A Randomized Clinical Trial Evaluating Plasma Rich in Growth Factors (PRGF-Endoret) Versus Hyaluronic Acid in the Short-Term Treatment of Symptomatic Knee Osteoarthritis

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Purpose: This multicenter, double-blind clinical trial evaluated and compared the efficacy and safety of PRGF-Endoret (BTI Biotechnology Institute, Vitoria-Gasteiz, Spain), an autologous biological therapy for regenerative purposes, versus hyaluronic acid (HA) as a short-term treatment for knee pain from osteoarthritis. **Methods:** We randomly assigned 176 patients with symptomatic knee osteoarthritis to receive infiltrations with PRGF-Endoret or with HA (3 injections on a weekly basis). The primary outcome measure was a 50% decrease in knee pain from baseline to week 24. As secondary outcomes, we also assessed pain, stiffness, and physical function using the Western Ontario and McMaster Universities Osteoarthritis Index; the rate of response using the criteria of the Outcome Measures for Rheumatology Committee and Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative (OMERACT-OARSI); and safety. **Results:** The mean age of the patients was 59.8 years, and 52% were women. Compared with the rate of response to HA, the rate of response to PRGF-Endoret was 14.1 percentage points higher (95% confidence interval, 0.5 to 27.6; $P = .044$). Regarding the secondary outcome measures, the rate of response to PRGF-Endoret was higher in all cases, although no significant differences were reached. Adverse events were mild and evenly distributed between the groups. **Conclusions:** Plasma rich in growth factors showed superior short-term results when compared with HA in a randomized controlled trial, with a comparable safety profile, in alleviating symptoms of mild to moderate osteoarthritis of the knee. **Level of Evidence:** Level I, randomized controlled multicenter trial.

Osteoarthritis (OA) is an heterogeneous disease that affects the structures of the joints. It has become one of the most common painful conditions affecting adults and the most frequent cause of mobility disability in the United States and Europe.[1] The incidence of OA is rising, influenced by the aging population and the epidemic of obesity.[2] Recent estimates suggest that symptomatic knee OA affects 13% of persons aged 60 years or older and a total of 20 million Americans, a number that is expected to double over the next 2 decades.[3]

Unfortunately, there are currently no agents available that can halt OA progression and reverse any existing damage. Analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) have suboptimal effectiveness, and there are some concerns regarding their safety, in light of the well-described gastrointestinal and cardiorenal side effects.[4] Current therapeutic approaches focus on developing less invasive procedures and applying them earlier

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in the disease when the structural changes of OA may be prevented or delayed.[5]

Synovial hyaluronic acid (HA) is a high–molecular weight glycosaminoglycan that acts as a fluid shock absorber, protecting cells and the intracellular collagen network from mechanical stress. The purpose of intra-articular injections of HA is to return the lost viscoelasticity to the joint, being frequently applied with some good results,[6] although several contradictory findings have also been reported.[7] Results from a clinical trial involving 306 patients showed that at the 40-month visit, significantly more patients responded to intra-articular injections of HA compared with placebo in the management of knee OA symptoms ($P = .004$).[8] Furthermore, a recent meta-analysis including 54 trials and involving more than 7,500 patients has also provided information about the therapeutic trajectory of HA for knee OA. Interestingly, HA was found to be efficacious by 4 weeks, reaching its peak effectiveness at 8 weeks but exerting a residual detectable effect at 24 weeks.[9]

Recent data support the application of platelet-rich plasma products as an effective and safe method in the treatment of the initial stages of knee OA.[10] Some growth factors present in platelet-rich plasma products, including transforming growth factor β, platelet-derived growth factor, and insulin-like growth factor 1, contribute to the maintenance of a homeostatic balanced status between anabolism and catabolism on the articular cartilage.[11-14] Others such as vascular endothelial growth factor and basic fibroblast growth factor show chondroinductive roles.

Platelet-rich plasma injections showed more and longer efficacy when compared with HA injections in reducing pain and symptoms and recovering articular functions.[15] In an interesting prospective study, Filardo et al.[16] compare, for the first time, the safety and efficacy of 2 different approaches of platelet-rich plasma production in the treatment of knee OA. In particular, they evaluated 2 platelet-rich plasma products prepared following either a single-spinning approach (PRGF-Endoret; BTI Biotechnology Institute, Vitoria-Gasteiz, Spain) or double-spinning approach (homemade leuko–platelet-rich plasma). Results showed that although both treatment groups presented a statistically significant improvement in all the scores evaluated at all follow-up times, significantly more adverse events (involving pain and swelling) were detected in the group treated with the platelet-rich plasma prepared with the double-spinning approach.

Plasma rich in growth factors (PRGF) is an autologous biological therapy based on using the patient's own plasma and platelet-derived growth factors and endogenous fibrin scaffold for regenerative purposes.[17] There has been increasing recognition of the potential role of this autologous cocktail of growth factors in stimulating tendon and synovial cell proliferation, migration, autocrine release of hepatocyte growth factors and HA, and even differentiation of tendon stem cells exclusively into tenocytes.[18-21] An absence or reduction in postsurgical inflammation is a consistent clinical observation associated with the use of this biological approach. A small retrospective cohort study showed that 3 intra-articular injections of PRGF-Endoret at 1-week intervals substantially reduced pain in patients with OA of the knee compared with those treated with HA.[22] In this randomized, double-blind, HA-controlled, multicenter trial, we explored the use of intra-articular injections of PRGF-Endoret as a novel, safe, and efficacious biological approach in the treatment of pain due to OA of the knee. The hypothesis was that PRGF-Endoret would improve pain symptoms compared with HA, possibly through the release of proteins and growth factors, in patients affected by knee degeneration.

METHODS

The study was carried out in accordance with the international standards on clinical trials: Real Decreto 223/2004, Declaration of Helsinki in its latest revised version (Tokyo, Japan; 2004), and Good Clinical Practice Regulations (International Conference for Harmonization). The study protocol was reviewed and approved by the Reference Ethic Committee. All patients provided written informed consent before entry into the study.

Patient Selection

One hundred eighty-seven patients were initially selected in the study. Patients were considered eligible if they were aged between 41 and 74 years and had OA of the knee diagnosed based on American College of Rheumatology criteria[23] with radiographic confirmation (Ahlbäck grades 1 to 3, on a scale of 1 to 4, with higher numbers indicating more severe signs of the disease).

Recruitment of patients began January 18, 2008, at 3 clinical centers. The recruitment finished November 12, 2009, and the study was completed on September 13, 2010. A preliminary assessment of each patient was carried out in the first basal visit by an orthopaedic surgeon, 30 days before randomization, and the