Tacrolimus Granules for Oral Suspension as Post-Transplant Immunosuppression in Routine Medical Practice in France: The OPTIMOD Study

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Background:
Different pharmaceutical forms of oral tacrolimus allow tailored administration. The granular formulation facilitates accurate dose adjustment of tacrolimus according to patient characteristics, such as weight, or potential concomitant drug interactions. Currently, there are no data describing the use of tacrolimus granules in transplant recipients in France.

Material/Methods:
OPTIMOD was a 6-month prospective, observational multicenter study that aimed to describe patient characteristics and conditions of use of tacrolimus granules. The 25 participating centers enrolled patients at time of tacrolimus granules initiation and were to collect patient and treatment data at initiation and after 6 months of follow-up. All analyses were descriptive.

Results:
Of 61 patients included, 55.7% were children (mainly kidney graft recipients) and 44.3% were adults (mostly lung graft recipients). Overall, 24.6% of patients (all children) initiated tacrolimus granules immediately post-transplant; the remaining 75.4% converted to tacrolimus granules from ciclosporin or immediate-release tacrolimus hard capsules. The main reasons for initiating tacrolimus granules, irrespective of whether first- or second-line therapy, were to offset potential drug–drug interactions in adults by adjusting dose, and to adapt to the particular needs of children as patients. Most patients (78.7%) underwent ≥1 dose modification during follow-up. Eleven rejection episodes occurred during follow-up, of which none led to graft loss. The adverse-event profile of the tacrolimus granules was similar to that of other tacrolimus formulations and 7 treatment-related adverse events were recorded.

Conclusions:
Results suggest that tacrolimus granules are well tolerated and effective in preventing transplant rejection when administered in routine practice in France.

MeSH Keywords:
Drug Utilization • Observational Study • Tacrolimus • Transplantation

Full-text PDF:
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Background

The current mainstay of immunosuppression after solid organ transplantation relies on triple therapies, comprising a calcineurin inhibitor (CNI), mycophenolate mofetil or mycophenolic acid (MPA), and corticosteroids. The most frequently used CNI is tacrolimus, which is prescribed to over 80% of transplant recipients [1–5] and is considered the standard of care. Indeed, a recent multinational study conducted in Australia found that tacrolimus utilization increased 2.2-fold between 2007 and 2013 [6]. However, the narrow therapeutic index exhibited by CNIs necessitate frequent therapeutic drug monitoring (i.e., trough blood concentrations (C_0)) to achieve the desired systemic exposure and minimize treatment-associated toxicity [7]. Different therapeutic combinations of individualized treatment regimens may be used to optimize immunosuppression, with dose modification of 1 or 2 of the constituent immunosuppressive agents being common practice in cases of potential pharmacokinetic drug–drug interaction [8].

Different pharmaceutical forms of oral tacrolimus are available, including twice-daily immediate-release capsules, once-daily prolonged-release capsules, and twice-daily immediate-release granules (Modigraf™, Astellas Pharma, Japan). A study conducted in 9 stable adult kidney transplant recipients converted from immediate-release tacrolimus capsules to granules found that the immediate-release formulations were comparable regarding maximum tacrolimus concentration (C_{max}; mean ±standard deviation (SD) ratio granules: capsules 1.18±0.50), time to C_{max}, and area under the concentration–time curve (AUC) over 12 h (ratio 1.08±0.51) [9]. There are no studies directly comparing the pharmacokinetics of tacrolimus granules with prolonged-release tacrolimus capsules. However, the prolonged- and immediate-release tacrolimus capsules have a comparable AUC in steady-state conditions following dose adjustment, while the C_{max} is lower with the prolonged-release formulation [10], owing to its extended absorption profile throughout the gastrointestinal tract [11,12].

The different formulations of tacrolimus allow tailored administration of the drug. However, while the smallest dose unit for immediate- and prolonged-release capsules is 0.5 mg, tacrolimus granules are available as 0.2 mg sachets that can be suspended in water and administered orally. The 0.2 mg sachet, therefore, allows for more precise dosing and dose titration than the capsule formulation. The granular formulation also facilitates accurate dose adjustment of tacrolimus according to patient characteristics, such as weight, or potential concomitant drug interactions (e.g., antiviral therapy for hepatitis C virus (HCV)- or human immunodeficiency virus (HIV)-positive recipients, or antifungal therapy) [13]. Additionally, tacrolimus granules offer an alternative for patients who are unable or unwilling to take a solid oral dosage form.

