Arch. Immunol. Ther. Exp. (2018) 66:267–271
DOI 10.1007/s00005-017-0493-3

REVIEW

Are We Right to Consider Mesenchymal Stem Cells to Be a New Perspective for Patients with Juvenile Idiopathic Arthritis?

Krzysztof Orczyk[1] · **Elzbieta Smolewska**[1]

Received: 8 February 2017 / Accepted: 30 August 2017 / Published online: 13 October 2017

Abstract Juvenile idiopathic arthritis (JIA) is the most common cause of chronic arthritis in childhood. Up to 50% of patients are resistant to standard therapy, which includes non-steroid anti-inflammatory drugs, corticosteroids, disease-modifying anti-rheumatic drugs and biologic therapies. Intra-articular injection of mesenchymal stem cells (MSCs) is proposed as a new approach to JIA treatment. MSCs can modulate inflammation via mechanisms of both adaptive and innate immune response. They are able to inhibit T and B cell proliferation, promote regulatory T cells, suppress the maturation of dendritic cells, stimulate macrophage differentiation into M2 phenotype and reduce effectiveness of natural killer cells. They also secrete plethora of soluble factors which influence joint inflammation. Recent clinical studies reviewed in the article provide promising results which may suggest including intra-articular injection of MSCs in therapy of patients with oligoarticular JIA.

Keywords Mesenchymal stem cells · Juvenile idiopathic arthritis · Pathogenesis

Introduction

Juvenile idiopathic arthritis (JIA) is the most common cause of chronic arthritis in childhood. It is not a homogenous entity as the definition applies to all forms of synovial joint inflammation without identified etiology which lasts for at least 6 weeks and with onset before the age of 16 years (Ravelli and Martini 2007). All possible causes of chronic arthritis, which are recognized to date, need to be excluded to make the diagnosis of JIA (Giancane et al. 2016). Classification of JIA encompasses seven categories of the disease based on the criteria set by the Pediatric Task Force of the International League of Associations for Rheumatology (Petty et al. 2004). Three main subtypes are presented by oligoarthritis, polyarthritis and systemic onset disease (sJIA) (Hahn and Kim 2010).

The detailed etiology of JIA remains unclear. According to Hinks et al. (2013), genetic factors constitute only 18% of the pathogenesis. Hence, JIA is considered to develop in genetically susceptible individuals due to environmental triggers, and primarily infections. Molecular mimicry of bacterial peptides is postulated to produce autoimmune arthritis (Verwoerd et al. 2016).

Pathomechanism of JIA involves both innate and adaptive immune response. Auto-reactive T lymphocytes, predominantly T helper 1 (Th1) and Th17 cells, play a crucial role in the development of arthritis as they cluster around antigen-presenting cells, secrete proinflammatory cytokines interferon (IFN)-γ and interleukin (IL)-17, and simultaneously stimulate the remaining synovial cells to induce inflammation (Hahn and Kim 2010). B cells produce immunoglobulins, specifically rheumatoid factor and antinuclear antibodies, without identified specific molecular targets, whereas macrophages, monocytes and synovial fibroblasts secrete plethora of inflammatory mediators (Huang 2012). The most significant of them, which are responsible for promoting autoimmune process, chronic inflammation and subsequent tissue destruction are, namely: tumor necrosis factor (TNF)-α, IL-1β and IL-6 (McInnes and Schett 2007).

Current treatment guidelines, which include non-steroid anti-inflammatory drugs (NSAIDs), corticosteroids, conventional disease-modifying anti-rheumatic drugs and biologic

✉ Elzbieta Smolewska
e.smolewska@wp.pl

[1] Department of Pediatric Rheumatology, Medical University of Lodz, Sporna 36/50, 91-738 Lodz, Poland

therapies, are not fully effective in up to 50% of rheumatic patients (Shin et al. 2016). They cannot explicitly repair the multifactorial immune response in JIA patients, what may provide as a reason of persistence and recurrence of arthritic symptoms (Wang et al. 2016). Therefore, new therapeutic approaches have been sought to reduce inflammatory activity of joints more adequately.

Intra-articular injection of mesenchymal stem cells (MSCs) has become one of novel perspectives for JIA patients. While recommended biologic agents are designed to hit a single molecular target, MSCs can adjust the secretion of numerous macrophage-derived cytokines and thus restore the balance of immune response (Shin et al. 2016).

