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Treatment of Undifferentiated Connective Tissue Disease with csDMARD's through Primary Care Providers in the Absence of Intervention via Rheumatology

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Treatment of Undifferentiated Connective Tissue Disease with csDMARD's through Primary
Care Providers in the Absence of Intervention via Rheumatology

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Table of Contents

Acknowledgments.....	3
Abstract.....	4
Chapters	
I. Introduction.....	5
Statement of the Problem.....	6
Research Questions.....	7
Research Methods.....	7
II. Undifferentiated Connective Tissue Disease.....	9
Clinical and Serological Presentation.....	9
Prevalence.....	11
Prescriptive Treatment Methods.....	14
Role of Primary Care.....	17
III. Discussion.....	18
IV. Clinical Application.....	20
V. Tables and Figures.....	23
References.....	29

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Abstract

Undifferentiated connective tissue disease (UCTD) was first defined by Leroy over 30 years ago. UCTD is described as an autoimmune disease which presents similarly to other rheumatic diseases but fails to meet laboratory requirements which indicate a specific disease such as rheumatoid arthritis, systemic lupus erythematosus, Sjogren's or scleroderma. Common signs and symptoms manifested by patients with UCTD include arthralgias, myalgias, fatigue, fever, Raynaud's phenomenon and sicca like symptoms in addition to having a positive antinuclear antibody (ANA) test. Often patients with these symptoms are referred to rheumatology. Unfortunately, there is a shortage of rheumatology providers across the nation. Although patients with UCTD have limited access to rheumatologists, there may be room for primary care providers to safely and adequately treat their symptoms with the use of disease modifying antirheumatic drugs (DMARDs) such as hydroxychloroquine. Evidence exists from recent studies that support the use of DMARDs, NSAIDs and low dose corticosteroids in UCTD patients to improve arthralgias, myalgias, fever, and functional limitations. Although the research indicates that the majority of rheumatologists and primary care providers feel UCTD patients should be referred to rheumatology, there is some evidence that primary care providers can also initiate and manage the treatment of UCTD patients. In the absence of rheumatology, primary care providers familiar with using DMARDs such as hydroxychloroquine can safely and effectively provide treatment for these patients.

Keywords: Arthritis, Undifferentiated Connective Tissue Disease, Undifferentiated Systemic Rheumatic Disease, Inflammatory Joint Disease, Disease Modifying Anti-Rheumatic Drugs, hydroxychloroquine.

Treatment of Undifferentiated Connective Tissue Disease with csDMARD's through Primary
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Undifferentiated connective tissue disease (UCTD) is a form of autoimmune disease which affects the adult population. Other terms for UCTD include incomplete lupus erythematosus, undifferentiated systemic rheumatic disease, latent lupus, and potential lupus. (Al Daabil, 2014). Rheumatology provides treatment to patients diagnosed with arthritic conditions and other autoimmune and inflammatory conditions, such as rheumatoid arthritis, Sjogren's syndrome, scleroderma and systemic lupus erythematosus. (Layton, 2015). Unfortunately, by 2025, data suggests that there will be a projected shortage of rheumatologists by 50% which will likely cause strain to the health care sector. (Basen, 2016). Subsequently, patients with UCTD face considerable wait times in pursuit of a consultation with a rheumatologist. West and West (2014) pointed out that this has emerged as problematic because early pharmacological intervention remains the standard of care for the majority of rheumatic disease patients.

The disease-modifying antirheumatic drugs (DMARDs), such as hydroxychloroquine, are provided to patients with UCTD, systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) and have been found to be effective. (West & West, 2014). Patients with these types of clinical and laboratory findings are often referred to rheumatology for consultation. Primary care providers play an essential part in early recognition and referral for patients presenting with UCTD. Unfortunately, a shortage of rheumatology providers exists across the nation. Shortages often result in rheumatology clinics screening patient referrals leading them to frequently accept only those patients who have laboratory findings which indicate a specific rheumatic disease such as RA or SLE.

The focus of this scholarly project is to review the available literature to determine whether intervention provided by primary care can effectively improve the symptoms of the UCTD patients treated with the csDMARD hydroxychloroquine. The projected outcome is that treatment of patients with UCTD using hydroxychloroquine in the primary care setting can decrease pain and functional impairment in the absence of rheumatology intervention.

Statement of the Problem

Primary care providers deal with a multitude of diseases and illnesses that are difficult to accurately diagnose. Often, patients display symptoms that are similar to certain diseases yet laboratory findings do not support the suspected condition. For instance, UCTD is one of the arthritis-related diseases with symptoms that are similar to other illnesses, yet laboratory findings do not point to any one particular rheumatic disease. Unfortunately, there is a shortage of rheumatologists to attend to the patients suffering from UCTD. (Bazsó et al., 2015). An article written by Ryan Basen in 2016 describes a study done by the American College of Rheumatology in 2015 which projected a decline in rheumatology labor force from 4,497 full-time equivalents to 3,455. The study projected a shortage of 4,729 rheumatologists by 2030. Additionally, 50% of the rheumatology workforce is expected to retire in the next 15 years which further limits patient's access to rheumatologists. (Basen, 2016). Consequently, the UCTD patients who do not have access to rheumatologists frequently look to their primary care providers for treatment. Nonetheless, it is not clear whether it is possible to decrease the inherent symptoms of UCTD by offering early interventions using csDMARDs such as hydroxychloroquine via a primary care provider. The use of csDMARDs by rheumatologists has the potential to control rheumatic diseases, but the problem for UCTD patients is the lack of

access to timely treatment by rheumatology. Delaying treatment may result in ongoing symptoms such as but not limited to arthralgias, myalgias, and functional impairment.

Research Question

In the absence of rheumatology, can primary care providers effectively initiate and appropriately manage patients with UCTD using conventional synthetic disease modifying antirheumatic drugs, such as hydroxychloroquine, to reduce patient's symptoms and functional impairment?