Although clinical studies have been conducted on tacrolimus granules [9,14], observational studies will help inform the medical community on its use in routine clinical practice. OPTIMOD was a prospective, non-interventional, 6-month study of post-transplant patients who received tacrolimus granules to prevent or treat organ rejection in routine clinical practice in France. The study objectives were to describe characteristics of patients in France who were taking tacrolimus granules, the efficacy and safety of tacrolimus granules, and patient adherence and satisfaction with treatment.

Material and Methods

Approximately 60 transplant centers in France with pediatric and adult renal, liver, and cardiopulmonary transplant activities were contacted for a feasibility assessment. Participating centers were invited to include all consecutive adult (≥18 years) or pediatric (<18 years) patients who received an organ transplant and for whom a decision to initiate tacrolimus granules had been made before enrollment (incident prescriptions only). The sole exclusion criterion was concomitant participation in an interventional clinical trial.

Patients received information about the study and were able to withdraw their consent at any time. Written informed consent was provided by adult patients or, in the case of pediatric patients, by their parents or their legal guardians. Due to the observational nature of the study, the dosing regimen of tacrolimus and care of the patients was left to the discretion of the investigator. The study was approved by the relevant ethics committees and conducted according to the Declaration of Helsinki.

Immunosuppressive therapy details were collected when tacrolimus granules were initiated (inclusion visit) and 6 months later (follow-up visit), although only the initially-prescribed tacrolimus dose was collected. C_0, measured during the 6-month follow-up, was reported once for the whole period, at the follow-up visit. Achievement of target tacrolimus concentrations was reported directly as 'yes/no' by the investigator and was not derived from reported C_0 values. Acute clinical rejections and organ loss, deaths and adverse events (AEs), including severe AEs, were recorded during follow-up. Adherence was assessed using the self-reported, 6-question, Girerd questionnaire. A positive answer was counted as 1 point in the overall score, which ranged from 0 to 6 (0, good adherence; 1 and 2, minor non-adherence; and ≥3, major non-adherence) [15]. Overall satisfaction, ease of use, and frequency of use were recorded by patients still under treatment at the follow-up visit, using generic 6-point rating scales, ranging from 1 (not at all satisfied) to 6 (extremely satisfied). For pediatric patients, questionnaires were completed by their parents or their legal guardians.

Table 1. Population characteristics.

Parameter	Children (N=34)		Adults (N=27)		Total (N=61)	
Sex, n (%)						
Male	27	(79.4)	17	(63.0)	44	(72.1)
Female	7	(20.6)	10	(37.0)	17	(27.9)
Age, years						
Mean ±SD	8±4		48±15		25±22	
Median (IQR)	7	(4–11)	51	(40–58)	15	(7–49)
Minimum; maximum	1;16		18;70		1;70	
Organs grafted, n (%)						
Kidney	24	(70.6)	1	(3.7)	25	(41.0)
Lung	0	(0.0)	21	(77.8)	21	(34.4)
Liver	8	(23.5)	3	(11.1)	11	(18.0)
Heart	1	(2.9)	2	(7.4)	3	(4.9)
Liver-kidney	1	(2.9)	0	(0.0)	1	(1.6)
Concomitant immunosuppression at inclusion, n (%)						
MPA	29	(85.3)	17	(63.0)	46	(75.4)
Corticosteroids	18	(52.9)	18	(66.7)	36	(59.0)
Other*	14	(41.2)	15	(55.6)	29	(47.5)
Treatment line, n (%)						
First-line initiation	15	(44.1)	0	(0.0)	15	(24.6)
Conversion	19	(55.9)	27	(100.0)	46	(75.4)

* Monoclonal antibodies (n=9); mTOR inhibitors (n=9); azathioprine (n=2); unknown (n=3); allocated incorrectly as receiving tacrolimus or non-immunosuppressive agent (n=6). IQR – interquartile range; MPA – mycophenolic acid; mTOR – mammalian target of rapamycin; SD – standard deviation.

Statistics

According to the Haute Autorité de Santé (the French National Authority for Health), the maximum number of new pediatric patients likely to benefit from tacrolimus granules in 2008 was 160 [16]; however, it was not possible to quantify the target population. The planned number of patients in this study was limited by the capacity of the contacted sites; it was anticipated that approximately 100 patients from 25 sites would be included during the 1-year recruitment period. In descriptive studies, the sample size calculation relies on the alpha risk and on the precision level desired for presenting observed frequencies (i.e., half of the total width of the expected confidence interval [CI]). A sample size of 100 patients would provide a precision level ranging from 4% to 10% for estimated percentages between 5% and 95% (e.g., the CI around an estimated incidence rate of 50% might be 50%±10%).

