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THE DYNAMICS OF INTRATHECAL BOLUS AND FACTORS OF INTRATHECAL PHARMACOKINETICS

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Synopsis: Intrathecal drug delivery is an established method in pain and spasticity management. However, the mechanisms of drug transport are not completely understood, which creates certain difficulties in the interpretation of the available data and hinders the development of new therapies. Our studies enable an integral mechanistic explanation of the transport phenomena within the cerebrospinal fluid as well as from the cerebrospinal fluid into the CNS and other compartments. This potentially opens new ways for optimization of delivery procedures for the existing drugs as well as for developing novel drugs specifically designed for cerebrospinal delivery.

Purpose: The goal of our studies was to investigate the dynamics of in vivo transport of solutes administered to the cerebrospinal fluid (CSF) and evaluate the potential routes of non-diffusional drug entrance from the CSF to the CNS.

Methods: To observe solute transport by PET, experimental large and small molecules were labeled with 124I or 89Zr and administered intrathecally (IT) to rats and cynomolgus monkeys. Dynamic imaging data (0-30 min post injection) and multiple whole-body images (over at least 48 hours) were acquired using Siemens MicroPET focus 220 imager; CT images were acquired for each PET session using CereTom NL 3000 CT scanner (Neurologica, USA). Images were analyzed to determine the rates and patterns of the label spread within the CSF from the injection site and farther into the CNS and towards the systemic circulation. To evaluate the potential routes of non-diffusional drug entrance from the CSF to the CNS, a model fluorescent macromolecule capable of labeling multiple cell types was administrated intrathecally in rats; the microdistribution of the label was studied by fluorescence photoimaging in unstained cryosections.

Results: PET studies showed that the initial solute distribution in the CSF greatly depended on the injected volume. Solutes injected at a low volume initially localized at the opening of the catheter/needle. Solutes injected at a high volume immediately translocated to the cervical/basal cerebral area (up to >90% of the injected dose). The subsequent solute spread depended on the initial location and was slow in the spinal CSF (millimeters per hour) but fast in the cerebral CSF (complete equilibration within 30 min). No evidence of directional solute flows anywhere in the CSF was found. The general patterns of solute transport in the CSF of rodents and monkeys were similar. The data suggest a strong size dependence of solute clearance from the CSF, likely through at least three different mechanisms, including two types of pores and diffusion. In monkeys, no evidence of significant lymphatic drainage from the CSF was found in any region. In rats some lymphatic drainage was detected in the deep anterior cervical area (lymphatic uptake of ca. 3% of the injected dose). Solute translocation into the brain and cerebellum from the CSF was observed by PET during the first 3-5 hours after the injection (depending on the probe), with subsequent biphasic clearance. The routes of translocation were further investigated with fluorophores labeling multiple cell types. Massive labeling of the perivascular channels entering the CNS from the outer as well as the inner boundaries was observed throughout the CNS (brain, cerebellum, spinal cord) with indications of probe exit to the parenchyma. The rate and depth of the entrance exclude diffusion-driven mechanisms. The “coverage” of the parenchyma by large and small transporting channels of various morphologies was found to be very significant; their exact density is a subject of an ongoing investigation.

Discussion: The overall mechanistic landscape of the cerebrospinal solute transport significantly differs from the paradigm suggesting that CSF bulk flows prevail outside the CNS, whereas interstitial flows prevail within. The major factor of the initial distribution of the administered drug is the hydrostatic compliance of the compartment. The secondary drug distribution in the CSF is an interplay of hydrostatic factors, molecular recognition and (for small molecules) diffusion. The subsequent phase of drug entrance into the CSF is an interplay of active perivascular transport, molecular recognition and diffusion.
Conclusions:
1. The observed transport phenomena can explain most, if not all, known but insufficiently understood effects of IT administered drugs.
2. The observed transport timeframes suggest a possibility for optimizing IT schedules of existing drugs, as well as a strong potential for developing highly effective, targeted novel intrathecal therapies in the near future.

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References:
IMPROVING RESPONSE TO TREATMENT FOR PATIENTS WITH DDD WITH THE USE OF THE FIBRONECTIN-AGGRECAN COMPLEX

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Abstract Introduction: Protein biomarkers associated with lumbar disc disease have been studied as diagnostic indicators and therapeutic targets. A cartilage degradation product, the Fibronectin-Aggrecan complex (FAC) identified in the epidural space, has been shown to predict response to lumbar epidural steroid injection in patients with radiculopathy from herniated nucleus pulposus (HNP) and identified in patients with degenerative disc disease (DDD). A therapeutic agent that prevents the formation of the G3 domain of aggrecan will reduce the fibronectin-aggrecan G3 complex and accordingly may be an efficacious treatment. Since the production of G3 domain of aggrecan is catalyzed by different known classes of proteases, a common inhibitor of all of these proteases could be an ideal therapeutic agent. Such a protease inhibitor is found in plasma and synovial fluid, alpha-2-macroglobulin (A2M). This investigation attempted to determine the ability of FAC to predict response to biologic therapy with concentrated autologous A2M for patients with LBP from Degenerative Disc Disease (DDD).

