Bone and joint disorders: screening and early clinical drug development
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General Discussion

Pathological conditions of the bones and joints cause great personal and societal burden. This thesis provides new insights for screening, diagnosis, and treatment of a selection of these conditions.

SCREENING

Screening for disease aims to discover those among the apparently well who are in fact suffering from disease. Early detection of disease through screening enables to treat or cure conditions which have already produced pathological change, but which have not so far reached a stage at which medical aid is sought spontaneously.[1] Testicular cancer has a high cure rate and survivors are relatively young.[2] Therefore, a population of young men is at risk of developing long-term effects of testicular cancer and its treatment for several decades.

The most efficient screening strategy for patients and society is screening those who are at increased risk of having the disease. Despite variations in methods and reporting, a review of available literature regarding the effects of testicular cancer to bone mineral density (**Chapter 2**) confirmed that survivors of testicular cancer are at increased risk to develop osteoporosis. Chemotherapy and/or a hypogonadal state can further aggravate this risk. Previous studies for the separate effects of hypogonadal state and chemotherapy to the bone, also indicated harmful effects to bone health.[3,4]

The literature review in **Chapter 2** also elucidates the need for more standardized outcomes and complete data availability. The included studies had large variations in their methods, definitions, and results. These variations precluded a direct comparison of results in a meta-analysis, which would have strengthened our outcomes.

DIAGNOSIS

The validity of a diagnostic test depends on its ability to identify those who suffer from a condition, ideally without failing to detect any of them.[1]

Calcaneal quantitative ultrasonography (QUS) cannot replace dual energy X-ray absorptiometry (DXA) scans as a diagnostic tool for osteoporosis as defined by the world health organization (WHO) in prostate cancer patients.[5] In **Chapter 3**, QUS had a high negative predictive value for DXA, but its positive predictive value was low. DXA is used as a gold standard for bone mineral density (bone quantity) measurements and the WHO definition of osteoporosis is an individual DXA outcome in relation to the DXA outcomes of a reference population. Bone quality is a measure of its architecture, geometry and material properties, thereby bone quality is another important predictor of fragility. DXA is unable to assess these outcomes. Alterations in bone architecture and composition together determine mechanical properties which can quantify fragility (bone's inability to resist fracture).)

It may be questioned which outcome is most relevant: bone quantity and osteoporosis as measured in DXA (often without symptoms), or other parameters such as bone quality and clinical outcomes: fragility fractures and associated morbidity and mortality.[6] Approximately 40% of fragility fractures occurs in patients with osteoporosis as defined by WHO.[7] In our study, it appeared that QUS outcomes were lower than DXA outcomes in those who had fragility fractures. QUS may thus gave more clinically relevant outcomes for the prediction of fracture risk than DXA. However, our study was not set-up to investigate this outcome. Studies in different populations found that DXA and QUS had similar predictive value for fractures.[8-10] The most important drawbacks of QUS are limited precision and calibration, but DXA shares these disadvantages.[11] The advantages of QUS, such as lower costs and accessibility, warrant further study of its applicability to further address its fracture-predictive value and to address practical issues related to its introduction in the clinic. Section II focusses on OA, which is commonly diagnosed by assessment of X-rays of the joint, but its suitability as a diagnostic tool for OA may be questioned. X-ray misses early OA changes and is poorly correlated with pain.[12] Synovitis, an early sign of OA, can be captured by magnetic resonance imaging (MRI) or ultrasound. However, MRI is rather expensive even in the Western world, and ultrasound does not capture cartilage- or osseous changes as well as X-Ray. Thereby, there are no established, affordable diagnostic tools available for OA, other than X-ray.

The development of novel compounds for OA could be optimized if precise diagnostic tools were available. Such diagnostic tools may be able to identify subtypes within OA and could be of aid in further decision making. The utility of such subtypes is under investigation.[13,14]

TREATMENT

Chapters 4 to 7 focus on studies for drug candidates of castration resistant, metastatic prostate cancer and OA. Both indications currently lack disease modifying drugs. In **Chapter 5**, information from a clinical trial registry was collected and reviewed to obtain a representative overview of the standings and developments in osteoarthritis treatment. The compounds under investigation target several pathways which play a role in OA development.

