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Undifferentiated Connective Tissue Disease: Comprehensive Review

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Abstract

Purpose of Review Undifferentiated connective tissue disease (UCTD) is characterized by the presence of clinical symptoms of a systemic autoimmune disease in addition to laboratory evidence of autoimmunity with the patients not fulfilling any of the widely used classification criteria for classic autoimmune diseases. The presence of UCTD as a separate entity versus an early stage of such diseases as systemic lupus erythematosus (SLE) or scleroderma has long been debated. Given the uncertainty regarding this condition, we performed a systematic review on the topic.

Recent Findings UCTD can be subcategorized as evolving (eUCTD) or stable UCTD (sUCTD) based on its evolution towards a definable autoimmune syndrome. Analyzing the data from six UCTD cohorts published in the literature, we found that 28% of patients have an evolving course with the majority developing SLE or rheumatoid arthritis within 5–6 years of the UCTD diagnosis. From the remaining patients, 18% do achieve remission. Published treatment regimens were similar to other mild autoimmune diseases with low-dose prednisone, hydroxychloroquine, and NSAID. One-third of patients did need immune suppressive medications. Importantly, the reported outcomes were excellent with survival rates of more than 90% over 10 years. It has to be noted though that as data on patient related outcomes are not available to date, the exact impact of this condition on quality of life is unclear.

Summary UCTD is a mild autoimmune condition with generally good outcomes. There is still great uncertainty though regarding diagnosis and management. Going forward, consistent classification criteria are needed to advance UCTD research and eventually provide authoritative guidance on the management of the condition.

Keywords Undifferentiated connective tissue disease · Early SLE · Criteria · Autoantibodies

Introduction: the Clinical Problem

Connective tissue disorder (CTD) is a term widely used to describe a group of diseases marked by inflammatory autoimmune response that can potentially affect any organ system. Diagnosing these conditions can be challenging as they share similar clinical manifestations, particularly at the early stages of the disease. Ultimately, physicians rely on their clinical acumen to make a definitive diagnosis. On some occasions, identifying the correct disease is unequivocal. For instance, when a young woman presents with malar rash, arthritis, leukopenia, a positive anti-nuclear, and double-stranded DNA antibody, the diagnosis of SLE is not in doubt. In practice though, rheumatologists often encounter individuals with clinical features suggestive of, but not unequivocally due to a CTD. It is common to label this presentation as an undifferentiated connective tissue disease (UCTD). It has been reported that up to 20–50% of patients who present at a rheumatology clinic are diagnosed with UCTD [1, 2]; however, the true prevalence is unknown primarily because of lack of consensus on UCTD definition. For the same reason, there is wide variation in the management of these patients.

To gain a better understanding on the clinical presentation, diagnostic uncertainty, and progression risk in UCTD patients, we performed a systematic literature review.

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Methods

Search Strategy and Data Sources

A systematic search was conducted in PubMed from the inception of the database through April 2022. The keywords used for the search included Undifferentiated Connective Tissue Diseases (UCTD), risk factors, and outcomes.

Study Selection

We included studies published in English that meet the following inclusion and exclusion criteria.

Inclusion:

1. UCTD patients with a disease duration of no less than a year,
2. At least one clinical manifestation suggestive of a CTD, and
3. A positive non-organ specific antibody or extractable nuclear antigen antibody (ENA). Anti-nuclear antibody (ANA) measured by immune fluorescence was considered positive at a titer ≥ 1:160.

Exclusion:

1. UCTD patients who fulfilled an established CTD classification criteria
2. Studies selecting only pregnant UCTD patients
3. Studies including patients with incomplete or latent SLE

If several studies were conducted at the same clinical center, we chose the publication with the longer follow-up time.

We combined and analyzed the data of patients found to evolve to definitive CTD or remained undifferentiated. In addition, we summarized the information about baseline clinical and immunological parameters.

