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Víctor Martínez Taboada  
Reumatology Service. Hospital Marqués de Valdecilla. Santander, Spain  

Javier Narváez  
Reumatology Service. Hospital Bellvitge. Barcelona, Spain  

Chamaida Plasencia  
Reumatology Service. Hospital La Paz. Madrid, Spain  

Luis Rodríguez  
Reumatology Service. Hospital Clínico San Carlos. Madrid, Spain  

Jesús Rodríguez  
Reumatology Department. Bellvitge Hospital. Barcelona, Spain  

Susana Romero  
Reumatology Service. Hospital de Lugo. Lugo, Spain  

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SUMMARY

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(BRIEF VERSION)

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Funding

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Extra-intestinal manifestations in inflammatory bowel disease: Etiopathogenesis and management

Clara Ramos-Belinchón, Luis Menchén, and Ignacio Marín-Jiménez*
Department of Gastroenterology, Hospital General Universitario Gregorio Marañón, Madrid, Spain

Abstract
Inflammatory bowel disease (IBD) can be considered a systemic inflammatory disease since it can present with a variety of extra-intestinal manifestations (EIMs). Arthropathies are the most common manifestation, but EIMs can occur in a wide variety of organs. The relevance of EIMs lies in its impact on quality of life. Even some EIMs may be associated with a decreased survival as occurs in primary sclerosing cholangitis (PSC), which is related to an increased risk of cholangiocarcinoma. The pathogen of EIMs is still partially unknown and treatments are not always effective. Some EIMs follow the course of the intestinal activity and may be treated as an intestinal flare. Others have an independent course and are difficult to treat. In this article, we review the pathogenesis of EIMs, their clinical manifestations, and the available treatments.

Keywords: Inflammatory bowel disease. Extra-intestinal manifestation. Crohn’s disease. Ulcerative colitis.

Introduction
Crohn’s disease (CD) and ulcerative colitis (UC) are systemic inflammatory diseases that mainly affect the gastrointestinal tract but can manifest with extra-intestinal symptoms in up to 50% of patients. These extra-intestinal manifestations (EIMs) have a significant impact on the quality of life of patients and, in the case of primary sclerosing cholangitis (PSC), on survival due to an increased risk of neoplasia. EIM can be diagnosed before, after, or simultaneously with inflammatory bowel disease (IBD). There are even some very specific EIMs (like PSC) that should make us actively search for an underlying IBD. EIMs affect multiple organs (such as skin, eyes, muscles, joints, liver, and bile duct) and can run a parallel or independent course from intestinal activity.

In this article, we review the epidemiology and pathogenesis of EIMs and describe the most frequent EIMs as well as their current management.

Epidemiology
Between 6 and 47% of patients with IBD develop at least one EIM throughout their lives, with arthralgia/arthritis being the most frequent EIM. The prevalence of the most frequent EIMs is described in table 1. It is more common in patients with CD than with UC and affects more women.

The likelihood of developing EIMs increases with the duration of bowel disease and is higher in patients who already have another EIM. In most patients, EIMs occur after IBD diagnosis, but about 25% of cases appear before it.

Pathogenesis
The pathogenesis of EIMs is still partially unknown. There are two theories that explain the development of these manifestations. The first describes the occurrence of extraintestinal symptoms as the extension of a specific immune response to other systems. The
second argues that EIMs are independent inflammatory processes but that appear as a consequence of IBD or by shared environmental or genetic factors. Most likely, several pathogenic mechanisms are involved in the development of EIMs.

**Extension of specific immune response from the intestine**

It has been demonstrated an ectopic expression of cytokines and adhesion molecules that in healthy patients are limited to the intestine. Specifically, the ectopic expression of MAdCAM-1 and CCL25 has been identified in the vascular endothelium of the portal tract of patients with PSC associated with IBD.

Another pathogenic mechanism in this sense is the increase in chemokines and adhesion molecules non-specific of the gastrointestinal tract that can lead to the recruitment of intestinal leukocytes at an extra-intestinal site. There could be an immune reaction on other systems mediated by circulating antibodies and immune complexes.

Finally, the translocation of microbial antigens derived from the intestinal microbiota could be another pathogenic mechanism. Patients with IBD-associated PSC have a different gut microbiota and the transport of microbial antigens into the portal circulation could activate an immune response through α4β7-MAdCAM-1.

**Independent inflammatory events**

Patients with IBD have increased mucosal and systemic levels of pro-inflammatory mediators such as interleukin (IL)-6, tumor necrosis factor (TNF-α), interferon, and vascular endothelial growth factor, as well as bacterial lipopolysaccharide (LPS) that can promote immune activation in other systems. The innate immune system is also involved through a phenomenon called “neutrophil priming,” which means that neutrophils present a greater response when activated and produce a higher amount of IL-1β and TNF-α. In addition, there could be an alteration in hematopoiesis.

The intestinal microbiota seems to be related to the development of EIMs. Some of the mechanisms that could be involved in this would be translocation of bacteria or microbial products such as LPS due to an alteration of the intestinal barrier, and the production of metabolites derived from the microbiota that stimulate the immune system.

**Musculoskeletal manifestations**

Arthropathies associated with IBD are the most frequent EIM and are included in the group of spondyloarthropathies. They are divided into axial and peripheral. They must be differentiated from arthralgias, which are a very common symptom in patients with IBD. In addition to these two forms that will be explained below, patients with IBD may have drug-induced joint symptoms. Treatment with corticosteroids increases the risk of osteoporosis and avascular bone necrosis, and anti-TNF treatment is associated with a lupus-like phenomenon.

**Axial arthropathy**

Axial arthropathy is usually independent of IBD. Axial involvement is characterized by sacroiliitis that can be accompanied by vertebral involvement and includes a spectrum of entities from non-radiological axial spondyloarthropathy to ankylosing spondylitis (Fig. 1). Its prevalence ranges between 12% and 46% of patients with IBD and an association with HLA-B27 has been demonstrated, especially in patients with ankylosing spondylitis.

**Peripheral arthropathy**

Peripheral arthropathy has been classically classified into pauciarticular or type 1 and polyarticular or type 2. Type 1 affects fewer than 5 joints and usually manifests in large joints, especially knees. The course of this type of arthropathy runs in parallel with intestinal activity and is usually self-limited, with a duration of < 10 weeks. Type 2 affects five or more small joints, the metacarpophalangeal joints being the most common. The course of type 2 arthropathy is independent of IBD activity, and symptoms tend to last longer than in type 1.
Treatment

The European consensus document of the European Crohn’s and Colitis Organization (ECCO) recommends for the treatment of axial arthropathy intensive physical therapy and short-term nonsteroidal anti-inflammatory drugs (NSAIDs). They do not recommend keeping NSAIDs in the long term because the use of these drugs has been associated with an increased risk of intestinal disease flares. COX-2 inhibitors are presented as an attractive alternative to NSAIDs in patients with IBD. Other treatments such as mesalamine are not effective in the treatment of arthropathies associated with IBD and therefore anti-TNF should be used early.

Recommendations for the treatment of peripheral arthropathy include treatment of intestinal inflammation, short-term NSAIDs, and local infiltration with corticosteroids. Other alternatives in these patients are short-term oral corticosteroids, sulfasalazine, methotrexate, or anti-TNF.

Oral and cutaneous manifestations

These manifestations are diverse and are divided into several groups: manifestations with the same histology as IBD (metastatic CD), reactive manifestations (erythema nodosum, pyoderma gangrenosum, and Sweet’s syndrome), dermatoses associated with IBD (psoriasis), and manifestations secondary to pharmacological treatment, especially secondary to anti-TNF (Table 2 and Fig. 2). The most frequent orocutaneous manifestations are described below.

Erythema nodosum

The diagnosis is based on the typical clinical presentation as raised subcutaneous nodules, red or purple, hot, painful and between 1 and 5 cm. Nodules are usually located in the pretibial region. The appearance of this lesion is mostly accompanied by intestinal disease activity, although the severity of the erythema nodosum does not correlate with the severity of the intestinal symptoms. When the presentation or location is not typical, a skin biopsy can be used. Metastatic CD, Behçet's disease, sarcoidosis, and skin infections should be considered in the differential diagnosis of EN.

Erythema nodosum usually resolves with an effective treatment for the bowel disease.

Pyoderma gangrenosum

It occurs more frequently in UC than in CD. Pyoderma gangrenosum presents as one or multiple erythematous and painful papules or pustules that progress to deep ulcers with sterile exudate. The most frequently affected areas are the pimples and the peristomal skin. The clinical course is not always parallel to that of intestinal activity. The diagnosis is made by the clinical presentation and by the exclusion of other diseases. Biopsy may help to exclude other cutaneous diseases even though findings are non-specific. Skin biopsy may not be needed if the clinical presentation is typical and if there is a good response to treatment. Treatment will include systemic corticosteroids and, in refractory cases, infliximab, adalimumab, or oral or topical calcineurin inhibitors.

