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UNDERSTANDING CUMULATIVE LIFE COURSE IMPAIRMENT IN PSORIASIS: IMPACT ON PATIENT MANAGEMENT

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UNDERSTANDING CUMULATIVE LIFE COURSE IMPAIRMENT IN PSORIASIS: IMPACT ON PATIENT MANAGEMENT

Increasing recognition of the life-altering burden of psoriasis, coupled with the availability of treatments that offer better efficacy, has raised the bar in psoriasis treatment

KEY TAKEAWAYS

- Psoriasis has a broad impact on the patient as a whole that accumulates over the individual's life course.
- This additive impact of disease over the lifetime of an individual is captured by the concept of cumulative life course impairment (CLCI).
- Targeted biologic treatments have revolutionized the psoriasis therapeutic landscape. Most guidelines now endorse complete or near-complete skin clearance as a realistic target.
- Biologics with the best efficacy and durability have the greatest potential to reduce CLCI.
- The current treatment paradigm emphasizes early diagnosis and intervention, ambitious targets, and treatment optimization to sustain response to optimize quality of life (QOL).
- Those most at risk for CLCI include patients with comorbidities, individual vulnerability and poor coping mechanisms/social support.

Psoriasis is a chronic inflammatory skin disease that occurs in an estimated 2% of individuals worldwide. Among the subtypes of the disease, plaque psoriasis is the most common, accounting for 90% of cases.[1] The disease is associated with numerous comorbidities and is now widely recognized as an immune-mediated inflammatory disorder.

PSORIASIS AND LIFE COURSE: A NEW WAY OF UNDERSTANDING IMPACT

Burden of psoriasis beyond the skin

Figure 1: The link between psoriasis and other comorbidities[2-7]

PSORIASIS HAS BEEN LINKED WITH A RANGE OF COMORBIDITIES	
Psoriatic Arthritis ✓ Present in up to 30% of people with psoriasis	Sleep Disorders ✓ 2.6 times higher risk of obstructive sleep apnea
Cardiovascular Disease ✓ Psoriasis is an independent risk factor for CV	Kidney Disease ✓ 2 to 4 times higher risk of death from kidney disease
Crohn's Disease ✓ 1.5 to 2.9 times higher risk of Crohn's Disease	Metabolic Syndrome ✓ 26% higher risk of diabetes ✓ Similar associations found for hyperlipidemia, hypertension, obesity and ischemic heart disease
Chronic Obstructive Pulmonary Disease ✓ 27% higher risk for COPD	Non-alcoholic fatty liver disease ✓ 2 times higher risk
Depression ✓ More than 10% clinically depressed	

The link between psoriasis and a range of comorbidities has been established (**Figure 1**). According to a large retrospective analysis, up to 41% of psoriasis patients develop psoriatic arthritis.[8] A 2019 meta-analysis of psoriasis patients described a more conservative psoriatic arthritis prevalence of 20%, and a higher likelihood of PsA in patients with moderate-to-severe psoriasis.[9] Skin lesions typically precede joint involvement—by an average of 12 years.[10] Patients with psoriasis also have increased rates of hyperlipidemia, hypertension, coronary artery disease, gastrointestinal (GI) disorders, non-alcoholic fatty liver disease (NAFLD), lymphomas and other neoplasms, and type 2 diabetes. Evidence suggests that psoriasis independently increases the risk of myocardial infarction and stroke.[1]

A population-based study confirmed the association between psoriasis and metabolic syndrome. The greater the severity of psoriasis, the stronger this association. Patients with severe psoriasis also have a higher risk of cardiovascular (CV) mortality, independent of traditionally considered risk factors.[12] Psoriasis is also associated with a high prevalence of anxiety (30%), depressive disorders (60%), and suicidality (10%).[11]

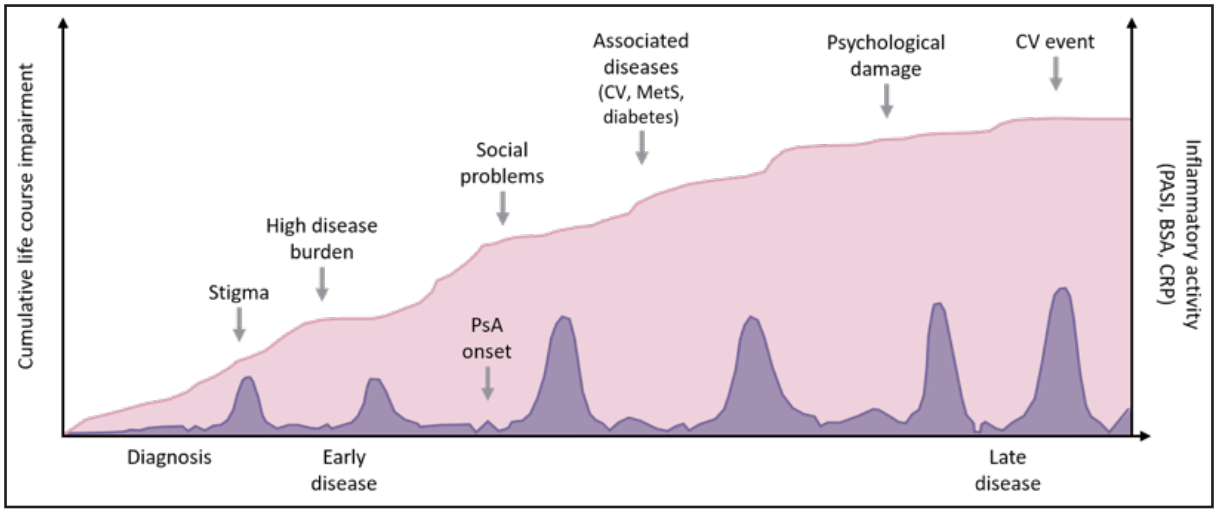
In a study of the impact of psoriasis on stigmatization and quality of life (QOL) involving 166 patients, researchers noted that the QOL in persons with psoriasis actually did not depend on sociodemographic parameters but instead correlated significantly with two stigmatization domains, ''Sensitivity to the opinions of others'' ($p = 0.0030$) and ''Positive attitudes'' ($p = 0.0115$).[13]

