

the ability of volar keratinocytes to retain their identity *in vitro* in a cell-autonomous manner. Moreover, the results also identify a platform to explore how positional identity and cell fate can be modulated *in vivo*. With the advent of gene- and cell-based therapy for many skin diseases, this study has important clinical implications for future human trials.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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Adalimumab in Psoriasis: How Much Is Enough?

Allison C. Billi and Johann E. Gudjonsson

Biologic therapies targeting tumor necrosis factor have revolutionized treatment of immune-mediated inflammatory diseases such as psoriasis, but optimal dosing and appropriate use of therapeutic drug monitoring are not yet fully understood. Wilkinson et al. explore these questions in a real-world psoriasis cohort on adalimumab monotherapy, defining a therapeutic range and finding value in early measurement for predicting clinical response.

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Growing costs of biologic therapy

Immune-mediated inflammatory diseases (IMIDs) are chronic conditions that can cause severe tissue damage, leading to increased morbidity and mortality. Biologic therapies have dramatically altered management of patients with IMIDs, but the prices of biologics are significantly higher than for traditional therapies. The active development of biosimilars brings hope that costs may decrease, but these alternatives are predicted to be only 20–30% less expensive than branded biologics. Availability of small-molecule chemical generics, in contrast, has historically lowered drug prices by as much as 90% (Blackstone and Fuhr, 2012). The majority of biologic therapies are prescribed with a “one size fits all” dosing, with variable data supporting doubling doses if sufficient clinical responses are not achieved or sustained. As this is frequently accompanied by a doubling of cost, substitution of another agent may be preferable, but can lead to development of anti-drug antibodies (ADAs) that may limit a patient’s future treatment options. On the other hand, adding methotrexate or another systemic medication for additional control exposes the patient to possible cumulative toxicity.

In the face of rising healthcare costs, researchers, clinicians, and policymakers must confront the significant

financial burden of biologic therapy. Early identification of patients who will respond to a biologic therapy and dosage adjustment to target an effective drug level represent potential cost-saving measures. In a large-scale, real-world multicenter cohort analysis, a study team led by Catherine Smith has investigated the utility of therapeutic drug monitoring in patients with psoriasis on adalimumab, an anti-tumor necrosis factor (TNF) biologic therapy (Wilkinson et al., 2018).

Defining a therapeutic range for adalimumab in psoriasis

Drawing from the Biomarkers of Systemic Treatment Outcomes in Psoriasis (BSTOP) cohort, Wilkinson et al. (2018) analyzed 544 patients with moderate to severe plaque psoriasis on adalimumab monotherapy, 69% of whom were naïve to biologic therapy (Wilkinson et al., 2018). From these patients, they collected Psoriasis Area and Severity Index (PASI) data and serum samples for testing of adalimumab levels. They defined analytic datasets of patients recently initiated on adalimumab (within 1–12 weeks) and post steady state (on therapy for at least 9 weeks). Comparing steady-state levels with same-day PASI scores, they found that an adalimumab serum level of 3.2 µg/ml or higher distinguished responders from nonresponders, with



Department of Dermatology, University of Michigan, Ann Arbor, Michigan, USA

Correspondence: Johann E. Gudjonsson, Department of Dermatology, University of Michigan, 6427C Medical Science I, 1301 Catherine, Ann Arbor, Michigan, 48109, USA. E-mail: johanng@med.umich.edu

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Clinical Relevance

- The therapeutic range for adalimumab is similar in psoriasis and other immune-mediated inflammatory diseases.
- Many psoriasis patients on adalimumab have drug levels outside the therapeutic range.
- Optimization of therapy for these patients requires further study.

approximately 65% of patients achieving their primary outcome of PASI75 (75% improvement in baseline PASI) at this threshold. A descriptive concentration effect curve generated from these data confirmed increased clinical response with increasing drug level; however, the effect plateaued at drug levels $\geq 4.6 \mu\text{g/ml}$. At $4.6 \mu\text{g/ml}$, a median percentage PASI change of 90.7% was observed, but probability of achieving the primary outcome of PASI75 was only 73%. For establishing a therapeutic range, [Wilkinson et al. \(2018\)](#) therefore specified a target drug level of $7 \mu\text{g/ml}$, at which 81% of patients achieved PASI75. Drug levels were measured at routine clinic visits, and the therapeutic range was comparable to that reported in another study of adalimumab in psoriasis derived from trough drug levels ([Menting et al., 2015](#)).

