may be resolved in the near future through recent reports on prospective trials and trials that are ongoing.[5] Since GnRH agonists are noninvasive, they would be acceptable to many physicians and patients; however, if the treatment is not effective or is effective only in some individual cases, patients will need alternatives that give the best probability of fertility preservation.

We appreciate the point raised by Chubak which highlights the importance of accurate assessment of sexual maturity in the pediatric population; this can be a difficult task, although it should be possible. Experimental techniques are under development for prepubertal boys.

In our article, we discussed all the points mentioned by Meirow and Wallace, and we reached the same conclusions. Thus, since we are in complete agreement, we cannot comment on any issue that was perceived as being misleading.

The threat to fertility that cancer treatments pose to young patients can be significant, and, if possible, mature techniques such as embryo banking and sperm banking should be considered before the initiation of cancer therapy. Raising the awareness of fertility-preservation options among clinicians and young patients with cancer is critical. New techniques are under development, and they may expand the range of options in the future. Where possible, multicenter studies should be initiated to ensure the most rapid completion of high-quality research so that authoritative guidelines for intervention can be created.

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B-Cell–Depleting Induction Therapy and Acute Cellular Rejection

TO THE EDITOR: B-cell depletion is an effective treatment for a number of autoimmune diseases in which B cells were not previously considered to be important, such as multiple sclerosis.[1] In renal transplantation, acute cellular rejection has been viewed as a T-cell–dependent process, but B cells are required for alloantibody production and may also play other roles, including alloantigen presentation to T cells.[2]

Published data on the use of B-cell depletion at induction in nonsensitized patients undergoing organ transplantation are lacking. We conducted an open-label, randomized, controlled trial comparing rituximab, a B-cell–depleting, chimeric, anti-CD20 monoclonal antibody, with an anti-CD25 monoclonal antibody (daclizumab) as induction therapy in patients undergoing renal transplantation. We planned to recruit 120 patients, but the study was suspended after recruitment of the first 13 patients, owing to an excess incidence of acute cellular rejection in the rituximab group. Five of six patients (83%) who received rituximab had an episode of biopsy-confirmed acute rejection in the first 3 months after transplantation, as compared with one of seven patients (14%) in the daclizumab group ($P=0.01$) (Table 1 and Fig. 1). All the episodes of rejection responded to intravenous methylprednisolone, and allograft function was similar in the two groups at 12 months (Table 1, and Fig. 1A in the Supplementary Appendix, available with the full text of this letter at NEJM.org). After rituximab treatment, peripheral B cells were undetectable in all patients (Fig. 1B in the Supplementary Appendix). Serum cytokines, including tumor necrosis factor α, interleukin-6, and interleukin-10, were increased after transplantation, as compared with baseline values, in some of the patients who were treated with rituximab (Fig. 2, 3, and 4 in the Supplementary Appendix).

Our findings are surprising; patients who received rituximab had a rate of acute rejection that

