showed the affinity of cells to the scaffold, a large extracellular matrix production, rich in collagen and proteoglycans and the efficacy of TGF-beta3. The presence of collagen type II and aggrecan was demonstrated by immunehistochemistry positivity for them. Through SEM, intense cellular growth and collagen fibers production, strongly adhered to the scaffold were observed.
Conclusions: The HAF SCs presented greater adhesion to the scaffold and resistance to the steps of the study than AT SC. Therefore we concluded that although both stem cells sources were feasible for application in chondrogenic experiments, as far as the chondrogenic differentiation into the scaffold of chitoman-xanthan under TGF-beta 3 stimuli, the HAF SC seems to be , at least qualitatively, better than AT SC.

562
RESPONSE TO TANEZUMAB, AS ASSESSED BY OUTCOME MEASURES IN RHEUMATOLOGY-OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL CRITERIA, IN PATIENTS WITH OSTEOARTHRITIS OF THE KNEE OR HIP

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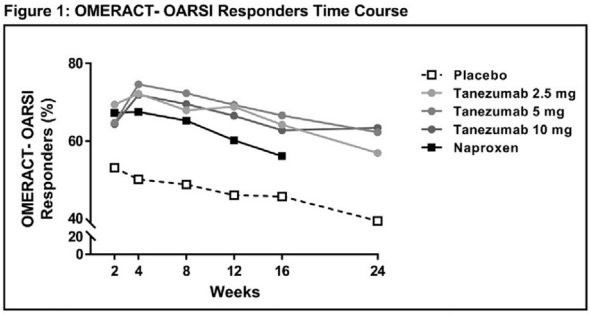
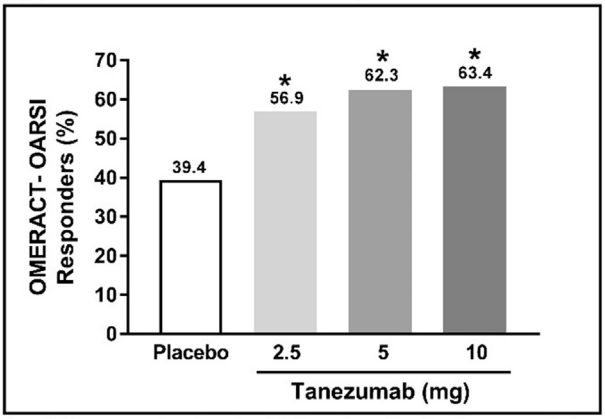
Purpose: The Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) responder index is used to assess treatment response in clinical trials of osteoarthritis (OA). The index comprises a combination of both absolute and relative changes in pain, function, and global patient's assessment. Tanezumab, a humanized monoclonal antibody with high selectivity and specificity for nerve growth factor, has been shown to decrease pain scores in patients with OA. The current analysis used the OMERACT-OARSI index to further assess treatment response to tanezumab in patients with OA.
Methods: Patient-level data were pooled from 4 randomized, blinded, placebo-controlled, 16-24 week studies in patients with OA of the knee or hip. In 2 studies patients received placebo or intravenous tanezumab (2.5 mg, 5 mg, or 10 mg at weeks 0, 8, and 16). In the other 2 studies patients received placebo, intravenous tanezumab (5 mg or 10 mg at 0 and 8 weeks), or oral naproxen (500 mg twice daily for 16 weeks). Treatment response was defined as: 1) improvements, from baseline, of $\geq$50% (relative) and $\geq$2 points (absolute) in either the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain or Physical Function subscales or 2) improvements, from baseline, of $\geq$20% and $\geq$1 point in two of the three following assessments: the WOMAC Pain subscale, the WOMAC Physical Function subscale, the Patient Global Assessment of Osteoarthritis. A logistic regression model including treatment, baseline WOMAC pain score, study, and study-by-treatment interaction as fixed effects was used to compare the percentage of OMERACT-OARSI responders across groups. Each tanezumab group was compared to the placebo group at weeks 2, 4, 8, 12, 16, and 24. The naproxen group was compared to the placebo group and to the 5 mg and 10 mg tanezumab groups at weeks 2, 4, 8, 12, and 16. The 2 trials with a 2.5 mg tanezumab group did not include a naproxen comparator; therefore, comparisons between the 2.5 mg tanezumab and naproxen groups were not made. Missing data were imputed using a baseline-observation-carried-forward approach.
Results: All active treatments exhibited a significantly greater percentage of responders, compared with placebo, at every time point examined (Fig. 1). At week 24 (Fig. 2), the placebo group responder rate was 39.4% (n = 129 of 327) compared with 56.9% for the tanezumab 2.5 mg group (n = 186 of 327; Odds Ratio [OR] = 2.10; P<0.001), 62.3% for the tanezumab 5 mg group (n = 203 of 326; OR = 2.65; P<0.001), and 63.4% for the tanezumab 10 mg group (n = 210 of 331; OR = 2.78; P<0.001). At week 16, the percentage of responders was 45.7% for the placebo group (n = 340 of 744) compared with 64.2% for the tanezumab 2.5 mg group (n = 210 of 327; OR = 2.28; P<0.001), 66.6% for the tanezumab 5 mg group (n = 495 of 743; OR = 2.43; P<0.001), 62.8% for the tanezumab 10 mg group (n = 469 of 747; OR = 2.11; P<0.001), and 56.1% for the naproxen group (n = 233 of 415; OR = 1.49; P = 0.004). Compared with the naproxen group, the percentage of responders was significantly higher in the 5 mg tanezumab group (OR = 1.47; P = 0.007), but not the 10 mg tanezumab group (OR = 1.12; P = 0.428), at week 16. In a subgroup of patients with severe pain (WOMAC Pain and Physical Function scores both $\geq$7 and Patient Global Assessment score of “poor” or “very poor”), all active treatment groups showed significantly higher responder rates than the placebo group at every time point assessed with the exception of the tanezumab 2.5 mg group at 16 and 24 weeks and the naproxen group at week 16.
Conclusions: Based on the OMERACT-OARSI index for treatment response, intravenous tanezumab (2.5-10 mg; every 8 weeks) provides sustained efficacy (up to 24 weeks) in patients with OA of the knee or hip.

