KIDENY TRANSPLANT RECIPIENTS RECEIVING MTOR INHIBITORS EXPERIENCED TWICE AS MANY THROMBOTIC EVENTS: A SINGLE COHORT OBSERVATIONAL STUDY.

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BACKGROUND and AIM

IS medications have been involved in the development of thrombosis in patients receiving a kidney transplant (KTR): KTRs receiving everolimus have been shown to have higher levels of circulating von Willebrand factor, prothrombin fragment 1+2, thrombin-activable fibrinolysis inhibitor and plasminogen activator inhibitor-1, leading eventually to a pro-thrombotic state, which may be associated with more thrombotic events.

Moreover, some case reports described devastating thrombotic events in solid organ transplant recipients treated with mTOR-I. However, RCTs on mTOR-I did not describe vascular complications as common adverse events. This could be due to a different subtype of CV events: for instance, in patients treated with mTOR-I the incidence of coronary artery disease was reported as significantly higher unlike overall CV adverse events.

	mTOR-I	Non mTOR-I	p
Coagulation			
PT	12,0	11,9	NS
aPTT	33,1	32,4	NS
vWF	315	178	<0,01
F1+2	556	356	0,03
Anticoagulation			
Prot. C	173	128	0,009
Prot. S	131	120	NS
Fibrinolysis			
PAP complex	657	488	NS
PAI-1	100	61	0,05
TAFI	122	102	0,01

Adapted from Baas MC, et al. Treatment with everolimus is associated with a procoagulant state. Thromb Res. 2013 Aug;132(2):307-11.

Therefore we retrospectively studied the incidence of major thrombotic events (MTE) in a cohort of unselected KTRs to evaluate if patients experienced more MTE while on mTOR-I.

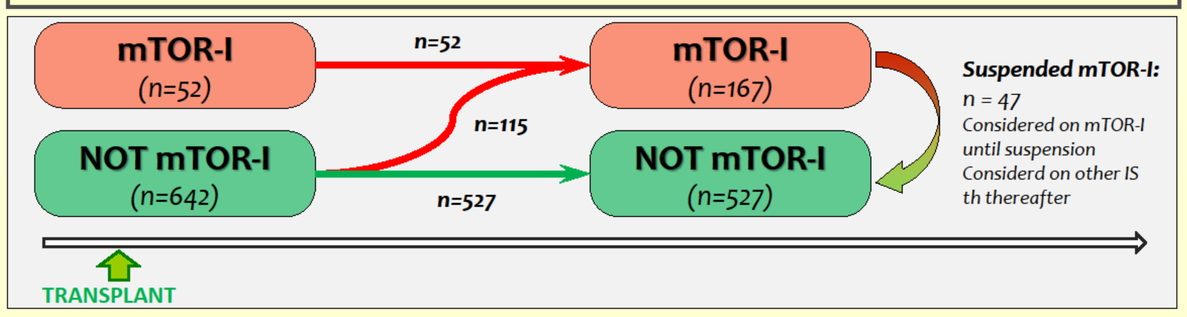
PATIENTS and METHODS

694 adult KTRs were enrolled, with a total follow-up of 3943 pt-years: patients **who started an mTOR-I at the time of transplant (n=52) and those who were later switched to an mTOR-I (n=115)** were compared to patients **who have never been on mTOR-I (n=527)**.

Major thrombotic events included:

- deep vein thrombosis (DVT)
- pulmonary or other vein thromboembolism (VTE)
- acute myocardial infarction
- ischemic stroke

The incidence rate of MTE was calculated on the total time on therapy for IS regimens including mTOR-I versus all the other IS regimens.



	Study population (n=694)	Never mTOR-I (n=527)	mTOR-I (n=167)	p-value
Age (years)	51.06±12.78	50.62±13.41	52.45±10.78	0.036
Male (%)	442 (63.7)	334 (63.4)	108 (64.7)	0.762
Sirolimus, at any time	119 (17.1)	0	119 (71.3)	n/a
Initial therapy with SRL (%)	26 (3.7)	0	26 (15.6)	n/a
Initial therapy with EVER (%)	26 (3.7)	0	26 (15.6)	n/a
Initial therapy with TAC (%)	610 (87.9)	492 (93.4)	118 (70.7)	<0.001
Initial therapy with CsA (%)	60 (8.6)	27 (5.1)	33 (19.8)	<0.001
Follow up time (years)	5.68±3.76	5.61±3.92	5.73±3.25	0.355

RESULTS - 1

KTRs who received an mTOR-I (n= 167) had a total follow up time of 985 pt-years (mean 5.73±3.25 yrs) and the total time on mTOR-I therapy was 575 pt-years (mean 3.34±2.57 yrs). No major clinical differences were noted between the two groups. Among mTOR-I treated patients, the other most common IS was with tacrolimus (81/167=48.5%), followed by mycophenolate (65/167=38.9%).

