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BRIEF COMMUNICATION

AJT

First-in-human use of a marine oxygen carrier (M101) for organ preservation: A safety and proof-of-principle study

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The medical device M101 is an extracellular hemoglobin featuring high oxygen-carrying capabilities. Preclinical studies demonstrated its safety as an additive to organ preservation solutions and its beneficial effect on ischemia/reperfusion injuries. OXYgen carrier for Organ Preservation (OXYOP) is a multicenter open-label study evaluating for the first time the safety of M101 added (1 g/L) to the preservation solution of one of two kidneys from the same donor. All adverse events (AEs) were analyzed by an independent data and safety monitoring board. Among the 58 donors, 38% were extended criteria donors. Grafts were preserved in cold storage (64%) or machine perfusion (36%) with a mean cold ischemia time (CIT) of 740 minutes. At 3 months, 490 AEs (41 serious) were reported, including two graft losses and two acute rejections (3.4%). No immunological, allergic, or prothrombotic effects were reported. Preimplantation and 3-month biopsies did not show thrombosis or altered microcirculation. Secondary efficacy end points showed less delayed graft function (DGF) and better renal function in the M101 group than in the contralateral kidneys. In the subgroup of grafts preserved in cold storage, Kaplan-Meier survival and Cox

Abbreviations: AE, adverse event; CIT, cold ischemia time; DGF, delayed graft function; ECD, extended criteria donor; IDSMB, independent data and safety monitoring board; SAE, serious adverse event.

regression analysis showed beneficial effects on DGF independent of CIT (P = .048). This study confirms that M101 is safe and shows promising efficacy data.

KEYWORDS

clinical research/practice, clinical trial, delayed graft function (DGF), ischemia reperfusion injury (IRI), kidney transplantation/nephrology, organ transplantation in general

1 | INTRODUCTION

The development of ischemia/reperfusion injuries is a multifactorial phenomenon that affects early graft function after organ transplantation[1,2] but also has deleterious effects on long-term graft survival.[3-5] The recent use of perfusion machines for kidney grafts showed that better organ preservation improved graft survival.[6] Today, organs are preserved at 4°C. The principle of hypothermic preservation is to slow metabolism and decrease the requirement for oxygen. However, the need for oxygen persists, and hypoxia and oxidative damage due to reperfusion remain key players.

M101 is an extracellular hemoglobin isolated from the marine lugworm *Arenicola marina*. This molecule has a large oxygen-binding capacity, releases oxygen according to a simple gradient, and possesses antioxidative properties.[7] This protein does not induce mutagenic, immunogenic, or allergenic responses and is degraded into polypeptide chains and heme.[7] The addition of M101 to preservation solution prevents the progressive decline of the dissolved oxygen concentration.[8] The efficacy of M101 used ex vivo as an additive to preservation solutions for preventing ischemia/reperfusion injuries has been demonstrated in preclinical studies in kidney,[9,10] heart,[11] and lung.[12] We designed the OXYgen carrier for Organ Preservation (OXYOP) study to analyze the safety and performance of the oxygen carrier M101 in renal transplantation.

2 | MATERIALS AND METHODS

2.1 | Production of M101

M101 ($HEMO_2Life^®$, Hemarina, Morlaix, France) is manufactured using a lugworm called *Arenicola marina* that colonizes the intertidal area on the west coast of France. Worms are bred in aquaculture under strict conditions of traceability and reproducibility on a dedicated farm (Noirmoutier Island, France) (Figure 1). The manufacturing begins by freezing the worm to create a hemorrhagic shock and to release its extracellular hemoglobin (M101). After successive steps of solid/liquid extraction, purification, filtration and gamma irradiation, the final product ($HEMO_2Life^®$) is a class III medical device containing M101. It is manufactured according to European Union Good Manufacturing Practice governing this category of product.

2.2 | Study design and participants

The evaluation of a marine OXYgen carrier for Organ Preservation was a national multicenter (six participating centers) open-label study investigating the safety of M101 used ex vivo as an additive to the preservation solution in kidney transplantation (Clinical Trial Registry No. NCT 02652520). A total of 60 consecutive grafts treated with M101 were planned. Grafts were preserved either in cold storage (standard donor) or on machine perfusion (extended criteria donor [ECD]) following the French recommendations. Inclusion criteria were grafts retrieved from an adult deceased donor after brain death and locally transplanted. Exclusion criteria included grafts from living donors, grafts from donors after cardiovascular death (DCD), and multiorgan transplantation. Recipients of the grafts had to be older than 18 years and on dialysis. To evaluate safety and performance (secondary efficacy end points), we made a control group consisting of the contralateral kidney (the paired kidney that did not receive M101).

