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Review Article

Mesenchymal Stem/Stromal Cells for Treatment of Rheumatoid Arthritis

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ABSTRACT

Rheumatoid Arthritis (RA) is a chronic, inflammatory, autoimmune disorder involving joint pathogenesis, cartilage and bone deformities, along with systemic comorbidities, affecting over 75 million people worldwide. At present there is no cure for RA and the current treatment modalities utilized have limitations and side effects. Over the last decades, mesenchymal stem/stromal cells (MSCs), both autologous and allogenic, have emerged as potential safe and effective alternatives. In this review, we highlighted the safety and efficacy of both autologous as well as allogenic MSCs to treat RA based on recently published clinical studies. These studies demonstrated that use of autologous or allogenic MSCs is safe and laid the foundation for multi-center prospective open label non-randomized trials and double blinded randomized controlled trials with larger sample size to further establish the safety and efficacy of these MSCs to alleviate symptoms of RA, thereby, ultimately justifying their clinical use.

1. Introduction

Rheumatoid Arthritis (RA) is a chronic, inflammatory, autoimmune disorder involving joint pathogenesis, cartilage and bone deformities, along with systemic comorbidities, affecting over 75 million people worldwide.[1,2] Common symptoms of RA consist of pain, stiffness and swelling which are regularly followed by gradual debility and joint disfunction.[3] Presently, there is no remedy for RA. Successful treatments regularly commence with the use of corticosteroids, which halt the disease process while managing symptoms, till disease modifying antirheumatic drugs (DMARDs), for example, methotrexate, begin to take effect. Patients devoid of an adequate response to non-biological DMARDs, either switch or augment with other synthetic DMARDs and/or with one of various increasingly accessible biological DMARDs, including TNF-α inhibitors, Anti-B/T cell and IL-6R therapies.[4–6] Even though not frequent, these remedies can have serious adverse effects, such as infections, hematologic, renal and hepatic dysfunction, as well as bone marrow suppression.[7,8] In addition, long-term use of DMARDs may lead to drug resistance, resulting in suboptimal therapeutic outcomes. Thus, need for safe and effective alternatives is warranted for those who respond inadequately to current treatment modalities.

Mesenchymal stem/stromal cells (MSCs) are multipotent progenitor cells which can differentiate into several tissue types.[9] MSCs ability to exert profound immunosuppression by modulating the proliferation and differentiation of B and

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T cells, dendritic cell maturation and NK cell activity; and promote regeneration contribute to the beneficial effects noted in several preclinical inflammatory studies.[10,11] Specifically, MSCs have been highlighted as a promising alternative for treatment of several immune-related diseases, such as graft-vs-host disease (GVD), multiple sclerosis, inflammatory bowel disease, atopic dermatitis, etc.[10] In addition, they have been associated to have therapeutic potential in preclinical models of RA.[11] The goal of this review is to highlight the safety and efficacy of both autologous as well as allogenic MSCs to treat RA based on recently published clinical studies.

2. Autologous MSCs and RA

2.1. Autologous Bone marrow-derived MSCs (BMSCs)

A study by Shadmanfar et al., assessed the safety, tolerability and efficacy of intraarticular knee implantation of autologous BMSCs in patients with RA. This study was a single-center, randomized, triple-blind, placebo-controlled phase 1/2 clinical trial where randomized RA patients with knee involvement received either an intra-articular knee implantation of 40 million autologous BMSCs per joint or normal saline (placebo). Patients were followed up for 12months to assess the therapy outcomes. A total of 30 patients, 15 in the BMSCs group and 15 in the placebo group, were enrolled in this study. No adverse effects were reported after BMSCs administration or during the duration of the study. Patients who received BMSCs showed improvements on the Western Ontario and McMaster Universities Arthritis Index (WOMAC), visual analogue scale (VAS), time to jelling, and pain-free walking distance compared to the placebo group, however the difference between the two groups was not statistically significant. In addition, this improvement was not significantly lasting past 12months. The BMSCs group exhibited improved standing time ($p= 0.01$). In addition, the BMSCs group showed reductions in methotrexate and prednisolone use ($p<0.05$). The results from this study, though preliminary, justified the need for further studies over an extended follow-up time with larger sample size of RA patients with involvement of knee.[12]