Trials conducted in adults diagnosed with rheumatoid arthritis (RA) support the effectiveness of MSCs in severe course of disease, refractory to aforementioned standard treatment (Ansboro et al. 2017). Besides, there is growing body of evidence on using MSCs in pediatric population (Norambuena et al. 2012). The aim of this article is to review the recent findings on using MSCs in patients with JIA.

Characteristics of MSCs

First isolation of MSCs dates back to 1968 (Friedenstein et al. 1974). These multipotential cells proved to have the capability of self-renewal and differentiate primarily into adipogenic, chondrogenic and osteogenic lineages (Pittenger et al. 1999). MSCs reside at the abluminal surface of sinusoidal blood vessels in bone marrow (BM) (MacFarlane et al. 2013), but they can also be harvested from periphery, including adipose tissue, synovium, umbilical cord (UC) and placenta (Zhang et al. 2012). Laboratory recognition of MSCs relies on their adherence to plastic (Colter et al. 2000) and expression of certain surface markers, such as CD44 (hyaluronate receptor), CD73 (ecto-5′-nucleotidase), CD90 (Thy-1), CD105 (endoglin) and CD106 (vascular cell adhesion molecule 1) (Jorgensen et al. 2003; Noel et al. 2002). MSCs do not present on their surface hematopoietic cell markers, including CD11a, CD14, CD19, CD34 and CD45 (Cipriani et al. 2013). Furthermore, human leukocyte antigen (HLA) class II molecules are not detectable on MSCs and they express low levels of HLA class I (Burt et al. 2002). Although the presence of human leukocyte antigens on the surface of MSCs can be stimulated by IFN-γ, they are unable to express HLA co-stimulants, specifically CD40, CD80 and CD86. Therefore, they manage to act besides the immune surveillance (Deans and Moseley 2000). Interestingly, they can be provided by universal donor as allogeneic MSCs, are not rejected and they retain their attributes (Di Nicola et al. 2002). Their potential to render immune response is reported in both in vitro and in vivo studies (Bartholomew et al. 2002; Di Nicola et al. 2002). MSCs can modulate inflammation using a vast array of mechanisms (Fig. 1) of both adaptive and innate immune response (Contreras et al. 2016). They are able to inhibit B and effector T cells, promote induction

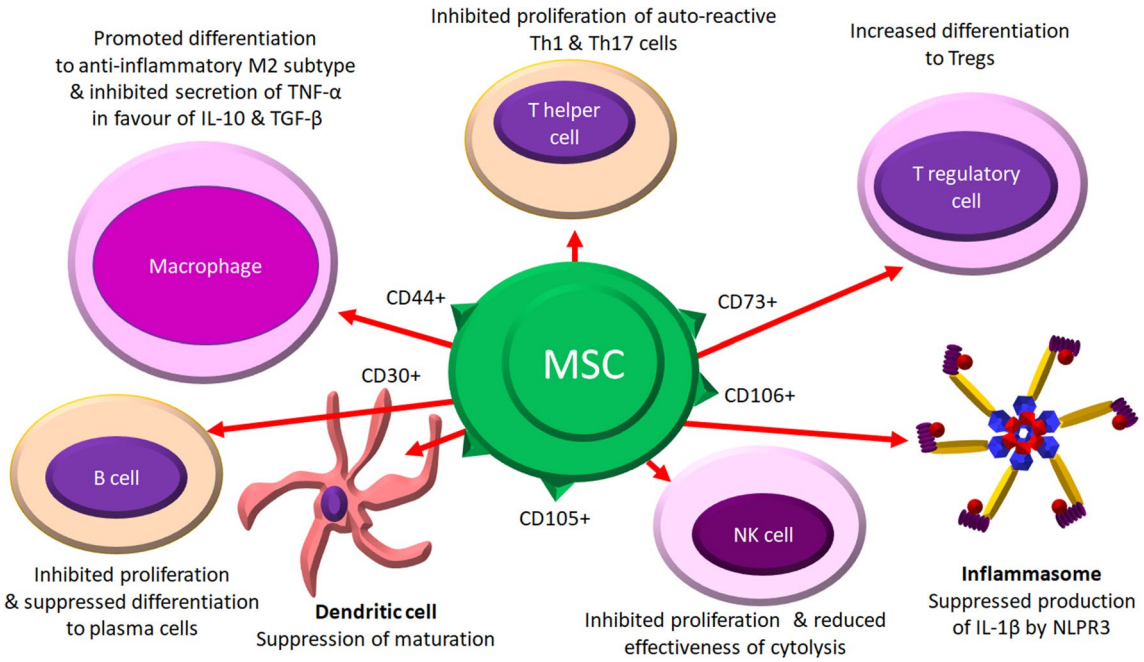

Fig. 1 Mechanisms of action of MSCs. *MSC* mesenchymal stem cell, *CD* cluster of differentiation, *Th* T helper cell, *Treg* T regulatory cell, *IL* interleukin, *TNF-α* tumor necrosis factor α, *TGF-β* transforming growth factor β, *NK* natural killer cell, *NLRP3* NACHT, LRR and PYD domains-containing protein 3