Sweet syndrome

Also known as acute febrile neutrophilic dermatosis, it is a rare cutaneous EIM. It presents as soft, erythematous papules or nodules. Sweet syndrome usually runs in parallel with the intestinal activity. Treatment is based on systemic corticosteroids and in refractory cases, immunosuppressants.
Oral lesions

Oral involvement is common in patients with IBD, and some of the following lesions may occur aphthous stomatitis, periodontitis, and vegetative peristomatitis. Oral lesions parallel intestinal disease activity, so the treatment will be that of the latter.40

Ophthalmological manifestations

After the joints and the skin, the eye is the organ most affected by EIMs. Within this kind of EIMs, episcleritis (Fig. 3) and anterior uveitis are the most frequent. Other ophthalmological manifestations such as scleritis (Fig. 4) or intermediate or posterior uveitis are much more infrequent. Episcleritis refers to the appearance of erythema in the sclera and conjunctiva and is usually painless. Anterior uveitis is less frequent and in patients with IBD, it is more frequently bilateral and of insidious onset. Associated symptoms are eye pain, blurred vision, photophobia, and headache. Normally, episcleritis parallels intestinal activity while uveitis runs an independent course.3

Treatment of episcleritis is the same as for IBD; topical or oral NSAIDs and topical corticosteroids are used to manage symptoms. On the other hand, uveitis deserves prompt referral to an ophthalmologist; topical corticosteroids may be used initially to reduce inflammation and topical cycloplegics to avoid spasms of the ciliary body and pupil and prevent the formation of synechiae. In refractory cases, systemic corticosteroids, immunosuppressants, or biologicals agents may be required.2,41

Primary sclerosing cholangitis

The diagnosis of PSC is made in a patient with cholestasis (elevated alkaline phosphatase is the most frequent laboratory finding) and typical features in magnetic resonance cholangiography (MRC), including multifocal intra- and extra-hepatic biliary strictures, once the causes of secondary sclerosing cholangitis have been ruled out (Table 3). In patients with normal MRC, a liver biopsy should be used to diagnose the small-duct PSC variant, which is characterized by normal appearance of the biliary tract in MRC.2,42

Between 24 and 96% of patients with PSC are positive for atypical perinuclear antineutrophil cytoplasmic autoantibody (p-ANCA).42 However, this marker is not specific to this disease nor do they have prognostic significance. In those patients with elevated antinuclear antibodies, anti-smooth muscle antibodies, or increased immunoglobulin G, we should suspect the existence of autoimmune hepatitis (AIH) and perform a liver biopsy. If IgG4 concentrations are high (more than 4 times the normal value) or the IgG4/IgG1 ratio is increased, we should suspect sclerosing cholangitis associated with IgG4.2,43

Table 2. Anti-TNF-induced skin lesions

<table>
<thead>
<tr>
<th>Paradoxical skin reactions:</th>
<th>Infusion reactions and injection site reactions</th>
</tr>
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<tbody>
<tr>
<td>- Eczematiform</td>
<td>- Lupus-like syndrome</td>
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<tr>
<td>- Psoriasiform</td>
<td>- Cutaneous malignancies</td>
</tr>
<tr>
<td>- Skin infections</td>
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</table>

Figure 3. Epiescleritis.

Figure 4. A: active scleritis. B: inactive scleritis with sclera thinning.
As previously described, MRC is the diagnostic test of choice. The typical image shows short multifocal strictures in the intra- and extra-hepatic bile ducts. Endoscopic retrograde cholangiopancreatography (ERCP) is reserved for the treatment of strictures and to rule out cholangiocarcinoma (taking biopsies and brushing). In the case of ERCP, it is recommended to use prophylactic antibiotic therapy in all cases.

The diagnosis of PSC in a patient with IBD significantly worsens the prognosis. Complications associated with PSC are cholestasis, cholangitis, cholelithiasis, cholangiocarcinoma, colorectal cancer, osteoporosis, vitamin deficiency, and steatorrhea.

Regarding treatment, there are no drugs that have proven to prolong transplant-free survival in these patients. Even so, ursodeoxycholic acid is routinely used at intermediate doses of 15–20 mg/kg/day. This drug has been shown to improve cholestasis but not survival. High doses should be avoided. Corticosteroids and immunosuppressants can be used in patients with evidence of autoimmune hepatitis. The indications for liver transplantation in patients with PSC are decompensated liver disease, intractable pruritus, and recurrent bacterial cholangitis. Transplantation could also be considered in patients diagnosed of biliary dysplasia.

The follow-up of patients with PSC will be done with annual (or biennial) colonoscopy for colorectal cancer screening. There are no established recommendations for the early diagnosis of biliary neoplasms. In general, annual abdominal ultrasound is recommended to assess gallbladder lesions and perform additional tests (MRC, ERCP, and CT) if cholangiocarcinoma is suspected.

### Cardiovascular manifestations

The incidence of cardiovascular events in patients with IBD is low but higher than in general population. This risk must be taken into account given the morbidity and mortality associated with these events. Even so, an increase in cardiovascular mortality has not been demonstrated in patients with IBD compared to the general population.

The cardiovascular manifestations are pericarditis, myocarditis, venous and arterial thromboembolism, arrhythmias, atrioventricular block, heart failure, endocarditis, valvular heart disease, and Takayasu arteritis. Pericarditis is the most common disease, representing 70% of cardiovascular manifestations. IBD patients have 1.2 times higher risk of myocardial infarctions than general population, 1.2 times the risk of stroke, and 3.5 times the risk of mesenteric ischemia.

### Pulmonary manifestations

In those patients with IBD who present pulmonary symptoms in the first place, infections and

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**Table 3. Causes of secondary sclerosing cholangitis**

<table>
<thead>
<tr>
<th>Condition</th>
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<tr>
<td>AIDS-related cholangiopathy</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
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<tr>
<td>Choledocholithiasis</td>
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<tr>
<td>Chronic biliary infestation (liver fluke, ascaris)</td>
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<tr>
<td>Congenital causes (choledochal cysts, Caroli’s syndrome, and biliary atresia)</td>
</tr>
<tr>
<td>Histiocytosis X</td>
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<tr>
<td>Cystic fibrosis</td>
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<tr>
<td>Eosinophilic cholangitis</td>
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<tr>
<td>IgG4-associated cholangitis</td>
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<tr>
<td>Ischemic cholangitis</td>
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<tr>
<td>Mast cell cholangiopathy</td>
</tr>
<tr>
<td>Portal hypertensive biliopathy</td>
</tr>
<tr>
<td>Recurrent pyogenic cholangitis</td>
</tr>
<tr>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Sclerosing cholangitis in critically ill patients</td>
</tr>
<tr>
<td>Surgical trauma</td>
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</tbody>
</table>

AIDS: acquired immune deficiency syndrome.
drug-induced lung injury, especially due to 5-aminosalicylic acid (5-ASA) and methotrexate, must be ruled out. Salicylates are associated with different types of interstitial lung disease. Methotrexate can cause hypersensitivity pneumonitis or pulmonary fibrosis. Lung damage has also been described with the use of aza-thioprine, 6-mercaptopurine, and anti-TNF. Treatment essentially lies in the suspension of the drug involved.\(^2,48\)

The pulmonary EIMs are rare. However, abnormalities found incidentally in respiratory function tests or chest imaging tests are relatively frequent. The EIMs of IBD usually affect the airway and can cause symptoms in any section of the respiratory tract from the glottis to small airways, most commonly affecting large airways. Lung interstitial damage can also occur, with organized pneumonia being the most common form. These manifestations usually respond adequately to treatment with inhaled or systemic corticosteroids. In refractory cases, immunosuppressants or biologicals may be used.\(^2,48\)

Renal and urological manifestations

Renal failure in patients with IBD may be due to drug toxicity or be an EIM of the disease, but this is difficult to differentiate. An association of IBD with the development of secondary amyloidosis, tubulointerstitial nephritis, and glomerulonephritis, especially IgA nephropathy, has been described. The risk of tubulointerstitial nephritis must be taken into account in patients treated with 5-ASA. Cyclosporine can cause acute and chronic kidney failure.\(^2,3,49\)

Patients with IBD, especially those with CD, have more commonly uric acid or calcium oxalate nephrolithiasis. An important proportion of IBD patients with nephrolithiasis has undergone surgery. Low urine pH and low urine volumes are risk factors associated with the development of uric acid stones. Patients with IBD have also a higher risk of calcium oxalate nephrolithiasis as a result of an increased intestinal oxalate absorption.\(^50\)

Osteopenia and osteoporosis

Osteopenia and osteoporosis are common in patients with IBD. The prevalence of osteoporosis varies between 4% and 9%. The diagnosis of osteoporosis is made when T-score is lower than −2.5 on a radiographic bone densitometry, whereas osteopenia is defined as a T-score between −1 and −2.5.\(^2,51\)

CD, a low body mass index, and low weight are risk factors associated with low bone mineral density (BMD) or osteoporosis.\(^1\) Some measures such as wear bearing exercise, smoking cessation, and an adequate intake of calcium in the diet (1 g/day) prevent the loss of BMD. The European consensus document of ECCO\(^2\) recommends systematically calcium and Vitamin D in patients receiving systemic corticosteroids. Control of intestinal inflammatory activity is necessary to reduce bone loss. Bisphosphonate treatment has been shown to reduce the risk of vertebral fractures in patients with IBD. Even so, this treatment cannot be widely recommended in young patients and premenopausal women.\(^2,52\)

Conclusion

IBD is a systemic inflammatory disease that affects multiple systems other than the intestine. The symptoms, treatment, and prognosis of different EIMs are varied. Its pathogenesis is still unclear and its deeper knowledge would help us to better treat them. Some EIMs run an independent course from the IBD and can affect severely patient’s quality of life, so the treating IBD physician should be aware to detect and control this EIM in due course.

Funding

No funding was needed for the writing of this manuscript.

Conflicts of interest

Ignacio Marín-Jiménez has served as a consultant, advisory member, speaker, or has received research funding from MSD, Abbvie, Takeda, Tillots, Ferring, Falk-Pharma, Faes Farma, UCB Pharma, Otsuka Pharmaceutical, Shire, Gebro Pharma, Pfizer, Biogen, Sandoz, Fresenius, and Chiesi.

