Longterm Survival and Cost-Effectiveness of Immunosuppression Withdrawal After Liver Transplantation

Tommaso Maria Manzia,[1] Roberta Angelico,[1,2] Luca Toti,[1] Cristina Angelico,[3] Claudia Quaranta,[1] Alessandro Parente,[1] Francesca Blasi,[1] Samuele Iesari,[3] Daniele Sforza,[1] Leonardo Baiocchi,[1] Jan Lerut,[4] and Giuseppe Tisone[1]

[1]Transplant and Hepatobiliary Unit, Department of Surgery, University of Rome Tor Vergata, Rome, Italy; [2]Division of Abdominal Transplantation and Hepatobiliopancreatic Surgery, Bambino Gesù Children's Research Hospital, IRCCS, Rome, Italy; [3]Department of Economics, Bocconi University, Milan, Italy; and [4]Starzl Unit of Abdominal Transplantation, Université Catholique de Louvain, Brussels, Belgium

Lifelong immunosuppression (IS) after liver transplantation is associated with severe adverse effects and increased recipients' morbidity and mortality. Clinical operational tolerance has been reported in up to 40% in very well-selected recipients. Longterm survival and cost savings within the Italian national health system in operational tolerant recipients is reported. Seventy-five liver recipients were enrolled for IS withdrawal at our institution during the period from April 1998 to December 2015. The study population comprised 32 (42.7%) tolerant patients; 41 (54.7%) nontolerant patients needing uptake of IS after clinical or biopsy-proven rejection; and 2 (2.7%) immediate nontolerant patients who developed early rejection after the first drug reduction. The primary endpoint of the study was to assess the longterm patients and graft outcome; the secondary endpoint was the assessment of cost savings in the context of IS withdrawal. The follow-up was 95.0 months (interquartile range, 22.5-108.5 months). IS withdrawal did not result in patient nor graft loss and resulted in a major cost savings reaching about €630,000. In conclusion, longterm IS withdrawal represents a remarkable cost savings in the health care of liver recipients without exposing them to graft loss.

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Liver transplantation (LT) is the therapeutic gold standard of acute and chronic end-stage liver diseases.(1) Development of surgical techniques, clinical management, and refinement of the immunosuppression (IS) schemes allow nowadays to obtain remarkable results. However, lifelong IS is associated with severe adverse events leading to major morbidity and mortality.(2) IS is indeed linked to a highly increased risk for lethal infectious, cardiovascular, renal, metabolic, and oncologic complications.(3-5) Therefore, multiple strategies have been explored to reach clinical operational tolerance (COT).(6) COT is the condition whereby a LT retains function and lacks histological signs of rejection in the absence of any IS.(7) Once achieved, it may not only be beneficial in relation to avoidance of the aforementioned complications(2,8-11) but also for improved quality of life (QoL).(5,12,13) In this scenario, another important corollary that is usually not taken into consideration is cost-optimization policies. US studies showed that lifelong IS results in an average yearly cost ranging from US $10,000 to US $14,000.(14)

This report looks at the impact of IS withdrawal on direct health cost savings in the Italian national health system.

Abbreviations: BPAR, biopsy-proven acute rejection; CNI, calcineurin inhibitor; COT, clinical operational tolerance; CsA, cyclosporine A; DRG, diagnosis-related group; ECMPS, enteric-coated mycophenolate sodium; EVR, everolimus; FPR, fibrosis progression rate; GFR, glomerular filtration rate; GGT, gamma-glutamyl transferase; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; i-non-COT, immediate non–clinical operational tolerance; IQR, interquartile range; IS, immunosuppression; ISTAT, Italian National Institute of Statistics; LT, liver transplantation; MDRD, Modification of Diet in Renal Disease; MMF, mycophenolate mofetil; mTORi, mammalian target of rapamycin inhibitor; NODAT, new-onset diabetes mellitus after transplant; non-COT, non–clinical operational tolerance; QoL, quality of life; TAC, tacrolimus.