Research Methods

An online databases search was carried out to complete this scholarly project. This scholarly project used current research findings related to interventions used for treating UCTD and the role primary care providers play in that treatment. Scopus, ScienceDirect, PubMed Central (PMC), and ResearchGate were searched to provide scholarly and peer-reviewed articles related to the treatment of UCTD patients with csDMARDs in primary care as part of early intervention. There were a number of search terms used to identify specific articles on UCTD treatment options and role of primary care in the management of connective tissue disease. Search terms used included interventions used with UCTD, treatment of UCTD patients in primary care, undifferentiated systemic rheumatic disease, early arthritis, the use of with csDMARD for UCTD treatment, and effects of early intervention of UCTD using csDMARDs. All article publications were written between 1999 and 2017, in English, and free to download were included in this literature review. The relevant themes are clinical presentation of UCTD, the prevalence of UCTD, treatment options for UCTD, prescription methods for UCTD, and primary care's role in managing UCTD. Frequently, undifferentiated connective tissue disease

was interrelated with undifferentiated systemic rheumatic disease. This often led to searches related to early arthritis which is also considered an aspect of UCTD.

Clinical and Serological Presentation of Undifferentiated Connective Tissue Disease

A wide array of physical findings can accompany a patient who presents to the clinic with signs and symptoms of UCTD. Some of these include but are not limited to arthralgias, Raynaud's syndrome, sicca syndrome, peripheral neuropathy, fatigue, vasculitis, malar rash, uraturia, alopecia, oral/nasal lesions, and muscle weakness.

In 1980, Dr. Leroy, a rheumatologist at Department of Medicine, Medical University of South Carolina, first identified undifferentiated connective tissue disease. At that time several studies began to look further into the disease. In 1999, Mosca et al. completed a systematic review of the current research data regarding the criteria in which a provider could use to diagnose a patient with undifferentiated connective tissue disease. With this data, Mosca et al. (1999) proposed criteria for undifferentiated connective tissue disease which included (a) signs and symptoms suggestive of a connective tissue disease, but not fulfilling the criteria for any defined connective tissue diseases (CTD), (b) positive antinuclear antibody (ANA); (c) a disease duration of at least one year, including early UCTD. Although the criteria was established in 1999, Bortoluzzi et al. (2017) found the classification criteria played a significant role in identifying 392 patients with UCTD to be used in a long term study.

Likewise, Conti et al. (2010) found Mosca et al. (1999) criteria to be useful as well in their study of UCTD patients. In addition to the criteria outlined in Mosca's 1999 study, they found several other clinical features which many UCTD patients had in common. The authors identified 41 patients with early UCTD and followed them over a three year period. They found the majority of their patients had more than 3 or 4 clinical symptoms simultaneously. Most prevalent of the clinical manifestations included fatigue (83%), Raynaud's syndrome (61%), arthralgias (56%), muscle pains (56%), fever (51%), and polyarthritis (51%) (Table 1). A

positive ANA and elevated ESR were the most frequent immunological findings. The study showed mild changes in the clinical manifestation over a period of three years, but none were statistically significant (p Value >0.05) except for erythema nodosum (p Value <0.05). However, the study was limited by its small sample size.

In 2004, Mosca et al. completed a review of thirteen existing UCTD studies which looked at a total of 1714 patients. The data was used to compile a profile of UCTD patients. The profile suggested a UCTD clinical course which includes Raynaud's phenomenon, sicca symptoms, arthralgias, arthritis and mucocutaneous manifestations such as photosensitivity, malar rash, and oral aphthous ulcers as well as a positive ANA. They determined that these disease manifestations and a positive ANA should be present at least three years. Additionally, these patients demonstrate no major organ involvement. Interestingly, the authors initially reported the UCTD symptoms should be present for at least one year to exclude transitory illnesses but then concluded at the end of their literature review that the symptoms and serological data should be present for at least three years. This was different than Mosca et al. (1999) criteria which stated that the symptoms had to be present for one year only.

A multicenter study by Danieli et al. (1999) researched 165 Italian patients diagnosed with UCTD ranging in ages from 14-70 years old from ten different clinics. They found that UCTD patients commonly presented with arthralgia, mucocutaneous abnormalities and Raynaud's phenomenon. The Danieli et al. (1999) study, also found evidence of a higher rate of major end organ damage to include kidneys, lungs, and heart than previously identified. This is opposite of the findings of Mosca et al. 2004, in which no end organ damage was identified. While Danieli et al. (1999) study revealed physical findings that were suggestive of UCTD and appeared to indicate possible specific autoimmune disease, laboratory findings did not always

match physical findings. For example, the study found that although patients may have had a positive rheumatoid factor (RF), the patients did not always have joint involvement.

Additionally, some patients were found to have positive anti-SSA/Ro and anti-SSB/La antibody but did not present with sicca symptoms. The study found that physical symptoms with non-specific immunologic abnormalities, otherwise known as UCTD, may ultimately develop into a specific connective tissue disease. The Danieli et al. (1999) study was strengthened by the large sample size involved in the study.

An article by Jessica Berman, MD, specializing in rheumatology at the Hospital for Special Surgery, offers clear insight into the relationship of UCTD and with other signs/symptoms of other well-known autoimmune diseases using a diagram (Figure 1). It highlights how there is much overlap SLE, Scleroderma and RA symptoms with UCTD making UCTD challenging to diagnose and treat. Although clinically, the patient presentation may appear to be directed at a specific diagnosis, lab data does not support clinical findings.

