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COMMENTARY

Living with Psoriasis Vulgaris and Multi-Treatment Failure: A Patient and Dermatologist Perspective

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ABSTRACT

Psoriasis vulgaris is a systemic, chronic inflammatory disease affecting 2–3% of the population. Recent advances in the understanding of the pathophysiology of psoriatic disease have facilitated the development of novel therapeutic options with improved safety and efficacy. This article is coauthored by a patient with a lifelong history of psoriasis who experienced multiple treatment failures. He details his diagnosis and treatment experiences, as well as the physical, mental, and social ramifications of his skin condition. He then goes on to elaborate how evolutions in the treatment of psoriatic disease have impacted his life. This case is then discussed from the perspective of a dermatologist specializing in inflammatory skin disorders. We highlight the clinical features of psoriasis, its medical and psychosocial comorbidities, and the current landscape of psoriatic disease treatments.

Keywords: Biologics; IL-17 inhibitors; IL-23 inhibitors; JAK inhibitors; Phototherapy; Psoriasis; Topical corticosteroids; TNF-alpha inhibitors

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Key Summary Points
Psoriasis vulgaris is a chronic inflammatory disease associated with medical and psychosocial comorbidities.
Reductions in psoriatic disease activity are associated with improvements in the symptoms of comorbid psychosocial disorders, including anxiety and depression.
There are numerous treatments available for the treatment of psoriasis, including topicals, phototherapy, oral systemic agents, and biologics.
Many patients living with psoriasis experience multi-treatment failure, which negatively impacts their health and quality of life.
With an improved understanding of the pathophysiology of psoriatic disease, translational immunology has facilitated the development of highly safe and effective treatments.

COMMENTARY

Patient's Perspective

I cannot remember a time when I did not have psoriasis. When I was eight years old, my skin broke out with rashes. My parents, immigrants from China, figured the rashes would go away on their own. Unfortunately, they did not. Soon after, a strep throat infection triggered a flare of guttate psoriasis, which spread over my entire body. My family doctor suggested I see a dermatologist at the University of California, San Francisco (UCSF). The dermatologist examined me in front of a large group of medical students and residents, which terrified me. He confirmed my psoriasis diagnosis and expressed his sympathy to my parents. I have had a dermatologist treating me ever since.

School became especially difficult. I lacked energy and felt too overwhelmed to focus on school or homework. Psoriasis took away part of my evenings. My dad helped me with tar bath treatments and applying coal tar solution in Aquaphor afterwards. I often did not sleep well, never quite feeling comfortable with the slimy and smelly tar ointment on my skin overnight. In the fourth grade, my dermatologist added ultraviolet light B (UVB) to my treatment regimen. Since we had to drive 45 min to Oakland Kaiser Permanente three mornings a week, I arrived at school late on treatment days. My well-meaning teacher told the class why I would be late. The students used the information to tease and bully me relentlessly. I became withdrawn and anxious. My self-esteem took a nosedive as did my grades.

By middle and high school, I decided to pour my energy into academics and sports. I became a straight-A student and two-sport varsity athlete. I drew some solace from those activities, but my struggles with psoriasis persisted. Upon graduating high school, my parents sent me to the Psoriasis Research Institute in Palo Alto, CA for anthralin paste and UVB treatments. I lived by myself at a family friend's house during those treatment weeks. Monday through Friday, I endured the burning anthralin paste on my skin for hours. While I appreciated meeting others with psoriasis for the first time, I resented spending a summer there while my peers traveled or took summer jobs. To make matters even worse, my psoriasis did not respond quickly to the anthralin treatments. One morning, my nurse took her frustration out on me, firmly and painfully applying the anthralin paste with a wooden tongue depressor. Her actions angered me, while at the same time I felt like a failure. After 6 weeks, my psoriasis improved enough to where I could return home before attending University of California, Davis (UCD).

