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COMMENTARY

Clinical Goals and Barriers to Effective Psoriasis Care

Bruce E. Strober · Joelle M. van der Walt · April W. Armstrong · Marc Bourcier · Andre V. E. Carvalho · Edgardo Chouela · Arnon D. Cohen · Claudia de la Cruz · Charles N. Ellis · Andrew Y. Finlay · Alice B. Gottlieb · Johann E. Gudjonsson · Lars Iversen · C. Elise Kleyn · Craig L. Leonardi · Charles W. Lynde · Caitriona Ryan · Colin T. Theng · Fernando Valenzuela · Ronald Vender · Jashin J. Wu · Helen S. Young · Alexa B. Kimball

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ABSTRACT

Engaging global key opinion leaders, the International Psoriasis Council (IPC) held a day-long roundtable discussion with the primary purpose to discuss the treatment goals of psoriasis patients and worldwide barriers to optimal care. Setting clear expectations might ultimately encourage undertreated psoriasis patients to seek care in an era in which great gains in therapeutic efficacy have been achieved. Here, we discuss the option for early treatment of all categories of psoriasis to alleviate disease impact while emphasizing the need for more focused attention for psoriasis patients with mild and moderate forms of this autoimmune disease. In addition, we encourage policy changes to keep pace with the innovative therapies and clinical science and highlight the demand for greater understanding of treatment barriers in resource-poor countries.

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B. E. Strober (✉)
University of Connecticut Health Center, Farmington, CT, USA
e-mail: brucestrober30@me.com

B. E. Strober
Probity Medical Research, Waterloo, ON, Canada

J. M. van der Walt
International Psoriasis Council, St. Louis, MO, USA

A. W. Armstrong
University of Southern California, Los Angeles, CA, USA

M. Bourcier
Faculty of Medicine, Sherbrooke University, Sherbrooke, QC, Canada

A. V. E. Carvalho
Moinhos de Vento Hospital Complex, Porto Alegre, Brazil

E. Chouela
University of Buenos Aires, Buenos Aires, Argentina

A. D. Cohen
Siaal Research Center for Family Medicine and Primary Care, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

A. D. Cohen
Department of Quality Measurements and Research, Chief Physician's Office, Clalit Health Services, Tel Aviv, Israel

C. de la Cruz
Clínica Dermacross, Santiago, Chile

C. N. Ellis · J. E. Gudjonsson
Department of Dermatology, University of Michigan Medical School, Ann Arbor, MI, USA

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INTRODUCTION

Psoriasis is an immune-mediated inflammatory skin disease with significant physical and psychosocial consequences. Visible skin disfigurement and the associated symptoms of itch, pain, scaling, bleeding, burning, and cracking have a significant impact on the patient's quality of life. Additionally, psoriasis is a systemic disease with multiple comorbidities, which increase the disease burden to beyond the realm of the skin [1]. Despite the current large inventory of effective treatment choices, including innovative biologics and oral therapy, undertreatment and non-treatment of psoriasis is prevalent worldwide, including in Europe and the USA [2]. This situation is even worse in developing countries where psoriasis patients with moderate-to-severe disease have poor access to the novel and costlier therapies [2–6]. The "Clear about Psoriasis" global study involving 31 countries (Western and non-Western) identified that 57% of moderate-to-severe psoriasis patients surveyed did not achieve clear/almost clear skin on current therapy [7], which recapitulates earlier findings that a majority of psoriasis patients worldwide are undertreated.

Key stakeholders agree that this global problem is driven by economics, market access, health policies, differences in the patient and physician perspectives on the disease, knowledge gaps, and the lack of established treatment goals. Councilors from the International Psoriasis Council (IPC) convened during a roundtable event, with the primary purpose to discuss clinical goals and specific barriers to optimal treatment and to highlight challenges for patients living in both Western and non-Western countries (Table 1). The event included dermatologists from ten different countries, and the intent was to reveal global perspectives and provide expert opinion.

This article does not contain any studies with human participants or animals performed by any of the authors.

