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Very early systemic sclerosis

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A B S T R A C T

The early diagnosis of systemic sclerosis (SSc) can be very difficult, when most of the typical signs and symptoms are absent. For this reason, the approach to SSc has changed during the last decades because the importance of an early diagnosis and treatment has been widely understood. *"Very early SSc"* is identified as a condition characterized by Raynaud's phenomenon, puffy fingers, disease-specific autoantibodies, and microvascular alterations at capillaroscopy. However, reliable biomarkers able to predict the disease evolution are missing, and decision whether to treat or not to treat in the earliest phase of the disease remains a dilemma. Presently, the only feasible clinical strategy in very early SSc remains a tight follow-up program to detect in "real time" the onset of internal organ involvement, which may thus allow an aggressive therapeutic agenda.

Introduction

Systemic sclerosis (SSc) is a connective tissue disease (CTD) characterized by widespread fibrosis of the skin and internal organs, small-vessel vasculopathy, and immune dysregulation with production of autoantibodies [1]. The disease may have different clinical features at onset as well as a heterogeneous course with time [1]: in fact, it is an unpredictable disease, which still presents considerable challenge for the rheumatologist. Despite many advances made in the understanding of the pathogenetic mechanisms and the development of new targeted therapies, diagnosis in the early oligosymptomatic phase of SSc remains a challenge for the physician. Taking into account a high individual variability in

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disease presentation and severity, identifying predictors of morbidity and mortality at disease onset is of high importance to identify high-risk groups and guiding treatment decisions [2,3]. To date, SSc has been easily diagnosed in an advanced phase when the skin is thickened, and disease-specific antibodies as well as microvascular changes are present; further, signs of internal organ involvement may be found. However, the diagnosis of SSc remains very difficult in the early phase, when most of the typical signs and symptoms are absent [4]. The earliest signs are Raynaud's phenomenon (RP) and puffy fingers (PF) (i.e., digital edema), recently identified as pivotal signs to suspect the presence of SSc [5,6]. Unfortunately, RP and PF are nonspecific signs, common also in other CTDs, in particular undifferentiated connective tissue disease (UCTD) and mixed connective tissue disease (MCTD). This evidence may limit the diagnostic capacity and early treatment as well. Therefore, the prevention of disease evolution and organ damage is impaired, thus favoring the progression to loss of function and impairment of quality of life with a significant increase in direct and indirect costs [4,7]. Data from a Canadian registry on 359 patients showed that the delay of SSc diagnosis was 6.1 years after the onset of RP and 2.7 years after the onset of extra-RP symptoms [8]. For this reason, it is important to underline that even if RP has a high sensitivity as an early sign, due to its low specificity (because it may be found in other diseases), the presence of RP should always prompt a thorough investigation. An efficient algorithm to approach a patient with RP to "diagnose" SSc is therefore of paramount importance: Johnson et al. have investigated the use of the health care system by patients with SSc by determining which physicians diagnosed and followed up patients, what tests were used, and what was the time to diagnosis. They observed that less than half of the patients were diagnosed by a rheumatologist, and the mean time to diagnosis during the 3 decades analyzed was 2.4 years. Less than 50% of patients visited sub-specialists or had baseline screening tests for organ involvement [9]. It is clear that in front of a patient with RP, SSc should be ruled out by the general practitioner by referral to a rheumatologist for more thorough investigation. Currently, a significant reduction in mortality is associated with SSc renal crisis due to early treatment with ACE inhibitors [10]. This evidence confirms that early diagnosis is a key objective for the rheumatologist to exploit the *window of opportunity* to start early therapy slowing or, even better, blocking the disease progression [11]. Ideally, treatment could be initiated in a timely fashion in such an early patient population [12] to preempt SSc-related vasculopathy complications, i.e., digital ulcers (DU), pulmonary arterial hypertension (PAH), and interstitial lung disease (ILD) [13].

