Study TPX-100-5: Intra-Articular TPX-100 Significantly Delays Pathological Bone Shape Change and Stabilizes Cartilage in Moderate to Severe Bilateral Knee OA

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Abstract

Background: TPX-100, a promotor of osteoblast and chondroblast differentiation, is a potential osteoarthritis (OA) therapy. This retrospective study compared MRI 3D femoral bone shape changes (B-scores) after intra-articular TPX-100 or placebo and analyzed the relationship between cartilage thickness and bone shape change over 12 months.

Methods: 104 participants with bilateral knee moderate to severe (ICRS 2-4) knee cartilage defects were randomized for evaluation of efficacy and safety of 200mg of TPX-100. Each subject's contralateral placebo-treated knee served as a paired internal control. After MRI quality control, 78/93 subjects (84%; 156 knees) were analyzed for quantitative femoral B-score and cartilage thickness. All analyses were centrally performed, blind to treatment assignment and clinical data.

Results: TPX-100-treated knees (n=78) demonstrated a statistically significant decrease in pathologic bone shape change compared with placebo-treated knees at 6 and 12 months: 0.0298 (95% C.I. -0.037, 0.097) vs 0.1246 (95% C.I. 0.067, 0.182) (P=0.02); and 0.0856 (95% C.I. 0.013, 0.158) vs. 0.1969 (95% C.I. 0.123, 0.271) (P = 0.01), respectively. The correlation between bone shape change and medial and total tibiofemoral cartilage thickness changes at 12 months was statistically significant in TPX-100-treated knees (P<0.01).

Conclusions: This is the first report of a potential therapy demonstrating a significant effect on bone shape measured by B-score in knee OA. These data, in combination with previously reported statistically significant and clinically meaningful improvements in WOMAC function versus placebo, support TPX-100 as a candidate for disease modification in knee OA.

Trial Registration: NIH clinicaltrials.gov, NCT01925261. Registered 15 August 2013, https://clinicaltrials.gov/ct2/show/NCT01925261?term=NCT01925261

Background

TPX-100 is a 23-amino acid peptide derived from Matrix Extracellular Phosphoglycoprotein (MEPE), a small integrin-binding ligand N-linked glycoprotein (SIBLING) family member. MEPE is highly expressed by osteocytes, is downregulated in osteoarthritis, and may play a role in osteoarthritic bone remodeling [1]. TPX-100 acts selectively on cells committed to hard tissue lineage, viz. bone, cartilage or dentin. In animal models, the actions of TPX-100 are limited to bone and cartilage formation and repair [2]. Based on preliminary *in vitro* data, the putative mechanism of action of TPX100 is via integrin binding with formation of TGF-β receptor complexes and activation of its effector, Smad3. Smad3 can regulate cartilage matrix synthesis via induction of type II collagen in chondrocyte lineage cells and play a role in homeostasis of knee joint bone [3][4].

TPX-100 has been shown to induce articular cartilage formation in goats (N = 8 / dose group) after a standardized full-thickness chondral defect and treatment with 4 weekly intra-articular (IA) injections of

TPX-100 (25, 125 or 250 mg/injection) vs. vehicle in a dose-dependent manner. After 6 months, histopathological staining in TPX-100-treated joints demonstrated robust articular (hyaline) cartilage formation and increased Type II collagen compared with vehicle-treated controls [2]. In a standardized rat model of ACL transection and partial medial meniscectomy, IA TPX-100 dose dependently reduced joint damage and improved osteoarthritis scores in actively treated animals compared with controls.