The overall impact of psoriasis on QOL approximates that of heart disease, diabetes, and cancer[12] and permeates all aspects of patients' lives. In a qualitative study of patients' experiences of living with psoriasis, 98% of respondents reported an impact on emotional life, 94% on social life, 70% on family life, 68% on professional career, 38% on physical functioning, and 21% on educational life.[13] Psoriasis has even been associated with a drop in income proportional to the severity of the disease. Low income (<$30,000) was significantly greater among patients with severe disease than those with mild disease ($P = .0002$) and significantly more patients with severe psoriasis (17%) versus mild (6%) reporting that psoriasis was the reason for not working ($P = .01$).[14] Taken together, these impacts may result in a "failure to achieve full life potential".[15]

Cumulative life course impairment

The overall burden of psoriasis does not remain static, but accrues over a patient's lifetime. The concept of cumulative life course impairment (CLCI) captures this longitudinal dimension of impact. First described in 2010[16], CLCI postulates that health is influenced throughout life by a range of social, environmental and economic determinants. These determinants inform not only disease status but overall well-being and QOL. As shown in **Figure 2**, suboptimal control of psoriasis and its physical comorbidities/psychosocial dysfunction/trauma intensifies the burden of disease as a whole, thereby, contributing to the individual's CLCI.

Figure 2: Cumulative burden of psoriasis over the life course.

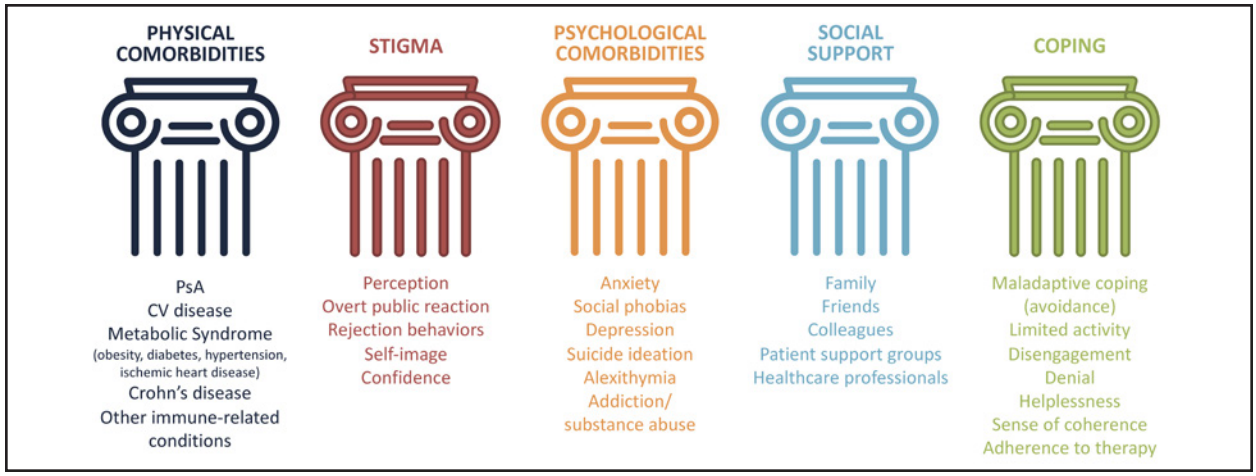


Adapted from Pariente JD, et al., Inflamm Bowel Dis. 2011;17:1415–22

Because of this cumulative burden, psoriasis lends itself especially well to a CLCI-based analysis. Research suggests that CLCI results from an interaction between (A) the burden of stigmatization, and physical and psychological co-morbidities as well as (B) coping strategies and external factors (**Figure 3**).