Methods: This study was a prospective cohort of 24 patients with low back pain and MRI positive for DDD. Outcome Measures included Oswestry disability index (ODI) and visual analog scores (VAS). They were noted at baseline and at 3- and 6-month follow-up. Primary outcome of clinical improvement was defined as patients with both a decrease in VAS of at least 3 points and ODI >20 points. All patients underwent lavage for molecular discography and delayed FAC analysis and injection of platelet poor plasma rich in A2M at the time of the intradiscal injection. Statistics using Anova with Bonferroni correction and Pearson correlation analysis was performed.

Results: Patients with FACT-positive assays were significantly more likely to show improvement in their VAS and ODI at follow-up. Mean VAS improvement in FACT-positive patients was 4.9 +/- 0.9 and 4.0 +/- 1.0 at 3 and 6-months, compared to 1.5 +/- 1.2 and 2.3 +/- 1.3 in those with negative FACT (p < 0.0001). Similarly, ODI improved on average 37 +/- 9.3 and 28 +/- 14 points at 3- and 6-months in FACT-positive patients compared to 9.4 +/- 11.9 and 12.6 +/- 11.8 points at 3- and 6-months in FACT-negative patients (p<0.0001). Correlation analysis demonstrated that a FACT-positive test correlates with improvement in 3-month VAS (Pearson r = 0.83; p < 0.0001) and ODI (Pearson r = 0.71; p<0.0001) and 6-month VAS (Pearson r = 0.58; p<0.0001) and ODI (Pearson r = 0.53; p<0.0001). When a 20-point ODI improvement cut-off is applied, 77% of FACT+ patients and 27% of FACTnegative patients meet this strict definition of clinical improvement.

Discussion: Patients who are “FAC+” within the disc are more likely to demonstrate clinical improvement following intradiscal autologous A2M injection. The results of this investigation suggest that autologous A2M may be an efficacious biologic treatment in discogenic pain and that FAC may be an important biomarker in patient selection for this treatment. We utilized a definition of clinical improvement that was in excess of the minimal clinically improved difference (MCID). Additionally, our defined outcome measure was a combination of two universally accepted outcome parameters (ODI and VAS). The current study provides evidence for a molecular biomarker that may improve patient selection and thus clinical outcomes in the treatment of discogenic back pain.

Significance: This study demonstrates that a platelet poor autologous concentrate rich is A2M is likely to result in clinical improvement of LBP in patients who demonstrate the FAC in the suspected disc. This pilot study shows that a combination of diagnostic and therapeutic may be the 1st theranostic application for CLBP of discogenic origin.
SAFETY AND EFFICACY OF INTRATHECAL ZICONOTIDE IN PATIENTS WITH COMPLEX REGIONAL PAIN SYNDROME

Authors: Mark Wallace, MD, I-Zu Huang, MD, Richard L. Rauck, MD

Synopsis: This analysis of a subpopulation of patients with complex regional pain syndrome who received intrathecal ziconotide in an open-label, multicenter study reports change from baseline in Visual Analog Scale of Pain Intensity (VASPI) score (ranging from 0 mm [“least possible pain”] to 100 mm [“worst pain imaginable”]). Mean (standard deviation) percentage change from baseline VASPI score was -16.8% (40.1%) at month 1 (n=57). The proportion of treatment responders (≥30% reduction from baseline VASPI) at month 1 was 29.8% (17/57 patients). The most common adverse events were nausea (70.7%), headache (61.3%), and dizziness (50.7%).

Purpose: This analysis evaluated the safety and efficacy of ziconotide in the subpopulation of complex regional pain syndrome (CRPS) patients who received ziconotide in a long-term (≥3 months), open-label, multicenter study.

Methods: The study enrolled patients with chronic, severe, noncancer pain with a demonstrable neurological basis, or pain related to cancer or AIDS or their treatment. Ziconotide was administered via continuous intrathecal infusion at an initial dose of ≤2.4 mcg/d, which was titrated to patient response (not to exceed 2.4 mcg/d every 24 hours). Efficacy was measured through Visual Analog Scale of Pain Intensity (VASPI) score (ranging from 0 mm [“least possible pain”] to 100 mm [“worst pain imaginable”]). Per protocol, VASPI was assessed twice weekly up to month 1, then at discontinuation of intrathecal ziconotide, post-discontinuation follow-up, and study termination. The efficacy outcome for this post hoc analysis was change in VASPI score from baseline to month 1.

Results: The overall study population consisted of 644 patients who received intrathecal ziconotide. Of 75 patients diagnosed with CRPS, 62.7% were female and mean (standard deviation [SD]) age was 42.2 (12.2) years. Mean baseline (SD) VASPI score was 74.9 (16.6) mm. Mean (SD) percentage change from baseline VASPI score was -16.8% (40.1%) at month 1 (n=57 CRPS patients with available data). The proportion of treatment responders (with ≥30% reduction in VASPI from baseline) at month 1 was 29.8% (17/57 patients). The most common adverse events among all-treated CRPS patients (≥25% of patients) were nausea (70.7%), headache (61.3%), dizziness (50.7%), pain (49.3%), confusion (40.0%), somnolence (38.7%), memory impairment (34.7%), arthralgia (28.0%), asthenia (26.7%), constipation (26.7%), hypertonia (26.7%), nystagmus (26.7%), vomiting (26.7%), and fever (25.3%). The most common serious adverse events (≥5% of patients) were depression (5.3%) and pneumonia (5.3%).