CURRENT STATE OF PATIENT SATISFACTION

In previous surveys psoriasis patients have reported treatment dissatisfaction [2] and failure to meet treatment goals with current therapy [3]. A recent review of 60 published studies/articles, which included 35,388 psoriasis patients, noted modest patient satisfaction, with those patients treated with biologics

A. Y. Finlay
Department of Dermatology and Academic Wound Healing, Division of Infection and Immunity, School of Medicine, Cardiff University, Cardiff, UK

A. B. Gottlieb
Icahn School of Medicine at Mount Sinai, New York, NY, USA

L. Iversen
Department of Dermatology, Aarhus University Hospital, 8000 Aarhus C, Denmark

C. E. Kleyn · H. S. Young
The Dermatology Centre, Manchester Academic Health Science Centre, Salford Royal NHS Foundation Trust, Barnes Building, Manchester, UK

C. L. Leonardi
St Louis University Medical School, St. Louis, MO, USA

C. W. Lynde
University of Toronto, Toronto, ON, Canada

C. Ryan
Blackrock Clinic Dublin and University College Dublin, Dublin, Ireland

C. T. Theng
Department of Dermatology, National Skin Centre, Singapore, Republic of Singapore

F. Valenzuela
Department of Dermatology, Universidad de Chile, Santiago, Chile

R. Vender
Dermatrials Research Inc & Venderm Innovations in Psoriasis, Hamilton, ON, Canada

J. J. Wu
Dermatology Research and Education Foundation, Irvine, CA, USA

A. B. Kimball
Harvard Medical Faculty Physicians, Beth Israel Deaconess Medical Center, Boston, MA, USA

Table 1 Approaches to advance psoriasis care worldwide

Approaches to advance global psoriasis care
Treatment goal: total skin clearance and reduction of symptoms (most importantly itch) are important to the patient (objective tool + psoriasis-specific PRO to assess symptom severity = impact of disease)
Early treatment with effective therapy; reduction in time to initiation of biologic or new oral therapies
Encourage policy changes to keep pace with innovative therapies and clinical science
Advocate and treat psoriasis as a lifelong, systemic inflammatory disease, incorporating comorbidity screening
Deeper understanding of unmet needs in countries outside of Europe and North America; need for realistic yet effective national treatment programs
Greater focus is needed on treatment of mild to moderate disease patients that do not meet criteria for biologics or new oral therapies

PRO Patient reported outcome

reporting higher satisfaction than those treated with oral therapies, phototherapy, or topicals [8]. How these data would differ today given the introduction of the newer biologic therapies, such as interleukin (IL) inhibitors (IL-17 and IL-23), which have excellent clinical efficacy but significant cost issues, is yet to be determined. Part of the problem is that the majority of recent innovation have been targeted to the moderate-to-severe patient population, with little new successful development for those psoriasis patients with mild and moderate disease.

Psoriasis severity is generally defined by clinicians using objective measures of body surface area (BSA), the Psoriasis Area Severity Index (PASI), or one of several Physician Global Assessment (PGA) measures [9]. Additionally, the impact of psoriasis on patients' quality of life may be evaluated by the Dermatology Life Quality Index (DLQI), a self-reported questionnaire assessing the physical, psychological, and social well-being of patients [10]. Psoriasis patients and their physicians differ with regard to which psoriasis symptoms are most important. For example, some patients have found itch to be most bothersome, while dermatologists reported the location and size of the skin lesions as paramount [11]. Itch, affecting 60–96% of patients, is the primary source of discomfort, negatively impacting daily physical and mental well-being [12–14]. Clinical studies with ixekizumab [15, 16], tofacitinib [17], apremilast [18], etanercept [19], and secukinumab [20] have shown a significant association of improvement of itch with a correlative improvement of the quality of life for patients. Not surprisingly, the reduction of itch and pain is strongly correlated with skin clearance [21] [15]. In addition to physical symptoms of itch and pain, the visible aspect of the disease impacts many psychosocial domains. Anxiety and depression can lead to avoidance and reduction of social interactions [7, 22, 23]. In a recent global study, 84% of psoriasis patients surveyed reported humiliation, discrimination, difficulty in social/work situations, sleep disturbance, and mental health issues. In addition, both the physical symptoms plus psychiatric morbidity can negatively impact intimate relationships and sexual activity [24, 25]. These important factors, if recognized by the dermatologist, can be used to guide treatment decisions and provide educational health resources to the patient.