C. R-B and LM declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

References


Present and future trends of biologic therapies and small molecules in hidradenitis suppurativa

Antonio Martorell**, Abdulhadi Jfri2, Gemma Ochando1, and Fatima Mayo1,3

1Inflammatory Diseases Unit, Department of Dermatology, Venereology and Surgery, Hospital de Manises, Valencia, Spain; 2Harvard Medical School, Boston, United States; 3Fundación Instituto Valenciano de Oncología, Valencia, Spain

Abstract

Background: Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease affecting areas with a high density of apocrine glands and characterized by subcutaneous nodules that may evolve into fistulas with pus secretion. Progressor and aggressive profiles will require the use of immunomodulatory therapies to fight against their disease outcomes. Various options have been proposed to treat HS. Unfortunately, no therapy has been fully successful. Methods: The aim of this review is to investigate all current knowledge on biologic and small molecule options for HS management. A systematic literature research using the words “biologic,” “small molecule,” “therapy,” and “HS” was performed in PubMed/Medline and Scopus/Embase databases. A search of the clinicaltrials.gov website for interventional recruiting and completed trials including the term “HS” was also performed up to August 2021. Results: At present, tumor necrosis factor TNF alfa blockers are considered the first therapeutic option based on clinical trials results and real-world evidence. However, new therapeutic options based on alternative pathway blockage, including interleukin (IL)-17, Complement and IL-23, seem to offer future alternatives for this condition. Conclusions: Several future studies and clinical trials are necessary to gain new knowledge about HS and to properly treat this complex condition. At present, IL-17 blockers such as secukinumab and bimekizumab represent the most promising alternative therapies for those patients who do not respond to adalimumab.

Keywords: Hidradenitis suppurativa. Biologic. Small molecule. Therapy. Clinical trials.

Introduction

Hidradenitis suppurativa (HS) is a chronic inflammatory condition primarily affecting apocrine-gland-rich regions of the body such as the axillary and groin areas1. HS presents with painful nodules and abscesses that may coalesce and form fistulas with pus drainage.

Lesions often evolve into scars, with patients suffering significant physical and psychological impact2. Various therapies have been proposed to treat HS. Unfortunately, no therapy has been fully successful in the control of this disease3.

At present, HS management is evolving to a more integral intervention in which a holistic evaluation of dynamic inflammatory lesions, static non-reversible structures and their related comorbidities will be mandatory to achieve the best results for patients (Fig. 1)2. One of the most important challenges in managing HS is to better understand the disease history to stop possible progression to irreversible lesions.

The window of opportunity for HS treatment is the period during which efforts to control inflammatory activity will be most effective. This period occurs in the early stages of the disease, before the onset of sequelae and established irreversible damage. Immunomodulatory therapy during this phase may alter the natural history of the disease by reducing the accumulation of tissue damage (Fig. 2).

Correspondence:
*Antonio Martorell
E-mail: martorelldermatologia@gmail.com
Received: 13-09-2021
Accepted: 25-10-2021
DOI: 10.24875/JIMIDS.M21000012
Available online: 25-01-2022
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Disease progression occurs in up to 30% of HS patients, so the early detection of aggressive cases is critical to changing the course of disease in these patients. Recently, Martorell et al. conducted an observational, descriptive, nonrandomized, prospective study with 197 patients and described a clinical phenotype referred to as “inflammatory” that showed an independent risk for disease aggressiveness in the multivariate analysis (odds ratio [OR] 0.034 [95% Confidence interval: 0.015, 0.072]) (Table 1 and Fig. 3). Early detection of these
progressive profiles will require the use of immunomodulatory therapies to address this outcome (Fig. 4). Various therapies have been proposed to treat HS. Unfortunately, no therapy has been fully successful at controlling the disease. Among immunodulatory therapies, multiple biologic therapies and small molecules have been suggested.

During the present review we will analyze the real evidence of current HS options and future options that are in the pipeline (Fig. 5).

<table>
<thead>
<tr>
<th>Follicular phenotype</th>
<th>Inflammatory phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>− Females &gt; males</td>
<td>− Males &gt; Females</td>
</tr>
<tr>
<td>− Frequent HS family history</td>
<td>− Rare HS family history</td>
</tr>
<tr>
<td>− Peripuberal onset (mean, 14–18 years)</td>
<td>− Adolescent and adult onset (18–25 or &gt;35 years)</td>
</tr>
<tr>
<td>− Typical sites: thighs/axillar folds</td>
<td>− Typical sites: inguinal/axillar folds and buttocks</td>
</tr>
<tr>
<td>− Presence of folliculitis and/or comedones</td>
<td>− Folliculitis/comedones, epidermal cysts and nodules are scarce</td>
</tr>
<tr>
<td>− The main active lesion is the nodule</td>
<td>− Main active lesions are abscesses and wide tunnels and fibrosing tracts</td>
</tr>
<tr>
<td>− Individual predisposition to develop epidermal cysts</td>
<td>− Tendency to confluence in poorly defined inflammatory and scarring plaques</td>
</tr>
<tr>
<td>− Post-inflammatory pigmentation may occur</td>
<td></td>
</tr>
</tbody>
</table>

| MIXED PHENOTYPE |
| Follicular progression to Inflammatory (heavy smokers, combined comedons and abscesses/tunnels) |

Table 1. Clinical features of HS phenotypes

HS: hidradenitis suppurativa; y: year. Adapted from Martorell, et al. (2020)

Material and methods

A systematic literature research was performed in PubMed/Medline, Scopus/Embase, and Google Scholar, to find articles relevant to this review. Keywords searched included “biologic,” “small molecule,” “therapy,” and “HS.” Duplicate articles were deleted and articles that introduced no new information were excluded from the study. A search of the website clinicaltrials.gov for interventional recruiting and completed clinical trials with the term “HS” through August 31, 2021 was also conducted.
Results

New data from current approved biologic therapy in HS

Adalimumab

Adalimumab is the only currently-approved biologic for the treatment of moderate-to-severe HS in several countries worldwide. Its inhibitory action prevents the movement of nuclear transcription factor nuclear factor kappa B into the nucleus, where it induces the production of cytokines that contribute to the inflammatory cascade. It also downregulates processes induced or regulated by tumor necrosis factor (TNF) as inhibiting endothelial-leukocyte adhesion molecule-1, intracellular adhesion molecule-1, and vascular cell adhesion molecule-1. All of these molecules are responsible for the migration of leukocytes.

Two studies, PIONEER I and II, had a primary endpoint of achieving HS clinical response (HiSCR). This was defined as a ≥ 50% reduction from baseline in total abscess and inflammatory nodule count (AN count) without increases in abscess or draining fistula counts relative to baseline. Each of the two was a similarly designed, randomized Phase III clinical trial, and both trials demonstrated that a significantly greater percentage of patients achieved HiSCR at week 12 with adalimumab than with placebo: 41.8% versus 26.0% in PIONEER I (p = 0.003) and 58.9% versus 27.6% in PIONEER II (p < 0.001). They also both showed that adalimumab significantly improved health-related quality of life.

Adults and adolescents weighing 60 kg and greater should be dosed at a level of 160 mg of adalimumab on day 1 followed by 80 mg on day 15. Following this, the dosage can be dropped to 40 mg at day 29 and every week thereafter. Treatment with adalimumab should be reconsidered for patients that show no improvement by week 12, and during treatment daily use of a topical antiseptic wash on HS lesions is recommended.

Recently, Marzano et al. published their real-world experience with adalimumab in HS patients. Preliminary conclusions included the fact that a window of opportunity, as previously proposed by Martorell, could exist due to the fact that administration of adalimumab in early phases improves the results achieved on HS patients in terms of HiSCR. These results, which encourage the use of biologics from the time of symptom onset in the most inflammatory forms of HS (such as the inflammatory or mixed phenotypes) to halt the disease progression, contradict the labeling of adalimumab as a second-line therapy after failure to respond to conventional systemic treatments (e.g., systemic antibiotics).
Adalimumab's safety profile in patients with HS is consistent with the known adverse effect profile of the drug, with the most common effects including infections (e.g., upper respiratory, sinusitis), injection site reactions, headache, and rash. The drug is linked to an increased risk of developing serious infections and may have an increased risk of developing malignancies. In the United States the drug carries a black box warning about the risk of serious infections (e.g., bacterial sepsis, invasive fungal infections, tuberculosis, infections due to other opportunistic pathogens), and malignancy (e.g., lymphomas in children and adolescents). Still, a recent assessment of the risk of adalimumab use for HS during the COVID-19 pandemic supported the use of adalimumab in otherwise healthy patients with HS as long as they were without risk factors, indicating that its use should not predispose them to infection or nasopharyngitis.

Data from off-label options used in the current clinical practice

**Infliximab (IFX)**

IFX has been used as an off-label treatment in patients whose HS is resistant to adalimumab. It is currently FDA-approved for use in inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis. It acts by binding and blocking both membrane-bound and soluble TNF-alfa that play a central role in the pathologic inflammatory response associated with HS.

A Phase II double-blind placebo-controlled randomized trial of IFX in moderate-to-severe HS demonstrated a 50% or greater decrease from baseline HS Severity Index score as well as a statistically and clinically significant improvement from baseline. This improvement was observed at week 8 using the Dermatology Life Quality Index (DLQI) score, visual analog scale (VAS) score, erythrocyte sedimentation rate, and C-reactive protein compared with placebo.