Study by Ghoryani et al, evaluated the effects of intravenous (i.v.) administration of autologous BMSCs on the immunological, clinical and para-clinical factors including, regulatory T-cells, Th17 cells, $CD8^+$ T-cells, $CD4^+$ T-cells, disease activity score 28-erythrocyte sedimentation rate (DAS28-ESR), VAS, ESR, C-reactive protein (CRP), rheumatoid factor (RF), and anti-cyclic citrullinated peptide (anti-CCP) antibodies in patients suffering with refractory RA. 9 refractory RA patients with no other rheumatologic disorders were enrolled in this study. All patients received a single i.v. dose of 1×10^6autologous BMSCs/kg, and were followed up at 1, 6 and 12months post-injection. The results showed a significant decrease in Th17 percentage and geometric mean fluorescence intensity for IL-17A following injection of BMSCs at 12 months compared to baseline. Additionally, a significant increase in regulatory T-cells percentage was reported at the end of the 1 month post-injection. DAS28-ESR also decreased significantly at 1 and 12 months post-injection. VAS score indicated a significant decrease during the follow-up periods. No significant differences were reported for serum CRP and anti-CCP levels post-injection. The results from this study suggested that clinical symptoms were significantly improved following the i.v. administration of autologous BMSCs in patients with refractory RA.[13]

Another study by Ghoryani et al, evaluated immunological elements after i.v. administration of a single dose of autologous BMSCs (1×10^6 per kg) in 13 patients suffering from refractory RA. These patients were followed for 12months post-injection. The results demonstrated that the gene expression of forkhead box P3 (FOXP3) in the peripheral blood mononuclear cells (PBMCs) was significantly increased at 12 months follow-up. A substantial increase in the culture supernatant levels of IL-10 and transforming growth factor-beta 1 (TGF-β1) in PBMCs compared to the baseline was also observed. The results from this study indicated sufficient immunoregulatory effect of autologous BMSCs on regulatory T-cells in patients suffering from refractory RA.[14]

2.2. Autologous Adipose-derived MSCs (ADSCs)

Vij et al. conducted a phase I/IIa non-randomized, open-label study to evaluate the safety and efficacy of a single, i.v. infusion of autologous ADSCs over a period of 52 weeks, in patients suffering with active RA. 15 eligible RA patients aged 18-65 years were enrolled and followed-up at 4, 12, 26 and 52weeks post administration of 2×10^8 ADSCs. Efficacy was assessed utilizing American College of Rheumatology (ACR66/68 score) criteria for swollen and tender joint counts (S/TJC), and serum TNF-α, IL-6, CRP, and ESR levels. Safety endpoints comprised of measures of hematologic, renal and hepatic function. ACR66/68 scores for both S/TJC demonstrated significant improvements with large effect sizes (ES) at 52weeks compared to the baseline ($p< 0.01$, $ES = 0.83$ and $p<0.001$, $ES=0.93$ respectively). Medium to large ES were also described for ACR66/68 scores measured at other timepoints. Levels of inflammatory markers, including, TNF-α, IL-6 and ESR stayed unaffected compared to the baseline. Though, a difference in CRP levels with a small effect size was observed at 4weeks ($p=0.229$, $ES=0.33$) with additional improvement at 52weeks ($p=0.183$, $ES=0.37$). Post injection, levels of hematologic, renal and hepatic function remained largely unchanged ($p>0.05$). No acute or long-term adverse or serious adverse events were observed.

The results from this study suggested that a single, i.v. injection of autologous ADSCs is safe and efficacious for improvement in joint function in patients with active RA. This study also lays the foundation for prospective studies to further explore the use of ADSCs as a therapeutic modality for patients suffering with active RA.[11]

3. Allogenic MSCs and RA

3.1. Allogenic ADSCs

Study by Alvaro-Gracia et al. evaluated the safety, tolerability and efficacy of the i.v. administration of Cx611, an allogeneic expanded ADSCs formulation, in patients with refractory RA in a multicentre, dose escalation, randomized, single-blind (double-blind for efficacy), placebo-controlled, phase Ib/IIa clinical trial. Patients with active refractory RA (failure to at least two biologicals) were randomized to receive 3 i.v. infusions of Cx611: 1million/kg (cohort A), 2million/kg (cohort B), 4 million/kg (cohort C) or placebo, on days 1, 8 and 15, and were followed for 24 weeks. 53 patients were treated (20 in cohort A, 20 in cohort B, 6 in cohort C and 7 in placebo group). A total of 141 adverse events (AEs) were reported. 17 patients from the cohort A (85%), 15 from the cohort B (75%), 6 from the cohort C (100%) and 4 from the placebo group (57%) experienced at least one AE. 8 AEs from 6 patients were grade 3 in intensity (severe), 5 in cohort A (lacunar infarction, diarrhea, tendon rupture, rheumatoid nodule and arthritis), 2 in cohort B (sciatica and RA) and 1 in the placebo group (asthenia). Only one of the grade 3 AEs was serious (the lacunar infarction). Due to small sample size, no statistical analysis was performed to compare clinical efficacy between the cohorts. The i.v. infusion of Cx611 was in general well tolerated, without evidence of dose-related toxicity at the dose range and time period studied. The result from this study warrants more investigations with higher sample size to determine efficacy of this therapy in patients suffering with RA.[15]