Those college years marked a significant turn in both my outlook on life and my psoriasis severity and treatment regimen. Through the encouragement of a friend in my dorm, I started going to a Christian group on campus. My faith grew, which helped me emotionally cope with my psoriasis. However, my psoriasis worsened. I started my first systemic psoriasis treatment,

methotrexate, in my second year at UCD. I also applied topical steroids and used my home UVB unit built from assembly instructions provided by UCSF. Later, I tried psoralen plus ultraviolet A (PUVA) at Sacramento Kaiser Permanente, although I stopped due to side effects from the psoralen. After graduating from UCD, I began working at an environmental engineering firm in the Bay Area, where I stayed for a couple of years before enrolling in graduate school to prepare for Christian work. I had dreams to apply for PhD studies but could not see the path forward due to the constant discomfort I experienced with my psoriasis. When methotrexate stopped working, my dermatologist started me on etretinate (then later switched to the new formulation, soriatane).

My lowest point with psoriasis came in 2005. During that flare I was a young minister with three children, ages ten, six, and four. Soriatane had stopped working, and my first experiences using the biologics Amevive and Enbrel proved ineffective. Over the next few months, I tried CellCept, hydroxyurea, and even went back to methotrexate, injecting into my hip to avoid the digestive side effects. My psoriasis did not respond to any of those treatments, leaving me despondent and depressed. Out of ideas, my dermatologist at Kaiser referred me to the UCSF Psoriasis and Skin Treatment Center.

In what felt like a miracle, my coworker knew a psoriasis specialist there and helped me book an earlier appointment. When the doctor came into the exam room, I broke down in tears hoping he could help me. He compassionately told me he had two treatment options for me, even though I was 95% covered with psoriasis: Goeckerman therapy and cyclosporine. I opted for the convenience of the latter. Cyclosporine began clearing my skin and became a go-to treatment option for over a decade. However, due to its side effects, I had to lower my dose and eventually add back Enbrel in combination. I suffered periodic bouts of viral and bacterial infections. Still, Enbrel with cyclosporine gave me some of my life back. It was too late to work on a PhD, but better-managed psoriasis allowed me to enroll in a Doctor of Ministry degree program. It took me a full 7 years, but I fulfilled my dream of earning a doctorate degree. At my hooding ceremony, I reflected on how I could not have made it as a minister, father, and student without the help of my healthcare providers and new psoriasis treatments.

Over the next few years, I sought a treatment that would allow me to stop cyclosporine. Humira cleared my psoriasis, but a full-body rash broke out after 2 months of treatment initiation. I did not notice much improvement with Stelara over the 6 months I tried it. Each new biologic gave me hope that I could simply inject and somewhat forget my psoriasis, but none of them did until IL-23 treatments became available.

My dermatologist told me about Tremfya a few months before its Food and Drug Administration (FDA) approval. It did not clear my psoriasis as I had hoped, but it allowed me to finally stop taking cyclosporine in 2017. Just under 2 years later, I switched to Skyrizi, which I have taken for more than 3 years now. I still need combination treatment, including a low dose of narrowband UVB from my home phototherapy unit. However, I do not worry as much about side effects as I did with previous systemic treatments. I have also dedicated myself to serving those in the psoriasis community. The IL-23 psoriasis therapies freed me to do more, as I felt better with fewer symptoms. For instance, I become a more active patient advocate and blogger. In 2007, I began writing a column hosted by Everyday Health called "The Itch to Beat Psoriasis." As my confidence grew with improved health, I accepted more writing opportunities and launched a personal website. Additionally, I increased my volunteer involvement with the National Psoriasis Foundation (NPF) and was named their 2021 Volunteer Leader of the Year. I have advocated with the NPF in both Sacramento and Washington, D.C. for bills that increase access to medical care for those with psoriatic disease and other chronic illnesses.

My family life also improved after starting biologic treatments. With less focus on my psoriasis, I had more energy to devote to my marriage and my children's needs and activities. We began to take annual family trips to places like Alaska, South Dakota, Florida, and Southern California. I felt able take the lead for my

daughter's care when she was diagnosed with a severe mood disorder and help my mom navigate cancer treatments.

It has been over four decades since I was diagnosed with psoriasis as an elementary school child. Psoriasis does not define me, but it has shaped me into the person I am today. I am grateful for the advances in psoriatic disease research that produced treatments such as biologics that gave me my life back. It is truly now a privilege to give back to others, including those living with this stigmatizing, visible, and potentially debilitating disease.