Dosage of IFX is established at 5 mg/kg body weight on weeks 0, 2, and 6 and thereafter every 8 weeks as an intravenous infusion. However, reports suggest that the dosing regimen for HS requires further refinement, and the North American Clinical HS Management Guidelines recently emphasized the need for dose-ranging studies to optimize management. Along these lines, Ghias et al. performed a prospective analysis of 42 patients initiating IFX 7.5 mg/kg every 4 weeks (IFX 7.5) and 16 patients receiving dose escalation to IFX 10 mg/kg every 4 weeks (IFX 10) between March 1, 2018, and February 28, 2019. The primary outcome measure (clinical response) was the proportion of patients with Physician Global Assessment (PGA) of clear, minimal, or mild (score of 0-2) HS with at least a 2-grade improvement from baseline scores. In the result analysis, the proportion of patients achieving a clinical response after initiating IFX 7.5 was 20 of 42 (47.6%) at week 4 and 17 of 24 (70.8%) at week 12. For patients receiving dose escalation to IFX 10 because of incomplete initial response, 6 of 16 (37.5%) achieved clinical response at week 4 and 6 of 12 (50%) at week 12. The main conclusion was that the initiation of IFX 7.5 every 4 weeks, with possible dose escalation to IFX 10 if needed, provides optimal mitigation of HS-related disease activity.

Herpes simplex infection and influenza-like illness were the most common adverse effects in the Phase II clinical trial. IFX has also been associated with paradoxical worsening of facial acne vulgaris, demyelinating neuropathies, and metastatic cutaneous squamous cell carcinoma in some cases, as well as a case of Gemella morbillorum bacteremia complicated by brain abscesses.

**Anakinra**

Anakinra is a recombinant interleukin (IL)-1 receptor inhibitor that competitively inhibits the binding of both IL-1α and IL-1β to the IL-1 type 1 receptor. It has been used off-label for managing HS, but further and higher-quality data is needed to clarify its therapeutic role. It is currently FDA-approved for use in rheumatoid arthritis and neonatal-onset multisystem inflammatory disease.

IL-1 is produced in response to various microbial and non-microbial stimuli and plays a key role in immune dysregulation in HS. A double-blind placebo-controlled randomized clinical trial included 20 patients with moderate-to-severe HS (Hurley II or III), and demonstrated that the use of anakinra created a significant statistical difference in the primary outcome, including a decrease in DLQI scores from weeks 0 to 12. Still, between weeks 12 and 24 there was no significant overall difference in DLQI between the study arms. The secondary endpoint showed anakinra delivered a significantly increased prolongation to new HS exacerbation. Another open-label trial of anakinra revealed that at week 8 there was a significant and clinically meaningful mean decrease in Sartorius score (a validated scoring system for symptom severity in HS).
Ustekinumab

Ustekinumab is a human monoclonal antibody that acts by binding to and inhibiting the p40 subunit on IL-12 and IL-23 which may be elevated in HS lesions. It is FDA-approved for use in plaque psoriasis, psoriatic arthritis, and Crohn’s disease and has been used off-label for managing HS.

A case series of patients administered ustekinumab demonstrated an improvement in the PGA score in 70% (7/10) of participants and an improvement in the Numerical Pain Rating Scale in 80% (8/10). A systematic review of ustekinumab reported that 76% (34/45) of patients experienced clinical improvement in disease severity, and 84% (38/45) experienced symptomatic improvement.

Dosing for patients weighing 100 kg and below is 45 mg per dose, while those weighing above 100 kg received a dose of 90 mg, though the Phase II study’s authors suggested that further intensification of the dosing regimen in HS may be necessary.

Real world experience with ustekinumab suggests the need to use it in Crohn’s posology with a single intravenous infusion dose of STELARA® using the weight-based dosage regimen followed by a subcutaneous regimen with a recommended maintenance dosage of 90 mg 8 weeks after the initial intravenous dose, then every 8 weeks thereafter to achieve better results in HS patients.

The systematic review reported headache, fatigue, and upper respiratory tract infection as the most frequently reported adverse events, none of which were severe. All spontaneously resolved and the case series reported observing no adverse events related to ustekinumab use.

Apremilast

Apremilast is a phosphodiesterase 4 inhibitor that exerts an immunomodulatory action. It partially blocks the expression of pro-inflammatory cytokines and induces the expression of anti-inflammatory cytokines. The drug has been used off-label for managing HS and is currently indicated in adult patients diagnosed with plaque psoriasis and/or psoriatic arthritis who do not respond to conventional systemic therapy.

Apremilast acts on T cells, natural killer cells, neutrophils, monocytes, dendritic cells, and various cells involved in the pathogenesis of HS. A double-blind, randomized clinical trial showed that 8-out-of-15 patients with moderate HS (53.3%) achieved a positive HiSCR at week 16 after being given apremilast compared to zero of five in the placebo group. These patients also showed a significantly lower abscess and nodule count and lower numerical rating scales for pain with no significant difference between both arms in the DLQI over the period of the trial. A case series of nine patients (with three patients dropping out) with moderate-to-severe HS treated with apremilast for 5-9 months showed that 5 out of 6 patients reported achieving significant improvement in terms of Sartorius score, pain, and in the DLQI scores. An open-label, phase 2 clinical trial that enrolled 20 patients with mild-to-moderate HS revealed that 65% of patients achieved HiSCR30 at weeks 16 and week 24, with patients reporting significant mean improvements in the overall Sartorius score, the PGA score, the VAS pain score, and the DLQI score.

Dosage of apremilast is either 30 mg twice daily or 30 mg once daily as long as creatinine clearance is > 30 ml/min. There were mild-to-moderate headache and gastrointestinal symptoms (diarrhea and nausea) reported by patients in the randomized clinical trial, as well as depression.

Ongoing clinical trials in HS

Phase I drugs

Sonelokimab (MoonLake)

Sonelokimab (also known as M1095) is a novel trivalent nanobody comprised of monovalent camelid-derived (i.e., from the Cameliidae family of mammals, such as camels, llamas, and alpacas) nanobodies specific to human IL-17A, IL-17F, and human serum albumin. Nanobodies are a novel class of proprietary therapeutic proteins based on single-domain, camelid and heavy-chain-only antibodies.

Its smaller size may allow them to penetrate deeper into solid tissues such as skin and joints. In addition, their high stability, strong antigen-binding affinity, water solubility and natural origin make them suitable for development into next-generation biodrugs.
This molecule is now being tested for different inflammatory diseases such as psoriasis, psoriatic arthritis, ankylosing spondylitis, and HS.

Phase II, multicenter, randomized, and placebo-controlled trials have already been published for psoriasis. Under this indication, sonelokimab in doses of 120 mg or less showed significant clinical benefit over placebo, with rapid onset of treatment effect, durable improvements, and an acceptable safety profile. Nasopharyngitis and pruritus are the most frequent adverse events.

**Phase II drugs**

**LY3041658 (Lilly) CXCR1/2 inhibitor**

CXC chemokines and their receptors play an important role in increasing inflammation in HS by attracting neutrophils, dendritic cells and memory T and B cells attractants. LY3041658 is a humanized monoclonal antibody that blocks CXCR1 and CXCR2 signaling. A multicenter, randomized, double-blind, placebo-controlled, Phase 2 study is underway to evaluate the efficacy and safety of LY3041658 in adults with moderate-to-severe HS. Currently the recruitment phase is still open, thus data about the drug efficacy and safety are not yet available.

**C5aR inhibitors**

Selectively blocking the action of C5a on its receptor is crucial to reducing the risk of impairing the formation of the membrane attack complex C5b-9 necessary for defense against encapsulated bacterial infections, including Neisseria meningitidis.

HS is characterized by inflammation and an abundant neutrophilic infiltrate. It has been described as a complementary system that plays a fundamental role in the infiltration and activation of neutrophils in the skin. It has recently been shown that circulating C5a and C5b5-9 are increased in HS, and consumption of circulating C5a is associated with disease severity. Moreover, C5a primes the overproduction of TNF-alpha by circulating mononuclear cells.

Avacopan and vilobelimab are the two C5aR inhibitors that are running clinical assays.

**Avacopan (ChemoCentryx)**

Avacopan (CCX168) is an orally administered selective and potent C5aR inhibitor. A randomized, double-blind, placebo-controlled, and parallel group Phase 2 study of avacopan in subjects with moderate (Hurley Stage II) to severe HS (Hurley Stage III) began in December 2018. The multicenter study randomized 398 patients to three treatment groups. One group was treated with 10 mg avacopan twice daily. The second group was treated with 30 mg avacopan twice daily, and the third group with placebo twice daily for 12 weeks. Primary efficacy analysis took place at 12 weeks. Avacopan 30 mg twice daily demonstrated a significant improvement compared to placebo in Hurley Stage III patients (42.6% vs. 22.2%, respectively).

The sponsor company plans to advance the drug into Phase III clinical trial for the treatment of severe HS.

Avacopan demonstrated a favorable safety profile, with fewer adverse events than placebo (48.5% vs. 55%, respectively).

In addition, after the first 12 weeks, subjects on placebo will be re-randomized 1:1 to receive 10 mg or 30 mg of avacopan twice daily for an additional 24 weeks. Subjects treated with avacopan will continue to receive the same dose during the additional 24 weeks. The subjects will be followed for 44 weeks for assessment of safety and efficacy.

**IFX-1 (Infla-Rx) C5aR inhibitor**

IFX-1 (vilobelimab) is an intravenous monoclonal IgG4 kappa antibody that selectively binds to C5a and blocks its biological activity. The prospective, open-label, and single-arm Phase 2a study of IFX-1 in HS showed a treatment response of 75% at the end of the treatment and 83.3% at the end of the 3-month follow-up period, with good tolerance and a decrease in fistulization.

