Dear Editor,

Please find our answers to the comments from the reviewers for manuscript 21396.

1 Reviewer 2446280

1.1 Reviewer has commented that, "recently a Nobel awarded third type of stem cells has emerged- induced or reprogrammed stem cells".

We agree with reviewer that indeed induced pluripotent stem cells have been developed and it represent a major advance in the field of stem cell therapy.

We have revised our manuscript to read.

"Stem cells have their origins in the embryo and during the process of organogenesis, these differentiate into specialized cells which mature to form tissues. In addition, stem cells are characterized by ability to indefinitely self-renewal. Stem cells are broadly classified into embryonic stem cells and adult stem cells. Adult stem cells can be genetically reprogrammed to form pluripotent stem cells and exist in an embroyonic like state. In the early phase of embroyogenesis, human embryonic stem cells only exist transiently. Adult stem cells are omnipresent in the body and function to regenerate during the process of apoptosis or tissue repair. Hematopoietic stem cells (HSC) are adult stem cells that form blood and immune cells."

1.2 Reviewer 2446280 has commented that "Authors also stated that "Currently there are no approved clinical uses of embryonic stem cells". However at least 5 FDA approved clinical trials of phase 1-2 are under way now and results are very encouraging."

As far as authors are aware currently there are no FDA approved human embryonic stem cells therapies available for clinical use. There are three open clinical trials listed on clinical trials.gov studying human embryonic stem cell based therapies in severe heart failure, and macular dystrophy respectively. We did not find published results of successful clinical use of embryonic cell based therapy on search of pubmed.

We have revised our manuscript as follows

"Embryonic stem cells have great promise as they have the capability to replenish every functioning cell in the human body. Uncontrolled replication of embryonic stem cells leads to teratomas. Embryonic stem cell biology is subject to ethical controversy. Currently there are no FDA approved embryonic stem cells based therapies available for clinical use. There are several clinical trials ongoing exploring use of human embryonic stem cell based therapies in regenerative medicine. Hematopoietic stem cells (HSC) are blood and immune cells that have their origin from adult stem cells. HSC can be isolated from the umbilical cord, peripheral blood or the bone marrow."

2. Reviewer 02928802

2.1 "General comments 1. The author reviewed the hematopoietic stem cell transplantation for autoimmune rheumatic diseases. It is better to summarized the advantages and the disadvantages of HSCT in the manuscript. Besides, it is better to add a picture of HSCT treatment procedure for better understanding."

We agree with the reviewer and we will revise our manuscript to include the paragraph:

"The major advantage of HSCT for autoimmune diseases is the ability to achieve a 'immune reset' i.e. the ability to eliminate the autoimmune T cell cells clones and alter the natural history of the disease. The major disadvantages of HSCT for autoimmune disease are the added toxicity of the high dose chemotherapy or radiation used as part of conditioning regimen."

We will include a picture to illustrate the principle of HSCT.

2.2 "2. Page 6, "most of the data available for HSCT in SSc has shown a significant improvement in skin scores in patients and moderate improvement in FVC and DLCO." "Survival data from ASTIS trial, however, show while HSCT was associated with increased treatment-related mortality in the first year after treatment, HSCT conferred a significant long-term event-free survival benefit". It is better if the author could provide these data in detail."

We have described the results from the trial in table 2. We will also add following paragraph to the manuscript.

"In ASTIS trial 156 patient with SSc and heart, lung or kidney involvement were randomized to HSCT (n=79) versus monthly cyclophosphamide (n=77) for 12 months. During the first year there were more events (death and irreversible organ failure) in the HSCT group, 13 (16.5%) versus 8 (10.4%) in the cyclophosphamide group. However during the second the cumulative events were similar in two groups 14 (17.7%) versus 14 (18.2%). By 4 year the cumulative events in HSCT group 15 (19%) were less than cyclophosphamide group 20 (26%). In the ASSIST trial 19 patients with SSc and organ

involvement were randomized to HSCT (n=10) or monthly cyclophosphamide for 6 months (n=9). 8/9 patients on monthly cyclophosphamide progressed versus none for HSCT group within the first year after randomization. 7 patients underwent HSCT after evidence of progression on monthly cyclophosphamide. For 11 patients who under went HSCT and had follow up for at least 2 years there was significant improvements in mRSS ($p < 0.0001$) and FVC ($p<0.03$) compared to baseline. This trial was closed early and there were no deaths reported in either arm."

2.3 Reviewer commented "On page 4, paragraph 2, the author mentioned "In the beginning the use of HSCT had been limited to refractory diseases due to ……. Later it became clear that transplant related mortality and morbidity is a function of the disease state and conditioning regimen". This paragraph should be provided more references.

More references will be added to the manuscript.

Thanking you,

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