In humans, a Phase II randomized, double-blind, placebo-controlled, 12-month trial of TPX-100 (NCT01925261) has been completed to evaluate safety, tolerability and efficacy of IA TPX-100 in subjects with bilateral, mild-moderate (ICRS grades 2–3) patellofemoral cartilage defects, with or without tibiofemoral cartilage defects [2][5]. Each subject's contralateral placebo-treated knee served as a paired internal control, intended to control for effects of age, sex, weight, genetic factors, and activity levels on outcome measures. The pre-selected primary efficacy outcome measure in this trial was the 6-month change in patellar cartilage thickness as measured using standardized magnetic resonance imaging (MRI) in TPX-100-treated knees compared with placebo-exposed knees (See Fig. 1; CONSORT diagram). Subjects were screened clinically and with MRI. Synovitis and meniscal damage were among the exclusion criteria for enrollment. Briefly, Part A of the study evaluated safety of four, once-weekly IA doses of TPX-100 in sequential dose cohorts (25, 50, 100 and 200 mg/injection) of 6–9 subjects, with progression to the next dose following Safety Review Committee approval. All doses were reasonably safe and well tolerated, and the highest dose, 200 mg/injection, was selected for Part B of the study for evaluation of efficacy and safety. Of the 118 subjects enrolled for Parts A and B, 93 subjects received 4 injections of 200 mg TPX-100 and had baseline MRIs with at least one follow-up scan. Per the statistical analysis plan, these subjects made up the primary analysis population. Efficacy outcome measures included MRI cartilage measures (6 and 12 months) and patient-reported outcomes (WOMAC, KOOS, NRS for pain at 3, 6 and 12 months). Semi-quantitative MRI analysis by central readers blind to clinical data and treatment assignment demonstrated that only 14% of knees had measurable patellar cartilage thickness changes, with no significant treatment differences at 6 or 12 months. MRIbased MOAKS evaluation, including cartilage defects, meniscal pathology and Hoffa's synovitis, did not show differences at baseline or follow up between TPX-100-treated knees and placebo-exposed knees, and there were no significant within-knee changes in bone marrow lesions at 6 or 12 months. In contrast, patient benefit, measured by WOMAC and KOOS scores, was statistically significant and clinically meaningful in favor of TPX-100-treated knees at 6 months compared with placebo, with robust functional benefits sustained through the end of the study at 12 months [2]. Posthoc analyses revealed that 68 (73%) of subjects had, in addition to bilateral patellofemoral cartilage defects, moderate to severe (ICRS 2–4) bilateral tibiofemoral cartilage defects. In these subjects, sustained, statistically significant and clinically meaningful clinical benefits in favor of TPX-100-treated knees were observed, nearly identical to those in the whole population [5].

The present study (TPX-100-5) was designed as a retrospective MRI study to investigate femoral boneshape change at 6 and 12 months after TPX100 or placebo administration and to analyze relationships between cartilage thickness and femoral bone shape change at 6 and 12 months after TPX100 or placebo administration.

Bone shape change, measured by MRI, has been shown to predict radiographic onset of OA [6], is associated with radiographic structural progression [7], discriminates people with knee OA from those without knee OA [8] and is more responsive to change over time than is radiographic assessment [9]. In each of these studies, the femur (defined as the whole of the lateral and medial femoral condyles) had greater discrimination and responsiveness to change than did the tibia or patella. The femoral bone shape ("B-score") metric is a form of statistical z-score that represents the position of a femoral bone shape along a shape vector from a non-OA knee shape (origin) towards an OA knee shape (positive direction). Non-OA and OA knees used to define this 3-dimensional (3D) shape vector were categorized using centrally-read and adjudicated Kellgren-Lawrence grading [10].

Bowes et al demonstrated that in a large observational cohort of over 4,500 subjects' knees from the Osteoarthritis initiative (OAI), MRI-measured B-score produced logistic regression models for clinically important outcomes that were very similar in terms of predictive validity to those using categorical Kellgren-Lawrence grading (KLG), which is the conventional radiographic standard for OA diagnosis. These data provide construct validity for this new, continuous scalar measurement. In addition, Bowes et al showed that bone shape is directly associated with the risk of clinical outcome measures such as knee pain, functional deficit and joint failure, as indicated by total joint replacement, with only small effect sizes from adjusting models for potential covariates such as age, sex, ethnicity, body mass index (BMI), alignment, previous knee surgery, non-steroidal anti-inflammatory drugs (NSAIDs) use and smoking status [10]. These findings support femoral B-score as a structural endpoint in clinical trials of disease-modifying osteoarthritis drugs (DMOADs).

Methods

Subjects between the ages of 25–75 years with bilateral knee OA were enrolled at 15 sites across the United States.

Written informed consent was obtained prior to study enrollment.
All subjects were screened by MRI, centrally read, to confirm structural inclusion criteria: bilateral PF cartilage defects (ICRS Grade 1–3) with intact menisci. One knee was randomly assigned to receive 4 weekly injections of TPX100, while the contralateral knee received placebo (saline) injections that were identical in appearance and viscosity. Investigators, subjects, sites and sponsor were blinded to treatment assignment.

