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Discontinuation of chronic renal dialysis following treatment with autologous bone marrow derived multi-potent mesenchymal stromal cells targeted with low energy acoustic shockwaves; the first successful case report

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Abstract
Bone marrow derived autologous mesenchymal stromal stem cells (MSCs) represent an important potential source of multi-potent cells that can induce anti-inflammatory effects and be differentiated into cells resembling many other tissues. As such, treatment using MSCs represents a potential future approach for repair of disease-associated tissue damage and possibly also age-dependent wear & tear. Considering the successful and safe use of MSCs for treatment of many different clinical conditions caused by inflammatory or immune mediated tissue damage on the one hand, and for cosmetic and orthopedic indications for repair of cartilage and bone defects and for successful treatment of neurologic diseases caused by neuroinflammatory or neurodegenerative disorders, on the other, supported by pre-clinical experiments in mice and rats confirming the potential therapeutic effects of MSCs for treatment of experimental kidney damage and successful prior clinical investigations confirming that treatment with MSCs is safe, we have decided to pioneer the use of multi-potent MSCs for repair of renal failure in a patient that could no longer tolerate the use of hemodialysis. This case report represents the first successful clinical experience of an elderly patient with end-stage renal disease dependent on hemodialysis x3/week for 2 years that responded to treatment with autologous bone marrow derived MSCs in parallel with treatment with low energy acoustic shockwave therapy and remained off dialysis for 6 years.

Keywords: ESRD, end stage renal disease, CRD, chronic kidney disease, Hemodialysis MSCs, autologous mesenchymal stromal stem cells

Introduction
Acute kidney injury (AKI) and chronic renal failure due to chronic kidney disease (CKD) are common causes for morbidity and mortality with devastating long-term consequences. Patients with progressive disease resulting in end stage renal disease (ESRD) depend on dialysis or limited supply of kidney transplantation [1,2]. While AKI complications and ESRD are effectively treated with dialysis, there is no clinical accepted specific treatment for preventing or reversing kidney damage [3]. One main mechanism responsible for AKI is ischemia-reperfusion (I/R) injury along with the resulting immunological consequences that include activation of the complement system and tubular damage [4,5]. Other known causes of ESRD among other resulting in chronic renal failure involving a decrease in the function of both kidneys resulting in gradual loss of ability to filter waste and fluid from the blood include diabetes mellitus and hypertension. Developing CKD is usually a very slow process with very few symptoms at first, but when kidney failure deteriorates and reaches a stage known as ESRD it also results in many symptoms, including nausea and vomiting, muscle cramps, loss of appetite, swelling of feet and ankles, dry, itchy skin, shortness of breath, trouble sleeping, urinating either too much or too little. In parallel with increased risks of other health problems like progressive anemia, hypertension and heart disease and stroke. Control of ESRD can be accomplished using dialysis or kidney transplant [1, 2] Unfortunately, kidney transplantation is limited by shortage of kidneys that can be obtained from deceased donors or from living related donors, but prevention of rejection depends on life-long

use of immunosuppressive agents with possible drug-induced adverse events and consequences of long-term immunosuppressive treatment, like tendency for infections and high risk of secondary malignant disorders. The most common known causes of CKD include diabetes, hypertension, glomerulonephritis of unknown cause or secondary to an autoimmune disease, pyelonephritis due to chronic bacterial infections, or polycystic kidney disease, a genetic disorder in which the renal tubules become structurally abnormal, resulting in the development and growth of multiple cysts within the kidney when the renal tubules become structurally abnormal, resulting in the development and growth of multiple cysts within the kidney [6].

CKD is usually irreversible and progressive. Other than better control of underlying autoimmune mediated cause of ESRD or better control of diabetes or elevated blood pressure, not much can be done to prevent deteriorating renal failure. In the U.S. alone, at least 35 million people have CKD in different stages, that is at least 1 in 7 adults, and many may become aware of it only during later stages of the disease. Taken together, CKD is a worldwide public health problem. Accordingly, finding new approaches for prevention of progression of renal insufficiency or even trying to reverse CKD and the need for dialysis or kidney transplantation that is available only for the small minority of eligible patients with advanced renal failure in need is highly desirable and remains an unmet need.