Discussion: Intrathecal ziconotide reduced mean VASPI scores at month 1 in patients with CRPS. The adverse event profile of ziconotide was consistent with the prescribing information.

Conclusion: Intrathecal ziconotide may be an effective treatment option for patients with severe chronic pain related to CRPS. Analyses are ongoing to assess the impact of ziconotide on pain reduction at later time points. Funding support provided by Jazz Pharmaceuticals.

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DEEP BRAIN STIMULATION FOR PAIN - AN UNDERESTIMATED THERAPEUTICAL OPTION?

Author: François Alesch, MD

Today, deep brain stimulation (DBS) is well known as a powerful and established therapy in the treatment of movement disorders (Parkinson’s disease, dystonia).

To little is known that the origins of DBS are close to Napa, at the University of California San Francisco, where Yoshio Hosobuchi developed this technique in the early 1970ies as a treatment for neuropathic facial pain. Based on the good results of spinal cord stimulation (SCS) in the treatment of chronic pain he was looking for an equivalent therapy for regions that are not connected to the spinal cord. In fact it was "spinal cord for the brain", using equipment for SCS. He called it “deep” in order to differentiate it from superficial cerebellar stimulation which was popular at that time. While Hosobuchi reported about the sensory thalamus as a target for stimulation, subsequent authors showed good effects of DBS in the centre médian, the nucleus parafascicularis, the periaquaeductal, and the periventricular gray.

The stereotactic technique used for implanting the DBS leads took full advantage of the somato- and functiotopy of the brain and allowed to reach pain circuits at many levels.

DBS in pain has been used in various conditions like neuropathic facial pain, thalamic syndrome, root avulsion, zoster, plexus lesions, and even in nociceptive pain. Unfortunately the published series were small, only retrospective and too heterogenous so that DBS for pain never got the role that it probably deserves. Problems in reliability, biocompatibility, and availability were other factors impacting negatively the acceptance of DBS in the treatment of pain.

Today, DBS in movement disorders outshines by far the use of DBS in pain. The implanted material is safe, and it also offers a multitude of technical features (constant current stimulation, multi source generators, segmented electrodes, user switchable programs, recharge-ability and thus miniaturization) improving the application of the therapy. Implantation tools like the use of high definition MRI, and diffusion tension imaging (DTI, fiber tracking) have further optimized targeting.

All these technical improvements can equally be used in DBS for pain.

Therefore the use of DBS in pain cases, where conservative and/or neuromodulative therapies fails, should be encouraged.
EFFECTIVENESS AND SAFETY OF INTRATHECAL ZICONOTIDE AS THE FIRST AGENT IN PUMP FOR ADULT PATIENTS WITH SEVERE CHRONIC PAIN

Authors: Michael F. Saulino, MD, PhD, Timothy Deer, MD, Richard L. Rauck, MD, Philip Kim, MD, Mark Wallace, MD, Eric Grigsby, MD, I-Zu Huang, MD, Geertrui F. Vanhove, MD, PhD, Gladstone McDowell, MD

Synopsis: This interim analysis of The Patient Registry of Intrathecal Ziconotide Management (PRIZM; an open-label, long-term, multicenter, observational study of adult patients with severe chronic pain) reports change from baseline through month 12 in Numeric Pain Rating Scale scores (NPRS; primary outcome) and Patient Global Impression of Change scores (PGIC; secondary outcome). Of 93 enrolled patients, 51 received ziconotide as the first agent in pump (FIP+) and 42 did not (FIP-). Greater treatment response was observed in FIP+ versus FIP- patients on both NPRS and PGIC scores. The adverse event profile of ziconotide was consistent with the prescribing information.

Purpose: The Patient Registry of Intrathecal Ziconotide Management (PRIZM) evaluates effectiveness and safety associated with intrathecal ziconotide use in clinical practice settings.

Methods: PRIZM is an open-label, long-term, multicenter, observational study of adult patients with severe chronic pain who meet ziconotide prescribing information criteria. This interim subset analysis (data as of July 10, 2015) of ziconotide as the first versus second-or-later intrathecal agent in pump reports percentage change from baseline to month 6 and month 12 in “average pain for the past 24 hours” on an 11-point Numeric Pain Rating Scale (NPRS; primary efficacy end point at week 12) and Patient Global Impression of Change (PGIC) score at months 6 and 12.

Results: Enrollment closed at 93 patients on June 30, 2015; data collection is ongoing. Fifty-one patients (54.8%) received ziconotide as the first agent in pump (FIP+), whereas 42 (45.2%) did not (FIP-). Mean (standard deviation) baseline NPRS scores were 7.4 (1.9) and 7.9 (1.6) in FIP+ and FIP- patients, respectively. Mean percentage change (standard error of the mean) in NPRS scores at month 6 were –29.4% (5.5%) in FIP+ (n=26) and 6.4% (7.7%) in FIP- (n=17) patients and at month 12 were –34.4% (9.1%) in FIP+ (n=14) and –3.4% (10.2%) in FIP- (n=9) patients. Improvement from baseline, measured by PGIC score, was reported in 69.2% of FIP+ (n=26) versus 35.7% of FIP- (n=14) patients at month 6 and 85.7% of FIP+ (n=7) versus 71.4% of FIP- (n=7) patients at month 12. The most common adverse events (≥10% of patients overall) were nausea (19.6% vs 7.1%; FIP+ vs FIP- patients, respectively), confusional state (9.8% vs 11.9%), and dizziness (13.7% vs 7.1%).

