333 TISSUEGENE-C (TG-C) IMPROVED CLINICAL SCORES IN PATIENTS WITH OSTEARTHRITIS: A PHASE 2B STUDY


Purpose: TG-C is a cell mediated gene therapy that contains non-transduced (hChon) and transduced (hChonβ#7) human allogeneic chondrocytes. The hChonβ#7 cells were transduced with TGF-β1 gene by using retroviral vector and irradiated with gamma-ray. TG-C has been proved its efficacy and safety in preclinical studies in vitro and in vivo. TG-C has been tested in Phase I and Phase IIa clinical studies in osteoarthritis (OA) patients and has proved its safety and efficacy in the patients.

Methods: The current placebo controlled phase IIb study was conducted to determine both safety and efficacy of TG-C in patients with OA of the knee. Participants (n = 54) with a confirmed diagnosis of knee OA by X-ray and MRI were randomized into the treatment group (TG-C, 18 \times 10^7 cells/knee, n = 27) and the placebo group (saline, n = 27). The primary evaluation parameter was International Knee Documentation Committee (IKDC) which measures pain, sports activities, and daily function. The secondary evaluation parameters were Western-Ontario and MacMaster University (WOMAC) score, Knee Injury and Osteoarthritis Outcome Score (KOOS), and 100 mm Visual Analogue Scale (VAS). These parameters were assessed at 12 and 24 weeks post treatment. For TG-C treatment group, we also evaluated the all evaluation parameters at 48 weeks post treatment. Additionally, changes in biomarkers were assessed in serum and urine samples. Safety measures, including physical exams, complete blood count, and serum chemistry were included up to 6 months post treatment. Blood samples were screened to detect the replication competent retrovirus (RCR), retrovirally transduced cells, and TGF-β1 DNA and protein starting from 2 weeks up to 6 months post treatment.

Results: TG-C treatment group showed improvement in IKDC, WOMAC, KOOS and 100 mm VAS scores compared to placebo group as shown in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment Group</th>
<th>Placebo Group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>IKDC, 24W</td>
<td>16.39 ± 15.63</td>
<td>8.05 ± 11.18</td>
</tr>
<tr>
<td>Secondary endpoint</td>
<td>WOMAC, 24W</td>
<td>-13.81 ± 19.23</td>
<td>-7.50 ± 13.02</td>
</tr>
<tr>
<td>KOOS, 24W</td>
<td>-22.96 ± 27.15</td>
<td>-13.92 ± 16.85</td>
<td>P = 0.0199</td>
</tr>
<tr>
<td>VAS, 24W</td>
<td>-29.15 ± 29.31</td>
<td>-20.33 ± 29.31</td>
<td>P = 0.0002</td>
</tr>
<tr>
<td>KOOS, 48W</td>
<td>-33.35 ± 29.10</td>
<td>-30.15 ± 29.10</td>
<td>P = 0.0002</td>
</tr>
</tbody>
</table>

1) Data for 48 weeks were TG-C treatment group.
2) The p value of 48 weeks were calculated with a comparison between baseline to 48 weeks.

Conclusions: In summary, this Phase IIb study indicated that TG-C treatment improved pain, sports activities, and quality of daily life in patients with knee OA when compared to the placebo control.

334 RANDOMIZED, SINGLE CENTER, OBSERVER-BLIND, PARALLEL-GROUP TRIAL TO EVALUATE THE SAFETY AND EFFECTIVENESS OF HYADD4-G: A VISCOELASTIC HYDROGEL, FOR THE TREATMENT OF MENISCUS TEAR

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Purpose: Injury to the meniscus may play a key role in the development of knee osteoarthritis (OA) and prior studies demonstrated that tear of the meniscus are more common in patients with knee OA. Tears present as severe pain, swelling and possible catching, difficulty on deep knee bending and locking of the knee in partial flexion. Basically, signs and symptoms of meniscal tears are those of any OA disease where the reduction of rheological properties of synovial fluid of the affected joint increases the susceptibility of the articular cartilage to damage. Clinical trials have demonstrated the efficacy of viscosupplementation in patients undergoing arthroscopic partial meniscectomy with results on pain reduction, better joint mobility and reduction of NSAIDs intake. On this basis we aim to investigate whether intra-articular injections of HYADD4-G (Hymovis®) in patients with meniscal tears could improve symptoms and knee functionality so to avoid arthroscopy surgery to the patient.

Methods: This is a single site, randomised, parallel groups, observer-blind, investigator initiated study. Upon signature of the informed consent and satisfaction of all inclusion and exclusion criteria, each patient was randomly assigned to control group, receiving only conservative treatment or to HYADD4-G group. Conservative treatment consisted in use of an immobilizer brace, a combination of rest and ice, knee off-loading and acetaminophen as per patient’s need. Patients allocated to HYADD4-G group in addition to the conservative treatment underwent to 2 injections of HYADD4-G two weeks apart: at visit V1 (day 0) and at visit V2 (day 14). Pain was investigated through a Visual Analogue Scale (VAS), knee pain stiffness and functionality through the WOMAC questionnaire. Secondary objectives are the evaluation of Quality of life by the SF-36 questionnaire, patient’s and investigator’s global assessment of the disease (PTGA/COGA), intake of analgesics and HYADD4-G safety. Meniscus tears were evaluated at baseline and at the following visits by magnetic resonance imaging scans. The study analyzed the relationship between the symptoms and the presence of a meniscus tears.