The idea to investigate the potential therapeutic role of multi-potent bone marrow derived autologous MSCs for treatment of ESRD was based on the following basic hypotheses:

- First, MSCs induce anti-inflammatory and immune regulatory effects that can successfully down regulate any primary or secondary inflammatory or immune-mediated reactions that play a role in any type of CKD that results in ESRD (7,8).
- Second, MSCs are truly multi-potent and in addition to their well-known anti-inflammatory effects they can also induce anti-fibrosis effects that could help improve the filtration capacity of the scaring renal glomeruli and alleviate renal injury [9, 13].
- Third, other investigators have already confirmed the capacity of MSCs to be differentiated into many other types of cells resembling other damaged tissues [14, 16].
- Forth, MSCs have natural property to migrate to sites of inflammation and tissue damage and homing of MSCs to the damaged kidneys could be facilitated by dilatation of renal afferent blood vessels using low-energy extracorporeal acoustic shockwave therapy (EAST) to increase the flow of circulating MSCs into the kidneys, also possibly using EAST to enhance angiogenesis [17, 18].

Finally, considering the lack of other treatment option available for a dialysis-dependent patient insisting he could no longer tolerate hemodialysis on the one hand, and considering our more than 5 years cumulative experience in patients with multiple sclerosis and other neuroinflammatory and neurodegenerative disorders successfully and safely treated with intravenous combined with intrathecal administration of MScs, we felt similar intravenous treatment with autologous MSCs could be safely accomplished [19]. More recently, subsequent patients with multiple sclerosis were exposed to EAST over the central nervous system following infusion of MSCs with no complications (unpublished observations). Accordingly, we felt there should be no risk applying a similar combination of MSCs in parallel with EAST for treatment of ESRD based on the same rationale.

The following report documents the first successful treatment of ESRD by combining autologous bone marrow derived MSCs and EAST in a 66-year-old patient previously dependent on hemodialysis x3/week that continued full time professional activities for 6 continuous years off dialysis following treatment with autologous bone marrow derived MSCs supported by EAST, for as long as he lived.

Table 1: Renal and Hematological Parameters with Urine Output

Date	BUN mg/dL	Creatinine mg/dL	Hgb g/dL	Hct %	Urine L/day	notes
2/19/2009-11/11/2009	43-99	2.24-7.35	11.5-8.9	33.9-26.6	1.80-2.10	Interstitial nephritis Failed steroids & MMF, renal function rapidly deteriorating
11/12/2009	136	9.30	7.1	22.1	1.1	1st hemodialysis
11/13/2009-12/14/2011	75-48	5.40-4.72	7.1-8.2	24.8-22.1	1.40-0.10	Hemodialysis x3/week
12/18/2011	53	3.13	8.2	25.2	0.20	1st MSCs treatment
03/25/2012	40	2.94	13.0	39.1	2.05	Hemodialysis discontinued
03/25/2012-02/18/2015	40-53	2.82-3.04	11.4-13.0	33.9-39.2	1.75-2.10	First 3 years period off dialysis
02/18/2015	92	4.90	9.1	28.7	0.95	2nd MSCs treatment*
02/18/2015-08/20/2018	89-51	4.90-3.70	9.1-10.7	28.5-32.3	0.90-1.05	Second 3 years period off dialysis

*2nd MSCs treatment was administered as soon as creatinine started to rise up to 4.90mg/dL but no dialysis was applied

Case report

Mr. M.K., a 66-year-old man was referred for consultation at the Biotherapy International Outpatient Clinic in Tel Aviv on November 2011, accompanied by his urologist, for consideration of any possible experimental treatment because he could no longer tolerate hemodialysis treatment x3/week for the past two years and refused continuation of treatment. In 2009 the patient was diagnosed with nephritic syndrome and kidney needle biopsy revealed interstitial nephritis. Pulsed steroid treatment was applied followed by Mycophenolate mofetil (MMF) for 6 months failed to improve his rapidly deteriorating kidney function. As can be seen in table 1, during this period, creatinine level increased to 9.3 mg/dL (normal levels 0.5 to 1.1 mg/dL), BUN level increased to136 mg/dL (normal levels 6 to 24 mg/dL), hemoglobin dropped down to 7.1 with hematocrit 22.1%, urine volume down to 1,1L and hemodialysis was started on December 2009.

Past medical history includes continuous heavy smoking (2 packs per day) from the age of 16, hypertension for 25 years

treated with Cardura (doxazosin), and type 2 diabetes for 16 years treated with insulin. In 2004, myasthenia gravis was diagnosed, and the patient was treated with Mestinon and remained under neurological follow-up.

