Biomedicine & Pharmacotherapy 104 (2018) 652–660

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Platelet rich plasma, stromal vascular fraction and autologous conditioned serum in treatment of knee osteoarthritis

Ali Fotouhi[a], Arash Maleki[a], Sanam Dolati[b,c], Ali Aghebati-Maleki[d], Leili Aghebati-Maleki[b,d,*]

[a] Department of Orthopedic Surgery, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[b] Department of Immunology, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[c] Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran
[d] Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

ARTICLE INFO

Keywords:
Cell therapy
Osteoarthritis
Platelet-rich plasma
Stromal vascular fraction
Autologous conditioned serum

ABSTRACT

Osteoarthritis (OA) is a multifactorial chronic disease, causing several problems on patients, hygiene and community care systems. Conventional therapies, such as non-pharmacological mediations, systemic drug treatment and intra-articular therapies are applying previously; however, controlling and management approaches of the disease mainly remain insufficient.

Injections of intra-articular therapies directly into the joint evade conservative obstacles to joint entry, rise bioavailability and minor systemic toxicity. Current progresses in osteoarthritis management have designed better diversity of treatment approaches. Innovative treatments, such as autologous blood products and mesenchymal stem cells, are in progress. Platelet-rich plasma (PRP) is one of the several novel therapeutic approaches that stay to progress in the field of orthopedic medicine. Stromal vascular fraction (SVF) comprises a lesser amount of mesenchymal stem cells and is a treatment for OA and cartilage damage. Based on novel opinions, an innovative therapy by autologous conditioned serum (ACS) from the whole blood was settled. The inoculation of ACS into tissues has revealed clinical efficacy for the treatment of osteoarthritis and muscle injuries.

Here, we make available historical perspective of PRP, SVF, and ACS and the other existing researches on using PRP, SVF and ACS for the treatment of knee OA. In conclusion, in current years, OA stem cell therapy has rapidly progressed, with optimistic consequences in animals and human studies. Additionally, PRP, SVF and ASC injection seem to be accompanied with numerous favorable results for treatment of patients with OA.

1. Introduction

Osteoarthritis (OA) is a chronic debilitating disease of synovial joints, influencing the cartilage, ligaments, joint lining, and surrounding bones [1,2]. Knee OA is described by articular cartilage degeneration, principally owing to alterations in chondrocytes from catabolic function. The incapability of chondrocytes to tolerate this tension prevents the extracellular matrix (ECM) formation and leads to production of intermediaries, such as matrix metalloproteinases (MMPs), nitric oxide (NO), and prostaglandin E2 (PGE2), resulting in matrix degradation [3,4]. Interleukin (IL)-1 might have a catabolic effect, causing cartilage deterioration. High levels of C-reactive protein (CRP) modestly but remarkably predict those whose disease will progress [5]. Little mitotic activity and insistent metabolic imbalances in chondrocytes lead to irretrievable articular cartilage impairment, providing an environment with a restricted reparative reactions [6]. Likewise, elevated systemic inflammatory markers have a role in joint destruction. Biochemically, OA patients present an enhanced amount of water and modifications in proteoglycans (elevated chondroitin/keratin sulphate ratio).

The aetiology of OA can be primitive, due to intrinsic deficiency or secondary, because of trauma, infection [7]. The risk factors related to OA are generally personal issues, including age, gender, obesity, heredities, race/ethnicity, and dietary regimen and joint-level factors, such as damage, physical activity, type of occupation that involves joints, and muscular power [8,9]. Elements accompanying with OA have also been categorized as those that affect OA development, such as age, gender, job, weight, and those in relation to disease progression, consisting of weight and nutrition [9–11]. Age is the main independent risk factor of OA; it is becoming obvious that aging makes changes in the musculoskeletal system, contributing to the progress of OA in line with other factors [12]. There is minute or no cell division or cell death in

* Corresponding author at: Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
E-mail address: aghebatil@tbzmed.ac.ir (L. Aghebati-Maleki).

https://doi.org/10.1016/j.biopha.2018.05.019
Received 20 February 2018; Received in revised form 30 April 2018; Accepted 7 May 2018

adult articular cartilage, therefore, chondrocytes are thought to be long-lived cells. Aging extremely changes chondrocyte function and matrix structure.

It appears to be an age-related reduction in the number of chondrocytes in articular cartilage [13]. Telomere shortening, can be caused by stress-induced senescence, which seems to be the much probable mechanism in cartilage damage, in which chronic inflammation and oxidative stress are further offending factors [14]. Increased production of cytokines and growth factors can contribute to tissue aging, through triggering the matrix degradation and decreasing matrix synthesis and repair [12]. Chondrocytes become less responsive to growth factors with aging, thus additional reducing matrix synthesis and repair. Oxidative stress plays an important role in aging and in the link between aging and OA [15,16]. Increased levels of reactive oxygen species (ROS) may also contribute to the reduced sensitivity of chondrocytes to Insulin-like growth factor 1 (IGF-I) [17].

It is well known that OA is a disease with a genetic susceptibility [18]. Genes related to OA are linked to those that are involved in the process of synovial joint mechanobiology. Mutations in these genes could directly cause OA [19]. They are mainly genes that encode proteins and mediators involved in the pathways like bone morphogenetic proteins (BMPs), transforming growth factor beta (TGF-β), the wingless-type (Wnt), thyroid pathway, and apoptotic and mitochondrial DNA (mtDNA) damage-related molecules [20]. A genetic variant in *growth differentiation factor 5* (*GDF5*) has been considered as the strongest genetic connotation with OA. Moreover, genetic variation also influences the joint replacement therapy on account of aseptic loosening [20].