According to the French authorities (Agence Nationale pour la Sécurité des Médicaments), all the patients on the waiting list in the participating centers received an information letter on the study design and procedures. Additionally, before transplantation, the recipients signed a consent form. The study was conducted in full compliance with the amended Declaration of Helsinki and with the Harmonized Tripartite Guideline for Good Clinical Practice in the European Community (CPMP/ICH/135/95) and was approved by an independent ethics committee and other relevant authorities (EUDRACT 2015-A00818-41). The data were monitored by an independent data and safety monitoring board (IDSMB) of three independent experts. After the 10th transplantation, a *stop-and-go* procedure was applied, and the inclusions were temporarily suspended until the IDSMB authorized the continuation of recruitment. Safety analysis by the IDSMB was based on the comparison of transplant outcomes of the M101 group with data from the French Registry (Agence Biomedecine), with results from large clinical trials and with the contralateral group.

2.3 | Procedures

The same perfusion solution was used in all the participating centers: 3-6 L of Belzer UW® cold storage solution (Bridge to Life Company, Columbia, SC). M101 is a red, sterile, apyrogenic

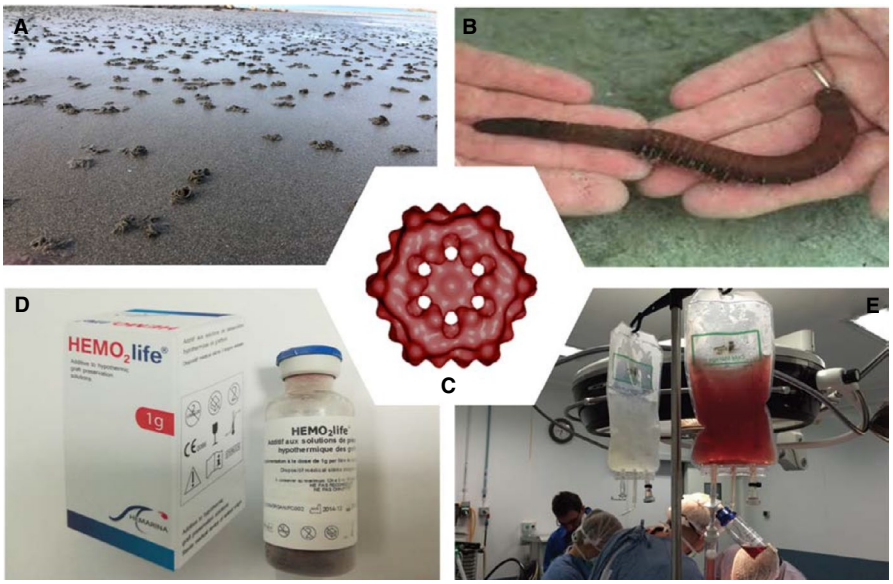

FIGURE 1 Production and use of M101. M101 is manufactured using a lugworm called *Arenicola marina*. This marine species belongs to the phylum Annelida, which appeared 450 million years ago. A, In the natural environment, *Arenicola marina* colonizes the intertidal area on the west coast of France. B, Today, worms are bred in aquaculture under strict conditions of traceability and reproducibility on a farm (Noirmoutier Island, France). C, $HEMO_2$Life® contains an oxygen carrier named M101, which is an extracellular hemoglobin fully described by Zal et al[26] in 1997. D, M101 is a class III medical device manufactured according to European Union Good Manufacturing Practice governing this category of product. E, M101 is meant to be used ex vivo as an additive to the preservation solution

solution conditioned in 20 mL glass vials holding 1 g and stored between −80 and −20°C (Figure 1). For cold storage, the kidney was perfused with 500 mL of Belzer UW® containing M101 (1 g/L) to allow the release of the carrier inside of the kidney. The kidney was then put in a container (Vitalpack®, E3 Cortex, Mitry-Mory, France) containing 1 liter of Belzer UW® and M101 (1 g/L). For machine perfusion, grafts were placed on a Lifeport 1.0 or 1.1 (Organ Recovery Systems, Diegem, Belgium), and M101 was added to the machine perfusion Belzer MPS® solution (1 g/L). Just before transplantation, the kidney was rinsed to flush out any residual molecules of M101. The immunosuppressive strategy was chosen by the renal transplant center.

