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Dosage of OKT3 independent of body weight: a mistake?

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Abstract. Comparing OKT3 and antithymocyte globulin (ATG) in a prospective study, the dosage difference in regard to body weight (ATG: dependent on body weight/OKT3: independent) does not introduce any obvious source of mistake concerning clinical effectiveness or side effects. One explanation for the lack of influence of body weight may be the high effectiveness of 5 mg of OKT3, reaching a maximal effect even with lower plasma levels in heavier patients. We wonder, therefore, whether the OKT3 dosage could be lowered.

Key words: Immunosuppression – Monoclonal antibodies – OKT3 – Antithymocyte globulin

In renal transplantation OKT3 is administered independently of body weight in fixed doses of 5 or 10 mg/day [1–4] for initial prophylactic immunosuppression or treatment of severe, methylprednisolone-resistant rejection. This obviously contrasts with the usual regimen of antithymocyte and antilymphocyte globulins (ATG, ALG), which are both administered per kilogram of body weight [3]. Therefore, we wondered whether light-weight patients were relatively overdosed or obese patients underdosed with OKT3.

Materials and methods

A total of 71 renal transplanted patients received either OKT3 or ATG in a randomized study from 1990 till 1991. Murine orthoclone OKT3 (Cilag/Ortho) was given prophylactically as a 5 mg i.v. bolus intraoperatively and over the following 6 days in 36 patients (mean age 50.8 years, range 17–70). Intravenous rabbit ATG (Fresenius) was administered to the other 35 patients (mean age 49.7 years, range 18–82) at a dosage of 4 mg/kg daily for the same period of time as OKT3. Both groups received in addition azathioprine (2 mg/kg daily), methylprednisolone i.v. (1.0, 0.5 and 0.25 g on days 0, 1, and 2), prednisone orally (from day 3 at 5 mg/kg daily), and cyclosporine A (2 × 300 mg/day from day 4 on). The i.v. doses of methylprednisolone were given 1–4 h prior to the OKT3/ATG administration. In each patient the free OKT3/ATG trough plasma levels were measured 2 to 3 times during the 1 week after transplantation, using an enzyme-linked immunosorbent assay (ELISA) technique (sandwich principal in solid phase technique) with antimouse/antirabbit globulin antibodies. The same plasma samples were also screened for human antimouse antibodies (HAMA) and human antirabbit antibodies (HARA). One OKT3 patient developed HAMA on the 4th day, and his plasma values were therefore excluded from the calculation. HARA did not develop in ATG-treated patients during this early period.

To evaluate the biological effectivness of OKT3 or ATG we measured the level of $CD3^+$ cells (FACS). In order to estimate the clinical success rate we took the plasma creatinine values on days 7 and 28, the number of i.v. methylprednisolone pulses of 0.5 g given for rejection, and the OKT3/ATG retherapies needed for steroid-resistant rejection during the first 30 days after transplantation. Episodes of viral and fungal infections were counted and expressed as the total sum.

The effect of body weight was analyzed in two ways: (a) by plotting the individual data corresponding to their body weight or (b) by dividing both patient groups close to their median body weight (69.5 kg) into a heavy (> 70 kg) or a light subgroup (< 70 kg) and comparing their parameters (median of individual mean values). Thus, the 36 OKT3-treated patients were divided into 18 light patients (L-OKT3) with a median weight 60.9 kg and 18 heavy patients (H-OKT3), with a median weight of 78.3 kg. Correspondingly, the 35 ATG-treated patients were subdivided in 20 light patients (L-ATG) with a median weight of 63.7 kg and 15 heavy patients (H-ATG) with a median weight of 76.4 kg.

The results of all parameters were correlated with individual body weight and compared as well in all 4 subgroups. Statistical significance was calculated by using the regression of all correlations, the Mann-Whitney U-test, and the χ^2 test.