The reason for the discrepancy between patients and physician regarding the most bothersome symptoms of the disease is possibly due to the objective approach taken to determine disease severity by the physician versus the subjective manner by which patients experience and monitor their disease symptoms. Consequently, the physician's use of the PASI could potentially miss the effect of a therapy on

the specific symptoms, such as itch, burning, pain, and stinging, that commonly affect psoriasis patients. The DLQI captures the symptoms of itching, soreness, pain, and stinging using one question, but it does not evaluate each separately. This points to the potential value of utilizing psoriasis-specific patient-reported instruments that assess individual symptoms in conjunction with quality-of-life inquiries.

DISEASE-SPECIFIC PATIENT REPORTED OUTCOME MEASURES ARE NEEDED TO DEFINE SUCCESS AND TO INFORM CLINICAL DECISIONS

Current outcome measures may not be helpful in distinguishing which psoriasis therapies are clinically meaningful unless they have established the minimal clinically important difference (MCID) for score change [26]. Certainly, the main goal of psoriasis treatment is to achieve skin clearance and to restore the patient's normal daily activities to where this disabling disease has no impact on work, family life, social connections, and well-being of the patient [7, 26].

To this end, patient reported outcomes (PROs) complement and qualify objective (observer only) tools [26, 27] and move the focus from objective to subjective (patient-experienced) measures. The DLQI, a PRO that is not specific for psoriasis, is composed of content that includes important and relevant concepts from the perspective of psoriasis patients [28] and is the most widely accepted PRO currently available to clinicians. Psoriasis-specific PROs should capture corresponding elements of the DLQI that have been clinically validated, that are responsive to change, and which are determined as well understood by patients [28, 29] but which may need to be expanded to include other elements. A thorough assessment of psoriasis-specific PRO tools has been systematically reviewed elsewhere [30, 31].

The International Dermatology Outcome Measures Group (IDEOM) is one initiative which aims to establish validated and standardized outcome measures that satisfy the needs of all stakeholders for use in clinical trials and clinical practice [32–34]. The core domains that have been identified are skin manifestations (surface area of involvement, location, redness, induration, and scale), investigator global assessments, psoriasis and psoriatic arthritis symptoms, patient global assessment, treatment satisfaction, and health-related quality of life [35].

Ideally, an effective PRO with regard to measuring both disease severity and treatment effects could replace objective metrics such as the PASI or PGA. Furthermore, the discussion of PRO results has the potential to significantly enhance the physician–patient interaction and contribute to the formation of valid treatment goals.

TREATMENT EXPECTATIONS AND CLINICAL GOALS

In the majority of cases, patient expectations are influenced by the clinician, but neither the patient nor the clinician may be fully aware of what the patient believes is most important. Dermatologists are generally calibrated to patient expectations that are highly related to factors such as age, gender, socioeconomic status, occupation, and geographic locale [36]. In a German registry, patients surveyed reported a wide range of highly valued treatment goals beyond skin clearance, which included improvement of itching, burning, and pain and normal life functioning [37]. In addition, many patients are unaware that there is a possibility of attaining 100% clearance over both the short term and long term, or of achieving substantial improvement or elimination of their most troublesome symptoms [7]. Treatment goal misalignment was reported in 67.9% of patient–physician pairs surveyed in a study conducted in Japan which examined skin clearance as a goal indicator [38]. The main reason for misalignment was that patients expressed a higher goal than physicians. This finding again highlights the importance of dermatologists recognizing patient expectations

in order to reach clinical goals. It is likely that this disconnect also contributes to the finding that adherence to treatment falls well below that for other chronic conditions [39, 40]. In part, adherence is negatively affected by patient psychological barriers related to past failed treatments, whereby the patient becomes resigned to modest or limited outcomes (inadequate skin clearance and relief from symptoms) [41].

WHAT DEFINES TREATMENT SUCCESS OR FAILURE?

