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EDITORIAL

ORIGINAL ARTICLES

Letter from the Guest Editor

Leon H. Kircik MD

As dermatologists, we are familiar with the importance of exploring the nuances of new or existing therapies such as biologic agents, which target immunologic responses. The articles in this supplement help to address various components of psoriasis and comorbidities as well as hidradenitis suppurativa and biologic treatments.

In my article with Dr. Neh Onumah, we cover psoriasis and its identified comorbidities or chronic proinflammatory disorders driven by similar immunopathologic expression of immune response mechanisms. There is growing and emerging evidence that psoriasis patients have a higher prevalence of associated comorbid diseases such as psoriatic arthritis, cardiovascular disease, metabolic syndrome, gastrointestinal disease and psychological disorders. This article aims to elucidate recent findings and provide guidance for clinical practice in terms of further management.

Dr. Joshua A. Zeichner covers immunologic therapies for treatment of psoriasis—tumor necrosis factor (TNF) inhibitors and interleukin (IL)-12 and IL-23 inhibitors: etanercept, adalimumab, infliximab, golimumab, and ustekinumab. Dr. Zeichner also considers therapeutic management prior to initiating biologic therapy.

Lastly, Drs. Elena Sotiriou MD PhD et al from Aristotle University in Thessaloniki, Greece provides perspectives on a prospective clinical trial of efficacy of adalimumab in the treatment of hidradenitis suppurativa. The study demonstrates the significant efficacy of the once weekly regimen, as well as its benefit regarding time to recurrence.

As we continue to determine the safest and most efficacious biologic therapies, it is important to explore past and current data, in order to mold our future approaches in clinical studies.

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Psoriasis and Its Comorbidities

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ABSTRACT

Psoriasis is a multi-systemic chronic inflammatory skin disease targeting 2% to 3% of the general population. It is a prototype of immune dysregulation mediated by TH1 proinflammatory cytokines such as TNF-α, IFN-Y, IL-6, and IL-12, to name a few. Psoriasis, traditionally viewed as an inflammatory skin disorder of unknown origin, is increasingly recognized as an inflammatory skin disease with far reaching systemic effects. There is growing and emerging evidence that psoriasis patients have a higher prevalence of associated comorbid disease with cardiometabolic dysfunction and psoriatic arthritis being at the forefront. It appears that psoriatic skin disease severity portends a serious risk for development of these comorbidities. As such, patients with moderate to severe psoriatic skin disease are found to have a higher association with these extracutaneous disease manifestations.

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INTRODUCTION

Psoriasis is a multi-systemic chronic inflammatory skin disease targeting 2% to 3% of the general population. It is a prototype of immune dysregulation mediated by TH1 proinflammatory cytokines such as TNF-α, IFN-Y, IL-6, and IL-12, to name a few. Psoriasis, traditionally viewed as an inflammatory skin disorder of unknown origin, is increasingly recognized as an inflammatory skin disease with far reaching systemic effects. There is growing and emerging evidence that psoriasis patients have a higher prevalence of associated comorbid disease with cardiometabolic dysfunction and psoriatic arthritis being at the forefront. It appears that psoriatic skin disease severity portends a serious risk for development of these comorbidities. As such, patients with moderate to severe psoriatic skin disease are found to have a higher association with these extracutaneous disease manifestations.

Conceivably, the unifying thread linking these diseases is their shared pathogenicity. In other words, psoriasis and its identified comorbidities are chronic proinflammatory disorders driven by similar immunopathologic expression of immune response mechanisms. However, it may be that their association is induced indirectly by the severe and persistent inflammation exemplified in moderate and severe psoriatic disease. Additional contributing factors include shared genetic susceptibility loci, environmental influences (i.e., smoking and alcohol use), and adverse effects of prescribed medications. Some of these comorbidities include cardiovascular disease (CVD) and its associated risk factors such as hypertension, obesity, cigarette smoking, alcohol consumption, dyslipidemia, type 2 diabetes, or impaired glucose tolerance and the metabolic syndrome. Other associated comorbidities of psoriasis include inflammatory bowel disease, nonalcoholic fatty liver disease and lymphoma. They can all cause serious morbidity and in certain cases increased mortality. For example, patients with severe psoriasis are at increased risk for early cardiovascular death and apparently die on average five years earlier than those without psoriasis.[1]

The discovery of biologicals targeting various components of the immune response and approved for the treatment of psoriasis and rheumatoid arthritis among other diseases has certainly improved or reinforced our understanding of immunopathogencity in psoriasis. They have also helped to elucidate the relationship between psoriasis and its proposed comorbidities. Due to the limited scope of this paper, we have chosen to discuss a few of the associated comorbidities of psoriasis. As such, this review is not inclusive of all of the comorbid diseases linked to psoriasis.

Psoriatic Arthritis

Psoriatic arthritis (PsA) is the most common comorbidity of psoriasis. However, it may be part of the natural clinical progression of psoriasis (i.e., the so-called "psoriatic march"—the a concept of how severe psoriasis may drive cardiovascular comorbidity) and not necessarily a comorbidity. In either case, if left undiagnosed, it can lead to progressive destructive joint disease and negatively impact the patient's quality of life.

PsA belongs to the group of spondyloarthropathies that includes ankylosing spondylitis, Reiter Syndrome, reactive arthritis, enteropathic arthritis associated with inflammatory bowel disease and undifferentiated spondyloarthritis. Distinguishing features of this group include seronegativity for rheumatoid factor, enthesitis or inflammation at the insertion point of tendon or ligament to bone, and HLA B-27+ (positive in 50% of cases of psoriatic spondylitis).

PsA is divided into five clinical subtypes based on the Moll and Wright classification scheme. They are: 1). DIP joint involvement, 2). Asymmetric oligoarthritis, often associated with sausage digits or dactylitis caused by enthesitis and joint inflammation of a single digit, 3). A symmetric polyarthritis like rheumatoid arthritis, typically RF negative but RF is positive in up to 24% of cases making the diagnosis difficult, 4). Arthritis mutilans, a rare destructive arthritis, and 5). Psoriatic spondylitis.[2,3] It is not unusual for a patient to present with several of these joint patterns simultaneously. The newer CASPAR classification criteria for PsA has a higher specificity for diagnosing the disease (98%).[3] (See box below)

Inflammatory Arthritis in the presence of at least three of the following: (Adapted from Gottlieb et al)[8]

1. Evidence of current psoriasis, or a personal or family history of psoriasis.
2. Typical psoriatic nail dystrophy, onycholysis, pitting, and hyperkeratosis.
3. Negative rheumatoid factor.
4. Current or past history of dactylitis.
5. Radiographic evidence of juxta-articular new bone formation (excluding osteophytes).