If a patient with psoriasis has an associated comorbidity, such as inflammatory bowel disease, the CLCI associated with the IBD may compound upon the CLCI of psoriasis.[17]

Figure 3: The pillars of CLCI in psoriasis



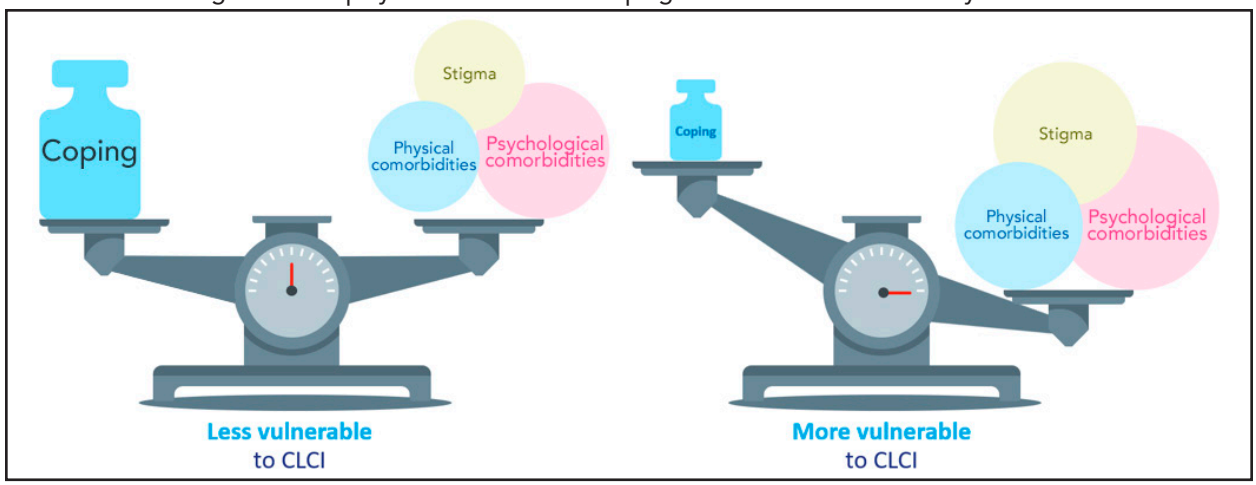
Adapted from Kimball AB, et al. J Eur Acad Dermatol Venereol 2010;24:989–1004.

Identifying psoriasis patients wth higher risk for CLCI requires a consideration of several clinical and psychosocial contributors, including:[18]

- Early age of onset
- More severe disease
- Significant comorbidities
- Perception of stigmatization
- Negative impact on work/profession
- Pessimistic personality structure
- Lack of social support
- Poor coping skills
- Engagement in risky behaviours

As illustrated below, overall vulnerability to CLCI is a balance between patient risk factors, individual vulnerability and the coping mechanisms available to the patient (**Figure 4**). Patients without support from family and friends, a multidisciplinary healthcare team, and/or support groups are more prone to CLCI. Understanding the aggregate risk factors facing each patient may help clinicians identify those with greater vulnerability to a high CLCI and inform treatment decisions earlier in the disease course.[19]

Figure 4: Interplay of risk factors and coping mechanisms in vulnerability to CLCI



Adapted from Kimball et al. JEADV 2010, 24, 989-1004.

CLCI patient cases

The two patients described below illustrate how negative impacts contribute to CLCI and how effective treatment can prevent this impairment from worsening.

SARA, 31, was diagnosed with severe plaque psoriasis at age 14 (BSA 12%). While most severe in the scalp, the plaques also affected other body areas including her hands, arms and legs. Throughout adolescence and early adulthood she was subject to various types of stigma, such as classmates avoiding physical contact with her and store attendants refusing to allow her to try on clothes. This eventually contributed to her development of depression and anxiety that was of sufficient severity to prevent her from forming close friendships and relationships. Following graduation from community college, Sara continued to live with her parents and worked part-time as a home-based bookkeeper. After failing topical therapy and being unable to tolerate the side effects of methotrexate and cyclosporine, she abandoned the pursuit of other treatments and became increasingly depressed.

At her family's insistence she finally returned to see her dermatologist, who prescribed her a biologic medication. Her skin cleared completely within 11 weeks, and she remained clear or almost clear as she continued on the biologic (BSA 0 to 0.5%, > PASI 90, DLQI improvement from a score of 12 at baseline to 0). Sara is working to change her learned avoidance behaviors. She is currently dating for the first time in her life and is completing her accounting credentials.

SAMIN, 42, developed extensive plaque psoriasis at age 18 and while he was in university he was picked on because of his psoriasis. He became obese (BMI 32) and developed problems with alcohol dependency. He dropped out of his engineering program, married and had two children, supporting his family by working at his father's appliance repair store. A diagnosis of psoriatic arthritis, followed by diabetes, led Samin to become less active and withdraw from his family and friends. Separated from his wife, his alcohol intake became a very significant issue, and he was admitted to hospital with hyperglycemic hyperosmolar syndrome.

Now living with a cousin, he is receiving mental health support and is slowly regaining his mental well-being. He has recently started a biologic treatment for his psoriasis, along with a diabetes-friendly diet and exercise plan and has experienced improvements in his psoriasis as well as his diabetes and depression. While satisfied with his progress, he expresses regret at not having begun treatment earlier.

