidemiological and clinical features as well as treatment. This task was essential to define inclusion criteria for patients to be enrolled in a prospective OT on the prevention and treatment of SHD by calcium channel blockers (CCB) and/or angiotensin converting enzyme inhibitors (ACEi).

Methods

Datasets of 10,183 SSc patients enrolled into the EUSTAR MEDSonline database until July 6, 2012 were analyzed. Only incidents of CB were reported in MEDSonline. Nevertheless, since CBs depend on myocardial fibrosis, which is the pathological hallmark of SSc heart disease, the analysis of CB should have identified patients who are also at risk for VA and/or CHF or to die from (cardiac) SD.

Results

The prevalence of CB was 10.2%. Multivariate analysis showed that sPAP ≥ 30 mmHg, DLCO $< 80\%$ of the predicted value, male sex, synovitis, proteinuria, joint contractures, and DU were independently associated with CB. With regard to treatment, the use of i.v. iloprost, diuretics, ACEi, angiotensin-receptor inhibitors, digitalis, and beta-blockers was positively associated with CB at univariate analysis. However, after adjusting for confounders for indication (arterial hypertension, SRC, DU, palpitations) and entering all these drugs into a multivariate regression model, none of these associations was still significant.

Conclusion

Based on the results of the multivariate regression analysis, the following inclusion criteria were developed for OT 5 to select SSc patients at risk of SHD: SSc patients who fulfilled the new ACR/EULAR diagnostic criteria and had at least one of the following risk factors: male sex and/or DLCO lower than 80% and/or sPAP > 30 mmHg and/or synovitis and/or joint contractures and/or DU and/or proteinuria.

Publication plan

No publications so far. The prospective OT 5 will provide more reliable data on the prevalence of SHD and its association with drug treatment. Therefore, no full-text publication of this subtask is planned.



III.3.6. Retrospective analysis of the epidemiology and off-label drug treatment of SHD in the EUSTAR cohort

Background

Heart disease in SSc patients can cause severe manifestations such as CBs, VA, and CHF which may require implantation of a pacemaker/defibrillator (PM/DF), are the cause of death or sudden death (SD) in about 20% of patients and can be collectively referred to as SHD. Since the EUSTAR MEDSonline database only provides data on CBs, this task was developed to address all items of SHD.

Methods

Seven EUSTAR/DeSSciphper centres provided clinical data at study entry including all items of SHD. The prevalence of any and each SHD manifestation was calculated. The associations with demographic, serological and clinical features and treatment with vasodilators (CCBs and /or ACEi), were investigated by univariate analysis and confirmed by multivariate logistic regression analysis.

Results

As of July 6, 2012, 1,119 SSc patients from the 7 EUSTAR centres had no missing data (995 females, 124 males; median age 53.6 years, range 14-86). Out of them, 211 patients (19%) had at least 1 SHD manifestation, 152 patients had CBs (14%), 71 had VA (6%), 132 had CHF (12%), and 27 received a PM/DF implant (2%). CBs were the only SHD manifestation in 100 patients, VA in 31, and CHF in 80. No association was found between SHD and clinical (limited or diffuse SSc subsets) and serological (anti-centromere or anti-Scl-70 antibody positivity) characteristics. No association was found between either CHF or PM/DF implant and any other disease feature. In multiple logistic regression analysis, CBs were associated with bibasilar lung fibrosis on chest X-ray (OR=2.6; 95%CI=1-6.4; p=0.04), while VA were associated with increased CK levels (OR=11; 95%CI=1-117; p=0.02) and, unexpectedly, current CCB use (OR 10; 95%CI 1.4-76.1; p=0.02).

Conclusion

This is the first study devoted to investigate SHD in a large series of carefully assessed SSc patients. SHD was detected in about 19% of the cases, CBs in 14%, VA in 6%, CHF in 12%. PM/DF implantation was needed in 2%. These data highlight the importance of an accurate cardiac assessment in SSc patients. Moreover, the associations between VA and CK elevation and current CCB use should stimulate further research to clarify the role of these drugs in patients with myositis/myocarditis.

Publications so far

Poster presentation at the EULAR congress 2015 entitled "Severe heart disease in systemic sclerosis: Prevalence, risk factors and current treatment. A EUSTAR/DeSSciphper study".

Publication plan

The prospective OT5 will provide more reliable data on the prevalence of SHD and its association with drug treatment. Therefore, no full-text publication of this subtask is planned.



III.3.7. Prospective identification of predictors for the development SHD in asymptomatic patients

Background

This subtask of OT5 assessed the incidence of SHD, i.e. CBs, VA, CHF, Q waves and SD in asymptomatic SSc patients enrolled into OT5. Furthermore, OT5 aimed to determine predictors for the development of SHD by means of a prospective longitudinal observation in contrast to the previous retrospective cross-sectional study in which estimated sPAP ≥ 30 mmHg, DLCO $< 80\%$ of the predicted value, male sex, synovitis, proteinuria, joint contractures, and DU had been found to be independently associated with CBs.

Methods

Clinical data of 259 SSc patients enrolled into OT5, who, at August 25, 2014, had at least one follow-up visit, were reviewed for the presence of any SHD manifestation both at baseline and at the end of follow-up (ranging from 0.08-1.33 years; mean 0.59 patient-years).

Preliminary Results

At baseline, 38 out of the 259 patients already had at least one SHD manifestation (prevalence 15%). At the end of follow-up, 39 new SHD manifestations occurred in 35 patients (incidence 23/100 pts/year). By multivariate analysis, the incidence of new SHD manifestations was found to be associated with age (HR 1.1, 95%CI 1.02-1.18) and the extent of skin sclerosis at baseline as evaluated by the modified Rodnan skin score (mRSS; HR 1.2, 95% CI 1.03-1.3).

Preliminary Conclusion

This subtask of OT5 provided the following significant results: 1) A high incidence of SHD during a short follow-up, which underlines the need to determine the effectiveness of any treatment. 2) The identification of previously unknown features predictive of the development of SHD manifestations over a short period. The age and mRSS should therefore be considered carefully in deciphering the optimal management of patients with SSc, suggesting a stricter follow-up in patients with any of these 2 features, notably in asymptomatic patients. 3) The consequent need to carefully investigate each patient for any SHD.

Outlook

The detected incidence would have likely increased if the number of missing values had been lower. A more detailed evaluation of potential risk factors associated with incident SHD will be available once the data of follow-up of patients will increase over time. Therefore, the patients who have been enrolled into OT5 until November 2015 will be followed up for two-years until November 2017 as a EUSTAR clinical project under the auspices of EUSTAR and WSF.

Publication plan

No publication so far. The continuation of the prospective OT 5 will provide more reliable data on the incidence of and risk factors for SHD. The results on risk factors predictive for the development of SHD will be either reported in combination with observed treatment effects or published as a separate full-text paper.



III.3.8. OT 5: Prospective observational trial on the development and prevention of SHD

Background

Asymptomatic heart disease is frequent in SSc patients. CBs, VA and CHF, collectively referred to as SHD, are frequent causes of death or sudden death. OT 5 was designed to examine and validate the potentially favourable effects of CCBs and/or ACEi in the treatment of adult and juvenile SSc heart disease.

Methods

The study protocol of this OT (study ID HEALTH-F5-2012-305495-OT6) has been published at ClinicalTrials.gov, identifier: NCT01829126.

Preliminary Results

Analysis of 406 patients who (i) had at least one follow-up (FU) visit (274 receiving vasodilator therapy; 132 without vasodilator therapy) and (ii) had been followed-up for 291 and 126 patient-years, respectively, showed a nearly significant protective effect of vasodilator therapy for CBs. This effect was particularly evident in patients receiving CCB+ACEi combination therapy. The identification of predictors of SHD in patients prospectively enrolled into OT5 was carried out on 272 patients who had had at least one FU visit (median FU time 1.0 years; range 0.18-1.99). Of these, 187 were prescribed vasodilator therapy (144 CCB, 13 ACEi, 30 a combination of both drugs). At baseline, 19.5% of the patients had at least 1 SHD manifestation 16% had CBs, 1% VA, 1% Q waves, and 1% a combination of CB + Q waves. In univariate analysis, newly developed SHD manifestations were associated with baseline SHD, dyspnea, chest X-ray fibrosis, FVC and DLCO <80% of predicted, echocardiography-assessed PH, mRSS and active disease (EScSG activity index). At multivariate Cox-regression analysis, mRSS and echocardiography-assessed PH were independent predictors of new SHD manifestations.

Preliminary Conclusion

OT5 addressing treatment/prevention of SHD has shown the following achievements so far:

- 1) The prevalence of SHD and of each manifestation in 228 patients (28.4%) showed CB in 123 (15.3%), VA in 58 (7.2%), and CHF in 105 (13%) patients. PM or DF had been implanted in 22 patients (2.7%).
- 2) Of the total 666 patients enrolled so far, 215 were treated with CCBs, 22 with ACEi and 37 with a combination of both drugs. Concomitant or isolated vasodilator therapy with endothelin receptor antagonists, PDE5 inhibitors and/or prostanoids were prescribed in about 10% of patients.
- 3) The incidence of SHD and of each of its manifestations (CB, VA, CHF, PM/DF implantation) was defined preliminary based on recruitment status on November 30, 2015, with incidence rates of 5.75/100 patient*year for any SHD, 4.5/100 patient*year for CB, 1.6/100 patient*year for VA, and 0 for CHF and PM/DF.
- 4) In the 406 patients, who were enrolled into OT5 and had completed at least one FU visit, a nearly significant difference in the incidence of SHD manifestations was detected in the patients receiving vasodilator therapy in comparison to those in the no-treatment arm.

