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Future trends in Orthobiologics for use in Osteoarthritis Knee

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Abstract

The focus has now shifted to newer biological approaches, after the success seen with use of Platelet rich plasma (PRP) and hyaluronic acid (HA) in early osteoarthritis of knee. This search for new approaches has come in due to the fact that effects of both PRP and HA tends to fade with time. Latest strategies have been tried with PRP like combining PRP with HA and other biomaterials, Use of allogeneic PRP and intra osseous PRP application for targeting subchondral pathology in OA. We also look at the role of autologous conditioned serum, alpha 2 macroglobulin and gene therapy in OA knee. In this review we discuss various of these strategies that have been explored and shown promising preliminary results.

Keywords: Orthobiologics, osteoarthritis, Knee joint

Introduction

Knee osteoarthritis has been a challenge for Orthopaedicians since time immemorial. Earlier the treatment options were limited to conservative management followed by total knee replacement as the end result. The last decade or so has been a major turning point in this regard. There has been a flurry of options to offer a middle path, especially in early osteoarthritis. Viscosupplementation and Platelet rich plasma (PRP) have been front runners in this race and have proven their efficacy time and again. But these treatment options have been plagued by the fact that the results these produce are for limited time and have limited efficacy. Is there anything beyond these options? In this article, we discuss various modalities to improve the efficacy of current frontline treatment options and new biological modalities in treatment of knee OA.

PRP and HA

PRP and hyalarunic acid (HA) are currently the most popular treatment options that have shown to have a disease modifying effect on early OA knee [1,2]. HA and PRP have been shown to act by different mechanisms of action by targeting different pathways inside the joint, and hence there is an evolving thought that the combined use of them can be synergistic. Apart from the main viscoelastic and lubrication properties [3], HA also exerts an anti-inflammatory effect on the synovium and anti-fibrotic andchondro-protective effects on the cartilage [4]. PRP also exerts a chondroprotective effects on cartilage[5], anti-inflammatory effect on synovium [6] and regulates the apoptotic pathway[7]. A number of in vitro as well as well as clinical studies have demonstrated the synergistic effects of combination of PRP and HA. Anitua et al.,and Marmotti et al.[8,9]have shown that PRP with HA is synergistic, by enhancing the migratory potential of fibroblasts in in vitro studies. Chen et al [10] have demonstrated that combination may increase cartilage growth apart from the anti-inflammatory effect in their in vitro study. Son et al [11] in their study noted better chondrocyte survival, cell count and cell proliferation with PRP encapsulated in Gelatin-HApolymer loaded in biphasic calcium phosphate. In contrast; Russo et al [12]while assessing the viscoelastic and biological properties of different combinations of PRP and HA in vitro, found that addition of PRP to HA leads to poor viscoelastic and lubrication properties due to dilutional effect on HA. It was also noted that proliferation rates were higher in PRP alone than in PRP an HA combination.

A number of clinical studies in knee OA have used the combination of PRP and HA. Lanaet al[13] in their RCT on early OA of knee on 105 patients compared PRP, HA and HA & PRP. They noted that the combination had better pain relief and decreased functional limitation at 1 year compared to HA and increased physical function compared to PRP at 1 and 3 months. Papalia et al[14] in their study on 60 patients with early OA knee compared 3 injections of HA with 3 injections of PRP +HA at weekly interval. They noted that VAS scores were significantly better at 3,6 and 12 months and KOOS scores were significantly better at 3 and 6 months in the combination group. Yu et al[15] in their RCT compared combination of PRP and HA with PRP, HA and placebo. They noted that PRP + HA combination treatment significantly improved arthralgia, reduced humoral and cellular immune responses and promoted angiogenesis as compared to PRP or HA alone.

Another interesting suggestion by some authors in improving the results of the combination is to use PRP and HA one after the other at a gap of few weeks and not simultaneously [16]. Combination of PRP and HA appear to be promising due to different mechanism of actions which appear to be synergistic, but further studies are needed to define the schedule, dosage and ideal concentration of PRP and HA.