Prevalence of Undifferentiated Connective Tissue Disease

Prevalence of UCTD is difficult to determine as many symptoms are vague which often leads to under-reporting or misclassification of UCTD. Additionally, laboratory results do not support a specific diagnosis which also can be frustrating for patient and provider alike. Often diagnosing UCTD takes many years. An article in *Autoimmunity Reviews* done by Doria et al. (2010) illustrated the difficulty in determining the onset of UCTD. Figure 2 demonstrates the progressive nature of the disease which also highlights the difficulty in identifying subclinical SLE or UCTD prevalence.

In 1999, Mosca et al. published a study of existing literature which determined that between 20%-52% of patients seen by a rheumatologist with a connective tissue disease may

have undifferentiated connective tissue disease. This range of patients is likely due to the variable criteria used to diagnose UCTD. Mosca et al. (1999) study proposed criteria for classification UCTD which is used today (Table 2). The study determined antinuclear antibodies must be present, along with a disease duration of at least three years. It also suggested that patient's symptoms and ANA lasting less than three years be classified as having early UCTD. In the study by Mosca et al. (2004), it was determined that the disease should have a duration of at least three years. Secondary to the criteria and classification, the prevalence of UCTD remains difficult to determine in the general population. The authors of the study found the absence of validated and internationally accepted criteria for UCTD resulted in a limited survey of the existing literature at that time. This remained consistent eleven years later with the study done by Doria et al. (2010) which highlighted the challenges of diagnosing UCTD.

Like many other connective tissue diseases, UCTD patients are predominantly middle-aged females. (Conti et al., 2010). Additional findings within the study concluded that after three years of follow up, 52% of patients with diagnosed with UCTD maintained this diagnosis while 27% demonstrated a clinical regression and 21% progressed to a defined connective tissue disease such as SLE or RA. (Conti et al., 2010). The author's study was limited secondary to that it was observational only and follow up was limited to three years.

Al Daabil et al. (2014) collected retrospective data on patients seen at Brigham and Women's Hospital Lupus Center between 1 January 1992 and 31 December 2012. Bivariable analyses and multivariable logistic regression models were used to analyze the data. They found that of the 264 "potential lupus" patients followed over 20 years in a rheumatology clinic, only 21% were diagnosed with SLE (per ACR criteria) at the end of 6.3 years. Of the remaining patients, 18% were diagnosed with another disease such as RA, Sjogren's, and mixed connective

tissue disease while 56% were still considered to have “potentials SLE” otherwise known as undifferentiated connective tissue disease. The study was strengthened by its study of a large population over a period of greater than six years and contained well documented clinical data.

A retrospective study by Bortoluzzi et al. (2017) reviewed the charts of 392 UCTD patients which were referred to their rheumatology clinic. The patients were selected using the criteria set by Mosca et al. 1999. They found that patients who presented with acute or subacute skin rash, inflammation of the serous tissue and positive antiphospholipid antibodies were the most likely to progress to SLE. Of the 283 patients originally classified as having UCTD, over the 15 year period 260 patients continued to be classified as having stable UCTD while 23 patients were eventually diagnosed with SLE. The study used 2012 Systemic Lupus Collaborating Clinics (SLICC) criteria to classify patients as having SLE (Table 3). This was an important aspect of Bortoluzzi et al. (2017) study due to the number of overlapping symptoms of UCTD and SLE. Using the more sensitive SLICC classification criteria for SLE, this increased the number of SLE diagnoses which were otherwise labeled as “stable” UCTD. The study by Bortoluzzi et al. (2017) was strengthened by its large population, and its lengthy duration yet was limited by its retrospective design.

A review of the literature by Mosca et al. (2011), suggested that 20% of newly referred patients to rheumatology may fall within the undifferentiated profile excluding rheumatoid arthritis. After surveying numerous studies, they concluded that the majority of UCTD patients were female (80-99%) and age of disease onset ranged from 32-44 years of age. After much review, they found that of those presenting with UCTD symptoms, up to 70% may remain undifferentiated. Although, this can be identified as stable UCTD authors suggested the importance that these patients be monitored for possible disease progression. The percentage of

patients which remained undifferentiated in Mosca et al. (2011) study was 70% which was considerably different than the Conti et al. (2010) in which only 52% of patients remained undifferentiated.

In studying the prevalence of UCTD, as with many other autoimmune diseases, Danieli et al. (1999) found that UCTD predominately affects females over males (12:1). They found that the majority of those affected began having significant symptoms in their 40's. The study suggested that a screening tool or scoring system could further help to identify those patients with UCTD. Likewise, Mosca et al. (2011) expressed some difficulty in determining the prevalence of UCTD and suggested adding exclusion criteria which could further help identify disease onset.

Prescriptive Treatment Methods for Undifferentiated Connective Tissue Disease

Data presented by Mosca et al. (2004) indicated that most UCTD patients were adequately treated by using low dose corticosteroids (53%) and hydroxychloroquine (11%). Additional studies conducted over time by Mosca et al. (2012) saw an increase in antimalarial use and rare use of immunosuppressive drugs in treating UCTD patients. Treatment consisted of low-dose corticosteroids (36%) and antimalarial drugs (52%) while 16% of UCTD patients were not being treated with prescription medications.

Conti et al. (2010) concluded that close follow up and use of hydroxychloroquine, NSAIDs, and low dose corticosteroids was sufficient to maintain UCTD in an inactive status. The treatment regime allowed for control disease activity which included reduction of arthralgias, functional limitations, myalgias and fever in many of their case study patients. Unfortunately, the study could not determine if a moderately aggressive form of therapy could prevent the evolution of the disease. However, the study did show that the prescriptive therapies

offered positive results concerning arthralgias, functional limitations, myalgias, and fever. The authors suggested early UCTD patients have strict follow up at least every six months. They also recommended clinical and diagnostic testing before starting treatment and during follow-up.

