Last but not least, the rigour of development was also assessed as suboptimal in two-thirds of the guidelines. This AGREE II domain evaluates the methodological process applied for conducting an appropriate and transparent evidence synthesis and selection process, and the approach for formulating trustworthy and credible recommendations. This methodological process is the core of guideline development and is the factor that defines a real evidence-based guideline. Without meeting these methodological standards, guidelines are prone to biased recommendations.

Using recommendations from low-quality guidelines may lead users to recommend treatments that are ineffective or harmful, are not implementable, are not acceptable by patients and have low or no value for money. Therefore, based on the work of Yen *et al.*, we may be confident that the guideline with the least risk of providing biased or problematic recommendations is that from EuroGuiDerm,[1] followed by the other British, French and German guidelines.[5–8]

This article provides an excellent summary of the available guidelines on psoriasis and describes their quality. Therefore, it should be a must-read article for dermatologists treating patients with psoriasis, for decision makers interested in psoriasis treatment and for anyone interested in using, adapting or implementing the best guidelines for their context.

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miR-378a: an amplifier of the interleukin-17A response in keratinocytes

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Linked Article: Xia *et al.* Br J Dermatol 2022; **187**:211–222.

MicroRNAs (miRNAs or miRs) are a group of single-stranded short noncoding RNAs of approximately 22 nucleotides in length. They regulate the expression of protein-coding genes at a post-transcriptional level. Through the RNA-induced silencing complex, miRNAs bind to the 3′-untranslated region of their target mRNAs, leading to translational inhibition or degradation of these targets.[1] miRNAs are known to play an important role in numerous biological and physiological processes, and abnormal miRNA expression has been discovered in many human diseases, including psoriasis.[2,3]

Psoriasis is a common chronic immune-mediated skin disease affecting approximately 125 million people worldwide. The pathogenesis of psoriasis is not fully understood but it is believed to be driven by an abnormal interplay between T cells and keratinocytes. In particular, the proinflammatory cytokine interleukin (IL)-17A is known to play a crucial role in psoriasis pathogenesis. This is shown by drugs targeting IL-17A, which have proven to be highly effective in psoriasis treatment.[4] Although the keratinocytes are believed to be the key cellular target of IL-17A-induced psoriasis,[5] the mechanism is not completely elucidated.

In this issue of the *BJD*, Xia and colleagues systematically investigated the interplay between miR-378a and IL-17A in human keratinocytes.[6] Sequencing of small RNAs showed miR-378a to be overexpressed in keratinocytes isolated from lesional psoriatic skin compared with nonlesional psoriatic skin and healthy skin, a finding that was also previously published by the same group.[7] In a psoriasis mouse model, intradermal injection of miR-378a was found to exacerbate psoriasis-like skin inflammation, suggesting that increased levels of miR-378a in psoriatic keratinocytes contribute to the pathogenesis.

To further characterize the molecular mechanism behind this observation, Xia *et al.* stimulated primary human keratinocytes with psoriasis-associated cytokines and found IL-

17A to be a strong inducer of miR-378a. IL-17A is known to mediate its psoriatic effects by acting on keratinocytes by a mechanism involving intracellular signalling molecules including nuclear factor (NF)-κB and IκBζ.[8] In line with this, Xia and colleagues reported that the IL-17A-induced expression of miR-378a observed in human keratinocytes was mediated by a mechanism involving NF-κB, C/EBP-β and IκBζ.

Interestingly, Xia and colleagues not only demonstrated that IL-17A activated NF-κB in keratinocytes, but also reported that overexpression of miR-378a by itself led to activation of NF-κB, which was mediated by directly targeting IκBα, a negative regulator of the NF-κB signalling pathway.

Taking the results together, the study by Xia *et al.* in a sophisticated manner unravelled a novel mechanism in human keratinocytes where IL-17A induces miR-378a, which then acts in a positive feedback loop further amplifying inflammation by activating the NF-κB signalling pathway. This is an important study because a better understanding of the underlying molecular mechanisms by which IL-17A mediates its psoriatic effects in human keratinocytes is greatly needed in order to identify new treatment targets. Based on the encouraging results of Xia and colleagues it is possible that modulation of miR-378a may be a future treatment strategy in inflammatory skin diseases such as psoriasis.

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Interleukin-17RA blockade by brodalumab decreases inflammatory pathways in hidradenitis suppurativa skin and serum

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Hidradenitis suppurativa (HS) is an inflammatory skin disease primarily affecting areas rich in apocrine glands, such as axillary and inguinal regions.[1] HS is characterized by painful inflammatory nodules and abscesses, which can progress to continuously draining fistulas and lead to extensive scarring.[2] The pathogenic concept of HS is currently changing from a disease originating in follicular occlusion to a systemic autoinflammatory, autoimmune keratinization condition, as seen in generalized pustular psoriasis.[3] Compared with other chronic inflammatory diseases, such as psoriasis, much less is known about the molecular processes driving inflammation in HS. As a result, current systemic treatment options are largely limited to courses of antibiotics and the tumour necrosis factor inhibitor adalimumab.[4]

Inhibition of interleukin (IL)-17 signalling has shown promise in clinical studies involving bimekizumab,[5] brodalumab[6] and secukinumab.[7] In this issue of the *BJD*, Navrazhina *et al.* characterize the molecular response to the IL-17 receptor agonist (IL-17RA) inhibitor brodalumab.[8] Their results offer potential clinical benefit and provide useful insights into the molecular pathophysiology of HS. To begin, the authors compared skin biopsies from the edge of inflammatory lesions (lesional) and from intact skin 2 cm (perilesional) and 10 cm away (control) using RNA sequencing and immunohistochemistry. They found that levels of inflammation based on differentially expressed genes are similar in lesional and perilesional skin compared with controls at baseline. However, inflammation decreases much more in perilesional vs. lesional skin at week 12 after initiation of biweekly treatments with brodalumab, suggesting that perilesional skin is more useful than lesional skin for monitoring treatment responses, which is consistent with previous studies.[9,10] An important question for future studies will be to determine the extent to which anti-inflammatory responses in perilesional skin predict clinical outcomes.

The authors derived further insights into the molecular response to brodalumab by conducting proteomic analyses in serum. Thereby, they identify downregulation of several neutrophil-related pathways. Together, these results then allowed the authors to identify the expression of neutrophil-related lipocalin 2 in the skin and IL-17A levels in the serum as potential biomarkers. In addition, they found several other pathways related to regulation of granulocytes, neutrophil migration and chemotaxis, as well as a reduction of B-cell infiltration. Taken together, these data point to IL-17