2.4 | Outcomes

The primary end point was the safety of M101, which we calculated by collecting all adverse events (AEs) (serious or not) within the first 3 months and all serious adverse events (SAEs) occurring between 3 and 12 months. Graft biopsies (preimplantation and at 3 months) were routinely performed in the 6 participating centers and classified locally according to the Banff classification.[13]

Secondary efficacy end points included patient survival and graft survival, renal function (creatinine level and estimated glomerular filtration rate based on Modification of Diet in Renal Disease formula[14]), and acute rejection. Different markers of delayed graft function (DGF) were also considered: at least one dialysis in the first week, more than one dialysis in the first week, the number of dialysis procedures per patient in the first month, and the number of days required to achieve a creatinine level lower than 250 μmol/L (a marker routinely used in the French organ transplant data system).

2.5 | Statistics

Renal survival was analyzed using the Kaplan-Meier method. The effects of donor and recipient age and sex, donor diabetes and hypertension, cause of death, cold ischemia time (CIT), and use of M101 on DGF were analyzed using the Cox proportional hazard model. Variables were entered into the Cox multivariate analysis when they were associated in the univariate analysis at a conservative threshold of 20%.

3 | RESULTS

As no issue appeared in the *stop-and-go* phase or in the later IDSMB reports, 60 graft kidneys from 60 deceased donors were preserved with M101. The use of $HEMO_2$life® was easy, even if a thawing time exceeding 1.5 hours was reported by the physicians in 15% of the cases.

The 58 kidneys grafted to 58 recipients represented the safety population (two were not transplanted) (Figure 2). Principal baseline characteristics of the donors and the recipients are presented (Table 1).

In the first 3 months, 490 AEs, including 41 SAEs, were reported. No allergic or hypersensitivity reactions or infections related to the product were reported. All SAEs (Table 2) were reviewed in the context of the medical history of the patients and by comparison with

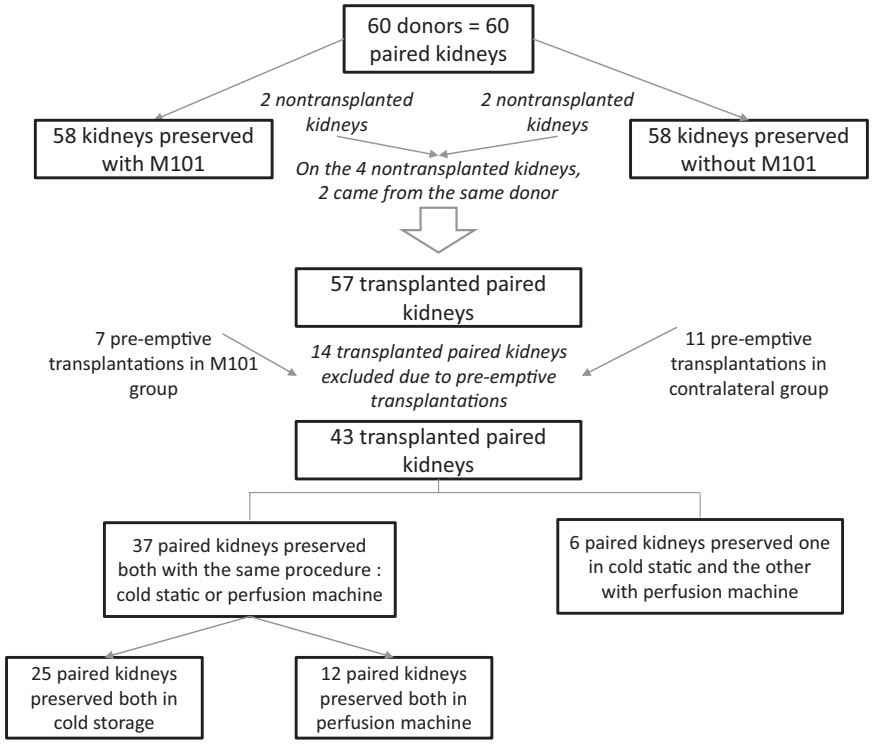

FIGURE 2 Flowchart

the French registry (data not shown). The IDSMB concluded that these events conformed in nature and frequency to a comparable population of transplant recipients. The IDSMB analysis of the SAEs occurring between 3 months and 1 year was also reassuring (data not shown).