Figure 1: OMERACT- OARSI Responders Time Course



P < 0.05 for all active treatments versus placebo at every time point and for the 5 mg tanezumab group versus naproxen at all time points except week 4. P = non-significant for the 10 mg tanezumab group versus naproxen at all time points. The 2.5 mg tanezumab group was not compared to the naproxen group. The total number of patients assessed at weeks 2-16 were as follows: placebo (n=744), 2.5 mg tanezumab (n=327), 5.0 mg tanezumab (n=743), 10 mg tanezumab (n=748), naproxen (n=417). The total number of patients assessed at week 24 was as follows: placebo (n=327), 2.5 mg tanezumab (n=327), 5.0 mg tanezumab (n=326), 10 mg tanezumab (n=331). Standard error <3% at each point, error bars not shown for clarity.

Figure 2: OMERACT- OARSI Responders at Week 24



*p < 0.01 versus placebo. The total number of patients assessed at week 24 was as follows: placebo (n=327), 2.5 mg tanezumab (n=327), 5.0 mg tanezumab (n=326), 10 mg tanezumab (n=331). Standard error <3% at each point.

Therapy — Biological

563
STRUCTURAL AND SYMPTOMATIC BENEFIT OF A HALF-LIVE EXTENDED, SYSTEMICALLY APPLIED ANTI-ADAMTS-5 INHIBITOR (M6495)

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Purpose: ADAMTS-5 (A Disintegrin And Metalloprotease with ThromboSpondin-motifs-5, or aggrecanase 2) cleaves joint cartilage aggrecans, which is pathologically increased in osteoarthritis (OA). We have generated the ADAMTS-5-inhibiting bifunctional Nanobody®, M6495, which binds albumin to extend plasma half-life. The two murine studies presented here, were designed to demonstrate preclinical proof of concept of M6495 as a disease modifying drug candidate for potential structural and symptomatic benefit.
Methods: In a destabilization of the medial meniscus (DMM) model in mice, M6495 was injected subcutaneously every third day at doses of 0.1, 0.3, 1, 3 and 10 mg/kg, starting 3 days after surgery and continued until necropsy at Day 56; the effect of M6495 on cartilage breakdown was investigated by histology (e.g., medial cartilage degeneration) 56

days after surgery (n = 20 mice/group). In a surgical rat OA model induced by anterior cruciate ligament transection with resection of the medial meniscus (ACLT+tMx), the effect on symptoms was investigated longitudinally by catwalk gait analysis. To stimulate spontaneous activity, rats were housed in stable groups of 48 rats in colony cages. M6495 was injected every other day at doses of 0.5, 5 and 50 mg/kg, from Day 3 after surgery until necropsy at Day 42 (n = 14-15 rats/group).