Results

Definition of UCTD

Approximately four decades ago, the term *undifferentiated* was introduced by LeRoy et al. [3] as a way to better categorize patients at an early phase of a CTD; these individuals would display certain manifestations that could be attributed to a CTD but did not have a clear cut presentation of a classic CTD. This observation besides introducing the UCTD entity provided the first evidence regarding its natural history and clinical spectrum. Since then, several observational studies on UCTD have been published but the interpretation of the results has been hindered by differences in the definition of UCTD and especially the patient selection criteria (Table 1). To complicate things further, other terms such as latent or incomplete CTD have been introduced adding uncertainty among practitioners as to the clinical significance and progression of the condition [4].

It is important to note that neither the American College of Rheumatology (ACR) nor the European Alliance of Associations for Rheumatology (EULAR) endorses any published definition or offer a general description, guidance, or guidelines about UCTD, denoting the challenges reconciling the available evidence on this subject. That being said, efforts have been made to introduce an accepted definition of UCTD.

Probably the most recognized definition is the one proposed by Mosca et al. [7, 18, 19••]. The authors suggested that to be classified as having UCTD, first and foremost, a patient should not fulfill any validated CTD classification criteria. If this is the case, a patient who presents with at least one clinical manifestation indicative of a CTD plus a positive ANA measured on two different occasions can be labeled as UCTD. A disease duration cutoff of 3 years was chosen to differentiate between two groups of patients. Patients who belonged to the first group, called evolving UCTD (eUCTD) developed a definable CTD within the first few years of their disease course. The second group of patients were those in whom the disease stayed undifferentiated for a longer period of time with only a few of them either eventually evolving to a definable CTD or having disease remission (stable UCTD, sUCTD). One critical point in the UCTD diagnosis and subgrouping used in these studies is the role of the established CTD classification criteria used. Not being able to meet an established CTD is the key determinant to classify a syndrome as UCTD. However, this assumption is tied to the accuracy of classification models to detect a definitive disease. For example, the initial studies in UCTD done between the 1980 and 1999 that used as a reference the 1982 revised SLE criteria may have failed to detect an early phase of SLE. To prove this, a recent study in 2021 demonstrated that the newer SLE classification criteria can re-classify 14–20% of patients previously labeled as UCTD as SLE [20••]. Hence, as our knowledge of CTDs evolves, improvement in classification criteria will inevitably lead to different views of the undifferentiated patients.

Therefore, we can conclude (as a general principle) that any patient who presents with *clinical manifestations suggestive of a CTD and evidence of autoimmunity but cannot be diagnosed or classified as a definitive CTD* can be assumed to have UCTD.

Table 1 UCTD definitions or selection criteria reported in the medical literature

Year	Author	Type of study	Definition/criteria *Patients with suggestive CTD's signs or symptoms…*
1980	Le Roy et al. [3]	NA	Undistinguishable autoimmune syndrome indicating a common early phase of a "classical" CTDs
1991	Alarcon et al. [2]	Prospective	…at least three clinical manifestations. Also included isolated RP, KCS, and unexplained arthritis. Disease duration < 1 year
1998	Mosca et al. [5]	Retrospective	…and at least one positive non-organ specific autoantibody. Disease duration of at least 1 year
1998	Danieli et al. [6]	Retrospective	…present for at least 1 year
1999	Mosca et al. [7]	NA	…and a positive ANA (on two separate occasions). Disease duration of three years (Stable UCTD). Those patients who progressed to a full-blown CTD in < 3 years were defined as having early UCTD
1999	Danieli et al. [8]	Prospective	…with at least two clinical manifestations OR one symptom/sign and presence of autoimmunity. Disease duration < 2 years
2001	Cavazzana et al. [9]	Retrospective	…and serological features. A positive SSA antibody must be present at onset. ANA ≥ 1:80 was considered positive. Disease duration of at least 1 year
2003	Bodolay et al. [10]	Prospective	Adopted Mosca's proposed definition (1998). ANA ≥ 1:160 was considered positive. Disease duration of at least 1 year
2005	De Angelis et al. [11]	Retrospective	Adopted Mosca's proposed definition (1998). ANA ≥ 1:160 was considered positive. Disease duration of at least 1 year
2009	Vaz et al. [12]	Prospective	Adopted Mosca's proposed definition (1999). ANA ≥ 1:160 was considered positive
2011	Castellino et al. [13]$^{\Delta}$	Prospective	Adopted Mosca's proposed definition (1999). ANA ≥ 1:160 was considered positive. Disease duration at least 1 year
2013	Guerrero et al. [14]	Retrospective	…and a positive ANA > 1:80 (on two different occasions). Disease duration of at least 1 year
2017	Garcia-Gonzalez et al. [15]	Retrospective	…and a positive autoantibody OR abnormal nailfold capillaries. ANA ≥ 1:80 was considered positive. Disease duration of at least 1 year
2020	Zucchi et al. [16•]$^{\Delta}$	Prospective	Adopted Mosca's proposed definition (1999). Disease duration of at least 1 year
2022	Radin et al. [17•]	Retrospective	… and a positive ANA ≥ 1:160 (on two separate occasions 2 weeks apart)