Among the 41 SAEs at 3 months, two were deemed to be possibly related to M101 by investigators. The first patient presented at day 1 with renal dysfunction and signs of thrombotic microangiopathy. The renal biopsy showed signs of acute humoral rejection (i2, cpt1, g1, negative C4d staining), but the patient did not develop donor-specific antibodies (DSA). The patient was treated by plasma exchanges, pulses of steroids and IV thymoglobulin, and renal function recovered. At 4 months, the transplant biopsy showed mild inflammatory glomerular lesions (g1), no allograft glomerulopathy and only rare and focal sequelae of thrombotic microangiopathy. This case was classified by IDSMB as a rare case of acute humoral rejection without DSA, as recently described.[15] The second patient presented venous graft thrombosis at day 1. Numerous risk factors were present: He had nephrotic syndrome still present at the time of transplantation, the hydration both preoperatively and during surgery was insufficient, venous anastomosis needed a venous reconstruction, blood pressure was low after surgery, and he did not receive preventive anticoagulation. The conclusion of the IDSMB was that this complication, even if rare, was classical and not related to the use of M101. Of note, a second graft loss due to venous thrombosis was reported. It was in a man treated for a long time with anti-vitamin K because of two previous histories of fistula thrombosis. After transplantation, the patient received anticoagulant medication. Graft function recovery was immediate. At day 9, the local thrombosis committee recommended stopping anticoagulation. Thrombosis occurred 2 days after suggesting a direct link between anticoagulation withdrawal and graft thrombosis.

We also had the opportunity to compare the AE rate in the treated group with the rate in the contralateral group (574 AEs reported, including 41 SAEs in the first 3 months). According to the international classification MedDRA, the types of events with a reporting rate of more than 5% were comparable between the M101 and contralateral groups: metabolic (16% vs 18.9%), hematological (12% vs 21%), accidents and procedural complications (10% vs 11%), gastrointestinal disorders (10% vs 5%), renal and urinary disorders (9% vs 8.1%), and infections (8% vs 10.7%). With a 12-month follow-up, four patients died in the contralateral group vs none in the M101 group, 1 graft was lost vs 3, and 4 acute rejection episodes were reported vs 5.

Finally, we focused on infectious AEs. In this OXYOP study, 41 infections were reported in 25 patients, with only 4 SAEs and no infectious deaths, which compared favorably with infection rates published in large clinical trials.[16,17] They all resolved after a few days of antibiotics, without sequelae. By comparison, in the contralateral group, 74 infections were reported, including 11 SAEs, and two patients died.

In this study, preimplantation (n = 50) and 3-month biopsies (n = 42) were routinely performed in the M101 group. Approximately 60% of the preimplantation biopsies presented various degrees of tubular necrosis. None of them presented signs of thrombosis in glomerular capillaries or in other vessels or alterations of the microcirculation. Interstitial fibrosis was absent (89%) or weak (11%), and 30% presented chronic vascular lesions inherited from the donor. At month 3, interstitial fibrosis progressed, but 70% of the biopsies were still free of interstitial

TABLE 1 Baseline characteristics of the donors and the recipients

Variable	Donors (n = 58)	Recipients of M101 (n = 58)
Age		
Median (q1-q3)	52.5 (39-61)	55 (43-62)
Mean ± SD	50.34 ± 16.09	51.64 ± 13.6
Minimum-maximum	18-89	21-72
Sex (male) n (%)	30 (51.7)	39 (67.2)
History of hypertension n (%)	18 (32.1)	49 (84.5)
History of diabetes n (%)	4 (7.1)	8 (13.8)
Cause of death		
Trauma	14 (24.1)	—
Intoxication	2 (3.4)	—
Cardiac-related anoxia	1 (1.7)	—
Stroke	34 (58.6)	—
Other	7 (12.1)	—
Last creatinine level (μmol/L)		
Mean ± SD	79.38 ± 58.87	—
Cold ischemia time (min)		
Mean ± SD	—	740 ± 258
Minimum-maximum	—	416-1920
BMI		
Mean ± SD	—	25.19 ± 4.19
Baseline nephropathy		
Polycystic kidney disease n (%)	—	7 (12.1)
Vascular nephropathy n (%)	—	12 (20.7)
Chronic interstitial nephropathy n (%)	—	3 (5.2)
Chronic glomerular nephropathy n (%)	—	7 (12.1)
Diabetic nephropathy n (%)	—	2 (3.4)
Other n (%)	—	27 (46.6)
Preemptive transplantation n (%)	—	7 (12.1)
First transplantation n (%)	—	52 (89.7)
Number of mismatch (A-B-DR-DQ)		
Mean ± SD	—	4.29 ± 1.54
PRA (%)		
Mean ± SD	—	13.24 ± 24.21
Minimum-maximum	—	0-97
PRA > 90 (%)	—	1 (1.72)
Presence of DSA n (%)		1 (1.7)

