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Allogenic BM-MSCs Transfusion for Treatment of r(LN)

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Abstract

Bone Marrow Mesenchymal Stem Cells (BM-MSCs) are very unique type of cells that have multipotency and immunomodulatory-regenerative properties. The aim of the present work is to evaluate the efficiency of (BM-MSCs) in controlling resistant Lupus Nephritis (rLN) in cases failing to respond to conventional immunosuppressive protocols and developing renal impairment. BM-MSCs withdrawn from three - four donors / patient was isolated and further cultured to maximize their proliferation reaching 70-80% confluence. They were infused Intravenously (IV) in ten lupus patients who were monitored for serum Creatinine (CR), Creatinine Clearance (CrCl) and twenty-four hr Proteinuria (PTN(U)) over six months to evaluate their response. Eight patients showed regression in proteinuria and improvement in renal functions while two failed to respond with progression of their disease due to late referral and possible inadequate BM-MSCs dose in conclusion, BM-MSCs may represent an additional therapeutic modality for LN particularly those resistant to other established lines of treatment. Their mechanism of action, duration of treatment and dose require further specifications

Keywords: Bone Marrow Mesenchymal Stem Cells (BM-MSCs); Creatinine Clearance (CrCl); Proteinuria PTN(U); resistant Lupus Nephritis (rLN)

Introduction

Systemic lupus erythematosus is a chronic autoimmune disorder that affects most of the body systems, especially the kidney which is rather lethal due to the inefficient current treatment. A persistent decline in renal activity is usually fatal, as not only most of the cases seek treatment late, but also, they remain resistant to the common therapeutic regimens. The known induction therapeutic modalities involving steroids with other immunosuppressive drugs may fail to control the activity in many LN cases [1]. As Mesenchymal Stem Cells (MSCs) have immunomodulatory functions, they may be considered in management of kidney diseases [2], endothelium [3], nerve and liver [4], bone, cartilage, fat [5], skin [6] and pancreatic cells [7]. They suppress the proliferation, differentiation and action of the B and T cells and hinder the secretion of antibodies and cytokine secretion respectively [8]. In addition, MSCs have been shown to reduce PTN(U) as they secrete retinoic acid and Retinoic Acid Response Elements (RARE), which in turn increase podocytes regenerations and renal progenitors [9]. Therefore, MSCs offer a promising regimen for most of patients suffering from deteriorating renal functions [10]. This study focuses on the use of BM-MSCs in rLN cases that not only failed to respond to the current therapeutic protocols but also accepted to be treated with MSCs. Those who didn't accept the BM-MSCs infusion were selected as control. This work is carried out by infusing around 15 million cells/ donor (after isolating-expanding them under sterile conditions) in renal SLE patients then assessing their kidney functions for almost six months interval for both groups.

Materials and Methods

Sampling and Specimen Collections

The present study was conducted on a total number of ten rLN patients. They were seven males (70%) and three females (30%) with their age ranging from 18 to 52 years. Their renal pathology data are summarized in (Table 6). Blood samples were collected

under aseptic conditions by means of clean venipuncture using vacuum collection tubes. Three ml blood were withdrawn from each patient into a sterile serum tube for Creatinine (CR) and a twenty-four hrs urine sample was collected in a sterile container for Creatinine Clearance (CrCl) and Protein Content (PTN(U)). Kidney functions were assessed at day 0 before MSCs injection, first month and sixth month after the initial infusion. Ten rLN patients of the same age range and with similar health conditions but refusing BM-MSCs treatment were taken as controls and monitored for the same kidney functions over six months