Results

By administering OKT3 in a fixed bolus the L-OKT3 patients received a 40% higher dosage (0.089 mg/kg daily) than the H-OKT3 ones (0.063 mg/kg daily). This was not the case in the two ATG-treated subgroups, since the median dosage did not differ (3.8 mg/kg daily vs. 3.9 mg/kg daily). The hyperbolic relation between OKT3 dosage and body weight (formula: dose pro kg = 5 mg/patients' body weight) follows an almost linear course in the observed range (Fig. 1), whereas ATG-treated patients of all

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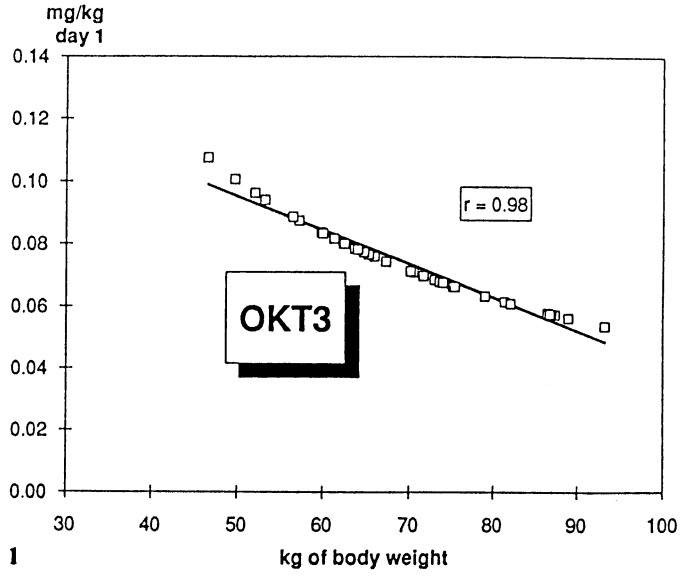

Fig. 1. Correlation of OKT3 dosage (mg/kg) and body weight ($n = 36$) on day 1 after kidney transplantation

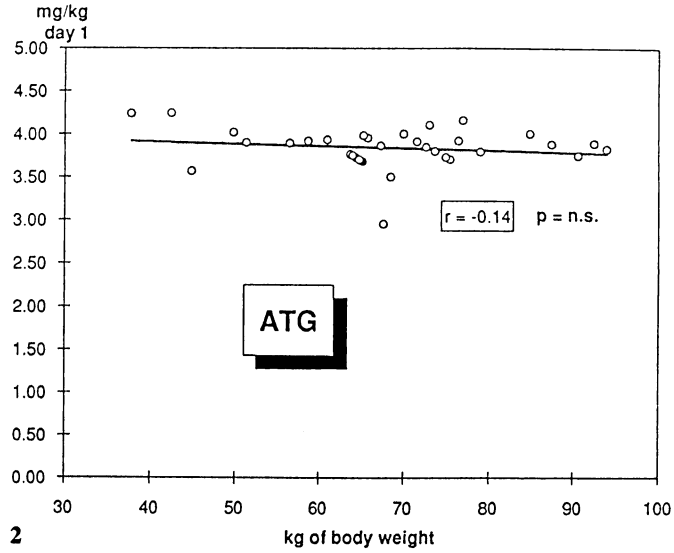

Fig. 2. Correlation of antithymocyte globulin (ATG) dosage (mg/kg) and body weight ($n = 35$) on day 1 after kidney transplantation