Outlook

After completion of the FU of patients who have been recruited until November 30, 2015, it is expected to identify differences between vasodilator and no vasodilator therapy and to highlight possible differences in the power of distinct vasodilator treatments to prevent CBs and other SHD manifestations.

Publication plan

No publication so far. A full-text paper, working title "Development and prevention of severe heart disease in SSc: a report of the prospective observational trial 5 of the DeSScipher project of the EUSTAR group" is planned to be submitted to The European Heart Journal (the official journal of the European Society of Cardiology).



III.4. Definition of appropriate measures to evaluate off-label prevention and treatment of SSc (WP4)

WP4 was lead by CHARITE and dedicated to the statistical analysis of the DeSScipher project.

III.4.1. Comparison of outcomes based on the analysis of the available data in MEDSonline

Objective

One part of the DeSScipher project was the analysis of “retrospectively” available documentations, meaning data collected in the EUSTAR MEDSonline database before and during the DeSScipher project. In a multi-organ disease such as SSc, success of therapy depends on numerous factors apart from the usual confounders such as age, sex and disease duration. Therefore, it was necessary to investigate individual confounders stratified by organ manifestations and different treatment regimens. Analysis of documentation frequencies in the MEDSonline database was expected to provide a first idea which laboratory markers, functional measures or clinical parameters are comprehensively used yet.

Methods

The change of MEDSonline variables under organ-specific therapies (which are not objective of the OTs of the project) were investigated and potentially treatment-sensitive parameters were detected.

Summary

The retrospective data were found to be insufficiently complete to safely test models with combined outcome measures under treatment conditions. However, it was possible to identify outcome measures with the potential of clinically meaningful changes over time. These potential outcome parameters will be re-evaluated after finalisation of the prospective OTs by application to the prospective dataset.

III.4.2. Confounder analysis

Confounder analysis comprised consideration of known and suspected confounders in analyses that have been conducted previously rather than novel evaluations of the impact of suspected confounders. In a comprehensive analysis of retrospective data regarding hand dysfunction, defined as presence of synovitis, joint contractures and tendon friction rubs, several potential confounders of treatment effects were evaluated in sub-analyses: subset of skin involvement, disease duration, positivity for anti-topoisomerase I, anti-centromere, and anti-nuclear antibodies, age, sex, elevated levels of inflammatory markers (ESR, CRP), and skin score (mRSS). In the analysis of lung function parameter development for SSc patients with ILD, subsets of skin involvement, disease duration, age and sex, initial FVC and DLCO status were identified as potential confounders of the development of lung function. Another issue of “analysis confounding” evolved in DeSScipher: (i) missing or unknown parameters of interest, in OT2 even concerning the primary outcome; and (ii) very diverse treatment combinations that were not expected prior to the study and hampered intended treatment arm allocation specifically in OT3 and partly in OT1.

In OT1, documentation of detailed information on DU distal to the proximal interphalangeal (PIP) joints turned out to be frequently missing or unknown, not allowing further or more sensitive analysis than the overarching question whether DU distal to the PIP joints were currently apparent or not. For OT2, collection of HAQs in clinical routine care turned out to be a limiting factor. HAQ baseline values differed remarkably between different treatment arms: while patients on MTX showed a wide range of baseline values, those on combination therapies showed initially rather high functional limitations compared to patients on CYC or other drugs. For OT3, treatment arm allocation turned out as a major challenge because of unexpected new treatment patterns which in general have been quite different from what was expected to be the current standard of care at the time of planning the DeSScipher project about 4 - 5 years ago. In order to adhere to clearly defined treatment groups allowing evaluation of treatment effects attributed to certain therapies, many patients could not be allocated due to very complex or rare combinations of therapies and thus have been omitted from the current analysis. OT4 still requires further patient recruitment and more



time to collect the necessary follow-up of 2 years to facilitate the intended evaluation of the prevention of PH in the selective group of high-risk patients. Of the 334 enrolled patients follow-up data is available for only 60% and their mean duration of observation is about 1 year. In OT5, 736 patients could be clearly allocated to the intended treatment arms. The quality of documentation of the several indicators of SHD (CBs, VA, PM/DF implantations, CHF and SD), which were merged into a combined endpoint, was variable. CBs and VAs were the most sensitive markers with regard to differences between treatment arms.

III.4.3. Comparison of outcomes using the prospectively collected data of the different OTs

Background

This subtask initially intended to use the prospectively collected data of the five OTs to identify important and sensitive indicators of treatment response based on the available data, and to test combinations of outcome measures to account for different aspects of SSc. However, given the delayed prospective data collection of the five OTs and ongoing data cleaning and completing by the several contributing study sites, the initial plan could not be implemented. Thus, the OT leaders plan a report on data quality of all OTs to be prepared by the team of WP4 at the end of the DeSSciphper project period, to further elaborate whether novel outcome measures based on which items could be developed.

Methods

As the development of novel outcomes measures could not be performed due to delayed patient recruitment and ongoing data collection, the activities of the WP4 team focused on measures to enhance data quality and on providing detailed reports on data quality for the five OTs.

Preliminary report on the data quality of the five observational trials

Overall, the availability of the general patient characteristics was good for the prospectively collected DeSSciphper data, apart from the items "History of DU" and "pulse". The item "Physician global assessment of articular disease activity" was rarely documented for any patient and its usefulness as an outcome measure and collection in MEDSonline should be discussed. In general, data quality was better for DeSSciphper cases when compared to the already existing data in the MEDSonline database.

Preliminary report on outcome measures of the five observational trials

In OT1, composite endpoints turned out to be difficult to build, since details of DU distal to the PIP joints had many missing values and unknowns, making it difficult to meaningfully construct and test combined endpoints. In OT2, the CHFS was hardly documented, whereas SHAQ and HAQ were almost always both there or missing, and the sensitivity of a binary combination of both (merging the information that either one of them was above a certain disability threshold) did not turn out as more useful than evaluating the continuous scale of the HAQ or its categorized version (disability threshold) itself. In OT3, DLCO/sb seemed to be more sensitive to differences in change than FVC, while DLCO/va did not show much differences in change for the treatment arms tested, so that only combining FVC and DLCO/sb might provide more insight. For OT4, so far only very few cases have reached the intended follow-up duration of 2 years necessary to reasonably assess development of PH. A composite endpoint was tested in OT5, where 5 single indicators of SHD (incidence of CBs, VA, PM/DF implantations, CHF and SD) were merged into one "any of" item, which turned out to show treatment differences already with the limited case numbers available so far.

Preliminary Conclusion

In summary, not all endpoints intended to be collected in the five OTs turned out as successful standard outcome measures with regard to availability in routine care and consequently documentation.



III.4.4. Aggregation of all results for preparation of therapy recommendations

Background

This subtask was designed to aggregate the preliminary results of the five OTs until project month 30 to provide the basis for the development of preliminary treatment recommendations for SSc (cf. WP6).

Methods

Due to delayed patient recruitment concerning all OTs, database freeze for the aggregation of the preliminary results of all OTs was postponed to September 1, 2015 (M33) for the actual report (while the results reported in the OT-specific deliverables may be based on a later database freeze due to individual OT leader decision to report updated latest results). By the end of project month 33, 2,180 patients had agreed to participate in DeSSciphер by signature of the patient informed consent form. Of those, 1,473 patients were enrolled into OT1, 208 into OT2, 1,282 into OT3, 348 into OT3 and 961 into OT5. 222 patients were not enrolled into any OT, since they did not fulfil eligibility criteria for any OT or were not included into any OT for reasons not known to the analysing statisticians. Given the low recruitment number of jSSc patients in the different OTs, jSSc patients have been excluded from analysis (data provided in a separate report, deliverable 1.5).

Preliminary Results

For OT1, differing healing and prevention effects of the investigated treatment arms were seen. For OT2, until present 39 patients could be evaluated at this preliminary analysis due to missing HAQ values or a not yet accomplished 10-month observation interval. HAQ baseline values differed remarkably between different therapy arms. Most patients reported an unchanged or improved functional capacity over time, only few patients deteriorated. For OT3, treatment arm allocation turned out as a major challenge, since many new treatment combinations were observed and treatment patterns in general were quite different from what was expected to be the standard of care 4 years ago. OT4 still requires further recruitment and more time to collect the necessary follow-up of 2 years to allow an evaluation of the prevention of PH in the selective group of high-risk patients. In OT5, especially the CCB+ACEi combination treatment group and the ACEi group need further recruitment to allow a robust verification of a first trend: the standardized incidence rate of the combined endpoint of several indicators of SHD turned out higher in the ACEi group compared to all other treatment groups. However, this alerting preliminary result is based on only 21 patients and thus required higher case numbers for verification.

Conclusion

Based on these preliminary results, preliminary treatment recommendations have been developed (cf. WP6).



III.5. Ethics and data monitoring (WP5)

WP5 was lead by UZH and designed to ensure that local, national and European ethical and regulatory requirements were fulfilled during the course of the project. In particular, standard operating procedures have been developed to harmonize study procedures between clinical centres and monitoring as well as audit visits have been performed to ensure that study procedures have been in accordance with ICH-GCP guidelines.

III.5.1. Development of written standard operating procedures

In order to ensure a high quality and credibility of the data collected, to ensure that all personnel involved in the DeSScIPHER project will follow the same standards and that the study conduct is in accordance with ICH-GCP, written standard operating procedures (SOPs) / working instructions (WIs) were necessary.