BM-MSCs' Collection, Processing, Harvesting and Injection

BM-MSCs' samples were aspirated and collected at two weekly intervals from the selected donors. Under complete aseptic conditions, using a preservative free heparin in a sterile syringe, 90 ml of BM blood was aspirated from iliac crest of the donors. The aspirate was then diluted at ratio 6: 1 with Phosphate Buffer Saline (PBS). Thereafter, the diluted cell suspension (35 ml) was carefully layered over 15 ml of ficoll hypage in 50 ml conical tubes. Mononuclear cells were separated and transferred to a new 15 ml conical tube. The cells were then washed, and the mononuclear cells were suspended in a 5 ml complete culture medium containing FCS (1 ml), α-MEM (4 ml), gentamycin (100 µl), fungi zone (100 µl), and fibroblast growth factor (2 µl). The mixture was mixed well and divided into tissue culture flasks. The flasks were incubated in 5% CO2 incubator at 37˚C for 48 hrs. Since MSCs have this unique phenomenon of plastic adherence, the medium was changed after 24 h by throwing the contents (the media and nonadherent cells); another complete medium was prepared as mentioned earlier and the flasks returned to the incubator. These cells were left for another 3-4 weeks in the incubator and the medium was changed every week using the same procedure as denoted earlier. After the third week, the cells were immunophenotypically tested for cell surface markers (CD29 and CD34) using Flow. The cells were also examined with an inverted microscope for confluence and morphology; besides, they were counted using a hemocytometer. In case of adequate number of cells (90% confluence), the contents were thrown, and the cells were harvested. On reaching such confluence, the media was discarded, and each flask was rinsed with PBS to remove any FCS. A volume of 3 ml of pre-warmed trypsin-EDTA solution (0.05%/0.53 µm EDTA) was added to each flask, and then incubated at 37˚C for 10 min. After trypsinization, the cells were dissociated from the adherent flask wall using a scrapper in a zigzag manner, followed by gentle tapping to detach the MSCs. Later, the MSCs were re-suspended in 5 ml of complete media. Finally, 15 million MSCs (which were isolated from a single donor) diluted in 5 ml saline were injected into the patient intravenously in two sessions with one week apart.

Immunophenotypic Characterization of BM-MSCs

After harvesting and counting MSCs using hemocytometer, the cells were tested for mesenchymal marker CD29 and hematopoietic stem cell marker CD34. Approximately 100 000-200 000 MSCs in DPBS were stained for 20 min at room temperature with 10 µl of antibody, as determined from the manufacturer's recommendation (mesenchymal markers) CD29 PE and exclusion marker CD34 FITC (hematopoietic stem cell marker). A volume of 2 ml of PBS was added to the MSCs and then the tubes were centrifuged at 200g for 5 min at room temperature. The supernatant was discarded and the labeled MSCs were finally re-suspended in 0.5 ml flow buffer (FACS wash) (5% FBS+95% PBS). The cells were analyzed on a flowcytometer Coulter Elite XL Caliber collecting 10,000 events. As a control, unstained cells were applied first to exclude the effect of autofluorescence of the cultured cells.

Results and Discussion

Measuring Renal Function Results (Figures and Tables)

	CR_0	CR_{1st}	CR_{6th}	$CRCL_0$	$CRCL_{1st}$	$CRCL_{6th}$	$PTN(U)_0$	$PTN(U)_{1st}$	$PTN(U)_{6th}$
1	**2**	**2.5**	**4.19**	**35**	**20**	**15**	**2.75**	**2.9**	**2.1**
2	**1.69**	**1.85**	**2.12**	**62**	**45**	**33**	**1.34**	**2.11**	**2.67**
3	**1.65**	**1.9**	**2.8**	**35**	**19**	**12**	**3.2**	**2.98**	**3.14**
4	**1.7**	**1.9**	**2.4**	**47**	**40**	**31.7**	**0.82**	**0.97**	**0.94**
5	**2.9**	**3.1**	**3.3**	**24**	**19**	**17**	**0.6**	**0.68**	**0.69**
6	**2.4**	**3.6**	**6.9**	**23**	**15**	**10**	**0.97**	**1.34**	**0.46**
7	**2**	**2.7**	**3.6**	**25**	**20**	**16**	**1.62**	**1.72**	**0.82**
8	**1.29**	**1.57**	**1.58**	**69**	**64.3**	**60.45**	**5.43**	**4.79**	**5.38**
9	**1.29**	**1.4**	**1.6**	**125**	**69**	**59**	**4.06**	**3.83**	**3.92**
10	**1.4**	**1.7**	**1.9**	**85**	**58**	**42**	**2.73**	**2.51**	**2.68**
Mean	**1.83**	**2.22**	**3.04**	**53.00**	**36.93**	**29.62**	**2.35**	**2.38**	**2.28**

