Gene therapy and cement injection for restabilization of loosened hip prostheses
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Introduction: The number of total hip replacement operations is likely to increase considerably in the next decade due to longer life expectancy of populations and the relative success at long-term follow-up. However, within ten years after primary hip replacement 7-13% of patients will require revision surgery due to loosening. The only treatment for this is revision surgery, which has a high morbidity and mortality rate, especially in elderly patients with comorbidity.

Hip prostheses can either be fixed with bone cement or have bone ongrowth properties. Bone cement can also be used during revision surgery. In some of these cases the old cement of the primary hip arthroplasty is left in place and a new prosthesis is inserted in this cement canal using new cement. These data led to the idea of a percutaneous technique for removal of the interface tissue and subsequent percutaneous cement injection in the periprosthetic cavity. Neither part of this technique has been described so far. As was shown by our group, the interface tissue can be transduced and killed by the viral vector HAdV-5-ntr in combination with the prodrug CB1954. In order to evaluate this concept of removal of interface tissue and cement re-fixation of the prosthesis, a phase 1-2 clinical trial was performed in 12 elderly patients with considerable co-morbidity. The feasibility and 6 months follow-up of the clinical results are described here.

Materials and Methods: In this phase-1 dose escalation study of the replication-deficient adenoviral vector CTL102 and the prodrug CB1954, safety is the primary objective. Secondary endpoints are viral shedding and clinical outcome.

Elderly patients with debilitating pain from a loosened hip prosthesis causing ADL-dependency, and with significant comorbidity were eligible for inclusion. These patients were informed orally and in writing before informed consent was obtained. The study protocol was approved by the Central Committee on Research Involving Human Subjects (CCMO), the Ministry of Housing, Spatial Planning and the Environment and the local ethical committee. For inclusion an arthrogram and the Environment and the local ethical committee. For inclusion an arthrogram

Discussion: This study provides the first description of the use of gene therapy and cement injection to stabilize loosened hip prostheses. The study was designed as an alternative to revision surgery for elderly patients with serious comorbidity and thereby a high morbidity- and mortality-risk peri-operatively.

Up to the maximal vector dose of 1x1011 particles no dose limiting toxicity was observed. A prodrug dose of 24 mg/m² resulted in nausea and vomiting and rises in AST and ALT, therefore the prodrug dose was lowered to 16 mg/m². Four serious adverse events occurred, which were not attributed to the study.

Results of this study show that part of the radiolucent zone can be filled with cement, but not all. However the stability of the prosthesis in the bone has increased. The question that remains unanswered in this short follow-up is whether stabilization of the prosthesis leads to increase of bone stock over time, due to reduction of stress-shielding of the bone, and consequent bone loading after fixation of the prosthesis. Analysis of clinical outcome show improvement of function and pain after gene therapy and cement injection, especially in the two highest dose groups. Whether this difference between dose groups is caused by the higher dose of adenoviral vector or by an increasing learning curve for percutaneous cement injection can not be differentiated.