Biomaterials and PRP

It has been proven in multiple studies that PRP works in OA knee, however the effects, seem to fade over time. This is because, the primary effects of platelet growth factors

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occur during the first 8 days (approximately the half-life of platelets). This has led many authors to use multiple PRP injection at weekly, biweekly, monthly injections to maximize the effects. However, this adds to the overall cost and the laboratory burden. This problem has led some authors to think of combining biomaterials with PRP, where in the biomaterials can act as carriers and increase the efficacy and lead to a sustained release of growth factors over time.

PRP has been used with a number of biomaterials like gelatin hydrogel, chitosan, PLGA (poly lactic-co-glycolic acid) mesh and β-tricalcium phosphate in various in vivo and invitro studies and have been shown to be significantly better than PRP for various application like healing of bone defects, wound healing and osteoarthritis knee. [17-20]Saito et al [17]used gelatin hydrogel impregnated with PRP in a rabbit model of knee osteoarthritis. They noted that gelatin hydrogel PRP resulted in significantly better results compared when compared to PRP and had preventive effects against OA knee.

Another biomaterial which has been of particular interest has been chitosan. Chitosan is a carbohydrate molecule which has structural similarities to cellulose. It consists of two repeating units, N-acetyl-d-glucosamine and d-glucosamine, linked by (1-4)-β-glycosidic linkage [21]. The combination of PRP and chitosan has been studied. Chitosan has been of particular interest and have been used widely with PRP for various applications. Depres-Tremblay et al [22] noted Chitosan PRP hybrid clots to have decreased retraction, higher cumulative release of PDGF and EGF and higher cell recruitment and granulation tissue synthesis compared to PRP clots. Chitosan also has been shown to increase platelet adhesion and aggregation. It also increases expression of glycoprotein IIIa expression and increases release of growth factors[23]. Dwivedi et al [24]in their study on rabbit created chronic defects in cartilage surgically and used bone marrow stimulation (BMS) with PRP or freeze dried Chitosan with PRP. They noted that animals treated with BMS+ Chitosan PRP had better articular scores at 8 weeks than BMS +PRP. They hypothesized Chitosan/PRP implants reside for several weeks in vivo and to have significant bioactivity, in contrast to PRP implants which are quickly degraded in a day. Segundo et al [25] in their study on surgically created cartilage defects in rabbit knees noted that composite base of PRP, hydroxyapatite and chitosan promoted better bone healing and cartilage healing compared to control. With emerging pre-clinical evidence, it is clear that the idea of use of biomaterials with PRP certainly has merit. However clinical evidence is lacking and it is to be seen in future, if the results can be translated to significant clinical benefit.

Intra articular and intra osseous application of PRP

The pathophysiology of Osteoarthritis and the involvement of synovium and cartilage is well known and has been the traditional target for intraarticular therapy. However, of late the role of subchondral bone in the pathogenesis of OA is becoming more clear and bone turnover, microfractures, marrow edema, osteoblast-osteoclast interaction is an emerging concept [26,27]. The most common method of application of PRP has been intra articular but this does not address the pathology in the subchondral bone and bone marrow. An emerging trend among surgeons is the use of Intra osseous injection of PRP along with intra articular PRP for Knee OA. The idea is that that the intraarticular injection will address the synovium the superficial layer of cartilage and synovial fluid while the intraosseous injection will address the deep zones of articular cartilage and the subchondral bone. Sanchez et al were the first to describe the technique and the concept of intra osseous delivery of PRP [28]. In an observational study on patients with severe knee osteoarthritis, they noted that the combination of intraarticular(IA) and intraosseous PRP was better than IA PRP at 6 and 12 months follow-up, but not at 2 months.[29] Su et al in their study on early OA knee noted that intraosseous and intraarticular PRP combination had superior VAS and WOMAC scores compared to intra articular PRP and HA alone at 1,3,6,12,18 months. [30]. Intra Osseous PRP technique thus appears very promising but further studies with large sample sizes are needed to establishthe true potential.