Table 1. Immunosuppression, Acute Rejection, and Allograft Function.*

Variable	Daclizumab Group (N=7)	Rituximab Group (N=6)
Immunosuppression		
Induction	Daclizumab, 1 mg/kg of body weight (day 0, day 7)	Rituximab, 10 mg/kg (day 0, day 7) and methylprednisolone, 10 mg/kg (day 0 and 7 before rituximab)
Maintenance (corticosteroid-free)	Tacrolimus (8–15 ng/ml) and mycophenolate mofetil (1 g twice a day)	Tacrolimus (8–15 ng/ml) and mycophenolate mofetil (1 g twice a day)
Tacrolimus level in months 1–3 — ng/ml	10.6±1.0	12.2±2.3
Mean no. of HLA mismatches	3.1	2.8
HLA-A	1.1	1.2
HLA-B	1.0	1.0
HLA-DR	1.0	0.7
First or second transplantation — no. (%)		
First	6 (86)	6 (100)
Second	1 (14)	0
Delayed graft function — no. (%)	2 (29)	1 (17)
Acute rejection at 3 mo — no. (%)	1 (14)	5 (83)
Banff grade for severity of acute rejection†	Patient 1, IB	Patient 1, IB; Patient 2, IB; Patient 3, IB and IA; Patient 4, IIB; Patient 5, IB
Peritubular capillaries on C4d immunoperoxidase staining of biopsy specimen — %	Patient 1, 0	Patient 1, <50; Patients 2–5, 0
Interval between transplantation and biopsy-confirmed rejection — days‡	Patient 1, 18	Patient 1, 12; Patient 2, 36; Patient 3, 11 and 35, respectively; Patient 4, 7; Patient 5, 23
Antibody-mediated rejection — no. (%)	0	0
Corticosteroid-resistant rejection — no. (%)	0	0
Development of donor-specific antibody — no. (%)	1 (14)§	0
Glomerular filtration rate as measure of graft function — ml/min/1.73 m^2		
At 3 mo	57.3±8.0	45.5±9.7
At 12 mo	48.9±10.6	44.4±8.1

* Plus–minus values are means ±SD.
† Banff grades for acute rejection range from I to III; I is defined as acute rejection with substantial interstitial infiltration with moderate (IA) or severe (IB) tubulitis, and II with mild-to-moderate (IIA) or severe (IIB) intimal arteritis.
‡ All biopsies were performed to investigate a rise in the creatinine level.
§ A weak class I antibody developed in a patient who had no biopsy-confirmed acute rejection.

was not only higher than the rate in the control group (83% vs. 14%) but also was higher than that previously observed among patients who have not received induction therapy (35%).[3] One possible explanation may be that proinflammatory cytokine release associated with B-cell depletion might prime antigen-presenting cells. A short-lived cytokine-release syndrome often occurs after administration of the first dose of rituximab[4]; in our study, some patients who were treated with rituximab had elevated levels of proinflammatory cytokines. However, we cannot exclude the possibility that the increased levels of cytokines were the result rather than the cause of acute rejection.

Although B cells may enhance immune re-

sponses, some B cells have immunoregulatory properties. In animal models, depletion of such B cells before disease induction can worsen autoimmunity,[5] and rituximab therapy can exacerbate ulcerative colitis and psoriasis. Similarly, depletion of immunoregulatory B cells may have contributed to the increased rejection in the rituximab-treated patients.

Recipients of renal transplants in whom rituximab is administered for desensitization do not appear to be at an increased risk for acute cellular rejection. Such patients usually receive rituximab well before transplantation, and rituximab treatment is often accompanied by plasma exchange and corticosteroid therapy; thus, any associated cytokine storm would probably resolve by the time of transplantation.

B-cell depletion has emerged as a powerful treatment strategy in autoimmunity; however, our results show that this strategy should be undertaken with caution when the precise role of B cells in a disease is unclear. (EudraCT Number, 2005-001496-35.)

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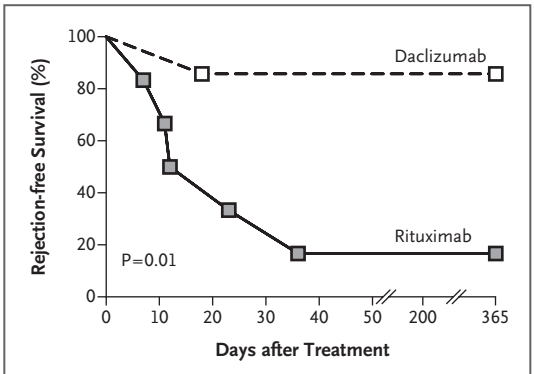

Figure 1. Increased Rate of Acute Rejection in Rituximab-Treated Patients.

Kaplan–Meier curves are shown for rejection-free survival at 1 year in patients who received rituximab as induction therapy, as compared with those who received daclizumab. The P value for the difference is based on a log-rank test.

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