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Case presentation

Oral manifestations of connective tissue disease and novel therapeutic approaches

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Abstract

Connective tissue diseases such as systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and Sjögren syndrome (SS) have presented many difficulties both in their diagnosis and treatment. Known causes for this difficulty include uncertainty of disease etiology, the multitude of clinical presentations, the unpredictable disease course, and the variable cell types, soluble mediators, and tissue factors that are believed to play a role in the pathogenesis of connective tissue diseases. The characteristic oral findings seen with these specific connective tissue diseases may assist with more swift diagnostic capability. Additionally, the recent use of biologics may redefine the success rate in the treatment and management of the disease. In this review we describe the oral manifestations associated with SLE, SSc, and SS and review the novel biologic drugs used to treat these conditions.

Keywords: systemic lupus erythematosus, systemic sclerosis, and sjögren's syndrome

Introduction

In the past few decades, connective tissue diseases such as systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and Sjögren syndrome (SS) have presented many difficulties both in their diagnosis and treatment. Many factors contribute to this complexity, some of which include uncertainty regarding the etiology of these diseases, the vast array of clinical presentations, the unpredictable course, and the variable number of cell types, soluble mediators, and tissue factors that are believed to play a role in the pathogenesis of connective tissue diseases.

SLE, SSc, and SS have characteristic oral findings, the early identification of which may allow for early diagnosis and treatment. Until recently, patients were routinely treated with non-specific immunosuppressive regimens. Although these medications were

efficacious in mortality reduction and in reducing medication-related morbidity, effective disease management has been limited [1]. Recently, the use of biologics, purified, modified, and/or reconstructed protein derived from the genetic sequences of living cells, have shown great promise in treatment. In autoimmune and rheumatologic diseases, biologics are used to suppress destructive and overly active inflammatory responses by targeting key mediators, cells, or cellular interactions. These agents have been studied for use as an adjunct to disease modifying anti-rheumatic drugs (DMARDs) by specifically targeting inflammatory cytokines, B cells, and co-stimulation molecules [2]. In this review we describe the oral manifestations associated with SLE, SSc, and SS and review the novel biologic drugs used to treat these conditions.

Systemic sclerosis (scleroderma)

SSc, an autoimmune connective tissue disease, is characterized by small vessel vasculopathy, autoantibody production, and excessive deposition of collagen in the skin and internal organs. Overproduction and accumulation of collagen and other extracellular matrix proteins is the hallmark of the disease, resulting in fibrosis and tissue dysfunction [3].

Although SSc is rare, affecting only 1 in 10,000, it has a very high morbidity rate and represents the highest case-specific mortality of any rheumatic disorder [4]. Like other autoimmune and connective tissue diseases, SSc has a higher prevalence in females with a greater incidence in women of childbearing age. The incidence is higher in blacks than in whites and tends to occur in blacks at an earlier age than in others [5]. It is estimated that as many as 50% of patients with SSc die or develop major internal organ complications within 3 years of diagnosis [4]. This disease entity is rare, has an unpredictable course, high mortality rate and is often resistant to therapy. A consensus on the most optimal approach to screening and diagnosis has been a topic of long debate [6].

Although the etiology of SSc is not well known, it is believed to be secondary to immunologic mechanisms, vascular endothelial cell injury, and activation of fibroblasts [3]. A proposed mechanism is microvascular dysfunction, represented by intermittent vasoconstriction, which may be triggered by infection, environmental exposure or genetic predisposition, which progresses to narrowing of the blood vessels leading to insufficient blood supply. The resulting alternating ischemia and reperfusion cause oxidative stress that further damages the endothelial cells. Activated endothelial cells secrete vasoactive mediators such as nitric oxide, prostacyclin, endothelin-1 (ET-1), platelet-activating factor, and soluble adhesive molecules such as vascular cellular adhesive molecules (sVCAM-1) and E-selectin. The damaged endothelial cells interact with T lymphocytes and induce local inflammatory cell activation. Antibodies produced against endothelial cells then develop. Ischemia also stimulates fibroblast activation and excessive extracellular matrix production. In most patients, endothelial cell damage is rectified by new vessel formation. In SSc patients, however, neo-angiogenesis is impaired while the ischemia stimulates growth factor production, fibroblast activation, and excessive extracellular matrix production [7]. When the inflammation later subsides, fibrosis of the skin and internal organs remain [8, 9]. The associated microangiopathy of SSc is widespread and assumed to be responsible for the life-threatening organ involvement, such as scleroderma renal crisis, pulmonary arterial hypotension, cardiomyopathy, vascular ectasia, and atrophy in the gastrointestinal tract [7].

Systemic sclerosis has been classified into two groups: limited cutaneous disease (LcSSc) and diffuse cutaneous disease (DcSSc) [10]. The limited form involves skin thickening limited to areas distal to the elbows and knees while the diffuse form includes sites both proximal and distal to the above areas. More severe organ damage is often associated with the diffuse form. Systemic sclerosis sine scleroderma is the term used to describe the involvement of visceral organs in the absence of skin involvement. This condition is very rare with an incidence of less than 1 per million and a 1:3 male to female ratio. An increase in prevalence correlating with advancing age has been shown with a peak in the third to fifth decade [11].