Additional analyses to account for possible confounding covariates identified serum drug level as the single most important determinant of response to treatment ([Wilkinson et al., 2018](#)). There was no additional clinical utility of

measuring ADAs, presumably because their effect is reflected in serum drug levels. Ethnicity emerged as a potentially significant covariate, with non-white ethnicity being associated with lower response rates, but the authors caution against over-interpretation of this finding, given the low representation of non-white patients in the study. While prior exposure to biologic therapy was not a predictor of achieving PASI75, biologic-naïve patients did show a trend in some analyses toward increased likelihood of clearance (PASI90 or absolute PASI ≤ 1.5).

Serum drug level as an early predictor of response

[Wilkinson et al. \(2018\)](#) then examined whether early serum drug level can predict therapeutic response at a later time point. They found that drug levels measured within 12 weeks of initiating adalimumab effectively predicted therapeutic response after 6 months of therapy. Patients who met the $7\text{-}\mu\text{g/ml}$ target drug level early in therapy had a 78% probability of achieving PASI75 at

6 months. Not unexpectedly, serum drug levels measured at steady state (after 9 weeks of therapy and beyond) also predicted therapeutic response 6 months later. The greatest value of these findings lies in the ability to identify responders early in the course of treatment when the full clinical response is often not yet apparent. Drug levels may even be informative within the first 4–5 weeks of therapy, according to this and a previous study from the same group ([Mahil and Smith, 2013](#)).

A therapeutic plateau suggests other mechanisms at play

Intriguingly, [Wilkinson et al. \(2018\)](#) observe a therapeutic plateau, with adalimumab serum levels $\geq 4.6 \mu\text{g/ml}$ conferring little additional clinical benefit, despite the persistence of active psoriasis. One possibility is that this represents the level at which TNF blockade is saturated, and an alternative inflammatory pathway independent of TNF is driving the residual disease. This alternative pathway may also be a more active driver of psoriasis in patients whose response plateaus at a lower level, and is therefore possibly more dominant in non-white patients, although this remains to be determined. An example of such a scenario may be the recently suggested mechanism underlying paradoxical psoriasis, wherein 5–10% of patients on anti-TNF agents develop psoriasiform dermatitis. Paradoxical psoriasis has long been

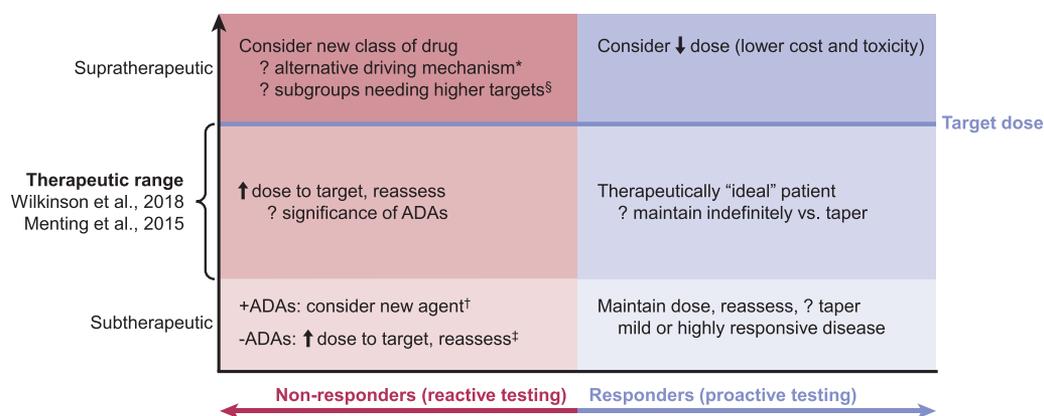


Figure 1. Speculative framework for biologic therapeutic drug monitoring in psoriasis. This was conceptually adapted from conditional recommendations in the field of inflammatory bowel disease ([Feuerstein et al., 2017](#)). The value of proactive testing is still under debate. Therapeutic ranges appear to be similar across immune-mediated inflammatory diseases including inflammatory bowel disease, suggesting shared pharmacodynamics. Much remains to be determined, including timing of monitoring, that is, during induction or at steady state, and whether particular subgroups of psoriasis patients exist who may require higher target doses. *Mechanistic failure. §Increasing the dose may also include decreasing the dosing interval or adding an immunomodulator. †Immune-mediated pharmacokinetic failure; transition to another class of drug is also reasonable. ‡Non-immune-mediated pharmacokinetic failure. ADA, anti-drug antibody.