The UZH team identified the major issues of the existing data collection practice and determined key aspects to be described in SOPs. Based on the DeSScIPHER Project Description, SOPs of the Clinical Trial Centre (CTC) UZH were adapted for the observational DeSScIPHER project. Drafts of the SOPs and related forms were reviewed by the head of Quality Management of the CTC, Jürg Lustenberger, the work package leader Oliver Distler and the Project Coordinator team at JLU GIESSEN.

Eight SOPs and related forms have been developed with regard to (i) document management, (ii) trial master file and investigator site file archiving, (iii) delegation, acceptance and confirmation of responsibilities of the project team, (iv) communication & reporting, (v) incidental findings, (iv) ethics committee approval, (vii) patient information and informed consent and (viii) data collection, data management and data protection. The final versions were provided by e-mail to the partners. ISF comprising SOPs and RUS (read, understand and sign) logs were established and/or reviewed during on-site monitoring visits.

III.5.2. Data management and reporting in accordance with GCP guidelines

During the DeSScIPHER Project, all information collected as part of the OTs was treated confidentially. Participant identifying data was coded when registered. Solely by signing the informed consent form, the subject authorized access by monitors, auditors, the ethics committee (EC) and regulatory authorities to the source data. Data protection pertinent to data management and reporting was in accordance with ICH-GCP and the applicable ECRIN (European Clinical Research Infrastructures Network) guideline. The project partner NEW WIN reviewed all internal processes and confirmed them to be in compliance with IT01-IT05 of the ECRIN guideline. In collaboration with the partners NEW WIN and UNIBAS several approaches to adopting the Soundex system without losing the one-to-one attribution of patient data were discussed (e.g. skipping one of the initials or masking the information have been considered to eventually compromise the data). NEW WIN and UNIBAS confirmed that the used version of the Soundex system combined with date of birth is solely visible at the level of the trial site and for authorized site personnel only.

III.5.3. Reporting incidental findings

The Ethics Review Report of the DeSScIPHER Project by the European Commission requested implementation of a reporting system for incidental findings in the DeSScIPHER OTs. To ensure a standardized handling and reporting of incidental findings, a corresponding SOP was developed by the UZH team. Incidental findings were defined as all study objective-unrelated findings generated at the time of study data entry, monitoring and/or analysing which apparently had not been noticed by the treating physician (missing medical record entry). All incidental findings had to be recorded in a dedicated incidental finding log together with a short description and had to be reported to the principal investigator (PI) and the Project Coordinator. Due to the observational nature of the DeSScIPHER project it was decided that it was the responsibility of the PI to decide in a case-by-case manner how to deal with incidental findings, including but not limited to reporting to the treating physician, and always in accordance with the patient's written informed consent. Within the DeSScIPHER project period no incidental findings were identified at any of the study sites, neither observed during the monitoring visits.



III.5.4. Monitoring and Audits

Routine monitoring visits comprised quality control measurements such as source data verification, review of trial documentation (investigator site file), IEC approvals and adequate trial staffing (e.g. data entry clerk). Sites for on-site monitoring were selected 3 months before the actual on-site monitoring date with respect to predefined criteria of targeted monitoring. A suitable sample size to meet the projected level of quality control was selected. Emphasis was put on the required organization and cooperation shown by the partners during those visits. Activities, findings and actions taken were captured in monitoring reports and reviewed by the UZH team, the PI and the Project Coordinator. In general, all monitoring visit showed that the sites complied with the SOPs provided.

In addition to routine monitoring, audits were performed on two sites, the Rheumatology Unit of the University Hospital Basel (USB), Switzerland, and the Kerckhoff-Klinik, Bad Nauheim, Germany. Both auditees were found to have, with minor corrective measures, the necessary systems and procedures in place required by ICH-GCP and applicable national regulations and international guidelines.



III.6. Dissemination and guidelines (WP6)

WP 6 was led by JLU GIESSEN and designed to inform physicians, patients, authorities and the general public about the DeSSciper project, its results and achievements. One of the key aims of the DeSSciper project was to translate the scientific results of the project into recommendations for the treatment of SSc.

III.6.1. Publications

As the OTs have not been completed yet, only preliminary results could be published as abstracts on national and international congresses (cf. section A, list of scientific publications). An overview of the projected publications of the DeSSciper project is provided in the following table.

DeSSciper partner	Working title	Target journal
JLU GIESSEN & all partners	Conducting observational studies in rare diseases: a report of the DeSSciper project of the EUSTAR group	The Journal of Scleroderma and Related Disorders (JSRD) (the official journal of the WSF)
UNIBAS	Predictors of disability in systemic sclerosis: an analysis of the DeSSciper cohort of the EUSTAR group	Annals of the Rheumatic Diseases (the official journal of the EULAR)
UNIFI & LEEDS	Best treatment for prevention of digital ulcers in SSc: a report of the prospective observational trial of the DeSSciper project of the EUSTAR group	The Journal of Investigative Dermatology (the official journal of the Society for Investigative Dermatology and The European Society for Dermatological Research)
UNIFI & LEEDS	Best treatment for healing of digital ulcers in SSc: a report of the prospective observational trial of the DeSSciper project of the EUSTAR group	
PECS	Validation of Disease Activity Indices using the 28 Joint Counts in SSc	Rheumatology (Oxford), submitted
PECS	Joint involvement and hand dysfunction in systemic sclerosis: a cross-sectional descriptive analysis of the multicentric prospective observational trial of the DeSSciper project of the EUSTAR group	Annals of the Rheumatic Diseases (the official journal of the EULAR)
JLU GIESSEN & PECS	Real life treatment patterns of arthritis in in systemic sclerosis: an analysis of the DeSSciper cohort of the EUSTAR group	The Journal of Scleroderma and Related Disorders (JSRD) (the official journal of the WSF)
CHARITE	Current state of the art of immunosuppressive treatment of SSc-related ILD: a merged analysis of the EUSTAR and DeSSciper	Rheumatology (Oxford), under revision
CHARITE	Immunosuppressive treatment of SSc related interstitial lung disease: a report of the prospective observational trial of the DeSSciper project of the EUSTAR group	The European Respiratory Journal (the official journal of the European Respiratory Society)
UPD	Development and prevention of pulmonary hypertension in SSc: a report of the prospective observational trial of the DeSSciper project of the EUSTAR group	
UNINA 2	Development and prevention of severe heart disease in SSc: a report of the prospective observational trial of the DeSSciper project of the EUSTAR group	The European Heart Journal (the official journal of the European Society of Cardiology)
JLU GIESSEN & CHARITE	Immunosuppressive and vasodilative treatment patterns in systemic sclerosis: a report of DeSSciper and EUSTAR	Annals of the Rheumatic Diseases (the official journal of the EULAR)
JLU GIESSEN & all partners	Safety of currently used off-label treatments in systemic sclerosis: a report of DeSSciper and EUSTAR	Annals of the Rheumatic Diseases (the official journal of the EULAR)

As DeSScipher originated from the EULAR funded EUSTAR consortium, the resulting publications should adhere to the EUSTAR publication rules. Beyond the author citation of the whole DeSScipher consortium and EUSTAR contributing centres, the FP7 funding by the European Commission will be adequately acknowledged in all upcoming publications usually as follows: "The DeSScipher project was funded by the European Community's Framework Programme 7 (FP7-HEALTH-2012.2.4.4-2 - Observational trials in rare diseases) under grant agreement N° 305495.

III.6.2. Recommendations

An international SSc expert meeting for the update of EULAR/EUSTAR recommendations for the treatment of SSc under the umbrella of EUSTAR was organized at the study site of the DeSScipher Project Coordinator in November 2014. Compared to the 14 EULAR/EUSTAR recommendations on the treatment of SSc published in 2009, a new set of 16 recommendations was developed which address treatment options for several SSc-related organ complications: Raynaud's phenomenon, digital ulcers, pulmonary arterial hypertension, skin and lung disease, scleroderma renal crisis, and gastrointestinal involvement. Compared with the previous recommendations, the 2015 recommendations include phosphodiesterase-5 inhibitors in the treatment of SSc-related RP and DUs, as well as riociguat and new aspects for endothelin receptor antagonists, prostacyclin analogues and PDE5 inhibitors for SSc-related PAH. New recommendations regarding the use of fluoxetine for SSc-related RP and the option of hematopoietic stem cell transplantation for selected patients with rapidly progressing SSc were added. In addition, a previous statement regarding sitaxentan for PAH was removed, because this drug has been withdrawn from the market. While the full-text paper of the update of the EULAR/EUSTAR recommendations has not been published yet, the updated recommendations have already been presented by the Project Coordinator Ulf Müller-Ladner to the public at the International Scleroderma Symposium in Berlin, September 2015, on the occasion of a special lecture and interactive discussion of symposium attendees with SSc experts of the EUSTAR recommendation task force.