47 pts (28.1%) suspended the mTOR-I, of which 23 (49%) due to major adverse events, while the others for infections or minor adverse events.

During the follow-up, there were globally 59 MTE (8.5%), of which 35 (5.0%) were arterial and 24 (3.5%) venous events. Among patients who ever received an mTOR-I, 16 events occurred during mTOR-I therapy (9.58%; M:F=11:5; males=68.8%, one lethal event), while 8 events occurred during the other mTOR-I free periods (4.79%; M:F=5:3; males=62.5%).

	Never mTOR-I (n=527)	mTOR-I (n=167)	p
Follow up time (years)	5.61±3.92	5.73±3.25	0.355
Time on mTOR-I	-	3.34±2.57	n/a
Dead at the last follow up (%)	13 (2.5)	10 (5.9)	0.027
CV death (%)	8 (1.5)	3 (1.8)	0.802
Major thrombotic events (%)	35 (6.6)	24 (14.4)	<0.001
Venous events (%)	14 (2.7)	10 (6.0)	0.040
Arterial events (%)	21 (4.0)	14 (8.4)	0.024
CVE incidence rate (ev/100-pt-yrs)	1,277	2,783	0,003
Venous CVE inc. rate	0,511	1,160	0,023
Arterial CVE inc. rate	0,766	1,623	0,040
Incidence rate ratio	**1**	**2,180**	**0,003**

The overall incidence rate of MTE was of 1.496 events per 100 pt-year: 2.783 during mTOR-I therapy and 1.277 while not on mTOR-I. The incidence rate ratio was 2.180 (95% confidence interval: 1.228–3.870, p = 0.003) with a mean incidence rate difference of 1.507 more events per 100 pt-year during mTOR-I.

MTEs occurred at a mean age of 57.30±8.39 years and at 4.28±3.79 years after starting mTOR-I therapy (range: 7 days – 10.8 years).

RESULTS – 2

Pts on mTOR-I with MTE did not experience more malignancies needing switch to mTOR-I (33.3% versus 46.8%, p 0.520), but had a significantly longer duration of mTOR-I therapy (5.82±3.48 vs 3.19± 2.47 years; p=0.003), as compared to pts on mTOR-I without MTE

	Ever mTOR-I (n=167)	MTE on mTOR-I (n=16)	mTOR-I, no MTE (n=151)	p
Age (years)	52.45±10.78	53.02±9.80	52.39±10.88	0.404
Male (%)	108 (64.7)	11 (68.8)	97 (64.2)	0.720
Follow up (years)	5.73±3.25	6.98±3.47	5.59±3.23	0.064
Initial therapy with SRL (%)	26 (15.6)	7 (43.8)	19 (12.6)	0.001
Initial therapy with EVER (%)	26 (15.6)	3 (18.8)	23 (15.2)	0.712
Malignancy or history of malignancy (%)	53/115 (46.1)	2/6 (33.3)	51/109 (46.8)	0.520
Time of switch to mTOR-I (mo)	21.16±30.26	6.85±14.00	21.95±30.2	0.991
Sirolimus as maintenance (%)	119 (71.3)	12 (75.0)	107 (70.9)	0.728
Sirolimus dose (mg/day)	1.54±0.86	1.70±0.95	1.52±0.85	0.267
Sirolimus BTL (ng/mL)	6.72±1.49	6.64±1.58	6.73±1.48	0.574
Everolimus dose (mg/day)	1.79±0.70	1.25±0.66	1.84±0.70	0.95
Everolimus BTL (ng/mL)	5.52±1.49	4.7±1.21	5.59±1.52	0.917
Time on mTOR-I (years)	3.34±2.57	5.82±3.48	3.19±2.47	**0.003**

CONCLUSIONS

1. The ***unadjusted incidence rate ratio of MTE is 2.2 during mTOR-I therapy***, **with an estimated increased risk of +1.5 ev./100-pt-year.**
2. **Interestingly, the *exposure time to mTOR-I seems to be a relevant risk* factor for MTE: patients on mTOR-I who developed an MTE had a longer drug.**
3. **While waiting for RCTs and novel cardiovascular risk models, we believe that *immunosuppressive drugs should be considered in the cardiovascular risk evaluation* and probably patients receiving sirolimus or everolimus could be considered as having a higher risk of MTE, especially for long time exposures.**

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