MR images were acquired at baseline, 6 and 12 months with 1.5T clinical MRI scanners using a sagittal T1-weighted 3D SPGR, FLASH or FFE sequence with fat saturation or water excitation. An identical scanner and knee coil were used for baseline and follow-up measurements of each participant. Acquisition parameters were as follows: contiguous slice thickness 1.5 mm, in-plane resolution of 0.31 mm, repetition time: 17 msec, echo time: 7 msec, flip angle: 15°. Identical acquisition parameters were used at baseline and follow-up.

In Study TPX-100-5, MRIs from all subjects (n = 93) who received, as randomly assigned, four weekly injections of TPX-100 (200 mg/injection) in one knee (Index) and placebo in the contralateral knee (Control) were eligible for inclusion. Image quality was assessed centrally and blind to clinical data and treatment assignment. Quality was sufficient to include bilateral knee images from 78 of the 93 subjects (84%) analyzed in study TPX100-1 (See Fig. 1; CONSORT diagram).

Cartilage measurement was performed centrally, blind to treatment assignment and clinical data, at a single center (Chondrometrics GmbH, Ainring, Germany). The subchondral bone and cartilage surface areas of the medial and lateral tibia and medial and lateral weight-bearing central femoral condyles were traced manually, excluding cartilage cover of osteophytes [11]. Quantitative measures of cartilage, including mean cartilage thickness averaged over the total area of subchondral bone, were computed using Chondrometrics software [12]. Mean cartilage thickness over the total area of subchondral bone for the medial tibiofemoral compartment was computed by summing the values of the medial tibia and those of the weight-bearing medial femoral condyle; and for the lateral tibiofemoral compartment by summing the values of the lateral tibia and those of the lateral weight-bearing femoral condyle. Definitions of the tibiofemoral subregions as well as measurement reliability (test–retest reproducibility with repositioning of the joint between acquisitions) have been published previously [12].

Femur bone surfaces were automatically segmented using active appearance models (AAMs) at a single center (Imorphics Ltd, Manchester, UK). An AAM is a type of statistical shape model trained using machine learning to search images. AAMs have proven to be a successful supervised machine learning method that can produce a segmented knee bone surface with sub-millimeter accuracy [8][13]. AAMs were constructed using a training set of 96 knee DESS sequence MRIs that were selected to provide examples of OA across KLG grades from subjects enrolled in the OAI [14]. The performance of the AAM has been tested with various other MRI sequences and slice thicknesses. Mean automated segmentation accuracy using MRI FLASH sequences is -0.0009 mm, with ± 95th percentiles of error of + 0.34/-0.43 mm, where a positive error represents the automated surface being outside the reference surface [15]. The construction of an AAM produces a “shape space,” spanned by the set of principal components used to describe the training set of examples. Within this shape space, an “OA vector” is defined as the line which passes through the mean shape of two populations: a population with OA (OA Group, defined as all knees with KLG ≥ 2 over 4 years of follow-up) and a population without OA (Non-OA Group, defined as knees with KLG of 0 in the same period). Distances along the femur OA vector are termed ‘B-score’, with the origin (B-score = 0) defined as the mean shape of the Non-OA Group for each sex, and 1 unit defined as 1 standard deviation of the Non-OA Group along the OA vector (positive values toward the OA Group). Each parameterized femur bone shape was projected orthogonally onto the OA vector to specify the corresponding B-score value [10]. Representative examples of differences in femur bone shape at various B-scores, and a heat map of the areas which change most with increasing B-score are shown in Fig. 2.

B-score changes over 6 and 12 months were graphically compared with the 12-month trajectories of “non-progressor” and “progressor” B-score groups from OAI data. The nonprogressor group was defined as all of those who do not change by more than 95% of the smallest detectable difference (SDD) using the

slope of change measured over 4 years. The average slope over this 4-year period is about 0.04 B-scores per annum. The progressor group was defined as all of those who *do* change by more than 95% of the SDD using the slope of change measured over slope over 4 years. The average slope over this 4-year period is about 0.24 B-scores per annum. SDD was calculated as the 95% limit of agreement between the first and second image measurements from test-retest data, using the Bland-Altman method [10].