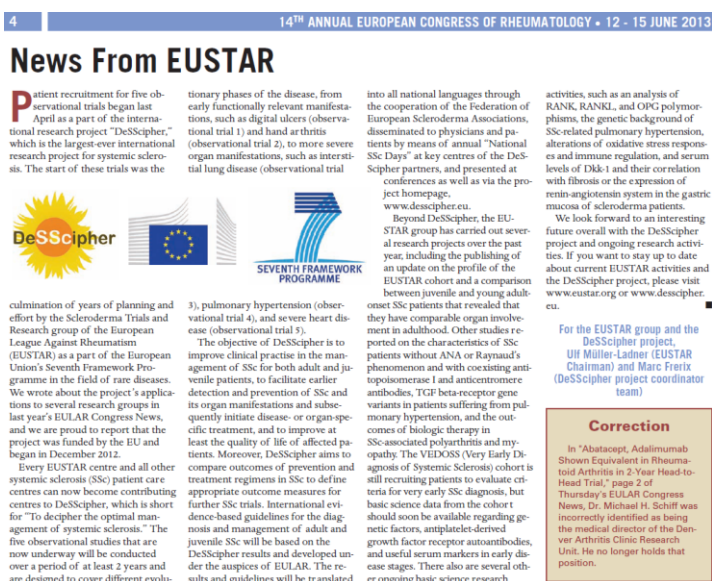
Presentation of the update of the EULAR/EUSTAR recommendations to the scientific community at the International Scleroderma Symposium in Berlin, September 2015

In addition, preliminary recommendations based on the interim analysis of four of the five prospective OTs of the DeSScipher project have been developed and voted on. However, the wide variety in the rating of the recommendations by the expert panel reflected the limited amount of data that could be collected as the scientific basis for the preliminary set of recommendations until the end of the DeSScipher funding period. Therefore, updated final recommendations based on the outcome of the five OTs of DeSScipher will be facilitated once the follow-up of the OTs will be completed in November 2017, and are planned to be integrated into the next update of the EULAR-endorsed EULAR/EUSTAR recommendations on treatment of SSc.



III.6.3. Dissemination activities

For transparency, accessibility and success of the DeSScIPHER project, several dissemination activities have been carried out by the Project Coordinator, FESCA and the DeSScIPHER consortium to foster awareness and understanding of juvenile and adult SSc, to improve patient care and management throughout Europe and to inform participants, physicians, patients, authorities and the general public about the DeSScIPHER project, its progress, results and achievements. Various dissemination activities have been organized in close collaboration with FESCA, a pan-European SSc patient organization and full partner in the DeSScIPHER project. A pivotal activity was the organisation of “National SSc Days” at key centres of the DeSScIPHER partners with interactive presentations on selected topics of SSc. Furthermore, the project was presented to the general public by preparing press releases at the launch of the project and biannual newsletters. In addition, a project specific webpage was launched in time in March 2013, which is hosted on the webserver of the JLU GIESSEN (www.desscipher.eu) and contains sections specifically designed for the scientific community as well as for the general public. Latest news about the DeSScIPHER project were also reported by use of the webpage of FESCA (www.fesca-scleroderma.eu) and have been updated on a routine basis, including different advertisement campaigns such as the dissemination of press releases and patient information newsletters. In addition, the DeSScIPHER project was advertised to the scientific community at large national and international conferences such as the annual scientific meetings of the European League Against Rheumatism (EULAR), the American College of Rheumatology (ACR) annual meetings, the biannual World Scleroderma Congresses or the annual European Workshops for Rheumatology Research by lectures, the use of DeSScIPHER project booths, posters, leaflets and roll-ups. Articles about the DeSScIPHER project have been published, for example in the EULAR NEWS journal.



Left panel: An example of the EUSTAR/DeSScIPHER booth at the 2013 EULAR congress in Madrid.

Right panel: Article in the EULAR congress NEWS journal 2013

In addition, the Project Coordinator took the opportunity of all EUSTAR business meetings to not only inform all EUSTAR members about the DeSScIPHER project but also invite them to contribute to the DeSScIPHER project. All SSc expert centres indicating their interest in contributing to the DeSScIPHER project were supported intensively in the process of becoming EUSTAR members and DeSScIPHER contributing centres, including the preparation of templates of patient information and informed consent forms, study manuals, assistance in ethics application for the DeSScIPHER project and database usage and the establishment of a mentorship program. Finally, an international dissemination meeting with a special focus on the needs of people with SSc was organized by the Project Coordinator in November 2015. An overview of the dissemination activities is provided below (cf. section A, list of dissemination activities).



IV. THE POTENTIAL IMPACT AND THE MAIN DISSEMINATION ACTIVITIES AND EXPLOITATION OF RESULTS

IV.1. Economic impacts

SSc is a disease with a high economic impact for (i) insurance companies, (ii) the society, and (iii) the affected families compensating disability and reduced quality of life. The severity of the disease and the unmet medical need often lead the treating physicians to using those therapies which are known to be effective in related diseases such as rheumatoid arthritis but are of unproven efficacy in SSc. These non-evidence based approaches bear some risks, as previously shown by accelerated interstitial lung disease in patients treated with TNF-alpha inhibitors. In addition, results of such attempts to treat SSc often remain unpublished and are consequently lost for the scientific community. Moreover, those therapies are often very expensive. After finalization of the OTs, DeSScipher will demonstrate the true efficacy of the currently used real-life treatment regimens and thus provide a rational basis for the use of the available medications in the future. The results of DeSScipher will enable rheumatologists to choose appropriate treatment regimens and to avoid inefficient, potentially harmful and costly therapies. In addition, it will be possible to better prevent treatment complications and associated costs.

In addition, the creation of the DeSScipher expansion of the EUSTAR MEDSonline database will also increase the attraction of Europe as a partner for the industry and for research work. The same can be envisioned for other specialties dealing with SSc as well.

IV.2. Social and ethical aspects

Social and ethical aspects were also key aspects of the DeSScipher project, primarily because of the strong involvement of the pan-European patients association FESCA, who facilitated not only the increasing recruitment rates but communicated also the progress of the OTs to a large number of affected people with SSc in Europe.

IV.2.1. Safety and efficacy of off-label use in SSc

The OTs will provide valuable data with regard to the safety and efficacy of off-label used drugs for treatment of SSc and will stimulate and facilitate the transfer from off-label to in-label status.

IV.2.2. Impact on quality of life in SSc

As reduction of quality of life is a dominant feature people affected by SSc the evaluation of the improvement of organ manifestations investigated in the different OTs will also reveal the treatment strategies which bear the highest potential for improvement of patients' well-being.

IV.2.3. Impact on the design of clinical studies of SSc in the future

While the DeSScipher OTs are still ongoing, the preliminary results already revealed important new information for the planning of further studies. For example, in OT2 an unexpectedly frequent use of biologics was observed, even though these agents are currently not recommended for the treatment of arthritis in SSc. Another example of lessons learned from DeSScipher was the unexpected diversity of immunosuppressive treatment patterns of SSc-ILD. Both preliminary results will alter the design of upcoming disease-modifying drug trials in SSc.



IV.2.4. Impact on EUSTAR and its activities in the future

Owing to the significantly expanded and quality-improved database, all EUSTAR projects will benefit from this upgraded EUSTAR database, which was specifically achieved by the several measures of the DeSScipher project such as automatic checks of invalid data entries or additional tools tips, the queries that which have been sent to the EUSTAR centres as well as the monitoring activities.

Beyond the improvement of the database, the DeSScipher project has supported the EUSTAR group and its 15.000 registered people with SSc in different ways, for example by means of fostering co-operation between different countries and geographical European areas, encouraging and assisting the foundation of national organizations, promoting educational programs, encouraging the publication of scientific proceedings of meetings, stimulating scientific research on SSc and finally establishing contacts with all other specialties interested in SSc.

Moreover, participation in the DeSScipher project of young clinicians and scientists in the DeSScipher core centres as well as all EUSTAR contributing centres and newly recruited EUSTAR centres, and the availability of a significantly enhanced EUSTAR database provided by the DeSScipher project has a strong potential to attract young talented researchers from SSc expert centres across Europe and to stimulate new research ideas in the field of this rare disease.

IV.2.5. Impact on other related orphan diseases

Beyond the impact on further studies in SSc, the EUSTAR/DeSScipher cohort also serves as a model case for other orphan diseases in the field of rheumatology and clinical immunology with similar issues in recruiting and documenting patients for testing novel drugs and establishing validated general international recommendations.

IV.3. Exploitation and dissemination

DeSScipher will address fundamental questions with the aim to reduce the risk for future clinical studies, e.g. due to excessive expectations concerning the changes of outcomes, underestimated numbers of patients needed, or by using incorrect inclusion criteria. DeSScipher results will provide several milestones providing data about validated outcomes, study protocols, impacts on quality of life, subgroup analyses and the impact of patient selection on outcomes, predictive factors to achieve outcomes, and information about the impact of current standard therapies on outcomes in a retrospective as well as prospective approach with real life data. The data will generate novel hypotheses that have to be proven in the future. The cooperation of the different experts will also provide a novel level by identifying composite outcomes.

DeSScipher has and will use the underlying pan-European interacting physician and patient network to disseminate the results that have been and will be published on a continuous and increasing basis in the upcoming years. Dissemination platforms will include not only the regular national and international meetings such as the annual EULAR congress and the biannual World Scleroderma Congress but also internet-based dissemination to all stakeholders involved. A specific focus will be the physician-aided dissemination by FESCA to all people with SSc in their native language.

The results of the OTs and additional general analyses as well as subanalyses are planned to be published accordingly in the publicly available journals as outlined above (cf. section III.6.1).



V. CONTACT AND ADDRESSES

V.1. Overview of project participants

The DeSSciper consortium consisted of 14 DeSSciper partners from 7 European Countries, which have been supported by several contributing EUSTAR centres.