Treatment success in managing chronic disease has been defined as control of a target that is quantifiable to a specified value or range (e.g., for certain conditions, glycated hemoglobin levels, lipid profiles, blood pressure ranges, or virus burden). The identification and acceptance of treatment goals require the establishment of minimal disease criteria through literature review and a subsequent expert consensus building exercise, such as the Delphi process. Target goals should be defined for both the initiation and maintenance phases of treatment and should also be easy to implement in clinical practice and feasible to attain. Ideally, treatment goals should correlate with meaningful effects on systemic comorbidities, such that achieving these targets has positive effects on either morbidity or mortality. Such targets for psoriasis therapy are yet to be identified.

Once target goals have been established, a "treat to target" approach can be compared to standard care to identify the best approach for disease management. For example, in psoriatic arthritis, the Tight Control of Psoriatic Arthritis study (TICOPA) investigated an intensive and early treatment protocol versus standard care [42]. First, the target goals of minimal disease activity (MDA) criteria were validated through observation and investigational studies and then these goals were applied in the TICOPA study. The results of the study determined that intensive care (review every 4 weeks, with escalation of treatment to MDA targets) provided greater patient improvement in disease activity and reduction in joint damage than standard care (review at 12 weeks).

Treatment goals for psoriasis have been defined by European [43], American [44], Canadian [45], and Australian [46] consensus committees according to shared criteria that define treatment success. The recently published consensus from the US National Psoriasis Foundation posits that an acceptable response to treatment at 3 months after initiation is $\leq$ 3% BSA or a BSA improvement of $\geq$ 75% from baseline; the target treatment response at 3 months after initiation is $\leq$ 1% BSA; and the target response at each 6-month maintenance appointment is $\leq$ 1% BSA [44].

These targets, which have been established to improve patient outcomes in diverse clinical settings within Western countries, may need modification in non-Western countries due to safety concerns in vulnerable populations. For example, Brazil has adopted the European targets with a few modifications due to the high local prevalence of human T-lymphotropic virus (HTLV) and tuberculosis infection burden, which demands screening before initiating treatment with immunosuppressive therapies [47]. More information is needed to establish the burden of psoriasis within populations of Latin America and the Caribbean in order to gain a stronger understanding of patient perspectives and barriers to care [48].

The Malaysian Ministry of Health lists treatment goals as minimum targets within therapy categories (topicals, phototherapy, conventional therapies, or biologics) and highlights the need for target goals to be based on patient severity and patient preference [49].

CLINICALLY MEANINGFUL TARGETS

It appears to be relatively straightforward to provide treatment with the target of skin clearance based on BSA, PASI, or PGA (minimal disease criteria), but the degree that is clinically meaningful to the patient should be clarified. A recent study examined the impact of total skin clearance on quality of life from the patient's perspective by investigating PSI and DLQI [26].

Patients that responded to treatment with total skin clearance (PASI 100 and PGA 0) demonstrated minimal or no impairment in dermatology-related quality of life factors or signs and did not experience symptoms of psoriasis. This outcome translates into a clinically meaningful treatment goal for patients. The study further revealed that even small areas of residual disease in patients that did not respond with complete clearance have a negative impact on patient quality of life and psoriasis symptoms.

Examination of other target goals below PASI100 might also be useful for determining the relationship between categories of PASI response levels. For example, data derived from clinical studies on secukinumab reveal that achieving a PASI response of 90 correlates with better quality of life (DLQI 0/1) at week 12 than achieving a PASI response of 75–89 [50]. When setting treatment goals, it should be understood that the concept of percentage PASI reduction as the only outcome measure might not be relevant for individual patients; rather, absolute change is usually more relevant. In this vein, the MCID score for absolute change of the metric being used should be better understood; for example, for the DLQI, the MCID is a score change of 4 [51].

Overall, current evidence supports the conclusion that greater skin clearance correlates with greater improvement of patient quality of life. However, studies have also shown that skin lesion severity on the head and upper extremities had disproportionately large impacts on DLQI compared with BSA, particularly for younger women and men. The impact was significantly greater in women aged < 45 years (higher DLQI) [52]. In addition, genital psoriasis, which affects over 60% of psoriasis patients, imparts significant impairment on the quality of life, feelings of stigmatization, and impact on sexual health [25]. These findings again point to the importance of patient perspectives on treatment goals and expectations.

