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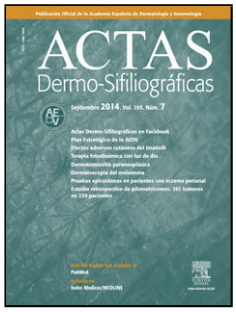

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Sección. Opinion articles

A Decade of Biologic Therapy for Hidradenitis Suppurativa: What Have We Achieved?

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Hidradenitis suppurativa (HS) is an immune-mediated dermatosis that affects 1%–2% of the population in our setting, causing a considerable health care, physical, and psychosocial burden.[1] Although genetic causes can be identified in about one-third of patients, there are pathogenic factors related to lifestyle (primarily overweight, sedentary behavior, and smoking) that may act as triggers or aggravating factors in virtually all cases. The pathophysiology of HS is marked by uncontrolled activation of multiple components of the immune system, including both innate and adaptive immunity, and the participation of various cellular lineages such as neutrophils, macrophages, Th1 and Th17 lymphocytes, and B lymphocytes, among others. In July 2015, the European Medicines Agency approved the first treatment for this disease: the monoclonal antibody against tumor necrosis factor (TNF), adalimumab. After 10 years of using the first immunomodulatory treatment for HS, this seems an opportune moment to reflect on what this new therapeutic approach has meant for clinical practice, as well as to consider what the future may hold.

Although HS is a well-known disease among dermatologists, management has traditionally been unevenly shared with general surgeons, plastic surgeons, primary care physicians, and other health care professionals. Our therapeutic arsenal was very limited prior to the approval of the first biologic treatment, and included antibiotics, retinoids, and dapsone as medical therapies, as well as excision of individual lesions or whole anatomic areas involved. Diagnostic delay is unfortunately the norm, given the limited awareness of the disease among both the general population and the medical community.

In the late 1990s, the emergence of biologic therapies in dermatology had a major impact on immune-mediated dermatoses, and even before 2015 they had been used "off-label" in HS with relative success. The approval of adalimumab following the PIONEER clinical trials[2] marked a milestone that generated considerable hope: the possibility of medical management of this disease with minimal adverse effects, and even the potential to avoid mutilating surgical procedures. More recently, 2 interleukin-17 (IL-17) antagonists—secukinumab and bimekizumab—have been approved for the treatment of HS. Dermatologists naturally recalled the achievements seen with other dermatoses such as psoriasis and chronic urticaria, as well as the progression of diseases with shared pathogenesis, such as inflammatory bowel disease. Several studies have shown that biologic therapy has reduced the need for surgery in Crohn's disease, although the same impact in ulcerative colitis remains uncertain.[3]

Since 2015, the concept of a "therapeutic window of opportunity" in HS has gained momentum—the idea that immunomodulatory treatment should be initiated as early as possible when certain markers of disease progression appear ("top-down" approach) to prevent permanent structural damage and the emergence of advanced lesions that respond

poorly to therapy. However, it is important to recognize that the available evidence is derived mainly from observational and retrospective clinical trials,[4] which carry inherent methodological limitations. Furthermore, the variability in individual responses and the lack of consensus on how to define and measure this "window of opportunity" highlight the need for prospective and randomized clinical trials to confirm these findings and establish stronger clinical practice guidelines. In medicine, the "top-down" approach means starting with more aggressive or advanced therapies from the outset, rather than the traditional "step-up" approach that begins with milder treatments and escalates based on response. The pharmaceutical industry has a commercial interest in positioning its products as first-line therapies. Through funded studies, conferences, continuing medical education, and marketing, the perception is promoted that these drugs offer superior early efficacy and structural-damage prevention. It is unsurprising that much of the key evidence supporting early "top-down" therapy comes from industry-sponsored trials. Notably, no randomized controlled trials have compared biologics with surgery or with rigorous control of well-established aggravating factors such as obesity or smoking. The potential benefits of the "top-down" approach must be weighed against costs, possible side effects, and the lack of robust data identifying patient subgroups who might benefit from a more conservative strategy—or simply from surgical management of lesions, which can be curative when the disease affects only a limited number of anatomic areas.