Physician's Perspective

It is an honor to provide my perspective on Howard's journey with psoriasis, as I have had the privilege of knowing Howard for several years now as a highly accomplished writer and fierce advocate for the psoriatic disease community.

I am a dermatologist and research scientist at UCSF, specializing in the care of patients with psoriasis and other inflammatory skin disorders. I decided to pursue a career in medicine to help patients overcome health barriers and allow them to live their best lives. Howard's description of the many challenges he has faced gives valuable insight into healthcare's many obstacles, but also provides examples of its progress and successes.

Psoriasis is a systemic, chronic inflammatory disease of the skin and joints affecting approximately 2–3% of the population [1]. Five psoriatic phenotypes have been described, with plaque psoriasis being the most common clinical morphology (90% of cases), defined by characteristic cutaneous involvement of well-demarcated, erythematous patches and plaques with overlying lamellar scales [2]. Guttate psoriasis, an acute form of psoriasis, often presents suddenly with small, erythematous, drop-shaped papules, and frequently occurs after streptococcal infections, as described by Howard during his childhood. Other psoriatic phenotypes include pustular, inverse, and erythrodermic psoriasis, the latter of which is considered a medical emergency [3]. Psoriatic arthritis (PsA), a chronic inflammatory disease of the joints and entheses, occurs in approximately 30% of psoriasis patients [4].

Owing to the systemic, chronic nature of inflammation in psoriasis, patients living with psoriasis are subject to an increased risk of medical comorbidities, including cardiovascular disease, type 2 diabetes, and metabolic syndrome [5]. Psoriasis also increases the prevalence of psychosocial comorbidities, with an improvement in psoriasis disease severity shown to correlate with a reduction in the symptoms of depression and anxiety [6]. The pathophysiology of psoriasis is a complex interplay between both genetic (e.g., susceptibility alleles) and environmental factors. An improved understanding of this multifactorial relationship between intrinsic and extrinsic elements has advanced the treatment options available for psoriatic disease [7]. Given its influence on both physical and psychosocial health, psoriasis should be considered as much more than just a disorder of the skin.

Howard's description of his initial psoriasis diagnosis is a striking example of how cultural, racial, and socioeconomic status may influence healthcare. When the rash that his parents thought would go away did not, he saw a primary care doctor who then referred him to a dermatologist at a large academic center. Luckily, Howard's parents had an established relationship with a primary care provider who was able to refer him to a knowledgeable dermatologist, a process which is often convoluted in patients with varying social strata. In medicine, we often see that cultural, linguistic, racial, and socioeconomic barriers prevent patients from accessing healthcare providers, and even more so specialists such as dermatologists [8]. I have seen patients in my clinic who were not diagnosed with psoriasis for over a decade after their symptoms first presented. Such delays in diagnosis can negatively impact the patient, especially in cases of PsA in which impediments in diagnosis may result in permanent, disfiguring joint destruction [9].

I noted that Howard was terrified by being viewed by a large group of medical students and residents. A person's skin is a very personal part of the body, and it is understandable that being

stared at by a large group of strangers may be uncomfortable. His experience highlights how doctors can and should explain to patients ahead of time the important role of trainees and learners in academic medical centers, while ensuring patients' willingness to participate [10]. While a patient at an academic medical center can typically expect to receive a physical exam from one or two trainees prior to being evaluated by an attending physician, it is important to ask patients if they are comfortable being seen by larger groups of learners. Howard's story aptly illustrates the devastating impact that skin disease can have on a person's psychosocial well-being. This is especially important for school-aged children who are trying to concentrate in class, navigate peer relationships, and who are in the process of forming their self-identity [11].

Depression, anxiety, and low self-esteem are common in patients with psoriasis [12]. Moreover, in Howard's case, the discomfort associated with psoriasis and his topical treatments resulted in poor sleep. We now know that poor sleep quality and quantity, which occurs in patients with psoriasis at higher rates, can increase the risk for high blood pressure, obesity, diabetes, heart attack, and mental health problems [13–15]. This issue is further compounded by the increased baseline risk of these disorders in patients living with psoriasis, leading to a vicious cycle [5].