DeSSciper partner organisation name	Part. Short Name	Country
Justus-Liebig-Universität Gießen	JLU GIESSEN	Germany
Universität Zürich	UZH	Switzerland
Université Paris Descartes	UPD	France
Università degli Studi di Firenze	UNIFI	Italy
Seconda Università degli Studi di Napoli	UNINA2	Italy
University of Basel	UNIBAS	Switzerland
University College London	UCL	United Kingdom
Charité - Universitätsmedizin Berlin	CHARITE	Germany
University of Pécs	PECS	Hungary
University of Leeds	LEEDS	United Kingdom
New win AG	NEW WIN	Switzerland
Federation of European Scleroderma Associations	FESCA	Ireland
Dr. Ivan Foeldvari	FOELDVARI	Germany
Novamen	NOVAMEN	France

EUSTAR member organisation name	Number	Country
Clinica Reumatologie, University of Medicine & Pharmacy "Iuliu Hatieganu" Cluj	16	Romania
Rheumatology Unit, Dept. of Clinical and Experimental Medicine, University of Padova	31	Italy
Istituto di Clinica Medica Generale, Ematologia ed Immunologia Clinica, Università Politecnica delle Marche Polo Didattico, University of Ancona	34	Italy
Universitätsklinik Köln	44	Germany
Division of Clinical Immunology and Rheumatology, Dept. of Internal Medicine Dubrava University Hospital	51	Croatia
Institute of Rheumatology Belgrade	55	Serbia
Medizinische Universitätsklinik Tübingen, Abteilung II	56	Germany
Kompetenz-Zentrum für Sklerodermie im Kindesalter, Hamburg Eilbek	64	Germany
Institute of Rheumatology, Russian Academy of Medical Science	78	Russia
Rheumatic Diseases Centre, Hope Hospital, University of Manchester	80	UK
Dept. of Internal Medicine Hôpital Claude Huriez	93	France
Divisione di Reumatologia, Università di Roma La Sapienza	94	Italy
Dept. of Internal Medicine and Rheumatology Clinic, Ion Cantacuzino Clinical Hospital	100	Romania
Dept. of Internal Medicine 3, Universitätsklinikum Erlangen	106	Germany
University of Ghent, Dept. of Rheumatology	113	Belgium
Endokrinologikum Frankfurt	124	Germany
University of Marmara, Dept. of Rheumatology	133	Turkey
II Chair of Rheumatology, University of Cagliari-Policlinico Universitario	142	Italy
GR.T. Popa Centre for Biomedical Research, European Centre for Translational Research, University of Medicine and Pharmacy Rehabilitation Hospital	162	Romania
Assiut and Sohage University Hospital, Dept. of Rheumatology	168	Egypt
Hospital Universitario Madrid Norte Sanchinarro	169	Spain
Rheumaklinik Bad Bramstedt	187	Germany
Clinic of Nephrology, Internal and Occupational Diseases, Dept. of Rheumatology	190	Russia
Krankenhaus St. Josef Hospital Wuppertal	192	Germany



V.2. List of beneficiaries and administrative contacts

Beneficiary number	Participant name	Address	Administrative contact
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3	UNIVERSITE PARIS DESCARTES (UPD)	Rue de L ecole de Medicine 12 75270 PARIS France	Adeline Lassaux Tel.: +33 176531748 Fax: +33 158412624
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5	SECONDA UNIVERSITÀ DEGLI STUDI DI NAPOLI (UNINA2)	VIALE BENEDUCE 10 81100 CASERTA Italy	Gabriele Valentini Tel.: +390815464487 Fax: +390815666747
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8	CHARITE – UNIVERSITAETS MEDIZIN BERLIN (CHARITE)	Chariteplatz 1 10117 BERLIN Germany	Eveline Fräßdorf Tel.: +49 30 450576024
9	PECSI TUDOMANYEGYETEM - UNIVERSITY OF PECS (PECS)	VASVARI PAL UTCA 4 7622 PECS Hungary	Józsefné Krutki Tel.: +36 72501510
10	UNIVERSITY OF LEEDS (LEEDS)	Woodhouse Lane LS2 9JT LEEDS United Kingdom	Martin Hamilton Tel.: +44 113 343 4090 Fax: +44 113 343 0949
11	NEW-WIN AG (NEW WIN)	TRAMSTRASSE 7 5034 SUHR Switzerland	Beat Fankhauser Tel.: +41 62 8558050 Fax: +41 62 8558031
12	FEDERATION OF EUROPEAN SCLERODERMA ASSOCIATIONS AISBL (FESCA)	LE VERSAILLES, AVENUE DES ETATS-UNIS 20, BOITE 32" 7500 TOURNAI Belgium	Beata Garay-Toth Tel.: +36 306377491
13	IVAN FOELDVARI (FOELDVARI)	Lange Reihe 83 20099 HAMBURG, Germany	Ivan Foeldvari Tel.: +49 40 20923697
14	ACIES CONSULTING GROUP(NOVAMEN)	Rue de la République 69 69002 LYON France	Marie-Laure Muiras Tel.: +33 4 78924000 Fax: +33 4 78924001



V.3. Project logo

The DeSSciper Project logo was designed by the patient organization FESCA, based on an idea of the Australian patient organization, which designed the original sunflower head. The Australian patient organisation Scleroderma Australia has adopted the sunflower symbolic for the warmth of the sun, because people with SSc usually feel more comfortable in warmer weather.



V.4. Project website

Background information on the DeSSciper project and preliminary results of the DeSSciper project have been published at the project website www.dessciper.eu hosted on the webserver of the Justus-Liebig-University of Giessen. The results of the DeSSciper project will be updated on a routine basis. In particular the final results of the five OTs will be added once the completion of the follow-up period has been facilitated.

V.5. Contact details of the scientific Project Coordinator

Prof. Dr. med. Ulf Müller-Ladner, MD (Scientific Project Coordinator)
Dr. med. Marc Frerix, MD, M.Sc. (DeSSciper Coordinating Office)



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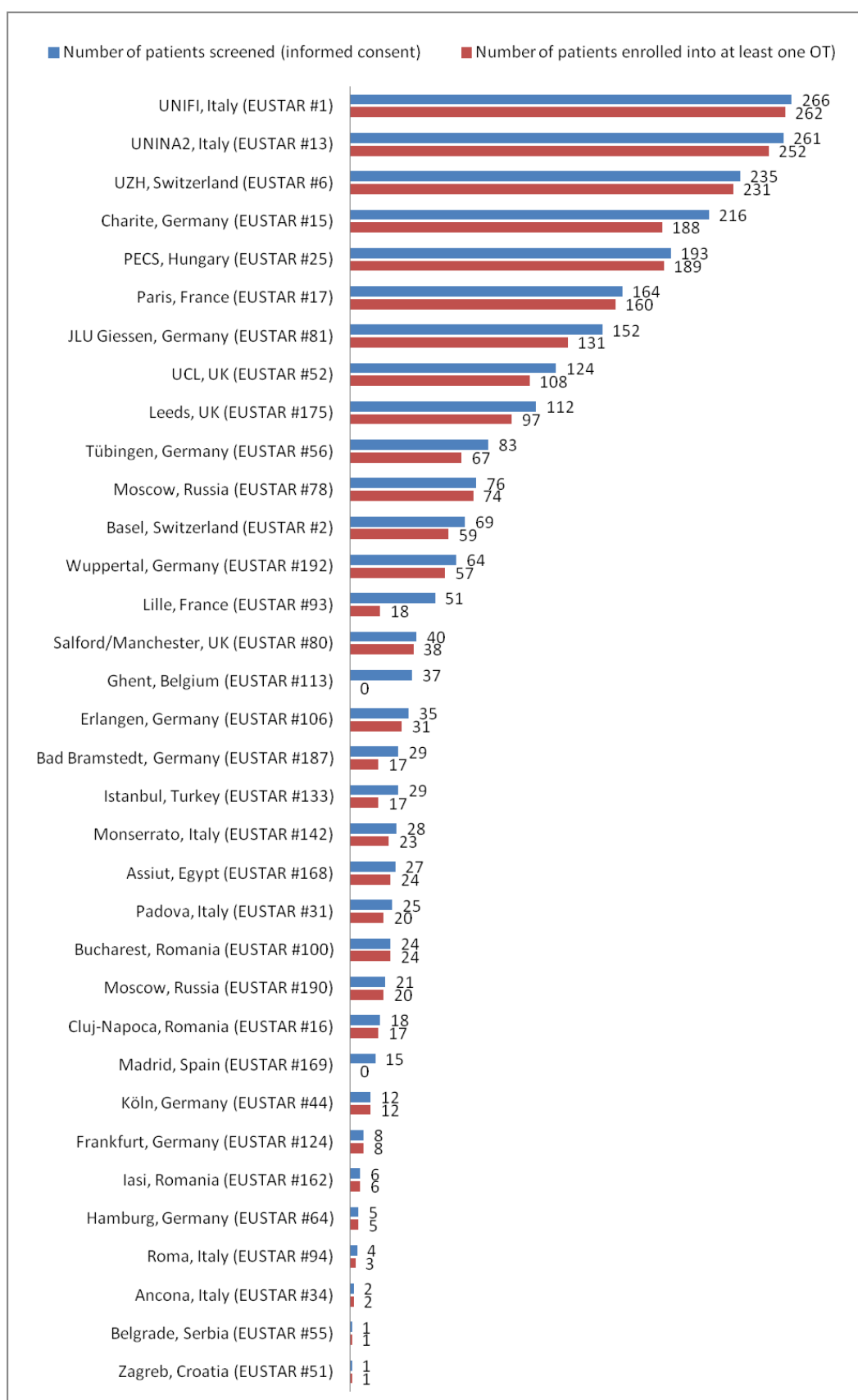