Allogenic PRP

Multiple studies have supported the use of allogeneic PRP in animals and have shown it to be safe, reliable and more consistent reliable with respect to concentration of platelets [31, 33]. Kastenet al [31] used allogeneic PRP and calcium deficient hydroxyapatite with or without mesenchymal stem cells. They showed that allogeneic PRP was effective in healing of radial diaphyseal bone defects in rabbits. No immunologic reactions were noted either clinically or histologically. They hypothesized that the lack of immunogenicity may be due to the fact that platelets do not express immunologically relevant surface antigens such as HLA 2. Crepper et al [32] in their in vitro study evaluated the effect of autologous and allogeneic PRP on fibroblast migration and noted no significant difference between the two in their cell function. Zhang et al 33 in their study on rabbits demonstrated that allogeneic PRP could be effectively used for treatment of bone defects. They noted that allogeneic PRP provided a more consistent product thus eliminating inter subject variation and also decreased the burden on the subjects. No adverse immune reactions were noted. Chouhan et al [34], in an recently published study on guinea pig knee OA model, also used allogenic PRP and reinforced its safety and efficacy. Where on one side the unique selling point of PRP was that it is made from one's own blood, but a lot of patients miss out due to the stringent exclusion criteria for preparation of PRP. However, these patients may benefit from the use of allogenic PRP. Bottegoni et al35 included 60 elderly patients affected by hematological disorders with mild to moderate OA knee in their study. They gave 3 injections of 5 ml homologous PRP at 2 weekly intervals. They did not note any severe adverse events. They also noted statistically significant improvement at 2 months follow up followed by significant worsening at 6 months follow up. Results were worst in patients over 80 years of age and those with bone attrition. They concluded that homologous PRP had an excellent safety profile but only a short clinical improvement. Further studies are needed in this field to substantiate these findings.

Autologous conditioned serum(ACS), Autologous Protien solution (APS) and knee Osteoarthritis

ACS and APS are blood based products which are based on the production of Interleukin 1 receptor antagonist protein (IRAP). Interleukin 1 (IL -1) has been known to be one of the major inflammatory makers of OA knee [36]. IL1 ra thus produced, when injected does not allow interleukin 1 to act, thus decreasing inflammation of the joint Autologous conditioned serum (ACS) is based on the principle that whole blood when incubated with medical grade glass beads coated with chromium sulphatefor 24 hours leads to the formation of Interleukin 1 receptor antagonist [36].

There are commercially available kits to prepare ACS. The ACS Orthokine (Orthogen, Düsseldorf, Germany) &Arthrokinex (Oklahoma City, Oklahoma) follow similar protocols. A total50 mL of venous blood is withdrawn in a syringe containing CrSO4-coated glass beads [40,41,44].The blood is then incubated for 24 hrs at 37 degrees Celsius. This followed by centrifugation for 10 minutes, after which the supernatant is aliquoted into 2 ml portions and frozen -20 degrees Celsius[36].

Baltzer et al [37] in their RCT on 376 patients used Orthokine ACS and compared it with hyaluronic acid and saline placebo. They concluded that ACS had better functional and pain scores at 7,13,26 and 104 weeks compared to HA and saline. The frequency of adverse events in ACS group was similar to saline. Similar positive results were published in a randomized study by Yang et al. [38] on 176 patients with OA of the knee, and by Baselga and Hernandez in a non-blinded 2-year prospective study [39].

Though ACS has given promising results but it still has not gained the popularity which it deserves. Long and cumbersome process involved in preparation, requirement of 6 injections at weekly intervals are some reasons for non-popularity. May et al [40] in their in vitro study have suggested that PRP instead of whole blood may be used for generation of ACS.The primary purpose of their study was to determine the minimum time required to produce more than 6ng IL-1ra while also producing detectable levels of sTNF-RI as both these are important for the desired effect. The results were promising as they demonstrated that neither time nor temperature significantly effected the IL-1ra production and that with shorter incubation time, same desired effects could be attained. This could significantly reduce the time of production of ACS [40].

Barreto et al [41] devised their protocol for preparation of ACS with a shorter incubation period of 30 min. They collected 60 ml blood with 3 ml ACD and it was centrifuged (3200rpm for 15 min). The resultant PRP and PPP were transferred and incubated for 30 min with medical grade beads. This was followed with a second spin (2000rpm for 3.5 min) which yielded the ACS product (Arthrokinex). It yielded a total of 6 injections collected in 6 syringes with 1 ml each. In their clinical trial on 100 patients [42], they injected 1 ml at the same day and stored the rest at -20 degree C. The other injections were received on day 7, 14, 90, 180, and 270. Compared to baseline, a total of 84% of patients reported better pain control at 6 months with 91% reporting improvement at 12 months (38). However, the study did not have a control arm.