A randomized, double-blind, placebo-controlled, and multicenter Phase 2 trial (SHINE) to determine the efficacy and safety of IFX-1 in 179 subjects with moderate-to-severe HS found HiSCR rates of 38.7%-51.5% across four dosing regimens at week 16. Remarkably, the placebo treated group reached similar response rates (47.1%).

**Bermekimab (Janssen) IL-1α inhibitor**

Bermekimab (MABp1), unlike anakinra, is a selective inhibitor of IL-1α. IL-1α, a highly pro-inflammatory cytokine with increased levels in HS lesions compared with healthy skin.
Four clinical trials have studied this fully humanized monoclonal antibody. The first clinical trial revealed a statistically significant improvement in patients treated with bermekimab compared to those receiving placebo (60% vs. 10%; p: 0.035). This result was supported by the open label extension of the study39,40. A new Phase 2a/2b, multicenter, randomized, placebo and active comparator-controlled, double-blind, dose-ranging study with bermekimab in moderate-to-severe HS is currently under way. Its primary outcome is to assess the percentage of patients who achieve HiSCR50 at week 1641.

IL-36R inhibitor

IL-36 cytokines are part of the IL-1 superfamily35,42. Evidence of IL-36 role in HS is increasing, similar to the well-known hyperactivation of the IL-1 pathway that contributes to the immune dysregulation in HS35. IL-36 cytokines are predominantly expressed in the skin, where the IL-36 receptor (IL-36R) pathway activates dendritic cells, affects neutrophil recruitment, and participates in polarizing Th1 cells and Th17 cells and their cytokines in serum and lesional HS skin35,42. At the moment there is no data about the efficacy of IL-36R inhibitors.

Two of such molecules are undergoing Phase 2 study: Imsidolimab (Anaptys Bio) and Spesolimab (Nochringer Ingelheim).

ImSidolimab (Anaptys Bio) IL-36R inhibitor

An ongoing Phase 2 multicenter, randomized, double-blind, placebo-controlled study of imsidolimab with HS patients will assess the efficacy and safety of this subcutaneous anti IL-36R monoclonal antibody. This study will also characterize the pharmacokinetic profile of imsidolimab and explore the immune response to imsidolimab in subjects with HS43.

Spesolimab (Nochringer Ingelheim) IL-36R inhibitor

Spesolimab is a subcutaneous IL-36R inhibitor that is currently being evaluated in two HS Phase 2 studies. The first study intends to evaluate the evolution of the disease considering the total abscess and inflammatory nodule count after 3 months44. The second trial attempts to target the emergent adverse events up to the end of a maintenance treatment period of 2 years and 4 months45.

PF-06650833 (PFIZER) IRAK4 inhibitor

The IL-1 receptor-associated kinase (IRAK) family mediates activating signals from TLRs and IL-1 receptor46. The IRAK family, comprised of four members, IRAK1, IRAK2, IRAK-M, and IRAK4, is closely involved in the pathogenesis of inflammatory autoimmune disorders46. The overexpression of IRAK4 encourages the generation of a pro-inflammatory environment, with increased production of IL-1β and tissue factor46. This explains the alleged involvement of the IRAK family in the complex pathogenesis of HS38.

A current Phase 2 multicenter study is evaluating the safety and efficacy of three kinase inhibitors (PF 06650833, PF 06700841, and PF 06826647) controlled with placebo in 192 randomized patients with moderate-to-severe HS. A primary outcome providing the percentage of patients with HiSCR is still pending47.

Iscalimab (Novartis) CD40 inhibitor

Iscalimab (CFZ533) is a fully human monoclonal antibody that blocks CD154 from binding to CD40 and therefore prevents CD40 pathway signaling and activation of CD40+ cell types35,48. A Phase 2 study to assess preliminary efficacy and safety of CFZ533 and LYS006 in moderate-to-severe HS is in the recruitment period49.

LYS006 (Novartis) LTA4 hydrolase inhibitor

LYS006 is a highly potent and selective LTA4H inhibitor with high whole blood potency and long-lasting pharmacodynamic effects50. Leukotriene A4 hydrolase is a cytosolic metalloenzyme involved in the biosynthesis of pro-inflammatory leukotriene B4 (LTB4). Furthermore, LTB4 is a strong inflammatory mediator engaged in innate and adaptive immune responses that has an important role in the recruitment and activation of neutrophils50. CFZ533 and LYS006 are currently being investigated in the same phase 2 clinical trial in HS49.

Brodalumab (Leo Pharma), IL-17 Receptor inhibitor

The IL-17 cytokine family consists of 6 cytokines (IL-17A to F) with five different receptor subtypes (IL-17RA to RE).
On ligation of ligand and receptor, tissue-specific transcription of genes for a host of different pro-inflammatory cytokines, chemokines, and matrix metalloproteases is initiated. In addition, IL-17 exerts its greatest inflammatory potential through its recruitment of immune cells such as TNF, IL-1β, IFNγ, and IL-23.

Increase in gene expression of IL-17 in lesional skin of HS patients has been shown to compare with healthy skin.

Brodalumab is a human monoclonal antibody binding to IL-17RA and thereby enables blockade of IL-17A, IL-17C and IL-17F. This drug was approved in 2019 for moderate-to-severe psoriasis treatment. (AMAGINE-2, ClinicalTrials.gov identifier: NCT01708603, AMAGINE-3, ClinicalTrials.gov identifier: NCT01708629).

A cohort study was performed in ten participants with moderate HS to assess the safety and clinical response. Brodalumab 210 mg/1.5mL was administered subcutaneously at weeks 0, 1 and 2 and every two weeks thereafter until week 24. No grade 2 or 3 adverse events were reported. All patients achieved HiSCR. Achievement occurred as early as week 2.

In another cohort study, brodalumab 210 mg/1.5mL was administered every week to a sample of ten patients with severe HS to provide better control for draining tunnels. All of the patients achieved HiSCR by week 4 sustained through week 24, without reporting serious adverse events.

At present, brodalumab is being studied in a Phase II clinical trial with ongoing patient recruitment, and no data from this study are yet available.

**P19 blockers**

IL-23 is a pro-inflammatory member of the IL-12 cytokine superfamily with a potent ability to enhance the production of Th17 cells. IL-23 is mainly secreted by dendritic cells and activated macrophages in peripheral tissues such as the skin. IL-23 and IL-17 form an axis through Th17 cells with a strong association to activation and pathogenicity of the immune system.

Two options, guselkumab and risankizumab, are currently under Phase II clinical assays.

**+GUSELKUMAB (JANSSEN)**

Guselkumab is a fully human IgG1-λ monoclonal antibody that binds to the p19 subunit of IL-23 and inhibits the intracellular and downstream signaling of IL-23. It is currently approved for psoriasis and psoriatic arthritis.

Case series following the psoriasis regimen have reported significant improvement in patients with severe HS.

A Phase II trial (NCT03628924) evaluating efficacy and safety has recently been completed with a primary endpoint of measuring the percentage of participants achieving HiSCR at Week 16. Some of the published results are displayed in Fig. 1 showing discrete results in achieving complete disease control.

**+RISANKIZUMAB (ABBVIE)**

Risankizumab is a humanized IgG1 monoclonal antibody targeting the p19 subunit of IL-23. It is currently approved for psoriasis and psoriatic arthritis.

So far, only retrospective data on the efficacy of risankizumab within small groups of patients with HS have been reported with acceptable results.

A Phase II (NCT03926169) trial evaluating efficacy and safety has recently been completed with results pending publication.

**Janus Kinase (JAK) inhibitors**

Kinases in the JAK family include JAK1, JAK2, JAK3 and non-receptor tyrosine-protein kinase TYK2 and are involved in signaling pathways affecting hematopoiesis, immunity and inflammation.

After JAKs are activated by diverse cytokines, signal transducers and activators of transcription (STATS) proteins are activated. STATS can then enter the nucleus and induce inflammation.

**+BREPOCITINIB (PFIZER)**

Brepocitinib is an orally available, selective inhibitor of non-receptor tyrosine-protein kinase tyrosine kinase 2 (TYK2) and tyrosine-protein kinase JAK1 (JAK1) with potential immunomodulatory and anti-inflammatory activities. On oral administration, brepocitinib selectively binds to and inhibits the activation of TYK2 and JAK1, thereby disrupting TYK2 and JAK-1-dependent cytokine signaling. This may reduce inflammatory responses and prevent inflammation-induced damage caused by certain immunological diseases.

According to Pfizer website information, brepocitinib has shown in vitro ability to inhibit IL-23, IL-12 and IFN-alpha. For this reason, it is being studied for use in HS patients.

Efficacy and safety are also being evaluated for Crohn’s disease, ulcerative colitis, psoriasis, psoriatic
arthritis, atopic dermatitis, alopecia areata, non-segmental vitiligo, and lupus erythematosus.

**+INCB054707 (Incyte)**

INCB054707 is a JAK1 inhibitor and has been tested for HS in two Phase II trials (NCT03569371 – NCT03607487). Safety and tolerability assessment were the primary endpoints of the trial.

A safety review was conducted at week 4, with a 30-day safety follow-up after the 8-week trial. A total of 35 participants were randomized to orally once daily of either placebo, 30 mg, 60 mg, or 90 mg doses of the drug. In the arm taking INCB054707 at 90 mg over an 8-week period, 87.5% of the patients achieved HiSCR.

**+Upadacitinib (AbbVie)**

Upadacitinib is a JAK1 inhibitor currently approved for atopic dermatitis. A clinical trial is now active but not recruiting to evaluate efficacy in HS.