Finally, the impact of psoriasis extends beyond the patient. Disease burden on family members and partners has garnered little attention in the past and, due to this lack of consideration, is a hidden and often ignored important aspect of the disease. However, observational studies have captured the degree of impairment in the quality of life of persons living with psoriasis patients using family quality reported outcome instruments, such as Psoriasis Family Index (PFI), Family Dermatology Life Quality Index (FDLQI), and Family Reported Outcome Measure (FROM-16) [23, 53–56]. Family members are burdened with psychological pressures, disruption of social, holiday, and sports activities, and disturbance in daily activities [23].

TREAT-TO-TARGET: A REALITY OR ASPIRATIONAL?

The treat-to-target approach may be difficult to implement in global clinical practices if the target goal is too ambitious and beyond the reach of the majority of patients. PASI100 should be considered to be an aspirational and important goal, as no current treatment can achieve it in more than 50% of patients. For example, in the UNCOVER-1 study, 35.3% of patients treated with ixekizumab reached PASI100 at week 12 [57]. PASI 90, on the other hand, is achievable in a larger percentage of patients treated with IL-17 inhibitors (ixekizumab 70.9% [57]; secukinumab 70.0% [58]; brodalumab 70.3% [59]) and IL-23p19 inhibitors (risankizumab 77% [60]; tildrakizumab 58% [61]; guselkumab 73.3% [62]). Other concerns regarding the treat-to-target approach include the possibility of inappropriate treatment if non-response or loss of response is not well understood, patient reluctance to undergo increased monitoring, dosing, or switching of therapies with a different mode of action, and potential increase in cost. Ultimately, therapy must be customized, as the definition of success will depend on the patient's perspective [63].

In addition, goals should be set to encourage physicians to optimize treatments and maximize long-term quality of life—while reducing the risk of important comorbidities. However, setting an actual number value within formal treatment guidelines used by physicians and private healthcare insurers may negatively impact access. For example, if a target is not met despite the patient being satisfied, insurers

might deny payment. In resource-poor countries, such as Brazil, where the government health agencies approve biologics but deny access to the public healthcare system due to economic reasons, physicians would be caught between the treat-to-target guidelines (and patient expectations) and divergent public healthcare policies [47].

CLEARANCE AND LONGEVITY

With the current broad spectrum of available psoriasis therapies, sustained and consistent clearance of psoriasis is a definite possibility [26]. In large patient populations, greater clearance translates to greater satisfaction, as patients who achieve full clearance (when compared to those who are "almost clear") more often report greater symptom resolution [64]. Importantly, psoriasis patients who are effectively treated may display a "reset" of the level of disease that can be tolerated. Treatment discontinuation after initial success results in a rebound dissatisfaction with returning disease (worsening of quality of life). Small recurrences of psoriasis therefore translate into disproportionately larger detrimental effects on quality of life reporting [65]. Reduction of drug dose after initial treatment success could result in a similar phenomenon [66].

These data would support the avoidance of unnecessary switching among therapies in order to increase the likelihood of long-term patient satisfaction. However, sustained efficacy is still a significant shortcoming with the biologic therapies, and corrective approaches to this problem are hindered by a lack of head-to-head studies between therapies and an understanding of the mechanisms by which therapies lose their effectiveness over time. Access to observational prospective registries has allowed some comparative assessments of long-term efficacy [67–69]. The use of concomitant immunomodulatory drugs, such as methotrexate, is inadequately studied, but it is well recognized from the rheumatology literature that this approach may lengthen treatment response [70, 71]. In this regard, it is important to realize that only monotherapy (including no potent topical steroids) is allowed in psoriasis clinical trials, whereas in rheumatology clinical studies, including those in psoriatic arthritis, more than 50% of patients in the clinical trials conducted to date are on concomitant systemic therapy (methotrexate, prednisone, etc.). In addition, because drug durability rates are possibly lower in the clinical setting than in controlled trials, more real-world studies [72] are needed to gauge the longevity of response of the novel biologics and oral therapies.