Discussion: In this interim PRIZM analysis, greater improvements in NPRS and PGIC scores from baseline to month 6 and month 12 were observed when ziconotide was initiated as first-line intrathecal therapy versus second-or-later intrathecal agent in pump. The adverse event profile of ziconotide was consistent with the prescribing information.

Conclusion: Intrathecal ziconotide provided clinically meaningful pain relief to a subset of patients who received ziconotide as the first agent in pump. The final analysis of the PRIZM study will provide additional information on the long-term effectiveness and safety of intrathecal ziconotide in the management of chronic pain.

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SUSTAINED EFFECTIVENESS OF INTRATHECAL ZICONOTIDE USE IN PATIENTS WITH SEVERE CHRONIC PAIN

Authors: Gladstone McDowell, MD, Eric Grigsby, MD, Michael F. Saulino, MD, PhD, Richard L. Rauck, MD, Philip Kim, MD, Mark Wallace, MD, I-Zu Huang, MD, Geertrui F. Vanhove, MD, PhD, Timothy Deer, MD

Purpose: The Patient Registry of Intrathecal Ziconotide Management (PRIZM) evaluates effectiveness and safety of intrathecal ziconotide use in clinical practice.

Methods: PRIZM is a long-term, multicenter, observational study of adult patients with severe chronic pain who meet ziconotide prescribing information criteria. This interim subset analysis (data through July 10, 2015) of ziconotide as the first versus second-or-later intrathecal agent in pump reports change from baseline over time (months 3, 6, 9, and 12) in “average pain for the past 24 hours” with an 11-point Numeric Pain Rating Scale (NPRS; primary efficacy end point at week 12).

Results: Enrollment closed at 93 patients. In this analysis, 61 patients had been enrolled for ≥12 months; 30 patients were still active in the study at month 12, of whom 21 had NPRS scores at months 3, 6, 9, and 12. Thirteen of 21 patients (61.9%) received ziconotide as the first agent in pump (FIP+), whereas 8 (38.1%) did not (FIP-). Mean (standard deviation) baseline NPRS scores were 7.4 (1.3) and 8.3 (1.2) in FIP+ and FIP- patients, respectively. Mean percentage change (standard error of the mean) in NPRS scores for FIP+ and FIP- patients were -19.2 (7.9)% and -12.2 (7.8)% at month 3, -30.8 (7.2)% and -4.3 (4.0)% at month 6, -22.8 (9.3)% and -22.3 (7.4)% at month 9, and -32.7 (9.7)% and -5.4 (11.4)% at month 12, respectively. The most common adverse events (≥5 patients overall) were peripheral edema (38.5% vs 0%; FIP+ vs FIP- patients, respectively), amnesia (30.8% vs 12.5%), and auditory hallucination (30.8% vs 12.5%), and auditory hallucination (30.8% vs 25.0%).

Discussion: Data from this small interim subset analysis of the PRIZM database suggest that there may be a greater sustained treatment response for up to 12 months when ziconotide is initiated as first-line intrathecal therapy versus second-or-later intrathecal agent in pump. The adverse event profile was consistent with ziconotide prescribing information.

Conclusion: Intrathecal ziconotide provided sustained pain relief to a subset of patients who received ziconotide as the first agent in pump. The final analysis of the PRIZM study will provide additional information on the long-term effectiveness and safety of intrathecal ziconotide in the management of chronic pain.

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EFFECTIVENESS AND SAFETY OF INTRATHECAL ZICONOTIDE: INTERIM ANALYSIS RESULTS FROM A SINGLE CENTER OF THE PATIENT REGISTRY OF INTRATHECAL ZICONOTIDE MANAGEMENT

Authors: Gladstone McDowell, MD, Michael F. Saulino, MD, PhD, Richard L. Rauck, MD, Philip Kim, MD, Mark Wallace, MD, Eric Grigsby, MD, I-Zu Huang, MD, Fannie Mori, MS, Geertrui F. Vanhove, MD, PhD, Timothy Deer, MD

Synopsis: This interim analysis of The Patient Registry of Intrathecal Ziconotide Management (PRIZM), an ongoing, open-label, long-term, multicenter (23 sites), observational study of adults with severe chronic pain, evaluated findings from the site with the highest enrollment (n=13). Use of ziconotide appeared to provide pain reduction through month 12 in patients with ziconotide as first-line intrathecal therapy. Favorable clinical outcomes observed at this PRIZM site may be related to use of ziconotide as the first intrathecal agent in pump and investigator-specific practices (such as high frequency of patient contact and opportunity for dose adjustment, and high use of patient-administered bolus dosing).

Purpose: The Patient Registry of Intrathecal Ziconotide Management (PRIZM) evaluates effectiveness and safety associated with intrathecal (IT) ziconotide use in clinical practice settings.

Methods: PRIZM is an ongoing, open-label, long-term, multicenter (23 sites), observational study of adult patients with severe chronic pain who meet ziconotide prescribing information criteria. Study assessments are scheduled at baseline, weeks 1, 2, 3, 4, 8, and 12, and every 3 months thereafter through month 18. The primary efficacy outcome measure assessed change from baseline to week 12 in “average pain for the past 24 hours” on an 11-point Numeric Pain Rating Scale (NPRS). This interim analysis reports change in NPRS score from baseline to month 12 from the site with the highest enrollment (site 9; n=13) in the PRIZM study. At the time of this interim analysis, sample sizes at later time points were too small to merit reporting.