UCTD undifferentiated connective tissue disease, *RP* Raynaud's phenomenon, *KCS* keratoconjunctivitis sicca, *ANA* anti-nuclear antibody

$^{\Delta}$Included pregnant patients with UCTD

The Natural History of UCTD

As briefly discussed above, once UCTD has been diagnosed, the disease can be separated into two distinct entities: eUCTD patients will evolve early on, to a well-defined CTD while sUCTD patients will not evolve and in some cases go in complete remission. To gain a better understanding on the progression risk in UCTD patients, we performed a systematic literature review. Based on our selection criteria (see Methods), six studies were included for the descriptive analysis (Table 2). Except for the study by Bodolay et al. [10] that was prospective, the others were retrospective single-center cohort studies with all but one conducted in Europe [2, 4, 14, 15, 21].

Altogether, 1118 subjects were classified as UCTD. Of these individuals, baseline data was available in 370

Table 2 Disease outcomes in UCTD patients

Study	Site	Follow-up, time years	Patients *n*	Evolved *n* %	Stable *n* %	Remission *n* %
Mosca [5]	Italy	15	83	30 (36)	53 (64)	NR
Bodolay [10]	Hungary	5	665	230 (35)	435 (65)	82 (19)
De Angelis [11]	Italy	1	78	3 (4)	75 (96)	2 (3)
Guerrero [14]	Colombia	4	94	13 (14)	81 (86)	NR
Garcia-Gonzalez [15]	Spain	11	98	14 (14)	84 (86)	23 (38)
Radin [17•]	Italy	6	100	21 (21)	79 (79)	NR
Total	-	7	1118	311 (28)	807 (72)	107 (13)

NR not reported, *n* number; %, percentage

patients. Most of these individuals was women (94%) in their fourth decade of life. There were no available data on race or ethnicity. To avoid including an early phase of a CTD, all patients carried a diagnosis of UCTD of at least 1 year. At disease onset, the most common (> 25%) clinical manifestations were Raynaud's phenomenon, sicca, and arthralgias/arthritis (Fig. 1). Conversely, fever, malar rash, subacute cutaneous lupus, livedo reticularis, sclerodactyly, myositis, lymphadenopathy, and CNS manifestations were infrequently reported (≤ 2%). At onset no kidney involvement was observed in any of these patients. Other symptoms with a wider range of frequency (> 2–25%) were cytopenia, photosensitivity, oral ulcers, telangiectasias, serositis, alopecia, esophageal dysfunction, myalgias, or weakness and peripheral neuropathy (Fig. 1).