Pathogenetically, TNF-α has a key function in driving osteoclast production and bone resorption through its upregulation of the NFκβ receptor and its ligand. It also promotes production of DKK-1, which inhibits osteoblastogenesis.[4] The role of TNF-α in disease progression is exemplified by the ability of the TNF-α blockers, adalimumab, infliximab, and etanercept to effectively halt radiologic progression of joint destruction.[5]

The onset of PsA may be insidious with an unpredictable relapsing and remitting clinical course ranging from mild to severe disease. PsA has a peak incidence of occurrence between ages 30 and 50 and a presumed prevalence of 7% with estimates up to 47% in psoriatics, although this has been subject to much debate. However, in the general population PsA has a documented prevalence of 0.1% to 0.25%.[6,7] Males and females are equally affected. Thirty-three percent of PSA patients have no obvious antecedent skin disease. In the majority, psoriatic skin disease precedes joint symptoms by up to 12 years.[8] Of significance, psoriatics with more severe skin disease are at greater risk for developing arthritis compared to patients with mild disease.[2] Regardless, severe joint destruction can develop in patients with limited skin disease. Exacerbation of psoriatic skin and joint disease can occur concomitantly or independently of each other. Also, there is evidence of increased mortality in patients with PsA. The evidence thus far suggests extensive radiographic damage early on, disease activity with high ESR, and high therapeutic dosages of immunosuppressives as major contributants.[4]

As an inflammatory arthritis, PsA has a predilection for the DIP and PIP joints not excluding the MCP and MTP joints and may also extend to the weight bearing joints of the hips, knees, elbows, and axial skeleton. Initially the DIP joint is most often involved. Patients present with joint swelling and pain, morning stiffness lasting a minimum of 30 minutes, sausage digits or dactylitis, and limited mobility. Nail pitting accompanied by other psoriatic nail changes such as transverse ridging, onycholysis, and splinter hemorrhages are said to be strongly associated with joint disease with nail pitting being the most common.[2]

The diagnosis of PsA is made by classic clinical and radiographic findings. The acute phase reactants CRP and ESR may be elevated, indicative of systemic inflammation. Typical radiographic signs include tenosynovitis, bone erosion, reactive bone formation, and enthesitis. Severe PsA is marked by the classic "pencil in cup" deformity of the PIP and DIP joints on imaging.

The rather long interval between the onset of skin disease and joint disease puts the dermatologist in a critical position for early diagnosis and aggressive management to arrest progression to debilitating destructive joint disease and deformity. This is substantiated by the small percentage of psoriatics (between 4 and 8%) who present with subclinical joint disease. Specifically, they have articular complaints yet a normal clinical joint examination. Of equal importance are asymptomatic patients with ensuing enthesitis who are likely to remain undiagnosed until progressive arthritis develops.[2]

To our point, in one study enthesitis was documented in 33% of psoriatics with normal clinical joint examination[9] underscoring the invaluable role of radiographic imaging in managing these patients. Hence, the clinical absence of obvious articular involvement does not exclude the presence of subclinical enthesitis.[2]

Thus, at each clinic visit, the onus is on the clinician to evaluate the joint(s) and ask about articular symptoms including arthral-

gia, joint swelling and erythema, repeated episodes of morning stiffness, and back pain as well as psoriatic nail changes. To optimize management, it may be beneficial to collaborate with a rheumatologist and as a multidisciplinary team decide on the appropriate intervals for radiographic surveillance and the initiation of treatment when necessary. Traditionally, MRI and ultrasound imaging have been employed as the primary diagnostic modes of imaging to assess joint damage. However, if the diagnosis of psoriatic arthritis is clear, one can initiate treatment with one of the TNF-α blockers if the patient is not already on one of these agents for their cutaneous psoriasis.

Cardiovascular Disease

Recently, the concept of psoriasis as an independent risk factor for cardiovascular disease has gained support. In an observational study—Swedish cohort (n=5,000)—of psoriasis in-patients, the risk of cardiovascular death in patients with severe psoriasis was 50% higher than rates in psoriasis outpatients.[10,11] Results from a population based study by Gelfand et al concluded that severe psoriasis is an independent risk factor for myocardial infarction.[12]

The causal relationship between psoriasis and cardiovascular disease is not firmly established as the biological mechanisms contributing to the progression from psoriasis to cardiovascular disease or stroke are largely unknown. It is accepted that patients with psoriasis appear to have a higher prevalence of conventional cardiovascular risk factors (e.g., obesity) relative to patients without psoriasis. This association does not necessarily establish a causal relationship. However, concepts increasingly supported by studies, describe a cascade where psoriasis is causally related to cardiovascular comorbidity have been presented in the literature. Common in these concepts is the role of systemic inflammation. For example, the concept of "the psoriatic march," suggests that the systemic inflammation in severe plaque-type psoriasis may cause insulin resistance which triggers endothelial cell dysfunction which drives atherosclerosis and then myocardial infarction or stroke.[13]

Boehncke et al coined the term "the psoriatic march" to help elucidate the cascade of events which may shape the relationship between severe psoriasis and the onset of cardiovascular comorbidity. As such, "the psoriatic march" is primarily focused on the pathophysiologic mechanisms leading from psoriasis to atherosclerosis involving the large vessels. They explain that severe psoriasis marked by chronic systemic inflammation imposes an increased inflammatory burden on the individual with the induction of insulin resistance. This insulin resistant state in turn promotes endothelial cell dysfunction and hardening of the cerebral, coronary, and carotid arteries with increased cerebral and cardiovascular events, namely stroke and myocardial infarction.[13]

The evidence presented to support the "the psoriatic march" includes the elevated level of the biomarkers (i.e., adipokines) that indicate system inflammation in psoriasis patients. Similarities in the adipokine milieu in the blood of psoriasis patients and in prediabetic individuals, who exhibit signs of insulin resistance, has been noted and supported by a recent study.[14] Results from two cross-sectional studies showed that psoriasis patients exhibit insulin resistance at clinical levels using both the homeostasis model assessment of insulin resistance and the more sensitive oral glucose tolerance test for insulin resistance.[14] Insulin resistance triggers endothelial cell dysfunction which predisposes the endothelium towards an atherogenic environment ultimately may cause vascular inflammation, atherosclerosis, and thrombosis.[14,15]

Metabolic Syndrome

The metabolic syndrome is a clustering of risk factors in one individual that increases overall cardiometabolic risk including the risk for type 2 diabetes and cardiovascular disease.[16] According to the revised National Cholesterol Education Program Adult Treatment (NCEP ATP) Panel III criteria, individuals presenting with three or more of the following five conditions (within the specified criteria) have the metabolic syndrome: abdominal obesity, hypertriglyceridemia, decreased levels of high density lipoprotein cholesterol [HDL], high blood pressure, and elevated fasting glucose levels.[15,16] The metabolic syndrome is defined by the World Health Organization (WHO) similarly to the NCEP ATP Panel III definition with some variation in the components of the definition.