One of the most difficult and painful aspects of Howard's story is the time he spent trying different psoriasis therapies, many of which failed or produced unwanted side effects. I counted no fewer than 16 therapies Howard tried, including topical creams and ointments, phototherapy, pills, and biologic injections. In many ways, the therapies Howard has tried reflect the slow but steady advancement of modern medicine. In the past decade, there has been rapid progress in the development of highly effective and safe psoriasis treatments. Howard's numerous medication trials also mirror the escalating therapies available for psoriasis patients with moderate-to-severe disease. After failing topical treatments and phototherapy, he began systemic treatment options including acitretin, PUVA, and immunosuppressants such as methotrexate and cyclosporine. While these may be highly effective for some patients, these older treatments all have significant potential for adverse effects [16].

Biologic treatments for psoriasis were first introduced in 2003 with the FDA-approval of alefacept, a drug which interferes with the activation and proliferation of T-cells [17]. Currently, 12 FDA-approved biologics belonging to three major families—tumor necrosis factor (TNF)-α inhibitors, interleukin (IL)-17 inhibitors, and IL-23 inhibitors—are available for the treatment of psoriasis. Many of these drugs have dual approval for the treatment of both psoriasis and PsA.

Howard tried numerous "first-generation" biologics, including alefacept, etanercept, and adalimumab, before eventually discontinuing them due to side effects or lack of efficacy. In randomized clinical trials (RCTs) of TNF-α inhibitors [etanercept, infliximab, adalimumab, certolizumab pegol, and golimumab (only approved for PsA)], the efficacy of this class of biologics in terms of 75% improvement in Psoriasis Area and Severity Index (PASI 75) ranged from 47% (etanercept) to 80% (infliximab) [18, 19]. TNF-α inhibitors may not be as efficacious as some of the "second-generation" biologics (IL-17 and IL-23 inhibitors), as evidenced by inferior efficacy in head-to-head RCTs [20–24]. Despite this, the efficacy and safety of anti-TNF agents are well established, as evidenced by the millions of patients worldwide benefiting from these medications [25].

The pathophysiology of psoriasis is characterized by excessive growth of the epidermis and aberrant differentiation of keratinocytes. The discovery of the roles of IL-17 and IL-23 in the development of psoriatic disease have further elucidated the molecular mechanisms underlying psoriasis and PsA, with translational immunology studies revolutionizing the treatment of these diseases [26].

Specifically, the IL-17/T helper 17 (Th17) pathway is critical in the pathogenesis of psoriasis, with IL-17A promoting epidermal hyperplasia and resulting in the formation of tenacious plaques seen in plaque psoriasis [27]. Currently, three FDA-approved IL-17 inhibitors

for the treatment of psoriasis are available, including secukinumab and ixekizumab (both IL-17A inhibitors) and brodalumab (an IL-17A receptor inhibitor). IL-17 inhibitors are highly safe and effective in the treatment of psoriasis, even more so than their "first-generation" predecessors. In placebo-controlled RCTs, these drugs were found to be significantly superior to both placebo and etanercept, with 81.6% and 89% of patients receiving secukinumab and ixekizumab, respectively, achieving a PASI 75 response at week 12 [21, 24].