Results: In mice and rats, pharmacokinetic analyses of serum samples confirmed that the dosing regimen resulted in dose-dependent systemic M6495 exposure. No treatment related body weight reductions or impact on general condition were observed, suggesting that M6495 was well-tolerated up to the highest dose used in either species. After DMM surgery in mice, therapeutic treatment with 1, 3 and 10 mg/kg M6495 decreased the medial cartilage degeneration sum score by up to 48.5% compared with the vehicle group. In rats, ACLT+tMx surgery caused gait disturbances reflecting abnormal weight bearing in the operated hindlimb to avoid pain. Administration of M6495 starting 3 days after surgery improved the gait performance in a dose dependent manner. At the highest dose of 50 mg/kg, gait performance improved by 42% (P=0.04) versus vehicle, and the benefit was observed as early as 4 days after the first treatment (7 days after surgery) and until necropsy (day 39 after first treatment).

Conclusions: Selective inhibition of ADAMTS-5 by M6495 commencing at early surgically induced OA was shown to prevent cartilage matrix breakdown and gait disturbance. M6495 is a promising candidate for development in OA as it demonstrated functional and structural effects – both endpoints required from a patient's point of view – in the preclinical setting in rodents.

564
THE EFFICACY AND SAFETY OF GENETICALLY ENGINEERED ALLOGENEIC HUMAN CHONDROCYTES EXPRESSING TGF-β1 IN PATIENTS WITH GRADE 3 CHRONIC DEGENERATIVE JOINT DISEASE OF THE KNEE

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Purpose: The purpose of this study was to evaluate the 24-month efficacy of an injectable mixture of normal human chondrocytes and genetically engineered chondrocytes virally transduced with a TGF-β1 expression vector (TissueGene-C [TG-C]) when compared to placebo in patients who have osteoarthritis of the knee. Specifically, we assessed: 1) functional outcomes; 2) analgesic usage and pain scores; 3) adverse events (AEs); and 4) magnetic resonance images (MRIs).

Methods: This is the 2 year follow-up of a multicenter, double-blinded, placebo-controlled, randomized study of adults with Kellgren-Lawrence grade III osteoarthritis of the knee. A total of 102 patients were randomized 2:1 to TG-C or placebo. Patients were recruited between May 2011 and October 2012 from five institutions and enrolled following approved informed consent procedures and institutional review board approval. Primary outcomes analyzed were knee joint function, scored by the International Knee Documentation Committee (IKDC) scores, and pain, measured by the Visual Analog Scale (VAS). Secondary endpoints included pain and analgesic use, quality of life, and adverse events (AEs), including the need for a total knee arthroplasty. Magnetic resonance images (MRIs) at approximately 3, 6, and 12 months were assessed using the Whole-Organ Magnetic Resonance Imaging Score (WORMS) system for cartilage damage; bone marrow lesions (BMLs); meniscal damage/extrusion; infrapatellar fat pad- and effusion-synovitis; and osteophytes. MRI analyses were performed at whole knee, compartmental, and subregional levels. This study was conducted in accordance with the International Conference on Harmonization Tripartite Guideline for Good Clinical Practice, ethical principles with origin in the Declaration of Helsinki, as well as the USA Code of Federal Regulations.