VI. APPENDIX

VI.1. Overview of the patient recruitment status of OT 1-5

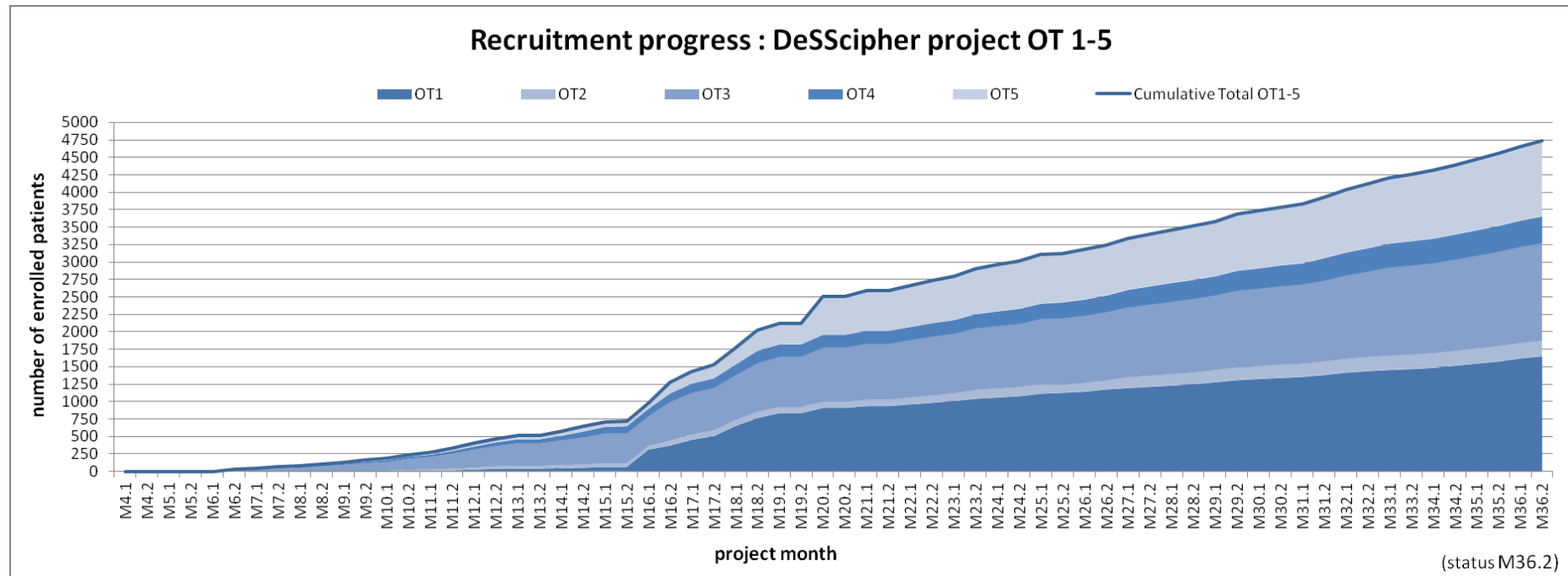
2162 (89%) of **2433** screened patients with SSc have been enrolled into at least one of the five OTs.

DeSSciper project recruitment status 30/11/2015 (M36.2)	Number of patients screened (informed consent)		Number of patients enrolled into DeSSciper OT 1-5	
	total	percentage of total screened patients	total	percentage of screened patients per center
UNIFI, Italy (EUSTAR #1)	266	11%	262	98%
UNINA2, Italy (EUSTAR #13)	261	11%	252	97%
UZH, Switzerland (EUSTAR #6)	235	10%	231	98%
Charite, Germany (EUSTAR #15)	216	9%	188	87%
PECS, Hungary (EUSTAR #25)	193	8%	189	98%
Paris, France (EUSTAR #17)	164	7%	160	98%
JLU Giessen, Germany (EUSTAR #81)	152	6%	131	86%
UCL, UK (EUSTAR #52)	124	5%	108	87%
Leeds, UK (EUSTAR #175)	112	5%	97	87%
Tübingen, Germany (EUSTAR #56)	83	3%	67	81%
Moscow, Russia (EUSTAR #78)	76	3%	74	97%
Basel, Switzerland (EUSTAR #2)	69	3%	59	86%
Wuppertal, Germany (EUSTAR #192)	64	3%	57	89%
Lille, France (EUSTAR #93)	51	2%	18	35%
Salford/Manchester, UK (EUSTAR #80)	40	2%	38	95%
Ghent, Belgium (EUSTAR #113)	37	2%	0	0%
Erlangen, Germany (EUSTAR #106)	35	1%	31	89%
Istanbul, Turkey (EUSTAR #133)	29	1%	17	59%
Bad Bramstedt, Germany (EUSTAR #187)	29	1%	17	59%
Monseurato, Italy (EUSTAR #142)	28	1%	23	82%
Assiut, Egypt (EUSTAR #168)	27	1%	24	89%
Padova, Italy (EUSTAR #31)	25	1%	20	80%
Bucharest, Romania (EUSTAR #100)	24	1%	24	100%
Moscow, Russia (EUSTAR #190)	21	1%	20	95%
Cluj-Napoca, Romania (EUSTAR #16)	18	1%	17	94%
Madrid, Spain (EUSTAR #169)	15	1%	0	0%
Köln, Germany (EUSTAR #44)	12	0%	12	100%
Frankfurt, Germany (EUSTAR #124)	8	0%	8	100%
Iasi, Romania (EUSTAR #162)	6	0%	6	100%
Hamburg, Germany (EUSTAR #64)	5	0%	5	100%
Roma, Italy (EUSTAR #94)	4	0%	3	75%
Ancona, Italy (EUSTAR #34)	2	0%	2	100%
Zagreb, Croatia (EUSTAR #51)	1	0%	1	100%
Belgrade, Serbia (EUSTAR #55)	1	0%	1	100%
Total	2433	100%	2162	89%



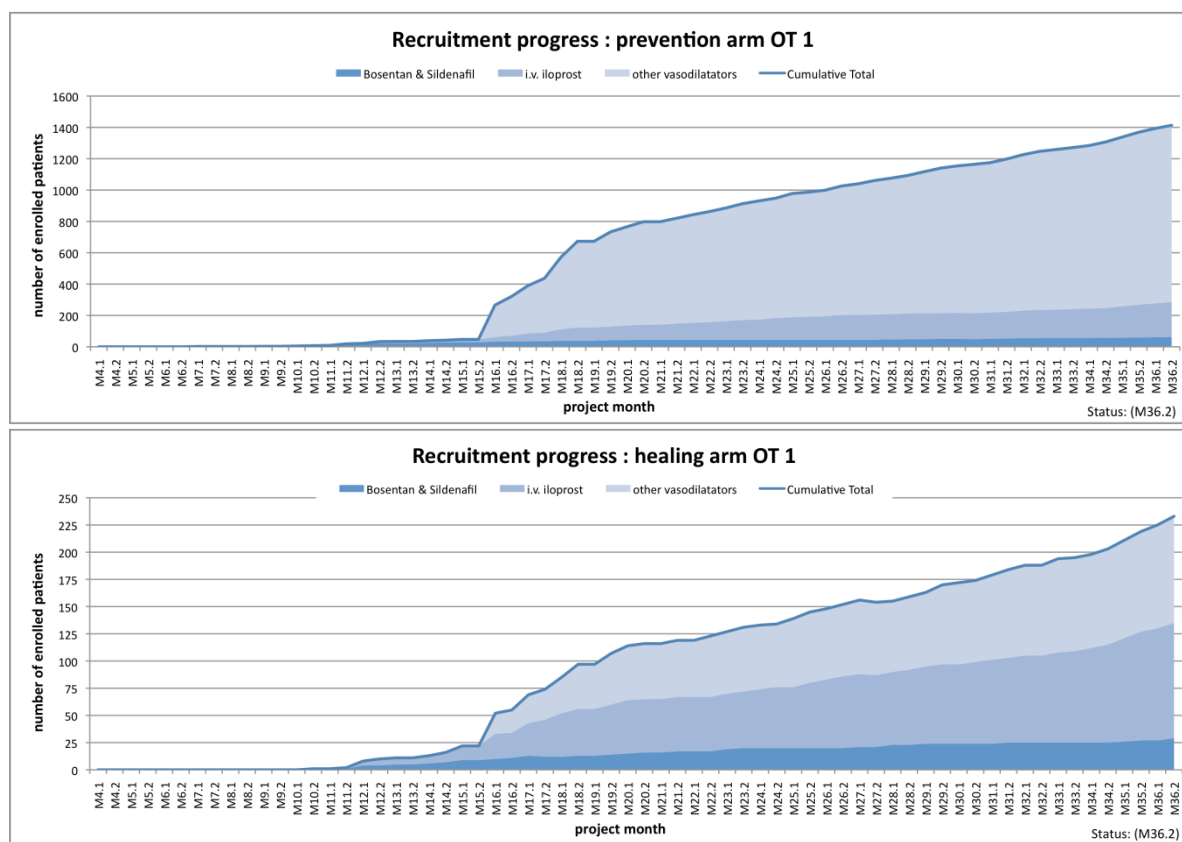


VI.2. Progress of patient recruitment of OT 1-5



Of note, one patient could be enrolled into multiple OTs at the same time.