Indeed, excision of affected areas—especially tunnels and scarring—has been the foundation of traditional treatment, supported by antibiotics. It is doubtful that immunomodulatory therapy can effectively target these types of lesions, because they involve permanent architectural disruption, unlike dermatoses with fully reversible lesions such as psoriasis or urticaria. Fistulas or tunnels, with epithelium lining their interior and often colonized by biofilms, act as persistent sources of inflammation. Current therapies may improve drainage, inflammation, and pain, but ultrasound studies[5] have demonstrated that tunnels persist and may flare again if medical treatment fails or is discontinued.

What is, in fact, the efficacy demonstrated by current treatments in the pivotal clinical trials? Adalimumab achieved the primary endpoint, HiSCR (Hidradenitis Suppurativa Clinical Response)—defined as ≥ 50% reduction in the total number of abscesses and inflammatory nodules with no increase in abscesses or draining tunnels vs baseline—at week 12 in 41.8% of patients on adalimumab vs 26.0% on placebo in the PIONEER I trial, and 58.9% with adalimumab vs 27.6% with placebo in PIONEER II. The NNT (number needed to treat) ranged from 6 to 8, depending on the trial. In the 2 pivotal secukinumab trials, HiSCR at week 16 was achieved in the SUNSHINE trial by 45% of patients on secukinumab vs 34% of those on placebo, and in the SUNRISE trial by 42% of patients on secukinumab vs 31% of those on placebo (NNT 8–10).[6] In the BE-HEARD pivotal trial, bimekizumab achieved 48–52% response at week 16 vs 29–31% with placebo[7] (NNT 6–7). These figures are nowhere near those achieved with biologic therapy in psoriasis, atopic dermatitis, or urticaria. In psoriasis, the NNT of the latest anti–IL-23 biologics ranges from 1 to 2 for an endpoint as ambitious as PASI 90. Although some of these clinical trials allowed concomitant treatments such as antibiotics, intralesional corticosteroids, or minor surgical procedures—thereby more closely reproducing real practice in HS—none has been able to replicate the combined medical–surgical management that HS truly requires. It is true that the purpose of clinical trials is to obtain regulatory approval, which requires testing the drug in isolation, without

additional adjuvant therapies, and with homogeneous trial groups. While we cannot deny the usefulness of these drugs, nor of those that will be approved in the future, the very figures presented—so modest in terms of achieving therapeutic success—point toward an ideal pathway: a combination of medical and surgical therapy, flare management with antibiotics or other short-duration treatments, and control of well-known proinflammatory factors such as overweight, sedentary behavior, and smoking.

Furthermore, randomized controlled trials do not account for the heterogeneity of HS and its phenotypes. These should be incorporated into post hoc analyses to define the most appropriate treatment for each patient profile. Response to medical therapy differs when dynamic lesions (abscesses and nodules) predominate vs static lesions (tunnels and scarring). It would also be desirable to better understand treatment response according to additional severity factors, particularly overweight.

As a final reflection on currently approved and reimbursed treatments, it should be noted that none of the anti–IL-17 agents appear to offer major advantages over the anti-TNF agent adalimumab. In a recent network meta-analysis published in JEADV,[8] neither secukinumab nor bimekizumab surpassed adalimumab in therapeutic endpoints or adverse event rates. Network meta-analyses must be interpreted with caution, as they can never replace a true "head-to-head" trial. The need for such studies is clear to better guide clinical practice and accurately determine the cost-effectiveness of these treatments. Moreover, there is concern about paradoxical reactions associated with both adalimumab and anti–IL-17 agents—including psoriasis, dermatitis, and alopecia—and the optimal therapeutic approach to these reactions remains undefined, even though they may require discontinuation of treatment. Moreover, the drug survival of biologic therapies in HS is limited, particularly for adalimumab.[9] It is reasonable to initiate treatment even in very young patients when there is clear progression toward severity, but it is concerning that the therapeutic arsenal may be depleted quickly, given that treatment is envisioned as indefinite for most patients.

