PERSPECTIVE

Testing failures

Promising drugs to treat diabetes stumble in the latter stages of clinical testing. **Thomas Mandrup-Poulsen** explains why — and how to fix it.

The development of certain diabetes drugs keep hitting a snag — phase III clinical trials. This final stage of clinical testing is designed to test the efficacy and safety of treatments in 300 to 1,000 or more patients to ensure that the results from earlier trial phases can be applied to a more general population. Recently, a striking pattern has emerged: trials are failing to confirm encouraging results obtained in earlier trials. In particular, recent phase II studies of short courses of immunomodulatory biologics have provided proof-of-principle that this strategy can at least transiently improve glycaemia, insulin sensitivity or beta-cell function in people with type 1 and type 2 diabetes (T1D and T2D). Four to six infusions of antibodies against the common T-cell surface marker CD3 (ref. 1) or the B-cell surface antigen CD20 (ref. 2) — both central determinants of adaptive immunity — preserved beta-cell function and/or reduced insulin needs after 12–18 months in groups of 80–90 patients with recent-onset T1D. In 70 long-term patients with T2D, a blocker of the receptor binding interleukin-1 (IL-1), the primary inflammatory mediator of innate immunity, resulted in an improvement in beta-cell function — an effect that lasted throughout the 39-week follow-up[3,4]. These trials created optimism for the success of these agents in later phase trials.

Disappointingly, the larger trials of these drugs have failed to meet their primary clinical endpoints — the measure of a trial's success. Careful analysis has pointed to important differences in the design of the phase II and III trials. In the case of anti-CD3 antibody, the Protégé phase III study of more than 500 patients with new-onset T1D used a dose regimen different from that of the companion phase II study[5]; moreover, this study, conducted by MacroGenics, selected glycaemia and insulin needs as primary endpoints, instead of beta-cell function (the phase II endpoint). Another anti-CD3 study, Defend-1, conducted by GlaxoSmithKline, used beta-cell function as an endpoint. Because the full study results have not been published, we do not know such important details as whether beta-cell function was measured during fasting or after meal stimulation as generally recommended. Furthermore, the study used a 15-fold lower dose than that effective in phase II.

Similarly, a large phase IIb trial of IL-1 blockade conducted by XOMA, a firm in Berkeley, California, and not yet published, enrolled more than 400 patients with T2D. The trial subjects were on average 6 years post-diagnosis, and were maintaining a baseline glycaemia of 7.8% on a single oral antidiabetic (less than 6% is considered a healthy level). In contrast, patients in the phase II trial were taking a combination of oral antidiabetics and insulin, and had a mean disease duration of 11 years and baseline glycaemia of 8.5% (ref. 3). So the subjects in the larger trial had a shorter disease duration and better glucose control than those enrolled in the proof-of-principle study.

THE DEVELOPMENT OF CERTAIN DRUGS KEEPS HITTING A SNAG — PHASE III TRIALS RARELY CONFIRM ENCOURAGING RESULTS

This experience prompts the question: were the right drugs tested at a wrong dose or in the wrong patients? Post-hoc analysis of the Protégé study did find significantly improved glycaemia and reduced insulin needs in the cohort receiving the highest dose[5], suggesting that patients with new-onset T1D are highly sensitive to the dosing of anti-CD3 antibody. This subgroup analysis also suggests that insufficient doses might account for the failure of the Defend-1 trial. Finally, there is preclinical evidence that IL-1 blockade is more effective at preserving insulin secretion when the glucose drive is high.

Changes in study rationale, dosage, patient selection and clinical endpoints may compromise the ability to confirm phase II findings in larger trials. The implications for drug development are clear, and organizers of new trials would be well advised to consider the following:

1. Recognizing that certain therapies may only be effective in subsets of patients, phase III trials should use entry criteria and endpoints as close as possible to those used in phase II, and generalization of the outcomes to the prescribed patient population could then be broadened by less restrictive exclusion criteria.
2. Phase III trials should include the doses and dosing regimens effective in phase II.
3. Negative results should be published to allow learning from failure.
4. Collaboration between academia and industry should be promoted to ensure that trial designs are based on the strongest experimental and empirical evidence.

These may be more general implications for developers of drugs to treat chronic degenerative diseases, for which current clinical classifications are too crude to discriminate between aetiologically and pathogenetically different populations of patients that may require different management.

Industry and academia are in this boat together. In these times of financial constraints, with growing rates of attrition in industry and funding sources drying up in academia, there has never been a greater need for trustworthy public–private partnerships. ■

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1. Keymeulen, B. *et al. N. Engl. J. Med.* **352,** 2598–2608 (2005).
2. Pescovitz, M. D. *et al. N. Engl. J. Med.* **361,** 2143–2152 (2009).
3. Larsen, C. M. *et al. N. Engl. J. Med.* **356,** 1517–1526 (2007).
4. Larsen, C. M. *et al. Diabetes Care* **32,** 1663–1668 (2009).
5. Sherry, N. *et al. Lancet* **378,** 487–497 (2011).