Classification versus diagnostic criteria

Almost all the SSc criteria proposed to date [14–16] are "classification" and not "diagnostic" criteria [17]. Classification criteria identify well-defined, relatively homogeneous cohorts of patients for use in randomized clinical trials, but they are also employed in practice to confirm the diagnosis of SSc. Conversely, diagnostic criteria are a set of symptoms, signs, and tests used in routine clinical practice that help to define the diagnosis of SSc. In clinical practice, often patients with early, mild, or limited expression of the disease are not considered for a precocious diagnosis of SSc. Population-based studies showed that mild SSc is a more frequent disease than that previously suspected [4] and that the involvement of internal organs is early and subclinical and can be also present in the very early and asymptomatic phase [18–20]. If started late, the currently available drugs are less effective, i.e., when the organ damage is already irreversible. For this reason, it is crucial to identify patients before organ damage is irreversible to adopt a tight follow-up and be ready to treat promptly the most aggressive cases.

SSc classification criteria: the past

The first classification criteria for SSc published in 1980 required skin fibrosis as major criterion with a high specificity but low sensitivity to identify patients with SSc, particularly in the early and limited SSc subset. In fact, the presence of skin sclerosis proximal to metacarpophalageal (MCP) or metatarsophalangeal (MTP) joints or the presence of two of three secondary criteria (sclerodactyly, DUs, or lung fibrosis) is required [15]. Consequently, approximately 10–20% of patients with a clear clinical

diagnosis of SSc that do not fulfill the ACR criteria have been undertreated or misunderstood [21]. Over the years, several criteria have been proposed to try to overcome these limitations, but all were ill suited for an early disease having as a prerequisite the presence of skin fibrosis. Furthermore, the semantic used to identify patients in the early phase of SSc has been significantly confusing. In the 1980s, Leroy and Maricq reported that a history or presence of RP, without other causes or disorders, a capillaroscopic "scleroderma pattern," and the presence of DU or decreased esophageal motility already allowed to identify patients with early SSc [22,23]. Since 1988, a dichotomic approach has characterized the management of patients with SSc. Two different subsets of disease – limited SSc (lSSc) and diffuse cutaneous SSc (dcSSc) – were proposed by LeRoy et al. [24], and they are still used in clinical practice, even if they cannot help to define or adequately understand the disease in the early phases. In fact, these criteria have been centered on skin extension even if other clinical features, course of disease, autoantibody profile, and prognosis distinguish the two subsets. This SSc subsetting has influenced and guided physicians in the management of the disease thus far, in particular for the known different evolution, faster and greater in the more aggressive diffuse subset. Data from the European League Against Rheumatism Scleroderma Trial and Research group (EUSTAR) show that the time between the onset of RP and the first non-RP symptom or sign of SSc is approximately 4.8 years in lcSSc and 1.9 years in dcSSc [8]. In 1996, the term pre-scleroderma was proposed to identify patients with RP, digital ischemic modifications, and typical nailfold capillary abnormalities or disease-specific circulating autoantibodies [25]. Five years later, in 2001, LeRoy and Medsger proposed the term limited SSc (lSSc) for patients with RP and either SSc-specific autoantibodies or SSc-type nailfold capillary pattern [16]. However, they did not mention which other symptom/sign/laboratory/instrumental finding should be considered as an exclusion criterion for the diagnosis of lSSc. Some patients with lSSc were without cutaneous involvement, but SSc nailfold videocapillaroscopy (NVC) abnormalities, specific antinuclear antibodies (ANAs), and visceral involvement were called SSc sine scleroderma even if none of the registries published thus far have considered it [26]. A few years later, in a large prospective follow-up study of 586 patients with RP and no definite CTD, 3197 person-years were evaluated, and it was observed that 12.6% of patients developed definite SSc (according to the 1980 SSc criteria). The results showed that patients with RP and abnormal SSc capillaroscopic pattern, together with an SSc-specific autoantibody at baseline, had a 79.5% probability of developing definite SSc up to 9 years of observation. This work highlighted the importance of RP, disease-specific antibodies, and NVC for SSc diagnosis [27]. In the wake of the results of Koenig's study, increasing attention has been focused on RP as a sentinel sign able to identify patients at higher risk of developing SSc potentially reducing the diagnostic delay.