A study of 130 military service members was done by James et al. (2007) in which serological, demographic and clinical manifestations data was collected on soldiers with non-organ damaging early lupus. The main focus of the study was to see if progression from early lupus to SLE was delayed by treatment with hydroxychloroquine, prednisone, or ibuprofen. Patients treated with hydroxychloroquine before being diagnosed with SLE had a statistically significant increase ($p = 0.018$) in the time between the symptom onset and SLE diagnosis compared to patients who were not treated with hydroxychloroquine before diagnosis (median time: 1.08 versus 0.29 years). (James, 2007). Additionally, the study showed using prednisone with UCTD delayed the development of SLE. The research appeared to indicate that the use of hydroxychloroquine and prednisone may have a synergistic effect and prove to be more beneficial in delaying the onset of SLE. The study was limited by the fact that it was not a randomized trial and that the natural evolutionary history of untreated possible SLE was unknown. The study would suggest that a more aggressive approach to treating non-organ early lupus with nontoxic hydroxychloroquine is warranted.

Puchner et al. (2016) carried out a study of Australian rheumatologists and general practitioners to measure the perceptions of the general practitioners and rheumatologists concerning the issue of the prescribing techniques for connective tissue disease. When concerning single or multi-joint inflammatory arthritis 1,215 of the general practitioners (100%) and 101 of the rheumatologists (92%) recommended lab tests before referring to a rheumatologist. With regards to connective tissue disease, 78% of general practitioners and 90%

of rheumatologists recommended referral to a rheumatologist even if the patient did not show signs of joint inflammation. When treating inflammatory rheumatic disease, 43% of general practitioners would always prescribe glucocorticoids, yet only 11% of rheumatologist were in favor of general practitioners prescribing glucocorticoids before to referral at all ($p < 0.001$). Additionally, 32% of rheumatologists discouraged general practitioners from prescribing glucocorticoids as the medication may mask disease symptoms. (Puchner et al., 2016). Overall, rheumatologists and general practitioners agree that only rheumatologists should initiate treatment using conventional synthetic disease-modifying drugs (DMARDs) such as hydroxychloroquine when treating rheumatic diseases, yet one-third of both also agreed that when rheumatology availability is limited, then csDMARDs could also be initiated by a general practitioner. (Puchner et al., 2016).

Smolen (2013) found that Target-to-Treat (TTT) approach in treating inflammatory rheumatic disease, specifically rheumatoid arthritis, via the use of DMARD was effective in improving the health and patient's outcomes. Smolen (2013) found using TTT (Figure 3) resulted in high response rates treating with DMARD plus glucocorticoid use. Often time's inflammatory disease activity is reflected with complaints of joint pain, fatigue, mucocutaneous irritations, etc. Up to 40% of patient with active disease complaints who have a normal CRP, ESR, and RF at disease onset. (Sokka et al., 2009). Disease activity can easily be assessed by using the RAPID3 questionnaire which is free online. This could be used by primary care providers to monitor disease activity allowing for treatment modifications during follow up visits.

Role of Primary Care in the Management of Undifferentiated Connective Tissue Disease

In the absence of rheumatologists, primary care providers play a crucial role in the management of suspected connective tissue disease and other rheumatic diseases. Badley, Canizares, Gunz, and Davis (2015) studied the significance of accessing primary care physicians when managing inflammatory rheumatic connective tissue disease, especially in the absence of rheumatologists. The multi-level study was conducted in Ontario, Canada. The findings indicated that the visits to physicians for any form of inflammatory joint pain remained at 130.4 per 1,000 population, compared to rheumatologists who were 13.4 per 1,000 population. (Badley et al., 2015). Thus, 10.3% of the patients made at least one visit to primary care for inflammatory arthritis. The findings further showed that most patients with low socioeconomic status or those living in areas with limited access to primary care physicians were less likely to have office visits to rheumatologists. Badley et al. (2015) showed that the median geographic availability index of rheumatologists indicated that 11 out of the 105 health planning areas located had no availability for a rheumatologist. In spite of skewed access to a rheumatologist, 75% of the population lived near a facility with a rheumatology department. The findings demonstrated that patients with limited access to physicians in the primary care setting are severely affected by the illness compared to those living within access areas. Additionally, primary care providers were less likely to use csDMARDs to treat connective tissue disease symptoms.

Puchner et al. (2016) established that DMARD treatment in primary care was imperative because unnecessary referrals of patients diagnosed with rheumatic condition increased the work overload in rheumatology practices. Badley et al. (2015) noted that adequate patient access to rheumatologists was critical because early treatment of early connective tissue disease with DMARDs and biologic agents improved clinical outcomes. Moreover, the use of DMARDs and

biologic agents improved a patient's quality of life, functional status, reduced sick leave and decreased job loss. Delayed treatment initiation of DMARDs therapy has the potential to result in poor outcomes according to James et al. (2007). Although disease-modifying therapy is not commonly initiated in primary care by primary care physicians, DMARDs are recommended, especially when timely access to rheumatologists is limited. On the other hand, timely access to rheumatologists can significantly reduce joint pain, swelling, global pain, morning stiffness, functional status, and improve symptom control.

Discussion

Current literature suggests that primary care providers play a significant role in UCTD treatment because they are frequently the only and first point of contact for many patients. Puchner et al. (2016) and Badley et al. (2015) identified the role of primary care providers to be significant in treating early connective tissue disease due to the rheumatology shortage. James et al. (2007) also found this to be true. Therefore, it may be up to the primary care physicians to make use of their clinical knowledge to establish a treatment regimen to meet patient's needs. Moreover, even when primary care physicians referred patients with UCTD, to rheumatologists in known shortage areas, the referral may be denied as the rheumatologists are frequently overwhelmed with treating known rheumatic diseases. Thus, a shortage of rheumatologists has resulted in long wait times in the healthcare setting for rheumatology visits. Yet Puchner et al. (2016) found that the primary consensus between rheumatologists and general practitioners is that a patient must be referred to a rheumatology expert to seek the necessary treatment. Similarly, a small percentage of the primary care physicians acknowledged having initiated DMARD therapy, but the majority of general practitioners pointed out that they would prescribe DMARDs.