ALL CLEAR: THE NEW TREATMENT TARGET

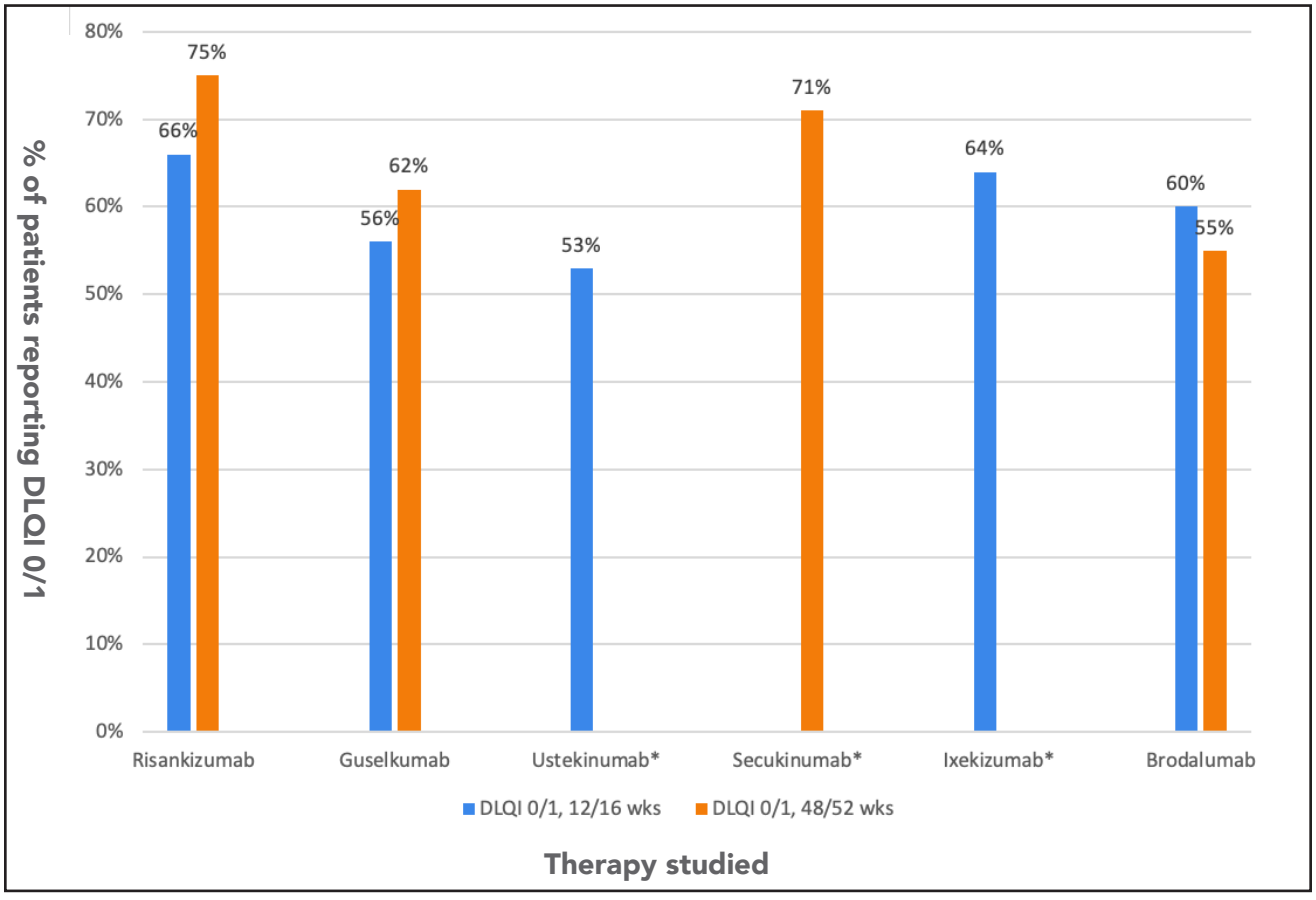
The evolution of biologic therapies available for the treatment of moderate-to-severe psoriasis has lead to a re-evaluation in treatment targets for both skin clearance and mental health/psychosocial functioning. Clear or almost-clear skin is considered an achievable target for most patients to support the broader goal of improving QOL and potentially reducing CLCI.[19]

The implications of clear skin

Clear skin contributes to an improvement in an individual's subjective well-being. In a survey of more than 8,000 patients from 31 countries with moderate-to-severe plaque psoriasis, respondents listed activities they most looked forward to doing if/when they achieved clear skin. Dominating the list were activities most people consider routine, such as hugging , sexual relations, dating, visits to the gym, and participating in outdoor sports.[20]

Treatment resulting in clear or almost clear skin has been demonstrated to improve patient QOL. Numerous studies have demonstrated that biologic therapies can help patients achieve a DLQI of 0/1, thereby indicating that patients experience little to no impact on their quality of life related to their psoriasis while on treatment (**Figure 5**). In addition, patient reported improvements in quality of life are greatest for patients with complete skin clearance. In three separate studies looking at the relationship between DLQI (0/1) and PASI response in patients treated with either ixekizumab, brodalumab or secukinumab, significantly more patients reported a DLQI 0/1 when they had clear skin (PASI 100) compared to almost clear skin (PASI 90).[21,22,23]