Two first-in-human studies with compounds targeting these pathways described in **Chapters 6 and 7**.

The clinical studies described in **Chapters 4, 6 and 7** all included early phase drug studies in patients from the target patient population, rather than healthy volunteers. Generally, patient recruitment is more difficult, slower and more expensive than recruitment of healthy volunteers. The selection of a patient population in an early stage of clinical development may have several reasons. Outcomes and symptoms of certain diseases can or should not be mimicked in healthy volunteers. Moreover, administration of compounds to healthy volunteers for which the risk analysis is unfavorable and particularly when the risk cannot be managed may not be justified.[15] In those cases, clinical development can be commenced in the patient population. Although more cumbersome, the inclusion of the target population has the potential to give an efficient drug development trajectory. By patient inclusion, a single study can provide valuable insights into safety, tolerability, pharmacokinetics, and preliminary efficacy in the target population, including the relevant variability.[16]

The opportunity to investigate efficacy should be considered in study design to maximally exploit the (challenging) fact of patient inclusion in an early-phase clinical trial. Thereby, aims and endpoints must be formulated bearing population-specific results in mind. Indeed, the clinical trials in this thesis brought information that could not have been obtained if healthy volunteers were included. Healthy subjects may: respond differently to liposomes (**Chapter 4**), have different PK of LRX712 after intra-articular administration (**Chapter 6**), or have a different response to ART-I02 due to absence of inflammation (**Chapter 7**). Thereby, the target patient populations were the most suitable for these studies.

The formulation of aims and endpoints to acquire new insights, is at least influenced by knowledge, ethics, and financial resources. With the current knowledge and additional resources, the clinical studies described in **Chapters 4, 6 and 7**, could have been further exploited. Ideally, liposomes would have been located *in vivo*, using a radioactive tracer (**Chapter 4**). Such imaging could have confirmed whether the compound reached the targeted osseous metastases. Furthermore, adverse event etiology could have been further clarified if tissue would have been obtained as an integral part of the studies in **Chapters 6 and 7**. Such information from an early phase of clinical development can give guidance to further studies and investments.[16]

However, it should be considered that in these cases the study designs and end points should be adaptive and flexible. Restrictively defined analyses and endpoints may hinder exploration of unexpected (adverse) outcomes and are not justified in in early phase drug studies. These studies are by definition exploratory and should be designed as such. This is also defined in regulatory documents and described in papers pertaining to this topic.[17–19] Administration site adverse events, as described in **Chapters 6 and 7**, ask for further analysis. Preferably, the required information to analyze setbacks, is obtained as an integral part of a study. In some study protocols, 'adverse events of interest' are defined, for which additional information is then collected. If tissue samples would have been available, the etiology of the adverse events could have been further studied. In the described studies, adverse event etiology was maximally studied by (additional) imaging (**Chapter 7**) and the use of back-up samples (**Chapter 6**).

Future perspectives

SECTION I – BONE IN MALE UROLOGICAL MALIGNANCIES

Screening and treatment of testicular cancer survivors for fracture risk, could prevent fractures and could thereby lower morbidity and mortality. To enable this, osteoporosis screening should be introduced in the urological guidelines. Currently, osteoporosis screening of testicular cancer patients is not mentioned in the European Association of Urology (EAU) guideline for testicular cancer.[20] Testicular cancer survivors have an increased risk of hypogonadism, and the Endocrine Society recommends osteoporosis screening for all hypogonadal men, regardless of their medical history.[21,22] It does seem that these guidelines should align on screening and anti-bone resorptive treatment.

We found that the available literature about bone health in testicular cancer patients is ambiguous. Future studies on this topic should choose their endpoints carefully (e.g. standardize reported clinical endpoints, make individual data available) and should preferably have a long follow-up to enable measurement of late effects.