All analyses were descriptive. Quantitative variables were reported using mean and SD, or the median and range, according to variable distribution; qualitative variables were reported using frequencies and percentages, not accounting for missing values.

Results

Patient characteristics

Of 25 participating sites, 18 enrolled 66 patients between March 2013 and June 2014. As 5 patients did not meet the selection criteria (tacrolimus granules were not initiated during the inclusion visit), 61 patients were analyzed: 34 (55.7%) children and 27 (44.3%) adults.

Table 2. Tacrolimus granules for oral suspension prescriptions according to period of initiation.

Parameter	First-line (N=15)	Conversion (N=46)	Total (N=61)
Indication for tacrolimus granules, n (%)			
Prevention of rejection	15 (100.0)	43 (93.5)	58 (95.1)
Treatment of rejection	0 (0.0)	3 (6.5)	3 (4.9)
Reason for tacrolimus granules prescription, n (%)			
Dose adjustments	2 (13.3)	39 (84.8)	41 (67.2)
Pharmaceutical form	13 (86.7)	1 (2.2)	14 (23.0)
Other	7 (46.7)	20 (43.5)	27 (44.3)
Dose at initiation, mg/day			
Mean ±SD	2.5±1.6	1.8±1.9	1.9±1.8
Median	2.4	0.8	1.2
Minimum; maximum	0.4; 5.8	0.2; 8.8	0.2; 8.8
Number of treatment modifications during follow-up, n (%)	15 (100.0)	33 (71.7)	48 (78.7)
Mean ±SD	4.7±3.3	2.4±1.7	3.1±2.5
Median	6	2	2
Type of treatment modification during follow-up (among those with modifications), n (%)			
Dose reduction	12 (80.0)	18 (54.5)	30 (62.5)
Dose increase	10 (66.7)	17 (51.5)	27 (56.3)
Temporary withdrawal	3 (20.0)	1 (3.0)	4 (8.3)
Definitive discontinuation	3 (20.0)	12 (36.4)	15 (31.3)

SD – standard deviation.

Patient characteristics are summarized in Table 1. Most patients were male (72.1%) in both pediatric (79.4%) and adult (63.0%) groups. The mean ±SD age of the pediatric population was 8±4 years (range: 1–16 years) and 48±15 years for the adult population (range: 18–70 years). Of the 34 pediatric recipients, 24 received a kidney graft (70.6%), 8 received a liver graft (23.5%), 1 received a heart graft (2.9%), and 1 received a combined kidney and liver graft (2.9%). Of the 27 adult recipients, 21 received a lung graft (77.8%), 3 received a liver graft (11.1%), 2 received a heart graft (7.4%), and 1 received a kidney graft (3.7%). All patients were taking concomitant immunosuppressant therapies at inclusion; most frequently MPA (75.4% patients) and corticosteroids (59.0%). Drugs with potential interactions with tacrolimus at initiation were antimycotics (13.1%), antivirals (6.6%), proton pump inhibitors (3.3%), and aspirin (1.6%).

Treatment characteristics

Treatment with tacrolimus granules was initiated during the inclusion visit. For 15 patients this was immediately after transplantation (first-line initiation; 24.6%) and was delayed for 46 patients (initiation at conversion; 75.4%). Patients receiving first-line treatment were all children, whereas those who converted were mainly adults (Table 1). The median delay between transplantation and initiation of tacrolimus granules was 1 day (range: 0–10 days) for patients receiving first-line treatment, and 16 months (1–168 months) for patients who converted to tacrolimus granules. For patients converting to tacrolimus granules, previous treatment was another tacrolimus formulation (immediate-release or prolonged-release tacrolimus) in 41 patients (89.1%), and ciclosporin in 4 patients (8.7%). The main reasons for prescribing the granules were dose adjustment, and specific pharmaceutical form in 14 patients (23.0%), of whom 13 were children receiving first-line treatment. The median dose prescribed at the inclusion visit

Table 3. Tacrolimus granules for oral suspension prescriptions by organ.