St. Dev.	**0.51**	**0.72**	**1.61**	**32.92**	**21.06**	**18.96**	**1.57**	**1.29**	**1.60**
Median	**1.695**	**1.9**	**2.6**	**41**	**30**	**24.35**	**2.175**	**2.31**	**2.385**
Max.	**2.9**	**3.6**	**6.9**	**125**	**69**	**60.45**	**5.43**	**4.79**	**5.38**
Min.	**1.29**	**1.4**	**1.58**	**23**	**15**	**10**	**0.6**	**0.68**	**0.46**

Table 1: Ten resistant LN patients (control) their CR, CrCl and PTN (U) over sixth month period initially at (0) first month (1) sixth month (6).

	Gender	**Renal Biopsy**	**CR_0**	**CR_{1st}**	**CR_{6th}**	**$CrCl_0$**	**$CrCl_{1st}$**	**$CrCl_{6th}$**	**$PTN(U)_0$**	**$PTN(U)_{1st}$**	**$PTN(U)_{6th}$**
1	**Male**		**1**	**0.8**	**0.8**	**74**	**130**	**133**	**0.6**	**1**	**0.43**
2	**Female**	**II (10%) int fibrosis**	**1.9**	**1.7**	**1.28**	**3 9**	**44.7**	**138.8**	**0.048**	**0.03**	**0.01**
3	**Male**	**IV (10)**	**2.9**	**2.2**	**4.8**	**31.7**	**43.3**	**8**	**1.28**	**0.84**	**4.8**
4	**Male**	**IV (25%)**	**1.8**	**1.8**	**1.8**	**38**	**62**	**43**	**0.5**	**0.2**	**0.2**
5	**Male**	**(III)**	**1.9**	**1.3**	**1.2**	**81**	**98**	**89**	**4.7**	**4.6**	**2.8**
6	**Male**		**1.9**	**1.3**	**1.2**	**89**	**120**	**136**	**2.7**	**1.6**	**1.5**
7	**Female**		**2.5**	**5.7**	**8.3**	**39**	**20**	**12**	**4.8**	**7.7**	**7.7**
8	**Male**	**IV (10%)**	**1.6**	**1.3**	**1.2**	**77**	**85**	**127**	**2.3**	**3.4**	**2.6**
9	**Female**	**III**	**1.3**	**1.2**	**1.2**	**66**	**115**	**158**	**0.5**	**0.32**	**0.25**
10	**Male**	**IV**	**1.9**	**1.3**	**1.1**	**89**	**120**	**158**	**2.7**	**1.6**	**0.3**
Mean			**1.87**	**1.86**	**2.29**	**62.37**	**83.80**	**100.28**	**2.01**	**2.13**	**2.06**
St. Dev.			**0.54**	**1.40**	**2.41**	**22.98**	**38.94**	**58.62**	**1.73**	**2.44**	**2.52**
Median			**1.9**	**1.3**	**1.2**	**70**	**91.5**	**130**	**1.79**	**1.3**	**0.965**
Max.			**2.9**	**5.7**	**8.3**	**89**	**130**	**158**	**4.8**	**7.7**	**7.7**
Min.			**1**	**0.8**	**0.8**	**31.7**	**20**	**8**	**0.048**	**0.03**	**0.01**

Table 2: Ten resistant LN patients (subjected to BM-MSCs) their CR, CrCl and PTN (U) over sixth month period initially at (0) first month (1) sixth month (6).