Paired Students' T-tests were used to compare B-score change from baseline between the knee receiving IA placebo (control) or TPX-100 (index) at 6-months and 12-months. For each knee (index, control) at 6months and 12-months, the Pearson coefficients of the changes from baseline between the femur B score and cartilage thickness of tibiofemoral variables were estimated. The two-sided p-value and 95% confidence intervals from the test of the null hypothesis (that the true correlation coefficient is equal to zero) were also computed. Statistical significance was set at $P < 0.05$. The data analysis for this paper was generated using SAS software version 9.

Results

Characteristics of the per-protocol (TPX-100-1) and B-score analysis (TPX-100-5) cohorts were as follows:

- All Per Protocol (PPT) subjects: TPX-100-1, N = 93

  Mean Age: 58.4 (95% C.I.: 56.4, 60.4)
  Sex: 38 Males, 55 Females (59.1% Females)
  Mean BMI: 30.4 (95% C.I.: 29.1, 31.7)
- Evaluable B-Score Analyzed Cohort: TPX-100-5, N = 78

  Mean Age: 58.4 (95% C.I.: 56.2, 60.6)
  Sex: 30 Males, 48 Females (61.5% Females)
  Mean BMI: 30.9 (95% C.I.: 29.5, 32.3)

Relative proportions of ICRS grades of Index and Control knees of the subjects analyzed in TPX-100-1 and TPX-100-5 studies are provided in Table 1.

Table 1. ICRS Grades of Index and Control Knees of the Subjects Analysed in TPX-100-1 and TPX-100-5 Studies, Respectively at Baseline. ICRS grade in each knee was determined as the maximum degree of cartilage defect observed in tibiofemoral knee compartment.

ICRS Grade	TPX-100-1 (N = 93)		TPX-100-5 (N = 78)	
	Index	Control	Index	Control
4	37%	37%	35%	34%
3	25%	21%	27%	19%
2	19%	21%	18%	22%
1	0%	0%	0%	0%
0	19%	22%	21%	25%
Total	100%	100%	100%	100%

Comparison of the 78 evaluable TPX-100-treated knees demonstrated a statistically significant decrease in B-score change in the femur compared with placebo-exposed knees at 6 months: 0.0298 (95% C.I. -0.037, 0.097) vs 0.1246 (95% C.I. 0.067, 0.182) (P = 0.02) and at 12 months: 0.0856 (95% C.I. 0.013, 0.158) vs 0.1969 (95% C.I. 0.123, 0.271) (P = 0.01). Graphical comparisons of Bscore change with progressor and non-progressor groups from OAI data showed B-score trajectories in TPX-100-treated knees that were strikingly similar to those of OA non-progressors, and, among placebo-exposed knees, B-score trajectories that were similar to OA progressors (Fig. 3).

Analysis of quartiles of index knee B-score change at 12 months showed a statistically significant association between cartilage thickness loss, particularly in the lower medial femoral condyle, and lower positive B-score change (Fig. 4).

In TPX-100-treated knees, correlation analyses revealed a statistically significant association between B-score change and medial femoral condyle cartilage thickness change at 6 months; and a statistically significant association between B-score change and cartilage thickness change in entire femoral condyle and entire TF compartments at 12 months (P < .05; Table 2). There was also a significant association between B-score change and cartilage thickness change in the medial femoral condyle and medial TF compartments at 12 months (P < 0.005; Table 2).

Table 2: Pearson Correlations between Femur Bone Shape Stabilization and Tibiofemoral Cartilage Thickening/Stabilization in TPX-100-treated Knee.

Change Period	Knee Compartment	n	Correlation Coefficient	p-value
Baseline to 6 months	Entire Femoral Condyle	78	-0.206	0.07
	Medial Femoral Condyle	78	-0.265	***0.02***
	Entire TF	78	-0.193	0.09
	Medial TF	78	-0.212	0.06
Baseline to 12 months	Entire Femoral Condyle	78	-0.303	***0.007***
	Medial Femoral Condyle	78	-0.329	***0.003***
	Entire TF	78	-0.296	***0.009***
	Medial TF	78	-0.320	***0.004***

Cartilage thickness change in the lateral femoral condyle and lateral TF compartments did not show an association with B-score changes at either 6 or 12 months. There was little or no association between B-score change and cartilage thickness change in control knees (Table 3).

Table 3
Pearson Correlations between Femur Bone Shape Stabilization and Tibiofemoral Cartilage Thickening/Stabilization in Control Knee.