Parameter	Kidney (N=25)	Lung (N=21)	Liver (N=11)	Heart (N=3)	Liver-kidney (N=1)	Total (N=61)
Indication for tacrolimus granules, n (%)						
Prevention of rejection	25 (100.0)	18 (85.7)	11 (100.0)	3 (100.0)	1 (100.0)	58 (95.1)
Treatment of rejection	0 (0.0)	3 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.9)
Reason for tacrolimus granules prescription, n (%)						
Dose adjustments	14 (56.0)	20 (95.2)	3 (27.3)	3 (100.0)	1 (100.0)	41 (67.2)
Pharmaceutical form	8 (32.0)	0 (0.0)	6 (54.5)	0 (0.0)	0 (0.0)	14 (23.0)
Other	12 (48.0)	8 (38.0)	5 (45.5)	2 (66.7)	0 (0.0)	27 (44.3)
Dose at initiation, mg/day						
Mean ±SD	2.6±1.8	1.2±1.6	1.8±1.9	1.3±0.9	4.4	1.9±1.8
Median	2.0	0.8	1.0	0.8	NA	1.2
Minimum; maximum	0.8; 8.8	0.4; 8.0	0.2; 5.8	0.2; 2.4	NA	0.2; 8.8
Number of treatment modifications during follow-up, n (%)	19 (76.0)	17 (81.0)	9 (81.8)	2 (66.7)	1 (100.0)	48 (78.7)
Mean ±SD	4.6±2.9	2.2±1.7	2.4±2.1	1.0±0.0	1	3.1±2.5
Median	5	1	2	1	NA	2
Type of treatment modification during follow-up (among those with modifications), n (%)						
Dose reduction	15 (78.9)	9 (52.9)	5 (55.6)	1 (50.0)	0 (0.0)	30 (62.5)
Dose increase	14 (73.7)	7 (41.2)	5 (55.6)	0 (0.0)	1 (100.0)	27 (56.3)
Temporary withdrawal	1 (5.3)	1 (5.9)	2 (22.2)	0 (0.0)	0 (0.0)	4 (8.3)
Definitive discontinuation	2 (10.5)	10 (58.8)	2 (22.2)	1 (50.0)	0 (0.0)	15 (31.3)

SD – standard deviation; NA – not applicable.

was 2.4 mg/day for first-line patients, and 0.8 mg/day for the conversion patients. During follow-up, treatment modifications were recorded for 48 patients (78.7%) with a mean of 3.1 adjustments per patient (4.7 in first-line patients; 2.4 in conversion patients), most of which were dose reductions (Table 2). All patients receiving a kidney graft were children, except 1. Kidney transplant patients received tacrolimus granules at a median dose of 2 mg/day at inclusion visit. Lung transplant recipients, all adults, received a median dose of 0.8 mg/day at inclusion visit. During follow-up, treatment modifications were frequent for kidney (76.0%) and lung (81.0%) patients, with means of 4.6 and 2.2 treatment adjustments per patient, respectively (Table 3).

Fifteen patients (31.3%) discontinued treatment during follow-up due to problems attaining tacrolimus target trough blood levels (n=10), the addition of a treatment potentially able to cause drug interactions (n=3), serious AEs (cardiotoxicity; n=1),

and withdrawn consent (patient did not like the taste of tacrolimus granules; n=1). Discontinuations were reported for 2 kidney patients (10.5%), 10 lung patients (58.8%), 2 liver patients (22.2%), and 1 heart patient (50.0%).

Tacrolimus trough blood concentration

During the 6-month follow-up, each patient had an average of 8 tacrolimus C_0 assessments. The median time to achieve target C_0, according to the investigators, was 20 days: 27.5 days in first-line patients and 20 days for conversion patients (Table 4). Three patients had C_0 <5 ng/mL or >20 ng/mL, which were both considered AEs. After first-line initiation of tacrolimus granules, mean ±SD C_0 was higher during than after the first month of follow-up (11.5±10.3 ng/mL vs. 6.5±2.3 ng/mL 1 week and in the 1st to 2nd month after initiation, respectively); C_0 was stable from the first month of follow-up until the end of the study. The variability in tacrolimus C_0 appeared higher

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565

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Table 4. Trough blood level (C_0) assessments.

	First-line (N=15)		Conversion (N=46)		Total (N=61)	
Mean number of C_0 assessments per patient	8.8		7.5		7.8	
Median (minimum; maximum) time to target C_0, days	27.5	(2; 171)	20.0	(0; 175)	20.0	(0; 175)
Patients with target C_0 within first 2 weeks, n (%)	6	(40.0)	21	(45.7)	27	(44.3)
Patients with a C_0 <5 or >20 ng/mL considered an AE*, n (%)	2	(13.3)	1	(2.2)	3	(4.9)
	Children (N=34)		**Adults (N=27)**		**Total (N=61)**	
Mean number of C_0 assessments per patient	8.2		7.3		7.8	
Median (minimum; maximum) time to target C_0, days	42	(0; 175)	10	(0; 121)	20	(0; 175)
Patients with target C_0 within first 2 weeks, n (%)	13	(38.2)	14	(51.9)	27	(44.3)
Patients with a C_0 <5 or >20 ng/mL considered an AE*, n (%)	2	(7.1)	1	(6.7)	3	(7.0)