The gastrointestinal (GI) tract is a frequent site of SSc involvement and may represent the second most common site of SSc organ damage [12]. The mortality rate attributable to GI involvement is estimated at 6-12% [13-18]. Specifically, one of the most frequently experienced oral manifestations of systemic sclerosis is microstomia or difficulty with opening the mouth as a result of sclerosis of the perioral tissues [19, 20] (Figure 1). A study of 21 patients with SSc found that 80% of patients were unable to open their mouth beyond 40 mm [21]. Many patients also experience xerostomia and loss of mobility to the tongue, which may result in difficulty swallowing, accelerated dental decay and increased predisposition to low-grade erythematous oral candidiasis [19, 20]. Loss of expression lines of the facies leading to a mask like appearance and thinned lips is yet another complication causing a “purse-string” appearance to the mouth [11, 19] (Figure 2). Pseudoankylosis (fixation of a joint) may also develop owing to fibrosis of the soft tissues around the temporomandibular joint. Other findings include effacement of the lingual papillae, pallor with blanching of the mucous membranes, and fibrosis of the buccal mucosa with loss of normal elasticity (Table 1) [11].

Table 1

Oral Manifestations of Systemic Sclerosis
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Microstomia Decreased tongue mobility Dental decay Mask-like facies Pseudoankylosis Mucous membrane pallor	Xerostoma Dysphagia Oral candidiasis "Purse-string" mouth Atrophic tongue Buccal mucosa fibrosis
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Figure 1. Limited oral aperture due to sclerosis of the perioral tissues. **Figure 2.** Characteristic mask-like facies and thinned lips.

Treatment for SSc has been a challenge owing to the unpredictable nature of the disease. Treatment is determined based on the extent of organ involvement [7]. Immunosuppressive treatments have proven to be effective in other autoimmune diseases such as rheumatoid arthritis suggesting that these agents may have a role in the treatment of SSc. This, however, has not been found to be the case [22].

Antifibrotic therapy for systemic sclerosis

In SSc, activation of fibroblasts leads to an excessive release of collagen, which accumulates in the interstitial space disrupting physiologic tissue architecture and causing organ failure [23]. Both internal and external stimuli have been shown to activate fibroblasts via inflammatory mediators of paracrine or autocrine self-stimulatory loops, respectively [24, 25]. Despite the fact that fibrosis represents a major clinical challenge in SSc and is a cardinal feature, effective antifibrotic therapies are currently unavailable [23]. There are, however, several drugs with the potential to be used as antifibrotic treatment. These novel antifibrotics are designed to be effective in the following methods: blocking inflammatory signaling pathways, inhibiting profibrotic growth factors, and modulating epigenetic codes.

Blocking inflammatory signaling pathways

Considering that both B cells and IL-6 appear to be involved in the development of fibrosis in SSc, anti-CD20 antibodies and anti-interleukin (anti-IL) 6 receptor antibodies have been studied as potential treatments [23]. B cells increase collagen release by secreting stimulatory autoantibodies against the platelet-derived growth factor (PDGF) receptor on fibroblasts. Therefore, B-cell depletion represents a reasonable approach to treatment due to the potential role in the disease pathogenesis. Yet clinical trials evaluating the efficacy and tolerability of the anti-CD20 antibody, rituximab, in SSc have been inconsistent to date. Four open-label trials with a range of 8-15 patients enrolled had inconclusive results with regards to efficacy and tolerability of rituximab, whereas three studies found symptom improvement during the same observation period, the largest study showed no significant

changes [2, 26-29]. Further randomized controlled trials are necessary to assess the clinical role of B-cell depletion in SSc and identify the predictors for a therapeutic response [23].

IL-6, released by B cells, can directly stimulate fibroblasts to release collagen [25]. A small study evaluating the response of 2 patients with SSc to treatment with the anti-IL6 receptor antibody, tocilizumab, showed a decrease in symptoms of skin fibrosis [30]. However, larger controlled studies are necessary to determine efficacy and tolerability.

Other inflammatory mediators and pathways involved in the pathogenesis of SSc may represent a viable target to treat fibrosis. Specifically, IL-13 and IL-33 may be an important pathway to target owing to their potential role in the development of skin fibrosis [31-33].

Inhibition of TGF-beta and other profibrotic growth factors

Recently, the role of transforming growth factor-beta (TGF- β) and connective tissue growth factor (CTGF) in the development of fibrosis has become more clearly understood. TGF- β stimulates cell growth, apoptosis, and differentiation. It also promotes collagen and matrix protein production, decreases the synthesis of collagen-degrading metalloproteinase, and stimulates fibroblasts. Additionally, TGF- β stimulates CTGF synthesis in fibroblasts, vascular smooth muscle, and endothelial cells. CTGF in turn, may trigger angiogenesis, apoptosis, chemotaxis, and extracellular matrix formation [20, 34, and 35]. The inhibition of TGF- β signaling, therefore, is thought to reduce tissue fibrosis in SSc. Imatinib mesylate, a tyrosine kinase inhibitor used to treat chronic myelogenous leukemia, is found to block two profibrotic signaling pathways. Clinical trials of imatinib mesylate in SSc patients were inconclusive but evidence of efficacy was present in the treatment of chronic graft versus host disease, which shares similar features with cutaneous SSc. Unfortunately, high rates of adverse events led to the withdrawal of imatinib in many patients [23]. Further clinical trials are therefore needed to prove the efficacy and safety of medications targeting TGF- β .