	CR_0	**CR_{1st}**	**CR_{6th}**	**$CrCl_0$**	**$CrCl_{1st}$**	**$CrCl_{6th}$**	**$PTN(U)_0$**	**$PTN(U)_{1st}$**	**$PTN(U)_{6th}$**
1	**1**	**0.8**	**0.8**	**74**	**130**	**133**	**0.6**	**1**	**0.43**
2	**1.9**	**1.7**	**1.28**	**39**	**44.7**	**138.8**	**0.048**	**0.03**	**0.01**
4	**1.8**	**1.8**	**1.8**	**38**	**62**	**43**	**0.5**	**0.2**	**0.2**
5	**1.9**	**1.3**	**1.2**	**81**	**98**	**89**	**4.7**	**4.6**	**2.8**
6	**1.9**	**1.3**	**1.2**	**89**	**120**	**136**	**2.7**	**1.6**	**1.5**
8	**1.6**	**1.3**	**1.2**	**77**	**85**	**127**	**2.3**	**3.4**	**2.6**
9	**1.3**	**1.2**	**1.2**	**66**	**115**	**158**	**0.5**	**0.32**	**0.25**
10	**1.9**	**1.3**	**1.1**	**89**	**120**	**158**	**2.7**	**1.6**	**0.3**
Mean	**1.66**	**1.34**	**1.22**	**69.13**	**96.84**	**122.85**	**1.76**	**1.59**	**1.01**
St. Dev.	**0.34**	**0.31**	**0.28**	**20.36**	**30.65**	**38.80**	**1.61**	**1.63**	**1.14**
Median	**1.85**	**1.3**	**1.2**	**75.5**	**106.5**	**134.5**	**1.45**	**1.3**	**0.365**
Max.	**1.9**	**1.8**	**1.8**	**89**	**130**	**158**	**4.7**	**4.6**	**2.8**

Min.	**1**	**0.8**	**0.8**	**38**	**44.7**	**43**	**0.048**	**0.03**	**0.01**

Table 3: Results of successful trials with BM-MSCs infusion.

	CR_0	CR_{1st}	CR_{6th}	$CrCl_0$	$CrCl_{1st}$	$CrCl_{6th}$	$PTN(U)_0$	$PTN(U)_{1st}$	$PTN(U)_{6th}$
3	**2.9**	**2.2**	**4.8**	**31.7**	**30**	**8**	**1.28**	**0.84**	**4.8**
7	**2.5**	**5.7**	**8.3**	**39**	**20**	**12**	**4.8**	**7.7**	**7.7**
Mean	**2.70**	**3.95**	**6.55**	**35.35**	**25.00**	**10.00**	**3.04**	**4.27**	**6.25**
St. Dev.	**0.28**	**2.47**	**2.47**	**5.16**	**7.07**	**2.83**	**2.49**	**4.85**	**2.05**
Median	**2.7**	**3.95**	**6.55**	**35.35**	**25**	**10**	**3.04**	**4.27**	**6.25**
Max.	**2.9**	**5.7**	**8.3**	**39**	**30**	**12**	**4.8**	**7.7**	**7.7**
Min.	**2.5**	**2.2**	**4.8**	**31.7**	**20**	**8**	**1.28**	**0.84**	**4.8**

Table 4: Results of resistant trials with BM-MSCs infusion.