Abdominal obesity and insulin resistance have been presented as underlying risk factors for the metabolic syndrome. Additionally, high levels of pro-inflammatory and/or pro-thrombotic factors (i.e., TNF-α, leptin, IL-6, C-reactive protein), and low levels of anti-inflammatory factors are associated with the metabolic syndrome and especially with the abdominal component of this syndrome.[16] Patients with the metabolic syndrome have a three to nine-fold increased risk of developing type 2 diabetes mellitus[16] and a two to three-fold increased risk for coronary heart disease, stroke, and myocardial infarction.[17]

Recent studies using the definition of the metabolic syndrome from the NCEP ATP Panel III or the WHO have concluded that psoriasis patients have an increased risk for the metabolic syndrome and for the individual components of the metabolic syndrome.[4] In results from an investigation of the increased prevalence of the metabolic syndrome in patients with moderate to severe psoriasis, using the WHO definition for the metabolic syndrome, Sommer et al showed that psoriasis patients hospitalized for treatment resistance or severe psoriasis from 1996 to 2002 were significantly more likely to have the metabolic syndrome when compared with the control group (stage I melanoma surgical patients) (OR: 5.92; 95% CI: 2.78–12.8).[18] The increased propensity for the metabolic syndrome in patients with psoriasis began around 40–49 years of age

and continued with increasing age.[18] Sommer et al noted that through an increased frequency of smoking and alcohol consumption was observed in the psoriasis patients, these factors alone did not explain the association of the underlying metabolic syndrome risk factors with psoriasis.[18] In results from an investigation of the prevalence of the metabolic syndrome in psoriasis using the revised NCEP ATP Panel III definition for the metabolic syndrome, Love et al concluded that the prevalence of the metabolic syndrome is high among psoriasis patients. The estimated the prevalence of the metabolic syndrome is 40% among psoriasis cases and 23% among the control group (patients without psoriasis) (OR: 2.16, 95% CI: 1.16–4.03) on univariate analysis and OR: 1.96 95% CI: 1.02–3.77 after adjustment for age, sex, race/ethnicity, smoking, and serum CRP levels).[19]The overall study population was the National Health and Nutrition Examination Survey participants from 2003–2006 (n=6549).[19] This overall population provides a nationally representative sample of men and women from the United States, aged 20 to 59 years. Approximately 50% of this overall population had been diagnosed with psoriasis. Data analysis by Love et al showed the prevalence of the metabolic syndrome among women with psoriasis was higher than among men; whereas prevalence of the metabolic syndrome among women in the control group was lower than among the male controls.[19] Love et al observed that among the individual components of the metabolic syndrome, abdominal obesity, which was present in 63% of psoriasis patients, was the most common abnormal metabolic feature. This was followed by hypertriglyceridemia (at 44%), decreased high density lipoprotein cholesterol levels (at 34%), and high blood pressure (at 28%). Love et al applied their analysis to the general U.S. population (using 2008 census data) and estimated that of the 6.6 million adults (age 20–59 years) with psoriasis, 2.7 million have the metabolic syndrome, which is nearly 1 million more than would be expected from individuals with psoriasis.[19] Love et al indicate that this prevalence estimate for psoriasis is consistent with previous reports.[19]

Gastrointestinal Disease

Nonalcoholic Fatty Liver Disease

The clinical spectrum of nonalcoholic fatty liver disease (NAFLD) extends from benign fatty liver disease to the more severe steatohepatitis, which may culminate in liver fibrosis, cirrhosis, and hepatocellular CA. It has been suggested that psoriasis, NAFLD, and the metabolic syndrome are strongly interrelated. In fact, NAFLD is increasingly recognized as the hepatic form of the metabolic syndrome, [20] a conceivable idea since NAFLD is believed to be derived from underlying obesity and insulin resistance (type 2 diabetes).

Gisondi et al showed psoriatics with NAFLD were at a higher risk for development of the metabolic syndrome and that these patients had higher levels of IL-6 and C reactive protein and higher levels of adiponectin compared with psoriatics without NAFLD. Several theories support a relationship between psoriasis and NAFLD. One theory suggests that proinflammatory cytokines help induce insulin resistance and psoriatics with the greatest resistance develop NAFLD. Another theory focuses on the role of visceral adiposity and its liberation of free fatty acids, hormones, and adipocytokines with resulting inflammation.[20]

Thus, it seems reasonable to monitor psoriatics for the onset of NAFLD. This argument is strongest for psoriatics with the metabolic syndrome, psoriatic arthritis, and elevated transaminase levels.[20] Initial monitoring may include labs, hepatic ultrasound, along with a thorough clinical examination. Liver biopsy may be indicated in the future.

Inflammatory Bowel Disease

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory bowel diseases (IBD). Bacterial, viral, and immunologic theories have all been postulated regarding their etiology. However, an overexuberant immune response to recognized microbial antigens leading to inflammation seems more probable. There is an increased prevalence of IBD in psoriasis patients. It is documented that patients with IBD develop psoriasis at a much higher rate than the general population. It is also said that the incidence of IBD in psoriasis is elevated seven fold versus the general population.[21] Their shared immunogenic pathway is reflective in the efficacy of the TNF-α blockers in the treatment of these diseases. Furthermore, genome-wide studies have shown that CD and psoriasis share genetic susceptibility loci localized to chromosome 6p21 locus housed in the MHC region. Other shared genes between psoriasis and IBD include the gene encoding the IL-23 receptor and IL-12B.21 A newer subset of T helper cells called Th17 cells release proinflammatory cytokines like Il-17, Il-21, and IFN-Y. Il-21 induces Il-23 production. In the lamina propria of Crohns patients as well as in the serum and skin of psoriatics, elevated levels of Il-17 and Il-23 are found.[22] According to Lee et al, psoriasis was much more common in CD patients and their first degree relatives compared to the control group.[23] The relationship between psoriasis and UC is not as strong, but still is statistically significant. Interestingly, cigarette smoking which is linked to psoriasis increases the risk of CD but decreases the risk of UC to 50% that of the general population.

Psychological Disease (Depression and Quality of Life)

The psychological burden of psoriasis can be significant and patients with more severe psoriasis appear to suffer a greater psychological burden. It is well documented that many psoriasis patients suffer depression or depressive symptoms.[24-27] Psoriasis causes significant physical and psychological morbidity. Results from a study assessing the psychiatric morbidity of psoriasis and vitiligo patients showed 53% of psoriasis patient had scores indicating the presence of psychiatric illnesses such as depression, anxiety, and sleep disturbances compared to 17% of vitiligo patients.[26]

It then follows that psoriasis patients with moderate to severe disease on health-related quality of life (QoL) measures often re-

port difficulties in performing their daily activities of living and the onset of depression. Also, joint disease in patients with psoriatic arthritis is associated with lower QoL scores.[28] Of note, patients with mild but persistent psoriatic disease may also report a significant negative impact from their disease on QoL measures.