Regarding their immunologic profile at diagnosis, as expected, ANA was highly prevalent in this population (Fig. 2). Of interest, the nucleolar pattern was reported in one study to be 7%. Anti-Ro and anti-RNP were the most frequent extractable nuclear antigens (ENA), in up to 35% and 29% of the individuals, respectively. The rest of the ENA panel (Scl-70, RF, anti-La, anti-centromere Sm, Jo-1) had a frequency below 20%. Antiphospholipid antibodies frequency ranged between 11 and 17%. Rheumatoid factor and anti-citrullinated peptide were observed in 7–8% of these cases. Lastly, hypocomplementemia was present in less than a fourth of the subjects.

Taking into account that the mean follow-up time was variable in the different studies (minimum of 1 year to a maximum of 15 years), we noted that of the 1118 UCTD cases, 311 (28%) UCTD patients evolved to a classifiable disease, and 807 (72%) did not (Table 2). Only 107 out of 594 (18%) individuals with sUCTD achieved remission (three studies did not report remission, and hence, the total number of patients is lower). Although UCTD evolution to definable CTD occurred at different time points, it is important to note that the largest proportion of these patients transitioned within the first 5–6 years from UCTD onset. Importantly, the time to evolution to CTD has been shown to be shorter in those patients who developed SLE when compared to other CTDs [14]. In our analysis, UCTD more commonly progressed to RA (29%) and SLE (25%) (Table 3). It is worth mentioning that 5 out of 6 studies had a larger number of patients evolving to a classifiable SLE, whereas evolution to RA was mainly observed in the study by Bodolay et al. [10]. These striking differences in rates of evolution might be related to methodology or unmeasured confounders. Other CTDs were also diagnosed: 18% of patients evolved to Sjogren syndrome (SS), 9% to systemic sclerosis (SSc) and mixed connective tissue disease (MCTD), 1% to Dermato- or Polymyositis (DM/PM) and < 1% developed an overlap syndrome (OS). The study by Bodolay et al. was the only one to captured systemic vasculitis in 7% of UCTD patients.