fibrosis, and the progression of the vascular lesions was limited. The results were comparable for tubular atrophy (Figure 3). In 17 patients in whom two biopsies were available, interstitial fibrosis and tubular atrophy remained stable or improved in 14 patients and progressed in three patients.

To analyze the performance of M101, secondary efficacy end points were analyzed in comparison with the contralateral kidneys in 43 pairs (after exclusion of the paired kidneys that had at least one recipient transplanted preemptively) (Figure 2). The baseline characteristics of the recipients were comparable except for CIT, which was longer in the contralateral group (Table 3). In a few pairs of kidneys, due to logistic reasons, one kidney was kept on machine perfusion, and the second kidney was kept in static mode (Figure 2).

We reported less DGF (at least one dialysis) in the M101 group, and the difference between the two groups (23% vs 33%) was clinically relevant but not statistically significant. When we used a more stringent definition (more than one dialysis), the difference

TABLE 2 Serious adverse events

Serious adverse event	Related or possibly related to the device (investigators)	Related or possibly related to the device (IDSMB)	Outcome
Acute humoral rejection	Yes	No	Resolved without sequelae
Acute cellular rejection	No	No	Resolved without sequelae
Venous graft thrombosis	Yes	No	Graft loss
Venous graft thrombosis	No	No	Graft loss
Severe *klebsiella* sepsis	No	No	Resolved without sequelae
Pyelonephritis (×2)	No	No	Resolved without sequelae
Contamination of perfusion solution	No	No	Resolved without sequelae
Congestive heart failure	No	No	Ongoing
Myocardial ischemia (×2)	No	No	Resolved without sequelae
Ventricular tachycardia	No	No	Resolved without sequelae
Delayed graft function (×2)	No	No	Resolved without sequelae
Bleeding after surgery (×5)	No	No	Resolved without sequelae
Increased creatinine level (×7)	No	No	Resolved without sequelae
Lymphocele (×4)	No	No	Resolved without sequelae
Vascular complication of the graft (×4)	No	No	Resolved without sequelae
Perfusion machine dysfunction (×2)	No	No	Resolved without sequelae
Error in perfusion solution use	No	No	Resolved without sequelae
Seizure	No	No	Resolved without sequelae
Peripheral edema	No	No	Resolved without sequelae
Hyperglycemia	No	No	NODAT
Basal cell carcinoma	No	No	Ongoing

(7% vs 26%) was statistically significant (P = .038). Interestingly, the number of dialysis sessions per patient during the first month was also significantly lower: 0.47 vs 1.33 (P = .008). This was also the case with the criterion "time to achieve a creatinine value of 250 µmol/L" (7 vs 13 days, P = .020) (Table 3). The difference between the two groups was mainly driven by the subgroup of paired kidneys that were both preserved in cold storage (n = 25), whereas for the limited group of paired kidneys on machine perfusion, no clear effect was seen (n = 12) (Table 4). In total, recovery of renal function was better in the M101 group, as expressed by the area under the concentration curve (AUC) of creatinine (day 0-7), was 1709 ± 873 vs 2717 ± 1878 in the contralateral group, P = .042 (Table 3).

To better understand the respective roles of CIT and M101 in the benefit suggested by our study, we performed subgroup analysis in the group of 25 paired kidneys that were both preserved in cold storage. Kaplan-Meier estimate curves of time to achieve creatinine below 250 µmol/L showed a clear benefit in the M101 group (log rank test: 0.006) (Figure 4). This result was confirmed using Cox multivariate analysis (P = .048), showing that the use of M101 and CIT were two independent factors predicting DGF (Table 5).