Patients may suffer from physical, emotional, psychosocial, and psychosexual stressors, leading to higher prevalence of anxiety and depression. There is evidence suggesting that the increased levels of cytokines such as TNF-α and interleukin 1 (IL-1) in psoriasis may be linked to depression and chronic fatigue.[6,7,16,32] TNF-α blockade leads to improved affect and clinical improvement. In a phase 3 clinical trial involving etanercept, psoriatic skin disease as well as physical and emotional well-being was improved.[29] This improved mood may be caused by both TNF-α blocker therapy and obvious clinical improvement in skin disease. It has been shown that patients with psoriasis perceive their disease to negatively impact their QoL to a degree that is comparable with patients suffering from other chronic illnesses such as cancer, major depression, and arthritis.[28]

Therefore, reducing these stressors through active therapeutic disease control and implementing methods of stress reduction such as meditation can be extremely beneficial. It is also important to counsel patients frequently. As well their perception of their skin and joint disease and related comorbidities should be reviewed, documented, and addressed frequently.

Also, increased alcohol consumption has been documented in psoriatics with severe disease. It may be secondary to the negative impact of the disease on their QoL leading to depression and thus heavy alcohol use or it may be coincidental but the latter seems less likely.

Insulin Resistance/Type 2 Diabetes

There is overall support for the association between psoriasis and insulin resistance/type 2 diabetes. TNF-α is a major inflammatory mediator in the induction of insulin resistance. Hence, it has been determined that TNF-α blocking agents can improve insulin sensitivity by blocking TNF-α and other proinflammatory cytokines. In fact, infliximab was found to improve insulin sensitivity as early as two hours after infusion and this effect is apparently sustained up to one year.[31] Results from a cross-sectional study (n=110) indicate that psoriasis patients are significantly more likely to be insulin resistant and to have impaired glucose tolerance, higher fasting insulin levels, and impaired β-cell function.[16,31] Obesity may be a confounding factor in the association between diabetes and psoriasis. Obesity is one of the metabolic abnormalities that lead to the metabolic syndrome and type 2 diabetes.

Lymphoma

Psoriasis is associated with an increased risk of lymphoproliferative malignancies. It is hypothesized that the abnormal immunogenic response operational in psoriasis may lead to an elevated risk of lymphoma (i.e., increased T and B cell activity as well as circulating Th-1 cytokines). Regarding causation, systemic medications used in psoriasis treatment such as methotrexate, cyclosporine, and the biologics have also been implicated. However, large prospective observational studies are needed to establish statistically significant causality. The strongest association has been documented between cutaneous T cell lymphoma (CTCL) and psoriasis especially severe psoriatic disease followed by Hodgkins lymphoma (HL).[34] This elevated risk of CTCL is important to consider when contemplating the use of biologic therapy in severe psoriatics since the immunosuppressive properties of these agents can upregulate lymphoma development.[33] The association between psoriasis and non-Hodgkins lymphoma (NHL) has been inconsistent.[33]

Multiple studies to date aiming at defining the association between psoriasis and lymphoma have been limited on several fronts. Firstly, these studies have not had adequate power, have examined a skewed patient population (i.e., hospitalized psoriasis patents) have failed to evaluate the subtypes of lymphoma, and lacked a population based design. Gelfand et al minimized these biases by designing a population-based study with adequate study size and with a broad representation of patients. They examined the risk of psoriatics developing all lymphoma types (NHL, HL, and CTCL) and found that the overall risk of lymphoma was increased in all psoriatics including those with mild psoriasis and across all age groups. Interestingly, the risk of all lymphoma was found to be slightly higher in those with severe psoriasis, but the results were not statistically significant.[32] Furthermore, it should be noted that despite an increased relative risk of lymphoma in psoriatics, the absolute risk of lymphoma is low. This is due to the fact that lymphoma is a rare disease and the strength of the association is modest.[33]

CONCLUSION

Psoriasis is a chronic inflammatory disease of the skin inflammatory skin disease targeting 2% to 3% of the general population and was traditionally viewed as an inflammatory skin disorder of unknown origin. However, recent scientific advances have led to an awareness of the systemic manifestations that psoriasis shares with other chronic inflammatory diseases hence enabling psoriasis to be classified as an immune-mediated inflammatory disease. Other diseases in this category include systemic lupus erythematosus, rheumatoid arthritis, Crohn's disease, multiple sclerosis, etc. Similar to other diseases in its class, psoriasis shares the characteristics of inflammation, immunopathogenesis, and a role for TNF-α, etc. This article provides an overview of the comorbidities of psoriasis and guidance for clinical practice in terms of further management.

DISCLOSURES

Dr. Onumah has no relevant conflicts of interest to disclose. Dr. Kircik has served as consultant for Amgen, Inc. and speaker for Abbott Laboratories.

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Considerations When Initiating Psoriasis Patients on Biologic Therapy

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ABSTRACT

Several types of systemic therapies exist to treat psoriasis. These include traditional immunosuppressive agents such as cyclosporine and methotrexate. Oral retinoids such as acitretin may also be appropriate in some patients. The scope of this paper, however, will focus on the use of targeted immunologic therapies, know as biologic agents.

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INTRODUCTION

Psoriasis is a chronic inflammatory disorder that affects approximately 2% of adults in the United States, including patients of all ages, genders, races and ethnicities. Psoriasis is a systemic disease with variable presentation. About 30% of psoriasis patients develop psoriatic arthritis, and 1.5 million adults with psoriasis have moderate to severe disease.[1-3]

Psoriasis had once been thought to be a disease of only the skin and joints, we now know that systemic inflammation affects the cardiovascular, liver, respiratory and hematological systems. Psoriasis patients, especially those with severe disease, are at risk for coronary artery disease, diabetes, fatty liver, stroke, sleep apnea, and lymphoma.[4,5] In addition, psoriasis is associated with other autoimmune diseases such as inflammatory bowel disease.[5] Finally, besides these medical comorbidities, psoriasis has a negative impact on quality of life and is associated with depression.[6]

Disease severity is usually defined by extent of body surface area (BSA) involved. Mild disease is commonly defined as less than 3% BSA affected, moderate disease as 3–10% BSA, and severe psoriasis >10% BSA.[7] These definitions do not take into account the affect of disease on quality of life, which also plays a significant role in defining disease severity.[8] Mild and some cases of moderate psoriasis may be treated with topical therapies. More severe cases, however, often require systemic therapies such as biologic agents, which suppress the abnormal immunogenic process that causes psoriasis.

Systemic medications may be necessary to treat psoriasis patients under several different conditions. Severe disease may be impossible to manage with topical agents or phototherapy because of the extent of involvement. In other cases, patients may be unresponsive to topical therapies. A phototherapy regimen may be impossible to follow because of personal life circumstances. Finally, some patients' quality of life may be significantly affected to the point that the benefits of systemic therapy outweigh its potential risks.[8]

Several types of systemic therapies exist to treat psoriasis. These include traditional immunosuppressive agents such as cyclosporine and methotrexate. Oral retinoids such as acitretin may also be appropriate in some patients. The scope of this paper, however, will focus on the use of targeted immunologic therapies, know as biologic agents.

