INVITED COMMENTARY

Tacrolimus exposure and intra-patient variability in paediatric and young adult kidney transplant recipients: one size does not fit all

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Paediatric practice recommendations on the use of tacrolimus following kidney transplantation are largely based on the experience from adult solid organ recipients. It has been reported that adequate tacrolimus exposure in adults can impact patient outcomes. As shown in the SYMPHONY trial, adult *de novo* kidney transplant patients with a target tacrolimus predose concentration (TAC C_0) of 3–7 ng/ml had a higher glomerular filtration rate and a lower incidence of acute rejection one year following transplantation compared to those treated with cyclosporine A or sirolimus [1]. On the other hand, a retrospective study in adult renal transplant recipients showed that a mean TAC C_0 of < 8 ng/ml was associated with the formation of donor-specific antibodies (DSA) and a graded increase in risk of DSA formation with lower mean TAC C_0 [2]. What is lacking, are studies comparing patient outcomes according to given target TAC C_0 head-to-head. In children and adolescents, the target TAC C_0 in stable kidney transplant recipients is usually set at 5–15 ng/ml [3]. This is rather a wide range, and the individual target TAC C_0 is tailored according to the state of over- and under-immunosuppression, clinically reflected as infections on the one hand and allograft rejection on the other. The study of Gold *et al.* [4] is the first to show an association between tacrolimus exposure and patient outcomes following paediatric kidney transplantation. The authors report that adolescents and young adults (12–23 years of age) with TAC C_0 between 4.0 and 10.9 ng/ml had a 5-year survival rate of 85.1% compared to 66.1% in patients with TAC C_0 < 4.0 ng/ml. Interestingly, there was no association between graft survival and TAC C_0 in children younger than 12 years. These results are important in patient risk stratification and may be helpful in tailoring the individual TAC C_0 target. Adolescents display a higher risk of allograft loss compared to younger children and the changes associated with the maturation of the immune system are one of the postulated contributing factors [5]. The findings of Gold *et al.* suggest that the poor allograft outcomes may be at least partially counterbalanced by adequate tacrolimus exposure.

Worse allograft outcomes in adolescents have traditionally been attributed to poor therapy adherence mirrored in high intra-patient variability (IPV). Again, our knowledge on the significance of tacrolimus IPV is to a

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large extent based on studies performed in adults. High tacrolimus IPV in kidney transplant recipients is associated with inferior allograft survival, higher incidence of acute rejection and increased risk of histologic lesions, such as fibrosis and tubular atrophy. Moreover, high tacrolimus IPV has been found to contribute to the development of DSA [3,6,7]. Hypothetically, higher tacrolimus IPV would be expected in adolescents given the higher prevalence of poor therapy adherence in this age group. However, in the study of Gold and co-authors the percentage of kidney recipients with high IPV was similar across all age groups. This indicates that strategies aimed at reducing IPV should also take into account its other determinants such as interactions with concomitant medications and food, diarrhoea and strict timing of administration. The relevance of high tacrolimus IPV is reflected in an association with the risk of graft loss in all age groups from 0 to 23 years [4].

In summary, the study of Gold *et al.* is an important contribution to the existing body of literature with emphasis on the customization of tacrolimus exposure according to recipients' age. Although the study included deceased donor kidney recipients only, a robust statistical analysis was feasible due to the large sample size. Paediatric research is often hampered by low numbers of patients as paediatric kidney transplantation is only a fraction of the overall transplant activity. In 2019 in the Eurotransplant area, only 135 out of 4144 kidney recipients were younger than 15 years of age (https://statistics.eurotransplant.org/). The study of Gold *et al.* is an excellent example of a valuable scientific report based on a large international registry. International collaboration is in my opinion the way to go in paediatric kidney transplantation research.

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REFERENCES

1. Ekberg H, Tedesco-Silva H, Demirbas A, *et al.* Reduced exposure to calcineurin inhibitors in renal transplantation. *N Engl J Med* 2007; **357**: 2562.
2. Davis S, Gralla J, Klem P, *et al.* Lower tacrolimus exposure and time in therapeutic range increase the risk of de novo donor-specific antibodies in the first year of kidney transplantation. *Am J Transplant* 2018; **18**: 907.
3. Prytula A, van Gelder T. Clinical aspects of tacrolimus use in paediatric renal transplant recipients. *Pediatr Nephrol* 2019; **34**: 31.
4. Gold A, Tonshoff B, Dohler B, Susal C. Association of graft survival with tacrolimus exposure and late intrapatient tacrolimus variability in pediatric and young adult renal transplant recipients – an international CTS registry analysis. *Transplant Int* 2020. doi: 10.1111/tri.13726. Online ahead of print.
5. Van Arendonk KJ, James NT, Boyarsky BJ, *et al.* Age at graft loss after pediatric kidney transplantation: exploring the high-risk age window. *Clin J Am Soc Nephrol* 2013; **8**: 1019.
6. O'Regan JA, Canney M, Connaughton DM, *et al.* Tacrolimus trough-level variability predicts long-term allograft survival following kidney transplantation. *J Nephrol* 2016; **29**: 269.
7. Vanhove T, Vermeulen T, Annaert P, Lerut E, Kuypers DRJ. High intrapatient variability of tacrolimus concentrations predicts accelerated progression of chronic histologic lesions in renal recipients. *Am J Transplant* 2016; **16**: 2954.