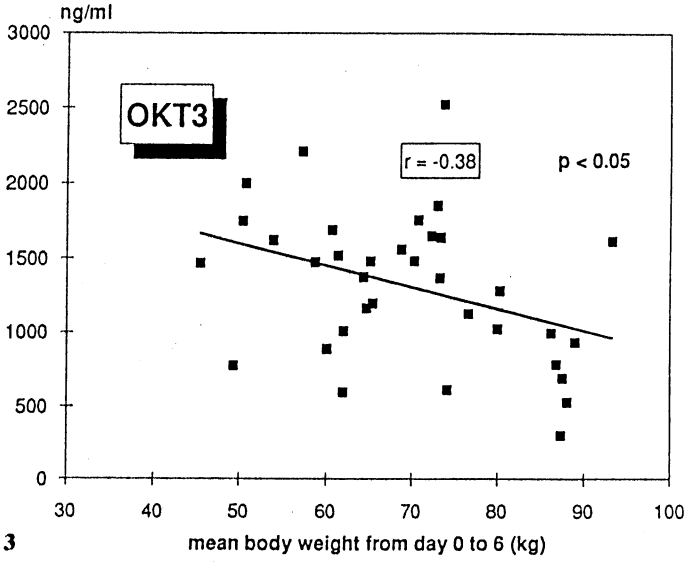

Fig. 3. Correlation of OKT3 mean plasma levels (day 0–6) and body weight

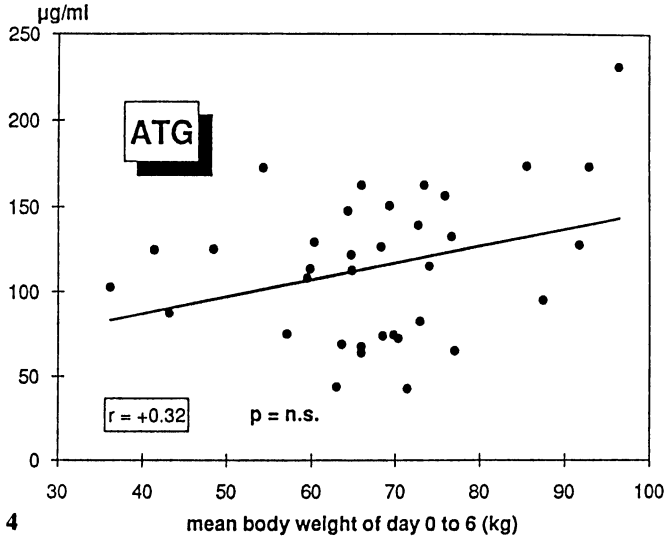

Fig. 4. Correlation of ATG mean plasma levels and body weight

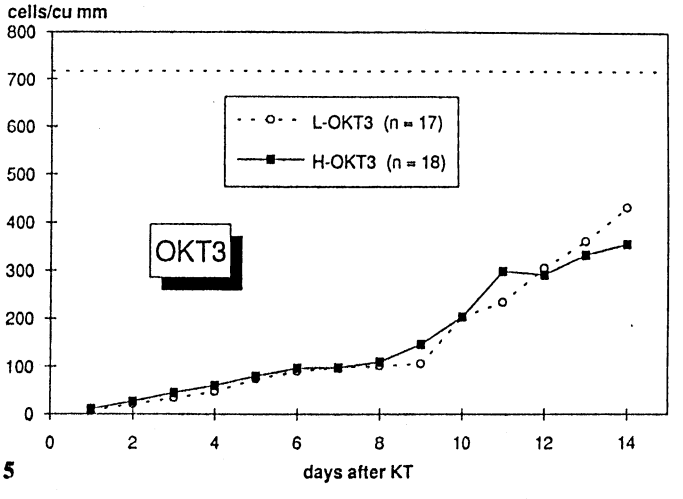

Fig. 5. Median of absolute CD3 count in OKT3-treated patients, below (L)/above (H) 70 kg in weight

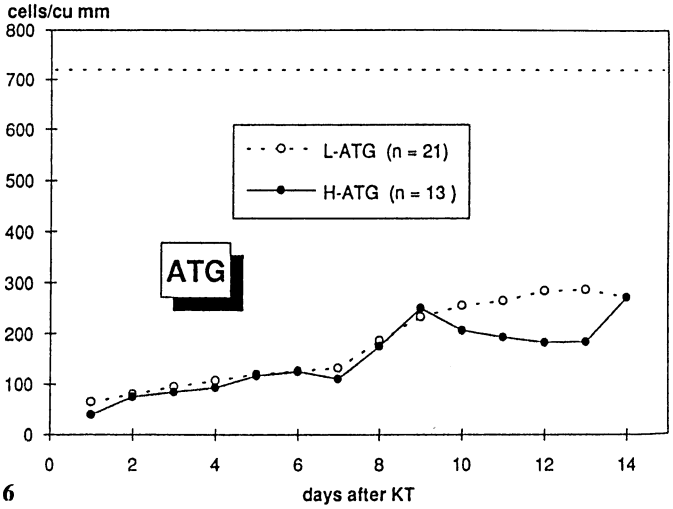

Fig. 6. Median of absolute CD3 count in ATG-treated patients, below (L)/above (H) 70 kg in weight

Table 1. Weight and plasma levels are indicated in median values of the individual mean (days 0–6)