Realizing the patient insisted to refuse continuous hemodialysis, seeking with his urologist any possible alternative treatment, we considered possible use of autologous bone marrow derived MSCs as a safe anti-inflammatory and immune regulatory treatment based on our experience using MSCs for different clinical indications as approved by IRB of the Hadassah University Hospital in Jerusalem and also by our local IRB at the Biotherapy International Center in Tel Aviv [19]. After reviewing all details of the suggested procedure and outcome of similar treatment for neurological indications, a consent form was signed by the patient and his urologist for compassionate intravenous treatment with autologous bone marrow derived MSCs in parallel treatment with extra-renal EAST in order to increase the flow of circulating MSCs into the kidneys by combining local vasodilatation and possible angiogenesis inducible by EAST [17, 18]. On 5th of November 2011 bone marrow aspiration was done under sedation. A total of 200 ml was aspirated from the posterior superior iliac crest and sent to our Cell-Processing Center for expansion of the number of MSCs as previously described [19].

On December 18th 2011, after confirming sterility and quality (CD73=99.16%, CD90=98.40%, CD105=98.80%, and were negative for CD34, CD45 and CD14), MSCs were transferred to the laboratory on dry ice, thawed in a 37°C water bath and washed twice with normal saline solution to remove any residual dimethyl sulfoxide. The cells were then resuspended in normal saline at a concentration of 10 × 10^6/mL. The total number of 69.75x10^6 viable MSCs, equivalent to 0.87x10^6/kg were slowly infused in parallel with extra-renal EAST applied over both kidneys in an attempt to dilate the afferent blood vessels and increase the intra-renal flow of MSCs. The entire procedure was uneventful and done on an outpatient basis.

Starting at two weeks after infusion of MSCs and improving towards the fourth month, the patient started to feel much better. His daily urine amount, which was around 100 ml before administration of MSCs started to increase. On December 30th, 2011, BUN was 54mmol/L, creatinine 2.93 mg/dL, Hct 40.2%, hemoglobin 13.2g/dL before dialysis. It was then decided to reduce the amount of dialysis from 3 times a week to once a week. Three months after treatment with MSCs and EAST, on 03/25/2011, the daily urine volume increased up to 2,050 ml/day. Despite the reduction in the number of hemodialysis to once a week, the creatinine before hemodialysis decreased to 2.6mg/dL and hemodialysis was completely discontinued. In parallel, blood pressure levels and metabolic parameters of diabetes also improved. For the next three years, creatinine levels ranged between 2.82 to 3.14 mg/dL, BUN levels went down and hemoglobin and hematocrit increased as shown in table 1 with no additional dialysis. The patient remained in excellent performance status and returned to full time managing his leather factory.

As shown in table 1, around three years after MSCs treatment the level of creatinine started to rise up to 4.90mg/dL and hemoglobin level fell down to 9.1g/dL with hematocrit 28.7% and therefore a second round of MSCs was accomplished on 02/18/2015 using cryopreserved bone marrow-derived MSCs. The total number of viable MSCs infused was 109.82x10^6 (CD45=0%, CD73=99.70%, CD90=98.50%, CD105=99.80%), equivalent to 1.29x10^6/kg. Again, outpatient cell infusion was uneventful. Patient's condition stabilized again with improved renal function and elevation of red blood cells and he remained off dialysis for the next 3 years (table 1).

Unfortunately, on March 2015, the patient was diagnosed with squamous cell carcinoma of lung and underwent right lower lobectomy with mediastinal lymph node dissection. The pathology was defined as PT2a with perineural invasion. Radiotherapy was applied between April and June 2015 and was followed by anti-cancer vaccination, but tumor progression persisted. During all these processes, the patient's creatinine levels ranged between 3.5 - 4.2 mg/dL. The creatinine level did not exceed beyond 4.2 although the patient never received any additional hemodialysis. Unfortunately, the patient passed away on August 20th, 2018, due to uncontrolled progressive metastatic lung cancer.

In conclusion, Mr. MK that was dependent on dialysis x3/week for two years prior to treatment with MSCs and EAST, remained fully functional off dialysis, initially for 3 years following the first infusion of MSCs and continuously for the next 3 additional years following a second infusion of MSCs, with a total of 6 consecutive years off dialysis since the first treatment with autologous MSCs and EAST.

Methods & procedures

Preparation of MSCs

Enrichment of cultured MSCs was accomplished in Dulbecco modified Eagle medium with low glucose levels (Qiagen, Valencia, California) supplemented with 10% fetal bovine serum, 1% L-glutamine, and 1% penicillin-streptomycin-nystatin solution (Biological Industries, Kibbutz Beit-Haemek, Israel) as previously described [19].

