Activin receptor ligand traps in chronic kidney disease

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Purpose of review
Sotatercept and luspatercept are recombinant soluble activin type-II receptor-IgG-Fc fusion proteins that are tested in clinical trials for the treatment of various types of anemias, including renal anemia. The mechanism of the action of the novel drugs is incompletely understood, but it seems to be based on the inactivation of soluble proteins of the transforming growth factor-ß (TGFß) family. This review considers pros and cons of the clinical use of the drugs in reference to the current therapy with recombinant erythropoiesis-stimulating agents (ESAs).

Recent findings
One or more activin type-II receptor (ActRII) ligands appear to inhibit erythroid precursors, for example growth and differentiation factor 11. Trapping of these ligands by the recombinant ActRII fusion proteins, sotatercept and luspatercept increases red blood cell numbers and hemoglobin levels in humans. Reportedly, the novel compounds were well tolerated in trials on healthy volunteers and patients suffering from anemia due to chronic kidney disease or malignancies. On approval, the drugs may prove particularly useful in patients suffering from ineffective erythropoiesis, such as in myelodysplastic syndrome, multiple myeloma or ß-thalassemia, where ESAs are of little use. Independent of their effect on erythropoiesis, ActRII ligand traps were found to exert beneficial effects on renal tissue in experimental animals.

Summary
ESAs are likely to remain standard of care in renal anemia. There is a need for a better understanding of the effects of ActRII ligand traps on TGFß-like proteins. The novel drugs have not been approved for sale as therapeutics so far. Their long-term efficacy and safety still needs to be proven, particularly with respect to immunogenicity. Antifibrotic effects may be worthy to be investigated in humans.

Keywords
activin receptor ligand trap, anemia, chronic kidney disease, transforming growth factor ß

INTRODUCTION

The activity of hematopoietic stem and progenitor cells is controlled by various hormones and cytokines. In the erythrocytic branch, at the differentiation step of the colony forming units-erythroid (CFU-Es), the hormone erythropoietin (Epo) is required for survival and proliferation. In the presence of Epo, CFU-Es and their progeny divide 3 to 5 times within 7–8 days. Each CFU-E can produce cell colonies of 8–64 polychromatic normoblasts, which accumulate hemoglobin (Hb). In addition to its action on erythrocytic progenitors, Epo activates the proliferation, differentiation and maturation of the morphologically identifiable proerythroblasts and normoblasts (syn. orthochromatic erythroblasts). The latter extrude their nuclei and become reticulocytes. As endogenous Epo is mainly of renal origin, there is a lack of Epo in chronic kidney disease (CKD), causing renal anemia.

About 25% of patients with CKD needed regular red blood cell (RBC) transfusions before recombinant human Epo (rhEpo, epoetin) became available. The replacement therapy with erythropoiesis-stimulating agents (ESAs) can prevent RBC transfusion-dependent anemia in virtually all CKD patients, provided that care is taken for sufficient iron supplementation. Investigational therapies for renal disease-induced anemia focus on stabilizers of the hypoxia-inducible transcription factors ('HIF

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Curr Opin Nephrol Hypertens 2018, 27:351–357
DOI:10.1097/MNH.0000000000000433

KEY POINTS

- ActRII ligand traps (sotatercept and luspatercept) are in clinical trials for the treatment of anemias, including those of CKD, MDS, multiple myeloma and ß-thalassemia.
- ActRII ligand traps exert anabolic effects in bone which may be beneficial in anemic individuals, including CKD patients.
- Results with ActRII ligand traps in CKD patients are not yet in the public domain.
- ActRII signaling is a possible target for therapy of CKD irrespective of anemia.

stabilizers'), which induce transcription of the endogenous Epo gene and can be administered orally [1].

Rating of the current therapy with recombinant erythropoiesis-stimulating agents

The target Hb level is generally set at 100–120 g/l in ESA-treated patients, and the target hematocrit (Hct) at 0.30–0.36. However, the present ESA labels in the United States warn that CKD patients experienced greater risks for death, serious adverse cardiovascular reactions and stroke in clinical trials, when ESAs were administered to target [Hb] more than 110 g/l. The major cause of resistance toward ESAs in CKD patients is reduced iron availability, due to the increased production of hepcidin which inhibits ferroportin. This situation is indicated by a low serum ferritin concentration (<100 μg/l), a low transferrin saturation (<20%) and a high proportion of hypochromic RBCs (>10%).