Very early SSc

"Very early SSc" was identified as a condition characterized by RP, PF, disease-specific autoantibodies, and microvascular alterations detected by capillaroscopy (requiring at least two, or better, all three items to be present) [6]. In 2011, the preliminary criteria for the very early diagnosis of SSc (VEDOSS) were proposed by the EUSTAR Group [28] and a 3-round multicenter web-based Delphi exercise was performed among 110 experts in the field of SSc to identify the potential predictors able to guide the rheumatologist in very early diagnosis of SSc. The presence of RP, PF, and ANA positivity were identified as the three "red flags" that should raise suspicion of very early SSc [6]. To confirm suspicion of the disease, it is necessary to look for the SSc pattern at nailfold capillaroscopy (NC) and/or of specific SSc antibodies (anti-centromere antibody (ACA) or antitopoisomerase I (TOPO-I)). VEDOSS criteria identified PF as an additional warning sign for very early SSc as compared to previous proposed criteria [6,15,16,28]. Although patients with RP, autoantibodies, and SSc capillaroscopic pattern could be easily followed up, an agreement on the predictors identifying patients that will evolve to established disease is still lacking. For this reason, patients must be followed up regularly even though the ideal frequency of such visits has not yet been established. The VEDOSS project, a multicenter study performed in 38 EUSTAR centers, throughout and outside Europe, has been designed to identify through an at-risk population the predictive factors for the progression toward a definite classification of SSc [6].

Preliminary results of the analysis of 516 patients with RP enrolled into the VEDOSS online database confirm the relevance of the "red flags" identified by EUSTAR and highlight the importance of PF in the identification of patients with a predisposition to develop very early SSc. Almost 90% of ANA-positive patients with RP with previous or current PF already had an NC SSc pattern and/or SSc-specific autoantibodies. It is interesting to note that ANA-negative patients with PF should be followed up and carefully investigated, as 20% of these patients presented with other SSc signs (esophageal symptoms, an SSc pattern on NC) and another 17% presented with an NVC SSc pattern, while 8% fulfilled the new SSc ACR/EULAR classification criteria [5].

SSc classification criteria: the present will change the future

A major achievement of the recent years has been the publication of the new SSc ACR/EULAR classification criteria [29]. Sensitivity and specificity in the validation sample were, respectively, 0.91 and 0.92 for the new criteria, which is significantly better than the 0.75 and 0.72 values, respectively, for the 1980 ACR classification criteria [15]. The new criteria should allow to identify patients in earlier phases of disease than the older criteria: Johnson et al. performed an analysis of a cohort of 304 patients with early or established SSc, demonstrating that the new criteria classified more patients as patients with definite SSc than the previous 1980ARA criteria [15,30], thus having a high sensitivity and specificity.

These new classification criteria not only confirm the important role of skin involvement for the diagnosis of SSc, according to the 1980 ACR criteria [15] but also introduce new features, usually found in the early phase, allowing to reach the diagnosis using a score system. In addition to the confirmation of the importance of skin thickening of the fingers extending proximally to the metacarpophalangeal or metatarsophalangeal joints, other items may be considered (skin thickening of the fingers, telangiectasia, digital tip ulcers, fingertip pitting scars, PAH, abnormal nailfold capillaries, ILD, RP, and SSc-related autoantibodies). Each item has a score from 1 to 3, and if the patient has a total score of 9 or more points, the patient should be classified as SSc [29]. It is important to remind that the fact that patients with different stages of disease may have the same score indicates that the value of the score does not correspond to the severity of the disease. Patients with a similar score may have a very different degree of disease severity: RP, PF, ACA/*anti*-topoisomerase-I positivity and abnormal NC (score = 10); PAH, DU of the tip, ACA/*anti*-topoisomerase-I positivity, RP (score = 10). However, these new criteria are very close to the criteria needed in clinical practice to make an SSc diagnosis by including many very early signs of SSc. The most important thing is that all these patients will be recognized as having SSc, allowing the rheumatologist to plan the best management and therapeutic strategies since the early phases. Furthermore, the new ACR/EULAR criteria add emphasis to the vasculopathic manifestations and this could indicate that a more aggressive therapeutic strategy should be started since the onset of the earliest vascular manifestation (i.e., RP) [29]. In fact, RP is the target for the vasodilating strategy (endothelin receptor antagonists, phosphodiesterase type 5 (PDE 5) inhibitors, calcium channel blockers, and iloprost) established early, with the aim to not only reduce the frequency and severity of RP attacks but also prevent or at least delay the onset of late severe complications, such as DU, PAH, and scleroderma renal crisis [31,32]. However, the greatest risk is overtreatment of those patients who will not evolve or will evolve very slowly to a full-blown picture of SSc with internal organ involvement. Some patients will remain in the limbo of UCTD or MCTD, despite that they may develop their own, separate spectrum of internal organ complications.