Passage 2 mesenchymal cells were harvested after reaching confluency and a sample was obtained for 2-weeks sterility testing and for quality control. A sample of the cells were analysed by fluorescence-activated cell sorter (FACS) for MSCs markers including CD73, CD90 & CD105, and negative markers for CD34, CD45 &CD14. The cells were then cryo-preserved in 10% dimethyl sulfoxide-containing medium in liquid nitrogen (−196°C) until sterility and quality were confirmed.

East device

Shockwave therapy is a safe non-invasive solution for improving the function of any targeted tissue. In order to try and improve the flow of MSCs circulating in the blood, extra-renal acoustic shockwaves therapy (EAST) was delivered using Medispec's ED1000™, a medical device that uses advanced acoustics technology based on electrohydraulic power. This technology has proven to be effective for treatment of erectile dysfunction [20, 21] and also in cardiology for patients with chronic ischemic heart disease [22] as well as for wound healing [23]. EAST utilizes low-intensity extracorporeal shock waves, focusing on blood vessels and encouraging neovascularization [17, 18]. The low-intensity shock waves help relieve low blood flow by vasodilatation to targeted organs and improving vascular deficiency. In addition to vasodilatation, shockwaves stimulate vascular endothelial growth factor (VEGF), eNOS endothelial nitric oxide synthase (eNOS), and PCNA

proliferating cell nuclear antigen (PCNA). These factors encourage greater blood flow to any targeted tissue [24].

Discussion

Improving renal function in patients with acute or chronic renal failure in an attempt to prevent the need for chronic dialysis and kidney transplantation is still considered an unmet need. Luckily, the patient reported could manage normal lifestyle for 6 years following two MSCs treatments supported by EAST until he passed away due to metastatic lung cancer, so it is important to analyze the case history and the type of treatments he received in greater details in order to try to understand if similar treatment may possibly also be applicable for other patients with ESRD in need. To start with, although the cause of renal failure as documented by histology was interstitial nephritis this patient had 3 additional disorders that could result in or facilitate the development of renal failure including diabetes mellitus, hypertension and susceptibility to develop autoimmune manifestations best documented by development of myasthenia gravis.

Using MSCs in combination with EAST was previously successfully applied for treatment of neuroinflammatory and neurodegenerative disorders using autologous bone marrow derived MSCs for combined intravenous and intrathecal treatment supported by extracranial application of low energy EAST in order to increase the flow of circulating MSCs into the brain and spinal cord. The combination of treatment using MSCs and EAST was well tolerated since except for self-limited subfebrile temperature, none of the patients developed any severe adverse effects [25]. Therefore, it seemed reasonable to apply similar treatment based on the same rationale for treatment of a different clinical indication. Encouraged by significant long-lasting clinical benefits that were observed, especially among patients with multiple sclerosis that have already failed any known treatment [25], we felt that in view of lack of any alternative treatment option except dialysis which the patient insisted to refuse, a safe alternative experimental treatment option could be justified for treatment of another incurable inflammatory interstitial nephritis.

Since initially the patient responded to the combine treatment with autologous bone marrow-derived MSCs and EAST it is impossible to know for sure the exact role of each of the two procedures. Although the therapeutic benefits of MSCs alone for different clinical indications was previously documented by us and many other investigators [14-16,19,26-29], the role of therapeutic angiogenesis by EAST alone cannot be ignored, although the treatment with EAST in our patient was applied only for one day to guide MSCs while they circulate into the kidneys, while normally therapeutic EAST for treatment of erectile dysfunction and coronary artery disease is time consuming [20, 22].

Although the patient did enjoy good quality of life off dialysis, he passed away 6 years after the first treatment with MScs, the question remains whether or not treatment with MSCs could induce or at least facilitate the development of metastatic lung cancer. Being a heavy smoker since the age of 16 with 2 packs a day, he was certainly at risk to develop lung cancer. In addition, he did receive previously immunosuppressive treatment in an attempt to treat the interstitial nephritis which also represent a risk factor. There's actually ongoing research on this topic, and so far, there's no solid evidence that treatment with MSCs causes cancer, however, recent observations suggest that MSCs produce and secrete a number of paracrine factors, such as chemokines, cytokines and growth factors, thereby regulating existing tumor progression and metastasis in many tumors by supporting tumor microenvironment, thus increasing tumor growth [30,31]. Since heavy smoking and immunosuppressive treatment can promote carcinogenesis and since progression of existing tumor cells can be facilitated by treatment with MSCs that can down regulate immune surveillance, the potential role of MSCs in tumor progressions in our patient cannot be ruled out. On the other hand, it should be noted that other investigators regard MSCs as double-edged sword because there also exist evidence for inhibitory effects on tumor development by anti-inflammatory effects or down-regulation of other tumor promoting factors [30, 32, 34].