Results: Fifty patients (25 in each of the two treatment groups) were enrolled in the study. All patients receiving HYADD4-G in addition to the conservative treatment completed the treatment. All patients in the control group attended the visit 4 (day 60). Reasons for discontinuing the study were lost to follow-up (4 patients), surgery before visit 3 (3 patients) and treatment failure (1 patient). Pain mean values decreases from 82.0 mm at baseline to 12.0 mm at V4 (day 60) in patients receiving HYADD4-G injection while in the control group VAS pain decrease from 83.6 mm to 57.9 at V4 (day 60). Among patients who completed the study a statistically significant difference was found between the groups at day 30 up to the end of the study at day 60 (P < 0.001). Results obtained on pain were confirmed by WOMAC assessment. WOMAC pain sub-score, stiffness and function showed the same trend. In particular considering WOMAC pain a statistiscal significant difference between two groups was found at day 30 and this difference persisted to day 60 (P < 0.001). No local or systemic serious adverse events were observed during the study. Five patients complained of local pain after injection. Four patients (3 included in control group and 1 in HYADD4-G group) reported a worsening of the baseline conditions; these events resulted in withdrawals from the study.

Conclusion: Although it should be noted that the gold standard for the evaluation of meniscus injuries is arthroscopic surgery, this study demonstrates that patients who have been administered HYADD4-G can improve their symptoms relief since 14 days after the first treatment and this decrease was maintained up to 60 days. Symptoms relief together with MRI data are favourable to HYADD4-G study group, suggesting a relationship of meniscus injury pain reduction and physical improvement in knee. In conclusion based on this study HYADD4-G seems to be indicated for the treatment of pain in patients affected by meniscal tear or degenerative signal but further investigations need to be conducted on other symptoms related to this condition to confirm these promising data.

335 Tibial slope and patellar height changes following high tibial osteotomy

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Objective: Improving the accuracy of high tibial osteotomy not only in the coronal plane but with considering it as a three dimension procedure can give better long term results in cases of medial compartment osteoarthritis associated with varus deformity and minimize the obstacles faced in future total knee replacement (TKR).

Design: Two different techniques of high tibial osteotomy: the opening wedge osteotomy (OW) and the hemiacellotomy osteotomy (HCO) were compared clinically in a prospective randomized clinical trial that was held in Ain Shams University hospitals in the period between December 2010 to
April 2013 on thirty knees of twenty-four patients suffering from medial compartment osteoarthritis associated with varus deformity. The patients were allocated randomly (single-blinded) in two groups; where thirteen knees of group (I) underwent high tibial osteotomy using the OWO technique, while those of group (II) underwent the procedure using the HCO technique.

Two important parameters were compared; the posterior tibial slope in lateral radiographs using the anatomical proximal tibial axis and the patellar height using the Blackburne-Peel method; to assess the accuracy of the procedure in the sagittal plane.

Results: OWO had proven lower accuracy than HCO as regard the change in tibial slope (P = 0.001 and 0.3 respectively), while both techniques preserved patellar height almost unchanged with optimizing the procedures’ techniques (P = 0.4 and 0.6 respectively).

Conclusion: HCO technique for osteoarthritic knees associated with varus deformity can give more accurate results for the sagittal limb alignment and this may improve the long term results of the procedure and facilitate future TKR.

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Purpose: Osteoarthritis (OA) is a multifactorial polygenic degenerative disease, mechanically induced, and whose progression might be attributable to pro-inflammatory signaling molecules (cytokines) overall leading to the synovial joint failure as organ, and where pain represents the clinical hallmark of disease. This study reviews the efficacy of the autologous biological therapy, Plasma rich in growth factor (PRGF) to regenerate tissue and reduce pain in patients with knee OA.

Methods: Using the interchangeable terms PRGF, or Plasma rich in growth factors, or autologous growth factors, or platelet rich plasma, and knee osteoarthritis, a comprehensive literature search was conducted using OVID, EMBASE, PASCAL, PubMed/MEDLINE electronic databases and the Cochrane Central Register of Controlled Trials on October 31, 2013. Studies were considered suitable if the participants were over 18 years and had been clinically diagnosed with OA of the knee according to the American College of Rheumatology. The studies had to include a PRGF group and a control group (Hyaluronic acid, placebo, or another PRP), and the design had to be a comparative retrospective study or randomized controlled trial (RCT). Pre- and post-treatment measures of joint pain, reduced function and stiffness were evaluated using WOMAC, KOOS, IKDC, LEQUESNE, or OMERAT OARSI responders, with a follow-up of at least 4 weeks. Studies conducted using methods other than PRGF (such as double centrifugation, presence of leucocytes, platelet activation by bovine thrombin) to elaborate the product treatment group, were excluded. Outcomes were categorized by types and by pre- and post-treatment numbers, and median, or mean values (SD) were extracted. Dichotomic variables were expressed by determination of absolute and relative frequencies and the measure of effect was calculated by ascertaining the relative risk or odds ratio with their respective 95% confidence intervals. Quantitative variables were summarized by using the mean and standard deviation with intervals confidence at 95%. The quality assessment encompassed study methods, participants, experimental intervention, and control treatment. Overall, the risk of bias was categorized as low, unclear, or high risk based on random sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting.