Very early SSc and prognosis

As all potential predictive factors of disease evolution are yet poorly known, VEDOSS patients should be followed up regularly even though the ideal frequency of such visits has not yet been established. In VEDOSS patients, Vasile et al. studied NVC characteristics that could predict progression toward established SSc: 66 patients with VEDOSS performed NVC once a year, with the evaluation of morphological parameters, pattern, and semiquantitative rating scale. In a mean follow-up time of 31

months, almost 32% of patients progressed to SSc. Patients who progressed very fast within one year showed a loop diameter and apex width significantly higher than all other VEDOSS subjects. Each unit increase of apex width was associated with an increasing risk of 1% for developing SSc and the cut-off value of 103 μm showed a positive predictive value of 56% and a negative predictive value of 71% [33]. Bruni et al. reported that patients with VEDOSS already present modifications of the microvasculature and complications such as DU [34]. This study evaluated the presence of digital lesions in 110 patients with VEDOSS and its possible association with internal organ involvement. It was found that 16 patients presented with active DU, while the other 9 patients reported a history of DU only. It is interesting to remark that both the history and the presence of DU showed statistically significant correlation with esophageal involvement. Therefore, the appearance of DUs may be a sentinel sign for early organ involvement in VEDOSS patients.

Utility of disease-specific autoantibodies

When laboratory features are considered, ANA positivity with no "specific SSc autoantibodies" was significantly more frequent in patients who did not progress, while a specific SSc autoantibody positivity was significantly more frequent in the progressors. This finding suggests that the positivity of ACA and *anti*-topoisomerase I indicates a high probability of developing SSc [35] and that the contemporary detection of specific NVC abnormalities and specific SSc autoantibodies further improves the predictive value [34]. Important indications from a prognostic point of view can also be obtained with the detection of other autoantibodies that can predict internal organ complications and guide the follow-up despite not having an ascertained pathogenetic significance. Of note, *anti*-RNA polymerase III antibodies are associated with an increased risk of renal crisis, gastric antral vascular ectasia, and rapid progression of skin involvement [36]. Interestingly, Lazzaroni et al. reported an increased risk of concomitant neoplasia at the time of SSc diagnosis in patients with RNA polymerase III positivity, suggesting the need for a regular and thorough screening every 2–5 years [36] to exclude cancer. It is also of note that ACA and Anti-Th/To antibodies are associated with lcSSc and to a higher risk of PAH development, while *anti*-topoisomerase I positivity is associated to dcSSc and a higher risk of severe ILD and DUs [37,38]. Moreover, the presence of anti-pm-scl, *anti*-ku, and *anti*-RuvBL1/2 may predict myositis [39–41]. Unfortunately, in practice, few laboratories can make a complete evaluation of ANAs, and this reduces their use and the possibility of studying and confirming the prognostic power of autoantibodies [42].

How to assess internal organ involvement since the earliest phases of disease

Several data have shown that internal organ involvement is present since the early and asymptomatic phase and determined the prognosis of the disease [18,19]. As shown previously, esophageal manometry, B-mode echocardiography, lung function tests, and esophageal manometry are recommended to detect preclinical subclinical alterations in internal organs in SSc [18]. In a high proportion of patients, the presence of SSc-related internal organ involvement, including an inverted mitral E/A ratio (i.e., diastolic dysfunction as a measure of early cardiac involvement) and/or a transfer factor for carbon monoxide (TLCO) < 80% of the predictive value (i.e., early lung interstitial/vascular involvement) and/or basal low esophageal sphincter pressure <15 mmHg (i.e., early esophageal involvement) may be found [18].

Esophageal involvement

Esophageal involvement is prevalent in SSc, in particular in the very early phases [43]. On esophageal manometry, typical findings include a weak lower esophageal sphincter (LES) and ineffective or absent esophageal motility [8,44,45]. The presence of an early internal organ involvement in patients with SSc along with an esophageal and anorectal involvement was found in the earliest SSc phase [19]. Lepri et al. evaluated 59 patients with VEDOSS who underwent esophageal and anorectal manometry.