Modulation of epigenetic codes

Histone deacetylase (HDAC) inhibitors may reduce the development of TGF- β and PDGF induced fibrosis in SSc. They also induce cell cycle arrest, cell differentiation, and apoptosis of tumor cells leading to their use in the treatment of several malignancies. Trials with the nonselective HDAC inhibitor trichostatin A, which inhibits TGF- β signaling, were poorly tolerated by patients [36]. Other HDAC inhibitors with better tolerability will be investigated in further clinical trials [37]. Another promising approach to SSc is the inhibition of DNA methyltransferases (DNMT), which regulate DNA transcription. The DNMT inhibitor 5-aza-2-deoxycytidine (5-aza) inhibits the stimulatory effects of TGF- β on collagen synthesis thereby decreasing the release of collagen. 5-aza effectively inhibited bleomycin induced dermal fibrosis in preclinical trials and may be a promising treatment [23, 38-40].

Systemic sclerosis summary

Systemic sclerosis poses a therapeutic challenge given its rare occurrence, unpredictable course and unresponsiveness to therapy. The oral symptoms manifested in this condition can result in considerable morbidity. To date, treatments effective in other connective tissue and rheumatic diseases have not proven efficacious in the treatment of SSc. Acknowledging fibrosis as a cardinal feature in this disorder has led to the search for effective antifibrotic therapies, which have yet to be developed. Further studies are required to determine the efficacy of medications designed to block inflammatory signaling pathways, inhibit profibrotic growth factors, and modulate epigenetic codes.

Sjögren syndrome

Sjögren syndrome, a systemic autoimmune disorder, is characterized by lymphocytic infiltration and destruction of the lacrimal and salivary glands. This exocrine gland destruction leads to “sicca” symptoms of xerophthalmia (dry eyes) and xerostomia (dry mouth). SS affects women more frequently than men with a female to male ratio of approximately 9:1 [19]. Women aged 50 years and older are afflicted more commonly than younger women. SS is classified as primary SS (pSS) when there is no other coexistent autoimmune disease while secondary SS (sSS) is the term applied when those affected with Sjögren syndrome also suffer from another autoimmune condition such as rheumatoid arthritis (RA) or SLE [41]. SS affects 1-3% of the general population. However, it is believed that up to 50% of pSS patients are undiagnosed and up to 30% of patients with other autoimmune disorders are diagnosed with sSS [42].

One hypothesis in the pathogenesis of SS is epithelial cell activation within affected organs by an epitheliotropic viral trigger. Specifically, Coxsackie virus has been identified in salivary gland tissues in association with SS, yet confirmatory studies are still

needed. This activation may trigger an autoimmune process and immunological derangements within the target organ consisting of local and systemic cytokine dysregulation with an increase in proinflammatory cytokines such as interferon-gamma (IFN- γ), tumor necrosis factor-alpha (TNF- α), IL-6 and B cell-activating factor (BAFF). This occurs in combination with B and T lymphocyte activation. The mainstay of therapy to date, therefore, has been through targeting these immune/inflammatory processes [41].

The American European Consensus Group (AECG) criteria have been established to aid in the diagnosis of SS (Table 2) [42, 43]. The 2002 criteria include keratoconjunctivitis sicca, xerostomia, and abnormal ophthalmologic tests. Schirmer's test is utilized to determine a quantitative decrease in tear production defined as less than 5 mm of moisture on filter paper inserted into the inferior fornix of the eye within 5 minutes. The Rose Bengal test is used to detect epithelia tissue damage of the conjunctiva and cornea with a positive test defined as a score greater than or equal to 4. Histopathologic changes of the salivary glands, salivary gland involvement, and the presence of autoantibodies to Ro/SSA or La/SSB antigens are also diagnostic criteria [44, 45, and 46]. Salivary gland biopsy is typically taken from the lower lip. The biopsy is considered positive with the presence of 1 or more lymphocytic foci per 4 mm² of glandular tissue on histological evaluation. The presence of any 4 of the 6 items is diagnostic granted that either histopathology or serology is positive [46]. It is understood, however, that neither of the autoantibodies are highly specific to SS and are commonly detected in other autoimmune diseases [47]. The specificity is 97.2% whereas the sensitivity is only 48.6% making it important to rule out other causes of sicca syndrome [48]. A limitation to the AECC criteria is that those with early disease may be missed through strict application of the criteria whereby qualifying symptoms may not appear for 10-15 years [49].