Moreover, early identification and treatment of UCTD by a primary care provider can result in a decline in disease progression, pain, possible joint destruction and functional impairment when compared to delayed intervention via rheumatology. Studies reviewed for this project indicated that possible delays in referrals to rheumatology resulted in long-term harm, including joint inflammation and destruction. Primary care providers can initiate treatment with DMARDs in the absence of treatment provided through rheumatology. Using csDMARDs are effective in the treatment of UCTD which can lead to improving a patient's quality of life. However, the reviewed literature indicates that primary care physicians will commonly continue to use DMARDs, although only a minority initiate them. Discomfort in prescribing DMARDs is linked with difficulties in accessing rheumatology referrals in primary care. Early administration of DMARD can improve the painful symptoms of UCTD and possibly reduce the progression of the disease from UCTD to a definitive connective tissue diagnosis. Limitations to early treatment by primary care providers would include the providers comfort level and knowledge of DMARD therapy use.

The literature on health outcomes for patients receiving care from rheumatologists compared primary care providers have supported the need for referrals. Timely consultation with a specialist can result in the initiation of medications and improved symptom control. The current literature has established that early use of DMARDs is common in primary care, but 40% of those primary care physicians who prescribe DMARDs reported that delayed initiation is suitable. Thus, this approach of 'wait and see' indicates a primary care physician's lack of urgency in the aggressive treatment of UCTD and may result in delayed referral to a rheumatologist.

Overall, the current studies have provided significant data supporting the use of DMARDs in treating UCTD, but there is minimal evidence that supports the use of DMARDs by primary care providers. Although there have been numerous studies siting criteria used to diagnose UCTD, no specific studies were found indicating how confident primary care providers are in diagnosing and treating the disease. Additionally, data indicates that rheumatologists overwhelmingly feel that it is the role of rheumatology providers to diagnose and initiate treatment of connective tissue disease. Studies show that in some cases of stable disease, it may be appropriate for primary care providers to continue with DMARD use. In searching for data, no studies were found indicating adverse patient outcomes nor positive patient outcomes in cases where primary care providers took the lead in diagnosing and treating UCTD with DMARDs. After a comprehensive review of the available and current literature, the role of the primary care provider in initiating treatment for these patients remains unclear. It can be surmised that the use of DMARDs is likely based in each providers comfort level and knowledge of DMARDs in treating UCTD. Future studies on the use of DMARDs by primary care providers in treating UCTD is recommended.

Applicability to Clinical Practice

Adequate patient access by patients to rheumatologists is critical because early treatment of connective tissue disease via DMARDs provides the opportunity to intervene and improve quality of life. Current literature has established that the use of csDMARD result in low disease activity and improve remission rates. On the other hand, delays treatment with DMARDs is linked to worse outcomes such as poor health and depression. Thus, in clinical practice, these findings are necessary as they can be used to encourage primary care providers to initiate

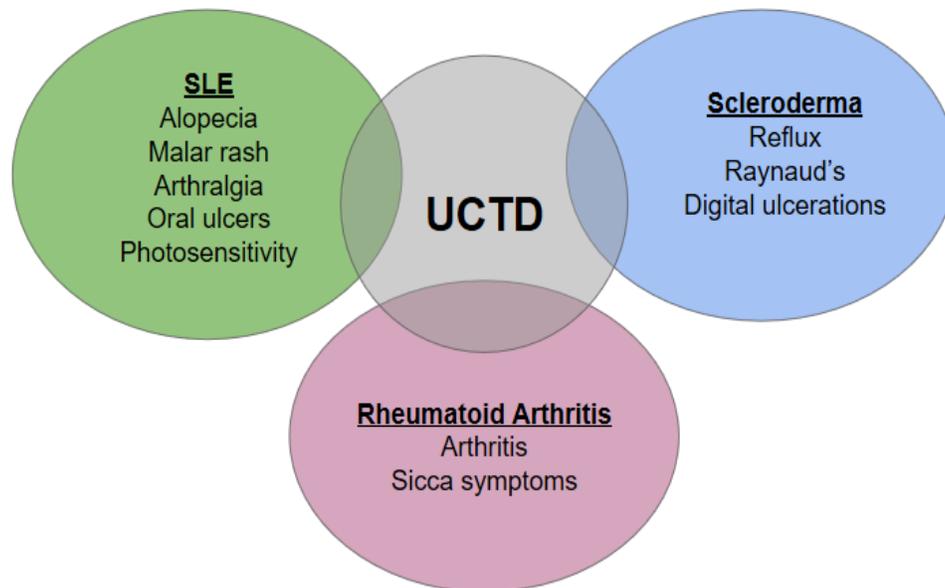
disease-modifying therapy in cases where timely access to rheumatologists is limited.

Subsequently, negative outcomes can be reduced, and health of patients with UCTD improved.

Given the gap and lack of accessibility to rheumatologists by patients with UCTD, health care sector could collaborate with primary care providers to offer formal training to improve patients' outcomes and reduce instances of joint pain, debility, decreased quality of life and depression. As recommended by Solomon et al. (2014), rheumatology organizations may put into consideration the possibility of working with physician assistant programs and schools of nursing to integrate rheumatology into the curriculum. Subsequently, primary care providers frequently have the first contact with patients and therefore could be in a position to provide services offered by rheumatologists. The presence of primary care providers skilled in rheumatology can reduce waiting times in rheumatology outpatient practices and clinics. Subsequently, earlier diagnosis and earlier incorporation of therapy could be realized thus leading to better patient outcomes. Additionally, delays in consulting a general practitioner, waiting times for appointments, delays in referral to a rheumatologist, and delays in identifying a correct diagnosis by rheumatology-trained personnel after referral could be improved.