* Of patients with at least one assessment with a C_0 <5 or >20 ng/mL (children, n=28; adult, n=15; total, n=43). AE – adverse event; C_0 – trough tacrolimus blood concentration.
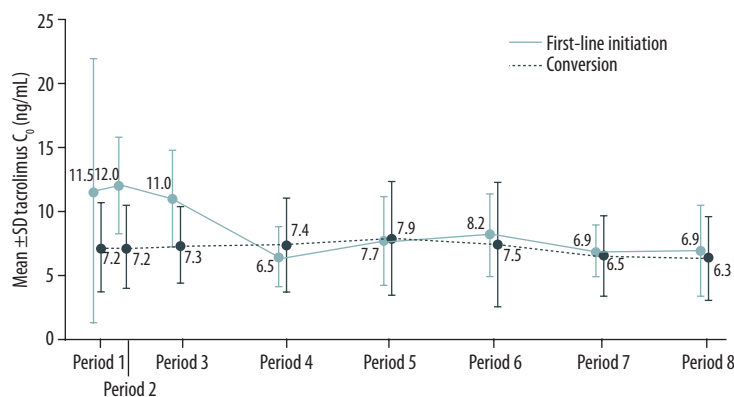
Figure 1. Evolution of the mean C_0 of tacrolimus during follow-up according to initiation type: first-line (N=15) or conversion (N=36). Period 1 – one week after initiation; period 2 – two weeks after initiation; period 3 – two weeks–1st month after initiation; period 4 – 1st–2nd month after initiation; period 5 – 2nd–3rd month after initiation; period 6 – 3rd–4th month after initiation; period 7 – 4th–5th month after initiation; period 8 – 5th–6th month after initiation. C_0 – trough tacrolimus blood concentration; SD – standard deviation.

during the first month after treatment initiation than during subsequent months (Figure 1). In conversion patients, mean ±SD tacrolimus C_0 remained stable during follow-up (Figure 1). Pediatric patients had a higher mean tacrolimus C_0 than adult patients during the first month after initiating tacrolimus granules, after which mean C_0 was numerically lower in the pediatric cohort until the end of the study (Figure 2).

Effectiveness and safety of tacrolimus granules

During follow-up, rejection episodes occurred in 10 patients (16.4%): 5/34 (14.7%) pediatric patients (4 liver recipients and 1 kidney recipient), and 5/27 (18.5%) adult patients (all lung recipients). One pediatric liver recipient had 2 episodes of rejection 26 days apart. Of the 11 rejection episodes, 10 were

biopsy-proven acute cellular rejections and 1 was antibody-mediated rejection in a lung recipient. Five of these episodes occurred in first-line patients and 6 occurred in conversion patients. Nine of the 10 patients with a reported rejection episode during follow-up had data available for the time between transplantation and rejection; the mean ±SD delay between transplantation and the rejection episode was 6.55±6.0 months (median: 6.7 months; range: 0.2–18 months). The average delay between tacrolimus granules initiation and the rejection episode was 2.4±2.2 months (range: 0.2–6.3 months); in conversion patients the mean delay was 6.4 months (median: 5.7 months; range: 1–13 months). One rejection episode (described as acute borderline cellular rejection by the local pathologist) was considered a treatment-related AE and was graded as non-serious. This occurred in a pediatric kidney recipient taking
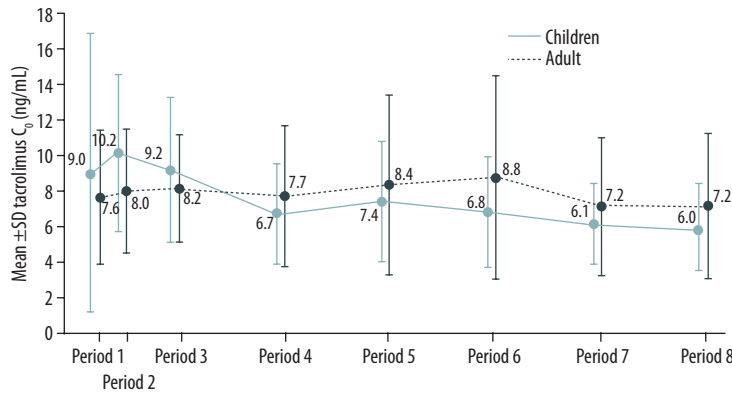
Figure 2. Evolution of the mean C_0 of tacrolimus during follow-up according to age group: adults (N=27) or children (N=34). Period 1 – one week after initiation; period 2 – two weeks after initiation; period 3 – two weeks–1st month after initiation; period 4 – 1st–2nd month after initiation; period 5 – 2nd–3rd month after initiation; period 6 – 3rd–4th month after initiation; period 7 – 4th–5th month after initiation; period 8 – 5th–6th month after initiation. C_0 – trough tacrolimus blood concentration; SD – standard deviation.