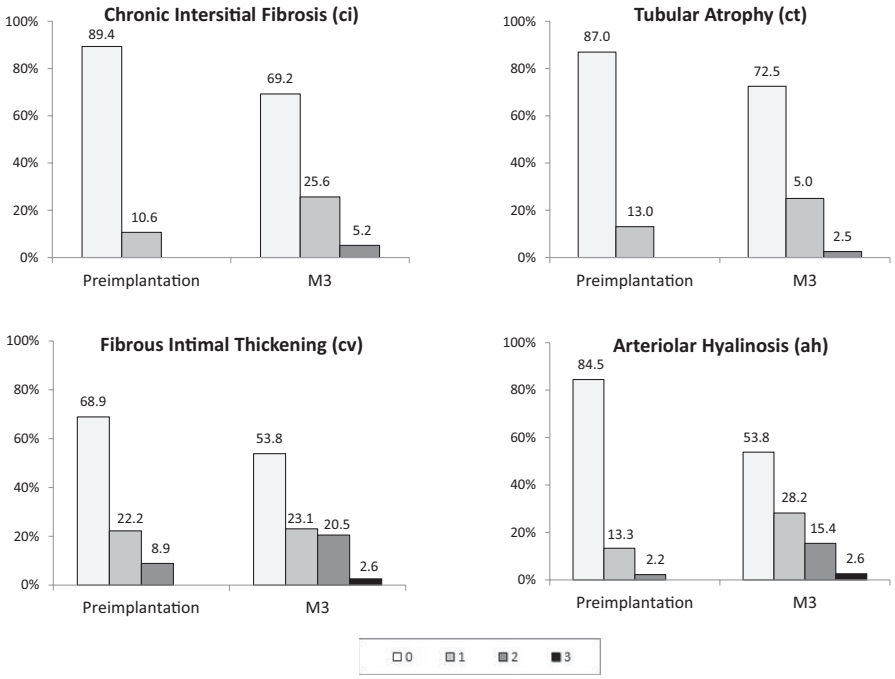

FIGURE 3 Protocol biopsy analysis (Banff classification). In this study, preimplantation (n = 50) and 3-mo biopsies (n = 42) were routinely performed in the M101 group and were classified locally according to the Banff classification. Tubular and interstitial damage, including tubular atrophy (ct score ranging from 0 to 3) and chronic interstitial fibrosis (ci score ranging from 0 to 3); vascular damage, including fibrous intimal thickening (cv score ranging from 0 to 3); and arteriolar hyalinosis (ah score ranging from 0 to 3)

TABLE 3 Comparison between the M101 and contralateral groups after exclusion of preemptive transplantation

	M101 n = 43	Contralateral n = 43	*P* value
Age, y (mean ± SD)	51.32 ± 13.49	49.54 ± 12.89	.051
Male, %	38 (66)	33 (57)	.523
Cold ischemia time (min)	713 ± 227	1082 ± 373	<.0001
Use of machine perfusion, %	21 (36)	20 (35)	1.000
Delayed graft function:			
At least one HD, %	10 (23.2)	14 (32.5)	.45
More than one HD, %	3 (6.9)	11 (26.1)	.038
Number of dialysis sessions	0.47 ± 1.18	1.33 ± 2.86	.008
Days for creatinine <250 µmol/L	6.9 ± 9.1	13.17 ± 13.8	.020
AUC of creatinine from day 1-7	1709 ± 873	2717 ± 1878	.042

TABLE 4 Subgroup analysis of the secondary efficacy end points (see flowchart)

	M101	Contralateral	*P* value
25 paired kidneys both preserved in cold storage			
At least one HD, %	4 (16)	8 (32)	.343
More than one HD, %	2 (8)	6 (25)	.218
Number of dialysis sessions	0.36 ± 0.99	0.92 ± 1.67	.194
Days for creatinine <250 µmol/L	4.7 ± 4.6	12.92 ± 14.06	.021
12 paired kidneys both preserved in perfusion machine			
At least one HD, %	4 (33.3)	3 (25)	1.000
More than one HD, %	1 (8.3)	3 (25)	.625
Number of dialysis sessions	0.75 ± 1.71	2.17 ± 4.71	.500
Days for creatinine <250 µmol/L	11 ± 16.3	13.8 ± 16.5	.0773