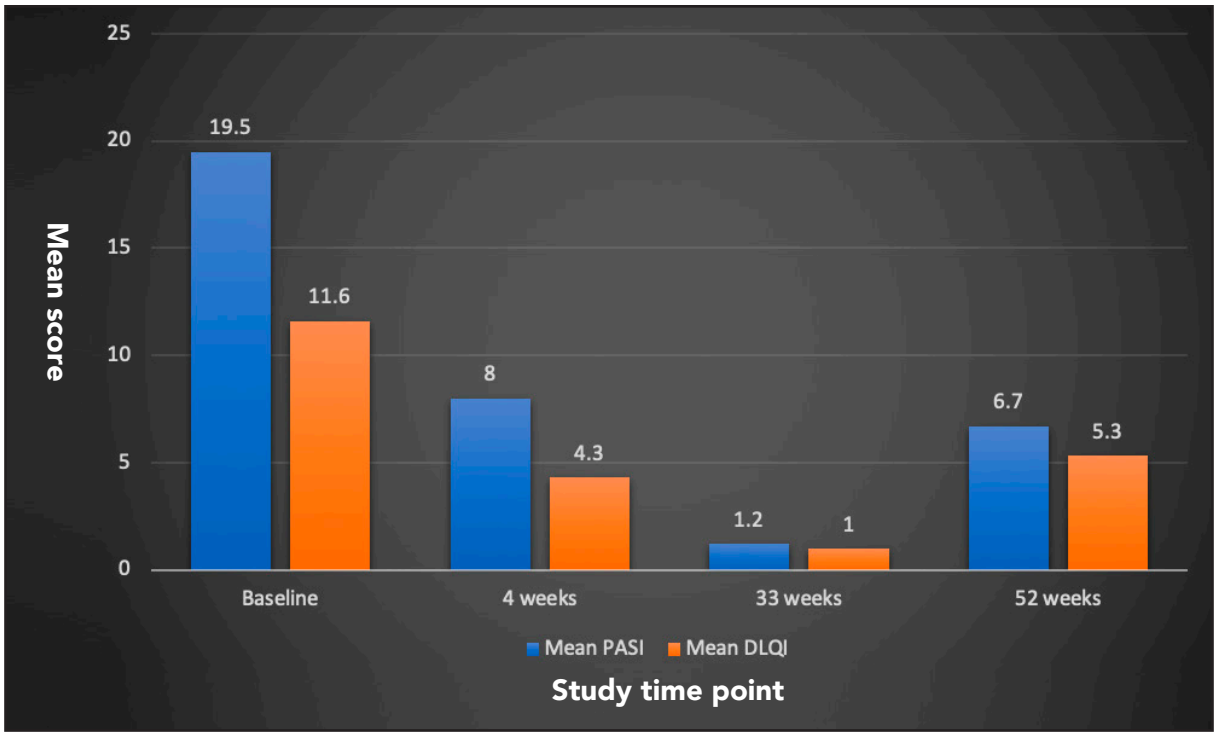
Figure 5: Percent of patients reporting DLQI 0/1 for various biologics at either 12/16 wks or 48/52 wks[24-29]



** study did not report short- and long-term DLQI 0/1 together*

It is not enough to achieve clear skin: maintaining the improvement is equally important, particularly since psoriasis is a chronic disease. In a study of psoriasis patients treated with a biologic agent, those who discontinued treatment after achieving a good response (defined as PASI 75) experienced a disproportionate larger increase (i.e. worsening) in DLQI score relative to the change in skin status (**Figure 6**).[30]

Figure 6: Maintenance of response is critical as relapse leads to disproprotionate worsening of DLQI



Adapted from Poulin et al, 2014

Treating to target

The treat-to-target approach entails setting treatment targets, choosing the appropriate treatment, regularly monitoring treatment response and adjusting the treatment plan when needed. This approach finds support in many psoriasis guidelines (**Table 1**), with therapeutic targets and management strategies becoming more ambitious as treatments continue to improve.