Results: PRIZM enrollment has closed at 93 patients; data collection is ongoing. Site 9 enrolled 13 patients, 12 of whom received ziconotide as the first agent in pump (FIP+) and 1 as the second-or-later intrathecal agent in pump (FIP-). Mean (SD) baseline NPRS score was 7.8 (1.5) in FIP+ patients; the FIP- patient had a baseline NPRS score of 4.0. At the time of this interim analysis, 10/12 FIP+ patients (83%) were enrolled ≥12 months prior; 80% (8/10) of patients were still active in the study at month 12 and 37.5% (3/8) of these patients remained on ziconotide monotherapy. The FIP- patient was not enrolled in the study at month 12. The number of patient visits corresponded with the study schedule through week 8, after which patients were seen approximately 2 to 5 times more frequently than the per-protocol visits scheduled at week 12 and every 3 months thereafter. In addition to continuous infusion dosing, all patients except for 1 in the FIP+ group had patient-administered bolus dosing enabled (via the Medtronic® Personal Therapy Manager [my PTM®]); the onset and duration of patient-administered dosing varied. Mean (SD) ziconotide dose in FIP+ patients was 1.03 (0.08) mcg/d (n=12) at baseline, 4.46 (5.76) mcg/d (n=10) at week 12, 3.44 (2.92) mcg/d (n=9) at month 6, and 1.52 (1.08) mcg/d (n=8) at month 12. Dosing in the FIP- patient was 1.20 mcg/d at baseline, 2.50 mcg/d at week 12, and 1.00 mcg/d at month 6; no available data at month 12. Mean (SEM) percentage change in NPRS score in FIP+ patients was -34.6% (9.0%; n=10) at week 12, -37.3% (9.3%; n=9) at month 6, and -46.1% (12.6%; n=8) at month 12. In the FIP- patient, percentage change in NPRS score was 100.0% at week 12 and month 6; no data available at month 12. In FIP+ patients, treatment response rates were 60.0% (n=10) at week 12, 55.6% (n=9) at month 6, and 75.0% (n=8) at month 12 for response defined as ≥2 unit decrease in NPRS score; and 50.0% (n=10) at week 12, 55.6% (n=9) at month 6, and 50.0% (n=8) at month 12 for response defined as ≥30% decrease in NPRS score. The FIP- patient did not respond to treatment. The most common adverse events (≥3 patients overall) were amnesia (38.5%), peripheral edema (30.8%), memory impairment (23.1%), nausea (23.1%), and vertigo (23.1%).

Discussion: In this interim analysis of the highest-enrolling PRIZM site, use of ziconotide appeared to provide pain reduction through month 12 in patients with ziconotide as first-line intrathecal therapy. Analysis limitations include the use of a small number of patients from a single site. The adverse event profile was consistent with ziconotide prescribing information.

Conclusion: Favorable clinical outcomes observed at this PRIZM site may be related to use of ziconotide as the first IT agent in pump, and investigator-specific practices (such as the high frequency of patient contact and opportunity for dose adjustment, and high use of patient-administered IT bolus dosing).

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EFFECT OF LEAD POSITION ON NEURAL RECRUITMENT DURING DORSAL ROOT GANGLION STIMULATION: COMPUTATIONAL MODELING ANALYSIS

Authors: Alexander R. Kent, Jeff Kramer, Xiaoyi Min

Synopsis: This work investigated the effect of dorsal root ganglion (DRG) lead position on neuronal recruitment. A finite element analysis model was used to calculate electrical potentials generated in the DRG and dorsal root (DR) during stimulation across lead positions, and was coupled to cellular models of Aβ-neurons to determine which neurons were recruited. Stimulation contacts that straddled the DRG generated greater recruitment than placement of a single contact over the DRG or both contacts over the DR. Moreover, recruitment decreased with dorsal shifts in the lead position. This indicates the importance of contact placement near the DRG for maximal recruitment.

Purpose: A clinical study demonstrated superior pain relief for dorsal root ganglion (DRG) stimulation over traditional spinal cord stimulation.1 Large variability in the DRG stimulation amplitude was observed across patients, which may be related to differences in lead placement. The goal of this work was to investigate the effect of Axium™ DRG lead position on neuronal recruitment using coupled finite element analysis (FEA) and cellular models.

Methods: The FEA model was built in Maxwell3D and implemented relevant anatomical structures. The four-contact lead was placed along the DRG midline and delivered bipolar stimulation. The first lead position (P1) used contact 2, centered 0.15mm cranial to the DRG, and contact 3 over the dorsal root (DR). The second lead position (P2) was characterized by a 3mm medial lead shift from P1, and used contacts 1 and 2 to straddle the DRG, while the third position (P3) had the same lead position as P2 but used contacts 3 and 4 above the DR. Additional lead positions were generated by shifting the lead dorsally away from the DRG by 3mm (P1’, P2’, P3’). Within the DRG and DR, 346 mammalian Aβ-neurons were randomly distributed, consisting of a soma, myelinated axons, and T-junction. The electrical potentials from FEA were coupled at the locations of the modeled neurons, and applied in a cellular model as a single biphasic stimulation pulse (150 μA amplitude, 200 μs pulse-width, 20 μs intra-pulse delay).