Other studies are also taking place for non-segmental vitiligo, lupus erythematosus, axial spondylitis, juvenile idiopathic arthritis, rheumatoid arthritis, Takayasu arteritis, giant cell arteritis, ulcerating colitis, and Crohn’s disease.

**+Ropsacitinib (Pfizer)**

Ropsacitinib (PF-06826647) is claimed as a TYK2 Inhibitor. However, its activity at clinically relevant concentrations to achieve TYK2 inhibition is suggestive of significant inhibition of at least JAK2, if not also of JAK1. Ropsacitinib is an ATP-competitive inhibitor.

NCT04092452 is a study with 3 kinase inhibitors (PF 06650833, PF 06700841, and PF 06826647) in participants with moderate-to-severe HS. The primary endpoint is the percentage of participants achieving HiSCR at week 16. Results are not yet published.

Phase I studies for plaque psoriasis showed significant improvement in disease activity within 4 weeks of dosing with an acceptable safety profile.

**Phase III drugs: IL-17 blockers**

**Secukinumab (Novartis)**

Secukinumab is an IL-17A inhibitor that is FDA-approved for moderate-to-severe plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis. Because the expression of IL-17 gene is increased in lesions and in perilesional skin, and IL-17 serum concentration in patients with HS is significantly increased, its blockade of the IL-17 pathway could be a potential target to treat HS.

Nine patients were enrolled and four completed an open-label pilot trial of secukinumab. Of the nine, six achieved HiSCR at week 24. Another retrospective study on a cohort of patients treated with secukinumab for their HS revealed a decrease in the median Sartorius score, the median inflammatory lesion count, and median DLQI score, and 75% of patients (15/20) achieved a successful HiSCR at week 16. There are two randomized double-blind multicenter trials (SUNRISE and SUNSHINE) currently being conducted of patients with moderate-to-severe HS. Their goal is to compare the efficacy, safety, and tolerability of secukinumab doses of 300 mg dosed 2-weekly and 4-weekly.

Dosing of secukinumab for patients with HS is 300 mg administered subcutaneously weekly for 1 month, then once every 4 weeks. A retrospective study showed two HS patients with no personal or family history of inflammatory bowel disease (IBD) developed Crohn’s disease (CD) after 3 and 5 months of treatment respectively, but the open-label pilot trial showed no new-onset inflammatory bowel disease or other serious adverse events. Still, HS is associated with IBD with a pooled OR for Crohn’s disease (CD) and 1.5 for ulcerative colitis (UC).

**Bimekizumab (UCB Pharma)**

Bimekizumab is a humanized, full-length IgG monoclonal antibody that selectively inhibits both IL-17A and IL-17F and which has demonstrated rapid and significant improvements in dermatologic and rheumatologic disease activity. It is a dual-cytokine blockade that may profoundly affect chronic tissue inflammation and confer additional efficacy in immune-mediated diseases such as HS.

Seventy-nine HS patients enrolled in a phase 2, double-blind, placebo-controlled randomized clinical trial that demonstrated that 46% of bimekizumab-treated participants achieved HiSCR75. Another 32% achieved HiSCR90 at week 12. In the other arm of adalimumab, 35% achieved HiSCR75 and 15% achieved HiSCR90 while 10% of placebo-treated participants achieved HiSCR75 and none achieved HiSCR90. Bimekizumab-treated participants reported greater improvements in skin pain at week 12 and no impact of disease on their quality of life compared with placebo-treated
participants. Improvements in IHS4, skin pain, and DLQI were numerically similar or smaller in adalimumab-treated participants than in those treated with bimekizumab.\(^{65}\) Dosing is 320 mg every 2 weeks (after a 640-mg loading dose at baseline)\(^{65}\). Most adverse effects were mild or moderate, though hospitalization for anemia and empyema did occur for one patient\(^{11}\).

**Discussion**

HS is a condition that involves several concomitant pathways. Although its pathogenesis remains unclear, more studies are being conducted to identify the triggers for this debilitating disease.

Although there are no current treatments that adequately control HS, immunomodulatory treatments targeting the Th17 pathway and the JAK/STAT pathways are now being explored. Anti-IL-17 drugs such as secukinumab, bimekizumab, brodalumab, and anti-IL-23 drugs such as risankizumab or guselkumab may represent possible treatments in the near future.

Preliminary data from ongoing clinical trials suggests that IL-17 blockers are the most promising options for HS management. Close safety monitoring to determine the risk of secondary IBD is necessary before considering these options beneficial to achieving an integral control of HS patients.

**Funding**

None.

**Conflicts of interest**

Dr Martorell has received honorariums from sponsored symposiums and advisory board meetings and has participated as principal investigator of Phases II, III, and IV from the following companies: AbbVie, Celgene, Janssen, Novartis, Merck Sharp & Dohme, UCB, Pfizer, Gebro Pharma, Leo Pharma, Lilly, Sandoz, Galderma. There are no conflicts of interest with respect to the research, authorship and/or publication of this article. Dr Jfri, Dr Ochando and Dr Mayo declare no conflicts of interest with respect to the research, authorship and/or publication of this article.

**Ethical disclosures**

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that no patient data appear in this article.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

**References**

Progressive systemic sclerosis, also known as scleroderma, is a rheumatic disease of autoimmune origin, in which the main affection occurs at the level of the arterioles and microvasculature, progressing toward fibrosis and vascular obliteration. At a skin level, a pathological increase in fibrosis causes the skin to harden and it also affects the subcutaneous cellular tissue, with the disappearance of the annex (hence, the name of scleroderma). In addition, there is an alteration of different internal organs, especially the lung and kidney, which gives it a poor prognosis although joint structures in the digestive system are also affected. The present article is an update of the current treatments for each affect, and of some up-to-date investigations that are improving the results and the prognosis. At present, there are different dilator drugs for treating Raynaud’s phenomenon, such as calcium channel blockers, prostacyclin analogs, and phosphodiesterase-5 inhibitors, among others. Immunosuppressants, such as mycophenolate and others, are used for cutaneous sclerosis. For pulmonary involvement in the form of interstitial lung disease, immunosuppressants such as cyclophosphamide, mycophenolate, and biological treatments such as nintedanib or rituximab (RTX) are used. Pulmonary hypertension is managed with endothelin receptor antagonists, such as bosentan, phosphodiesterase inhibitors, or prostacyclin. The prognosis for scleroderma renal crisis has drastically changed since the initiation of treatment with angiotensin-converting enzyme inhibitors. Finally, bone marrow, lung, and heart transplants are used in extreme cases.

an age-standardized mortality rate (ASMR) for SSc and non-SSc (all other causes), women and African-American persons had higher SSc ASMRs to non-SSc ASMR ratios than men and Eurasian persons, respectively. In less than 5% of those affected, renal impairment occurs in the form of a renal crisis, which also carries a poor prognosis.

Skin involvement serves as a prognostic marker in ESP, with diffuse forms having the worst progression.

In recent years, the use of bone marrow transplantation, as well as lung transplantation, has been a valid alternative for some patients. It is also possible that stem cell transplantation will be a therapeutic alternative for these patients in the future.

To address the treatment, the clinical manifestations in scleroderma are (Table 1):

- Raynaud’s phenomenon (RP), digital ulcers and sclerosis of the skin, often accompanied by telangiectasia (Figure 1) and in the most advanced forms, leads to limited mobility, even opening the mouth (Figure 2)
- Scleroderma renal crisis
- PAH
- ILD
- Alteration of the gastrointestinal tract
- Heart disease
- Arthritis

The objectives of treatment are:
- Limiting or stopping progression of the disease
- Reducing sequelae
- Improving quality of life by managing disability and functional limitation.

### Treatment for Raynaud’s phenomenon (RP)

The treatment for RP depends on its severity. The objectives are to reduce the number and severity of crises, to improve the quality of life, and to avoid structural damage.

There are a series of vasoconstrictor drugs that should be avoided or used with great caution in the presence of RP:
- Nasal decongestants for local or general use, such as ephedrine compounds
- Anti-migraine ergotamine derivatives
- Beta-blockers, including glaucoma drops
- Drugs for hyperprolactinemia.
- Anti-Parkinson drugs.

In the treatment itself, it is important to consider some non-pharmacological measures such as protection against cold and micro-trauma, and avoiding tobacco. Alternative treatments such as biofeedback techniques have not been sufficiently studied from a scientific point of view.

### Pharmacotherapy

1. Calcium channel blockers (CCB). They are the first line treatment, including nifedipine, diltiazem, lido-
nicardipine, nimodipine, amlodipine and felodipine. They are effective in reducing both the number and severity of RP seizures. Its effect varies with dose, and higher doses tend to show greater efficacy. An example would be nifedipine, at doses of 30 mg/day with a 30% reduction in seizures.

2. Prostacyclin analogs. Iloprost administered intravenously at doses of 0.05 mg each day, has shown efficacy in the treatment for RP secondary to scleroderma by reducing the severity and frequency of attacks and as prevention for digital ulcers. Oral iloprost appears to be less effective.

3. 1-5-phosphodiesterase inhibitors. Sildenafil, tadalafil, and vardenafil have been used as an alternative in the case of resistance or intolerance to CCBs. They have shown limited efficacy.

4. Angiotensin blockers. Losartan at single doses of 50 mg/day has been proposed as compassionate use in the treatment for RP in cases of intolerance to calcium channel inhibitors.

5. Angiotensin converting enzyme inhibitors. Captopril and enalapril at doses of 20 mg/day have been used as compassionate use, in case of coexistence with PAH.

6. Serotonin receptor antagonists. Fluoxetine at doses of 20 mg/day is proposed for compassionate use, based on a small, randomized study, which showed it to be somewhat superior to nifedipine.