3.2. Allogenic Umbilical Cord Blood-derived MSCs (UCB-MSCs)

Park et al. performed a (phase I, uncontrolled, open-label trial (CURE-iv) for RA patients with moderate disease activity despite treatment with methotrexate. The patients were administered a single i.v. infusion of 2.5×10^7, 5×10^7, or 1×10^8 cells of UCB-MSCs for 30minutes, with 3 patients in each cluster, with an increment of cell numbers when there was no dose-limited AE. Safety and clinical measurements were recorded during the study period, and serum cytokines were assessed at baseline and 24hours post-administration. 9/11 screened RA patients were enrolled. The participants were primarily female (78%) with a mean age of 57.4 years. The average duration of disease was 9.5 years, and baseline DAS28-ESR was 4.53. No major toxicity in all clusters up to 4weeks post-injection was reported. Serum ESR changes at 4weeks (n = 9) were -7.9±10.4 (p=.0517) and DAS28 changes were -1.60±1.57 (p=.0159). Decreased levels of IL-1β, IL-6, IL-8, and TNF-α at 24hours were noted in the cluster infused with 1×10^8 UCB-MSCs. The results from this study revealed no short-term safety concerns.[10]

3.3. Umbilical Cord MSCs (UC-MSCs)

Study by Wang et al. assessed the safety and efficacy of UC-MSCs in the treatment of RA. In this study, 172 patients with active RA who had insufficient responses to conventional medication were enrolled. Patients were divided into 2 groups for different treatment: either DMARDs plus medium without UC-MSCs, or DMARDs plus UC-MSCs group (4×10^7 cells per time) administered intravenously. AE and the clinical information were recorded. Tests for serological markers to assess safety and disease activity were also performed. In addition, serum levels of inflammatory chemokines/cytokines, and lymphocyte subsets in peripheral blood were examined. No serious AE were observed during or after i.v. administration. The serum levels of TNF-α and IL6 decreased after the first UC-MSCs treatment ($p<0.05$). The percentage of CD4(+)CD25(+)Foxp3(+) regulatory T-cells of peripheral blood was also increased ($p<0.05$). The treatment also led to a significant remission of disease per the ACR improvement criteria, the DAS28, and the Health Assessment Questionnaire (HAQ). The therapeutic effects were sustained for 3-6months without continuous infusion, relating with the increased percentage of regulatory T-cells of peripheral blood. On the contrary, no such benefits were observed in the control group. The results from this study indicated that treatment with DMARDs along with UC-MSCs may provide safe, significant, and persistent clinical benefits for patients suffering with active RA.[16]

In the follow-up study, Wang et al. evaluated the long-term safety and efficacy of UC-MSCs along with DMARDs for the treatment of RA. 64 RA patients aged 18-64 years were enrolled in the study. During the treatment, patients were treated with 40mL UC-MSCs suspension product (2×10^7 cells/20mL) via i.v. injection immediately after the infusion of 100mL saline. The serological markers tests were used to determine safety and the DAS28 and HAQ to assess efficacy. The blood routine, kidney and liver function and immunoglobulin examination demonstrated no abnormalities (all values in the normal range), 1 and 3years post-treatment. The ESR, CRP, RF of 1 and 3 years and anti-CCP of 3years post-treatment were reported to be significantly lower ($p<0.05$) than that of pre-treatment. DAS28 and HAQ also showed significant decrease ($p<0.05$) 1 and 3 years post-treatment vs pre-treatment.

Table 1: Ongoing clinical trials registered on ClinicalTrials.gov till September 18, 2022 utilizing Mesenchymal Stem/Stromal Cells for treatment of Rheumatoid Arthritis.

Study Identifier	Cell Type	Study Phase; Estimated Enrollment (N)	Primary Outcome Measure(s)	Recruitment Status	Country
NCT01985464	UC-MSCs	Phase I/II; N=20	Number of participants with adverse events [Time Frame:12 months]	Unknown	Panama
NCT01547091	UC-MSCs	Phase I/II; N=200	Safety of MSC treatment. [Time Frame: 6 months]: Adverse Events will be recorded in a patient or clinical investigation subject who administers MSC and will be evaluated a causal relationship with the treatment.	Unknown	China
NCT03067870	Autologous BMSCs	Phase I; N=100	Evaluation of Pain Reduction measured by VAS scaling [Time Frame: 1 month]: measured by VAS scaling	Unknown	Jordan
NCT02643823	UC-MSCs	Phase I; N=40	Severity of adverse events [Time Frame: 12 months]: According to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE)	Unknown	China
NCT04170426	Autologous ADSCs	Phase I/II; N=54	Adverse Events and Sever Adverse Events [Time Frame: 52 weeks]: The total number of adverse events and severe adverse events related and non-related with ADSCs will be recorded to indicate the safety and tolerability.	Not yet recruiting	USA