Results: Recruitment of DRG neurons was assessed for different lead positions. With cathodic-first stimulation delivered to the distal contact, 30% and 72% of neurons within the DRG were recruited for P1 and P2, respectively. After the lead was moved dorsally, neuronal recruitment decreased to 1% and 37% for P1’ and P2’. Using anodic-first stimulation, 18% and 56% of neurons were recruited for P1 and P2, and this decreased to 1% and 29% following a dorsal shift (P1’ and P2’). With both electrodes placed above the DR (P3), 3% of neurons were recruited for both cathodic- and anodic-first stimulation, and this decreased to 0% with the dorsal shift (P3’).

Discussion: Stimulation contacts that straddled the DRG generated greater recruitment than placement of a single contact over the DRG or both contacts over the DR. Moreover, dorsal shifts in the lead position led to declines in recruitment. This indicates the importance of contact placement near the DRG for maximal recruitment, and may influence future lead designs. In this future, this model may be used to study the effect of DRG stimulation at the single cell level, which may help to improve our understanding of the mechanisms of sub-sensory DRG stimulation.

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ACHIEVING PARESTHESIA-FREE ANALGESIA WITH SUBTHRESHOLD STIMULATION OF
THE DORSAL ROOT GANGLIA

Author: William Cusack, PhD

Synopsis: This retrospective review investigates the therapeutic efficacy of utilizing paresthesia-free dorsal root ganglion (DRG) stimulation for the management of chronic pain. Forty subjects met the selection criteria for this analysis. Changes in pain relief were measured using a Visual Analog Scale (VAS) between baseline and measurements over 12 months. On average, subjects reported continued pain relief of 59.0%, 68.1%, 64.5%, 64.1% and 58.9% at the postimplantation, 1, 3, 6, and 12-month follow-ups, respectively. DRG stimulation programmed at amplitudes below the perceptual level yielded significant overall pain relief over 12 months. Importantly, these patients did not experience paresthesias.

Purpose: Dorsal root ganglion (DRG) stimulation has become an attractive option for the treatment of chronic intractable pain.1 Neuromodulation of specific regions of the dermatome, that are otherwise difficult to reach with traditional spinal cord stimulation (SCS), is possible due to the somatotopic organization of the DRG at each segmental level of the spinal cord.2 Further, anecdotal clinical observations and preliminary data suggest that paresthesia can be eliminated by decreasing the stimulation amplitude below the perceptual level (subthreshold) without loss of analgesia.3 This is significant, as recent focus in the literature has been placed on achieving paresthesia-free pain relief in patients using traditional SCS.4,5 The purpose of this retrospective review is to investigate the therapeutic efficacy of a patient cohort utilizing subthreshold DRG stimulation for the management of intractable chronic pain.

Methods: Forty subjects (22 female, 18 male) at a single site met the selection criteria for this retrospective analysis. Patients had at least one DRG stimulation lead placed between spinal levels C6-S1. Six subjects required revisions of either the trial or permanent leads, and three subjects became deceased. Changes in pain relief were measured using a Visual Analog Scale (VAS) between baseline and measurements post-trial, post-implant, and 1, 3, 6, and 12-month follow-ups.

Results: All subjects were programmed according to the regional standard of care, which includes maintaining stimulation amplitudes below the perceptual threshold. Subjects in this cohort selfreported in a survey that they did not experience paresthesia at any of the follow-up visits. On average, subjects reported a reduction of overall pain of 66.2% after the trial stimulation phase was completed. Subjects reported continued pain relief of 59.0%, 68.1%, 64.5%, 64.1% and 58.9% at the post-implantation, 1, 3, 6, and 12-month follow-ups.

Discussion: DRG stimulation programmed at amplitudes below the perceptual level yielded significant and sustained overall pain relief for a period of 12 months after neurostimulator implantation. Importantly, these patients also reported experiencing paresthesia-free analgesia. These outcomes are suggestive of several mechanisms of action underlying subthreshold stimulation, including the inhibition of supraspinal regions involved in somatic paresthesia sensation, as well as local attenuation of pathological neural activity at the DRG.6,7

Conclusion: The retrospective results presented here posit that future prospective study of subthreshold DRG stimulation is warranted. This work was supported by St. Jude Medical.
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Conference Tracks: Neuromodulation of the Brain and Central Nervous System

Conflict of Interest: This work was supported by St. Jude Medical.
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Submission Category: Therapeutic Options for Pain Management

Funding: Boston Scientific

Background: Chronic pain disorders can be inherently complex and significantly differ in presentation and etiology from patient to patient. Therefore, customizing spinal cord stimulation therapy offers the prospect of addressing patient variability by tailoring disease treatment to each patient. The recent availability of different treatment modalities in Spinal Cord Stimulation (SCS) such as standard rate, 1 kHz, 10 kHz, burst, anode intensification, Multiple Independent Current Control (MICC), and 3D Neural Targeting SCS now enables for the potential real world, clinical application of highly customized SCS therapy. To begin to understand how patients utilize different modalities when empowered with different targeting and waveform options from a single SCS device, we embarked on a device utilization registry study. In this specific analysis, the usage of novel stimulation waveforms is examined.