Another product, nSTRIDE APS injection (Zimmer Biomet) can be injected immediately after preparation and they recommend only a single injection. In their procedure, 60 mL of anticoagulated blood yielded is put into the nSTRIDE Cell Separator and centrifuged once for 15 minutes at 3,200 rpm, after which the plasma is removed. The remaining cell solution is injected into the nSTRIDE Concentrator containing polyacrylamide beads, centrifuged once for 2 minutes at 2,000 rpm, and extracted into the administered treatment syringe [36].Kon et al [43] in their study on RCT on 46 patients compared APS with saline placebo and followed up patients at 2 weeks, 1,3,6 and 12 months. They established the safety profile and found no difference in adverse effects between these 2 groups. There was no difference between the VAS scores at any time point. At 12 months the WOMAC pain score was significantly better than saline placebo. At 12 months the APS group reported significant reduction in bone marrow lesion size on MRI and osteophytes in central zone. They concluded that both APS and saline injection provide significant pain relief over course of study with differences becoming apparent at 6 and 12-month time points. Few case series have also shown positive effects of APS nSTRIDE kit[44,45].

In conclusion, Interleukin 1 receptor antagonist products (IRAP) have the potential of providing a disease modifying solution to osteoarthritis. ACS has been clearly shown to be better than saline and HA. However, no studies comparing PRP with ACS are available. The use of PRPfor production of ACS also is a promising idea and an evolving trend. However, the data is still preliminary and there is a need for good RCT to establish their true role.

Alpha 2 macroglobulin

Alpha 2 macroglobulin (A2M) is homotetrameric glycoprotein which is present in serum and synovial fluid of all healthy individuals [46].It is a protease inhibitor which helps to decrease harmful proteases like ADAMTS-1, ADAMTS-4,ADAMTS-5, ADAMTS-7, and ADAMTS-12 in a dose dependent manner [47, 48]. Additionally they are also known to decrease cytokine induced collagenases up regulation by trapping IL-1β and TNF-α.[49]. A few commercial kits are available for concentration of A2M from patient's blood. A2M is a major component of platelet rich plasma and is believed to be one of the major contributors towards effect of PRP [50].Prominent amongst these is Autologous Platelet Integrated Concentration (APIC) kit, developed by Cytonics (West Palm Beach, Florida) [49]. It is an office based procedure and requires less than an hour to make.

There are many animal studies which have shown the positive effects of A2M in osteoarthritis models in animals. Wang et al[51] in their study on posttraumatic osteoarthritis in rats analyzed the effect of A2M. They noted that synovial fluid of rats injected with alpha 2 microglobulin had significantly reduced amount of MMP 13 protein which is known to cause osteoarthritis. Cuellar et al[52] studied OA progression following Anterior cruciate ligament transection, in white rabbits. The treatment group rabbits received an intra-articular injections of autologous platelet integrate concentrate (APIC) on days 1, 4, and 14 post ACLT. They noted that the control group had significantly more femoral and tibial degeneration than the treatment group. They also found that A2M levels were 5 to 10 fold higher in the treatment group than the control group.

The rationale for use in OA Knee is that A2M is supposed to be a scavenger molecule which traps all the deleterious catabolic and inflammatory proteins called proteases which are found in the synovial fluid. The final pathway of OA degradation process is through these proteases and hence by targeting them the desired effect could be achieved. Theoretically, A2M being a plasma protease inhibitor appears to be an important therapeutic agent for acute flares in OA as that is the phase where proteases have high concentration. However, most of the data are preliminary and clinical trials are underway.

Gene therapy and OA knee

The major limitation with all the injectable options discussed so far is that they have a time bound effect and with time, as the effect fades, there will be relapse. Osteoarthritis on the contrary is an ongoing process which is expected to progress. An ideal therapy is one which will enable in a sustained supply of required mediators (growth factors, cytokines) to provide an overall anabolic environment favorable for cartilage regeneration and Joint modulation. This is

where gene therapy finds its place in OA management. By introduction of certain genes which can modulate positive environment within joint, a long term effect may be obtained.