Biologic Agents

Biologic agents are laboratory engineered drugs therapies that have specific immune system targets. Biologic therapies currently available for psoriasis can be broadly divided into two categories: tumor necrosis factor (TNF) inhibitors and interleukin (IL)-12 and IL-23 inhibitors. Two T-cell inhibitors had previously been available, but have been withdrawn from the U.S. market. In November 2011, Astellas Pharma U.S. Inc. voluntarily discontinued the production and sale of Amevive® (alefacept), due to finances rather than health concerns.

TNF is a major pro-inflammatory cytokine implicated in the pathogenesis of many inflammatory disorders, including psoriasis. TNF antagonists currently available for the treatment of psoriasis include etanercept (Enbrel®, Amgen), adalimumab (Humira®, Abbott), and infliximab (Remicade®, Janssen). Golimumab (Simponi®, Janssen) is another TNF blocker approved to treat psoriatic arthritis. IL-12 and IL-23 are pro-inflammatory cytokines that promote Th1 and Th17 inflammatory pathway. Ustekinumab (Stelara®, Janssen) is a fully human IgG1 monoclonal antibody that binds to p40, a subunit of IL-12 and IL-23.

Adalimumab is a recombinant IgG1 monoclonal antibody that binds to TNF-alpha. It is FDA-approved for psoriasis, psoriatic arthritis, and rheumatoid arthritis. Adalimumab is administered as a subcutaneous injection, with a loading dose of 80-mg followed by 40-mg one week later. Thereafter, a 40-mg dose is administered every other week.[9] A dosing increase to 40-mg once weekly in patients with an inadequate response to every other week dosing has been shown to be effective.[10]

Etanercept is a fusion protein, combining a TNF-alpha receptor bound to the Fc portion of IgG. It is approved to treat moderate to severe plaque psoriasis and psoriatic arthritis. Besides psoriasis, etanercept is approved for ankylosing spondylitis, juvenile rheumatoid arthritis, and rheumatoid arthritis. Etanercept is a subcutaneous injection, dosed for plaque psoriasis as 50-mg once or twice weekly for three months, followed by a maintenance dose of 50 mg once weekly.[11] Injection sites should be rotated to minimize injection site reactions.

Infliximab is a monoclonal antibody against TNF approved to treat severe psoriasis, psoriatic arthritis, Crohn's disease, rheumatoid arthritis, and ankylosing spondylitis. The drug is an intravenous infusion, given at a weight based dose of 5 mg/kg. Infusions are given at weeks 0, 2, and 6, then every 8 weeks.[12] In patients who lose response, dosing may be increased up to 10 mg/kg and frequency of infusions can be reduced to every four weeks. Patients should be observed for one hour after infusion to monitor for infusion reactions and offices should be prepared with such reactions with emergency kits.[8]

Ustekinumab is a monoclonal antibody targeted against the p40 subunit common to both IL-12 and IL-23. The medication is given as a subcutaneous injection administered in the office. Dosing is weight-based. Patients weighing less than 100 kg (220 lb) receive a 45-mg dose and those over 100 kg receive a 90-mg dose. Patients receive injections at weeks 0, 4, and then every 12 weeks thereafter.[13] In patients with an inadequate response to that dosing regimen, doses as frequent as every 8 weeks has been shown to be effective.[14]

Considerations Prior to Initiating Biologic Therapy

Once biologic therapies have been initiated, most patients continue their use for long periods of time, so a baseline history, physical examination, and laboratory evaluation is important. While there is no specific guideline for therapy, most dermatologists obtain a complete blood cell count with platelets, a complete metabolic panel with liver function tests, and a hepatitis panel.

Reactivation of latent tuberculosis and susceptibility to new infection is a risk with the TNF and IL 12/23 blockers.[5,13,15] This risk has been shown to be higher in the monoclonal antibodies to TNF (e.g., adalimumab, infliximab) as compared to the soluble receptors (e.g., etanercept).[16] Tuberculosis testing [in the form of a purified protein derivative (PPD) or a QuantiFERON®-TB Gold test] should be performed before initiating therapy.[5,17] The National Psoriasis Foundation recommends a nine-month prophylactic course of isoniazid for carriers of latent tuberculosis. Patients should finish at least one month of isoniazid therapy prior to initiating biologic therapy.[18]

Biologic agents target the immune system and lower its ability to protect the body from infections. Treatment with biologics is contraindicated in patients who have active, serious infections. Moreover, if a patient on a biologic develops serious infections (defined as one requiring antibiotic therapy), it is recommended that the medication dose be held until the infection has resolved.[5] It is important to ensure that patients are properly vaccinated prior to initiation of biologic therapy, as the medications may impair immunologic response to vaccinations.[5] Studies evaluating patients on TNF blockers show an adequate, but attenuated response to pneumococcal and influenza vaccines.[19-21] The recommended vaccinations for psoriasis patients on biologics are similar to those for other immunosuppressed patients. They include pneumococcal, hepatitis A and B, influenza, and tetanus-diphtheria vaccines prior to initiation of therapy.[5,22] Patients on biologics should not be treated with live vaccines (e.g., varicella, mumps, measles, rubella) and live-attenuated vaccines (e.g., intranasal influenza and the herpes zoster).[5,23]

Patients with hepatitis must be carefully evaluated prior to considering biologic therapy. There is evidence that TNF may be involved in the pathogenesis of hepatitis C virus destruction of hepatocytes.[24] Small studies have suggested that anti-TNF therapy is safe in patients with hepatitis C.[25,26] However, TNF antagonists, such as etanercept, are still considered second line therapy in these patients.[5] Caution should be used in prescribing infliximab, as there are rare reports of drug-related hepatotoxicity.[12] There have also been reports of hepatitis B reactivation after TNF blockade, and this therapy should be avoided in patients with Hepatitis B infection.[5] Data on the use of ustekinumab in patients with hepatitis infections in lacking.

Special considerations should be taken into account before initiating biologic agents in women and children. All of the currently available biologics are pregnancy category B, and there is mini-

mal data on these agents during pregnancy. The biologics are all approved for psoriasis in patients at least 18 years old. One study has demonstrated safety and efficacy of etanercept in a pediatric population (ages 4-17 years old); however its use is off-label.[27] Infliximab and adalimumab have approvals in pediatrics populations for other conditions. Inflixmab is approved for pediatric patients with ulcerative colitis,[12] and adalimumab for juvenile rheumatoid arthritis.[9]

The immune system monitors the body not only for infection but also for neoplasia. Immune suppression with biologic agents, particularly TNF inhibitors, carries the risks of developing a malignancy. Patients with psoriasis have an increased risk for developing lymphoma at baseline.[28,29] While lymphoma rates in anti-TNF treated psoriasis patients are not elevated above those of rheumatoid arthritis patients on similar medications, there are anecdotal reports of lymphomas developing in these psoriasis patients.[30] Expert guidelines recommend extreme caution in prescribing TNF-blockers to patients with a history of lymphoproliferative disorders.[5] Little data exist on the relationship between ustekinumab and lymphoma; however four years of cumulative exposure to the drug did not increase malignancy risk as seen in the setting of severe immunosuppression.[31]

