issues may reveal, in the authors' words, "new targets for immune-based interventions to slow HIV-1 disease progression." The methodology used here provides opportunities for experimental manipulations in human lymphoid tissue aimed to normalize "abnormal" profiles and to identify irreversible damage.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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TRANSPLANTATION

Comment on Hockenbery et al, page 4557

At last, an "ointment" for gastrointestinal GVHD?

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Intestinal graft-versus-host disease (GVHD) has been notoriously difficult to treat. A simple measure such as topically active oral steroids can halt its progression, reduce systemic steroid use, and improve survival.

Too many studies have shown "promising" results in treatment of acute graft-versus-host disease (GVHD) during early phase 1/2 trials over the last decades; none has yet stood the test of a prospective randomized comparison. Trials did include drugs such as monoclonal and polyclonal antilymphocyte antibodies, anti–TNF alpha antibodies, proinflammatory cytokine-modifying agents, or more complex approaches such as extracorporeal photopheresis or infusion of mesenchymal stromal cells.[1-3]

Sometimes results were even worse with the new treatment than with steroids alone. The latter, steroids, still form the mainstay of GVHD treatment. They induce a response in about 50% of the patients with acute GVHD of grade II or higher.

Still, relapse of GVHD is frequent, steroids are associated with significant morbidity, and response is mainly seen in skin GVHD. Moreover, any reduction of GVHD is immediately linked with reduced graft-versus-leukemia (GvL) and increased relapse rate.[4]

Alternatives are urgently warranted. Hockenbery and colleagues from the OrBec GVHD Study Group have now identified a surprisingly simple but successful approach. In a prospective, randomized, placebo-controlled group, they tested efficacy and safety of oral beclomethasone diproprionate (BDP) in patients with steroid refractory gastrointestinal GVHD. The authors chose an elegant design, forcing rapid steroid tapering after 10 days of treatment.

Their postulate was that a topically active "ointment" should reduce symptoms, hence reduce the need for systemic drugs. Of eligible patients, risk of GVHD treatment failure was indeed significantly reduced in the BDP group. This approach did translate into a significantly improved survival in the BDP group, with a reduction in mortality by more than 50% at 1 year after transplantation.

Effects were even more pronounced in recipients of mismatched or unrelated transplants.

The results are clear and significant. There is no doubt. In addition, ease of application and relatively low costs make oral BDP an attractive treatment for gastrointestinal GVHD. It should be tested in any case of gastrointestinal GVHD, before more toxic or more expensive therapy is used. Still, questions remain, and it is premature to consider oral BDP as established from now on. Topical treatment is an accepted therapy for acute and chronic GVHD of the skin, oral mucosa, eyes, and vagina.[1-3] Why did it take so long from the first reports and from the first randomized study to the present results?

The answer lies probably in the outcome results. The authors present difficulties in interpretation. Reduction in mortality was primarily due to a reduction in deaths from infections and deaths from relapse, not in deaths from GVHD. The authors give their interpretation. Local treatment, by avoiding systemic immunosuppression, should more likely result in fewer serious infections. Vice versa, protracted exposure to systemic steroids, should result in an abrogation of T-cell response in the GVL direction in the placebo group. There is some logic in this view, but questions remain. No data on absorption, or "nonabsorption" of the drug are provided. Furthermore, it would be the first time that any reduction in GVHD would not be associated with a reduction in GVL.

Above all, numbers in the trial were small and the statistical analysis was skewed. Survival difference was mainly based on an exceedingly low mortality in the mismatched or unrelated transplants (1 of 23, 4%) in the BDP group compared to 10 (42%) of 24 in the placebo group. This cannot reflect reality. As it stands, BDP has become an attractive alternative for severe gastrointestinal GVHD. Still a confirmatory trial needs to be done before BDP can be declared as the new standard of care in gastrointestinal GVHD.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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