of $CD4^+CD25^+FoxP3^+$ regulatory T cells (Tregs), suppress maturation of dendritic cells, stimulate macrophage differentiation into anti-inflammatory M2 phenotype and reduce effectiveness of natural killer T cells (Abdelrazik et al. 2011; Ansboro et al. 2017). Moreover, in response to stimulation by IFN-γ, MSCs secrete soluble factors including prostaglandin-E2 (PGE_2), transforming growth factor (TGF)-β, indoleamine 2,3-dioxygenase (IDO), hepatocyte growth factor and IL-10 (Di Nicola et al. 2002; English 2013; Nemeth et al. 2009; Spaggiari et al. 2008; Uccelli and de Rosbo 2015). The specific role of each molecule was listed in Table 1.

Tissue source of MSCs is postulated to affect the immunosuppressive effects of MSCs. Specifically, BM-derived and adipose-derived MSCs appeared to have greater chondrogenic potential, whereas synovium-derived MSCs are more likely to differentiate into osteogenic lineages (Djouad et al. 2005). MSCs harvested from adipose tissue are reported to have greater impact on T cells and monocytes compared to BM-MSCs. In a study performed by Melief et al. (2013), application of adipose-derived MSCs resulted in higher level of functional suppression of peripheral blood mononuclear cells, stronger inhibition of dendritic cells formation and higher production of aforementioned cytokines. Additionally, adipose-derived MSCs are easier to be isolated and expanded. Thus, they seem to have the greatest capability of being included in new therapeutic strategies (MacFarlane et al. 2013).

Potential Role of MSCs in JIA

During a focal injury, MSCs tend to migrate to sites of local damage, demonstrating high motility and paracrine production of cytokines to improve the repair of damaged tissues (Wang et al. 2016). Subsequently, these cells promote angiogenesis and inhibit fibrosis (Norambuena et al. 2012). According to Swart et al. (2008), systemic administration of MSCs supported the healing of incisional wounds.

Table 1 Molecules secreted by mesenchymal stem cells after IFN-γ stimulation

Molecule	Role in immune response
PGE_2	iTregs
TGF-β	iTregs
IDO	Major factor in contact-dependent suppression of effector T cells
HGF	Mediator of expansion of myeloid-derived suppressor cells
IL-10	Inhibition of Th1-related cytokines

HGF hepatocyte growth factor, *IDO* indoleamine 2,3-dioxygenase, *iTregs* induction of regulatory T cells

While MSCs are normally present in human synovial fluid, their count is much lower in RA than in osteoarthritis. There is growing body of evidence that native MSCs in patients with autoimmune diseases might be impaired (Cipriani et al. 2013). Nie et al. (2010) reported early signs of senescence in culture of these cells in systemic lupus erythematosus patients. Likewise, MSCs harvested from RA patients manifest limited proliferation capacity, presumably due to decreased telomere length (Kastrinaki et al. 2008). Whole-genome analysis of synovial MSCs in RA patients and healthy donors performed by Hou et al. (2016) showed difference of expression in 4828 genes. Notwithstanding, despite their functional aberrations, MSCs seem to sustain their suppressive capability in vitro (Bocelli-Tyndall et al. 2007). According to Calkoen et al. (2013), MSCs from patients with systemic JIA did not show significant differences in anti-inflammatory effect when compared to healthy controls. Overall, administration of MSCs might improve a disease course of inflammatory arthritis.

Heretofore, clinical trials involving the MSC therapy were limited to patients with severe RA refractory to standard treatment. It might re-establish the systemic immune balance and produce better outcomes when given within the early phase of rheumatoid process before the development of sequelae (Ansboro et al. 2017). To date, there are no specific criteria assessing the effectiveness of using MSCs in rheumatoid diseases. Shalev-Malul et al. (2016) postulated that measuring of the overall inhibition level of effector T cells may be used as the functional biomarker of the effects of cell-based therapy in RA patients. Since the long-term results of MSCs are not fully elucidated yet, there are only a few published studies involving pediatric population (Table 2). Nonetheless, similarities in autoimmune background between RA and JIA allow to extrapolate the findings of reports on using MSCs in RA into pediatric patients with JIA.