In 4 patients and 17 patients, esophageal manometry and anorectal manometry were not performed, respectively, because of intolerance. They found that several esophageal abnormalities were common in patients with VEDOSS. In particular, the maximum pressure and mean pressure of LES were significantly lower in patients with VEDOSS as the anal resting pressure; further, the maximum voluntary contraction was significantly abnormal. Interestingly, esophageal and anal involvement seems to be correlated with lung involvement in the very early phases of disease. In fact, patients with a DLCO <80% showed a hypotonic LES and an abnormal peristalsis, while in case of DLCO >80%, they showed only abnormal peristalsis [19]. Furthermore, a prospective longitudinal cohort study of 68 consecutive patients with SSc evaluated whether high-resolution manometry (HRM) with a test meal can detect clinically relevant, abnormal motility already in very early SSc. The authors showed that patients with SSc had less frequent effective esophageal contractions during the test meal than healthy controls, even in very early disease [45]. These data recommend routine manometry studies in patients with SSc since disease onset to detect early loss of esophageal contractile reserve that may aid in diagnosis and risk stratification. The importance of gastrointestinal involvement assessment was also demonstrated for prognostic purpose. Trapiella-Martínez et al. retrospectively evaluated 1632 patients included in the Spanish Scleroderma Registry (RESCLE) who were considered as pre-scleroderma (RP and either specific SSc autoantibodies or positive ANA with nucleolar immunofluorescence (IF) pattern or a SSc capillaroscopy pattern) and were reclassified as very early (VEDOSS) and early SSc. Patients who met the VEDOSS criteria presented esophageal involvement (gastroesophageal reflux or hypotonic LES without esophageal body dysmotility), decreased diffusion of carbon monoxide (DLCO) without ILD or PAH, diastolic dysfunction excluding hypertension, ischemic heart disease or age, and/or DU or pitting scars, telangiectasia, calcinosis, or arthritis). The authors reported that the early subset has a higher risk of progression to definite SSc than the very early subset and that gastroesophageal involvement is an independent risk factor of progression [21].

Heart involvement

Regarding heart involvement, as it potentially presents since early and asymptomatic phases, all patients with SSc should regularly undergo an annual cardiovascular evaluation with echocardiography and ECG Holter and, when positive, should perform cardiac magnetic resonance (MRI) in search of myocarditis and/or fibrosis in early stages of the disease [46,47]. In fact, increasing interest had been paid to cardiac MRI as a reliable and sensitive technique to diagnose early heart involvement in SSc and to analyze its mechanisms, including its inflammatory, microvascular, and fibrotic components [48]. Gargani et al. reported that the presence of myocardial fibrosis, elevated uCRP, and higher maximum mRSS are predictors of cardiovascular outcomes (heart failure, coronary artery disease, arrhythmias, vasculopathy, elevated systolic pulmonary artery pressure, and death) in patients with SSc [49]. Arrhythmias are one of most severe and potentially fatal complications in SSc. Kostis et al. reported that ventricular tachycardia was associated with a 2-fold increase in the risk of death, whereas frequent ventricular ectopy, defined as more than 100 premature ventricular contractions (PVCs) per 24 h, was associated with a 4-fold increase in the risk of death, and ectopy, defined as more than 1000 PVCs per 24 h, was associated with a 6-fold increased risk of death [50]. Recently, the role of high levels of NT-proBNP has been reported. Muresan et al. [51] found a statistically significant correlation between the NT-proBNP levels and the total number of PVC, total number of ventricular couplets, total number of isolated PVCs, and the number of PVC morphologies. In particular, NT-proBNP serum level >287 pg/ml showed a sensitivity of 55% and a specificity of 93% in predicting the presence of complex ventricular arrhythmias on 24-h Holter ECG monitoring. For this reason, NT-proBNP levels could become a useful ventricular arrhythmia marker for assessing the arrhythmic risk in patients with SSc since the early phase of disease, as it allows a PAH risk stratification, suggesting its potential role as a first-line tool in the primary care setting for the overall cardiac assessment of SSc [52–54]. In fact, initial screening evaluation for PAH in patients with SSc includes pulmonary function tests (PFT) DLCO, transthoracic echocardiogram (TTE), and NT-proBNP; TTE and PFT should be performed on annual basis while full screening panel (TTE, PFT, and NT-roBNP) should be performed as soon as any new signs or symptoms are present [55].