TNF inhibitors are contraindicated in patients with demyelinating disorders and congestive heart failure (CHF). Demyelinating diseases such as multiple sclerosis (MS) have been unmasked by TNF blockade. Patients with a personal history or a first-degree relative with MS should not be treated with TNF inhibitors.[5] In addition, caution should be exercised in treating patients with CHF, as there have been reports of new onset and worsening of CHF in patients on TNF blockers. Patients with CHF should be evaluated by a cardiologist. If the patient's ejection fraction is lower than 50%, then TNF inhibitors should be avoided if possible.[15]

While CHF exacerbation has not surfaced as an adverse event associated with anti-IL12/23 drugs, major adverse cardiovascular events (MACE) are potential concerns. MACE are defined as cardiovascular death, myocardial infarction, or stroke. Seven MACE were reported in phase 3 clinical trials for briakinumab.[32] Subsequently, Abbott Laboratories withdrew the drug's FDA application in January 2011. However, four years of follow-up data in patients in ustekinumab have demonstrated rates of myocardial infarction and stroke to be low, remain stable over time, and be comparable to rates reported with traditional immunosuppressive medications and other biologics.[31]

CONCLUSION

The development of biologic agents has revolutionized the treatment of psoriasis. These drugs can be divided into two major classes, TNF inhibitors and IL-12/23 inhibitors. They have excellent efficacy and safety profiles; however, selection of appropriate candidates for these medications is extremely important. Caution should be used in prescribing biologics to pregnant women, children, patients with infections such as hepatitis, patients with demyelinating diseases or CHF, and those with a history of lymphoproliferative disorders.

DISCLOSURES

Dr. Zeichner is an investigator for CORIA and Medicis and an Advisory Board Member for Coria, Galderma, and Ortho Dermatologics.

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A Prospective Open-Label Clinical Trial of Efficacy of the Every Week Administration of Adalimumab in the Treatment of Hidradenitis Suppurativa

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ABSTRACT

Background: Hidradenitis suppurativa (HS) is a debilitating disease refractory to treatment. As its impact on patients' quality of life is strong, it requires effective treatment.

Objectives: To evaluate the efficacy and safety of adalimumab using a higher dosage regimen for HS treatment and establish the recurrence-free interval after treatment discontinuation.

Material and Methods: Patients with moderate to severe HS were treated with 80 mg adalimumab at baseline, followed by 40 mg every week for 24 weeks. Subsequently, patients entered an observational period for another 24 weeks. Clinical evaluation took place every 4 weeks during the study period. Sartorius scoring system was used as assessment tool regarding disease activity. At the same time points patients evaluated disease activity by Visual Analogue Scale (VAS). They completed a Dermatology Life Quality Index (DLQI) questionnaire at baseline and at weeks 24 and 48.

Results: Fifteen patients completed the study. Significant reduction in Sartorius score was obtained by week 24 with a marked improvement during the first month. Mean time to relapse was 11 weeks after treatment cessation, but even at the final visit Sartorius score was significantly lower than at baseline. VAS score and DLQI showed a significant decrease at week 24. There was significant worsening at week 48, however both scores remained significantly lower than baseline levels.

Conclusions: Our study data demonstrate the significant efficacy of the once weekly regimen, as well as its benefit regarding time to recurrence. However, the question if benefit outweighs the risk of a long-term anti-TNF-α antagonist's administration needs still to be answered.

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INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic recurrent inflammatory disease of the apocrine gland-bearing areas of the skin, presenting with painful subcutaneous nodules, abscesses, sinus tracts, and scarring.[1]

Taking into account that HS is not uncommon, affecting about 1% of the general population,[2] and since it has a profound impact on patients' quality of life, effective treatment is mandatory.[3] Common therapeutic approaches, such as antibiotics,[4,5] retinoids,[6] dapsone,[7] hormones,[1] and immunosuppressives[8] are unsatisfactory, as they do not accomplish complete remission, or lead to relapse after discontinuation.

Trying to develop the optimal therapeutic strategy for this debilitating disease, understanding pathogenesis plays a key role. Recent data provide a rationale for treatment with biologic agents targeting TNF-α.[9,10]

Recent studies proved that TNF-α, a proinflammatory cytokine, which activates and recruits inflammatory cells, is significantly elevated in HS skin and serum of these patients. Thus, the hypothesis of a possible role of TNF-α in the pathogenesis of HS is reasonable, justifying the use of anti-TNF-α agents.[9,10]

Several clinical studies and case reports demonstrate a favorable outcome using the anti-TNF-α agents infliximab,[11-15] etanercept,[16-20] and adalimumab[21-32] for HS treatment. However, maintenance of the curative effect after discontinuation of treatment still remains an issue.[13,17,19,20,28,30]

TABLE 1.

Patients' Characteristics and Demographics at Baseline	
Sex, n (%)	
Male	5 (33.3%)
Female	10 (66.6%)
Age(y), mean±SD (range)	36.27±5 (28-45)
BMI (kg m-2), mean±SD (range)	33.3±3.96 (25.95-38.94)
Disease duration (y), mean±SD (range)	5.13±2.13 (2-9)
Smokers, n (%)	9 (60%)

BMI=Body Mass Index, y=years

Considering the role of TNF-α in the pathogenesis of HS, and based on promising, but not ideal results of former studies, we decided to conduct a prospective open-label clinical study evaluating the efficacy, safety and tolerability of adalimumab, using a higher than the usual dosage regimen for the treatment of recalcitrant HS. We chose adalimumab because of its home- and self-administration convenience. Our aim was to optimize efficacy and define recurrence-free interval after discontinuation of therapy.

MATERIALS & METHODS

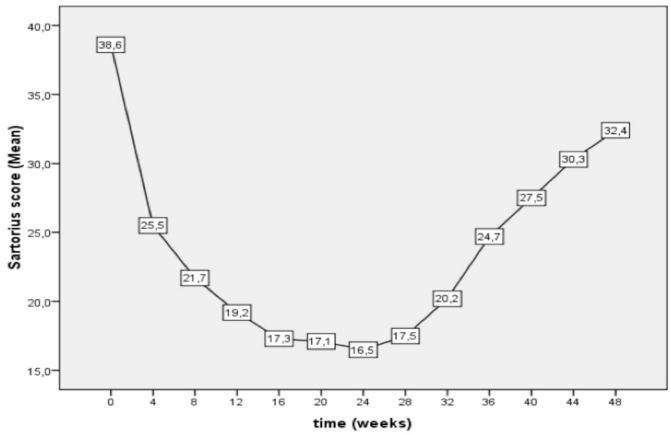
Patients

Men or women older than 18 years of age with a clinical diagnosis of moderate to severe HS were enrolled in this prospective open-label study. The study was held in our department between September 2010 and November 2011. All patients provided written consent to participate, after receiving detailed information on the purpose and design of the study. The latter was approved by the local ethics committee and was conducted in accordance with the latest revision of the Declaration of Helsinki. Eligibility requirements for enrolment included: clinical diagnosis of moderate to severe HS defined as Hurley stage II or III,[33] disease duration above two years and failure of at least three systemic treatments (oral antibiotics, retinoids, cyclosporine or antiandrogens). Wash-out period was a minimum of four weeks prior to baseline assessment. Exclusion criteria were treatment with biologics within the previous six months, chronic or recurrent infections, latent or active tuberculosis, demyelinating disease, congestive heart failure, poorly controlled medical conditions, history of malignancy, and pregnant or lactating women.