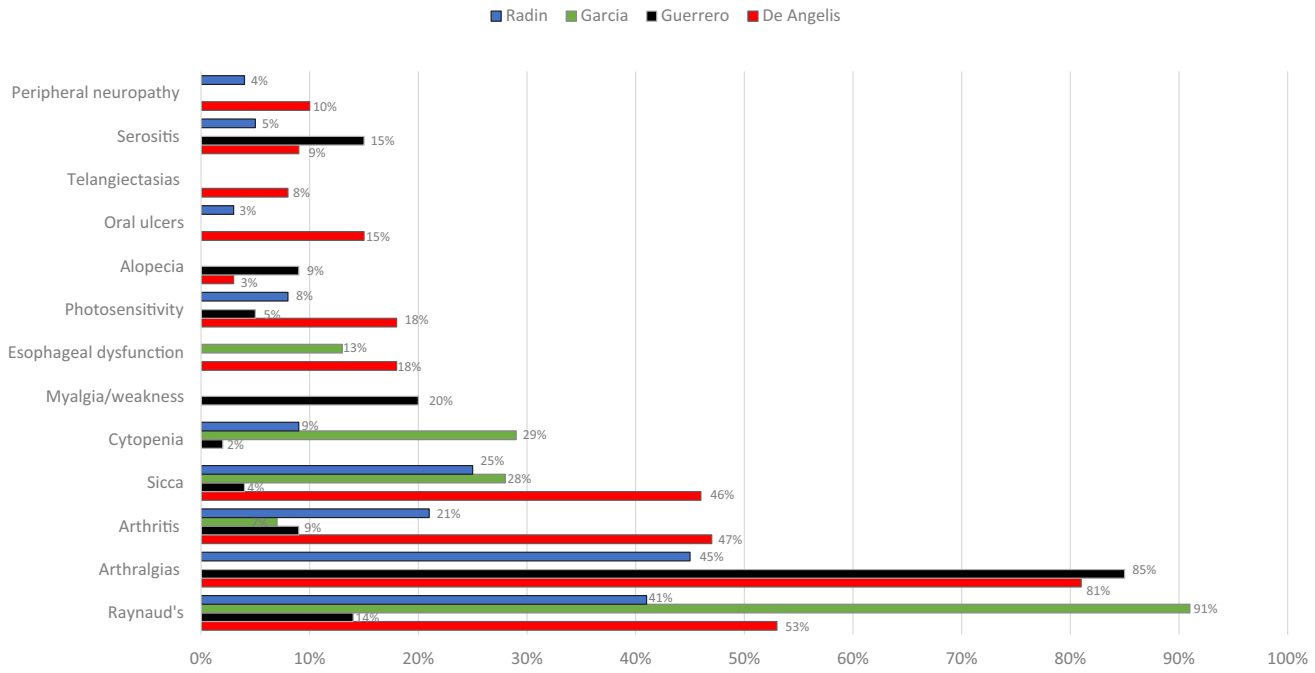

Fig. 1 Frequent clinical manifestations of UCTD at diagnosis. Manifestation prevalence is depicted from select publications identified by the first author's name (Radin [17•], Garcia [15], Guerrero [14], DeAngelis [11])

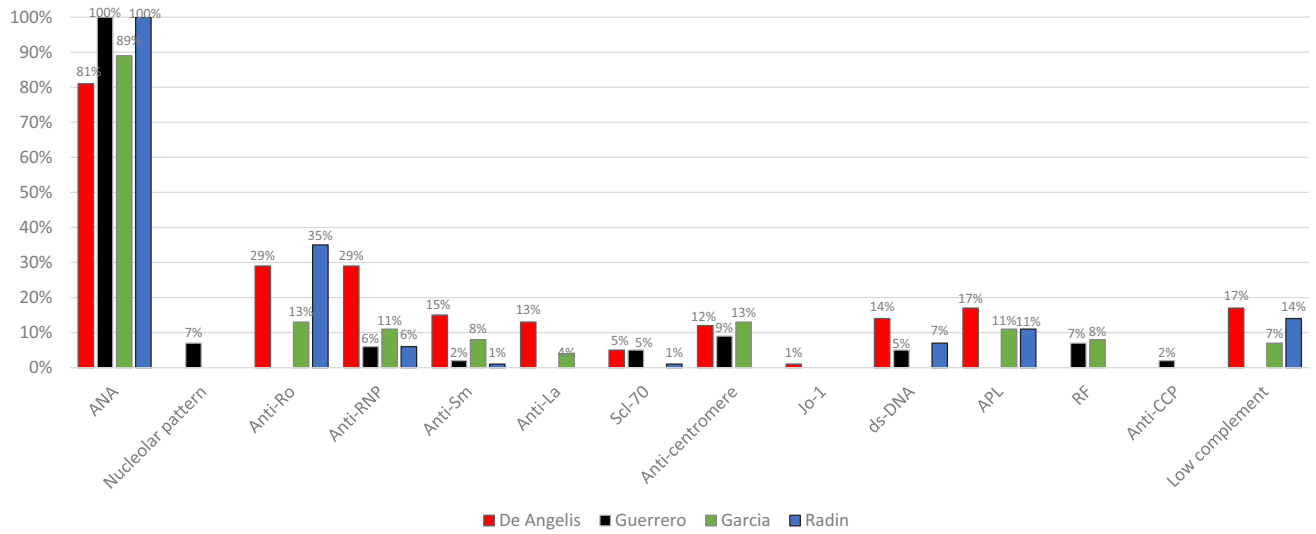

Fig. 2 Immunologic profile at diagnosis. Laboratory findings prevalence are depicted from select publications identified by the first author's name (DeAngelis [11], Guerrero [14], Garcia [15], Radin [17•])