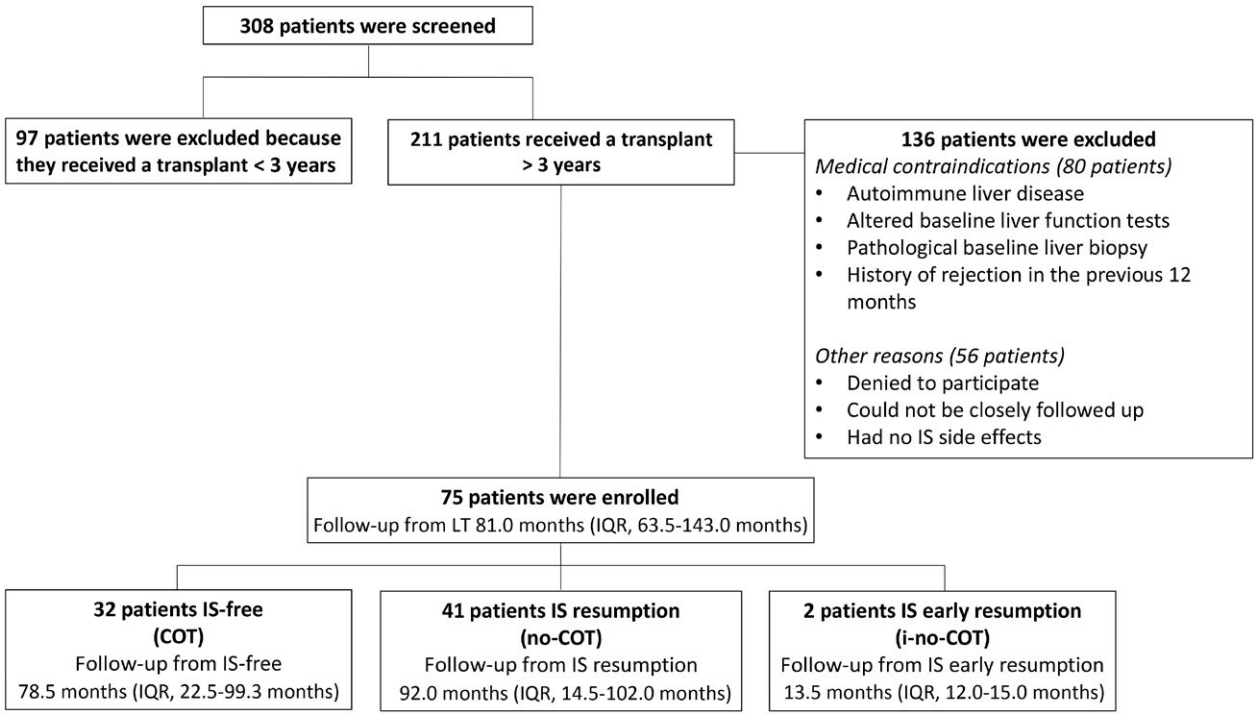

FIG. 1. Screening and enrollment of IS withdrawal in the LT population.

Patients and Methods

Inclusion and exclusion criteria for the IS weaning approach have been previously well described.[5-8] There were 308 patients who were screened for potential enrollment. Out of these patients, 97 patients were excluded because they did not reach 3 years of follow-up from LT. Of the remaining 211 patients, 136 patients did not fulfil the inclusion criteria because of medical contraindications (n = 80) or for other reasons (n = 56; Fig. 1).

There were 75 LT recipients (53 [70%] male) who had a median age of 50.0 years (interquartile range [IQR], 44.5-57.0 years) and who underwent LT at University of Rome Tor Vergata during the period from April 1998 to December 2015 (unpublished data).[5,9] Their median follow-up from LT was 193.0 months (IQR, 143.0-241.0 months). Also, 32 (42.7%) patients achieved COT following complete IS withdrawal; 41 (54.7%) patients had non–clinical operational tolerance (non-COT) as they developed a clinical and/or biopsy-proven acute cellular rejection (BPAR) during the tapering process needing resumption of IS. Finally, 2 (2.7%) patients developed clinical or BPAR after the first drug reduction and needed immediate readjustment of their IS (immediate non–clinical operational tolerance [i-non-COT]).

Initial IS was based on calcineurin inhibitors (CNIs). At the time of weaning, the IS regimen was as follows: 56 (74.7%) patients had CNI, 13 (17.3%) had mycophenolate mofetil (MMF), and 3 (4.0%) patients each had mammalian target of rapamycin inhibitor (mTORi)

Address reprint requests to Tommaso Maria Manzia, M.D., Ph.D., Transplant and Hepatobiliary Unit, Department of Surgery, University of Rome Tor Vergata, Viale Oxford 81, 00133 Rome, Italy. Telephone: +39062090289; E-mail: tomanzia@libero.it

Tommaso Maria Manzia designed the research and wrote the manuscript. Luca Toti, Roberta Angelico, Claudia Quaranta, Francesca Blasi, and Alessandro Parente collected data. Cristina Angelico analyzed data and cost savings. Samuele Iesari and Daniele Sforza performed the research. Leonardo Baiocchi, Jan Lerut, and Giuseppe Tisone critically revised the manuscript for intellectual content.

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and combined CNI or mTORi and MMF-based IS. This study was approved by our local ethical committee board. Authors declare no conflicts of interest.

STUDY ENDPOINTS

The primary endpoints of the study were the composite endpoint comprising graft and patient loss, longterm liver function, and BPAR. The secondary endpoint was to identify the cost savings of such a strategy for the Italian national health system. As the results of the primary endpoints have already been reported previously,[9,10] this article focuses on the secondary economic-related endpoint.

STUDY DESIGN

Primary Endpoint: Composite Survival and Clinical Outcome

The longterm weaning of IS was assessed considering patient and graft status; liver tests; renal function; lipid profile; glycemia; and the occurrence of BPAR. All data were extracted from a prospectively collected database and were retrospectively analyzed.

Secondary Endpoint: A Cost-Effectiveness Calculation in the Context of IS Withdrawal

This cost evaluation took into consideration the cost savings of IS minimization or withdrawal, the cost of weaning protocol liver biopsies, and the cost of supplementary protocol blood tests and outpatient visits.

All drug prices were recorded from the official site of the Italian drug agency.[15] Data on the IS cost before the start of weaning, during weaning, and for each subsequent visit were adjusted for inflation using the consumer price index for blue- and white-collar worker households provided by the Italian National Institute of Statistics (ISTAT).[16] In particular, each amount of money was converted to the 2015 currency using annual coefficients of monetary re-evaluation. Using this method is equivalent to using the percentage change in the consumer price index during the studied period. From 2002 onward, final amounts were obtained by computing the product of the original values and the described coefficients. For the period 1998-2001, the original data were expressed in lira, being the Italian currency until 2002; afterward, as suggested by ISTAT, the re-evaluation coefficients were applied, and the prices were converted to 2015 euros using the fixed currency rate of 1936.3 lira for €1. Notably, at the time the empirical analysis was made, the official statistics on 2016 annual consumer price index were not available; hence, prices could not be converted to the current currency. Still, we verified a posteriori that in 2016, the percentage change in the consumer price index from the previous year was –0.1%. Therefore, we do not expect this minor variation to affect our results.

IS Tapering–Related Cost. Since the start of the weaning process until complete IS withdrawal (COT group) or weaning stop (non-COT and i-non-COT), the daily dose cost of each drug type, ie, cyclosporine A (CsA; Sandimmun Neoral, Novartis, Basel, Switzerland), tacrolimus (TAC; Advagraf or Prograf, Astellas, Tokyo, Japan), everolimus (EVR; Certican, Novartis), sirolimus (Rapamune, Pfizer, New York), and MMF (CellCept, Roche, Basel, Switzerland; Myfortic, Novartis, Tokyo, Japan; and Myfenax, Teva Petah Tigwa, Israel), and dose prescribed at each outpatient visit were recorded and inflated related to the current year (as stated previously). This cost was multiplied for each patient by the number of days elapsed between the start of weaning and each outpatient (where the IS dose was progressively reduced) until IS off (i.e. IS permanetly discontinued, COT) or stop weaning (non-COT; Figs. 2 and 3).