Change Period	Knee Compartment	n	Correlation Coefficient	p-value
Baseline to 6 months	Entire Femoral Condyle	78	-0.068	0.55
	Medial Femoral Condyle	78	-0.053	0.65
	Entire TF	78	0.043	0.71
	Medial TF	78	0.011	0.93
Baseline to 12 months	Entire Femoral Condyle	78	-0.174	0.13
	Medial Femoral Condyle	78	-0.246	0.03
	Entire TF	78	0.011	0.92
	Medial TF	78	-0.085	0.46

Discussion

In this study, we measured femoral bone shape using the B-score metric that describes changes along a vector tracing a linear path from a normal, non-osteoarthritic state to the pathological shape of the osteoarthritic knee. Pathological shape change is characterized by the broadening and flattening of the femoral condyles and tibial plateaus and the growth of osteophytes. The vector is defined by KLG=0 at its origin and KLG≥2, where a higher B-score is more radiographically pathologic, and, as demonstrated in previous work, is associated with progressive knee OA. Knees treated with IA TPX-100 had a bone shape change at 6 and 12 months similar to that of knees classified as KLG=0. This was substantially different from the trajectory of control knees, which was similar to that of knees classified as KLG≥2. There were no significant baseline group differences in any clinical or MRI measures.

These data represent, to our knowledge, the first report of an investigational agent demonstrating a significant treatment difference compared with placebo on pathologic bone shape (B-score) change in the knee. A previous study of the novel Cathepsin K Inhibitor MIV-711 demonstrated a reduction of pathological bone *surface area* change in subjects with knee OA at 6 months, with no group differences in clinical outcomes [16]. While clinically meaningful, treatment-related differences in B score changes have not been defined, the difference in the rate of B-score change between TPX-100-treated knees and placebo-exposed knees were notable, suggesting a slowing of the OA-related bone pathology associated with OA progression and predictive of joint failure. In addition, treatment-associated reductions in B-score

correlated significantly with reduced cartilage thickness loss in medial and total tibiofemoral cartilage in TPX-100-treated knees.

There were limitations in this study. TPX-100-5 was a retrospective analysis of the subset of Study TPX-100-1 subjects including those with tibiofemoral OA, mild to severe, in addition to PFOA, whose MRI images were qualified for bone shape analyses. However, the statistical analysis plan for the study was finalized prior to image qualification and analysis, and all analyses were performed blind to timepoint, treatment assignment and all clinical information. As bone-shape analysis was not part of the original (TPX-100-1) study plan, the MR image sequence used was designed for manual cartilage segmentation and therefore was not optimal for automated bone segmentation and shape analysis, for which thinner, 0.75mm slices would have been preferred. Nevertheless, all the image data that could be utilized were included in the analysis without any specific subject selection. The severity of OA in the subject population was defined by using MRI-based cartilage defect (ICRS) scoring after clinical inclusion/exclusion criteria were met. ICRS grading was performed by central readers blind to clinical information in order to establish a baseline of structural severity, and to exclude significant meniscal pathology and synovitis, per study exclusion criteria.

Conclusions

These results of structural imaging in TPX-100-treated knees compared with placebo-exposed knees, in combination with previously reported robust improvements in established clinical outcomes (as measured by WOMAC and KOOS scores), support the potential of TPX-100 as a candidate disease modifying drug in knee OA.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained prior to study enrollment. Institutional Review Board approval was obtained from Western IRB with approval ID #20131394.

Consent for publication

Not applicable.

Availability of data and materials

Osteoarthritis Initiative (OAI) source data are available from https://data-archive.nimh.nih.gov/oai/. The datasets generated and/or analyzed within this publication are available from the corresponding author on reasonable request.

Competing Interests

AB and **MB** are employees of Imorphics, Manchester, UK. **DM**, **MM**, **DR**, and **YK** are employees of OrthoTrophix, Inc., Oakland, CA. **NS** reports no competing interests.

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Author Contributions

DM was responsible for the conception and design of the study. **AB** was responsible for initial drafting the article. **DM**, **YK**, **MM**, **DR**, **AB**, **MB** and **NS** provided critical revision of the article for important intellectual content. All authors were responsible for analysis and interpretation of the data and for final approval of the article and take responsibility for the integrity of the work.

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