In accordance with Shin et al. (2016), infusion of UC-MSCs generally down-regulated serum levels of TNF-α, IL-1β and IL-6. As MSCs secrete PGE_2, they effectively suppress NLRP3 inflammasome-mediated IL-1β secretion. Furthermore, they also disturb the balance between subtypes of macrophages in favor of anti-inflammatory M2 cells, which secrete, among others, IL-10 and TGF-β, and subsequently inhibit the production of TNF-α (Swidrowska-Jaros et al. 2016).

Clinical Studies

Most published clinical studies have used intravenous infusions of MSCs to control systemic inflammatory disease. Similarly, this kind of procedure may be considered for future use in children with sJIA (Calkoen et al. 2013).

Table 2 Clinical studies on using MSCs in patients with JIA

References	No. of patients	Subtype of MSCs	Way of administration	Results
Wang et al. (2016)	10	UC-MSCs	Intravenous (2 times with a 3-month interval)	↓DAS28 ↓WBC, ESR, CRP ↑Tregs ↓↓IL-6, TNF-α
Swart et al. (2015)	6	Not given	Intra-articular	↓JADAS ↓ESR in 3 patients*
Wakitani et al. (2011)	4	BM-MSCs	Intra-articular	No complications during a 6-year follow-up

* Preliminary results; *MSCs* mesenchymal stem cells, *UC-MSCs* umbilical cord-derived MSCs, *BM-MSCs* bone marrow-dervied MSCs, *JIA* juvenile idiopathic arthritis, *WBC* white blood count, *ESR* erythrocytes sedimentation rate, *CRP* C-reactive protein, *IL-6* interleukin 6, *TNF-α* tumor necrosis factor alpha, *JADAS* juvenile arthritis disease activity score, *DAS28* 28-joint disease activity score

Although, patients with oligoarticular JIA may get more benefits from local intra-articular administration. Intra-articular injection of $CD146^+$ UC-MSCs is reported to alleviate collagen-induced arthritis in mice through promoting chondrogenesis, suppressing activation of Th17 cells and inhibiting excretion of IL-6 (Wu et al. 2016). However, the authors did not observe the difference in production of anti-inflammatory IL-10 between $CD146^+$ and $CD146^-$ cells. A proof-of-concept clinical trial reported by Jo et al. (2014) involved the intra-articular injection of autologous adipose-derived MSCs in the osteoarthritic knee in adults. Function improvement without causing adverse effects has been noted. Furthermore, Park et al. (2016) proposed experimental overexpression of soluble receptor for advanced glycation end products to optimize immunoregulatory properties of adipose-derived MSCs.

Ten cases of JIA patients were treated in two time-points with intravenous infusion of UC-MSCs in a study conducted by Wang et al. (2016). Patients continued their conventional treatment within the follow-up period. Three months after first infusion, authors noted significant improvement of disease activity and laboratory tests results—decrease of white blood count, erythrocytes sedimentation rate and C-reactive protein, increase of Tregs and decline of TNF-α and IL-6—whereas no statistical difference between two assessed time-points was observed.

Intra-articular injection of autologous BM-derived MSCs in four children was reported by Wakitani et al. (2011). There were no complications observed during a 6-year follow-up study. Most recently, a phase II clinical trial has been proposed by Swart et al. (2015). Six children with JIA resistant to treatment with local prednisone, NSAIDs and methotrexate were set to be injected intra-articularly with allogeneic MSCs to study their immunosuppressive effects. The current midway report suggested a slight improvement of disease activity and magnetic resonance image.

Conclusions

Mesenchymal stem cells seem to deserve a regular place in therapeutic strategies of JIA as a rational alternative for patients who did not respond properly to non-invasive treatment. Intra-articular injection is specifically worth considering in patients with oligoarticular JIA, where local reduction of inflammation may outweigh benefits of long-term systemic therapy.

Consistent results of clinical trials are essential to eliminate unforeseen side effects and introduce MSCs into everyday practice of pediatric rheumatologists.

Acknowledgements This work was partially supported by the grant No. 503/8-000-04/503-81-002 from Medical University of Lodz, Poland.