Results: The literature research yielded 91 citations, but only publications using eligible PRGF met the inclusion criteria, consisting of 3 RCT, 1 prospective and 1 retrospective analysis (n = 5). Two studies were rated as having a low risk of bias, and the remaining three studies as having high risk of bias. In two randomized clinical trials, it was observed that after six months of treatment the number of patients with a pain reduction of more than 50% was significantly higher in the group treated with PRGF than in the control group (HA). In two other studies (one retrospective and one prospective) the patients treated with PRGF showed a significant pain reduction compared with the patients treated with HA (WOMAC scale for pain, function, and stiffness, LEQUESNE, KOOS, scale and OMERAT OARSI responders) showed a statistically significant superiority of the group treated with PRGF in two studies (Vazquez et al, 2013, and Say et al, 2013).

Conclusions: The current clinical evidence suggests that pain reduction of PRGF intra-articular infiltrations in patients with knee OA is significantly higher compared with HA, and lasting for a longer period of time (24 weeks after the last infiltration). Despite the high risk of bias of the other three studies, their results are consistent with those coming from the two RCT. There exist three key limitations in this review: the heterogeneity of the studies that met the inclusion criteria, the small number of publications included in the study, and the absence of a placebo in the control group.

337 Low cost minimalist shoe as a mechanical treatment for algo-functional aspects and analgesic medicine intake in Elderly Women with Knee osteoarthritis
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Purpose: To evaluate the therapeutic effect of a low cost, flexible non-heeled shoe on the WOMAC domains and paracetamol intake of elderly women with knee OA.

Methods: A randomized, parallel and controlled clinical trial, with blind assessor was carried out. Fifty-six elderly women with knee OA graded 2 or 3 (Kellgren and Lawrence), assessed at baseline (T0), after three (T3) and after six months (T6), were randomly allocated into the intervention group (IG, n = 28) or the control group (CG, n = 28). We adopted the WOMAC pain as a primary outcome, and stiffness, function, and total WOMAC score, and paracetamol intake as the secondary outcomes. As intervention, the patients wore a minimalist, flexible and low-cost shoe (Moleca® shoe; Calçados Beira Rio S.A., Novo Hamburgo, RS, Brazil) for average daily usage time of 7 h 40 min. This intervention shoe is a woman’s double canvas flexible flat walking footwear without heels, and with a 5-mm anti-slip rubber sole. Paracetamol (500 milligrams), as a rescue medication, was allowed for both groups only in case of pain. The time effects (baseline, 3 and 6 months) of group (IG and CG) and interaction (time and group) were tested by two-way casewise ANOVA.

Results: The IG showed an improvement in pain (effect size between-group of 1.41), function (effect size of 1.22), and stiffness (effect size of 0.76) in WOMAC. The within-group results show that the IG improved the WOMAC pain by 51% (p = 0.001) at T3 and 66% (p = 0.001) at T6. The CG improved the WOMAC pain by 34% (p = 0.001) at T3 and 28% (p = 0.001) at T6. The IG improved the WOMAC stiffness by 55% (p = 0.001) versus the CG that worsened 22% (p = 0.001) at T3; at T6, the IG presented a reduction of 62% (p = 0.001) for WOMAC stiffness. In the IG, the reduction was only by 15% (p = 0.001). The IG increased the WOMAC function by 52% (p = 0.001) at T3 and 62% (p = 0.001) at T6. In the CG, this variable was improved by 29% (p = 0.001) at T3 and 19% (p = 0.001) at T6. In the IG, WOMAC total score was improved by 53% (p = 0.001) at T3 and 62.4% (p = 0.019) at T6. In the CG the improvement was of 26% (p = 0.001) at T3 and 19% (p = 0.001) at T6. The CG increased significantly the intake of rescue medication throughout the study, which possibly influenced their pain reduction and function improvement. The IG showed a slight increase in the paracetamol intake at the end of the 1st, 2nd and 3rd month; nevertheless, in the 4th, 5th and 6th month, the paracetamol intake was again similar to the initial assessment. From the 2nd to 6th month paracetamol intake was significantly higher in CG compared to IG.

Conclusion: We can recommend the use of this low cost minimalistic shoe as another conservative mechanical treatment that aims to minimize pain, improve functional aspects, and reduce the rescue medication intake.