Table 2

American European Consensus Group criteria for Sjögren syndrome	
Keratoconjunctivitis sicca	Histopathologic changes
Xerostomia	Salivary gland involvement
Abnormal ophthalmologic tests	Autoantibodies to Ro/SSA or La/SSB antigens

Note: 4 out of 6 criteria is considered diagnostic for SS provided that either histopathology or serology is positive.

Oral symptoms most commonly associated with SS include xerostomia secondary to destruction of the major and minor salivary glands, and difficulty swallowing as a result of mouth dryness, which can affect phonation and the ability to chew as well. The presence of thick, stringy saliva can lead to an increased risk of dental decay, premature periodontal disease, and risk of mucosal infections, such as oral candidiasis [50]. These symptoms arise as a result of functional impairment of the salivary glands [51]. Moreover, xerostomia may result in chapped lips, angular cheilitis, parotitis, and unilateral or bilateral enlargement of the parotid glands [46] (Figure 3). The oral mucosa may have a dry, red, and wrinkled appearance with a “bald” or “cobblestone” appearance to the tongue related to loss of the lingual papillae (Figure 4). Effacement of the lingual papillae can lead to increased sensitivity of the tongue with patients often complaining of an intolerance to hot and spicy foods. The decrease in salivary secretion is confirmed by an inability to express saliva from the parotid glands by physical examination [52]. The increase in dental caries and tooth decay seen in SS patients is due to a decrease in salivary gland secretion, which normally dilutes dietary sugars and bacteria. Some patients complain of sensitivity to acidic and spicy foods whereas some may exhibit hoarseness [47].



Figure 3. Dry chapped lips as a result of chronic xerostomia. **Figure 4.** Dry appearance of the tongue with evidence of fissuring.

Currently, there are no effective treatments available that can control the progression of SS. The therapeutic approach to date has been based on replacement therapy or stimulation of glandular secretion. This is done with the use of topical agents and secretory sialogogues such as pilocarpine and cevimeline, both of which stimulate muscarinic cholinergic receptors [53]. Pilocarpine, a muscarinic cholinergic parasympathomimetic agonist, binds to M3 muscarinic receptors and stimulates exocrine glands thereby increasing salivary flow and improving symptoms [54]. Pilocarpine appears to have a more rapid onset and shorter duration of action thus often requiring 4 times daily dosing. Such dosing can lead to increased side effects of sweating. Cevimeline is dosed at three times daily with the most prominent side effect being increased symptomatic gastric acidity. Other measures that can be taken to alleviate oral dryness is encouraging multiple sips of water during the day to keep the mucous membranes moist, sucking on sugar-free lemon drops to stimulate saliva production, and the use of artificial saliva products to lubricate the mucosal surfaces. Maintaining meticulous oral hygiene with daily brushing and flossing and the use of high fluoride containing dentrifices are particularly important in minimizing the risk of dental caries as a result of chronic xerostomia. Patient education with special emphasis given to the increased risk of dental caries as a result of decreased salivary flow and the accumulation of plaque and calculus as well as risk of gingivitis, periodontitis and premature loss of the dentition is of utmost importance. Twice daily rinsing with chlorohexidine gluconate 0.12% mouthwash can be helpful in decreasing the oral bacterial load and in treating signs of gingivitis. However, some patients may not tolerate it well because of side effects of dysgeusia (abnormal taste sensation) and unpleasant yellow discoloration of the teeth from chronic use, which usually resolves with routine in-office cleanings.

As the potential efficacy of biological therapies in the treatment of autoimmune-rheumatic diseases has been explored over the past few decades, clinical trials have been conducted to investigate their use in SS. Therapeutic approaches in primary SS using biological agents were directed at B-cell targets (rituximab, ocrelizumab, epratuzumab, belimumab); T-cell targets (efalizumab, alefacept, abatacept); and cytokine-targets (infliximab, etanercept, tocilizumab, Anti-IL 10, Anti-IL 17, Anti-IFN γ).

B-cell targeted therapies

The role of B cells in the pathogenesis of SS include autoantibody production, associated hypergammaglobulinemia, B-cell infiltration of salivary glandular and extraglandular tissue, and the association with B-cell lymphomas. Rituximab has been identified as an extremely promising treatment for SS and has been used to treat B-cell lymphoma and non-neoplastic autoimmune disorders. Rituximab binds to the B cell surface antigen CD20, a B cell marker, highly expressed on the surface of pre-B lymphocytes and mature B cells but not on other cells [55]. The efficacy of rituximab in the improvement of sicca symptoms has been reviewed in studies with reports of significant improvement in subjective feelings of dryness and an increase in salivary gland function [56-58]. A randomized, double blind, placebo-controlled trial published in 2010 showed evidence that rituximab was an effective and safe treatment for patients with primary SS [59]. The study included 30 patients (20 treated with intravenous infusions of rituximab and 10 treated with intravenous infusions of placebo). End points were defined as a significant improvement in the secretion of stimulated whole saliva with multiple secondary end points. Results showed that patients treated with rituximab had improved salivary gland function, decreased fatigue, and a reduced number of extra-glandular manifestations. Safety was also established with the acknowledgment that a larger scale, controlled trial would be of great value [59]. In fact, it has been utilized in multiple studies evaluating a number of different clinical outcomes, measuring glandular and extraglandular outcomes using both objective and subjective parameters. Most studies showed some improvement in sicca symptoms. Thus, rituximab may be considered an effective treatment option in patients with pSS; however additional studies are ongoing to determine long-term risks and benefits [41].