4 | DISCUSSION

This study reports the first use in humans of the oxygen carrier M101. Providing oxygen directly to tissue is a therapeutic tool with potentially important indications, and the development of M101 in organ preservation is only the first step. The lack of oxygen during the CIT is deleterious for grafts; ionic imbalance, mitochondrial uncoupling, coagulation, endothelium activation, activation of various programs of cell death, and proinflammatory immune responses participate in this deleterious process.[1,2] Hypothermic preservation at 4°C reduces enzyme activities 10-fold and the oxygen requirements by 95%. Transcriptomic analysis, however, has revealed that metabolic pathways related to hypoxia are still the major pathways enriched after cold ischemia in human kidney transplantation.[18] Several approaches have been investigated to supply oxygen to the organ (reviewed in[19]). The two-layer preservation method using perfluorocarbons[20] is effective in preserving different organs.[21,22] Active gaseous oxygenation of the preservation solution by retrograde persufflation is also possible.[19] More recently, a portable device for oxygenated perfusion showed, in a pig model of autotransplantation, a benefit in terms of renal function recovery and fibrosis at the 3-month kidney biopsy.[23] In addition, some papers have reported

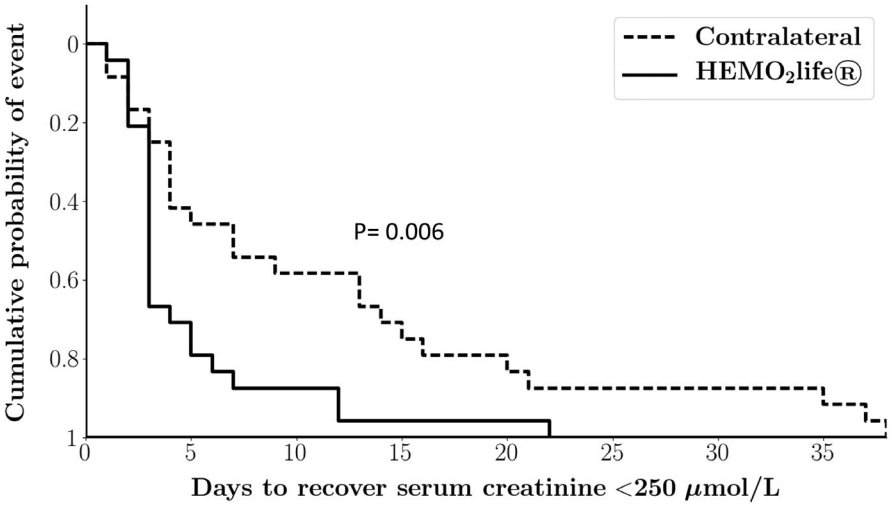

FIGURE 4 Delayed graft function: comparison between the 2 groups. Kaplan-Meier estimate curves of cumulative probability to achieve creatinine below 250 μmol/L in the group of 25 paired kidneys that were both preserved in cold storage. There was a significant difference in time to achieve the event between the 2 groups (M101 vs contralateral)

TABLE 5 Multivariate Cox analysis

	Univariate analysis				Multivariate analysis			
	Coeff	Lower 0.95	Upper 0.95	*P* value	Coeff	Lower 0.95	Upper 0.95	*P* value
Donor sex	−0.27	−0.87	0.32	.37				
Donor age	−0.02	−0.04	0.01	.18				
Donor diabetes	−0.58	−2.02	0.87	.43				
Donor hypertension	0.08	−0.69	0.85	.84				
Cause of death (stroke)	−0.24	−0.82	0.33	.41				
Cold ischemia time	−0.001514	−0.002346	−0.000683	.000357	−0.001341	−0.002198	−0.000483	.002188
Recipient age	−0.00	−0.03	0.03	.89				
Recipient sex	−0.04	−0.62	0.55	.9				
Recipient race	−0.14	−1.01	0.73	.76				
Group (M101 vs contralateral)	−0.88	−1.50	−0.26	.01	−0.66	−1.305809	−0.004945	.048284

Note: The effects of donor and recipient age and sex, donor diabetes and hypertension, cause of death (stroke), cold ischemia time (CIT), and use of M101 on delayed graft function were analyzed using the Cox proportional hazard model. Variables were entered into the Cox multivariate analysis when they were associated in the univariate analysis at a conservative threshold of 20%. Lower 0.95, upper 0.95 confidence interval.