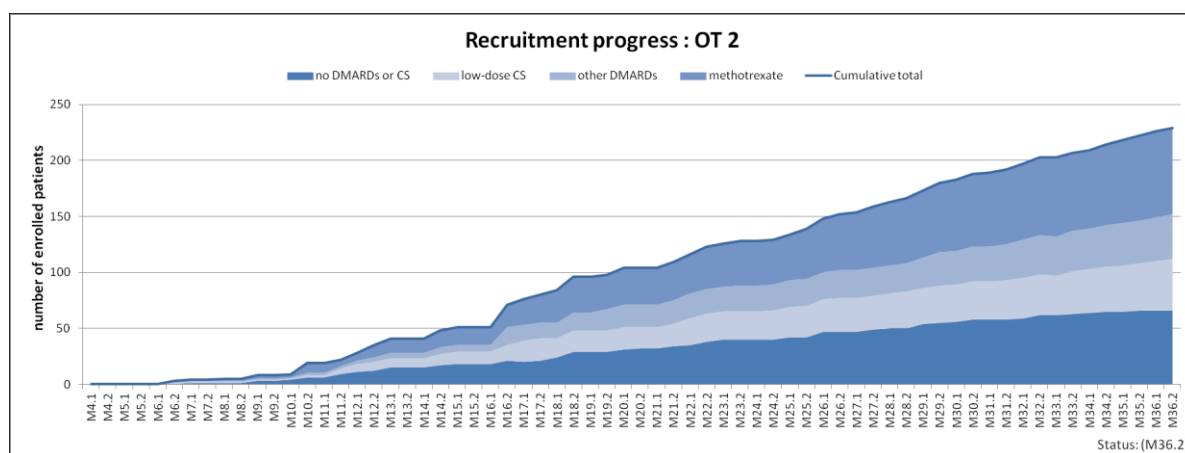
VI.3. Progress and status of patient recruitment of OT 1



OT1: Prevention and treatment of digital ulcers PI: Marco MATUCCI-CERINIC (UNIFI), Francesco DEL GALDO (LEEDS)	Number of patients enrolled in OT1								
	Total	Prevention arm				Healing arm			
		Bosentan and Sildenafil	i.v. iloprost	other vasodilators	Total prevention arm	Bosentan and Sildenafil	i.v. iloprost	other vasodilators	Total healing arm
UNINA2	237	1	3	216	220	1	3	13	17
UNIFI	236	36	18	151	205	17	3	11	31
UPD	151	4	3	139	146	0	1	4	5
PECS	138	0	0	127	127	1	0	10	11
UZH	109	4	7	86	97	2	5	5	12
Charite	107	3	44	39	86	3	17	1	21
JLU Giessen	102	2	14	69	85	1	11	5	17
Leeds	90	1	17	57	75	0	10	5	15
UCL	89	0	57	11	68	1	19	1	21
Moscow, Russia	53	0	2	39	41	0	5	7	12
Wuppertal, Germany	52	1	26	14	41	0	9	2	11
UNIBAS	45	1	0	38	39	1	2	3	6
Tübingen, Germany	42	3	2	30	35	0	3	4	7
Salford/Manchester, UK	29	0	0	25	25	0	0	4	4
Erlangen, Germany	24	2	3	13	18	1	2	3	6
Assiut, Egypt	23	0	0	18	18	0	2	3	5
Monseerrato, Italy	22	0	14	2	16	0	6	0	6
Bucharest, Romania	20	0	1	13	14	0	0	6	6
Istanbul, Turkey	15	2	0	6	8	0	2	5	7
Cluj-Napoca, Romania	11	0	0	8	8	0	0	3	3
Padova, Italy	10	0	2	6	8	0	2	0	2
Köln, Germany	10	1	4	2	7	1	1	1	3
Moscow, Russia	9	0	0	7	7	0	0	2	2
Frankfurt, Germany	5	0	0	5	5	0	0	0	0
Iasi, Romania	5	0	2	0	2	0	3	0	3
Bad Bramstedt, Germany	5	0	1	4	5	0	0	0	0
Roma, Italy	3	1	2	0	3	0	0	0	0
Ancona, Italy	2	0	1	1	2	0	0	0	0
Belgrade, Serbia	1	0	0	1	1	0	0	0	0
Földvár, Hungary	1	0	0	1	1	0	0	0	0
Lille, France	0	0	0	0	0	0	0	0	0
Zagreb, Croatia	0	0	0	0	0	0	0	0	0
Total	1646	62	223	1128	1413	29	106	98	233
Needed until M18	261	37.5	37.5	37.5	112.5	49.5	49.5	49.5	148.5
Needed (total)	522	75	75	75	225	99	99	99	297

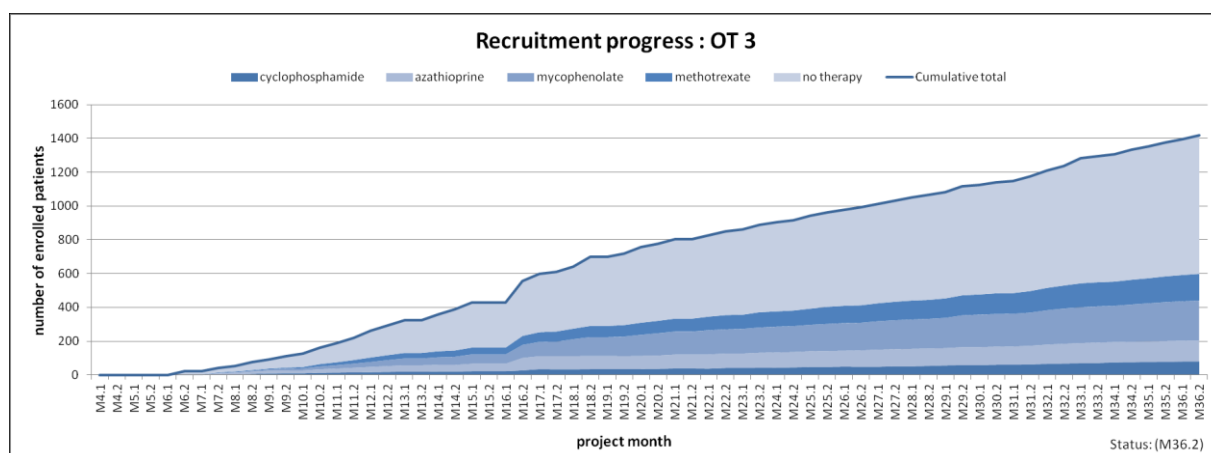
OT1 recruitment rate: 315.3% Prevention arm recruitment rate: 628.0% Healing arm recruitment rate: 78.5%

VI.4. Progress and status of patient recruitment of OT 2



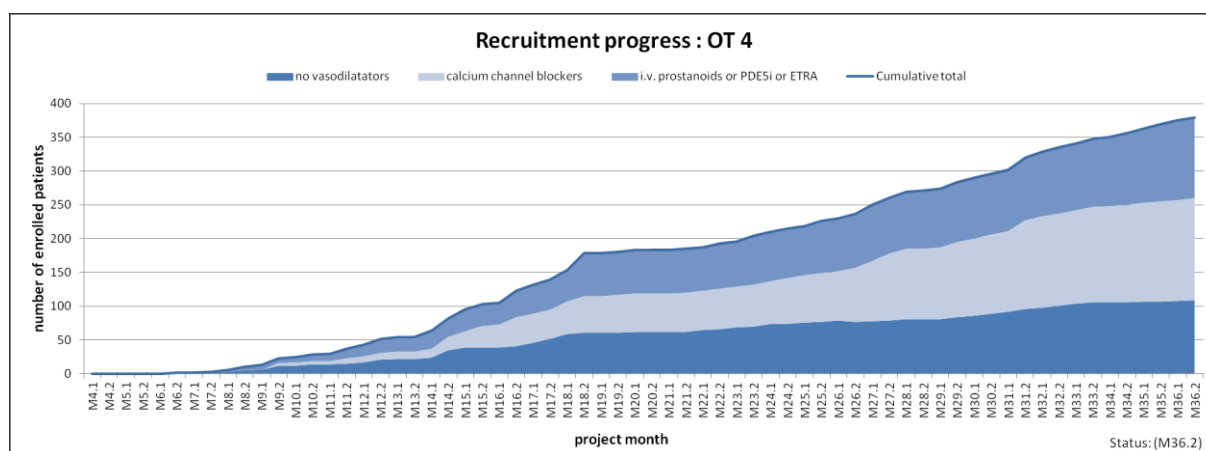
OT2: Improvement of hand dysfunction by arthritis PI: László CZIRJÁK	Number of patients enrolled in OT2								
	Total	Methotrexate		Other DMARDs		Low-dose CS		No DMARDs or CS	
		total	without concomitant biologics	total	without concomitant biologics	total	without concomitant biologics	total	without concomitant biologics
Charité	36	6	6	5	5	17	14	8	5
UZH	26	9	4	4	1	4	3	9	8
PECS	21	3	2	4	4	1	1	13	13
UNIFI	19	5	4	6	6	4	1	4	2
UNINA2	19	11	10	3	2	4	4	1	1
JLU Giessen	17	9	6	2	2	2	1	4	3
UPD	15	10	5	3	0	1	0	1	0
Moscow, Russia	10	3	3	2	0	1	1	4	2
Assiut, Egypt	9	9	9	0	0	0	0	0	0
UCL	8	2	2	3	3	1	1	2	2
Istanbul, Turkey	8	1	1	4	4	2	2	1	1
Wuppertal, Germany	8	3	3	1	1	2	1	2	2
UNIBAS	6	1	0	1	1	1	0	3	2
Iasi, Romania	6	2	2	0	0	1	1	3	2
Moscow, Russia	4	0	0	1	1	2	2	1	1
Leeds	3	0	0	0	0	1	1	2	2
Cluj-Napoca, Romania	2	1	1	0	0	0	0	1	1
Monseratto, Italy	2	0	0	0	0	2	2	0	0
Zagreb, Croatia	1	0	0	0	0	0	0	1	1
Tübingen	1	0	0	1	1	0	0	0	0
Bucharest, Romania	1	1	1	0	0	0	0	0	0
Bad Bramstedt, Germany	1	1	0	0	0	0	0	0	0
Földvari	0	0	0	0	0	0	0	0	0
Salford/Manchester, UK	0	0	0	0	0	0	0	0	0
Lille, France	0	0	0	0	0	0	0	0	0
Frankfurt, Germany	0	0	0	0	0	0	0	0	0
Total	223	77	59	40	31	46	35	60	48
Needed until M18	80	20		20		20		20	
Needed (total)	160	40		40		40		40	
DMARD = disease-modifying antirheumatic drug; CS = corticosteroids									
173 patients without concomitant biologics									
OT2 recruitment rate: 139.4% 108.1% (recruitment rate of patients without concomitant biologics)									