Table 5. List of reported treatment-related AEs following initiation of tacrolimus granules for oral suspension.

Patient number	AEs	Age (years)	Organ transplanted	Treatment line of initiation	Severity	Outcome
1	Acute borderline cellular rejection	2	Kidney	First-line	Non-serious	Recovered
	EBV-associated lymphoproliferative disorder	2	Kidney	First-line	Serious	Recovered
2	CMV infection	13	Kidney	Conversion	Serious	Recovered
	Diabetes	13	Kidney	Conversion	Serious	Ongoing
3	Haemophilus pneumonia	10	Kidney	Conversion	Serious	Recovered with sequelae
	Herpes infection	10	Kidney	Conversion	Serious	Recovered with sequelae
	Lung infection	10	Kidney	Conversion	Serious	Recovered with sequelae

AE – adverse event; CMV – cytomegalovirus; EBV – Epstein-Barr virus.
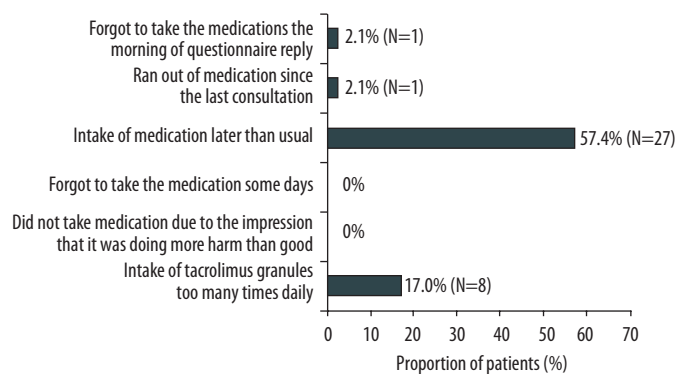
tacrolimus granules as first-line treatment 3.5 months after transplantation. No rejection episodes led to graft loss during the study. During follow-up, one 40-year-old female lung recipient (second graft) with cystic fibrosis died 15 months after transplantation and 3.5 months after tacrolimus granules were initiated. The cause of death was chronic respiratory insufficiency considered unrelated to tacrolimus granules.

During the study, 30 AEs were reported by 16 (26.2%) patients. Seven AEs in 3 (4.9%) patients were considered treatment-related: 4 infections (3 in 1 patient), Epstein-Barr virus (EBV)-associated lymphoproliferative disorder that occurred 3.5 months after initiation of tacrolimus granules, diabetes, and an acute cellular rejection. All treatment-related AEs were assessed as serious, except for the acute cellular rejection (Table 5). No significant changes in metabolic profile (including hepatic enzymes, serum creatinine, and proteinuria)

were observed in any patient for up to 6 months after tacrolimus granules were initiated. Of note, no cases of polyomavirus-associated nephropathy were reported.

Self-reported adherence and patient satisfaction

Responses to the adherence questionnaire at the 6-month visit were obtained for 47 patients (77.0%): 25 (53.2%) children, and 22 (46.8%) adults. All respondents reported good adherence or minor non-adherence: 15 patients (31.9%) had good adherence (score: 0) and 32 (68.1%) had minor non-adherence (score: 1 or 2). No respondent had a score >2 (major non-adherence). For patients scoring 1 or 2 points, the main issues were taking medicine later than usual and the perception that they had to take tacrolimus granules too many times daily (Figure 3). Adherence rates and reasons for minor non-adherence were similar to the overall population when patients
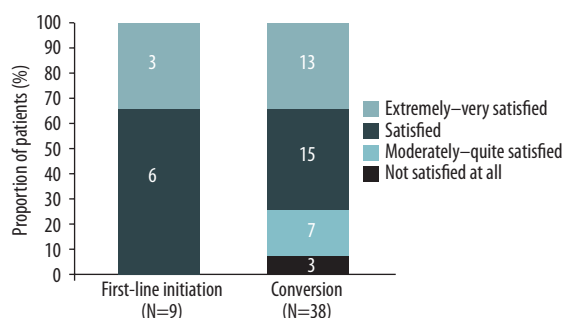
Figure 4. Patient satisfaction with tacrolimus granules according
to line of treatment (N=47).

were stratified by first-line *vs.* conversion treatment with ta-
crolimus granules.

