Case study: complex regional pain syndrome

Maria E. Sheean, Giuseppe Capovilla, Dinah Duarte, Andreas Farkas, Matthias Hofer, Michel Hoffmann, Julian Isla, Armando Magrelli, Segundo Mariz, Ana Mingorance, Benedetta Polsinelli, Mario Ricciardi, Evyenia Shaili, Violeta Stoyanova-Beninska, Josep Torrent-Farnell, Stelios Tsigkos, Bruno Sepodes

Introduction

The joint EMA/COMP Preclinical Models Working Group focuses on an in-depth literature and experience-based review of preclinical models that may be used to support orphan drug designations. Here we would like to highlight pre-clinical models which exist for complex regional pain syndrome and to evaluate assays pertinent to the core features of this condition. The work should also provide guidance regarding the COMP's views in required pre-clinical data to support orphan drug designation (ODD) applications.

There are two types of complex regional pain syndrome: Type I (reflex sympathetic dystrophy, Sudeck's atrophy, reflex neurovascular dystrophy or algoneurodystrophy) does not exhibit demonstrable nerve lesions. Type II (causalgia) has evidence of obvious nerve damage.

Breakdown of the condition:

- Aetiology: unclear, history of peripheral nerve injury or hemiplegia. Correlates with cigarette smoking
- Pathophysiology: aberrant inflammatory mechanisms, vasomotor dysfunction, and maladaptive neuroplasticity
- Clinical characteristics: severe pain in a limb accompanied by autonomic, sensory, motor and trophic changes, oedema, sweating asymmetry. The sensory changes include allodynia and hyperalgesia, are accompanied by movement disorders and joint stiffness and local osteoporosis.
- Prevalence: 3 in 10,000
- Core outcome measures (clinical):

  Pain and tenderness, oedema, joint mobility, dystrophic symptoms, sudomotor activity, bone density

Preclinical models

Model	Features	Relevance	Used for ODD / Available?	Limitations
Tibia fracture in rats	Chronic hind paw pain, oedema, warmth, and regional osteopenia	Pain, oedema, warmth and weight bearing can be measured	Yes/yes	No knowledge of exact mechanism of disease (genetic component?), limited knowledge of translatability , Selected symptoms or selected mechanism of action can be tested, no perfect model exists
Neuropathic pain induced by partial ligation of the sciatic nerve	Neuropathic pain and mechanical hyperalgesia – only supportive	Partial representation of type II CRPS, which is not just a neuropathic pain	Yes/yes	
Model of inflammatory pain induced by injection of CFA* in the rat	Inflammatory pain – only supportive	Anti-nociceptive effects can be tested in a non-bone related pain	Yes/yes	
Rat model of bone cancer pain - inoculation into the tibia of a mammary tumour cell line	Pain (osteoclast-mediated bone resorption and the development of allodynia and hyperalgesia) - only supportive	Pain, bone density can be tested	Yes/yes	
Chronic post-ischemia pain produced by prolonged hind paw ischemia and reperfusion	Hyperemia, acute plasma extravasation, pain (hyperalgesia, cold-allodynia and mechano-allodynia, but not heat-hyperalgesia)	Pain, oedema, warmth and weight bearing can be measured	**No**/yes	

Clinically relevant endpoints in models

Pain (pain threshold - mechanical hyperalgesia using the von Frey fibre paradigm), number of osteoclasts vs. hyperalgesia, oedema, warmth and weight bearing and molecular markers.

Conclusions

Since a better understanding of the disease is needed to fully evaluate each of these models and it is hard to identify models with a clear predictive value, a combination of experiments in several models would be recommended to support the medical plausibility.