Table 1: Therapeutic targets in recent psoriasis guidelines

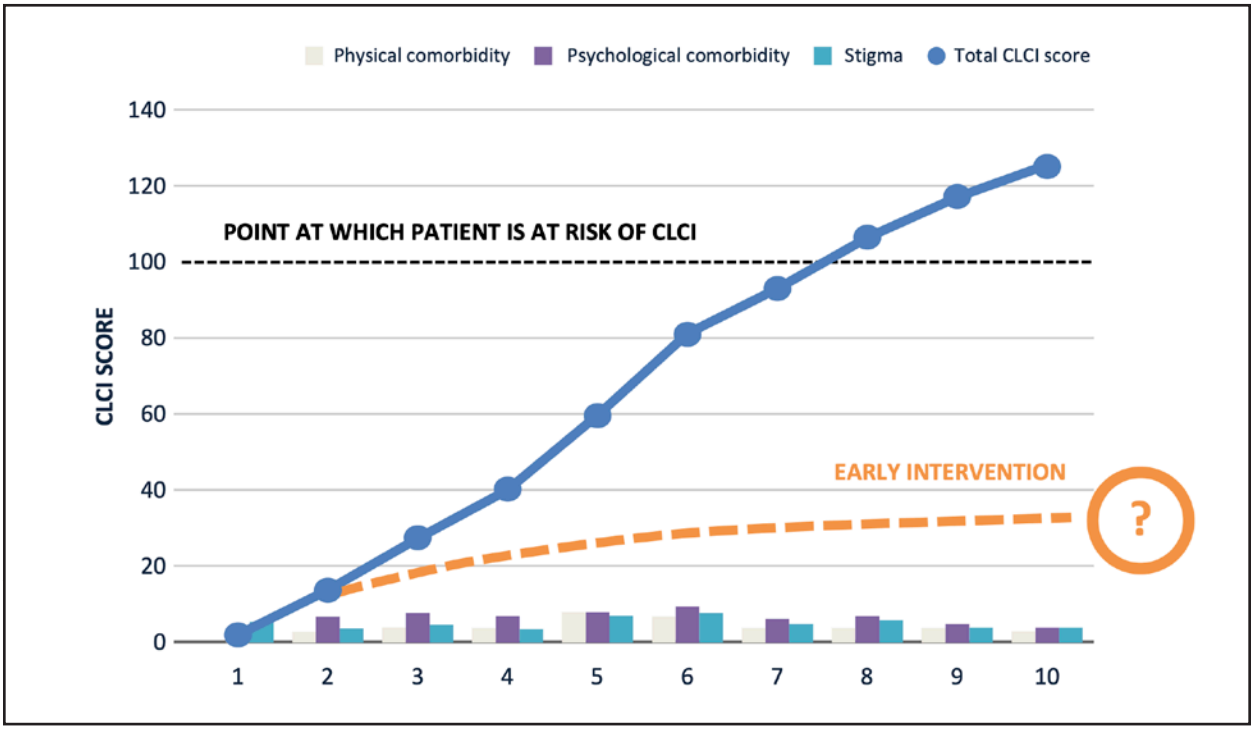
Guidelines	Target
2017 Canadian position paper on treat-to-target[31]	Clear or almost clear skin, improvement in QOL
2017 National Psoriasis Foundation guidelines[32]	Body Surface Area (BSA) ≤1% after 3 months of treatment
2019 National Psoriasis Foundation/American Academy of Dermatology guidelines[33]	PASI 100 as achievable goal (based on studies showing complete clearance in 24-45% of psoriasis patients on biologic treatment)
2019 Societé Française de Dermatologie guidelines[34]	PASI ≥ 90 and Physician Global Assessment (PGA) 0/1
2019 Japan Dermatological Association guidelines[35]	PASI 90 and DLQI 0/1

In parallel with these guidelines, clinical trials have shown an upward trend in the use of PASI 90 and PASI 100 endpoints over the past ten years, while the use of previous lower targets of PASI 50 and PASI 75 has decreased.[36]

The right treatment at the right time

Timely and appropriate treatment does more than improve symptoms: it can impact overall life course.[16] **Figure 7** illustrates how early intervention can mitigate the cumulative CLCI impact that results from the symptoms, comorbidities, stigmatization, and psychological scarring associated with moderate-to-severe psoriasis.[16] A systematic review suggests that effective treatment of psoriasis can help alleviate depression,[37] which in turn creates the conditions for better work productivity.

Figure 7: Early intervention can lower CLCI score



Adapted from Kimball AB, et al. J Eur Acad Dermatol Venereol 2010;24:989.

Thus, proper management of comorbidities and collaboration between different specialists, as well as leveraging community resources are key to disease control and maximizing the potential for a successful outcome.

Reaching target without biologics?

Traditional systemic agents are frequently prescribed for moderate-to-severe psoriasis and are often mandated by payers, despite limitations in their safety, efficacy and durability (**Table 2**).

Table 2: Therapeutic targets in recent psoriasis guidelines

Study design	Medication(s)	Results
16-week RCT	Methotrexate vs. adalimumab	Significantly fewer patients on methotrexate achieved complete clearance at week 16 (7.3 % versus 16.7%, p < 0.001).[38]
16-week observational study	Cyclosporine	40% of patients reached PASI ≥ 90 at 12 weeks, but close to 30% permanently discontinued treatment, most often due to poor tolerability.[39]
52-week RCT Results at week 16	Apremilast vs. placebo	20% of subjects attained PASI ≥ 90 at 16 weeks.[40]

Biologics for psoriasis

While early biologic therapy for psoriasis focused on TNF inhibitors, biologic agents that inhibit IL-23 (tildrakizumab, guselkumab, risankizumab) and IL-17 (secukinumab, ixekizumab, brodalumab) offer more targeted immune mediation and a better overall risk-benefit profile.[41] They have also demonstrated an excellent efficacy and safety profile in clinical trials.