Early intervention using csDMARDs offered by primary care providers can improve the symptoms of UCTD patients. Primary care providers have an opportunity to greatly impact the progression and detrimental effects of UCTD using early csDMARDs therapy. Education can be used to increase knowledge and awareness which can improve access to safe and timely treatment. (Brennan-Olsen et al., 2017). The majority of primary care physicians are uncomfortable with the identifying and managing UCTD with DMARDs, but recommendations by clinical organizations could improve the confidence. Future directions for research that focuses on UCTD care improvement may include altering the design of educational programs for

primary care providers such that they have greater comfort prescribing DMARDs. (Gerneau et al. 2012). There continues to be a need for improving awareness and education regarding diagnosing and treating UCTD patients in primary care where early treatments with DMARDs make a significant impact on a patient's health and quality of life.

Tables and Figures**Figure 1: UCTD Overlap**

Berman, J. R. (2017, July). Undifferentiated Connective Tissue Disease: In-Depth Overview.

Retrieved from https://www.hss.edu/conditions_undifferentiated-connective-tissue-disease-overview.asp.

Table 1: Clinic Features of UCTD

Clinical Features	% Patients
Fatigue	83
Raynaud's syndrome	61
Arthralgia	56
Muscle pains	56
Fever	51
Polyarthritis	51
Xerophthalmia	29
Xerostomia	27
Weight loss	24
Thyroiditis	19
Oral aphthosis	17
Lymphadenopathy	17
Urticaria	17
Synovitis	15
Serositis	14
Photosensitivity	12
Erythema nodosum	9
Other	7

Conti, V., Esposito, A., Cagliuso, M., Fantauzzi, A., Pastori, D., Mezzaroma, I., Aiuti, F. (2010).

Undifferentiated Connective Tissue Disease-An Unsolved Problem: Revision of Literature and Case Studies. *International Journal of Immunopathology and Pharmacology*, 23(1), 271-278. doi:10.1177/039463201002300125.

Table 2: Suggested preliminary classification criteria for UCTD.

1. Signs and symptoms suggestive of a connective tissue disease, but not fulfilling the criteria for any of the defined CTDs for at least three years.

2. Presence of antinuclear antibodies determined on two different occasions.

* If the disease duration is less than three years, patients may be defined as having an early undifferentiated connective tissue disease (EUCTD).

Mosca, M., Neri, R., Bombardieri, S. (1999). Undifferentiated connective tissue diseases (UCTD): a review of the literature and a proposal for preliminary classification criteria. *Clinical and Experimental Rheumatology* 1999 (17):615–620. Retrieved from <https://pdfs.semanticscholar.org/233b/6c55c10fb5c8b880f57e039de07be53f80d6.pdf>.

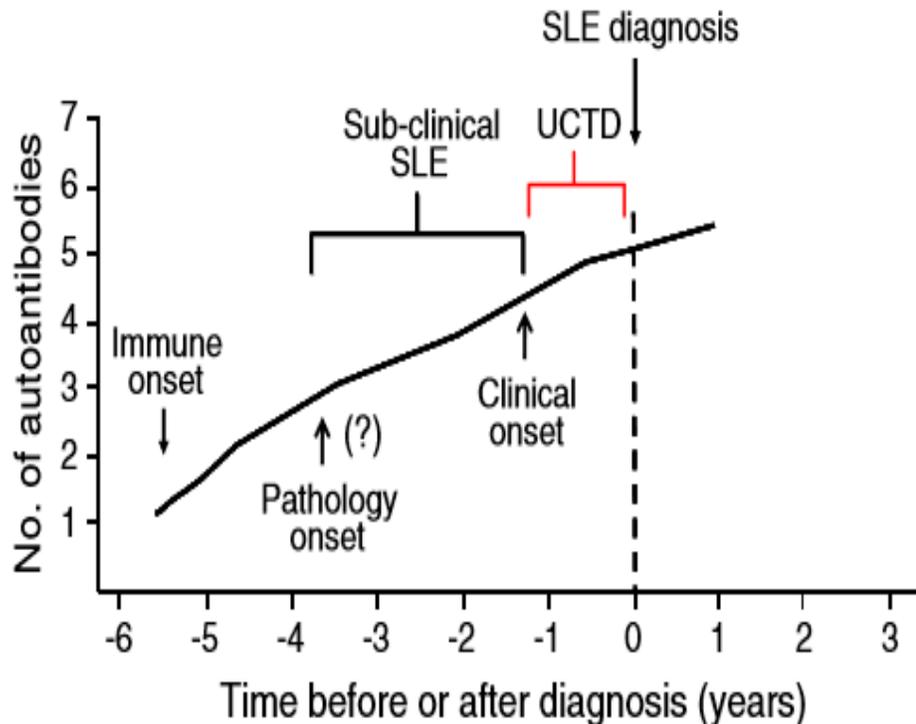
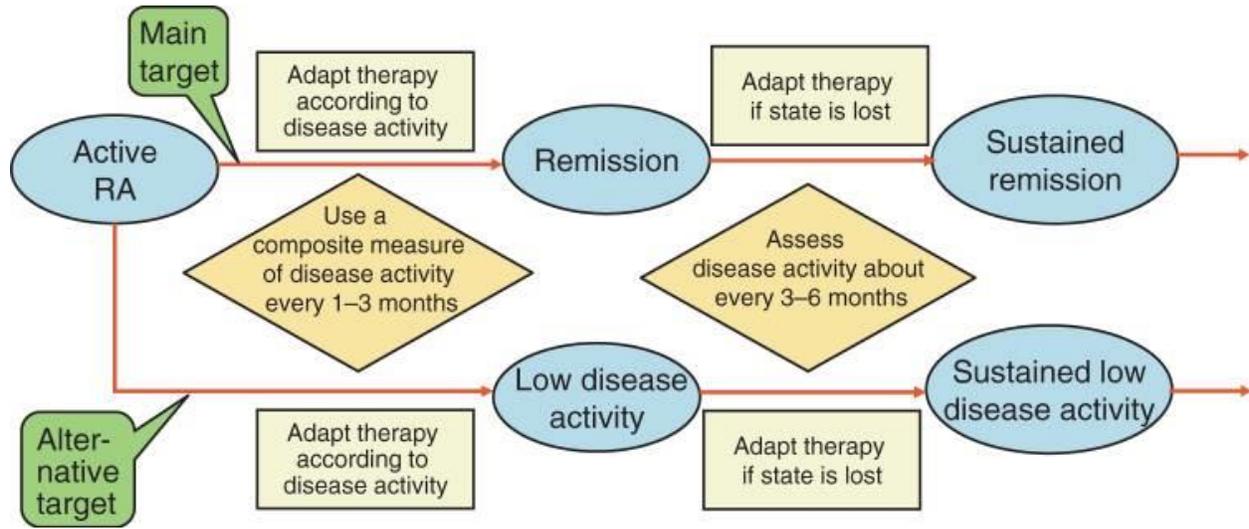
Figure 2: Autoantibodies Related to Onset of Diagnosis