Results: There were significant improvements in IKDC scores in the TG-C, when compared to placebo cohort at week 12 (least mean square difference [LSMD]: 10.4; P = 0.0337), at week 52 (LSMD: 13.4; P = 0.0100), at week 72 (LSMD: 15.9; P = 0.0031), at week 104 (LSMD: 14.2; P = 0.0076), and overall (LSMD: 10.7; P = 0.0101). Pain analyses showed significant improvements at week 12 (LSMD: -14.4; P = 0.0119), at week 52 (LSMD: −15.5; P = 0.120), at week 72 (LSMD: −16.6; P = 0.0074), and overall (LSMD: −12.2; P = 0.0106). Reduction in severity of pain by study specific questionnaire was seen at weeks 12 and 52 and frequency of pain at 24 hours, weeks 12, and 104. Whole-knee MRIs at 12 months showed less progression of cartilage damage in the TG-C group when compared to placebo (34.6% vs. 47.9%; adjusted RR 0.7, 95%CI [0.5–1.1], P = 0.077). Less progression of infrapatellar fat pad synovitis and effusion-synovitis also was observed in the TG-C group when compared to placebo (9.6% vs. 21.1%, adjusted RR 0.5, 95%CI [0.2–1.2], P = 0.115). Statistically significant differences were not seen for BMLs, meniscal damage, and osteophytes. No severe AEs related to treatment with TG-C were observed. Common AEs related to treatment with TG-C were arthralgia, joint inflammation, and joint effusion, which were similar to the control cohort.

Conclusions: In the TG-C cohort, patients had significant improvements in IKDC score, VAS, and reported less severe and frequent pain. A number of subscores among the secondary efficacy endpoints were also more positive in TG-C patients. Patients in the TG-C group showed a lower percentage of joints with progression of cartilage damage as well as less progression of infrapatellar fat pad- and effusion-synovitis. Treatment with TG-C was generally well-tolerated with minor AEs.

565
TUMOR NECROSIS FACTOR-INHIBITOR TREATMENT DURATION IS ASSOCIATED WITH LOWER RISK OF HAND OSTEOARTHRITIS PROGRESSION IN PATIENTS WITH RECENT-ONSET RHEUMATOID ARTHRITIS AFTER 10-YEAR FOLLOW-UP

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Purpose: Increasing evidence indicates involvement of the pro-inflammatory cytokine TNF-α in hand osteoarthritis (OA) pathogenesis. The BeSt study, a randomized controlled trial primarily designed to investigate targeted treatment in recent-onset rheumatoid arthritis (RA) patients, enabled to study the long-term effects of TNF inhibitors (TNFi) on the development and progression of hand osteoarthritis. The distal interphalangeal joints (DIPJs) are rarely affected in RA, which allowed to evaluate primary OA separately. The purpose of this study was to investigate the effect of TNFi on incidental and progressive radiographic hand OA after 10-year follow-up in recent-onset RA patients.

Methods: At baseline and 10-year follow-up 262 patients (mean age 52 years, 66% women) were available for radiologic assessment of hand OA. Eighteen interphalangeal joints (IPJs) were scored for osteophytes using the Osteoarthritis Research Society International (OARSI) atlas (0–3; summated score 0–54), and according to the Kellgren-Lawrence (KL) scoring method (0–4; summated score 0–72). Incidental OA was defined as an increase ≥1 in summated osteophyte score or ≥2 in summated KL score in absence of OA at baseline, and progressive OA as an increase ≥3 in summated osteophyte or KL score in presence of OA at baseline, based on the smallest detectable change. TNFi treatment and disease activity score (DAS) were assessed on standardized visits at a three-monthly interval. Associations between TNFi treatment duration in months and incidental and progressive hand OA were analyzed using generalized linear models with Poisson distribution and robust standard errors, while adjusting for age, gender, time averaged DAS, time averaged Sharp-van der Heijde score and hand OA severity at baseline.

Results: Based on the osteophyte score, 126 patients (48%) were classified with OA at baseline in the DIPJs and 82 patients (31%) in the proximal IPJs (PIPJs). Incidental OA developed in 33% of patients in DIPJs and in 42% in PIPJs. Progressive OA occurred in 30% of patients in DIPJs and in 38% in PIPJs. Of patients with and without OA at baseline, irrespective of joint location, 63% and 55% were treated with TNFi, with a median treatment duration of 47 and 36 months, respectively. No effect of TNFi treatment duration was seen on incidental hand OA. On progressive hand OA, every month of TNFi treatment resulted in a reduced relative risk (95% confidence interval) of 0.987 (0.978-0.996) of osteoarthritis progression in DIPJs, but not in PIPJs. The results from the analyses with the KL scoring method were comparable to the osteophyte score, as shown in Table 1.