Group	Weight (kg)	*n*	drug plasma level	Plasma creatinine level		CD3 count absolute (cells/μl)	Methylprednisolone pulses/ patient	OKT3/ATG retherapies	Viral and fungal infections
				Day 7 (μmol/l)	Day 28 (μmol/l)				
OKT3	< 70 (60.9)	18	1478 ng/ml	121	124	52	41/12	5	8
	> 70 (78.3)	18	1205 ng/ml	335	132	55	36/11	5	11
ATG	< 70 (63.7)	20	113 μg/ml	90	99	96	45/11	2	4
	> 70 (76.4)	15	128 μg/ml	124	122	96	27/9	2	3

Methylprednisolone pulses, retherapies, and infections were counted during the first 30 days after kidney transplantation

weight classes had a similar "per kilo dosage" ($r = -0.14$, n.s.) (Fig. 2). Small aberrations were due to the fact that the dosage was calculated with the initial weight and stayed so for the next 6 days independent of weight changes after operation.

As expected, OKT3 mean plasma levels of the first 7 days after kidney transplantation correlate significantly ($P < 0.05$) and inversely with the patients' mean body weight of the same period (Fig. 3). This was not the case in the ATG-treated patients (Fig. 4).

However, despite body weight-dependent blood level differences in OKT3 patients, the CD3-cell count was almost identical for the L-OKT3 and H-OKT3 patients over the first 2 weeks (Fig. 5). This was – not surprisingly – also the case for the L-ATG and H-ATG patients (Fig. 6). All other parameters for the clinical effectiveness of OKT3 (plasma creatinine level at days 7 and 28, number of methylprednisolone pulses, retherapies with OKT3) were not different in the L-OKT3 and H-OKT3 subgroups (Table 1), similar to the L-ATG and H-ATG subgroups.

Finally, the sum of episodes of viral and fungal infections showed no weight-related differences, i.e., was not different among all 4 subgroups.

For all mentioned parameters, correlations with individual body weight were calculated, but the regression analysis was found not to be significantly different in all of them (not shown), besides the OKT3 blood levels and body weight (Fig. 3) noted above.

Discussion

When two antilymphocytic substances like ATG or OKT3 are compared with regard to success in a clinical trial of renal transplantation, one might be disturbed by the fact that one substance is given in a weight-dependent dosage (ATG: 4 mg/kg daily) and the other independent of body weight (OKT3: 5 mg/day). This is particularly the case if the effective body weight among the patients ranges from 36 to 96 kg (ATG) and 45 to 93 kg (OKT3), as in our study. One may anticipate that OKT3 is more effective in lowering the CD3 counts or rejection rate in lighter than in heavier patients. The side effects of overdosage like viral or fungal infection may occur more frequently in light, relatively overdosed patients.

Our findings confirm only a weight-dependent difference in the average OKT3 plasma levels ($P < 0.05$) and – as expected – no such difference in the ATG-treated patients. For ATG there is even a tendency for the plasma concentrations to increase with body weight (n.s., Fig. 4). This might be explained by the higher proportion of adipose tissue in obese patients, which is associated with a relatively smaller volume of distribution of ATG.

The range of our mean OKT3 plasma levels is in agreement with the measurements of Chatenoud et al. [1] and Goldstein et al. [2], but higher than those of Todd and Brogden [4]. As far as we know, there are no published data on ATG Fresenius plasma levels, but our calculated levels with a factor difference of 100 for ATG look reasonable.

Measurements of OKT3 or ATG plasma levels by an ELISA technique have a common error source. The measured plasma level may not represent true free plasma levels of unbound substance; it can also comprise inactivated complexes with antimouse or antirabbit antibodies [1]. However, we tried to avoid this mistake by excluding the plasma samples from the calculation whenever the simultaneous search for HAMA or HARA was positive. Whether our measured plasma levels represent true "free plasma levels" of active OKT3 still remains unclear, since we failed to find a weight-dependent correlation with the CD3 counts. There was no weight dependency either for all parameterse of clinical relevance such as plasma creatinine level or the number of methylprednisolone pulses needed for the treatment of rejection. Another meaningful parameter for effectiveness is the number of retherapies with OKT3 or ATG for the rescue of steroid-resistant rejection. Again, there was no difference in the OKT3 patients above or below 70 kg of body weight. Viral and fungal infections were not increased in the light patients on OKT3 as compared with the heavy ones.

The number of patients in the two groups may be too small to evaluate properly significant differences correlated to body weight. We were even unable to show any trend in favour of body-weight dependency in the OKT3 patients, with the exception of the plasma levels.

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