Ruprecht-Karls-Universität Heidelberg
Medizinische Fakultät Mannheim
Dissertations-Kurzfassung

Characterization of anti-RGMa/c mAbs and their influence on iron regulation

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Discovery of hepcidin's function in iron metabolism in year 2001 revolutionized research of iron physiology because the pathophysiology of many iron disorders could be better understood. High levels of hepcidin are generally associated with iron-restrictive diseases such as ACD, IRIDA and Anemia of CKD etc. Treating these patients with recombinant erythropoietin (rhEPO) therapy is not optimal because rhEPO only stimulates the hormone erythropoietin resulting in stimulation of erythropoiesis without reducing hepcidin. Many strategies had been taken in developing anti-hepcidin antibodies therapy but the drawback of this approach is the high turn-over rate of hepcidin. Due to this drawback very high doses of antibodies would be required to downregulate the hepcidin level to baseline for a longer period. Therapies targeting the BMP6 on the other hand are extremely risky due to the high possibility of nonselective targeting since there are large amounts of other BMPs that regulate diverse functions. Two mAbs ABT-207 and affinity maturated h5F9-AM8 which have high affinity towards RGMc were developed at AbbVie.

In this thesis the potential of these mAbs to work as therapeutics were determined. In order to investigate if the mode of effects of the mAbs, single dose studies in rats were performed. The effects of these mAbs were determined by measuring parameters such as the liver hepcidin mRNA expression, the serum hepcidin protein level, serum iron and the UIBC level. Histological evaluations (including morphometric analysis) to study the mAbs effect were also carried out. Through these studies, it could be determined that a single dose of ABT-207 or h5F9-AM8 could downregulate hepatic hepcidin expression and serum hepcidin levels for several weeks. The antibody effects were also very specific since a higher affinity towards RGMc resulted in a significant increase in therapeutic effect i.e. h5F9-AM8 which has higher affinity towards RGMc showed stronger decrease in hepcidin downregulation with lower dose. These effects were also effective for a long period because both these mAbs have long half-lives. A good PK/PD relationship was also obtained from all these results using both these antibodies. The antibodies also showed low immunogenic potential (low incidence of ADA induction). Through these studies, the mode of action of these anti-RGMa/c antibodies through the BMP/SMAD pathway could be demonstrated and the proof of concept of the Hemojuvelin/RGMc-Hepcidin-Iron cascade was provided. Through the subchronic toxicology studies, it could be shown that application of these mAbs does not participate in any non-mode of action related pathway. Dose related iron accumulation in the liver and iron decrease in the spleen was seen but this effect was reversible over time.

In order to determine the therapeutic effect of these mAbs, they were tested in different preclinical animal models that mimic human diseases. The DSS study showed that they were able to shift the macrophages in the intestine of the animals with colitis from the M1 (pro-inflammatory) to the M2 (anti-inflammatory) state diseases. In cooperation with Mathias Hentze's group from the EMBL that is specialized in iron metabolism, it could be shown that these antibodies were able to rescue the hemoglobin level in animals with arthritis and severe anemia due to the PGPS application. With this cooperation work, it could furthermore be shown that the h5F9-AM8 mAb was able to reduce the hepcidin in liver and serum and correct the hemoglobin level in the Tmprss6 mice with high hepcidin levels. These mice mimic the human IRIDA condition. Dosing of these mAbs in animal models proved the therapeutic potential of these antibodies for the use in diseases which are related to or induced by high hepcidin expression. With these results it could be shown that ABT-207 and h5F9-AM8 have long half-lives, excellent safety profile and good therapeutic effect. Therefore they could serve as excellent clinical candidates.