	Successful M±SD	Resistant M±SD
CR_0	**1.66±0.34**	**2.7±0.28**
CR_{1st}	**1.34±0.31**	**3.95±2.47**
CR_{6th}	**1.22±0.28**	**6.55±2.47**
$CrCl_0$	**69.13±20.36**	**35.35±5.16**
$CrCl_{1st}$	**96.84±30.65**	**25.00±7.07**
$CrCl_{6th}$	**122.85±38.8**	**10.00±2.83**
$PTN(U)_0$	**1.76±1.61**	**3.04±2.49**
$PTN(U)_{1st}$	**1.59±1.63**	**4.27±4.85**
$PTN(U)_{6th}$	**1.01±1.14**	**6.25±2.05**

Table 5: Results of successful vs. resistant cases to BM-MSCs infusion.

	class	% of fibrosis
1	**II**	**10**
2	**III**	**10**
3	**IV**	**10**
4	**IV**	**25**
5	**III**	**10**
6	**II**	**10**
7	**IV**	**25**
8	**IV**	**10**
9	**II** **III** **II**	**10**
10	**IV**	**10**

Table 6: Results of class and % of fibrosis for renal biopsy of all the cases.

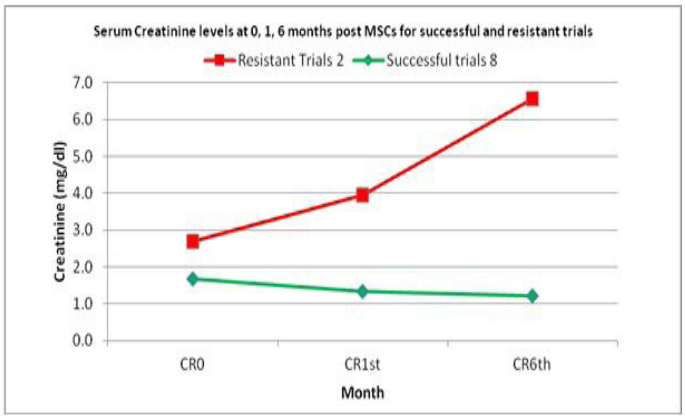

Figure 1: Serum Creatinine levels at 0, 1, 6 months post BM-MSCs for successful and resistant trials.

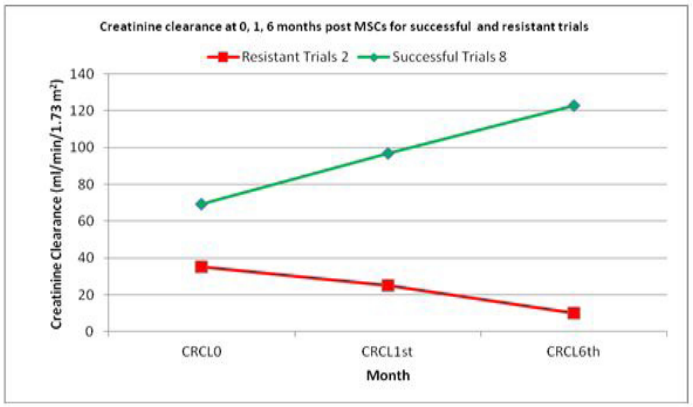

Figure 2: Creatinine clearance levels at 0, 1, 6 months post BM-MSCs for successful and resistant trials.

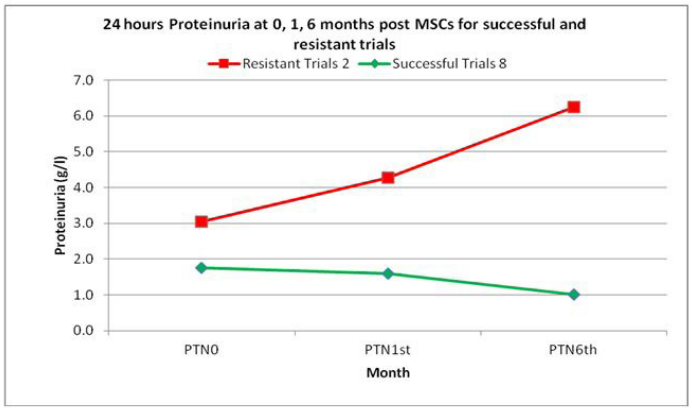

Figure 3: 24-hour Proteinuria levels at 0, 1, 6 months post BM-MSCs for successful and resistant trials.