Study Design and Protocol

The trial included a six months treatment period followed by a six months follow-up period. All eligible patients received 80 mg of adalimumab subcutaneously (s.c.) at baseline (week 0), followed by weekly dosages of 40 mg, for the next six months.

FIGURE 1. Mean Sartorius score over treatment and follow-up period, as evaluated by the examiners.



After the six-month treatment phase, and during the observational period, no systemic treatment was administered. Topical antibiotics were applied, if necessary.

Patients were assessed at screening, baseline (week 0) and weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48. At each visit, all patients had a thorough clinical examination, while disease severity was evaluated by the physicians using the Sartorius score.[34]

Patients were asked to complete a Dermatology Life Quality Index (DLQI) questionnaire at baseline and at weeks 24 and 48. A numeric (0=no disease activity, 10=very severe disease activity) visual analogue scale (VAS) was used to evaluate the subjective degree of disease activity, as perceived by the patient at baseline and weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48.

Efficacy and Safety Evaluation

Primary efficacy endpoints included: a) changes in Sartorius score from baseline to the end of treatment phase (week 24) and to the end of the follow-up period (week 48) as well as from week 24 to week 48 and b) the recurrence –free interval after treatment discontinuation. Recurrence was defined as 50% increase of Sartorius score achieved at week 24.

Secondary efficacy endpoints were a) alterations in disease activity as perceived by the patients (VAS score) and b) in DLQI between baseline and weeks 24 and 48 but also between weeks 24 and 48.

Safety assessment was based on monitoring all adverse events, e.g., clinical and laboratory abnormalities, occurring during the treatment and follow-up period.

Statistical Analysis

Differences of objective (Sartorius score) and subjective (VAS) disease activity and DLQI between different time points were

FIGURE 2. Mean disease activity score (Visual Analog Scale, VAS) as evaluated by the patients over treatment and follow-up period.

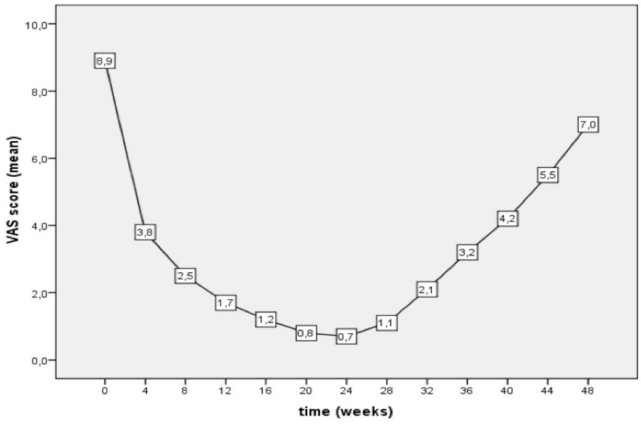
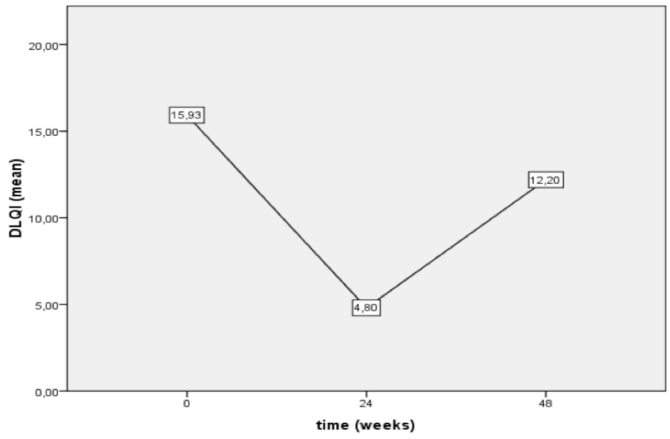


FIGURE 3. Changes in Dermatology Life Quality Index (DLQI)



evaluated by Wilcoxon Signed Ranks Test. The significance level was $P<0.05$. Data are expressed as mean (SD).

RESULTS

Among 20 patients initially screened, 15 patients—10 female and 5 male—were eligible for enrollment in the study. All of them completed both treatment and observational phase. Their ages ranged from 28 to 45 years (mean±SD 36.27±5). Disease duration ranged from two to nine years (mean±SD 5.13±2.13). Nine patients were active smokers. None of them gave up their habit during the trial, although they were strongly advised to do so. All of our patients had BMI>25 and despite the fact that they were referred to a specialist they did not manage to decrease to a lower BMI category. Baseline patients' characteristics and demographics are summarized in Table 1.

Primary Efficacy Endpoints

Mean Sartorius score declined rapidly from 38.6 at baseline to 25.5 at week 4 and then gradually reached 16.5, until the end of the treatment period (week 24). Changes in Sartorius score from baseline to week 24 were statistically significant (P=0.001, Z=-3.411). During follow-up period, mean Sartorius score progressively increased up to 32.4 at the final post-treatment visit (week 48). This change was statistically significant (P=0.01, Z=-3.297). Furthermore, there was a significant reduction (P=0.002, Z=-3.066) between baseline and final Sartorius score.

Changes in mean Sartorius score, as assessed by the physicians at each visit, are summarized in Figure 1.

Recurrence ranged from 32 to 38 weeks (mean±SD 35±1.65), which indicates that mean time interval to recurrence was 11 weeks after treatment discontinuation.

Secondary Efficacy Endpoints

Mean VAS score diminished rapidly from 8.9 at baseline to 3.8 at week 4 and further to 0.7 at the end of the treatment period. A statistically significant change was recorded between baseline and week 24 (P=0.001, Z=-3.458). During the follow-up visits VAS increased up to a final score of 7 at week 48, showing significant change from week 24 (P=0.01, Z=-3.426). Comparing baseline to week 48, a significant decrease in VAS score was observed (P=0.008, Z=-2.663). Alterations in VAS, corresponding to disease activity as evaluated by the patients at each visit during treatment and observational phase of the study, are demonstrated in Figure 2.

Mean DLQI declined significantly from 15.9 at baseline to 4.8 at week 24 (P=0.001, Z=-3.415). At the end of the follow-up period (week 48) mean DLQI increased to 12.2 showing a significant change compared to week 24 (P=0.001, Z=-3.423). Comparison between baseline and final DLQI, revealed a significant reduction (P=0.005, Z=-2.817).

Modifications in DLQI over treatment and follow-up phase are shown in Figure 3.