suspected to reflect altered immunological homeostasis due to imbalance of inflammatory and regulatory cytokines and immune cells. Recently, lesions of paradoxical psoriasis were found to show selective overexpression of type I IFNs, increased dermal plasmacytoid dendritic cells, and reduced T-cell numbers compared to classical psoriasis (Conrad et al., 2018). Furthermore, in paradoxical psoriasis, TNF blockade prolongs type I IFN production, leading to a T-cell-independent psoriasiform phenotype. It is possible that the adalimumab therapeutic plateau reflects a point at which TNF blockade triggers or unmasks the overactive plasmacytoid dendritic cell-driven innate immune response. In addition, TNF has anti-inflammatory effects that may underlie other paradoxical inflammatory reactions observed during anti-TNF therapy. TNF- α limits acute intestinal inflammation by inducing local intestinal steroidogenesis (Noti et al., 2010), which could explain a possible association between cases of de novo inflammatory bowel disease (IBD) in patients on anti-TNF therapy. However, there is no evidence for a similar mechanism in the skin, and we have shown that TNF- α decreases local cutaneous glucocorticoid biosynthesis (Sarkar et al., 2017). With cases of paradoxical psoriasis related to IL12/IL23 blockade now accumulating, it will be interesting to evaluate these agents for a similar therapeutic threshold and interrogate the underlying molecular mechanisms.

Impact on current practices

Adalimumab is currently one of the most commonly measured biologic therapies in routine practice, often accompanied by ADA testing. Adalimumab quantitation is frequently performed using classic ELISA, but multiple ELISA methodologies are employed and other methods are available, complicating use of standard therapeutic ranges.

Based on their therapeutic range for adalimumab in treatment of psoriasis, Wilkinson et al. (2018) note that a large proportion of their study population would benefit from treatment modification. Half of nonresponders showed subtherapeutic levels, and >40% of patients achieving 90% improvement in

baseline PASI showed supratherapeutic levels (Wilkinson et al., 2018). Their findings additionally suggest that providers may consider proactive testing during induction to identify nonresponders sooner. Whether the patients with subtherapeutic levels are better suited for dose escalation or transition to another agent is not specifically addressed in this study, but is of great practical interest. The therapeutic ranges for adalimumab in psoriasis defined by Wilkinson et al. (2018) and Menting et al. (2015) are similar to those reported for other IMIDs (Pouw et al., 2015; Roblin et al., 2014; Yarur et al., 2016), suggesting common disease pharmacodynamics. In applying the therapeutic range to psoriasis patients, we may look to other IMIDs for guidance.

During care of IBD patients, assessment of trough levels of anti-TNF agents and ADAs is commonplace. Therapeutic drug monitoring, including ADA testing, may be performed at any point during induction or maintenance therapy, in both nonresponders (referred to as reactive testing) and responders (proactive testing). Target trough concentrations have been established for patients on maintenance therapy, but may not apply to other groups, such as patients with secondary loss of response or patients with perianal disease, who may require higher target concentrations (Feuerstein et al., 2017). Higher targets may also be required during induction, and patients with suboptimal response during induction may benefit from empiric dose escalation, unless failure due to ADAs is suspected. Data for adalimumab are overall less robust than for infliximab, and many questions remain.

Current evidence supports the use of reactive testing to classify IBD patients failing anti-TNF therapy in order to guide treatment modification (Feuerstein et al., 2017). Among nonresponders, three broad causes of drug failure are recognized:

1. In mechanistic failure, drug level is optimal, but clinical response is inadequate, indicating an alternative disease mechanism, such as the presence of inflammatory mediators not targeted by the therapy. Such patients are unlikely to benefit from transition to another drug of the same class.

2. In immune-mediated pharmacokinetic failure, drug level is subtherapeutic in the presence of high titers of drug-neutralizing ADAs.
3. In non-immune-mediated pharmacokinetic failure, drug level is subtherapeutic in the absence of ADAs, often due to rapid drug clearance in the setting of high inflammatory burden (Vande Casteele et al., 2017).

Distinguishing among these causes of drug failure can help to identify nonresponders who may benefit from dose escalation versus transition to a different anti-TNF agent or an alternative therapeutic class altogether.