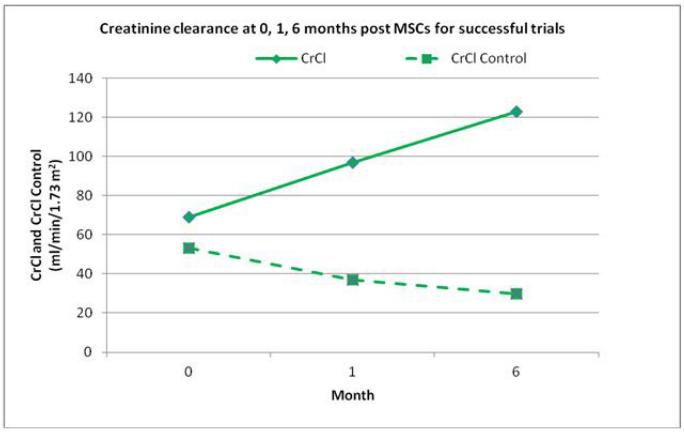

Figure 4: Creatinine clearance at 0, 1, 6 months post BM-MSCs for control (10) & successful trials (8).

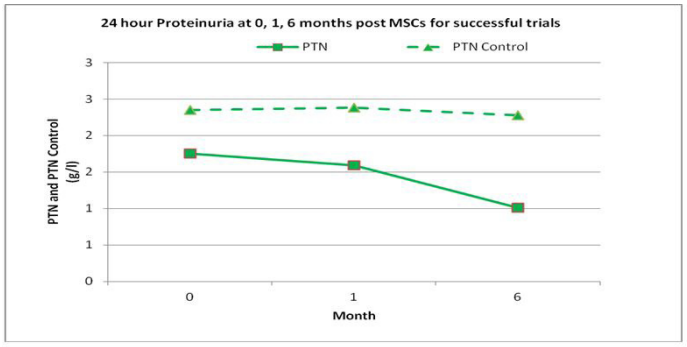

Figure 5: 24- hour Proteinuria at 0, 1, 6 months post BM-MSCs for control (10) & successful trials (8).

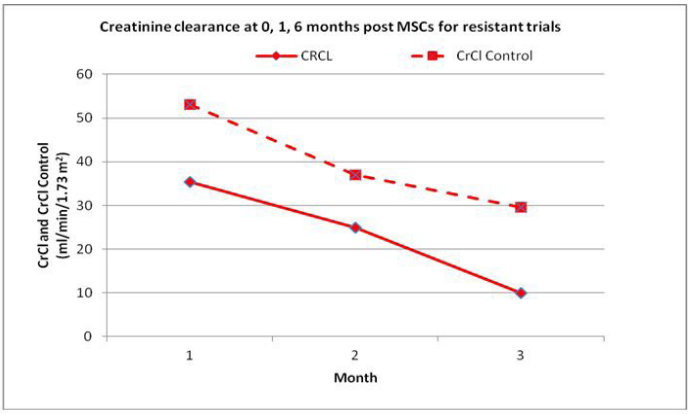

Figure 6: Creatinine clearance at 0, 1, 6 months post BM-MSCs for control (10) & resistant trials (2).

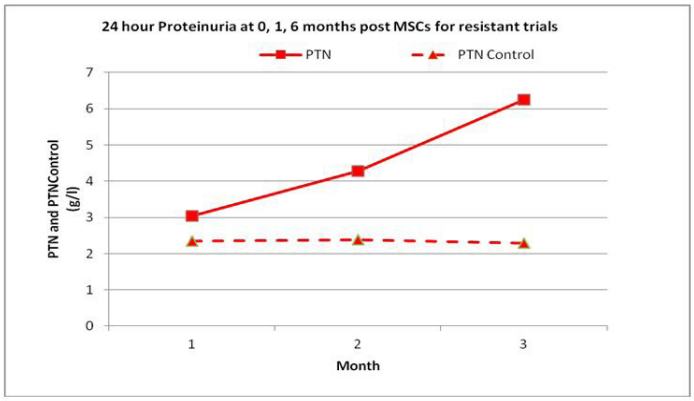

Figure 7: 24-hour Proteinuria at 0, 1, 6 months post BM-MSCs for control (10) & resistant trials (2).