Other recently developed biologics targeting B-cells have shown promise in the treatment of SS. Epratuzumab, a humanized antibody against CD22, which is thought to act as a homing receptor for re-circulating B cells, also has B-cell depleting capabilities and was found to be effective and safe in treating SS. Phase I and II studies showed a reduction in B-cell levels with epratuzumab giving hope for further clinical trials [60]. Specifically, in a study of 227 patients with SS, 67% of patients responded to 6 months of epratuzumab therapy. In this clinical trial no significant difference in adverse events occurred between those treated with epratuzumab and placebo. Further studies are ongoing [61].

The B-cell activity factor (BAFF), a member of the TNF-ligand family, is essential in controlling B-cell maturation and survival [62,63] as it specifically regulates B-lymphocyte proliferation and survival. Studies show a higher expression of BAFF in SS and an association with the presence of anti-SSA antibodies [64]. Belimumab, a human monoclonal antibody against the human protein B-lymphocyte stimulator (BLyS) and the first biological drug approved for the management of SLE, has shown promising efficacy in trials [60].

Cytokine-targeted therapies

Initial studies of TNF- α blockers in patients with SS showed great potential, but to date conflicting evidence exists for infliximab and etanercept as subsequent randomized controlled trials of TNF- α blockers showed no improvement in sicca symptoms or salivary and lacrimal gland function [41]. Nor did the larger multicenter, randomized, double blind, placebo-controlled trial known as the Trial of Remicade in Primary Sjögren's Syndrome (TRIPSS). One hundred three patients with primary SS were randomly assigned to receive either infliximab (remicade) or placebo. After 10 weeks of treatment favorable results were seen in 26.5% of the placebo group and 27.8% of the infliximab group. At week 22 only 16.7% of the infliximab group had a favorable response as opposed to 20.4% of the placebo group. The study therefore found no evidence of efficacy for infliximab in primary SS [65]. Treatment with TNF- α blockers for SS has subsequently diminished as further studies failed to show efficacy [41]. Conclusions were drawn that although infliximab might play a therapeutic role, TNF- α blockers should not be considered as a first-line option [60]. The anti-TNF agent, etanercept, showed no clinical efficacy in sicca symptoms in a 12-week randomized, double blind, placebo-controlled trial and no significant difference between the treatment and placebo group in oral or ocular symptoms. Etanercept, therefore, was not determined to be an efficacious treatment for SS [66].

T-cell targeted therapies

In primary SS, the autoimmune process includes expression of autoantigens on epithelial cells with migration of T lymphocytes to exocrine tissue. The analysis of T-cell dysfunction in primary SS has led to the possibility of T-cell targeted therapy [60]. Efalizumab, alefacept, and abatacept have been developed for this purpose (Table 3). Efalizumab, a humanized monoclonal antibody, targets the CD11a component of leukocyte function-associated antigen-1 (LFA-1). This prevents the binding of CD11a to intercellular adhesion molecules thus interfering with T-cell activation and reactivation, leukocyte extravasation and adherence to keratinocytes [67]. Thus there is a possible role for efalizumab in the treatment of primary SS [60]. Alefacept blocks the LFA-3/CD2 interaction necessary for the activation and proliferation of memory T cells. It is used to treat moderate to severe chronic plaque psoriasis with few reported side effects and thus may prove to be helpful in SLE, RA, and SS. Abatacept, a soluble fusion protein, blocks the CD80 and CD86 ligands on the surface of antigen-presenting cells that interface with the CD28 receptor to activate T cells. It has been approved for the treatment of RA but has an increased rate of serious adverse events. It is viewed as a potential treatment for other autoimmune conditions given its ability to suppress T-cell function [68].

Table 3

T-cell targeted therapy mechanism of action	
Efalizumab	blocks binding of CD11a to intercellular adhesion molecules
Alefacept	blocks LFA-3 & CD2 interaction
Abatacept	blocks CD80/CD86 ligand interaction with CD28 receptor on T cells

Sjögren's syndrome summary

SS, a disease of lymphocytic infiltration and gland destruction, causes multiple oral symptoms associated with salivary gland involvement. Historically, the primary treatment focus has been placed on identifying and targeting the causative autoimmune and inflammatory processes. Although no efficacious treatments are currently available to modify the evolution of SS, many clinical studies are now underway with biological agents targeting B-cells, T-cells, and cytokines. Initial studies show some improvement in oral symptoms of SS with B-cell targeted therapies but further clinical trials are necessary. Similarly, the use of cytokine-targeted therapies in initial clinical studies resulted in a decrease in oral symptoms yet subsequent larger trials did not confirm the results. Clinical trials are needed to determine the safety and efficacy of T-cell targeted medications in the use of SS. With the current uncertain efficacy of biologic therapy in the treatment of SS, replacement or stimulation of glandular secretions has been the main therapeutic approach to date.