Fig. 2. Early steps in the development of SLE. After a variable period of time from autoantibody appearance, immune deposits can be found in tissue where they can potentially initiate an inflammatory process. The development of immune deposits can be considered as the pathology onset of lupus and all immune histopathological changes occurring between pathology and clinical onset can be defined as “subclinical SLE”, whereas all clinical and immunological abnormalities occurring between clinical onset and diagnosis represents what is known as undifferentiated connective tissue disease.

Doria, A., Zen, M., Canova, M., Bettio, S., Bassi, N., Nalotto, L... & Iaccarino, L., (2010). SLE

diagnosis and treatment: When early is early. *Autoimmunity Reviews* 10(1): 55-60.

doi:10.1016/j.autrev.2010.08.014.

Figure 3: Target to Treat- Generic Model

Solomon, D. H., Yelin, E., Katz, J. N., Lu, B., Shaykevich, T., & Ayanian, J. Z. (2013). Treatment of rheumatoid arthritis in the Medicare Current Beneficiary Survey. *Arthritis Research & Therapy*, 15(43), 1-7. doi:10.1186/ar420.

Table 3: 2012 SLICC Classification Criteria for SLE

2012 SLICC CLASSIFICATION CRITERIA FOR SYSTEMIC LUPUS ERYTHEMATOSUS	
Biopsy proven LUPUS NEPHRITIS and ANA or anti-DNA	
CLINICAL	IMMUNOLOGIC
<ul style="list-style-type: none"> • Acute cutaneous LE • Chronic cutaneous LE • Oral ulcer • Alopecia • Synovitis • Serositis • Renal • Neurologic • Hemolytic anemia • Leucopenia/ lymphopenia • Thrombocytopenia 	<ul style="list-style-type: none"> • ANA • Anti-dsDNA • Anti-Sm • aPL antibodies • Low complement • Direct Coomb's test
<div style="background-color: #d4edda; padding: 5px; border: 1px solid #c3e6cb;">AT LEAST 4 CRITERIA (1 Needs to be IMMUNOLOGIC)</div>	

Petri M, Orbai AM, Alarcón GS, et al. *Arth & Rheum* 2012; 64 (8): 2677-86.

Petri, M., Orbai, A.-M., Alarcón, G. S., Gordon, C., Merrill, J. T., Fortin, P. R., ... Magder, L. S.

(2012). Derivation and Validation of Systemic Lupus International Collaborating Clinics Classification Criteria for Systemic Lupus Erythematosus. *Arthritis and Rheumatism*, 64(8), 2677–2686. <http://doi.org/10.1002/art.34473>.

References

- Al Daabil, M., Massarotti, E., Fine, A., Tsao, H., Ho, P., Schur, H.& Costenbader, K. (2014). Development of SLE among “Potential SLE” Patients Seen in Consultation: Long-Term Follow-Up. *International Journal of Clinical Practice*, 68(12), 1508–1513.
doi:10.1111/ijcp.12466.
- Badley, E. M., Canizares, M., Gunz, A. C., & Davis, A. M. (2015). Visits to rheumatologists for arthritis: The role of access to primary care physicians, geographic availability of rheumatologists, and socioeconomic status. *Arthritis Care & Research*, 67(2), 230-239.
doi:10.1002/acr.22413
- Basen, R. (2016). Rheumatology faces serious manpower shortage: Supply of full-time docs will drop over the next 15 years. *American College of Rheumatology: MedPage Today*.
Retrieved from <https://www.medpagetoday.com/meetingcoverage/acr/61442>.
- Bazsó, A., Szodoray, P., Szappanos, Á., Korda, J., Pálfi, P., Kiss, E., Poór, G. (2015). Systemic autoimmune, rheumatic diseases and coinciding psoriasis: Data from a large single-center registry and review of the literature. *Mediators of Inflammation*, 2015(1), 1-9.
doi:10.1155/2015/657907.
- Berman, J. R. (2017, July). Undifferentiated Connective Tissue Disease: In-Depth Overview.
Retrieved from https://www.hss.edu/conditions_undifferentiated-connective-tissue-disease-overview.asp.
- Bortoluzzi, A., Furini, F., Campanaro, F., Govoni, M. (2017). Application of SLICC classification criteria in undifferentiated connective tissue disease and evolution in systemic lupus erythematosus: analysis of a large monocentric cohort with a long-term follow-up. *Lupus* 2017(26), 616–622. doi:10.1177/0961203316671814