Compliance with Ethical Standards

Conflict of interest Authors declare no conflict of interests.

References

Abdelrazik H, Spaggiari GM, Chiossone L et al (2011) Mesenchymal stem cells expanded in human platelet lysate display a decreased inhibitory capacity on T- and NK-cell proliferation and function. Eur J Immunol 41:3281–3290

Ansboro S, Roelofs AJ, De Bari C (2017) Mesenchymal stem cells for the management of rheumatoid arthritis: immune modulation, repair or both? Curr Opin Rheumatol 29:201–207

Bartholomew A, Sturgeon C, Siatskas M et al (2002) Mesenchymal stem cells suppress lymphocyte proliferation in vitro and prolong skin graft survival in vivo. Exp Hematol 30:42–48

Bocelli-Tyndall C, Bracci L, Spagnoli G et al (2007) Bone marrow mesenchymal stromal cells (BM-MSCs) from healthy donors and auto-immune disease patients reduce the proliferation of autologous- and allogeneic-stimulated lymphocytes in vitro. Rheumatology 46:403–408

Burt RK, Slavin S, Burns WH, Marmont AM (2002) Induction of tolerance in autoimmune diseases by hematopoietic stem cell transplantation: getting closer to a cure? Blood 99:768–784

Calkoen FG, Brinkman DM, Vervat C et al (2013) Mesenchymal stromal cells isolated from children with systemic juvenile idiopathic arthritis suppress innate and adaptive immune responses. Cyto-Therapy 15:280–291

Cipriani P, Carubbi F, Liakouli V et al (2013) Stem cells in autoimmune diseases: Implications for pathogenesis and future trends in therapy. Autoimmun Rev 12:709–716

Colter DC, Class R, DiGirolamo CM et al (2000) Rapid expansion of recycling stem cells in cultures of plastic-adherent cells from human bone marrow. Proc Natl Acad Sci USA 97:3213–3218

Contreras RA, Figueroa FE, Djouad F et al (2016) Mesenchymal stem cells regulate the innate and adaptive immune responses dampening arthritis progression. Stem Cells Int 2016:3162743

Deans RJ, Moseley AB (2000) Mesenchymal stem cells: biology and potential clinical uses. Exp Hematol 28:875–884

Di Nicola M, Carlo-Stella C, Magni M et al (2002) Human bone marrow stromal cells suppress T-lymphocyte proliferation induced by cellular or nonspecific mitogenic stimuli. Blood 99:3838–3843

Djouad F, Bony C, Haupl T et al (2005) Transcriptional profiles discriminate bone marrow-derived and synovium-derived mesenchymal stem cells. Arthritis Res Ther 7:R1304–R1315

English K (2013) Mechanisms of mesenchymal stromal cell immunomodulation. Immunol Cell Biol 91:19–26

Friedenstein AJ, Chailakhyan RK, Latsinik NV et al (1974) Stromal cells responsible for transferring the microenvironment of the hemopoietic tissues. Cloning in vitro and retransplantation in vivo. Transplantation 17:331–340

Giancane G, Consolaro A, Lanni S et al (2016) Juvenile idiopathic arthritis: diagnosis and treatment. Rheumatol Ther 3:187–207

Hahn YS, Kim JG (2010) Pathogenesis and clinical manifestations of juvenile rheumatoid arthritis. Korean J Pediatr 53:921–930

Hinks A, Cobb J, Marion MC et al (2013) Dense genotyping of immune-related disease regions identifies 14 new susceptibility loci for juvenile idiopathic arthritis. Nat Genet 45:664–669

Hou J, Ouyang Y, Deng H et al (2016) Whole-genome expression analysis and signal pathway screening of synovium-derived mesenchymal stromal cells in rheumatoid arthritis. Stem Cells Int 2016:1375031

Huang JL (2012) New advances in juvenile idiopathic arthritis. Chang Gung Med J 35:1–14

Jo CH, Lee YG, Shin WH et al (2014) Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: a proof-of-concept clinical trial. Stem Cells 32:1254–1266

Jorgensen C, Djouad F, Apparailly F et al (2003) Engineering mesenchymal stem cells for immunotherapy. Gene Ther 10:928–931

Kastrinaki MC, Sidiropoulos P, Roche S et al (2008) Functional, molecular and proteomic characterisation of bone marrow mesenchymal stem cells in rheumatoid arthritis. Ann Rheum Dis 67:741–749