However, if successful treatment of renal failure by MSCs and/or EAST can be confirmed, the risk of induction of *de novo* cancer by such treatment should not be considered as contra indication, to the same extent that treatment with MSCs may be indicated for treatment of other indications such as for treatment of life-threatening autoimmune diseases or for otherwise resistant acute graft-vs-host disease (GVHD) after allogeneic stem cell transplantation for patients with existing cancer to start with [35].

Unfortunately, once ESRD develops due to unknown cause or despite optimal control of treatable diseases that may result in ESRD, chronic dialysis or kidney transplantation represent the only possible treatment option. The chance to benefit from kidney transplantation was always reserved to a relatively small minority of patients in need due to shortage of organ donation, so life-long dependency on chronic dialysis remans the treatment of choice for most patients in need. Yet, some patients in need may not even be eligible for chronic dialysis, e.g. after stroke, due to Parkinson's disease or due to severe peripheral vascular disease, to name just a few, whereas in many countries' dialysis may not be available for elderly patients above a ceratin age limit. Once the potential use of autologous MSCs and EAST, or even EAST alone, could be confirmed in prospective clinical trials many additional patients in need with chronic dialysis may benefit. The successful and safe use of MSCs, both autologous and even allogeneic was already confirmed for neurologic disorders [19, 26], musculoskeletal disorders in addition to general regenerative medicine indications [15, 27], and even cosmetic indications [25, 26] including for skin regeneration and rejuvenation [28, 29] with no serious adverse effects further supported the potential use of autologous MSCs for additional clinical indications.

Our investigations in pre-clinical animal models in both mice [36] and rats [37] support the beneficial therapeutic role of bone marrow derived multi-potent MSCs to facilitate repair of kidney damage induced by AKI. Our initial observations in murine models of ischemia-reperfusion injury were confirmed more recently by other investigators [38, 39]. Additional recent publications suggest different mechanisms to explain the therapeutic effects of MSCs in AKI [40] or diabetic nephropathy [41].

Furthermore, since it seems that many of the therapeutic benefits of MSCs could be replaced by the use of their secreted extra cellular vesicles or exosomes, it may not be impossible that some of the therapeutic benefits induced by MSCs could be replaced by administration of MSCs-derived

nanoparticles, as already been suggested and confirmed by our investigations using AKI in rats [42].

Unless confirmed by prospective clinical trial, no solid claims can be made based on a single successful case featuring therapeutic effects of MSCs supported by EAST as possible replacement of renal dialysis. However, the existing report seems to justify a prospective clinical trial for studying the effects of MSCs and EAST used alone or in combination for treatment of patients with progressive renal failure in an attempt to prevent the need for renal dialysis and for patient already treated by renal dialysis. However, considering the supportive information from pre-clinical animal models, clinical observations about safe application of MSCs for different indications and considering the present report certainly justify future clinical trials for treatment of ESRD induced by known or unknow cause.

In addition, it would be most important to investigate if improvement of ESRD may be induced by non-specific anti-inflammatory and anti-fibrosis effects, by repair induced by extra cellular vesicles or exosomes provided by MSCs, or by replacing damaged glomeruli and/PR renal tubules by differentiated or trans-differentiated MSCs. Theoretically, the therapeutic benefit induced by MSCs could also be mediated in part by exosomes secreted by MSCs that could activate locally residing MSCs or other cells present in the kidney [43].

In conclusion, the potential beneficial effect of MSCs combined with EAST observed in our patient with ESRD deserves to be further investigated in prospective clinical trials. The therapeutic outcome induced by MSCs combined with EAST may be attributed to multifaceted anti-inflammatory, immunomodulatory and regenerative capacity induced by multi-potent cell-mediated effects and paracrine effects induced by MSCs, although the role of vasculogenic effects induced by EAST cannot be ruled out. Considering the fact that both treatments with MSCs and EAST are safe, inexpensive and potentially effective, our hope is that future patients in need could also benefit from successful control of ESRD. Taken together, the potential feasibility to replace the need or delay the use of hemodialysis for treatment of ESRD documented by our case report justifies prospective clinical trials for the benefit of a large number of future patients in need.

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Disclosures and Declaration of any conflict of interest

The authors have no relevant financial or non-financial interests to disclose.

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