Table 3 Disease progression in UCTD patients

Study	Evolved *n*	SLE *n*	RA *n*	SS *n*	SSc *n*	MCTD *n*	PM/DM *n*	OS *n*	Other* *n*
Mosca [5]	30	22	3	3	1	1	-	-	-
Bodolay [10]	230	28	87	45	19	26	3	0	22
De Angelis [11]	3	-	-	2	1	-	-	-	-
Guerrero [14]	13	8	1	4	-	-	-	-	-
Garcia-Gonzalez [15]	14	9	-	-	3[1]	1	-	1	-
Radin [17•]	21	13	-	2	5	1	-	-	
Total %	311	80 (25.7)	91 (29.2)	56 (18)	29 (9.3)	29 (9.3)	3 (0.9)	1 (0.2)	22 (7.4)

UCTD undifferentiated connective tissue disease, *SLE* systemic lupus erythematosus, *RA* rheumatoid arthritis, *SS* Sjogren's syndrome, *SSc* systemic sclerosis, *MCTD* mixed connective tissue disease, *PM* polymyositis, *DM* dermatomyositis, *OS* overlap syndrome

[1]Includes 2 patients with pre-scleroderma and one patient with diffuse systemic sclerosis

*Systemic vasculitis

Risk Factors Associated with Progression of UCTD to Definable CTD

The studies included in this systematic review differ significantly in their approach to assess risk factors linked to UCTD progression, making it difficult to analyze the combined data. However, separately these and other studies have identified potential causal associations between some baseline clinical or serological features and the development of a CTD (Table 4) [4, 9, 10, 14, 15, 21–23]. In general, comparing UCTD patients who evolved to a CTD to those who did not, the former patients were more likely to have Raynaud's phenomenon (RP), polyarthritis, photosensitivity, sicca, cytopenias, a high titer ANA, a positive anti-Ro, anti-centromere, antiphospholipid, or RNP antibodies at baseline. Progression to SLE was more likely in young African American women with fever, serositis, photosensitivity, discoid lupus, positive anti-ds-DNA, anti-Smith, anti-cardiolipin antibody, or multiple antibody specificities. In the case of RA progression, arthritis, a positive rheumatoid factor (RF), or bone erosions on magnetic resonance imaging were predictive. In systemic sclerosis, RP, sclerodactyly, and a positive ANA with a nucleolar pattern were the strongest risk factors. Sicca or a positive anti-Ro/La antibody were more likely to be present in those patients who evolved to Sjogren's syndrome. A positive RNP antibody or arthritis increased the risk to progress to MCTD. Lastly, factors that changed during the study period such as the accrual of autoantibodies and nailfold capillaroscopy progression have been found to

Table 4 Baseline risk factors associated with evolving UCTD

Risk factors	Evolved UCTD	SLE	RA	SSc	SS	MCTD
Younger age [4]		SA				
African American [4]		SA				
RP [10, 14]	5.70^{OR}			5.39^{RR}		
Fever [5, 10]		5.49^{RR}				
Sicca [5, 9, 10, 14]	7.18^{OR}				$5.64–18.54^{RR}$	
Esophageal dysfunction [5]				SA		
Serositis [4, 10]		$4, 10–7.50^{RR}$				
Photosensitivity [10, 14]	11.80^{OR}	3.49^{RR}				
Polyarthritis [10, 14]	12.03^{OR}		3.39^{RR}			6.75^{RR}
Discoid lupus [4]		15.80^{RR}				
Sclerodactyly [5, 10]				4.28^{RR}		
Cytopenias [9, 15]	4.20^{OR}					
Multiple antibody specificities [22]		SA				
ANA ≥ 1:640 [15]	7.00^{OR}					
ANA (nucleolar pattern) [10]				40.19^{RR}		
Anti-centromere [15]	3.77^{OR}					
ds-DNA [5, 10]		$5.08–64.74^{RR}$				
Anti-Sm [4]		$25.70, 28.20^{RR}$				
Anti-Ro [5, 10, 15, 17•]	SA				12.96^{RR}	
Anti-La [10]					22.69^{RR}	
Anti-RNP [10]						16.69^{RR}
Rheumatoid factor [10]			12.42^{RR}			
aPL antibody [22]		SA				
Bone erosions on MRI [10]			3.03^{RR}			