MacFarlane RJ, Graham SM, Davies PS et al (2013) Anti-inflammatory role and immunomodulation of mesenchymal stem cells in systemic joint diseases: potential for treatment. Expert Opin Ther Targets 17:243–254

McInnes IB, Schett G (2007) Cytokines in the pathogenesis of rheumatoid arthritis. Nat Rev Immunol 7:429–442

Melief SM, Zwaginga JJ, Fibbe WE et al (2013) Adipose tissue-derived multipotent stromal cells have a higher immunomodulatory capacity than their bone marrow-derived counterparts. Stem Cells Transl Med 2:455–463

Nemeth K, Leelahavanichkul A, Yuen PS et al (2009) Bone marrow stromal cells attenuate sepsis via prostaglandin E(2)-dependent reprogramming of host macrophages to increase their interleukin-10 production. Nat Med 15:42–49

Nie Y, Lau C, Lie A et al (2010) Defective phenotype of mesenchymal stem cells in patients with systemic lupus erythematosus. Lupus 19:850–859

Noel D, Djouad F, Jorgense C (2002) Regenerative medicine through mesenchymal stem cells for bone and cartilage repair. Curr Opin Investig Drugs 3:1000–1004

Norambuena GA, Khoury M, Jorgensen C (2012) Mesenchymal stem cells in osteoarticular pediatric diseases: an update. Pediatr Res 71:452–458

Park MJ, Lee SH, Moon SJ et al (2016) Overexpression of soluble RAGE in mesenchymal stem cells enhances their immunoregulatory potential for cellular therapy in autoimmune arthritis. Sci Rep 6:35933

Petty RE, Southwood TR, Manners P et al (2004) International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 31:390–392

Pittenger MF, Mackay AM, Beck SC et al (1999) Multilineage potential of adult human mesenchymal stem cells. Science 284:143–147

Ravelli A, Martini A (2007) Juvenile idiopathic arthritis. The Lancet 369:767–778

Shalev-Malul G, Soler DC, Ting AE et al (2016) Development of a functional biomarker for use in cell-based therapy studies in seropositive rheumatoid arthritis. Stem Cells Transl Med 5:628–6321

Shin TH, Kim HS, Kang TW et al (2016) Human umbilical cord blood-stem cells direct macrophage polarization and block inflammasome activation to alleviate rheumatoid arthritis. Cell Death Dis 7:e2524

Spaggiari GM, Capobianco A, Abdelrazik H et al (2008) Mesenchymal stem cells inhibit natural killer-cell proliferation, cytotoxicity, and cytokine production: role of indoleamine 2,3-dioxygenase and prostaglandin E2. Blood 111:1327–1333

Swart J, Martens A, Wulffraat N (2008) Mesenchymal stem cells: a future for the treatment of arthritis? Joint Bone Spine 75:379–382

Swart J, Wulffraat N, Prakken BJ et al (2015) Mesenchymal stromal cell treatment in juvenile idiopathic arthritis: a pilot study [abstract]. Arthritis Rheumatol 67:3813–3814

Swidrowska-Jaros J, Orczyk K, Smolewska E (2016) Macrophages - silent enemies in juvenile idiopathic arthritis. Postepy Hig Med Dosw (Online) 70:743–750

Uccelli A, de Rosbo NK (2015) The immunomodulatory function of mesenchymal stem cells: mode of action and pathways. Ann N Y Acad Sci 1351:114–126

Verwoerd A, Ter Haar NM, de Roock S et al (2016) The human microbiome and juvenile idiopathic arthritis. Pediatr Rheumatol Online J 14:55

Wakitani S, Okabe T, Horibe S et al (2011) Safety of autologous bone marrow-derived mesenchymal stem cell transplantation for cartilage repair in 41 patients with 45 joints followed for up to 11 years and 5 months. J Tissue Eng Regen Med 5:146–150

Wang L, Zhang Y, Li H et al (2016) Clinical observation of employment of umbilical cord derived mesenchymal stem cell for juvenile idiopathic arthritis therapy. Stem Cells Int 2016:9165267

Wu CC, Liu FL, Sytwu HK et al (2016) CD146 + mesenchymal stem cells display greater therapeutic potential than CD146- cells for treating collagen-induced arthritis in mice. Stem Cell Res Ther 7:23

Zhang Y, Khan D, Delling J et al (2012) Mechanisms underlying the osteo- and adipo-differentiation of human mesenchymal stem cells. Sci World J 2012:793823