- Brennan-Olsen, S. L., Cook, S., Leech, M. T., Bowe, S. J., Kowal, P., Naidoo, N., & Mohebbi, M. (2017). Prevalence of arthritis according to age, sex and socioeconomic status in six low and middle income countries: analysis of data from the World Health Organization study on global aging and adult health (SAGE) Wave 1. *BMC Musculoskeletal Disorders*, *18*(1):271. doi:10.1186/s12891-017-1624-z.
- Bykerk, V., & Emery, P. (2010). Delay in receiving rheumatology care leads to long-term harm. *Arthritis Rheum.* *62*(12):3519-3521. doi:10.1186/ar3517.
- Conti, V., Esposito, A., Cagluiso, M., Fantauzzi, A., Pastori, D., Mezzaroma, I., Aiuti, F. (2010). Undifferentiated Connective Tissue Disease-An Unsolved Problem: Revision of Literature and Case Studies. *International Journal of Immunopathology and Pharmacology*, *23*(1), 271-278. doi:10.1177/039463201002300125.
- Danieli, M., Fraticelli, P., Franceschini, F., Cattaneo, R., Farsi, A., Passaleva, A.....& Danieli, G. (1999). Five-year follow-up of 165 Italian patients with undifferentiated connective tissue diseases. *Clinical and Experimental Rheumatology*. *17*(5):585-91. Retrieved from <https://www.semanticscholar.org/paper/Five-year-follow-up-of-165-Italian-patients-with-u-Danieli-Fraticelli/48a2f33d87a12869f019ec9a9b7253a81542080b>
- Doria, A., Zen, M., Canova, M., Bettio, S., Bassi, N., Nalotto, L...& Iaccarino, L., (2010). SLE diagnosis and treatment: When early is early. *Autoimmunity Reviews* *10*(1): 55-60. doi:10.1016/j.autrev.2010.08.014.
- Garneau, K.L., Iversen., M.D., Tsao, H., & Solomon, D.H. (2012). Primary care physicians' perspectives towards managing rheumatoid arthritis: room for improvement. *Arthritis Research & Therapy* *13*(6):R189. doi:10.1186/ar3517.

- James, J.A., Kim-Howard, X.R., Bruner, B.F., Jonsson, M.K., McClain, M.T., Arbuckle, M.R.,..... & Harley, J.B. (2007). Hydroxychloroquine sulfate treatment is associated with later onset of systemic lupus erythematosus. *Lupus* 2007(16) 401-409. doi:10.11h77/0961203307078579.
- Layton, K. (2015). Evaluation of a Rheumatology Patient Prioritization Triage System. *DNP Projects* 48. Retrieved December 19, 2017, from http://uknowledge.uky.edu/cgi/viewcontent.cgi?article=1048&context=dnp_etds.
- Mosca, M., Baldini, C., Bombardieri, S. (2004). Undifferentiated connective tissue diseases in 2004. *Clinical and Experimental Rheumatology* 2004 (22):S14-S18. Retrieved from <https://www.semanticscholar.org/paper/Undifferentiated-connective-tissue-diseases-in-200-Mosca-Baldini/2129036df2dfbc8be8b80395cf79388e52ae5509>.
- Mosca, M., Neri, R., Bombardieri, S. (1999). Undifferentiated connective tissue diseases (UCTD): a review of the literature and a proposal for preliminary classification criteria. *Clinical and Experimental Rheumatology* 1999 (17):615–620. Retrieved from <https://pdfs.semanticscholar.org/233b/6c55c10fb5c8b880f57e039de07be53f80d6.pdf>.
- Mosca, M., Tani, C., Carli, L., Bombardieri, S. (2012). Undifferentiated CTD: a wide spectrum of autoimmune diseases. *Best Practice & Research: Clinical Rheumatology* 26(1):73-77. doi:10.1016/j.berh.2012.01.005.
- Mosca, M., Tani, C., Talarico, R., Bombardieri, S. (2011). Undifferentiated connective tissue diseases (UCTD): simplified systemic autoimmune diseases. *Autoimmunity Reviews* 10(5):256-258. doi:10.1016/j.autrev.2010.09.013.
- Petri, M., Orbai, A.-M., Alarcón, G. S., Gordon, C., Merrill, J. T., Fortin, P. R., ... Magder, L. S. (2012). Derivation and Validation of Systemic Lupus International Collaborating Clinics

- Classification Criteria for Systemic Lupus Erythematosus. *Arthritis and Rheumatism*, 64(8), 2677–2686. doi.org/10.1002/art.34473.
- Puchner, R., Edlinger, M., Mur, E., et al. (2016). Interface management between general practitioners and rheumatologists-results of a survey defining a concept for future joint recommendations. *PLoS One 11*(1): 1-12. doi:10.1371/journal.pone.0146149.
- Smolen, J.S. (2012). Treat-to-target: Rationale and strategies. *Clinical and Experimental Rheumatology*. 30(4):2-6. Retrieved from <http://www.clinexprheumatol.org/article.asp?a=6475>.
- Sokka, T, Pincus, T. (2009). Erythrocyte sedimentation rate, C-reactive protein, or rheumatoid factor are normal at presentation in 35%-45% of patients with rheumatoid arthritis seen between 1980 and 2004: analyses from Finland and the United States. *Journal of Rheumatology 36*(7):1387-1390. doi:10.3899/jrheum.080770.
- Solomon, D. H., Yelin, E., Katz, J. N., Lu, B., Shaykevich, T., & Ayanian, J. Z. (2013). Treatment of rheumatoid arthritis in the Medicare Current Beneficiary Survey. *Arthritis Research & Therapy*, 15(43), 1-7. doi:10.1186/ar420.
- West, L. E., & West, S. (2014). *Rheumatology Secrets 3rd*. New York: NY: Elsevier Health Sciences.