UCTD undifferentiated connective tissue disease, *SLE* systemic lupus erythematosus, *RA* rheumatoid arthritis, *SS* Sjogren's syndrome, *SSc* systemic sclerosis, *MCTD* mixed connective tissue disease, *PM* polymyositis, *DM* dermatomyositis, *RP* Raynaud's phenomenon, *ANA* anti-nuclear antibody, *ds-DNA* double-stranded DNA, *anti-Sm* anti-Smith, *anti-RNP* anti-ribonucleic acid protein, *aPL* antiphospholipid, *MRI* magnetic resonance imaging, *RR* relative risk, *OR* odds ratio, *SA* statistically significant association

be predictors of a definitive disease, with the latter being highly associated with systemic sclerosis.

Despite the fact that several variables that may predict progression of a UCTD have been described, none of these has been truly studied using predictive models. Consequently, a risk prediction tool is not available to date.

UCTD Treatment and Outcomes

UCTD usually follows a benign course, even in those cases that eventually develop a definable CTD. Interestingly, a study found that kidney involvement, an independent predictor of SLE morbidity and mortality, was three times more common in patients with SLE without the UCTD phase compared to those patients in which UCTD preceded SLE, suggesting that the latter presentation is milder with less organ damage (9) [10]. This hypothesis is further supported by the limited use of immunosuppression in these populations [14].

When evaluating mortality rates in UCTD patients, Mosca et al. reported only 2 deaths out of 91 patients (2%) over a mean follow-up of 15 years [21]. Another study conducted by Williams et al. concluded that the survival rate of UCTD patients at 10 years was 91% [23].

Given the benign nature of UCTD, it is unsurprising that these patients receive less intense immunomodulatory or immunosuppressive therapy compared to the typical CTDs. Hydroxychloroquine has been the most commonly prescribed drug for arthritis, and photosensitive rashes, used in 39–77% of cases [6, 14, 17•, 21, 24]. The use of low doses of glucocorticoids for a short period of time was also common (41–69 %) [6, 17•, 21, 24]especially to treat arthritis or serositis after NSAID failure. Less than a third of UCTD patients were treated with chronic immune suppression, with azathioprine, methotrexate, and mycophenolate mofetil being the most commonly used medications [14, 21, 25].

The assessment of pregnancy outcomes within the UCTD spectrum has also been analyzed. It is generally

thought that pregnancy may trigger flares of certain autoimmune diseases. Several studies have suggested that the rate of miscarriage/stillbirth is around 5 to 21% of the pregnancies [13, 17•]. The incidence of other obstetric complications was found to be 2 to 9% for premature membrane rupture, and between 2 and 3% for preeclampsia and intrauterine growth restriction. Notably, congenital heart block or neonatal lupus was rarely observed among the 30% of UCTD patients who had a positive anti-Ro antibody. In women with sUCTD, it was noted that flares occur in 13 to 32% of patients during pregnancy or postpartum period. Additionally, during the early postpartum phase, about 6% of patients evolved to a classifiable CTD, more specifically RA or SLE.

Patient-reported outcomes have recently become more widely used and are important outcome measures for studies. A group of investigators longitudinally assessed the quality of life in UCTD patients [24]. At enrollment, individuals were found to have worse physical and mental scores compared to the general population. During the follow-up period, these scores improved significantly in those UCTD patients who were on hydroxychloroquine or immunosuppression. Fibromyalgia, a well-recognized co-morbidity among autoimmune diseases, was also found to have a detrimental impact on UCTD physical domain. Moreover, a different group that focuses on patient's advocacy surveyed UCTD patients to get more insight on their perceptions and opinions [1]. The investigators found that these patients in general feel uneasy not only with the name of the disease but also with its unpredictability. At times, they can also feel their concerns ignored by healthcare professionals as the disease does not support the need for frequent testing or follow-ups. They finally noted that all these emotions can significantly impact their well-being. An ongoing single-center prospective study that is assessing quality of life and co-morbidities in UCTD patients will hopefully provide more insights in patient-reported outcomes (NCT02234388).