The involvement of IL-23 in psoriasis is well established, demonstrated in part by IL-23 expression being significantly elevated within psoriatic lesions [28]. At the cellular level, IL-23 promotes the differentiation of Th17 cells and production of IL-17 in a self-amplifying, positive feedback loop that stimulates psoriatic pathogenicity [29]. Ustekinumab, which also inhibits IL-12 due to a shared p40 subunit, was the first FDA-approved biologic that inhibited IL-23 [30]. Three FDA-approved IL-23 specific inhibitors are currently available for the treatment of psoriasis, including guselkumab, tildrakizumab, and risankizumab. Similar to IL-17 inhibitors, IL-23 inhibiting agents are highly safe and effective in the treatment of psoriasis and have demonstrated superior clinical response rates compared with TNF-α inhibitors in head-to-head RCTs [22, 23]. In terms of disease clearance (PASI 90) at week 16, 85% of patients treated with guselkumab versus 66% patients receiving adalimumab achieved clearance [22]. In another study, 72% of patients receiving risankizumab achieved PASI 90 at week 16 versus 47% patients treated with adalimumab [24]. Furthermore, these IL-23 specific inhibitors may be more effective than their IL-12/IL-23 inhibiting predecessor, ustekinumab. Patients treated with risankizumab achieved PASI 90 at a significantly greater rate versus ustekinumab at week 12 (77% versus 40%) [31]. Howard described how the IL-23 inhibitors were life changing for him, enabling levels of side-effect-free skin clearance he had never experienced previously using a laundry list of treatments. This narrative is corroborated by head-to-head RCTs comparing the efficacy of IL-17 and IL-23 agents with "first generation biologics," as well as network meta-analyses contrasting numerous RCTs, enabling comparisons among multiple drugs and classes [20].

Aside from their efficacy, there are many important aspects to consider when prescribing these medications. While all currently FDA-approved TNF-α inhibitors are approved for PsA, only certain IL-17 and IL-23 inhibitors are approved for PsA (e.g., risankizumab, secukinumab, brodalumab, ixekizumab, and guselkumab). For patients prescribed TNF-α inhibitors, they should be counseled on the increased risk of serious infections or malignancy associated with these medications [32]. The increased risk of infections with TNF-α inhibitors were exemplified by Howard's recounts of suffering periodic bouts of viral and bacterial infections while taking etanercept. The safety profile of IL-17 and IL-23 agents may be considered as preferable to the anti-TNF drugs. The safety of IL-17 and IL-23 inhibiting drugs is well supported by registry data of real-life data from patients taking biologics [33, 34]. The most common adverse events for patients taking IL-17 or IL-23 inhibitors include nasopharyngitis, upper respiratory infections, injection site reactions, and headaches. In RCTs of IL-17 and IL-23 agents, the increased incidence of minor infections was modest compared with placebo (~ 30% versus ~ 20%) [24, 35]. In the real world, choosing between biologics, especially IL-17 and IL-23 inhibitors, often comes down to which medication the patient's insurance is willing to cover.

Even newer agents are becoming increasingly accessible. For patients preferring orally administered agents, deucravacitinib is a member of the Janus kinase (JAK)-inhibitor family of medications, which selectively inhibits tyrosine kinase 2 (TKY2). JAK-inhibitors act by inhibiting the signal transduction pathways downstream of cytokine-receptor interactions (e.g., IL-23) [36]. In a phase 3 RCT investigating deucravacitinib in moderate-to-severe plaque psoriasis, significantly greater proportions of patients treated with deucravacitinib (59%) achieved a PASI 75 response at week 16 versus placebo (13%), and apremilast (35%), another orally administered agent FDA-approved for the treatment of psoriasis [36].

Advances in treatment now enable the possibility that patients living with psoriasis in the USA can achieve clear or almost-clear skin if the appropriate treatment is accessible and affordable—a stipulation that is often still a major hurdle. The development of these modern miracles required significant contributions from academic researchers, federal health agencies such as the National Institutes of Health, nonprofit organizations, and pharmaceutical companies. Continued investment in research, discovery, and clinical translation is critical for fueling the next generation of improved therapies [37].

Despite decades of constant struggle, Howard was able to find moments of solace with friends, family, his faith, and patient organizations such as the NPF. These support structures are critical for patient well-being, and physicians would be wise to encourage their patients to engage with these resources [38]. I greatly admire that Howard was able to turn his personal struggles with psoriasis into a great strength, using his experience to help others through writing, community volunteerism, and legislative advocacy. Patients with psoriasis are among the most resilient and courageous individuals I know, and Howard embodies these ideals.

As I reflect on Howard's long journey, I am happy he has finally achieved a measure of relief and is able to enjoy time with his family. Stories like Howard's remind me of why I chose a career in medicine. I am optimistic that if physicians and patients continue to partner together, we will one day develop a cure for psoriasis [37], alleviating much suffering and making our world a better place.

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