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Table 1 continued

NCT04971980	UC-MSCs	Phase I/II; N=9	1. Number and frequency of adverse events (AEs) [Time Frame: Up to day 28±3]: Adverse events are assessed by CTCAE 5.0 up to 28±3 days. The flexible change of ±3 days is set for the convenience of patients. Day 1 refers to the day the participant accept BC-U001 infusion. 2. Changes of vital signs from 1 hour after infusion to day 28±3 [Time Frame: Up to day 28±3] 3. Changes of complete blood count (CBC) from day 1 to day 28±3 [Time Frame: Up to day 28±3] 4. Changes of blood biochemical from day 1 to day 28±3 [Time Frame: Up to day 28±3] 5. Changes of coagulation function from day 1 to day 28±3 [Time Frame: Up to day 28±3] 6. Routine urine analysis [Time Frame: Up to day 28±3] 7. Urine pregnancy test (female only) [Time Frame: 28±3 days] 8. Cardiac rate measured by twelve-lead electrocardiogram [Time Frame: Up to day 28±3]	Recruiting	China
NCT03798028	UC-MSCs	Not Applicable; N=250	1. Improvement rate of blood routine hemoglobin (HGB) compared to baseline [Time Frame: 24 weeks]: The HGB increases by 10g compared to the baseline is considered improvement. 2. Improvement rate of forced vital capacity (FVC) and/or carbon monoxide diffusing capacity (DLCO) compared to baseline. [Time Frame: 24 weeks]: FVC increases by 0.5% and DLCO increases by 10% compared to baseline are considered improvement.	Unknown	China

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Table 1 continued

NCT03186417	Allogenic MSCs	Phase I; N=20	1. Safety assessed by dose limiting toxicity (DLT) [Time Frame: 14 days following infusion]: In addition, a DLT will be assigned if through 14 days after the infusion any grade 3-4 adverse event for pulmonary, cardiac, renal, oral mucosal or hepatic, and grade 4 adverse events for other organs occurred per the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. 2. Safety assessed by dose limiting toxicity [Time Frame: 48 hours following infusion]: A DLT is triggered by occurrence through 48 hours after infusion of grade ≥2 infusion-related allergic toxicities, which include rash, flushing, urticaria, dyspnea, fever ≥38°C (≥100.4°F) as scored according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse events (CTCAE) version 4.03. 3. Safety assessed by change in spirometry [Time Frame: 30 minutes following infusion]: Changes in spirometry following infusion compared to baseline. 4. Safety assessed by all adverse events [Time Frame: 52 weeks following infusion]: Incidence and severity of adverse events	Recruiting	USA
NCT05003934	UC-MSCs	Phase I; N=20	Safety (adverse events) [Time Frame: Four year follow-up]: Clinical monitoring of possible adverse events or complications	Recruiting	Antigua and Barbuda
NCT03828344	UC-MSCs	Phase I; N=16	Frequency of Adverse Events (AE) and Serious Adverse Events (SAE) [Time Frame: 12 months after infusion]: Total number and rate of AEs and SAEs, related and non-related with BX-U001 infusion will be recorded as a measure of tolerability and safety.	Not yet recruiting	USA
NCT03618784	UCB-MSCs	Phase I/II; N=33	Safety of FURESTEM-RA Inj. - number of adverse events [Time Frame: 4 weeks follow-up after treatment]: Evaluate the number of adverse events Safety of FURESTEM-RA Inj.	Unknown	Korea

The results from this study further emphasized that treatment with DMARDs along with UC-MSCs is safe, effective and a potential therapeutic option to treat patients suffering with RA.[17]

4. Conclusion

In conclusion, these studies demonstrated that use of autologous sources including BMSCs and ADSCs or allogenic sources including UCB-MSCs and UC-MSCs is safe and laid the foundation for multi-center prospective open label non-randomized trials and double blinded randomized controlled trials with larger sample size to further establish the safety and efficacy of these MSCs to alleviate symptoms of RA, thereby, ultimately justifying their clinical use. There are certain clinical trials which are designed and/or are ongoing. As of September 18, 2022, there are 11 ongoing (or status unknown) clinical trials registered on clinicaltrials.gov (search terms: "Rheumatoid Arthritis" and "stem cells" or "Stromal Cells"). These are summarized in Table 1.

5. Author Contributions

A.G. conceptualized the manuscript and wrote the initial manuscript draft. A.G. and M.K. reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

6. Conflicts of Interest

None

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