It is safe to assume that UCTD is a mild condition within the spectrum of CTDs. Nevertheless, it is not a disease that a physician should overlook as it can still have significant negative consequences.

Discussion

In the absence of formal recommendations for the care of UCTD patients, it is complicated to systematically report the gaps in care of these patients. It is widely perceived though that variability in treatment is the norm. Below, we outline a list of current gaps in clinical and research care and discuss potential solutions.

1. Definition

To begin with, it is problematic to call a disease *undifferentiated*. The name itself creates a sense of doubt for the clinician, while patients might feel worried that an "unknown" disease was diagnosed or is about to happen. Nonetheless, UCTD is probably the most common term used in clinical practice and most likely will continue to be so. Before embarking on new research projects on the topic, researchers in the field should agree on a standardized definition and thus create relatively homogenous cohorts for clinical research. Once this has been agreed upon, the research community can create multicenter registries and repositories that would help collect meaningful data on the clinical and molecular basis of the disease.

2. Diagnosis

Not different from other diseases, the process for the correct identification of UCTD patients relies on obtaining an accurate history, performing a comprehensive physical examination, and diagnostic testing. In general, when there is a clinical suspicion on a CTD, one looks for immunologic abnormalities including elevated inflammatory markers (Sedimentation rate or C-reactive protein), low complement levels and positive ANA, other autoantibodies associated with CTD (anti-Ro, anti-Smith, anti-RNP, Scl-70), anti-ds-DNA antibodies, rheumatoid factor, or antiphospholipid antibodies. If after a thorough evaluation, a CTD diagnosis cannot be made, but there are features highly suggestive of it, physicians diagnose a patient as having UCTD, evolving or stable: to date, there is no available diagnostic tool that would help distinguish the two. However, there are currently under investigation serological (soluble mediators, complement products, gene signatures) [26, 27] and imaging (ultrasonography) [28] biomarkers, aiming at identifying the early stages of a CTD and differentiate between a potentially evolving vs. a stable UCTD. For now, close monitoring by clinical examination and immunologic testing may help quickly diagnose patients who transition from UCTD to a definable CTD. Two open questions that remain are the frequency and length of monitoring. Although definite answer cannot be given on either question, twice a year monitoring for the first 5–6 years is reasonable with less intense or even no scheduled monitoring in mild cases that have not progressed over this period of time.

3. Management

There is no approved treatment for UCTD; thus, the use of therapy is guided based on the clinical manifestations. For example, if the patient primary complaint is arthralgia,

treatment with NSAID, low-dose corticosteroids, and potentially hydroxychloroquine would be appropriate.

Probably the most intriguing question about management of these patients is whether therapy can halt or delay the progression of a UCTD; this hypothesis that has been previously studied by James et al. while assessing patients with unclassifiable SLE. The authors concluded there is a delay in the development of SLE in those patients who received hydroxychloroquine compared to those who did not [25]. An ongoing randomized clinical trial (NCT03030111) may be able to answer this question in patients at risk of SLE.

Conclusion

UCTD is now recognized as a mild autoimmune disease within the CTD continuum, with a good prognosis. Still a myriad of questions regarding diagnosis and management remain unanswered and undoubtedly influence the way we practice. For this reason, the creation of consistent criteria for the diagnosis of UCTD is imperative; this will help advance UCTD research and eventually provide authoritative guidance on the management of the condition. In the meantime, it would be helpful to generate interim clinical guidelines and much-needed patient educational resources to enhance communication and avoid misunderstandings about the disease.

Author Contribution Vasileios C. Kyttaris together with Jose Rubio performed the literature search, analysis, and prepared the manuscript.

Data availability The authors confirm that the data supporting the findings of this study are available within the article.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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• Of importance
•• Of major importance

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