COT IS Cost Savings. The cost of daily drugs employed before the weaning start for each enrolled patient was multiplied by the time (days) of IS off stay. Namely, the saving evaluation was calculated considering the cost of IS dose before the enrollment since it represented the standard longterm dosage that would otherwise have been given (lifelong).

Non-COT Patient IS Cost Savings. For the non-COT group, the IS cost savings was evaluated based on the difference, or Δ dose, between the daily dose of IS before the start of weaning and the IS maintenance daily dose after the resumption of the drug. Seven patients switched to a different IS drug at the time of IS resumption, so no cost benefit evaluation was attempted.

I-Non-COT Patient IS Cost. The i-non-COT patients (n = 2) showed liver test deterioration 1 week after the drug reduction so that the IS resumption at the preweaning start of the daily dose resulted in no savings.

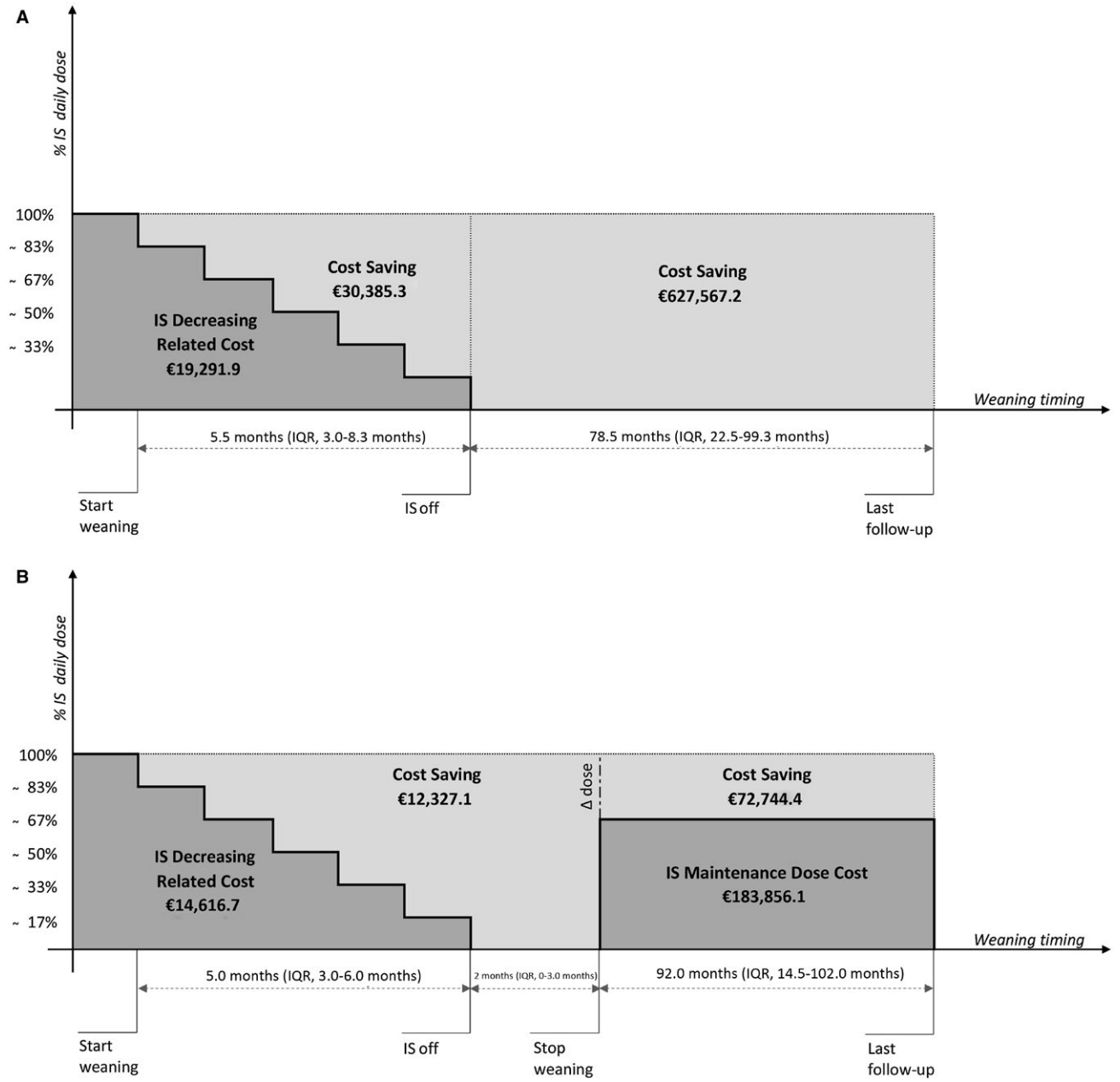

FIG. 2. Model of immunosuppressive drug management and cost-effectiveness in patients with cost savings. Continuous variables are expressed as median and IQR; IS cost during tapering = ∑ ([IS daily dose cost] × [number of days between the start of weaning process and complete IS withdrawal]); IS maintenance dose cost = ∑ ([daily cost of the lower IS dose at which no liver function test deterioration was detected] × [number of days between weaning stop (non-COT) and the last follow-up]); Δ dose therapy = (IS preweaning start daily dose) – (IS maintenance daily dose); cost savings = ∑ ([IS pre-start weaning daily dose cost] × [number of days between the start of weaning process and last follow-up]) – ([IS cost during tapering] + [IS maintenance dose cost]); Δ dose cost in non-COT patients with postresumption dose 50% higher than the baseline = €53,969.1.