Methods: This is a retrospective, multicenter device utilization registry study. All subjects have been implanted with a commercially-approved neurostimulator (Precision Spectra, Boston Scientific) equipped with MICC and 3D Neural Targeting technology and programming options for novel stimulation waveforms (1 kHz subperception, burst stimulation, and anode intensification) as well as standard rate stimulation (≤ 1 kHz). To date, 1,820 patients have been evaluated for utilization.

Results: Subjects evaluated so far have been observed to use a large number of different programs from 0-30 days postimplant (~6 programs) but stabilize by 6 months post-implant (~2-3 programs). Seventy percent of subjects were found to have used one or more novel stimulation waveforms (1 kHz subperception, burst stimulation, and anode intensification). In addition, more than half of the patients evaluated (53.5%) were found to have frequently utilized these novel stimulation waveforms on multiple days. The proportional patient usage of these novel stimulation waveforms was identified to be the following: anode intensification, 60.1%; 1 kHz subperception, 53.3%; burst stimulation, 37.3%.

Conclusion: Analysis of collected patient utilization data demonstrates that multiple SCS programs/waveforms are used by patients long-term when provided with programming options within a single device. This and other utilization data obtained so far in this study underscores the clinical relevance of a single device capable of multiple programming options that enables patients to highly customize stimulation for different waveforms as well as specific anatomical targets. This study also suggests that additional on-going data collection, advanced analytics, and objective preclinical research will likely even further drive understanding of how best to customize SCS to each patient.
REAL WORLD DISABILITY AND PRODUCTIVITY OUTCOMES FOLLOWING 3D NEURAL TARGETING SPINAL CORD STIMULATION

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Category: Patient Evaluations, Monitoring and Ongoing Assessment

Funding: Boston Scientific

Background: Successful spinal cord stimulation (SCS) therapy in patients with chronic pain may not only improve pain intensity but may also reduce disability and increase activities of daily living (ADL). A recently introduced SCS paradigm using a 3-dimensional (3D) algorithm to customize stimulation (3D Neural Targeting SCS) has enabled SCS treatment of pain areas which have historically been challenging, such as low-back pain. This has potentially opened up new possibilities for functional improvement in patients suffering from predominant back pain.

Objective: We undertook a large observational study to characterize real-world disability and physical, functional outcomes using 3D Neural Targeting SCS out to 2 years post implant.

Methods: This sub-study of the larger LUMINA clinical study is a multi-center, consecutive, observational assessment of 100 subjects using Precision Spectra SCS (Boston Scientific Corporation) for chronic, intractable pain of the low back and/or legs out to 2 years post-implant. The majority of subjects in this sub-study (72%) reported severe pain at baseline. In addition, 62% percent of subjects reported only experiencing low back pain at baseline.

Results: To date, significant reductions in Oswestry Disability Index (ODI) scores and Numeric Rating Scale (NRS) scores, with increases in walking tolerance and an approximately 90% satisfaction rate, have been observed. Relative to baseline, these reductions include a 21.3 point decrease in mean ODI score, a 51% increase in mean walking time, and a 3.3 point drop in mean NRS score.

Conclusion: In subjects with moderate or severe low back and/or leg pain, 3D Neural Targeting SCS provided reduced disability (as measured by ODI and walking tolerance), reduced pain intensity (as measured by NRS), and produced generally high satisfaction rates.
COMPREHENSIVE ASSESSMENT OF THE SPINAL CORD STIMULATION PATIENT EXPERIENCE: A DATA ANALYTIC APPROACH COMBINING ESTABLISHED PAIN AND QUALITY OF LIFE OUTCOME MEASURES FROM THE RELIEF GLOBAL REGISTRY STUDY

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Category: Patient Evaluations, Monitoring and Ongoing Assessment

Funding: Boston Scientific

Introduction: Patient satisfaction with spinal cord stimulation therapy would depend on both pain relief and improvements in quality of life. Surprisingly, however, many studies report only weak to moderate correlation between pain control and patient satisfaction, such that some patients with minimal pain reduction still report treatment satisfaction (Pellino and Ward, 1998; Phillips et al., 2013; Shah et al., 2015; Silvemark et al., 2008), suggesting that pain ratings may not account for all facets of the patient experience. Here, we examine the relationships between pain ratings and quality of life responses following spinal cord stimulation (SCS) to identify the key factors driving patient satisfaction. We also identify groups of patients whose experiences cannot be adequately expressed by a single pain numeric rating scale (NRS).

Methods: RELIEF is a prospective, multi-center, global clinical data registry that collects patient outcomes for neurostimulation systems utilized on-label to treat chronic pain in routine clinical practice. Our study utilizes data across all assessments collected on patients who have completed their 12 month visit post-implantation.

Results: Two hundred and sixteen SCS patients provided responses on patient satisfaction, pain, and quality of life during the 12 month post-implant visit. The questionnaires were not scored and responses were analyzed using Spearman’s rho correlations to achieve a more finely grained assessment of the results. Patients’ perception of pain at follow-up was found to be more closely tied to patients’ satisfaction of overall therapy than with quality of life measurements. In addition, medical history profiles of the 42 patients who reported a discordant relationship between pain control and satisfaction with overall therapy (less than 1 point reduction in NRS yet are completely or somewhat satisfied) were compared to the medical history profiles of the other patients. A logistic model selection of 86 medical history variables was performed using lasso. Daily or near daily usage of opioids at Baseline was found to be a contributing factor to patients feeling satisfied despite little to no pain control.