The satisfaction questionnaire was completed for the same 47
patients: 16 (34.0%) were extremely or very satisfied with treat-
ment, 21 (44.7%) were satisfied, and 10 (21.3%) were moder-
ately satisfied to dissatisfied. All moderately satisfied or dis-
satisfied patients were in the conversion group (Figure 4), of
whom 6 (60%) were children, and 4 (40%) were adults.

Discussion

Most solid organ transplants, with the exception of pancreat-
ic and intestinal, were represented in this observational study,
although patient enrollment was 40% lower than planned.
Consistent with the overall transplant population, most pa-
tients had a kidney graft, but the proportion of lung recipients
in our population (34.4%) was higher than generally seen in
the overall population of organ recipients (6% in 2013) [1]. This
increased proportion of lung recipients may be because this
patient population requires particularly accurate and tailored
dose adjustment, such as that provided by tacrolimus gran-
ules-based regimens, and close monitoring due to the poten-
tial for drug interactions [17,18]. Since only patients receiving

tacrolimus granules were included in the study, the represen-
tation of lung patients may be proportionately greater than
in the general transplant population.

The dosing regimen of tacrolimus and its adaptations was left
to the discretion of the treating physician in this non-inter-
ventional study. When used in children, tacrolimus often re-
quires small dose adjustments. Indeed, a heterogeneous pedi-
atric population requires individualized dosing [19] according
to characteristics such as age, weight, and genetic variation
in metabolic enzymes, including polymorphisms in the cyto-
chrome P450 3A5 (CYP3A5) family [20]. Such dosing can be fa-
cilitated by the granular formulation of tacrolimus [13], which
also provides patients with an alternative way of taking their
treatment in the event of (transient) swallowing difficulties.
Accordingly, treatment with tacrolimus granules was started
immediately after transplantation as first-line treatment in 15
of the 34 children.

In the adult population, all of whom converted to tacrolimus
granules, treatment initiation was related to the need for dose
adjustments. As previously mentioned, many of these patients
were lung recipients, who have specific requirements. For ex-
ample, there are significant drug interactions between tacro-
limus and CYP450 inducers and inhibitors [13,17,18], such as
antifungals (mainly CYP450 inhibitors), which are often pre-
scribed to lung recipients for prophylaxis or treatment for in-
fections [21]. Indeed, 3 patients in this study were treated with
antiviral therapy for concomitant hepatitis C and required dose
adjustment owing to drug interactions between boceprevir/
telaprevir and tacrolimus [21].

Mean tacrolimus trough blood levels were higher during the
first month after first-line initiation of tacrolimus granules than
during subsequent months. As all patients receiving first-line
tacrolimus granules were children, clinicians may have been
reluctant to risk under-immunosuppression in this vulnerable
patient cohort. In contrast, mean tacrolimus trough blood levels
were generally stable in patients who converted to tacrolimus

granules. During the follow-up period, dose increases or decreases were reported for most patients, mainly to reach target C_0. This is consistent with requirements for graft recipients, owing to the narrow therapeutic index of CNIs [22–24]. However, it is reassuring that only 3 patients in this cohort had C_0 <5 ng/mL or >20 ng/mL.

During the 6-month follow-up period, graft and patient survival rates were 100% and 98.4%, respectively. A 40-year-old female lung recipient who had cystic fibrosis died during follow-up (15 months after transplantation) from chronic respiratory insufficiency. Patients with pulmonary fibrosis or compromised airways have a higher risk of death following lung re-transplantation [25], and this death was considered to be unrelated to treatment. Limited data from patients treated with tacrolimus granules are available with which to compare our results. However, the high graft and patient survival rates in this study are aligned with those from a 12-month, open-label, randomized Phase 3 study conducted in *de novo* pediatric liver transplant recipients, in which 12-month graft and patient survival rates were 92.3% and 93.4%, respectively [14]. Similar high rates of graft and patient survival have also been reported for pediatric and adult solid organ transplant recipients for up to 1 year after initiating immediate- or prolonged-release tacrolimus capsules *de novo*, or following conversion from immediate- to prolonged-release tacrolimus capsules [26–34].

In a small (N=9), 4-week study of adult stable kidney transplant recipients converted from immediate-release tacrolimus capsules to tacrolimus granules, no patients experienced graft rejection or dysfunction [9]. The incidence of rejection in our 6-month study was also low, with only 11 rejection episodes occurring among 10 patients (16.4%): 5 children and 5 adults, none of which led to graft loss. Furthermore, only 1 rejection episode was assessed by a participating physician as probably related to tacrolimus treatment. This was an acute borderline cellular rejection, 3.5 months after transplantation and treatment initiation, in a pediatric kidney transplant patient receiving tacrolimus granules as a first-line treatment; however, details of the relationship with tacrolimus treatment were not provided.