Liver Biopsy Cost. All patients underwent day-hospital liver protocol biopsies at the time of the enrollment, 12 months after IS withdrawal (COT), and whenever acute rejection was clinically suspected (non-COT). The cost of each liver biopsy was evaluated according to the diagnosis-related group (DRG) classification system of the Lazio area. This classification system provides the principal means of reimbursing hospitals

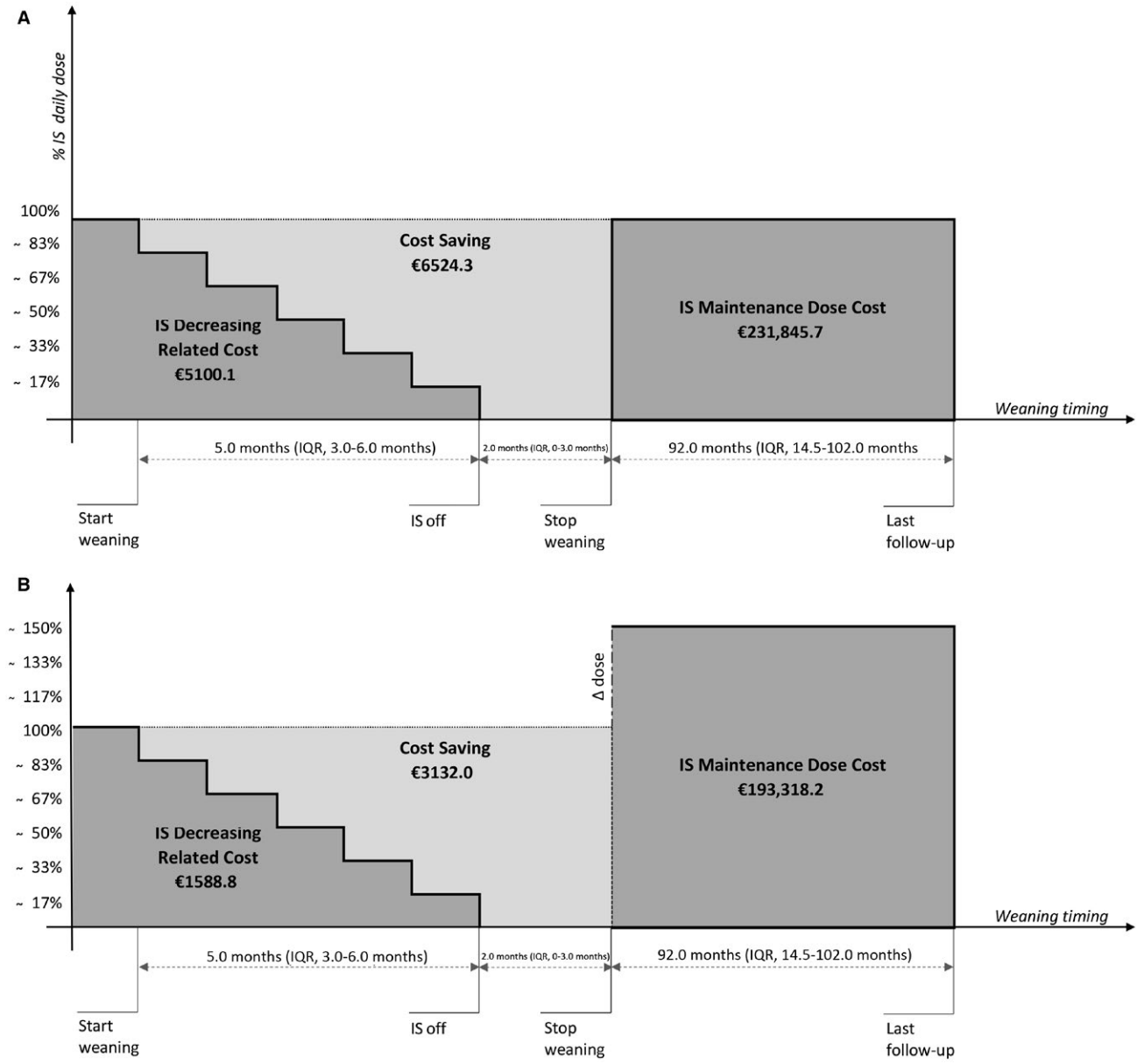

FIG. 3. Model of immunosuppressive drug management and cost-effectiveness in patients with no cost savings. Further explanation is given in Fig. 2.

for the acute inpatient. This payment system classifies hospital cases into DRGs of patients with similar clinical characteristics and comparable costs, and it is used to refund hospitals with a flat fee for each DRG that reflects the national average of treatment costs in a same grouping care.[17] According to DRG, the cost of a liver biopsy was €273.0 and €236.0 in 2009 and 2015, respectively. The costs of liver biopsies in the group of 37 (49.3%) hepatitis C virus (HCV)–positive recipients in this weaning project were not taken into consideration as supplementary costs because they had yearly routine liver biopsies to monitor HCV-disease evolution.

Cost of Blood Tests and Outpatient Visits. Strict follow-up of these patients is mandatory for early diagnosis of rejection and eventual necessary treatment. All patients were assessed every 4 weeks,

and IS was gradually discontinued aiming at complete withdrawal within 12 months from the beginning of the IS withdrawal. The cost of each blood sampling (including liver tests, renal function, lipid profile, glycemia as well as blood trough levels of the immunosuppressive drugs) and outpatient protocol visit were collected because they represented an additional financial burden. According to the DRG system, the cost of blood tests changed from 2013 onward from €69.9 to €46.7; the outpatient protocol visit costs increased from €12.9 to €26.9.

STATISTICAL ANALYSIS

Data were collected retrospectively from a prospective database (Microsoft Excel 2016, Microsoft Corporation, Redmond, WA). The normal continuous data were analyzed using a parametric test (Student *t* test); categorical variables were evaluated according to the nonparametric test (Fisher's exact test). A *P* value of <0.05 was considered significant.