VI.5. Progress and status of patient recruitment of OT 3



OT3: Prevention and treatment of ILD PI: Gabriela RIEMEKAŠTEN (CHARITÉ), Christopher DENTON (UCL)	Number of patients enrolled in OT3					
	Total number (including no therapy arm)	CYP	AZA	MYC	MTX	No therapy
UNIFI	150	2	3	51	6	88
UNIBAS	26	0	2	2	4	18
UZH	226	0	3	11	34	178
UNINA2	180	1	27	57	14	81
Charite	126	20	23	7	18	58
Cluj-Napoca, Romania	10	4	3	0	3	1
UPD	51	0	3	5	11	32
PECS	160	17	11	7	8	119
Padova, Italy	12	0	0	3	1	8
Ancona, Italy	1	0	0	1	0	0
Köln, Germany	10	1	0	2	3	4
UCL	55	1	9	19	4	22
Belgrade, Serbia	1	0	0	0	1	0
Tübingen, Germany	42	2	4	7	3	27
Földvari	1	0	0	0	1	0
Moscow, Russia	67	9	4	22	2	30
Salford/Manchester, UK	26	0	2	5	0	19
JLU Giessen	67	1	3	1	13	49
Lille, France	0	0	0	0	0	0
Roma, Italy	3	0	0	1	1	1
Bucharest, Romania	24	2	4	0	5	13
Erlangen, Germany	17	1	0	2	3	11
Frankfurt, Germany	2	1	1	0	0	0
Istanbul, Turkey	13	3	4	6	0	1
Monserato, Italy	17	3	1	1	0	12
Iasi, Romania	2	1	0	0	0	1
Assiut, Egypt	21	1	8	7	16	0
Leeds	36	2	5	16	0	13
Bad Bramstedt, Germany	14	4	2	1	3	4
Moscow, Russia	19	2	1	2	0	14
Wuppertal, Germany	23	2	2	0	4	15
Total	1402	80	125	236	158	819
scenario 1 needed until M18	835	167	167	167	167	167
scenario 1 needed (total)	1670	334	334	334	334	334
CYP = Cyclophosphamide, AZA = Azathioprine, MYC = Mycophenolic acid, MTX = Methotrexate						
OT3 recruitment rate scenario 1: 84.0%						

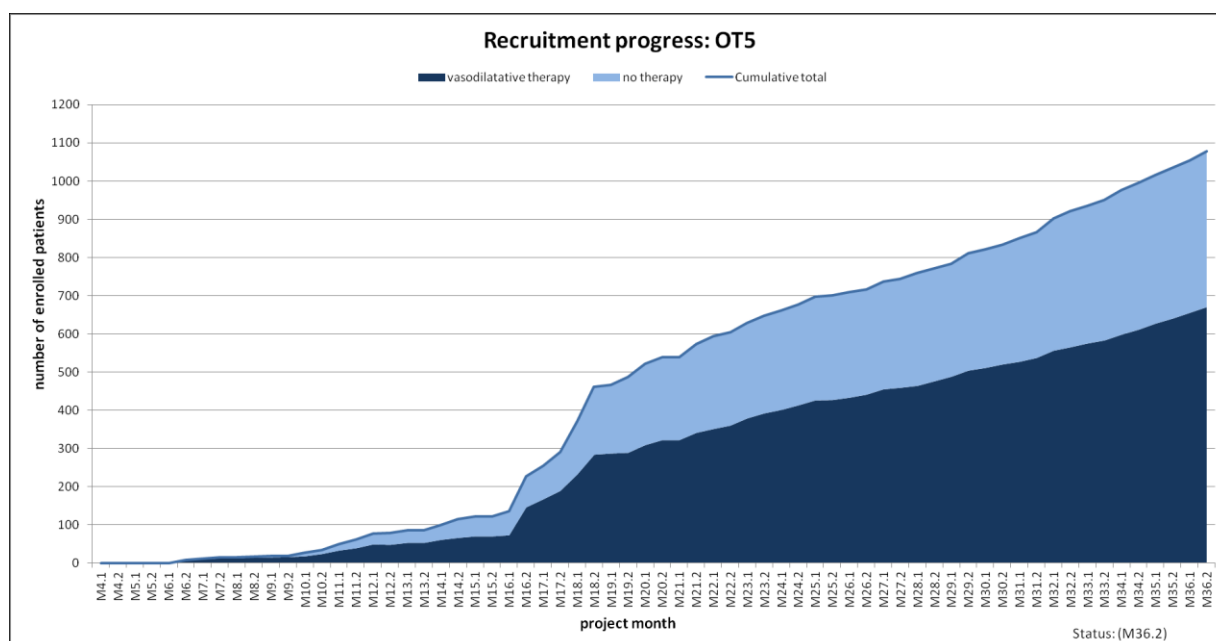
VI.6. Progress and status of patient recruitment of OT 4



OT4: Development and prevention of PH PI: Yannick ALLANORE (UPD)	Number of patients enrolled in OT4			
	Total	No vasodilators	CCB	i.v. prostanoids or PDE5i or ETRA
UNINA2	52	5	41	6
Charite	47	19	13	15
UZH	39	21	9	9
UNIFI	35	9	2	24
JLU Giessen	35	7	15	13
UPD	30	3	24	3
PECS	23	13	10	0
Moscow, Russia	22	4	14	4
Lille, France	18	7	10	1
UCL	13	5	2	6
Monserato, Italy	11	1	0	10
Assiut, Egypt	11	0	1	10
Bad Bramsted, Germany	10	5	2	3
Tübingen	8	4	1	3
Leeds	8	3	3	2
UNIBAS	6	2	0	4
Bucharest, Romania	4	0	3	1
Cluj-Napoca, Romania	2	0	0	2
Erlangen, Germany	2	1	0	1
Wuppertal, Germany	2	0	0	2
Moscow, Russia	1	0	1	0
Földvari	0	0	0	0
Salford/Manchester, UK	0	0	0	0
Iasi, Romania	0	0	0	0
Total	379	109	151	119
Needed until M18	480	160	160	160
Needed (total)	960	320	320	320

First value: current total; values in brackets: changes since last month.
 CCB = calcium channel blocker, PDE5i = phosphodiesterase-5 inhibitors, ETAs = endothelin receptor antagonists.
OT4 recruitment rate: 39.5%

VI.7. Progress and status of patient recruitment of OT 5



OT5: Development and prevention of SHD PI: Gabriele VALENTINI (UNINA2)	Number of patients enrolled in OT5								
	Total number	vasodilative treatment						No therapy	
		CCB		ACEi		CCB+ACEi			
		without risk factors	with risk factors	without risk factors	with risk factors	without risk factors	with risk factors	without risk factors	with risk factors
UNIFI	200	28	27	9	15	3	9	49	60
UNINA2	195	29	110	2	5	5	24	9	11
UZH	135	11	24	2	9	0	7	34	48
JLU Giessen	81	14	28	1	3	1	7	10	17
Charite	77	8	25	2	6	0	4	9	23
UPD	72	18	45	0	0	2	3	2	2
UCL	66	6	16	1	5	0	1	5	32
PECS	43	2	11	0	2	0	6	3	19
Tübingen, Germany	33	3	1	4	6	2	2	10	5
UNIBAS	28	2	6	0	3	0	1	1	15
Wuppertal, Germany	26	2	13	0	3	0	0	2	6
Erlangen, Germany	23	5	5	0	2	0	2	7	2
Salford/Manchester, UK	15	6	2	0	0	1	2	2	2
Moscow, Russia	15	0	11	0	2	0	1	0	1
Moscow, Russia	14	4	4	0	2	0	0	4	0
Leeds	10	0	4	1	1	0	4	0	0
Bucharest, Romania	9	0	7	0	0	0	0	0	2
Cluj-Napoca, Romania	7	1	1	0	1	0	0	2	2
Monseratto, Italy	6	2	3	0	0	0	0	0	1
Assiut, Egypt	6	0	5	0	0	0	0	1	0
Foeldvari	5	0	0	0	0	0	0	1	4
Padova, Italy	5	1	2	0	0	0	0	1	1
Frankfurt, Germany	4	1	1	0	0	0	0	0	2
Ancona, Italy	2	0	0	1	0	0	0	1	0
Bad Bramstedt, Germany	1	0	0	0	1	0	0	0	0
Lille, France	0	0	0	0	0	0	0	0	0
Iasi, Romania	0	0	0	0	0	0	0	0	0
Total	1078	143	351	23	66	14	73	153	255
Needed until M18	393	670						408	
Needed (total)	786	196.5						196.5	
OT5 recruitment rate: 137.2% vasodilative arm recruitment rate: 170.5% no therapy arm recruitment rate: 103.8%									