The concept of using gene therapy in osteoarthritis is based on the principle that expression of certain genes in the lesion can help in its repair. There are 2 ways to transfer genes for expression, in vivo and ex vivo. In in vivo method, the vector and transgene are introduced directly into the joint. In ex vivo methods the vector is introduced into chondrocytes /cells and these cells are than re introduced into the joint [53].

A number of animal studies have shown gene therapy to be effective in small as well as large animals. Nixon et al [54] in their study on mouse and horse knee OA model used helper-dependent adenovirus (HDAd) mediated intraarticular gene therapy for interleukin-1 receptor antagonist (IL-1Ra)gene. They noted significant improvement in cartilage volume, cartilage surface and bone surface in mouse.In the horse OA model, HDAd–IL-1Ra therapy significantly improved lameness parameters, indicating efficient symptomatic treatment. Macroscopic cartilage and synovial improvement was noted. They were able to demonstrate the safety and effectiveness of the treatment with an HDAd-expressing IL-1Ra. Phase I clinical trials are currently underway in knee osteoarthritis based on IL 1Ra based gene therpy [55].

Lee et al [56] in their RCT on 54 patients who either received TGF beta 1 expressing chondrocytes or placebo and followed up the patients at 4, 12 and 24 weeks, They found significant improvement with respect to IKDC scores and VAS scores in the treatment groups. However, WOMAC score and KOOS score were not significantly better. One patient has an anaphylactic reaction to the preservative medium and no other significant adverse effects were noted.

In a phase II multi center, double blind, placebo controlled randomized study involving 102 patients to determine the efficacy and safety of genetically engineered allogeneic human chondrocytes expressing TGF-β1 (GEC-TGF-β1) in patients with grade 3 chronic degenerative joint disease of the knee, Cherian et al [57] noted significant improvement in GEC-TGF-β1group than placebo in terms of IKDC and VAS scores at 12 weeks and 52 weeks post injection.

Kim et al [58] in their RCT(Phase 3 trail) on 163 patients in kellgrenlawrence grade 3 OA compraredTissueGene-C (TG-C) or Invossa, (a cell and gene therapeutic for osteoarthritis consisting of non-transformed and transduced chondrocytes (3:1) retrovirally transduced to overexpress transforming growth factor-b1) with placebo. The treatment group had significant improvement over placebo in terms of IKDC and VAS scores at 26,39 and 52 weeks. WOMAC and KOOS scores also improved in the treatment group over placebo. The treatment group patients also showed trend towards thicker cartilage and slower growing rates of subchondral bone. Serum C-terminal telopeptide of type I collagen (CTX-I) were significantly lower in the treatment group. No significant adverse events were noted. These studies show the great potential of TG- C or Invossa to be a disease modifying drug for osteoarthritis.

Gene therapy definitely holds promise and appears to be the only disease modifying treatment option for OA knees. South Korea in fact has approved gene therapy for OA knee treatment [59,60] on 12 July 2017.

PEARLS OF WISDOM

- Knee osteoarthrosis is an age-old disease which needs a fresh perspective to prevent or retard disease progression.
- Interleukin 1 receptor antagonist products like autologous conditioned serum (ACS) and autologous protein solution (APS) have been approved for intra-articular use and have shown early promise.
- Alpha 2 macroglobulin is a protease inhibitor which has shown early promise in animal studies and is another potential biological therapy.
- Gene therapy is the next frontier which holds the promise of providing an actual disease modifying solution for knee OA which is not dose dependent and possibly free from the vagaries of orthobiologics.
- Cost of therapy, compliance, confidence in safety and ethical consideration of these products are problems to be sorted out.
- Good data from randomized controlled trials to support or disprove these newer therapies are needed before any recommendations can be made for more widespread use.

Conclusions

OA Knee still is a major challenge to treating physicians and the research scientists are in search of the holy-grail to prevent Knee degeneration which could truly halt the disease process. However, we are nowhere near to it though our understanding of the complex problem is evolving. The existing products and the upcoming products mainly tend to provide symptomatic relief by targeting at various sites of catabolic and inflammatory pathways which explains the positive clinical results obtained.

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