Survival rates were calculated following Kaplan-Meier. The program used for statistical analysis was SPSS, version 13.0 (SPSS, Chicago, IL) for Mac.

Results

LONGTERM CLINICAL OUTCOME

Characteristics of the study population are displayed in Table 1. The overall median follow-up from the start of weaning was 95.0 months (IQR, 22.5-108.5 months). The overall composite survival rates in COT and non-COT were 90.6% versus 86.0%, respectively (log-rank, 0.5; Fig. 4). Among 43 (57.3%) patients who had IS resumption (non-COT), 3 died due to recurrent HCV allograft disease at 3, 8, and 16 years after LT, with 1 each dying of lung cancer, acute myocardial

TABLE 1. Characteristics of LT Patients Enrolled in Weaning Protocol

Variables	Overall (n = 75)	COT (n = 32)	Non-COT (n = 41)	I-Non-COT (n = 2)	*P* Value
Age at LT, years	50.0 (44.5-57.0)	50.0 (45.8-56.0)	52.0 (43.0-57.0)	43.5 (42.3-44.8)	0.42
Age at weaning start, years	61.0 (53.5-64.0)	62.0 (58.0-65.0)	58.0 (50.0-63.0)	53.5 (50.8-56.3)	0.37
Sex, male	53 (70.7)	24 (75.0)	28 (68.3)	1 (50.0)	0.86
Indications to LT					
Cirrhosis related to HCV	27 (36.0)	10 (31.3)	17 (41.5)	0 (0.0)	0.59
Clrrhosis related to HBV	10 (13.3)	6 (18.8)	4 (9.8)	0 (0.0)	0.31
Hepatocellular carcinoma	9 (12.0)	6 (18.8)	3 (7.3)	0 (0.0)	0.31
Alcoholic cirrhosis	4 (5.3)	3 (9.4)	1 (2.4)	0 (0.0)	0.23
Cryptogenic cirrhosis	7 (9.3)	5 (15.6)	2 (4.9)	0 (0.0)	0.31
Cirrhosis related to HBV-HDV-HCV	8 (10.7)	2 (6.3)	6 (14.6)	0 (0.0)	0.86
Cirrhosis related to HBV-HCV	2 (2.7)	0 (0.0)	2 (4.9)	0 (0.0)	0.35
Mixed etiology cirrhosis	2 (2.7)	0 (0.0)	1 (2.4)	1 (50.0)	0.16
Fulminant hepatitis	3 (4.0)	0 (0.0)	3 (7.3)	0 (0.0)	0.59
Other diseases	3 (4.0)	0 (0.0)	2 (4.9)	1 (50.0)	0.35
IS at weaning start					
CsA	38 (50.7)	14 (43.8)	23 (56.1)	1 (50.0)	0.83
TAC	18 (24.0)	5 (15.6)	13 (31.7)	0 (0.0)	0.25
EVR	3 (4.0)	1 (3.1)	2 (4.9)	0 (0.0)	0.16
ECMPS	13 (17.3)	12 (37.5)	1 (2.4)	0 (0.0)	0.75
TAC-ECMPS	2 (2.7)	0 (0.0)	2 (4.9)	0 (0.0)	0.35
EVR-ECMPS	1 (1.3)	0 (0.0)	0 (0.0)	1 (50.0)	0.34

NOTE: Data are given as n (%) and median (IQR).

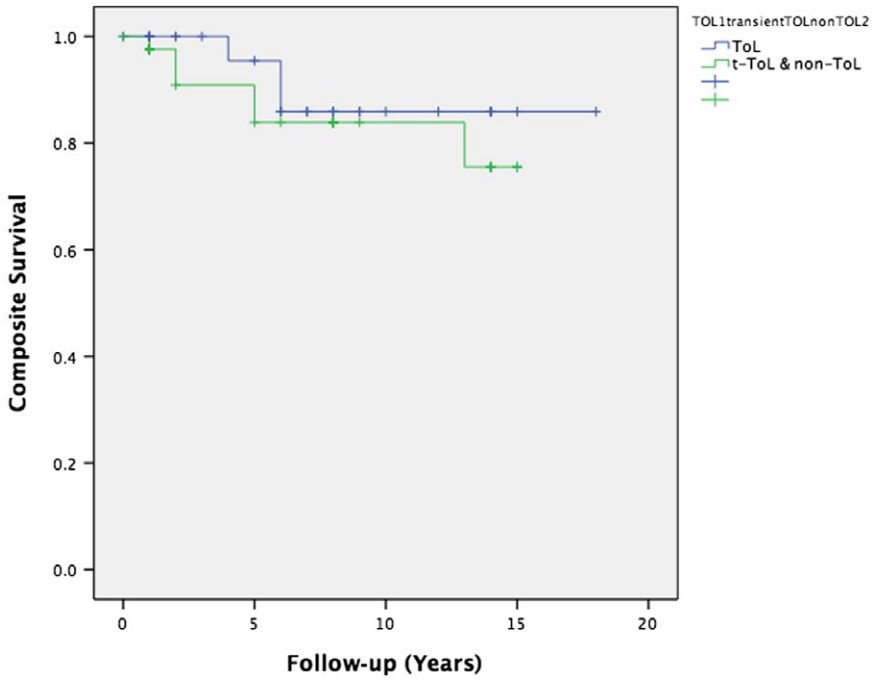

FIG. 4. Composite survival of the protocol IS-weaned patients versus those who required IS resumption.

infarction, and pancreatitis. Of the 32 COT recipients, 1 died from recurrent HCV allograft disease (12 years after LT and 5 years after complete withdrawal of IS), 1 each died due to heart failure and heart and end-stage renal failure. Participation with the weaning off protocol did not result in any patient or graft loss.