Systemic lupus erythematosus

SLE, the most common autoimmune connective tissue disease in the US, affects more than 1.5 million people. Its estimated prevalence is 20-150 per 100,000 with a female-to-male ratio of 9:1 [69,70]. Genetics, ethnicity, hormones and environmental factors have been identified as having a possible role in the development of SLE though the exact etiology of the disease is unknown.

In SLE, autoantibodies to nuclear components and immune complexes are produced, which lead to inflammation and/or destruction of organs and tissues. Specifically, antinuclear antibodies (ANAs), anti-double-stranded DNA (anti-dsDNA), anti-Ro (a ribonuclear protein complex), anti-La (an RNA-binding protein), anti-C1q, anti-Smith (anti-Sm), and antiphospholipid antibodies are associated with SLE [71,72]. Autoantibodies tested are frequently associated with non-disease and thus are not diagnostic in the absence of other disease findings. The diagnosis of SLE is therefore a clinical diagnosis relying heavily on a careful history and physical examination findings.

Although SLE has multiple clinical presentations (listed in Table 4), oral lesions occur in approximately 7-57% of patients. Oral ulceration, one of the eleven criteria in the diagnosis of SLE is a common sign, which tends to precede severe systemic disease flares. Oral lesions occur in 3 different types: erythematous (35%), discoid (16%), and ulcerative (6%) [73]. In 9% of patients, more than one lesion type is present at the same time and lesions may merge with one another with associated erythema and petechiae. Discoid lesions are identified as a central area of erythema with white dots surrounded by rays of white striae and telangiectasia. They can be painful with well-defined, elevated borders occurring most frequently in the buccal mucosa. Erythematous lesions, on the other hand, are classically flat, red, and painless with ill-defined borders that most often occur on the hard palate. The ulcerative lesions, also found in the buccal mucosa (Figure 5), may involve the pharyngeal mucosa in up to 30% of patients. Oral ulcerations of SLE are characteristically shallow in appearance with a tendency to occur in crops on the hard palate. They are typically 1-2 cm in diameter and often painful with associated symptoms of burning and tenderness. The associated oral ulcerations may persist for years or occur intermittently with cyclical remissions and exacerbations [74] (Figure 6). SLE patients may also experience lupus cheilitis of the lower lip, areas of erythema and hyperkeratosis of the soft or hard palate or buccal mucosa, stomatodynia, dysgeusia, xerostomia, candidiasis, and periodontal disease [19].

Table 4

Clinical Symptoms of Systemic Lupus Erythematosus	
Fatigue	Gastrointestinal
Fever	Pulmonary
Weight loss	Cardiac
Arthritis/Arthralgia	Lymphadenopathy
Rash	Splenomegaly
Renal involvement	Hepatomegaly
Central nervous system	



Figure 5. Mucosal ulcerations involving the left buccal mucosa, inferiorly. **Figure 6.** Ulceration of the lower labial mucosa.

Other lesions associated with SLE are acute necrotizing ulcerative gingivitis (ANUG) characterized by ulceration, bleeding, facial swelling, dysphagia, halitosis, and sloughing of the gingival tissue with loss of the teeth. ANUG is thought to occur in patients with SLE due to their altered host immune mechanisms in addition to further suppression by immunosuppressive treatment agents [74]. Raynaud's phenomenon involving the tip of the tongue can present with well-demarcated areas of blanching as well as the development of tense bullae in the oral cavity [74]. Oral hairy leukoplakia has also been associated with SLE [48]. Finally, oral candidiasis and herpes simplex virus has also been seen in patients with SLE [74]. It is unclear if this association is due to an increased risk for developing infections or due to an immunocompromised host from immunosuppressive therapy, or a combination of both.

Recently, much investigation has occurred in the potential utilization of biologic therapies for the treatment of autoimmune rheumatic diseases. In March 2011, the US Food and Drug Administration (FDA) approved belimumab as a new treatment for adult patients with active, autoantibody-positive SLE despite ongoing standard therapy [75]. Belimumab is a recombinant human immunoglobulin (Ig) G1- γ monoclonal antibody that binds to soluble BLyS preventing it from binding to its receptors on the surface of B cells. The soluble mediator BLyS belonging to the TNF ligand superfamily [76], plays a role in the generation and maintenance of autoreactive B cells. BLyS is expressed as a membrane protein and binds to its receptors that are expressed exclusively on B cells. This in turn prolongs B-cell survival, maturation and differentiation toward immunoglobulin and autoantibody production [77]. The binding of belimumab to soluble BLyS results in a reduction of anti-apoptotic proteins and a reduction in the production of immunoglobulin and autoantibodies [75]. Early studies of belimumab in the treatment of SLE were inconclusive. However, subsequent randomized controlled trials showed modest but consistent improvements across various clinical outcome measurements [78]. Rituximab, although not approved for use in SLE, has been used as off-label therapy in refractory cases [79,80].

