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Among the brightest antipsoriatic stars

DOI: 10.1111/bjd.18867

Linked Article: Thaçi *et al.* *Br J Dermatol* 2020; **183**:265–275.

Genome-wide association studies, immunological studies and clinical studies have identified interleukin (IL)-23 as the key cytokine in psoriasis pathogenesis. IL-23 stimulates the production of IL-17A by innate and adaptive immune cells infiltrating the skin and joints during psoriatic inflammation. Chemical compounds and biologics that improve psoriasis usually interfere with the IL-23/IL-17-dominated immune response. Fumaric acid esters (FAE), and especially their active ingredient dimethylfumarate (DMF), have been shown to impair IL-23 expression by activated dendritic cells.[1] Improvements of psoriasis and quality of life in patients treated with FAE/DMF are fair. Around 35–40% of patients achieve ≥ 75% improvement in Psoriasis Area and Severity Index (PASI 75) at week 16.[2] A comparable PASI 75 response is achieved by classical antipsoriatic drugs like methotrexate.[3] Antibodies targeting IL-17A or IL-23 have recently been approved and set the bar for efficacy higher than before. The vast majority of patients treated with such biologics achieve a PASI 90 response, demanding the definition of new treatment goals in psoriasis.

In this issue of the *BJD*, Thaçi *et al.* present the results of the POLARIS study, a German multicentre, randomized, open-label phase IIIb trial comparing the efficacy and safety of the IL-23-neutralizing antibody guselkumab with those of FAE in treatment-naive patients with plaque psoriasis.[4] Patients were treated with either subcutaneous guselkumab injections or FAE tablets. The primary endpoint – PASI 90 response at week 24 – was achieved in 82% of patients receiving guselkumab vs. 14% receiving FAE. Likewise, guselkumab was superior in secondary endpoints. As expected, guselkumab achieved a much faster onset of efficacy as measured by PASI 90 responses than FAE. The incidence of adverse events was significantly lower in the guselkumab group than in the FAE group (147 vs. 309 events).[4]

However, there are some caveats when interpreting the data. While biologics act very fast, treatment with FAE or DMF shows significant clinical effects beginning at week 12 at the earliest.[5,6] Full-dose guselkumab is given from week 0, while FAE are typically uptitrated over a period of 9 weeks (maximum dosage six tablets per day). The PASI 75 response rate for patients treated with FAE in this study was lower than that in the BRIDGE trial.[2] In regard to the adverse event rates, one has to mention that the high number of events in the FAE group is due to drug-specific common events like gastrointestinal symptoms, flushing and lymphopenia. These often lead to discontinuation of FAE treatment. Infections that required treatment were rare but more frequent in the guselkumab group (eight vs. four).

From a scientific perspective, it appears not quite reasonable to compare a monoclonal antibody like guselkumab with oral FAE. If any, it would be more interesting to compare the efficacy and safety of guselkumab with those of selective tyrosine kinase 2 inhibitors,[7] which interfere directly with IL-23 signalling and have different pharmacokinetics than FAE/DMF. Yet the very rapid and overwhelming efficacy of anti-IL23 antibodies like guselkumab is remarkable and takes the therapeutic spectrum for our patients with psoriasis into a bright light. With the POLARIS study presented in this issue we gain another high-quality and detailed insight into modern antipsoriatic treatment strategies.

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Conflicts of interest: K.G. has been advisor for and/or received speaker's honoraria from and/or received grants from and/or participated in clinical trials for Almirall, Biogen Idec and Janssen. K.M. has received speaker's honoraria from and/or received grants from and/or participated in clinical trials for Almirall, Biogen Idec and Janssen.

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Repurposing existing trial data to infer relative efficacy of biologics: guselkumab vs. ustekinumab for psoriasis

DOI: 10.1111/bjd.18848

Linked Article: Diels *et al.* Br J Dermatol 2020; **183**:276–284.

Clinical trials require significant investment. An average phase III clinical trial in dermatology costs around 11·5 million U.S. dollars,[1] with each trial a culmination of work from multiple contributors ranging from physicians, methodologists and pharmaceutical companies to trial centre staff. More importantly, hundreds of patients volunteer significant time and effort through multiple clinic visits, and are potentially exposed to unknown adverse effects. Therefore, trial data are a high-value resource, and it is arguably unethical for trial data to be unreleased for further research purposes once the primary trial analyses have been completed. However, accessing clinical trial data is challenging; a recent cross-sectional study suggests only 33% of large pharmaceutical companies adhere to data-sharing guidelines.[2]

Diels *et al.*[3] should be commended for conducting an individual participant data (IPD)-adjusted analysis, published in this issue of the *BJD*, which leveraged data from five large phase III clinical trials to indirectly compare efficacy between guselkumab and ustekinumab for the treatment of psoriasis. The five trials are NAVIGATE,[4] which compared guselkumab with ustekinumab in a selected population of ustekinumab nonresponders; PHOENIX 1 and PHOENIX 2,[5,6] which compared ustekinumab with placebo; and VOYAGE 1 and VOYAGE 2,[7,8] which compared guselkumab with adalimumab and placebo.

The original design of the NAVIGATE trial[4] included a ustekinumab-responder cohort to continue ustekinumab (cohort 1); and a ustekinumab nonresponder cohort randomized to either start guselkumab (cohort 2) or to continue ustekinumab (cohort 3) after 16 weeks of treatment. An innovative idea utilized in this study was to use weighting to allow all of the NAVIGATE trial data to represent the outcome for treatment with ustekinumab at week 40, with cohort 3 upweighted to represent both cohorts 2 and 3. This counterfactual outcome is valid, as cohorts 2 and 3 were comparable groups created using a 1 : 1 randomization, with the caveat that randomization and allocation concealment were implemented without potential for bias. However, the limitation was that cohort 1 was conducted open-label, with information bias likely leading to an overestimation of ustekinumab treatment efficacy.

Using weighted multivariable logistic regression, the authors then adjusted for a number of prespecified covariates to allow for cross-trial comparisons between ustekinumab and guselkumab in two separate analyses, comparing NAVIGATE against VOYAGE 1 and VOYAGE 2[7,8] in the primary analysis, and PHOENIX 1 and PHOENIX 2[5,6] against VOYAGE 1 and VOYAGE 2 in the validation analysis. The authors found that the predicted probability of achieving a 90% reduction in baseline Psoriasis Area and Severity Index (PASI 90) for guselkumab was 74·2% compared with 54·4% for ustekinumab [adjusted odds ratio 2·40, 95% confidence interval (CI) 1·89–3·13] at week 40, with a corresponding risk difference of 19·7% (95% CI 14·7–24·1). The secondary validation analysis yielded remarkably consistent results.

Although IPD meta-analysis can be limited by heterogeneity in complex trial designs,[9] this rigorously performed study is an excellent example of how it can be a substantial addition to the existing evidence base. Future network meta-analyses across all biological therapies[10,11] in psoriasis, especially for indirect comparisons between treatments with a closer margin of clinical difference, e.g. p19 inhibitors, may similarly benefit hugely if IPD could be provided by industry partners to independent researchers in a judicious but expeditious and collegiate manner.

Acknowledgments: I am grateful to Professors Christopher Griffiths and Richard Warren for their critical review and helpful suggestions in the preparation of this commentary.

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Funding sources: Z.Z.N.Y. is funded by the National Institute for Health Research as an Academic Clinical Lecturer at The University of Manchester.

Conflicts of interest: none to declare.

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