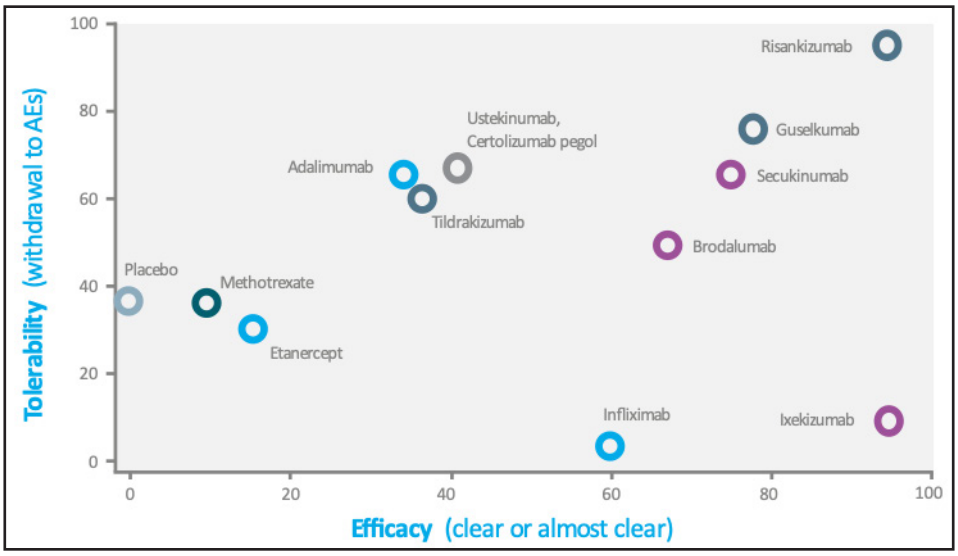
A meta-analysis examined the comparative efficacy for moderate-to-severe psoriasis patients on IL-17 and IL-23 inhibitors vs anti-TNF and oral agents. Seventy-one trials used an efficacy endpoint of 10-16 weeks and 11 used an efficacy endpoint of 48-52 weeks. The highest PASI 90 and PASI 100 response rates at weeks 48 to 52 were seen with risankizumab, brodalumab, guselkumab, and ixekizumab (**Table 3**).[42]

Table 3: Estimated response rates from the NMA of long-term PASI response

Treatment	Posterior median, % PASI 90	(95% CrI) PASI 100
Risankizumab 150 mg at weeks 0, and 4, then Q12W	85.3 (81.4, 88.7)	65.4 (59.3, 71.1)
Brodalumab 210 mg at weeks 0, 1, and 2, then Q2W	78.8 (74.0, 83.0)	55.7 (49.4, 61.8)
Guselkumab 100 mg at weeks 0, and 4, then Q8W	78.1 (72.5, 83.0)	54.8 (47.6, 61.9)
Ixekizumab 160 mg at week 0, 80 mg Q2W until week 12, then 80 mg Q4W	72.1 (62.7, 80.1)	47.2 (37.0, 57.6)
Secukinumab 300 mg at weeks 0, 1, 2, 3, and 4, then Q4W	67.0 (62.8, 71.0)	41.5 (37.0, 46.1)
Ustekinumab 45 mg B 100 kg, 90 mg [100 kg at weeks 0, and 4, then Q12W	55.0 (52.7, 57.3)	29.8 (27.6, 32.1)
Adalimumab 80 mg at week 0, then 40 mg Q2W	51.6 (41.8, 61.3)	26.9 (19.3, 35.7)
Etanercept 50 mg BIW until week 12, then QW	37.9 (30.4, 45.8)	16.7 (12.1, 22.4)

A recent network meta-analysis compared biologics, methotrexate and placebo efficacy using endpoints of PASI 90 or Physician's Global Assessment 0 or 1; PASI 75; Dermatology Life Quality Index improvement) and tolerability (defined as drug withdrawal due to adverse events) outcomes at 10-16 weeks. As shown in **Figure 8**, risankizumab demonstrated the overall best profile.[43]

Figure 8: Risk-benefit profile of biologic therapies and methotrexate



Adapted from Mahil SK et al. Br J Dermatol 2020;183:638.

The new biologics have also been compared to each other in head-to-head randomized controlled trials (RCTs) (**Table 4**).

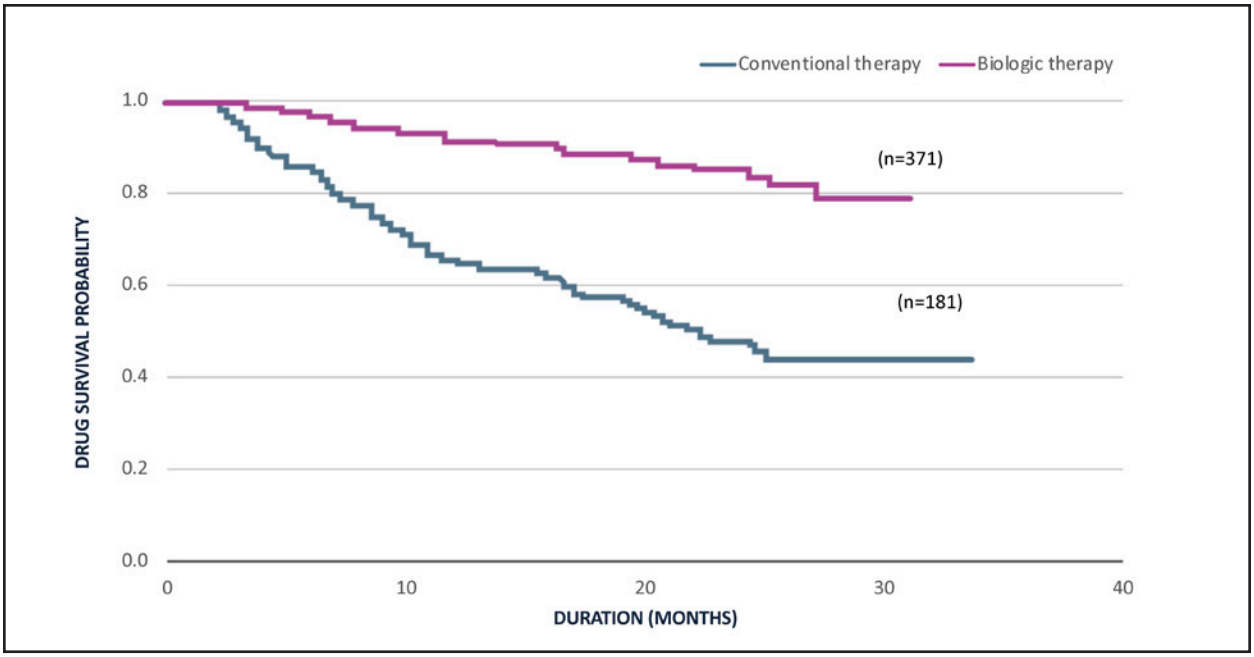
Table 4: Head-to-head RCTs of biologics for psoriasis