Patients with active SLE have increased IL-6 levels in the serum, which directly affect both B and T-cells by promoting their differentiation and maturation [81]. It is also involved in promoting inflammatory responses. Tocilizumab, the humanized monoclonal anti-IL6 receptor antibody, has been proven effective in rheumatoid arthritis and is showing promise in SLE as well [82]. Studies showed a decrease in acute-phase reactants and a minor decrease in immunoglobulin and anti-dsDNA levels. However, further studies are needed to determine the safety and efficacy of tocilizumab [1].

T-cells secrete IFN- γ , a Th1 cytokine. The interferon pathway has shown to be highly active in patients with SLE [1]. Studies have shown that blocking IFN- γ can lead to a significant decrease in autoantibody production [83,84]. Rontalizumab, a humanized monoclonal IgG1 antibody, was shown to be safe and effective in trials of SLE patients. Phase II trials are currently underway where sifalimumab, a fully human monoclonal antibody, is being tested for efficacy and safety [74].

TNF- α inhibitors, well studied for use in arthritis, have not been proven to be helpful in the treatment of SLE. Although there are case reports of severe cutaneous lupus responding to TNF- α inhibition and phase II trials with etanercept are currently underway [1]. Table 5 reviews biologic agents for the treatment of SLE.

Table 5

Biologic therapy in SLE	
Belimumab	Adult patients with active autoantibody-positive SLE despite ongoing therapy
Rituximab	Not approved for use in SLE
Tocilizumab	Further studies needed to determine safety and efficacy
Rontalizumab	Shown to be safe and effective in SLE trials
Sifalimumab	Ongoing studies

In a study of 227 patients with moderate to severe SLE treated with epratuzumab, significant clinical improvement was noted based on the British Isles Lupus Assessment Group (BILAG) scale [61]. In the study, most of the reported adverse effects were minor including nausea, fatigue, general pain, and infusion reaction [85]. Studies in SLE patients using abatacept suggest possible therapeutic efficacy. However, further investigation is necessary to determine its safety [86].

Systemic lupus erythematosus summary

SLE, the most common vascular collagen disorder in the US, has suspected causative factors yet the exact etiology is still not clearly understood. With oral symptoms occurring in up to 57% of SLE patients, it is of considerable significance with regards to treatment. Studies with immunoglobulin monoclonal antibodies have shown modest symptom improvement whereas those with humanized monoclonal antibodies and TNF- α inhibitors still require further studies to ensure safety and efficacy.

Adverse effects of biologics

The arsenal of biologic therapies available to treat autoimmune diseases is quickly expanding. Although only one is FDA-approved for use in SSc, SS, and SLE, continued clinical trials may soon prove efficacy. It must be noted, however, that these medications come with the potential for significant adverse effects (AE).

Though biologic therapies are generally well tolerated, AEs can arise. There are 5 categories of known AEs: overstimulation, immunodeviation, cross-reactivity, hypersensitivity [both immediate and delayed] with acute infusion reactions, urticaria, anaphylaxis, and risk of opportunistic infections (Table 6). The vast majority of AEs associated with biological agents have been with TNF- α inhibitors. One of the most frequently reported AEs is the development of an infusion reaction or injection site reaction. Most occur within 24 hours, often within minutes to a few hours. These symptoms are generally mild, but can be severe and even life threatening in some instances. Accepted contraindications for the use of biologics include pregnancy, nursing, significant cardiac failure, and previous history of malignancy [87]. Additionally, patients should be screened for tuberculosis risk factors, HBV, HCV, and HIV prior to starting biologics [88].

Table 6

Adverse effects of biological agents
Overstimulation
Immunodeviation
Cross-reactivity
Hypersensitivity
Risk of opportunistic infections

Rituximab, most frequently given as an IV infusion of 1000 mg/m² on days 1 and 15 in combination with methotrexate then every 24 weeks as necessary, may cause symptoms of fever, chills, rash, swelling of the hands, feet, and face, bronchospasm, and hypotension [2]. The reaction is often immediate (30 minutes to 2 hours) and usually occurs during the first infusion. Typically, it is less severe and occurs less frequently with subsequent infusions. Pre-treatment with acetaminophen and anti-histamine prior to infusion can be helpful in preventing these reactions. In a study analyzing the safety of rituximab, 123 of 2578 patients withdrew secondary to severe cardiac reactions. Rituximab is contraindicated in pregnancy, breastfeeding, active infections, live vaccination, severe congestive heart failure, those with a history of a demyelinating disease, or a 5-year history of non-lymphoproliferative cancer [89]. General recommendations are to screen for HBV, HCV, HIV, and TB whereby therapy should not be started if any significant infection exists.