The negative effect androgen deprivation therapy has on the bones of prostate cancer patients is well established and addressed in guidelines.[23,24] In clinical practice, however, it does not receive the attention it claims in the guidelines.[25,26] The education of treating physicians will further enhance awareness and increase screening rates.

The utility of QUS in clinic practice is dependent on several factors. First, more and larger studies are required to evaluate its utility in predicting fragility fractures (rather than BMD). If the value of QUS is confirmed, it must be recognized in guidelines and definitions of organizations such as the WHO and endocrine societies. If both conditions are met, it can be implemented widely, and may contribute to low-threshold screening for osteoporosis, even in remote areas.

With regards to PEG Liposomal treatment of osseous metastases, the first step forward, would be a study for the actual targeting of the liposomes, as was done in mice.[27] These studies are ideally executed in patients with osseous metastases, but who are more treatment-naïve than the population included in **Chapter 4**. Such a population could give information about targeting of the liposomes and about efficacy if e.g. concomitant medication is also standardized.

SECTION II – OSTEOARTHRITIS

As repeatedly mentioned, osteoarthritis is a multifactorial, heterogenous disease. The future of OA therapy is likely to be multifactorial too.

There are opportunities in the measurement of endpoints in OA clinical studies. The development of validated set of wet-, digital-, or imaging- biomarkers enables distinction of phenotypes and accurate measurement of disease modifying effects. Both would greatly benefit drug development.

By precisely defining phenotypes, interventions can be developed to target certain subgroups. Chances for successful drug development can be enhanced by targeting certain phenotypes. Potential phenotypes should be based on the causality of OA, and could e.g. be: obesity, trauma-induced OA, hereditary factors, and speed of progression.

Progress in the development of DMOADS is ongoing, and DMOADS will become reality with the increasing knowledge on pathophysiological processes, at least for certain phenotypical subtypes of OA.

Considerations

Testicular cancer patients were found to be at risk of fragility fractures, although the reported studies had their limitations and should be interpreted carefully. QUS was found to be a worthy candidate tool to prescreen prostate cancer patients for osteoporosis and further studies are required to study the ability of QUS to predict fragility fractures in this- and other populations.

In the clinical studies in this thesis, liposomal dexamethasone, LRX712 and ART-102 were administered without systemic adverse reactions. Insights were obtained regarding these compounds' safety and pharmacokinetic profiles. The local tolerability of ART-102 was found insufficient to complete study enrollment.

Meanwhile, we identified opportunities for the optimization of screening processes, and development of compounds targeting osteoporosis and osteoarthritis. The lack of complete- and comparable outcomes amongst clinical studies hindered the compilation of osteoporosis study results, limiting firm conclusions and transition into guidelines for clinical practice. Reporting standards and, especially in case of osteoarthritis, representative biomarkers are to be developed and should be reported in a uniform manner across studies. In the review of ongoing studies for OA medication, we found that new insights into OA pathophysiology already led to targeting pathways as treatment strategies. Further development of this knowledge will aid the development of a DMOAD.

In some areas, such as prostate cancer research, a framework of standard reporting guidelines for researchers is already provided.[28] Such guidelines allow a good start to define aims and endpoints. However, guidelines can only temporarily fulfill the reporting requirements in a world of ever-evolving techniques and interdisciplinary research. Investigators are therefore dependent on up-to-date expert knowledge of guidelines and techniques, recent literature, and interdisciplinary connections to define aims, methods and endpoints.

Having mentioned the need for standardized reporting, it must also be addressed that unexpected outcomes can devaluate excellently set aims, methods, or endpoints during a study in a matter of a single analysis or the occurrence of an adverse events, as we encountered in the study with ART-102. Therefore, aims and endpoints of (especially early phase) clinical studies should take the options of 'failure' and adverse events into account, and should leave room for anticipation in case of unexpected events. As such, research for screening- diagnostic- and treatments can be further optimized.

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