

Complete skin clearance and beyond

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Linked Article: Warren *et al.* *Br J Dermatol* 2021; **184**:50–59.

Before the introduction of biologics, the treatment of moderate to severe psoriasis was Sisyphean. Today, interleukin (IL) inhibitors have made it possible in many cases to achieve complete skin clearance/100% improvement from baseline in Psoriasis Area and Severity Index (PASI 100). To investigate which IL inhibitors are most potent at the group level is essential. Randomized controlled trials show their particular strength in the head-to-head setting – the collection of real-world evidence in this domain is not trivial. However, head-to-head trials are unfortunately rare, giving the article by Richard Warren *et al.* from Manchester in this issue of the *BJD* particular importance.¹

The AbbVie-funded, multicentre, phase III, randomized open-label, efficacy-assessor-blinded trial (IMMerge) compared both efficacy and safety between the IL-23 inhibitor risankizumab (Skyrizi®, AbbVie) and the IL-17 inhibitor secukinumab (Cosentyx®, Novartis) under 1 year (52 weeks) of treatment in a total of 327 included patients. Risankizumab met both primary endpoints – it was, in the proportion of patients achieving PASI 90, both noninferior at week 16 and superior at week 52. Even the secondary endpoints were met by risankizumab, including PASI 100 at week 52. That risankizumab only needs to be administered after initiation every 12 weeks (secukinumab every 4 weeks) is an additional advantage.

With several new molecules in each class of biologics it is not feasible to have evidence from comparative studies for all molecules. However, it is hazardous to regard one molecule as representative for a class. Correctly, the authors did not speculate on class effects but clearly restricted their conclusions to risankizumab vs. secukinumab. We know from everyday practice that patients may have a very different response to molecules within one class. To build evidence for personalized medicine, patient registers are of utmost importance to understand the therapeutic effectiveness of the various molecules in real life.²

Two patients treated with risankizumab experienced non-fatal myocardial infarctions confirmed as major adverse cardiovascular events (MACEs) (no MACE occurred in patients treated with secukinumab). Both patients had a smoking history extending decades. Neither event was considered to have a causal relationship with risankizumab treatment, and both patients remained in the study without treatment interruption. The authors conclude that no new safety signals were detected during this trial, which is correct, as MACE signals for risankizumab were described in independent trials before.^{3,4} At this stage, it is of course difficult to exclude a causal relationship between risankizumab and MACEs in particular risk groups – careful follow-up in phase IV studies have to address this question. Patient registries are important here, too, to capture

these rare adverse events and to retrieve the information for all molecules within each class of biologics.

But, in a larger sense, this study confronts us with the paradox of the interleukin era – that a patient with psoriasis who has achieved complete skin clearance is not necessarily healthy. This is particularly important now as the Coronavirus disease 2019 (COVID-19) pandemic clarifies the vital importance of general health and fitness. In the delicate interplay between psoriasis of the skin, and somatic and psychiatric comorbidity,⁵ we cannot take comfort in the belief that pharmaceutical psoriasis treatment will also take care of comorbidities. In particular, as this study insinuates, pharmaceutical psoriasis treatment will not be able to compensate for poor lifestyle choices such as smoking.

Are we not obligated to explain to a patient with, for example, a MACE risk that we can treat the skin successfully with IL-inhibitors, but that her overall health needs to be improved by optimizing lifestyle factors too?

We dermatologists are often the central caregiver for patients with psoriasis, and we interact directly with our patients. In this encounter, an excellent opportunity arises to raise and discuss health challenges beyond the skin. Let us be ambitious in the management of psoriasis, aiming for clear skin, optimal quality of life and last, but not least, optimal health in its broadest sense.

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Survival is excellent for most patients with thin melanoma, but patients may die from thin melanoma

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In this issue of the *BJD*, Isaksson et al. describe the (conditional) melanoma-specific survival (MSS) of over 30 000 Swedish patients with thin melanoma (≤ 1 mm Breslow thickness).¹ While MSS is heavily influenced by patients who die rather soon after diagnosis, conditional melanoma-specific survival (CMSS) provides updated survival estimates during follow-up, given that a patient has already survived a number of years. This information is informative for patients and clinicians during follow-up visits, and also for health policymakers to determine a suitable frequency of follow-up visits. In this study, long-term MSS and CMSS were both excellent (above 95%) and close to the survival of the general population.

Although this study does not compare different follow-up schedules or assess the impact of follow-up on MSS, these population-level survival estimates support the assumption that follow-up is not very beneficial from a mortality perspective.² The current Swedish national follow-up recommendations [a single postoperative visit (stage IA/IB) plus 3 years of annual follow-up visits (stage IB)] seem appropriate, but they might benefit patients' anxiety and possible subsequent tumours more than they increase survival rates.^{3,4}

The relative numbers are very good, but the volume of patients with thin melanoma is very high, resulting in 727 deceased Swedes due to thin melanoma during the 27-year study period.¹ Due to the high volume of thin melanomas, more people died due to thin melanoma than due to thick melanoma in Australia.⁵ In the era of personalized medicine, patients with thin melanoma should be further stratified as being at high or low risk, because now it has diagnostic and therapeutic consequences. Currently, sentinel lymph node biopsy (SLNB) is recommended for stage IB melanoma onwards.⁶

Although it is very rare, death due to melanoma can even occur among people with very thin tumours (< 0.6 mm), as can be seen from the MSS curve.¹ Those patients may not have been offered SLNB, as only 4% of all patients with thin melanoma underwent biopsy.¹ SLNB in specific subpopulations of patients may upgrade their stage, making them eligible for adjuvant immunotherapy, which may affect long-term survival.

Gene expression profiles (GEPs) of the primary melanoma may be used in the future to guide SLNB decisions.^{7,8} A GEP

of six classes with prognostic value in patients with stage I melanoma was identified.⁹ Unfortunately, the class that was associated with a poor prognosis was also associated with nonresponse to immunotherapy.⁹ GEPs should also be used to identify patients who might benefit from adjuvant therapy, because stage shifts towards lower stages occur for adjuvant therapy (e.g. stage IIC; see the KEYNOTE-716 trial: [clinicaltrials.gov NCT03553836](https://clinicaltrials.gov/NCT03553836)). The use of GEPs may allow acceptable risk–benefit ratios in high-risk patients with melanoma of lower stages, without exposing all patients of a certain stage to adjuvant therapy.

To conclude, although the prognosis for patients with thin melanoma is excellent on a population level, there are some patients who die due to thin melanoma. Future research should enable practitioners to identify those patients in order to provide personalized care pathways.

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