Treatment of digital ulcers

The treatment of digital ulcers, in addition to local care and the prevention or treatment of infections when they occur, does not differ from the treatment of RP, with which they are also usually associated. Endothelin receptor antagonists such as bosentan have proven to be effective in preventing ulcers, but they have not shown an effect on the on the speed of healing ischemic wounds. There is no indication on prescribing bosentan as a curative treatment for digital ulcers. The use of cellular therapy techniques by digital injection of stromal vascular fraction or mesenchymal stem cells is still under investigation. These techniques are, therefore, not currently recommended.

Treatment for cutaneous sclerosis

There is no approved treatment for treating skin sclerosis specifically. Different immunosuppressants are used based on the autoimmune pathogenesis of the disease and some inconclusive clinical trials.

Methotrexate

There are some trials that showed improvement in scleroderma of short evolution (<3 years), without statistical significance, and it is used on the recommendation of expert groups and therapeutic guidelines at weekly, oral or subcutaneous doses of 0.3 mg/kg, and for a period of 2 years.
Cyclophosphamide

Although there are different trials for its use in pulmonary involvement, there are limited and inconclusive experiences for skin involvement. The SLS-I study evaluated oral cyclophosphamide and showed a discrete improvement at the cutaneous level, which was significant after one year of treatment, and which disappeared after discontinuation of treatment.\(^1\)

Mycophenolate mofetil (MMF)

There is no direct study on the use of MMF as disease-modifying anti-rheumatic drugs (DMARD) for SSc, but there are observational and also controlled studies for lung damage. In the SLS-II trial, MMF use was associated with a 4.9-point reduction in the modified Rodnan score versus 5.3 for cyclophosphamide at 24 months. The results are only significant in diffuse forms of SSc. Analysis of SLS-II compared with the SLS-I placebo group would suggest that MMF use was associated with an improvement of the modified Rodnan score compared with the placebo group after 24 months. Considering these data, it is considered to use MMF DMARD in the diffuse cutaneous forms of SSc with or without lung damage. The recommended dosage of MMF is from 2 to 3 g/day.

The skin must be treated locally for good hydration. It is recommended to use moisturizing and softening creams and lotions several times a day. Paraffin baths for the hands or the use of castor oil have not been rigorously and scientifically studied. Personalized physiotherapy with massages aimed at softening the skin or subcutaneous tissues can be proposed, although no rigorous study on the subject has been conducted to date.

Treatment of locomotive apparatus damage

Locomotive apparatus damage is frequent with SSc: arthralgia, arthritis, and tenosynovitis are especially common in the 1st years of the disease. Fibrous tenosynovitis is included in the disease activity score and is considered a sign of worsening development. No randomized study has specifically addressed musculoskeletal damage.\(^2\)

- Arthralgia and arthritis can be treated by analgesics and by nonsteroidal anti-inflammatory drugs in the short term, with monitoring of renal function and after evaluation of digestive bleeding risk.
- Oral corticosteroids are commonly proposed at an initial dosage of prednisone equivalent to but not exceeding 10-15 mg/day, then at a lower long-term dosage of less than 10 mg/day.
- Corticosteroid shots can be proposed in case of articular or tenosynovial damage.
- Tenosynovitis can benefit from the same treatments as articular damage, but there has not been any specific trial dedicated to this type of damage.
- Rehabilitation programs can reduce disability, but they have not been shown to have significant long-term efficacy.
- Calcinosis: the frequency of this complication is high (near 25% of all patients) and is the source of pain and disability (Figure 3). No treatment has been shown to be effective. In certain situations, surgical excision of calcium deposits can be proposed to promote healing and avoid secondary infections after making sure that the peripheral vascular condition allows for it.

Interstitial lung disease treatment

- Total and definitive smoking cessation.
- It is recommended to give an annual flu vaccination and an anti-pneumococcal vaccination.
- Oxygen therapy: as with other causes of chronic respiratory failure, long-term oxygen therapy is recommended in the event of severe respiratory failure.
defined by PaO₂ ≤55 mmHg (7.3 kPa), or PaO₂ between 55 and 60 mmHg (7.3–8.0 kPa) with at least one of the following criteria: polycythemia (hematocrit > 55%), signs of pulmonary hypertension, and signs of right heart failure.

- Respiratory rehabilitation: a respiratory rehabilitation program must be discussed on a case-by-case basis.

- Despite the conflicting efficacy data, the use of intravenous cyclophosphamide remains the most widely used treatment for SSc-ILD. The schedule of administration every 4 weeks is that usually used. The dose is 0.7 g/m² or 0.5 g/m² in patients over 65 years of age or with GFR <30 ml/min/m², at the rate of one treatment every 28 days for 12 months. The dose of cyclophosphamide is capped at 1200 mg/injection. Intravenous uromitexan is administered concomitantly for dose. The total duration of 1 year of treatment is justified by the fact that, after a 6-month treatment of intravenous cyclophosphamide followed up with PO azathioprine for 18 months, some initially responsive patients subsequently worsened. MMF at a dose of 1500 mg, twice a day for 2 years has shown non-inferiority in a randomized study carried out versus oral cyclophosphamide and may be an alternative as a first-line treatment, especially for forms of ILD with a poorer prognosis.

- Low-dose corticosteroid doses are recommended in association with cyclophosphamide or MMF. Given the risks of a renal crisis occurring in scleroderma patients, we recommend the use of corticosteroids at dosages ≤15 mg/day of oral prednisone.

- RTX. For patients not responding to first-line therapies, consideration is given to RTX as rescue therapy. To assess the effect of RTX on the lung function parameters in SSc-ILD patients, PubMed and EMBASE were searched to identify studies on SSc-ILD treated with RTX, confined to a predefined inclusion and exclusion criteria. A systematic review and meta-analysis were performed on the included studies on changes in forced vital capacity (FVC) and diffusion capacity of carbon monoxide (DLCO) from baseline to six and 12 months of follow-up. A total of 20 studies (two randomized controlled trials [RCT], six prospective studies, five retrospective studies, and seven conference abstracts) were analyzed. In conclusion, the treatment with RTX in SSc-ILD was associated with a significant improvement of both FVC and DLCO during the 1st year of treatment. RTX use was associated with lower infectious adverse events.

### Pulmonary arterial hypertension

In the treatment for PAH, the sequential for mild and severe form of the disease was proposed (Table 2).

### Endothelin receptor antagonists

Bosentan is an orally active mixed endothelin A and B receptor antagonist approved for PAH associated
with a connective tissue disease by the New York Heart Association (NYHA) functional Class II or III. Bosentan is started at a dosage of 62.5 mg mornings and evenings for four weeks, then increased to a dosage of 125 mg mornings and evenings according to hepatic tolerance (monthly hepatic testing obligatory [SGOT, SGPT] and routine monitoring of hemoglobin).

The benefit also provided by bosentan on the secondary prevention of digital ulcers can lead to recommending first-line use of bosentan in case of SSc-associated PAH if the patient has a severe digital ulcer disease.

Ambrisentan is an orally active endothelin A receptor antagonist approved for PAH associated with connective tissue disease of NYHA functional Class II or III. The dosage is 5 mg once per day and can be increased to 10 mg/day.

**Phosphodiesterase-5 inhibitors**

Sildenafil and tadalafil are approved in the treatment of idiopathic, familial, or SSc-associated PAH with dyspnea of NYHA functional Class II or III. The dosage used is 20 mg 3 times/day for sildenafil and 2 × 20 mg once a day for tadalafil. There is no specific biological monitoring for these treatments.

**Continuous intravenous prostacyclin injection**

Epoprostenol is approved in the treatment of PAH associated with connective tissue disease of NYHA functional Class III or IV. It is administered in continuous intravenous perfusion through a portable Perfusor connected to a tunneled central venous catheter. In urgent situations, it can be administered through a peripheral venous route for a short duration while the central venous route is being set up. Epoprostenol constitutes the reference treatment for severe forms of SSc-associated PAH of functional classes III/IV.

**Prostacyclin receptor agonists**

Selexipag is a selective prostacyclin receptor agonist that is used orally. It is approved for treating PAH associated with connective tissue diseases of NYHA functional Class III and insufficiently controlled by treatment associating an endothelin receptor antagonist and a phosphodiesterase-5 inhibitor. It is prescribed at a progressive dose over several weeks up to the maximum tolerated dose, to a maximum of 1600 μg twice a day, based on tolerance. Special monitoring for the occurrence of adverse effects is crucial (headaches, flushing, and digestive disorders).

**Lung or heart-lung transplant**

This is the last recourse in case of severe PAH insufficiently improved by maximum medical treatment. The indication of transplant is systematically posed by reference centers or a competence center.

**Treatment for scleroderma renal crisis (SRC)**

- Preventive treatment: prophylactic administration of angiotensin-converting enzyme (ACE) inhibitors has not yet been shown to be effective in preventing the occurrence of SRC. In contrast, treatment with prednisone at a dosage >15 mg/day within the previous three months appears to be associated with the occurrence of SRC. In this context, the prescription of corticosteroids should always be subject to expert advice.
- Curative treatment: ACE inhibitors are the only therapeutic class to have demonstrated efficacy and to have modified the SRC prognosis. This demonstration is based on cohort follow-up studies. In the absence of hemodynamic instability, it is recommended the use of an intermediate half-life ACE inhibitor such as enalapril or ramipril in graduated doses. Captopril (short-acting ACE inhibitor) is only used in cases of hemodynamic instability. Conventional increases in creatinine levels with ACE inhibitors (lowering of renal perfusion pressure) should not result in a decrease in dosage.
- Nicardipine or urapidil can be used early if blood pressure is not controlled by ACE inhibitors alone. The use of iloprost is recommended by some authors, but has not been validated. Use of bosentan cannot currently be recommended in the absence of clinical studies demonstrating its efficacy. At present, there is no demonstrated indication for first-line plasma exchange, eculizumab, or immunosuppressants. Corticosteroid therapy is contraindicated.