The development of new therapies for HS brings considerable hope. Phase II and III clinilcal trials are underway for monoclonal antibodies such as sonelokimab (anti–IL-17 A and F), lutikizumab (anti–IL-1), izokibep (anti–IL-17A), and small molecules such as remibrutinib (anti-BTK), upadacitinib, and povorcitinib (anti-JAK). Moreover, clinical trials are being conducted for mild and moderate HS using topical JAK inhibitors such as ruxolitinib. Time will tell whether the efficacy profile of these drugs will allow their approval and incorporation into our therapeutic arsenal. Of note, monoclonals such as spesolimab (anti–IL-36) and risankizumab (anti–IL-23) were withdrawn from development due to insufficient efficacy in clinical trials. These failures highlight the complexity of HS pathophysiology and the need to identify more effective therapeutic targets. Because HS involves activation of numerous pathways in both innate and adaptive immunity, effective treatments may need to target multiple pathways simultaneously—a strategy that almost certainly increases the risk of adverse events. The expected introduction of small molecules such as JAK inhibitors will force us to address this issue more directly, as biologic therapies—supported by decades of experience in HS, psoriasis, and arthritis—have thus far shown a comparatively favorable safety profile. Another possibility is the combination of biologics with small molecules, but safety would need to be established through robust evidence.

The future of HS management is therefore oriented toward cautious optimism with the development of new pharmacologic therapies. At the same time, it highlights the need not to overlook surgical treatment and even to improve existing surgical techniques. Although many hospitals in Spain now have dedicated HS clinics, not all dermatologists who oversee these units possess the surgical expertise required to perform HS surgery, nor have they established the necessary collaborations with other surgical specialties—such as general surgery, colorectal surgery, plastic surgery, gynecology, or urology—which are equipped to manage complex lesions or those located in anatomical areas where dermatologic surgeons may lack sufficient operative capability to offer an optimal outcome. Furthermore, in public health systems, dermatology departments often prioritize oncologic surgery in their operative schedules, to the detriment of conditions such as HS, which is less urgent and not typically included on surgical waiting lists. To effectively undertake the surgical management of HS, it is preferable for the same dermatologist to oversee timing and scheduling, prepare the patient with appropriate medical therapy, and determine the most suitable moment for surgery. Ideally, any referral center should have an agile and motivated medical–surgical committee[10] capable of evaluating patients comprehensively and committing to identifying the most appropriate therapeutic approach at each stage.

In conclusion, we must not overlook the profound change brought by having approved treatments for HS, even though their efficacy remains limited. Although the concept of a "window of opportunity" is appealing, it requires reliable markers of disease progression and drugs that—through prospective clinical trials—demonstrate an ability to halt that progression. In the meantime, prospective national registries, such as the one promoted by the Spanish HS Working Group,[11] can generate robust long-term data on disease progression. These registries will ultimately be far more valuable than retrospective "real-world" studies of lower methodological quality. Of note, the importance of surgical management, which remains indispensable, as well as the need to address comorbidities—many of which act as triggers and aggravating factors in HS.

We can certainly congratulate ourselves on the progress made over the past 10 years regarding disease visibility and the increasing presence of dedicated HS clinics in most dermatology departments. Although interest in HS among dermatologists has grown, this expansion has not been uniform across the other specialties involved. There is still room to improve access to specialized clinics, ensure that primary care physicians can recognize HS and refer patients promptly, and reduce the persistent diagnostic delay.[12] We should aspire to a scenario—perhaps achievable in the medium term—in which we can control the disease through a combination of medical and surgical treatment that prevents progression, sequelae, and the profound psychosocial impact of HS.

CONFLICTS OF INTEREST

The author declares the following conflicts of interest: lectures, advisory roles, and clinical trials for Novartis, UCB Pharma, Moonlake, Boehringer, AbbVie, and Almirall.

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