The value of proactive testing in IBD is still under intense investigation. Indirect evidence from the TAXIT (Trough Concentration Adapted Infliximab Treatment) study suggests one-time testing for initial dose optimization may be beneficial, as it may increase the number of responders by identifying patients with low drug levels who require escalation of therapy (Vande Casteele et al., 2015). It may also yield cost savings by enabling dose reductions in patients with supratherapeutic drug levels. Subsequent work has expanded upon these findings. Of particular interest is a recent investigation of early (4 weeks) testing during adalimumab therapy in Crohn's disease to guide dose optimization. The findings from this study suggested that sufficient drug level during induction may prevent ADA development (Verstockt et al., 2018). There may, however, be risks associated with proactive testing for ADAs, as the significance of low-titer ADAs is still unclear. ADA measurement is considerably more variable across assays, and there is no standardized reporting. In patients with ADAs and immune-mediated pharmacokinetic failure, dose escalation poses the risk of immediate and delayed hypersensitivity that may be severe (Vande Casteele et al., 2017). Clinicians may therefore overinterpret the significance of low-titer ADAs, leading to a premature switch from the index therapy.

The wealth of data in IBD patients has spurred development of guidelines addressing appropriate use of therapeutic drug monitoring during anti-TNF therapy. The American Gastroenterological Association has developed an algorithm for reactive testing and

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management of nonresponders (Feuerstein et al., 2017), and guidelines addressing proactive monitoring may be on the horizon. The psoriasis community will benefit from similar guidance, and parallel research across IMIDs may help to advance the field rapidly. We present a speculative framework (Figure 1) conceptually adapted from conditional recommendations in the field of IBD (Feuerstein et al., 2017). For all future guidelines focusing on anti-TNF therapy, cost will and should be a critical consideration. Given the money at stake, recommendations may be motivated by cost-effectiveness to an unprecedented degree.

CONFLICT OF INTERESTS

The authors state no conflict of interests.

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KLHL24: Beyond Skin Fragility

Maria C. Bolling¹ and Marcel F. Jonkman¹



KLHL24 mutations have recently been associated with epidermolysis bullosa simplex. Initial studies focused on skin fragility. However, the picture of KLHL24 mutations causing extracutaneous human disease is emerging, with dilated cardiomyopathy as a strong association. In addition, neurological disease is suspected as well. Careful clinical follow-up and functional studies of (mutated) KLHL24 in these tissues are needed.

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KLHL24, encoded by the gene *KLHL24*, is the “new kid on the block” in the hereditary skin fragility disorder epidermolysis bullosa simplex (EBS) (He et al., 2016; Lin et al., 2016). The basal variant of EBS with a level of blister formation through the basal keratinocytes is caused by mutations in genes encoding the basal cell keratins keratin (K) 5 or K14 in the majority of cases. However, approximately 25% of EBS cases were unsolved on the DNA level before next generation sequencing techniques emerged (Bolling et al., 2011). In 2016, Lin et al. (2016) and He et al. (2016), using whole-exome sequencing, discovered dominant acting point mutations in the start codon of *KLHL24* caused basal cell skin fragility. Since then, several other

patients with basal EBS caused by *KLHL24* mutations, all affecting the same start codon, have been reported (Alkhalifa et al., 2018; Lee et al., 2017; Yenamandra et al., 2018). *KLHL24*, unlike K5 and K14, is not a structural protein. *KLHL24* belongs to a family of proteins with a Kelch-like motif that is part of a ubiquitination-ligase complex and is involved in tight regulation of its substrate levels. Lin et al. (2016) suggested that *KLHL24* was the substrate receptor of the cullin 3 (CUL3)—RBX1—*KLHL24* ubiquitin-ligase complex, with K14 being the ubiquitination substrate based on in vitro experiments with recombinant proteins. They showed that the EBS-associated *KLHL24* start codon mutation caused an N-terminal truncation of *KLHL24*,

¹University of Groningen, University Medical Center Groningen, Department of Dermatology, Center for Blistering Diseases, Groningen, The Netherlands

Correspondence: Marcel F. Jonkman, Center for Blistering Diseases, Department of Dermatology, University Medical Center Groningen, Hanzplein 1, 9713 GZ Groningen, The Netherlands. E-mail: m.f.jonkman@umcg.nl

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