Bone and joint disorders: screening and early clinical drug development

Vrouwe, J.P.M.

SUMMARY

The aim of this thesis was to gain new insights on the diagnostic process- and treatment of pathological conditions of the bone (section I) and joints (section II).

Section I focuses on the impact of male urological malignancies and their therapies on bone health (**Chapters 2, 3**) and in an early phase clinical study, a compound targeting osseous metastases of prostate cancer was investigated (**Chapter 4**). In section II the focus is on inflammatory arthritis and the early clinical development of compounds targeting inflammatory joint disease (**Chapters 5-7**). **Chapters 2 and 5**, are reviews using peer-reviewed literature and registered clinical trials to gain new insights and overall conclusions. For the remaining **Chapters: 3, 4, 6 and 7**, new data was collected.

SECTION I – BONE IN MALE UROLOGICAL MALIGNANCIES

Section I describes if and how testis- and prostate cancer may affect the bone, whether quantitative ultrasonography is of aid to diagnose bone loss in patients with prostate cancer, and whether PEG-liposomal targeted therapy can be safely administered to patients with prostate cancer and osseous metastases.

Chapter 2 is a systematic review using data of testicular cancer survivors to describe the effects on bone quality due to testicular germ cell tumors (TGCT) and its treatment modalities. Both testicular cancer itself and therapies, in particular orchiectomy and chemotherapy, can have a detrimental effect on bone mineral density (BMD), and hence an increased risk for fragility fractures, which may be associated with morbidity and mortality. It does appear that these patients are at risk of developing osteoporosis. This particularly concerns patients treated with chemotherapy. The data also suggest that osteoporosis is more prevalent in patients for whom longer follow-up data are available, which probably reflects that osteoporosis progresses over time.

All included studies reported DXA outcomes, but due to large variations in the study designs and reported endpoints, a direct comparison of results of the included studies was difficult, and a meta-analysis was impossible. In addition, outcomes on important clinical endpoints (fragility fractures) were mostly kept unreported. Notwithstanding these limitations, screening of testicular cancer patients for osteoporosis, in particular those who have had chemotherapy, may prevent fragility fractures and associated morbidity and mortality. Screening programs should be set-up such that its utility and cost-effectiveness can be evaluated unambiguously.

This can be achieved by using the gold standard for the diagnosis of osteoporosis dual-energy X-ray absorptiometry (DXA)-scan. However, DXA-scans are relatively expensive, as it requires a DXA scanner, and cumbersome for patients, as it requires an additional visit to the hospital. Alternatives for this standard can be developed.

Availability of an easy and accessible screening tool would aid in screening high volumes of patients who are at risk, e.g. in the general practitioner's, medical oncologist, urology practice. An example of a larger population at risk of developing osteoporosis, are patients with prostate cancer, especially those who undergo androgen deprivation therapy. In **Chapter 3**, we investigated the utility of quantitative ultrasonography (QUS) as a pre-screening tool for osteoporosis as diagnosed in DXA. QUS is a quick and cheap tool which may be used to assess osseous content and microarchitecture. In addition, the patients were followed-up, to collect data about which patients fractured and whether this was to be expected by their DXA and QUS outcomes.

In summary, calcaneal QUS had a good negative predictive value to identify patients at risk of low bone mineral density, could differentiate between those not at risk, and those who need further diagnostic and treatment follow-up for osteoporosis. Additional studies about the predictive value of QUS for fractures (rather than BMD) in prostate cancer patients are required to learn whether this modality could replace DXA in this population.

In **Chapter 4** of this thesis, a strategy for targeted treatment of osseous metastases is studied. Patients with castration resistant prostate carcinoma who have osseus metastases, are currently treated with corticosteroids. This is in general well-tolerated but can have serious side-effects. These side effects may be improved by pharmacological targeting of the corticosteroids towards osseous metastatic sites. Targeting may be achieved by using liposomal encapsulation of the corticosteroids which utilizes the so-called 'enhanced permeability and retention effect'. With this approach a relatively high local exposure of the active compound can be achieved compared to the systemic exposure, potentially resulting in higher efficacy and lower toxicity. **Chapter 4** describes a first-in-human study of the safety and pharmacokinetics of liposomal dexamethasone, which aims to target osseous metastases of patients with metastasized, castration resistant prostate carcinoma. No safety issues were found, and the pharmacokinetic properties of this formulation are now sufficiently known for further clinical (efficacy) studies.

SECTION II – OSTEOARTHRITIS

Section II focuses on osteoarthritis (OA): OA is a multi-factorial, heterogeneous chronic disease, which involves a chronic low-grade inflammatory state of the joint tissues. The synovium, subchondral bone and cartilage are affected, and cause slow joint degeneration. Clinically, it presents as progressive joint pain and impaired function. Currently, there are no registered disease modifying osteoarthritic drugs.

In a review of recently registered and completed studies as described in **Chapter 5** provides insight in the treatment approaches that are currently under investigation for OA treatment. Four treatment targets are distinguished: pain, inflammation, therapies involving bodily materials, and compounds influencing cartilage metabolism. It appears that many compounds are under investigation, some of which seem promising. However, in the completed studies very few reported a disease modifying effect, let alone without important side effects. It is also recognized that there are limited tools to differentiate between patient phenotypes, and measure disease modifying effects in clinical studies.

It is therefore concluded that although the development of disease modifying OA drugs (DMOADs) is at full throttle some deficiencies were noted. This includes further knowledge on the pathophysiology, development and use of relevant biomarkers to aid drug-candidate selection and evaluation and guide the development of such compounds. These biomarkers should include patient-reported outcomes, based on pain and function, and quantifiable structural outcomes responsive to the disease state. The latter set could include (a set of) soluble biomarkers, novel and existing imaging modalities with standardized acquisition and evaluation protocols, and data obtained through wearables.

PHASE I-II STUDIES FOR DMOAD'S

Chapters 6 and 7 describe two clinical studies: one study concerns an intervention targeting cartilage metabolism of arthritic joints, and the second study focuses on inflammation in osteoarthritic joints.

In **Chapter 6** a double blind, randomized, placebo controlled, single ascending dose, first-in-human study with LRX712 is described. The mode of action of LRX712 is to stimulate cartilage-progenitor cells to develop to mature cartilage cells and restore damaged cartilage. The study was performed in patients with confirmed OA in the knee. Drug administration was by an intra-articular injection in the affected knee. From this study it could be concluded that this approach is feasible and that high doses caused more local and systemic (elevation of CRP) adverse events of mild and moderate severity than lower doses and placebo. It thus appears that further studies to study the disease modifying effect of LRX712 should be performed with doses up to 25 mg.

Another approach for a potentially disease modifying OA compound targeting inflammation is described in **Chapter 7.** Here, we studied ART-IO2, a recombinant adeno-associated viral vector, containing a human gene which expresses IFN- β. This expression is under the transcriptional control of a promotor responsive to the pro-inflammatory Nuclear Factor kappa B (NF-κB). As such, it has an inflammation-driven, anti-inflammatory effect. ART-IO2 was administered by an intra-articular injection into a target hand joint of patients with inflammatory arthritis. The study was prematurely terminated because the local tolerability of ART-IO2 in the first 4 patients was too poor to pursue the inclusion of the intended 12 patients. The mechanism responsible for the limited local tolerability issue could not be unraveled. Nevertheless, it does appear that more research is needed to determine the place of recombinant adeno-associated viral vectors as a tool for gene therapy.