As previously stated, all patients underwent liver protocol biopsies at the start of weaning, at 1 year after IS withdrawal (COT), or at weaning stop (non-COT). Further biopsies were taken throughout the study as a local policy (out of COT protocol) in order to investigate any change in inflammation or fibrosis score or to detect any subclinical rejection. At the last biopsy available, none of COT or non-COT recipients showed signs of acute or chronic rejection. All histological findings are reported in Tables 2 and 3.

At last follow-up, out of non-COT recipients, 26 (60.5%) experienced arterial hypertension (defined as systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg under at least 2 antihypertensive drugs); 24 (55.8%) were on insulin and/or oral hypoglycemic agents due to new-onset diabetes mellitus after transplant (NODAT). No difference in terms of liver and renal function were seen between the COT and non-COT group at last available follow-up (Table 4).

TABLE 2. COT Group (n = 32): Liver Histological Findings

Variables	Baseline	1 Year After IS Off	Last Follow-up	*P* Values
Number of biopsies	32	32	25	—
Grading	1.0 (1.0-4.0)	2.0 (1.0-4.0)	1.5 (1.0-4.0)	0.40
Staging	1.0 (1.0-2.0)	1.0 (1.0-1.5)	1.0 (1.0-2.0)	0.83
Yearly FPR	—	—	0	—
BPAR	None	None	None	—

NOTE: Data are given as median (IQR).
Median follow-up (IQR), 77.0 (34.0-88.0) months.
In 7/32 (22%) LT recipients, the last biopsy available overlapped with those of 1 year after IS off.

IS COST-EFFECTIVENESS

COT Recipients

The overall cost of IS during the discontinuation time (median time, 5.5 months; IQR, 3.0-8.3 months) was €19,291.9 instead of €49,677.2 (corresponding to the cost of IS for a period 5.5 months) resulting in a savings of €30,385.3. The IS cost savings from IS off until last clinical follow-up (median follow-up from IS off, 78.5 months; IQR, 22.8-99.3 months) was €627,567.2 (€95,933.8 per year; Fig. 2A).

TABLE 3. Non-COT Group (n = 41): Liver Histological Findings

Variables	Baseline	IS-Resumption	Last Follow-up	*P* Value
Number of biopsies	41	41	33	—
Grading	2.0 (1.0-4.0)	3.0 (3.0-5.0)	3.0 (1.5-4.0)	0.88
Staging	1.0 (1.0-2.0)	1.0 (1.0-2.0)	3.0 (1.0-3.5)	0.01
Yearly FPR	—	—	0.3	—
Severity of BPAR				
Mild	None	4 (9.8)	None	—
Moderate	None	7 (17.1)	None	—
Severe	None	1 (2.4)	None	—

NOTE: Data are given as n (%) and median (IQR).
Median follow-up (IQR), 92.0 (14.5-102.0) months.
In 8/41 (19%) recipients, the last biopsy available overlapped with those of 1 year after IS off.

TABLE 4. IS Weaning for LT Patients: Outcome at 95 Months Follow-Up

Variables at Last Follow-up	COT	Non-COT	*P* Value
AST, IU/L	22.5 (20.0-33.3)	32.0 (20.0-51.5)	0.16
ALT, IU/L	36.5 (23.8-49.0)	36.0 (23.5-60.5)	0.34
GGT, IU/L	41.5 (22.0-66.5)	58.0 (35.8-195.3)	0.08
Total bilirubin, mg/dL	0.8 (0.5-1.0)	0.7 (0.6-1.3)	0.66
GFR (MDRD), mL/minute/1.73 m^2	58.3 (50.3-67.0)	56.6 (48.4-74.7)	0.85

NOTE: Data are given as median (IQR).
Non-COT group includes all LT recipients who required IS resumption (namely, i-non COT + non-COT).

There were 36 protocol liver biopsies performed, representing a cost of €9162.0 ([€273.0 × 18 liver biopsies performed] + [€236.0 × 18 liver biopsies performed]). The cost of blood tests including serum biochemistry and immunosuppressant blood trough levels during the study period as well as the cost of the increased number of outpatient visits was €24,600.2. This amount included 157 protocol visits performed during IS tapering ([€82.8 × 137 visits] [before 2013] + [€73.6 × 20 visits] [2013 onward]) and 179 ones since IS off ([€66.6 × 161 visits] [before 2013] + [€59.0 × 18 visits] [2013 onward]; these amounts did not take into account the drug level tests since IS was stopped).

Non-COT Recipients

As previously stated, a cost-saving evaluation could be performed only for 34 (82.9%) of 41 patients since 7 patients switched IS therapy at the time of IS resumption.

The IS decreasing–related cost from the start of weaning up to its stop was €21,306.0 resulting in a cost savings of €21,982.9.

The IS resumption resulted in a cost savings of €31,984.9 (total amount of €4171.9/year); the IS maintenance dose cost was €609,020. The cost of 50 protocol liver biopsies summed up to a cost of €13,021.0 ([€273.0 × 33 performed liver biopsies] + [€236.0 × 17 performed liver biopsies]). Protocol blood tests and outpatient visits, consisting of 148 visits required during IS tapering ([€82.8 × 106 visits] + [€73.6 × 42 visits]) and 139 after stopping the weaning process ([€82.8 × 100 visits] + [€73.6 × 39 visits]) amounted to €23,018.4.

In 16 (47.1%) recipients, the IS resumption dose was 33% lower than the dose given before IS weaning was attempted (Fig. 2B), 10 (29.4%) returned at the same dose (Fig. 3A), and 8 (23.5%) at 50% higher than baseline (Fig. 3B).

I-Non-COT Recipients

Two patients presented clinical signs of rejection immediately after the first IS reduction, so no cost savings could be observed since IS was resumed at the preweaning daily drug dose. The amount of 3 liver biopsies was €708.0 (€236.0 per biopsy). The cost of blood tests and outpatient visits was €662.7; 2 protocol visits were performed at the attempt of weaning and 7 after the IS uptake.

