preventing lethal infection. However, although commonly used immunosuppressive agents, such as the calcineurin inhibitors and mycophenolate, probably do not interfere with CMV control by adoptively transferred T cells, steroids have a devastating impact, rapidly reducing the number of circulating virus–competent lymphocytes and promoting viral proliferation. Clearly, the ability to use steroids and at the same time deliver potent antiviral cell-mediated immunity would fulfill an important therapeutic need.

An international collaboration of colleagues from London and Birmingham, United Kingdom; Paris, France; and Seattle, Washington, have now achieved this goal. In the paper, Menger et al describe the successful use of TALEN gene transfer to inactivate the GR on CMV-specific CD8+ T cells to render them steroid resistant. The technique involves the selection and expansion from donor blood of CMV-specific CD8+ T cells recognizing the immunodominant HLA A2-restricted CMV-pp65 9-mer peptide. These highly specific oligoclonal T-cell populations are then electroporated with a TALEN mRNA selected to bind specifically to the GR gene by virtue of their highly specific 17-bp targeting domains. TALEN causes site-specific double-stranded DNA breaks in the GR gene and then triggers repair through nonhomologous end joining recombination. Such recombinations are error prone and result in the inactivation of the GR gene by random insertion or deletion, altering the reading frame and leading to the failure to form a functional GR protein (see figure, panel B). The authors first tested the system in the T2 cell line and showed that, after selection by culture in dexamethasone, the TALEN-modified cells could proliferate normally in medium containing high concentrations of dexamethasone. Repeat experiments with CMV-specific CD8+ T-cell lines showed that TALEN-electroporated and dexamethasone-selected CMV-specific T cells retained full cytotoxicity against pp65-expressing targets when cultured in dexamethasone, whereas nonelectroporated controls in dexamethasone did not even survive adequately to test their function. Recognizing that the downside to their approach would be the risk of conferring steroid resistance on CD8+ T cells that cause GVHD, the authors also studied the effect of GR-suppressed T cells in a humanized mouse xeno-GVHD model. CD8+ T cells caused severe GVHD, which could be abrogated by steroids in this model. However, GVHD in mice receiving TALEN-electroporated T cells was completely unresponsive to steroid treatment.

What are the clinical implications from this technology? Although the approach appears highly intricate, the components of the process are already being developed in clinical practice. A number of clinical approaches to generating CMV-specific T cells (and indeed for several other viruses) are in clinical trials, and TALEN electroporation is easy to scale up. The pathway to clinical translation and early phase trials thus appears uncomplicated. In addition, the absence of viral vectors and the short survival of TALEN in the targeted cells are attractive to regulatory bodies concerned with potential risks of gene modification in transduced cells. A proof-of-principle study of TALEN-modified T cells in HSCT recipients would be a significant next step for broader applications of gene silencing with TALEN. Nevertheless, there are some important concerns about modification of T cells to resist the very agents that might be needed to suppress unwanted and off-target cytotoxicity, and the authors rightly point out that incorporation of a suicide gene into the final cell product would be required in circumstances where desired specificity of the T-cell population cannot be guaranteed.
In their study, Forero–Torres et al treated 27 patients with a new diagnosis of classical HL. All were aged 60 or older, with a median age of 78 years, and 5 patients were aged 85 or older. Fifty-two percent were deemed ineligible for treatment with conventional multiagent chemotherapy due mainly to heart disease comorbidity, 67% of patients reported being “limited a lot” for at least one physical activity, and 30% had fallen at least once in the previous 6 months. Hence, there is no doubt that this was a frail, comorbid, and vulnerable group of patients.

Overall response rate to brentuximab vedotin, an antibody-drug conjugate targeting CD30, was 92% among the 26 evaluable patients, with 19 patients (73%) achieving complete remission, 5 (19%) achieving partial remission, and 2 patients having stable disease (see figure). With a median observation time of 17 months, median progression-free survival was 10.5 months for all patients and 11.8 months for those achieving complete remission. Six patients have remained alive and progression-free for >12 months, with a median duration of time off treatment of 6.5 months. Overall survival ranged from 4.6 to 24.9 months with the median not yet reached.

Patients received a median of 8 cycles of treatment, with 8 patients completing 16 cycles. In general, brentuximab vedotin was well-tolerated and no infusion-related or hypersensitivity reactions were reported. All patients reported at least one adverse event, with peripheral neuropathy (21 patients, 78%), fatigue (12 patients, 44%), and nausea (12 patients, 44%) being the most common. Although these events were typically grade 1 or 2, 8 patients (30%) developed grade 3 neuropathy, most usually in the presence of coexisting diabetes mellitus or hypothyroidism. Myelosuppression was minimal and there was no thrombocytopenia or febrile neutropenia reported.

In terms of disease control rates and toxicity, these are very promising results, but the small number of patients treated mandates confirmatory studies. The investigators should be congratulated, however, for considering the needs of a group of patients poorly served by conventional treatments for HL who have been under-represented or absent from large randomized trials of therapy. They have shown that brentuximab vedotin, which already has an established role in the relapsed/refractory setting, is an effective single agent in the first-line treatment of older patients with classical HL and an extremely welcome new option for these individuals. It is encouraging that myelosuppression was not a significant toxicity in this study. However, physicians need to be aware of the risk of peripheral neuropathy, especially in patients with coexisting diabetes and hypothyroidism, and be ready to reduce and/or delay treatment for moderate toxicity and discontinue use if the symptoms become severe.

The challenge now is to determine whether these results, particularly in terms of duration of response, can be improved by combining brentuximab vedotin with other agents without adversely affecting patient tolerability. Good candidates for this role are the noncardiotoxic bendamustine—which has already been used in combination to very good effect in relapsed/refractory patients—and dacarbazine. These doublet drug approaches are currently under evaluation. Results will be awaited with interest, but the outcome of this study of brentuximab vedotin monotherapy makes clear that important progress has already been made in the treatment of older patients with HL, for whom therapeutic options have historically been extremely limited.

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REFERENCES
Treatment of Hodgkin lymphoma in older patients

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