Lung involvement

Today, SSc-ILD or PAH are the major causes of mortality [56,57], with up to 30% of deaths directly ascribable to pulmonary fibrosis [57]. In up to 90% of SSc patients, ILD is diagnosed by high resolution computed tomography (HRCT). As previuosly indicated, lung involvement could be present since the early phases of the disease [18,19]. Main risk factors for development of lung fibrosis and progression are: male gender, dcSSc subset, *anti*-topoisomerase I, and FVC % <70%. However, even as HRCT is the gold standard for diagnosis of lung involvement, PFTs are always recommended, either for diagnosis or for follow-up, and are the main tool in the evaluation of patients with very early SSc. HRCT should be repeated in case of new pulmonary symptoms and/or when FVC or DLCO <80% presents for the first time or there is a decrease of FVC >10% from predicted or a decrease of DLCO >15% from predicted [56,57]. Recently, lung ultrasound (LUS) has emerged as a new promising noninvasive and radiation-free tool for ILD evaluation in patients with SSc. Several studies showed that LUS may be a useful tool to determine the best timing for HRCT execution, thus preventing a continuous and useless exposure to ionizing radiation for many patients [58,59]. Gigante et al. found that the number of B-lines increased with the progression of both HRCT score and with digital vascular damage represented by capillaroscopic damage and presence of DU [60].

For this reason, in patients with VEDOSS, the follow-up to detect lung involvement should be performed with PFTs and LUS.

Musculoskeletal involvement

In the early phases of SSc, musculoskeletal involvement is common, and symptoms may be aspecific with body pain, hand pain, and joint swelling. Literature data showed that patients with early disease and synovitis are more likely to have the dcSSc, while palpable tendon friction rubs (TFRs) have been associated with diffuse SSc, increased disability, and poor survival [61–64].

In a prospective study on 1301 patients with SSc from the EUSTAR database (disease duration $\leq$3 years at inclusion and a follow-up of at least 2 years), Avouac et al. found that synovitis and tendon friction rubs were predictive of overall disease progression in patients with early SSc [62,63]. For this reason, these clinical signs should be evaluated in all patients with early SSc. Their detection may allow the identification of a subset of patients at risk of skin progression, which, in turn, predicts internal organ involvement [63].

Summary

The diagnosis of very early SSc is presently fundamental because it is the main tool to try to change the natural course of the disease. The red flags provided by the VEDOSS study help to raise the suspicion, while the presence of NVC abnormalities and specific antibody positivity may identify a very early disease at risk of evolving to a definite SSc. In these patients, the lack of reliable predictors of disease evolution suggests the need for a tight follow-up and a careful screening of internal organ involvement [65]. Therefore, the present-day challenge is deciding whether to treat or not to treat patients in the earliest phases of the disease. In very early SSc, the only feasible clinical strategy remains a tight follow-up program to detect in “real time” the early internal organ involvement, which may allow an aggressive therapeutic agenda. In fact, all patients may potentially progress, but everyone has their clock, and it is fundamental to identify those who are progressing faster. Therefore, a flexible management algorithm accounting for the different SSc phases and with a wide array of therapeutic measures seems most appropriate [7]. In fact, SSc can appear with heterogeneous clinical scenarios and requires different therapeutic strategies.

Conflicts of interest

None.

Funding statement

None.

Practice points

- "*Very early SSc*" is a condition characterized by Raynaud's phenomenon, puffy fingers, disease-specific autoantibodies, and microvascular alterations detected by capillaroscopy (requiring at least two, or better, all three items to be present)
- Internal organ involvement might be present at the earliest phases of disease; for this reason, the following examinations should be performed at diagnosis to predict visceral complications and guide follow up:
  - Esophageal manometry
  - Specific disease autoantibodies
  - Lung ultrasound and pulmonary function tests (repeated every 6 months)
  - Lung HRCT
  - ECG and echocardiography (repeated annually)
- The presence of gastroesophageal involvement in the earliest phase of the disease seems to be an independent risk factor for progression of the disease

Research agenda

- Validated predictive factors of disease evolution are still missing. For this reason, the VEDOSS patient should be followed up regularly even though the ideal frequency of such visits has not yet been established

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