Screening protocol liver biopsies were taken in 119/308 patients. The cost of screening patients who were ultimately not eligible to undergo IS weaning was €10,532.0 ([€273.0 × 4 performed liver biopsies] + [€236.0 × 40 performed liver biopsies]).

Discussion

The cost of medical care, including drug management and hospitalization, nowadays represents a major point of interest for health care managers and clinicians. The purpose is to give the best patient care at the lowest possible cost, considering thereby the safety on longterm survival.

Ten-year graft and patient survival after LT reaches 54% and 61%, respectively.[18] Hypertension, diabetes, hyperlipidemia, cardiovascular diseases, infections, renal failure, and de novo malignancy contribute to longterm morbidity in patients taking IS. We believe that in order to improve longterm outcome and QoL,[13] minimization or even discontinuation of IS should be always considered.[8,19,20]

In 2006, the Tor Vergata Transplant Unit reported the results of IS withdrawal in 34 longterm HCV-positive liver recipients. Complete IS withdrawal was obtained in 23.4% of patients. After 4 years of follow-up, COT patients showed a stabilization of their histological fibrosis and liver tests as well as reduced necroinflammation. NODAT was seen in 50% of non-COT patients, and infectious disease or cardiovascular disorders in 63% of them.[9] The beneficial effects of the IS-free state in terms of fibrosis progression, NODAT, infection, and cardiovascular disease were confirmed after 10 years.[10] In 2013, the European Consortium of Transplant Tolerance identified longterm follow-up after LT and older age at LT as the clinical predictors of successful IS withdrawal, obtaining an IS-free rate in almost 40% of these highly selected recipients.[5]

Recently, an ongoing US trial reported the early results of 275 adult liver recipients who tried early discontinuation of IS therapy 12-24 months after LT. The authors showed that minimization was mostly well tolerated, although complete weaning could only be achieved in 13% of them.[21]

The lifelong IS therapy in transplantation represents an important health cost. Even if the cost of longterm IS has not been well established, it is estimated that the cost covering the first 180 post-LT days encompasses over US $25,000.[22]

The Gordon et al. report revealed that the impact of IS expenses is responsible for the financial strain in almost one-third of transplanted patients and that more than 30% reported that the IS-related expenses had a great adverse impact on their lives. Recipients indeed faced difficulties in affording their daily life necessities, and they had to look at cost-cutting methods, such as buying generic instead of name brands, cutting hobbies, or avoiding restaurant visits, and so on.[23] This study suggests that IS therapy indeed negatively influences the lifestyle of the recipient due to costs itself.

It is obvious that one should also take into consideration not only IS costs itself, but also their adverse events. The incidence of NODAT reaches 20% of liver recipients and 50% of kidney recipients.[24,25] In this context particularly, corticosteroids and CNI therapy play a considerable role.[25,26] Furthermore, diabetes itself is a risk factor for developing complications such as hypertension, metabolic syndrome, and cardiovascular disease; all of them further increase costs and influence longterm patient and graft survival rates.[27] In Italy, the average yearly patient cost of diabetes is about €2300. This number further increases when complications occurred.[28,29]

De novo tumor formation is raised by a factor of 2-4 compared with the general population.[30,31] Skin cancer, posttransplant lymphoproliferative disorder, and solid organ tumors[32] still represent a great longterm challenge both in terms of recovery and costs.[33-35] Again, IS minimization or withdrawal may help to reduce adverse events occurrences and thus costs.

This study showed that approximately 43% of well-selected LT recipients can complete and permanently discontinue IS and that almost half of the patients who required IS resumption received a lower dose (33.3%) than before the weaning attempt (ie, IS-minimized recipients).

In this scenario, IS weaning represented a €711,992.3 cost savings versus an expense of €80,333.6 (screening/protocol liver biopsies and blood samplings) required to achieve COT. This resulted in a cost savings of more than €630,000 in a median period of 8 years. Thus, we can argue that, in order to be economically favorable, the minimum success rate for drug withdrawal should be approximately 10% in order to reach a cost savings of at least €80,000.

Although not investigated in the current study, we believe IS reduction decreases costs by reducing IS-related complications[10] both in COT and IS-minimized patients.

Our study presents the tolerance follow-up results of the longest reported clinical operation liver recipient group, and it is the first study to address the economic impact of longterm IS withdrawal. IS-free status resulted in a 10-year composite survival rate of 90.6% (versus 61% reported by the European Liver Transplant Registry).[18] Even if IS is not the only modifiable variable[13] that can lead to the improvement of longterm

outcome after LT, we argue that longterm IS minimization or withdrawal will be the main postoperative variable that could improve the results of LT and this even at a lower cost.