Belimumab, given in a slow infusion over 1 hour, at a dose of 10 mg/kg at 2-week intervals for three cycles, then once every 4 weeks, has AEs including nausea, diarrhea, headaches, and upper respiratory tract infections. Less common are fever, cystitis, leukopenia, infusion reaction, and infections. Studies show, however, that the number of AEs associated with belimumab was similar to that of the placebo group [90,91].

Epratuzumab used in the treatment of SLE and Sjögren syndrome has a recommended therapeutic dose of 360 mg/m² IV over 1 hour every 2 weeks for up to four cycles [2]. Typical AEs include infections, upper respiratory tract symptoms, nausea, headache, infusion reaction, fever, hypertension, and back and limb pain. In a long-term safety study, 96% of patients experienced AEs; however most were mild to moderate and were mostly represented by infections [92].

Studies have confirmed that infliximab and adalimumab are associated with a markedly higher risk of tuberculosis [93]. Infliximab was also associated with a higher risk of histoplasmosis, listeriosis, and coccidiomycosis. Cases of tuberculosis are observed at a relatively constant rate throughout treatment with etanercept, whereas the rate of infection in patients undergoing treatment with infliximab is highest within the first few months after the initiation of therapy [93]. This suggests that many cases of tuberculosis during infliximab therapy represent reactivation of latent disease, whereas cases occurring during etanercept therapy are more likely to be newly acquired disease [93].

The development of lupus or lupus-like diseases has been shown to occur within a few months of starting therapy with TNF- α blockers [85-86,89-90,]. The distribution of clinical features varies widely between reports, but malar rash, arthritis, serositis, and hematological abnormalities are common. Lupus-like symptoms resolved with discontinuation of therapy often requiring corticosteroid and/or immunosuppressive therapy [94]. Several cases of new onset psoriasis in patients treated with biologic agents have been reported [95]. Most of these cases occurred with adalimumab, infliximab, or etanercept [91]. Fortunately,

discontinuation of the TNF- α blocker resulted in resolution of psoriasis symptoms in most patients. Sarcoidosis has been reported in relation to treatment with infliximab, adalimumab and etanercept. Case reports are limited thus this is a rare AE [96]. The delay between initiation of therapy to the onset of signs and symptoms of sarcoidosis is highly variable, with a median duration of approximately 21 months with a range of < 1 month to 4 years. In almost all cases, discontinuation of the TNF- α blocker resulted in spontaneous resolution whereas others required corticosteroid treatment. Among published case reports, vasculitis is the second most common autoimmune manifestation associated with the use of biological agents representing approximately 17% of cases. Almost all cases emerged during treatment with TNF- α blockers, with etanercept and infliximab being implicated in approximately 42% of cases. Additionally, subsequent development of lymphoma has been associated with the use of biologics requiring further investigation [97].

Finally, because biologic agents may be fully human or chimeric, patients may develop immunogenicity to the biologic agents. This may lead to the development of antibodies to the biologic agent itself, or the development of pathogenic autoantibodies that can lead to the development of another autoimmune disease [97]. Human anti-chimeric antibodies (HACA) is the term used to describe antibodies targeted against the biologic. HACAs may therefore cause a decrease in the efficacy of the medication, at which time a DMARD is recommended as co-treatment. With the availability of fully humanized biologic agents, the development of HACA may be negligible. The development of frank SLE after biologic therapy is infrequent but the development of antinuclear antibodies and anti-double-stranded DNA antibodies secondary to biologic treatment has been reported [2]. The newly developed drugs, however, may not cause significant immunogenicity.

Conclusion

Substantial progress has been made in the development of biologic agents to treat connective tissue disorders. Although not yet FDA approved for use in the treatment of SSc, SS, and SLE, these medications show great promise for future use. The initiation of biologic therapy should be followed by a thorough history and complete physical exam with a detailed discussion of risks and benefits given the potential AEs. As further clinical studies are performed to determine safety and efficacy of biologic agents we inch closer to effectively controlling these difficult to treat conditions.

Abbreviations

5-aza	5-asa-2-deoxycytidine
AECC	American European Consensus Group
Anti-IL	Anti-interleukin
BAFF	B-cell activating factor
BLyS	B-lymphocyte stimulator
CTGF	Connective tissue growth factor
DcSSc	Diffuse cutaneous Systemic Sclerosis
DMARD	Disease modifying anti-rheumatic drug
ET-1	Endothelin-1
DNMT	DNA methyltransferase
GI	Gastrointestinal
HDAC	Histone deacetylase
IFN- λ	Interferon Gamma
IL-6	Interleukin-6
LcSSc	Limited cutaneous Systemic Sclerosis
LFA-1	Leukocyte function associate antigen-1
PDGF	Platelet derived growth factor
pSS	Primary Sjögren's syndrome
RA	Rheumatoid arthritis
SLE	Systemic lupus erythematosus
SS	Sjögren's syndrome
SSc	Systemic sclerosis
sSS	Secondary Sjögren's syndrome
sVCAM-1	Vascular cellular adhesive molecules
TGF- β	Transforming growth factor-Beta
TNF- α	Tumor necrosis factor-Alpha
TRIPSS	Trial of Remicade in Primary Sjögren's Syndrome

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