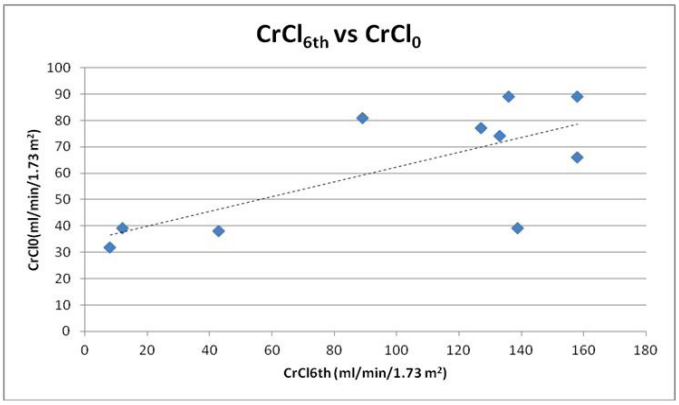

Figure 8: Mean of $CrCL_0$ vs. $CrCl_6$.

Ten SLE cases, showing resistance to control their renal activity by either one or several sequential known immunosuppressive regimens, were considered for trial with BM-MSCs. The cases were given variable doses of BM-MSCs from autologous and/or allogenic sources according to their response [11] demonstrated that the BM-MSCs' transdifferentiation into somatic cells can produce therapeutic benefits without engraftment into the injured tissues. Initial BM-MSCs infusions from three donors (average 15 million cells / donor) were intended. Additional infusion sessions were prescribed if the patient showed improvement or incomplete response. Further treatment was not considered if the patient failed to respond with deterioration of his/her renal parameters. Kidney functions (Cr, CrCl, PTNU) were measured at day (0), 1st month and 6th month after BM-MSCs treatment. (Table 1) shows that almost most of the cases in the control group deteriorated in their kidney functions with variable degrees. In other words, both resistant cases and control ones showed decline in the tested functions as per (Figures 6,7). However, the cases infused with BM-MSCs demonstrated a success rate of 80% as only 2 cases were resistant, as per (Table 2), (Figures 4,5) illustrate the significant improvement in the successful cases in contrast to the deterioration of the control with respect to both the CrCl and PTNU. Some LN cases which showed initial response were prescribed for more frequent infusion. For example, in (Table 2), case (4) and (5) showed incomplete progress to treatment in spite of having the higher four donor's regimen, so they were considered for furthermore intense BM-MSCs infusion. Besides, case (3), which was eventually resistant to BM-MSCs showed an initial improvement. This, in turn, might delineate the requirement of a higher and/or more frequent dosage of the BM-MSCs to get a better sustained response in worse cases with late referral. Thus, it can be concluded that extending infusions beyond initial scheduled three donor regimens can show improvement in kidney functions.

Moreover, it is apparent from (Tables 2,4,5) that those cases which showed resistance to BM-MSCs had much worse initial kidney functions. For instance, the mean of $CrCl_0$ is 69 and 35 ml/min/1.73 m^2 for successful and resistant cases respectively; however, after six months the former increased to 122 ml/min/1.73 m^2 while the latter's mean deteriorated to 10 ml/min/1.73 m^2 as per (Tables 3,4). Therefore, it could be suggested that early intervention is an important factor to achieve a positive response. (Figure 8) demonstrated the importance of starting treatment early, as can be noticed among the eight successful cases. To illustrate, there exists a positive correlation between $CrCl_0$ and $CrCl_6$; the higher the initial CrCl, the better the response to BM-MSCs after six months. This is in agreement with [12] who showed that an initial low CrCl is sometimes associated with poor outcomes. The higher male propensity among the included cases is a reflection of the common treatment response in lupus nephritis known to be more prevalent and responsive to treatment in females [13]. There are six males among the eight cases who responded to BM-MSCs, indicating an effective therapeutic modality for such category of lupus cases, as can be noticed in (Table 2).