Notably, the rate of rejection reported in this study with tacrolimus granules is within the range of rejection rates cited in *de novo* and conversion studies of solid organ transplant patients receiving immediate- or prolonged-release tacrolimus capsules for up to 1 year [26–31,34]. For example, 20.9% of adult *de novo* kidney transplant recipients experienced graft rejection at 6 months with prolonged-release tacrolimus in the ADVANCE study [31]. However, considering the small population size in our study, comparisons of the rejection incidence with those reported in previous studies should be made with caution.

During follow-up in our study, 2 patients recorded treatment-related infections (one with cytomegalovirus, and the other with separate events of pneumonia, herpes, and lung infection). The other treatment-related AEs were single cases of acute borderline cellular rejection (see above), diabetes mellitus, and EBV-associated lymphoproliferative disorder in a first-line pediatric kidney recipient who recovered after tacrolimus withdrawal and rituximab treatment. The incidence of diabetes mellitus and EBV-associated lymphoproliferative disorder was similarly low in *de novo* pediatric liver transplant patients receiving tacrolimus granules in the Phase 3 study by Kelly et al. [14], and in pediatric and adult solid organ transplant patients receiving immediate- or prolonged-release tacrolimus [26,27,29,30]. In our study, no significant changes in metabolic profile, including hepatic enzymes, were observed up to 6 months after starting therapy.

Although adherence to immunosuppressive therapy is essential to avoid rejection, non-adherence is frequent among transplant recipients, with rates ranging from 2% to 68% [35,36]. Tacrolimus granules require more preparation before taking than other tacrolimus formulations, which could have impacted adherence. However, self-reported adherence to treatment was either good or there were only minor issues related to delayed treatment ingestion. Overall, patients were generally satisfied with their treatment, and less than one-quarter of the patients who converted to tacrolimus granules reported low levels of satisfaction with the treatment. It is possible that the converted patients who reported lower levels of satisfaction had been content with their original regimen, and the unfamiliarity with their new, post-conversion, regimen could have negatively affected their levels of satisfaction.

The present study has some limitations, such as patient selection bias, which is inherent to observational studies. Although the study planned to enroll 100 patients, only 66 were enrolled, and 61 were included in the analysis population, leading to reduced precision of the estimates reported in the study. This was possibly a consequence of the relatively short enrolment period (15 months) and that only 'new' (i.e., incident) users of tacrolimus granules could be included in the study. As this treatment had been available for 3 years in France at the time of inclusion [16], patients who were likely to benefit from tacrolimus granules were probably already using it (i.e., prevalent patients) and were thus excluded. In our clinical experience, prevalent patients show similar results to those reported here. At the time of the study, new anti-HCV treatments had been launched with fewer potential drug–drug interactions with tacrolimus than those previously available [37]. Therefore, the demand for the very small doses delivered by the granule formulation (0.2 mg) of tacrolimus may have decreased as a consequence. Additionally, collection of tacrolimus dosing data during follow-up would have been useful

to interpret tacrolimus dose adjustments and trough levels. Studies assessing efficacy, target tacrolimus trough level, tacrolimus dose, need for dose adjustments, and cost-effectiveness of tacrolimus granules *vs.* other tacrolimus formulations would be useful to further elucidate the benefits of the tacrolimus granules in clinical practice.

The lower-than-expected sample size may impact extrapolation of findings to the overall population of patients treated with tacrolimus granules. However, as the first cohort study to describe the use of tacrolimus granules in transplant recipients in France, the results offer an important insight into the use of this formulation. A 6-month follow-up period is a limited timespan for the observation of long-term outcomes regarding effectiveness and safety. Nevertheless, the results observed during this period did not differ meaningfully from those published in clinical trials [9,14].

In the absence of a pediatric-specific questionnaire to assess adherence to immunosuppressive agents at the time of the study, the Girerd questionnaire was used, although it had not been validated in this setting [15]. This should be taken into account when interpreting adherence results.

Conclusions

In conclusion, this study appears to show that tacrolimus granules for oral suspension, when administered in routine practice in France, has an acceptable tolerability profile and is effective in preventing transplant rejection. Tacrolimus granules may also prove a useful alternative for children and patients who have trouble swallowing and would benefit from this

formulation, as well as for patients requiring accurate dose adjustments due to drug–drug interactions.

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