The prevalence of hand, knee, or hip joint OA has enhanced from 21 million in 1995 to an expected 27 million amongst United States (US) adults [21]. OA can cause a decreased quality of life (QoL) and greater death rates [22]. There is no straightforward and precise blood test for the diagnosis of OA. Even though OA can be diagnosed clinically, the significance of imaging of OA in diagnosis and longitudinal evaluation of this chronic disease are well acknowledged by both rheumatologists and radiologists [23]. While basic radiographs confer the gold standard and preliminary examination imaging approach for OA diagnosis, magnetic resonance imaging (MRI) and multi detector computed tomography (MDCT) have come to be necessary for OA classification and follow-up assessment in research [24–26]. Along with MRI, kinematic and weight-bearing evaluations of the peripheral joints are currently performed by four-dimensional computed tomography (4DCT) and cone-beam CT (CBCT) [27,28]. Besides advanced cross-sectional imaging techniques, positron emission tomography (PET) examinations may reveal fundamental metabolic activities correlated with synovial inflammation in OA [27]. Radiographs remain the imaging modality of choice in OA in clinical practice. In addition, MRI is being used for detection and quantification of various OA features and has been considered as a vital investigation tool. 4DCT and CBCT have special uses once a diagnosis of fundamental motion anomaly or dynamic variations in weight-bearing condition is supposed. Clinical use of ultrasound and PET for OA imaging has been less-recognized compared with radiography and MRI [29].

2. Treatment of osteoarthritis

The specifications of OA demonstrate that there is a multi-tissue, multi-cell involvement that contribute to the development of the disease. This implies a multi-treatment attitude that distinguishes the variety of the fundamental manifestations and signs in the OA syndrome [30]. Recent treatment choices are according to a composition of patient learning, physical exercise, knee braces, and shoe orthotics; nonsteroidal anti-inflammatory drugs (NSAIDS) to mitigate pain and inflammation; intra-articular inoculations of hyaluronic acid (HA); corticosteroid injections; ultrasound-guided and fluoroscopic-guided nerve block and radio frequency ablation processes; weight regulators; and, ultimately, aggressive joint replacement surgery [30]. Weight controlling and physical therapy are too advantageous [31]. Corticosteroid injection decreases synovitis and, therefore subside the pain in OA patients.

Endogenous hyaluronan is found in the synovial fluid and is involved in its viscoelasticity, and play a role in sustaining the tissue hydration and protein homeostasis through inhibiting great fluid movements and by performing as an osmotic buffer [31]. These types of treatments are typically palliative and only cause relief of disease symptoms and pain, preventing cartilage injury and devastation of other joint tissues [32].

Surgical treatments for knee OA include arthroscopy, cartilage repair, osteotomy, and knee arthroplasty [33]. The suitability of these techniques is determined by numerous factors, scuh as the location and stage of OA, comorbidities, and patients discomfort. Arthroscopic lavage and debridement are repeatedly carried out, but do not have positive impressions in the disease development [33].

Joint arthroplasty is a well-accepted, harmless, and profitable technique for treatment of progressive knee OA. Because of its irreparable nature, joint arthroplasty is suggested only in patients, for whom other treatment modalities have been unsuccessful or contraindicated [33,34]. Permanence of prosthetic mechanisms is restricted to about 15–20 years but endurance of unicompartmental knee arthroplasties (UKA) is generally inferior [34]. Therefore, arthroplasties should be circumvented in patients younger than 60 years. If OA is limited to one compartment, UKA or unloading osteotomy can be considered, then Total arthroplasty of the knee (TKA) with or without patellar resurfacing is observed [35]. Surgical treatment comprising fractional or complete joint knee arthroplasty and, infrequently, osteotomies are held in reserve to be carried out after failure of conventional treatments [36].

All of these methods are restricted to the repair of focal injuries. Consistent with organized clinical trials, surgical treatments have restricted long-term influence on the treatment of OA [37,38].

The use of Platelet-rich plasma (PRP), mesenchymal stem cells (MSCs), and blood products in orthopedics have improved disease course exponentially over the previous few years because of its autologous nature, proposed efficacy, and absence of side-effects [39]. PRP and Stromal vascular fraction (SVF) are progressively used frequently to treat a range of knee osteoarthritis, though its efficacy is dubious [40,41]. The cartilage is an exclusive avascular and aneural tissue that has restricted capability of self-repairing after being injured [42,43]. The aim of this article is to discuss about use of PRP, SVF and ASO to treat OA with the emphasis on the probable role of PRP and SVF in the properly restricted pharmacological approach.

2.1. Platelet-rich plasma

Platelet-rich plasma (PRP) has been used from 1950s, currently, the musculoskeletal effects of PRP have been the emphasis of substantial attention, particularly in orthopedics [44,45]. PRP is autologous plasma augmented with platelets that could be released after triggering wiht growth factors and cytokines [46,47]. The platelet concentration in PRP is different 5-fold from 300,000/mm^3 to over 1,500,000/mm^3 and these differences are as a result of dissimilarities in donors, total blood volumes, mediators designed for platelet stimulation (thrombin or calcium-chloride), amount of centrifugations, and freezing method of product [48–50]. Direct injection of PRP inside the joint could control the inflammatory response and cause healing over a long period [51,52]. PRP prevents the nuclear factor (NF)-κB cascade, by inhibiting the stimulation of NF-κB through IκBα, by avoiding the activation of NF-κB target genes [53]. NF-κB is stimulated by IL-1β in chondrocytes acquired from OA patients and obstructs the synthesis of anabolic pathways related genes, such as type II collagen and aggrecan [53,54]. Growth factors components in PRP have special effects such as anti-inflammatory properties and also could decrease pain. PRP comprises a