encouraging results from the use of a hemoglobin-based oxygen carrier perfusion solution (HBOC-201) for ex situ liver normothermic preservation in animal and preclinical models.[24,25]

M101 is a biopolymer of high molecular weight (~3600 kDa) that has a large oxygen-binding capacity, carrying up to 156 oxygen molecules when saturated (vs 4 for human hemoglobin). It releases oxygen according to a simple gradient and exhibits intrinsic superoxide dismutase-like activity, preventing both the occurrence of potentially harmful heme-protein-associated free radical species and the release of hemoglobin degradation products.[7,26] Interestingly, this molecule is able to work in a broad range of temperatures, in contrast to hemoglobin from vertebrates. In vitro, in a cold static preservation model of porcine LLCPK1 renal proximal tubular cells, M101 improved the structural and metabolic integrity and energetic content of LLCPK1 cells.[23] In vivo, in a preclinical porcine model of autologous transplantation after 24 hours of cold ischemia, M101 significantly improved renal function and decreased interstitial fibrosis in 3-month kidney biopsies.[9] In a model of isolated perfused heart in rats, M101 significantly improved the postischemic recovery of heart function and provided a higher coronary flow.[11] In a pig lung allotransplantation model, M101 led to significant improvement in functional parameters: graft vascular resistance and graft oxygenation ratio.[12]

We designed the OXYOP study to assess the safety of the ex vivo use of M101 as an additive to preservation solution in renal transplantation. We proved that the use of M101 is safe for the graft and for the recipient. No allergic or hypersensitivity reactions or infections related to the product were reported. Two graft losses due to venous thrombosis were reported, and the IDSMB conclusion

was that no relationship existed between these two events and M101. The rate of acute rejection was low, confirming that M101 did not activate the immune system. On protocol biopsies, no capillary thrombosis or alteration of the microcirculation was reported. Furthermore, comparison of the preimplantation and 3-month biopsies showed that interstitial fibrosis, tubular atrophy, and vascular lesions remained stable. All together, these data suggest that the oxygen carrier M101 has a good tolerance profile.

All the secondary efficacy end points studying DGF suggested the superiority of the M101 group compared with the contralateral group. DGF is usually defined as the need for dialysis during the first week after transplantation.[27] It has been shown that the difference in DGF between centers may reflect differences in dialysis indication rather than patient risk populations.[28] For this reason, we focused on other markers of DGF, which were all in favor of M101. However, the number of included grafts had not been calculated to prove the efficacy of M101. Furthermore, due to the study design, kidneys conserved with M101 were transplanted locally, whereas the contralateral kidneys were allocated to other centers, explaining their shorter CIT. Even if CIT is a strong predictor of DGF, the relationship between CIT and DGF is complex because numerous factors from the donors and the recipients may interfere.[4,29] In 14 230 ECD kidney pairs from the Scientific Registry of Transplant recipients, a 5-hour difference in CIT between two paired kidneys translated into a 4% increase in DGF (from 31% to 35%).[30] This small difference in the worst situation (ECD) might suggest that the difference in DGF observed in our study with the same CIT difference (5 hours) could be due at least in part to the beneficial effect of M101. To explore the performance of M101, we performed a multivariate analysis in the subgroup of paired kidneys that were both preserved in cold storage, and we found that M101 had a positive effect independently of CIT. These results, together with the preclinical data, argue for the efficacy of the oxygen carrier M101 in the prevention of ischemia reperfusion injuries.

In conclusion, this study demonstrated that the addition of the oxygen carrier M101 to preservation solution is safe. Although our study was not designed to show the superiority of M101, the analysis of the secondary efficacy end points is highly promising, with significantly less DGF and better renal function in recipients of the kidneys preserved with M101. This study argues for the use of M101 in organ preservation and for further investigations evaluating the cost/efficacy ratio and the long-term benefit of M101. It also justifies new avenues of research into hypoxia-related diseases.

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DISCLOSURE

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AUTHOR CONTRIBUTIONS

YLM and BB designed the study; all authors participated in the clinical trial as transplant physician or transplant surgeon; YLM and FR analyzed the data; FR made the figures; YLM drafted and all authors revised the paper; all authors approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings will be available on request from the corresponding author following an embargo from the date of publication to allow for commercialization of research findings.

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