There is also a need for variable dosing in studies of the various drugs to better understand how long-term clearance might be sustained. Internationally, methotrexate is the most widely used systemic therapy due to its reasonable efficacy and low cost. A recent survey administered across 63 countries demonstrated significant differences on dosing, route of administration, and safety monitoring of methotrexate [73]. In fact, an intensified dosing schedule of subcutaneous methotrexate over 52 weeks was found to be effective and well tolerated in moderate to severe patients [74].

CLINICAL INERTIA AND PATIENT BARRIERS

Clinical inertia, a concept coined in early 2000s, is defined as the failure to initiate and/or to intensify care when treatment goals are not met [75]. Evidence for clinical inertia in the treatment of psoriasis has been established; for example, in the studies (described above) in which only 31% of patients report that the target goal of skin clearance is reached.

Recent observational evidence suggests that patients, on average, seek referral to a secondary care (specialist) 15 years after presentation [76]. The authors of this study report that this delay in seeking help can be attributed to several barriers, including familial experience of the disease (acceptance that many family members have psoriasis); previous failed therapies and thus a sense of hopelessness; lack of follow-up to assess treatment response after initiation; and difficulty in obtaining a secondary care referral. Strikingly, patient conception of psoriasis as being neither curable nor life-threatening, and

thus unworthy of treatment, was also identified as a strong barrier to seeking effective treatment [76]. The barriers identified here are modifiable and have the potential to lead the patient to early treatment.

Access to expert care for patients with moderate to severe disease is affected by several factors. First among these is the inadequate supply of or limited access to dermatology practitioners in countries worldwide. Second, the framework in which patients receive care may not support the complexity needed for appropriate evaluation and management of psoriasis. Given the time constraints of the average dermatology clinic visit (5–15 min), arriving at effective treatment that maximizes both physician and patient outcomes and satisfaction may be challenging. Third, access to medications is frequently constrained. While psoriasis is a systemic disease associated with chronic inflammation and, in a number of patients, end-organ damage, it continues to be viewed by patients, physicians, and payors as a cosmetic or "itchy skin" problem and not of equal health significance as, for example, rheumatologic disorders. For example, US payers make decisions on physician and drug quality based on claims databases in community practices that do not assess either patient severity, associated comorbidities, or disease-specific outcomes [77]. Treatment regimens for psoriasis patients should be tailored to meet specific needs based on disease severity, impact on quality of life, response to previous therapies, and presence of comorbidities. With regard to comorbidities such as psoriatic arthritis, it is important to ensure that the appropriate agent not only improves the disease symptoms but also has the potential to inhibit the radiographic progression of disease [78]. In addition, since psoriasis is a chronic systemic and incurable disease that affects all age groups, special populations, such as pregnant women, pediatric patients, elderly patients, and those with chronic infections, must be considered [79].

Disparate treatment access for psoriasis patients is especially high for those who seek biologic treatment and new oral therapies in developing countries. In 2016, the World Health Organization issued a global report to emphasize that psoriasis is a serious, disfiguring, and disabling non-communicable disease and set forth actions to improve healthcare across all countries [6]. Communicable diseases still contribute significantly to disease burden in most developing countries, and a majority of the financial resources is dedicated to providing these treatments. However, recent studies have reported that the occurrence of non-communicable disease doubles the overall health burden [80, 81]. In some developing countries the economic burden of modern, highly effective therapies will drive the discussion. Unless pharmaceutical companies, payers, and regulators reach a consensus on how to adequately fit treat-to-target guidelines into the healthcare general budget, achieving excellent standard of care will be challenging. A better understanding of factors that influence disparity is critical to narrowing the healthcare gaps for patients.

CONCLUSIONS

Over 125 million people living with psoriasis depend on feasible approaches to attain treatment goals in order to reverse the current state of untreated and undertreated patient populations. Delivering comprehensive treatment information to the patient will help develop realistic expectations and lead to improved health outcomes [36, 43]. Further, patients and healthcare providers should appreciate that even though skin clearance is achieved in the short term, clearance must be maintained and a long-term strategy must be implemented in the form of a multidisciplinary approach that limits the comorbidities associated with psoriasis [11, 82, 83].

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