REFERENCES

1) Meirelles Júnior RF, Salvalaggio P, Rezende MB, Evangelista AS, Guardia BD, Matielo CE, et al. Liver transplantation: history, outcomes and perspectives. Einstein (Sao Paulo) 2015;13:149-152.
2) Whitehouse GP, Sanchez-Fueyo A. Immunosuppression withdrawal following liver transplantation. Clin Res Hepatol Gastroenterol 2014;38:676-680.
3) Dharnidharka VR, Stablein DM, Harmon WE. Post-transplant infections now exceed acute rejection as cause for hospitalization: a report of the NAPRTCS. Am J Transplant 2004;4:384-389.
4) Dantal J, Soulillou JP. Immunosuppressive drugs and the risk of cancer after organ transplantation. N Engl J Med 2005;352:1371-1373.
5) Benítez C, Londoño MC, Miquel R, Manzia TM, Abraldes JG, Lozano JJ, et al. Prospective multicentre clinical trial of immunosuppressive drug withdrawal in stable adult liver transplant recipients. Hepatology 2013;58:1824-1835.
6) Lerut J, Sanchez-Fueyo A. An appraisal of tolerance in liver transplantation. Am J Transplant 2006;6:1774-1780.
7) Sánchez-Fueyo A, Strom TB. Immunologic basis of graft rejection and tolerance following transplantation of liver or other solid organs. Gastroenterology 2011;140:51-64.
8) Tisone G, Orlando G, Cardillo A, Palmieri G, Manzia TM, Baiocchi L, et al. Complete weaning off immunosuppression in HCV liver transplant recipients is feasible and favourably impacts on the progression of disease recurrence. J Hepatol 2006;44:702-709.
9) Orlando G, Manzia T, Baiocchi L, Sanchez-Fueyo A, Angelico M, Tisone G. The Tor Vergata weaning off immunosuppression protocol in stable HCV liver transplant patients: the updated follow up at 78 months. Transpl Immunol 2008;20: 43-47.
10) Manzia TM, Angelico R, Baiocchi L, Toti L, Ciano P, Palmieri G, et al. The Tor Vergata weaning of immunosuppression protocols in stable hepatitis C virus liver transplant patients: the 10-year follow-up. Transpl Int 2013;26:259-266.
11) Curry MP, Forns X, Chung RT, Terrault NA, Brown R Jr, Fenkel JM, et al. Sofosbuvir and ribavirin prevent recurrence of HCV infection after liver transplantation: an open-label study. Gastroenterology 2015;148:100-107.
12) Tisone G, Orlando G, Angelico M. Operational tolerance in clinical liver transplantation: emerging developments. Transpl Immunol 2007;17:108-113.
13) Neuberger JM, Bechstein WO, Kuypers DR, Burra P, Citterio F, De Geest S, et al. Practical recommendations for long-term management of modifiable risks in kidney and liver transplant recipients: a guidance report and clinical checklist by the Consensus on Managing Modifiable Risk in Transplantation (COMMIT) group. Transplantation 2017;101(suppl 2):S1-S56.
14) Kasiske BL, Cohen D, Lucey MR, Neylan JF. Payment for immunosuppression after organ transplantation. American Society of Transplantation. JAMA 2000;283:2445-2450.
15) Agenzia Italiana Del Farmaco, Ministero della Salute Italiana, www.agenziafarmaco.org. Accessed August 12, 2017.
16) Istituto Nazionale di Statistica. www.istat.it. Accessed July 3, 2018.
17) Ministero della Salute. www.salute.gov.it. Accessed July 3, 2018.
18) European Liver Transplant Registry. www.eltr.org. Accessed July 3, 2018.
19) Lerut J, Mathys J, Verbaandert C, Talpe S, Ciccarelli O, Lemaire J, et al. Tacrolimus monotherapy in liver transplantation: one-year results of a prospective, randomized, double-blind, placebo-controlled study. Ann Surg 2008;248:956-967.
20) Lerut J, Bonaccorsi-Riani E, Finet P, Gianello P. Minimization of steroids in liver transplantation. Transpl Int 2009;22:2-19.
21) Shaked A, Feng S, Punch J, Reyes J, Levitsky J, Klintmalm G, et al. Early post-transplant immunosuppression (IS) withdrawal - final outcomes of the ITN030ST AWISH study. Am J Transplant 2016;16.
22) Transplant Living: Financing a Transplant. www.transplantliving.org/financing-a-transplant/
23) Gordon EJ, Prohaska TR, Sehgal AR. The financial impact of immunosuppressant expenses on new kidney transplant recipients. Clin Transplant 2008;22:738-748.
24) Lane JT, Dagogo-Jack S. Approach to the patient with new-onset diabetes after transplant (NODAT). J Clin Endocrinol Metab 2011;96:3289-3297.
25) Kuo HT, Sampaio MS, Ye X, Reddy P, Martin P, Bunnapradist S. Risk factors for new-onset diabetes mellitus in adult liver transplant recipients, an analysis of the Organ Procurement and Transplant Network/United Network for Organ Sharing database. Transplantation 2010;89:1134-1140.
26) Song JL, Gao W, Zhong Y, Yan LN, Yang JY, Wen TF, et al. Minimizing tacrolimus decreases the risk of new-onset diabetes mellitus after liver transplantation. World J Gastroenterol 2016;22:2133-2141.
27) Parekh J, Corley DA, Feng S. Diabetes, hypertension and hyperlipidaemia: prevalence over time and impact on long-term survival after liver transplantation. Am J Transplant 2012;12:2181-2187.
28) Marcellusi A, Viti R, Sciattella P, Aimaretti G, De Cosmo S, Provenzano V, et al. Economic aspects in the management of diabetes in Italy. BMJ Open Diabetes Res Care 2016;4:e000197.
29) Pons JA, Ramírez P, Revilla-Nuin B, Pascual D, Baroja-Mazo A, Robles R, et al. Immunosuppression withdrawal improves long-term metabolic parameters, cardiovascular risk factors and renal function in liver transplant patients. Clin Transplant 2009;23:329-336.
30) Piselli P, Serraino D, Segoloni GP, Sandrini S, Piredda GB, Scolari MP, for, , et al. Immunosuppression and Cancer Study Group. Risk of de novo cancers after transplantation: results from a cohort of 7217 kidney transplant recipients, Italy 1997–2009. Eur J Cancer 2013;49:336-344.
31) Collett D, Mumford L, Banner NR, Neuberger J, Watson C. Comparison of the incidence of malignancy in recipients of different types of organ: a UK registry audit. Am J Transplant 2010;10:1889-1896.
32) Doycheva I, Amer S, Watt KD. De novo malignancies after transplantation: risk and surveillance strategies. Med Clin North Am 2016;100:551-567.
33) Vajdic CM, McDonald SP, McCredie MR, van Leeuwen MT, Stewart JH, Law M, et al. Cancer incidence before and after kidney transplantation. JAMA 2006;296:2823-2831.
34) Buell JF, Brock GN. Risk of cancer in liver transplant recipients: a look into the mirror. Liver Transpl 2008;14:1561-1563.
35) Katabathina V, Menias CO, Pickhardt P, Lubner M, Prasad SR. Complications of immunosuppressive therapy in solid organ transplantation. Radiol Clin North Am 2016;54:303-319.