Study medication	Comparator	Primary Endpoint	Results
Risankizumab	Secukinumab	PASI90	Non-inferiority at week 16; superior efficacy at week 52[44]
Guselkumab	Secukinumab	PASI90	Superior efficacy at week 48[45]
Ixekizumab	Guselkumab	PASI100	Superior skin clearance at week 12[46] Non-inferiority at week 24, with no significant difference in PASI 100[47]

Benefits of biologics beyond efficacy

Biologics have a better drug survival profile than conventional systemic therapies for psoriasis.[48] In a 2020 study evaluating 2-year drug survival of conventional systemic agents methotrexate, cyclosporine and acitretin compared with the biologics etanercept, adalimumab and ustekinumab, the overall drug survival probability at 30 months was significantly higher with biologics than with conventional therapy (**Figure 9**).[48]

Figure 9: Drug survival with biologics vs conventional therapies



Adapted from Puig L et al. J Dermatol Treat 2020; 31:344.

Most significantly, biologcs can mitigate the impact of psoriasis on CLCI. Many biomarkers of inflammation have been identified including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).[49] Research has demonstrated that CRP levels are positively correlated with disease severity as measured by PASI.[49] Treatment with biological agents decreases systemic inflammation as measured by the ESR and CRP levels in several different disease states.[49] In patients with moderate-to-severe psoriasis treated with systemic therapies, including methotrexate, adalimumab, etanercept, infliximab and ixekizumab, studies have reported reductions in ESR and/or CRP levels.[49] In addition, numerous studies have demonstrated the use of biologics and reduction in depression and anxiety symptoms and improved work productivity in psoriasis patients.[50] In an ongoing observational study entitled the Psoriasis Atherosclerosis Cardiometabolic Initiative (PACI; NCT01778569), 209 participants aged 37-62 were enrolled with 124 receiving biologic therapy, and 85 in the control group treated only with topical creams and light therapy. After one year of treatment, researchers noted that patients who received biologic therapy had an 8% reduction in coronary plaque compared with subjects in the control group who experienced slightly increased coronary plaque progression. Even after adjusting for cardiovascular risk factors and psoriasis severity, patients treated with biologic therapy had reduced coronary plaque.[51] Research has demonstrated the potential role of a shared pathogenic mechanism involving psoriasis, cardiovascular disease and metabolic syndrome. This pathogenesis is believed to center on IL-17A and its proinflammatory role, thereby improving not only skin manifestations but also cardiovascular inflammation and metabolic factors.[52] In a 2019 prospective, observational study, researchers demonstrated that treatment of psoriasis with biologic therapy is associated with a reduction of non-calcified coronary plaque and improvement in plaque morphology compared with those not treated with biologic therapy.[53]

AN APPROACH TO MINIMIZING CLCI

In summary, a treat-to-target approach using highly efficacious treatment aims to help achieve the long-term objective of maximizing QOL and minimizing CLCI. In support of this objective, the therapeutic approach should include:

- Early diagnosis coupled with timely and successful collaborative management of psoriasis
- Setting a treatment target of clear or almost clear skin
- Regularly monitoring treatment response
- Optimizing treatment when clear or almost clear skin is not achieved
- If optimization strategies do not work, moving to another treatment in a timely fashion

When deciding on a systemic agent, relevant factors include not only the potential to improve symptoms, but also the ability to alter life course. Clinical response to treatment should be assessed regularly and modified promptly if insufficient. Clincians are reminded that psoriasis patients most at risk for the development of CLCI include those with a combination of clinical and psychosocial factors including, but not limited to, prolonged disease duration, disease that is more severe, the presence of comorbidities, lack of social support and poor coping skills.

While early diagnosis and intervention is ideal, opportunities for clinically meaningful interventions exist at many points across the treatment arc. It is never too late to set high treatment goals and implement a treatment plan that aims to optimize both symptom management and provide the patient with the greatest opportunity for a positive life trajectory.

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UNDERSTANDING CUMULATIVE LIFE COURSE IMPAIRMENT IN PSORIASIS: IMPACT ON PATIENT MANAGEMENT

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