The current study revealed that the more the frequency of shots of infused autologous/ allogenic BM-MSCs in SLE patients, the better the results. The scheduled three donor regiment (15 million per donor) may occasionally be inadequate to result in either a full recovery or an incomplete improvement [14]. This is clearly noticed in patient # (3) (Table 4) who initially started with a (Cr_0 2.9, $CrCl_0$ 31.7 & PTN $(U)_0$ 1.28) but sooner worsened to (Cr_6 4.8, $CrCl_6$ 8& PTN$(U)_6$ 4.8). Such deterioration might reflect inadequate therapy, in other words the frequency of donor collection was insufficient. Also, this patient in particular started rather late after a very prolonged treatment with cyclosporine; that is why his response to MSCs was not as expected. Therefore, not only the few shots given but also the delay to start MSCs therapy resulted in the failure of this patient (Gu et al, 2010) [15]. In contrast to patients (4) and (5) with low $CrCl_0$ (39) and PTN$(U)_0$ (4.8) respectively who showed improvement in renal functions as they were not only subjected to more frequent shots but also started early enough before creatinine (CR_0) drops. Moreover, MSCs seem to affect kidney differently with respective to the glomerular and tubular functions; with faster progress of the later; as both the creatinine Cr_1 and $CrCl_1$ showed much rapid improvement in comparison to Cr_6 and $CrCl_6$. As per (Figures 1,2). This is in agreement with a previous search conducted by [10] that showed a highly statistically significant difference for both serum creatinine and creatinine clearance levels before and after MSC injection at 1, 3 and 6 months for SLE cases; showing a greater decline of the former and elevation of levels after injection.

In this search for instance, while the mean creatinine level (for successful cases) dropped 20% after one month from starting treatment, it decreased by only 10% for the rest of the five months (CR_1 to CR_6). This magnifies the rapid tubular response to treatment as demonstrated in (Figure 1). Furthermore, creatinine clearance showed a similar progress in the first month (40% increase) when compared to the last five months improvement (only 27%), as shown in (Figure 2). Such an initial rapid response is very encouraging to give and maintain more frequent shots for the patients, consequently improving their results [14]. The immunomodulatory effect of MSCs not only decreases the intake of immunosuppressive drugs, but also improves the patients' renal functions and eventually their long-term survival. It is their homing criteria that makes them migrate towards renal tissue and repair the tubular injury [16]. On the other hand, glomerular function of the kidney showed a slower effect in comparison to the tubular one. For example, proteinuria dropped by 10% only in the first month which is almost more than tripled in the subsequent five months (36%) as shown in graph (3). This concludes that the MSCs therapy has rather slower effect when it comes to glomerular than

the tubular function.

Conclusion

In conclusion, current systemic therapies are rarely curative for patients with severe life-threatening forms of Autoimmune Diseases (AD). During the past decade, BM-MSCs infusion has been demonstrated to cure some patients with severe AD refractory to all other available therapies. BM-MSCs display specific immunomodulation and anti-inflammatory properties and appear as an ideal adjuvant tool to treat such diseases. One can conclude that the MSCs are not a replacement therapy but rather a complementary one. Finally, this investigation had 3 main conclusions. Firstly, gender plays a significant role regarding the response to traditional versus MSCs treatment. Secondly, glomerular and tubular functions responded differently during the course of treatment. Finally, the frequency and timing to start therapy is a factor that affects the results. MSCs therapy holds great hopes for lupus nephritis patient only if given at the right timing with no pace for fibrosis, with the right dose and frequency of donors. However, more and more research should be conducted to set the appropriate dose and frequency of cells for each patient.

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