Adverse Events

Treatment was well tolerated by all patients. No serious adverse events were observed. Four patients reported self-limited erythema at the injection site. One patient complained of fatigue that lasted only during the first four weeks of treatment.

DISCUSSION

In the current clinical study we administered adalimumab for 24 weeks in an every-week scheme, followed by an equal observational period. Fifteen patients with moderate to severe HS were enrolled and all of them completed the study.

We decided to document clinical efficacy using "Sartorius score," which is a validated tool for assessing disease severity in HS patients with a low inter-observer variability.[34,35] A striking decline

of mean Sartorius score was observed by week 4, followed by a further significant decrease during the second month, achieving a 50% reduction at week 12. Only minimal further improvement was observed from this point until treatment discontinuation with mean Sartorious score declining approximately three more units.

After treatment cessation, mean time to recurrence was 11 weeks. However, even at the final follow-up visit at week 48, Sartorius score did not reach initial levels, retaining significant reduction from baseline.

Both primary efficacy endpoints reached statistical significance. These results clearly demonstrate the significant efficacy of the once weekly regimen, as well as its benefit regarding time to recurrence.

Secondary efficacy endpoints, including quality of life and disease activity as perceived by the patients reached also statistical significance. It is worth mentioning that difference remained significant between baseline and week 48, although both DLQI and VAS score increased after treatment discontinuation. These results are consistent with previous findings.[30,31]

Adalimumab was, in general, well-tolerated. Neither infections, nor any serious adverse events were observed during study period, which is in accordance with all previous studies.

Since smoking and obesity are considered to be important risk factors for HS,[36] it is not surprising that the majority of our patients were active smokers and that all of them had BMI>25.

Differences in treatment protocols and objective severity score systems do not allow direct comparison between the already available studies.

The once weekly treatment scheme was used as initiate treatment only by Harde et al[23] in a case of severe, longstanding HS. The patient achieved good reduction in inflammatory activity within six weeks, and the result was maintained during the six months of administration.

The effect of the every other week administration following an induction dose of 80 mg at week 0 and a dose of 40 mg at week 1 is reported in one RCT,[30] in a few case series,[25,27-29] and some case reports.[22,24,26] Despite variabilities in the reported clinical outcomes, investigators converge to the need for optimization of the treatment protocol.

Miller et al[30] conducted a randomized placebo-controlled trial, where 15 patients received adalimumab every other week. Significant reduction in HS severity, using Sartorius and Hurley scoring system, was observed after six weeks in the actively treated group. This reduction was inferior than the one achieved at week 4 in our study. Moreover, after 12 weeks of active treatment, Sartorius score did not reach 50% reduction as in our study. Treatment cessation in the active group resulted in HS relapse, exceeding the baseline disease severity within the next 12 weeks. The latter is not in line with our observations, since we recorded only a 50% increase in Sartorius score, 11 weeks after treatment discontinuation. By the end of our study, Sartorius score remained significantly lower compared to the baseline. This discrepancy might be related to the higher disease severity at baseline in Miller's active group.

Based on their results investigators speculated that the dosage may have been suboptimal and that either a reduced interval between injections or a higher dose may be necessary.

There is a rather remarkable diversity concerning the results of the previously published case series and case reports.

The every other week dosage regimen used by Scheinfeld et al[24] for the treatment of a patient with seronegative arthritis and HS was increased to 40 mg weekly after three months, because of worsening of HS, with good results. Treatment and follow-up duration are not mentioned.

In a case series of Blanco et al. the initial treatment regimen was 40 mg every other week.[27] Based on the patients' response, treatment intervals were either reduced to once weekly, or increased to once every three weeks. According to the study results, significant improvement was observed one month after treatment in the number of affected regions, nodules and fistulas. The lack, however, of the use of a comprehensive system that assesses disease severity as well as the lack of definition of remission and relapse pose difficulties to compare the results of this study with those of other trials.

Previous data of a small clinical study conducted in our department demonstrated marked improvement in all evaluated parameters with Sartorius score reaching a greater than 50% reduction at two months. Moreover, although all three patients relapsed three months after treatment discontinuation Sartorius score did not increase more than 50% compared to that achieved at the time drug administration was discontinued.[28] This favorable outcome could be explained by the small number of patients included as well as by milder disease severity, as shown by mean Sartorius score, at baseline.

Arenbergerova et al reported eight patients, who were treated for one year with the every-other-week dosage regimen and were followed-up for another year. According to the study, all patients improved within 4–6 weeks and achieved further significant improvement at 4–6 months. Mean time to recurrence

was 9.5 months with disease severity being significant lower at recurrence than at baseline.[29] The favorable outcome in this study could be due to the longer treatment period but again the variety of methods assessing disease severity and clinical outcome makes it difficult and in some cases impossible to compare treatment efficacy between trials.

In a very recent trial[15] comparing efficacy of infliximab and adalimumab, nine patients received adalimumab every other week for a year. Significant reduction of Sartorius score was achieved at the end of the treatment period, however the majority of patients showed recurrence during treatment phase. Moreover, at the 1-year follow-up mean score of treatment efficacy as rated by the patients on a 10-point scale was high—5.1—and reflected the moderate treatment outcome. On the contrary, in our study the score of disease severity as perceived by the patients, also on a 10-point scale, diminished rapidly and showed very important reduction at the end of the treatment period. The authors concluded that higher induction and maintenance doses are needed to achieve better response.

As it is speculated that pathogenetic mechanisms leading to HS may be related to those of Crohn's disease[37] there are trials reporting the efficacy of the induction regimen used in Crohn's disease.[31-32]

In a study conducted by Amano et al[31] the dose employed was 160 mg at week 0, 80 mg at week 1 and 40 mg every other week for a 12-week period. Efficacy was evaluated using the Hidradenitis Suppurativa Severity Index (HSSI). Out of the 10 enrolled patients, four withdrew because of lack of efficacy and disease worsening. None of the remaining patients achieved ≥50% decrease of the score at the end of the treatment period and could thus not be classified as responders. Moreover, improvement based on the Physician's Global Assessment scale was proved to be moderate as only slight improvement was observed only in three of the six patients. According to the authors, higher doses, particularly after the induction phase, are required.

An ongoing double-blind, placebo controlled study comparing different induction and maintenance doses could demonstrate in the near future the most efficacious treatment regimen of adalimumab in the management of HS.[32]

In conclusion, we believe that our data strongly suggest that every week administration of adalimumab remarkably enhances efficacy and outcome maintenance. The rapid and significant improvement within the first treatment weeks indicates that an induction dosage of 80 mg is efficacious. No further improvement after four months of treatment might indicate a suppressive rather than an eradicating effect of adalimumab in HS. Approaching the disease with combined treatment modalities might lead to better results.

Given the chronic and refractory nature of HS, prolonged therapeutic modalities are usually required. Under this scenario, the long-term side effects and the treatment cost of biologics should be considered. The question if benefit outweighs the risk of a long-term anti-TNF-α antagonist's administration needs still to be answered. In this context, more studies with longer treatment and follow-up periods are warranted.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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