**Corticosteroid therapy**

**Treatment of digestive disorders**

**Esophagitis and esophageal motor disorders**

- Hygienic-dietary measures, such as reduced sized meals, reducing or even stopping consumption of tobacco, alcohol, tea, coffee, and chocolate.
Consultation with the nutrition team or a dietician is recommended.
- Postural rules.
- Anti-secretory therapy: double- and even quadruple-dose proton-pump inhibitors.

**Gastroparesis**

Dietary management is always necessary (fragmentation of meals, mixed diet). Low-residue diets and vitamin supplements have been recommended based on empirical evidence.

Stomach prokinetics accelerate gastric emptying, but can have a negative effect on motility of the small intestine when prescribed at too high a dose. Treatment with erythromycin is, therefore, recommended at a daily dosage not to exceed 125-250 mg × 2/day. Concomitant use of erythromycin and colchicine is not recommended due to the potential for potentiation of colchicine side effects.

Should erythromycin fail, one can try amoxicillin/clavulanic acid contained clavulanic acid which is prokinetic for the stomach.

Prokinetic treatment with metoclopramide or metopimazine may be proposed if there are no neurological and/or electrocardiographic contraindications.

Gastroparesis can lead to a state of severe undernutrition, requiring prolonged enteral (jejunal) feeding.

**Intestinal disorders**

1. Motor disturbances causing malabsorption syndrome and/or pseudo-obstruction of the intestine: in the case of acute occlusion, the first-line treatment consists of rehydration, analgesia (preferably avoiding opioids, which tend to exacerbate intestinal dysmotility), and relief of the small intestine by nasogastric aspiration. Nutritional management should not be delayed. Intestinal prokinetic agents can be used. Metoclopramide and domperidone often have little efficacy. The action of erythromycin on the motility of the small intestinal is less well known. Intravenous neostigmine can be used in acute episodes, but cardiac and cholinomimetic adverse events limit its use in frail patients.

2. Malabsorption syndrome by chronic bacterial colonization of the small intestine: the treatment is based on monthly sequential oral antibiotic therapy with alternating courses of different treatments, or even periods without treatment. The alternation of antibiotic molecules is proposed to avoid the emergence of a multiresistant intestinal bacterial flora. The durations are 10-14 days/month, and an alternation of three antibiotic molecules from different families is usually proposed. Commonly used antibiotics are amoxicillin (500 mg × 3/day) or ciprofloxacin (250 mg × 2/day) or other quinolones, doxycycline (100 mg/day) (and other tetracyclines), metronidazole (250 mg × 3/day), gentamicin (80 mg/day) or neomycin (500 mg × 4/day), and sulfamethoxazole 800 mg-trimethoprim 160 mg (1 tab 2 × per day).

3. Colonic disease: the treatment of constipation is based on hygiene-dietary measures (balanced diet of fiber and mucilage, satisfactory hydration, and regular physical activity), laxatives, and evacuating enemas. The advice of the nutrition team and/or a dietician is recommended for severe forms. Prokinetic drugs can be combined to improve colon motility (and to a lesser extent symptoms): metoclopramide 20-30 mg daily, domperidone (the maximum daily dose is currently 30 mg daily in three doses), and prucalopride once daily (2 mg before the age of 65 and 1 mg over). Their use must be limited in time.

**Future and investigative treatment**

A recent study carried out in mice in which an experimental SSc is induced, investigated the effect of B cell depletion on fibrosis in systemic sclerosis (SSc) and its mechanism of action. Mice with bleomycin-induced SSc (BLM-SSc) were treated with anti-CD20 antibody, and skin and lung fibrosis were histopathologically evaluated. T cells and macrophages were co-cultured with B cells, and the effect of B cells on their differentiation was assessed by flow cytometry. B-cell depletion inhibited fibrosis in mice with BLM-SSc. B cells from mice with BLM-SSc increased pro-inflammatory cytokine-producing T cells in co-culture. In mice with BLM-SSc, B-cell depletion before BLM treatment (pre-depletion) inhibited fibrosis more strongly than B-cell depletion after BLM treatment (post-depletion) (p < 0.01). However, the frequencies of pro-inflammatory T cells were lower in the post-depletion group than in the pre-depletion group. This discrepancy suggests that the effect of B-cell depletion on fibrosis cannot be explained by its effect on T-cell differentiation. On the other hand, profibrotic macrophages were markedly decreased in the pre-depletion group compared to the post-depletion group (p < 0.05). Furthermore, B cells from mice with BLM-SSc increased profibrotic
macrophage differentiation in coculture (p < 0.05). In SSc patients, the extent of profibrotic macrophage induction by B cells correlated with the severity of fibrosis (p < 0.0005). In conclusion: these findings suggest that B-cell depletion inhibits tissue fibrosis through suppression of profibrotic macrophage differentiation in mice with BLM-SSc, providing a new rationale for B-cell depletion therapy in SSc.

Chimeric antigen receptor-T (CAR-T) cell therapy is based on the specific targeting of tumor antigens, leading to lysis and the destruction of tumor cells. The high potency of CAR-T cells in the management of B-cell malignant neoplasms has been demonstrated. Following the success of this therapeutic strategy, new constructs derived from CAR-T cells have been developed that can eradicate pathogen B cells or restore tolerance.

The knowledge and technology generated using CAR-T cells can be translated and integrated into ongoing therapeutic strategies for autoimmune rheumatic diseases, such as rheumatoid arthritis, generalized lupus erythematosus, and SSc.

To assess the preclinical efficacy and mechanism of action of an anti-CX₃CL1 monoclonal antibody (mAb) in systemic sclerosis (SSc), cultured human dermal fibroblasts were used to evaluate the direct effect of anti-CX₃CL1 mAb on fibroblasts. Anti-CX₃CL1 mAb treatment significantly inhibited Smad3 phosphorylation (p < 0.05) and expression of type I collagen and fibronectin 1 (p < 0.01) in dermal fibroblasts stimulated with transforming growth factor β1 (TGFβ1). In the bleomycin model, daily subcutaneous bleomycin injection increased serum CX₃CL1 levels (p < 0.05) and augmented lesional CX₃CL1 expression. Simultaneous administration of anti-CX₃CL1 mAb or CX₃CR1 deficiency significantly suppressed the dermal thickness, collagen content, and capillary loss caused by bleomycin (p < 0.05). Injection of bleomycin-induced expression of pSmad3 and TGFβ1 in the skin, which was inhibited by anti-CX₃CL1 mAb. Further, the dermal infiltration of CX₃CR1+ cells, macrophages (inflammatory and alternatively activated [M2-like] subsets), and CD3+ cells significantly decreased following anti-CX₃CL1 mAb therapy (p < 0.05), as did the enhanced skin expression of fibrogenic molecules, such as thymic stromal lymphopoietin and secreted phosphoprotein 1 (p < 0.05). However, the treatment did not significantly reduce established skin fibrosis. In the second model, simultaneous anti-mCX₃CL1 mAb therapy significantly diminished the skin fibrosis induced by serial subcutaneous injection of TGFβ and connective tissue growth factor (p < 0.01). In conclusion, this study suggests that anti-CX₃CL1 mAb therapy may be a novel approach for treating early skin fibrosis in inflammation-driven fibrotic skin disorders such as SSc.

A Phase II study, carried out in the USA, studied the efficacy of abatacept in SSc with diffuse skin involvement, in an early phase. It was a multicenter, double-blind, randomized, placebo-controlled study; however, the results did not allow us to establish changes between the groups of statistical significance.

A meta-analysis carried out in Portugal assessed the use of botulinum toxin to treat peripheral vascular disease, which includes RP and digital ulcers. The authors conducted a review of the literature on the subject and identified 30 results, of which five original papers were included: two RCTs, two case series, and one case-control study, from a total 133 patients. Only one RCT showed negative results, with worse blood flow in the treated arm, but with lower dose of botulinum toxin. Despite this, all five included studies reported improvement of at least one RF/hand function outcome measure. Concerning digital ulcer healing, resolution of baseline digital ulcer at the end of follow-up was reported in 75-100% of the patients, with one RCT showing superiority over placebo. Botulin toxin protocols were highly heterogeneous. In conclusion, botulin toxin is a valid option in the treatment of SSc-related peripheral vasculopathy. However, future large prospective trials are necessary.

The autologous hematopoietic stem cell transplantation (HSCT) allowed a rapid and sustained improvement in skin and lung fibrosis, proved for early phase I/II studies, along with improved long-term survival of up to seven years after HSCT. The Canadian Scleroderma Research Group has done a recent study to quantify the magnitude, domains, and duration of change in health-related quality of life (HRQoL) in patients with systemic sclerosis (SSc) who underwent autologous HSCT as compared to SSc patients with similar characteristics who did not undergo autologous HSCT. In total, 41 SSc patients who underwent autologous HSCT and 65 SSc patients treated with conventional care were compared. This study provides robust complementary HRQoL data, including overall and event-free survival data, to expand on the standard repertoire of biomedical variables, thus potentially supporting the physical benefits of autologous HSCT in patients with SSc.
Funding
None.

Conflicts of interest
None.

Ethical disclosures
Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.
Confidentiality of data. The authors declare that no patient data appear in this article.
Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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