Discussion: We analyzed a large array of variables to provide a comprehensive assessment of patients’ reporting patterns on SCS effectiveness in chronic pain treatment. Although the NRS score is the most commonly reported metric for assessing SCS effectiveness, given the complexity in reporting pain, a single NRS measure is not adequate for summarizing a patient’s entire pain experience.

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LONG-TERM OUTCOMES OF 3D NEURAL TARGETING SPINAL CORD STIMULATION:
FINAL RESULTS OF THE LUMINA STUDY

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Synopsis: This study sought to characterize the long-term, real-world outcomes of Neural Targeting SCS in the treatment of chronic pain. LUMINA is a retrospective, multi-center, consecutive, observational study across 13 clinical sites of 213 patients treated out to 2 years post-implant using the Precision Spectra SCS system (Boston Scientific). The mean overall pain reduction in all subjects and a subset of subjects classified as “severe” (NRS >8.0) decreased 4.2 and 5.3 points from baseline (7.17 and 8.75), respectively. Using this new technology paradigm, this study demonstrated long-term evidence of pain relief out to 2 years.

Category: Clinical Advancements in Pain Medicine

Funding: Boston Scientific

Background: Anatomically-guided neural targeting or 3D Neural Targeting SCS is a recently introduced paradigm consisting of a software algorithm that computationally derives 3-dimensional field potentials coupled with current fractionalization technology to customize neurostimulation with precise specificity. We undertook this clinical study (LUMINA), to characterize the long-term, real-world outcomes of 3D Neural Targeting SCS in the treatment of chronic pain including leg pain only, leg and back pain, and predominant back pain.

Materials/Methods: LUMINA is a retrospective, multi-center, consecutive study across 13 clinical sites of 213 patients treated out to 2 years post-implant using the Precision Spectra SCS system (Boston Scientific Corporation). Only “on label” treatment for low back and leg pain was required. After implantation, programming was performed using a patient-specific, model-based algorithm to adjust for lead position (3D neural targeting) or previous generation software. Pain intensity was measured on a 0-10 numerical rating scale – NRS. Responder rates (≥ 50% pain reduction) out to using a previous generation system (non-3D Neural Targeting SCS) versus those using 3D Neural Targeting SCS were determined.

Results: The mean overall pain reduction in all subjects and a subset of subjects classified as “severe” (NRS >8.0) decreased 4.2 and 5.3 points from baseline (7.17 and 8.75), respectively. All subjects (and “severe” subset) reporting low back pain only displayed a decrease in mean low back pain of 4.1 and 5.6 points from baseline (7.21 and 8.60), respectively. Responder rates were greater than 70% for overall and low back pain. Compared to a previous generation SCS system, statistically significant increases in response rates were observed using 3D Neural Targeting SCS.

Conclusion/Discussion: 3D Neural Targeting SCS is a novel SCS variant based on anatomical placement using a unique software algorithm. Using this technology, the results of this study demonstrated longterm evidence of significant overall and low-back pain relief out to 2 years.

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LOW BACK PAIN RELIEF WITH A NEW 32-CONTACT SURGICAL LEAD AND 3D NEURAL TARGETING ALGORITHM

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Synopsis: Advances in surgical lead capabilities are thought to be essential for improving SCS outcomes for low back pain. This study evaluates the real world outcomes of a new 32-contact surgical lead that combines MICC with 3D neural targeting SCS. Results demonstrated that significant overall and low back pain relief was achieved. These data provide support for the notion that advances in surgical lead design and associated technology/programming capabilities can lead to better SCS outcomes for use in treating low back pain.

Category: Clinical Advancements in Pain Medicine

Funding: Boston Scientific

Background/Purpose: Treatment of low-back pain using Spinal Cord Stimulation (SCS) has been historically challenging. Advances in surgical leads and programming capabilities have been thought to potentially enable improved low-back pain relief using SCS. A recently introduced 32-contact surgical lead, which couples multiple independent current control (MICC) and anatomically-based 3D neural targeting stimulation algorithms, allows for patient-specific programming optimization. We present here a real world, observational study of this 32-contact surgical lead.

Methods: A multi-center, consecutive, observational study of a new 32-contact surgical lead was carried out using the Precision Spectra SCS System (Boston Scientific) in 100 subjects out to 12 months post-implant. We examine medical history, procedural information, programming parameters, and clinical outcomes including pain reduction (NRS), activities of daily living, and change in pain medications.

Results: Surgical lead placement distribution was between T7 and L2, with most at T9 (26%). A mean reduction of 5.1 points (SD 2.15, p<0.001) from 7.8 (baseline) to 2.6 in overall pain was observed. A subset of subjects reporting low-back pain only exhibited a mean decrease of 6.0 points (SD 2.12, p<0.001) from 8.3 (baseline) to 2.2. Of these, 83.1% percent of subjects showed ≥50% back pain reduction. Increases in activities of daily living and reduction in pain medication usage were also observed in a majority of subjects.

Discussion: Subjects implanted with a 32-contact surgical lead using a 3D neural targeting algorithm demonstrated significant low-back pain reduction. These results support the postulate that advanced surgical leads and programming capabilities can foster improved low-back pain relief in subjects treated using SCS.

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