In ESA-treated CKD patients, the most common unwanted effect is an increase in arterial blood pressure, and possibly hypertension. The higher blood pressure can be partly explained by the elevated blood viscosity and the reversal of hypoxia-induced vasodilatation in association with the increase in [Hb]. In addition, ESAs may stimulate thrombopoiesis in an indirect way, as thrombocytosis occurred in the course of iron depletion due to stimulated erythropoiesis in hemodialysis patients [2] and in cancer patients with chemotherapy-induced anemia [3]. Of note, meta-analyses have shown that the use of ESAs does not generally impact disease progression in cancer patients [4]. The immunogenicity of established ESAs is very low, with exposure-adjusted incidence of neutralizing anti-Epo antibodies-induced pure red cell aplasia amounting to less than 0.03 per 10 000 patient-years in ESA-treated CKD patients [5].

Activins: members of the transforming growth factorβ superfamily

Activins are dimers of inhibin β-type chains. They signal through type I (ActRI) and type II (ActRIIA or ActRIIB) serine/threonine kinase receptors [6]. Activin binding to ActRII causes activation of ActRI, which catalyzes the phosphorylation of cytoplasmic 'small mothers against decapentaplegic proteins' (SMADs). Activins belong to the transforming growth factorβ (TGFβ) superfamily of proteins that includes bone morphogenetic proteins (BMPs), growth and differentiation factors (GDFs), and others. Several of these proteins affect erythropoiesis.

Activin A is also called 'erythroid differentiation factor' [7], as it stimulates erythropoiesis. GDF11 modulates the differentiation of late erythrocytic progenitors and erythroid precursors [8]. The number of RBCs increased in transgenic chimeric mice, in which the soluble IgG_1-Fc fusion protein of three BMP type II receptors (ActRIIA, ActRIIB and BMPRII) was highly expressed [9]. GDF15 is produced by erythrocytic precursors and expressed at high levels in patients with ineffective erythropoiesis. Although GDF15 acts predominantly as hepcidin-suppression factor, it can also directly modulate erythropoiesis [10].

Excess hepcidin is the root cause of the hypoferremia and iron-restricted erythropoiesis in CKD. The hepcidin promoter contains BMP-responsive SMAD-binding sites [11] in addition to interleukin-6 responsive elements. Recent studies have shown that activin A and B levels in blood increase in various inflammatory and infectious states, which are associated with increased hepcidin expression [12].

Effects of ActRII ligand traps

Two ActRII ligand traps, namely sotatercept (ACE-011; Acceleron Pharma Inc., Cambridge, Massachusetts /Celgene, Summit, New Jersey, USA) and luspatercept (ACE-536) are in clinical trials for the treatment of various types of anemias, including CKD, myelodysplastic syndromes (MDS) and thalassemias. The novel compounds have not been approved for sale as therapeutics so far. Pharmacological basics of sotatercept have been described by Fields *et al.* [13]. In brief, the active substances are recombinant soluble ActRII-IgG_1-Fc fusion proteins that stimulate RBC production. The drugs trap circulating members of the TGFß superfamily, thereby

preventing their action on the endogenous, membranous, ActRII.

Sotatercept

The potential of sotatercept to increase RBC production was detected in a trial of postmenopausal osteoporosis almost a decade ago [14]. In that study, single intravenous (IV) injections of the highest doses of sotatercept [3 mg/kg body weight (b.w.)] resulted in increased [Hb], RBC numbers and Hct [14]. Adverse events were reportedly mild and no antidrug antibodies were detected. Follow-on studies in healthy female individuals have confirmed that sotatercept produces dose-dependent, clinically significant increases in [Hb], RBC numbers and Hct without detectable changes in the levels of leukocytes or platelets. These findings led to the concept that one or more ActRIIA ligands are negative modulators of RBC formation in humans under normal conditions (reviewed in [13]).

Chronic kidney disease

Provided that ActRII ligand traps stimulate erythropoiesis in patients with renal anemia, less conventional ESAs may be necessary for their care. The pharmacokinetics and pharmacodynamics of sotatercept as well as its safety, efficacy and tolerability are currently tested in two multicenter, randomized phase II trials in anemic patients with end-stage renal disease on hemodialysis. Both trials consist of two parts. In part 1 of the first trial (NCT01146574), approximately eight individuals are randomized to receive either a single 0.1 mg/kg subcutaneous (SC) dose of sotatercept or matching placebo in a 3 : 1 ratio, and part 2 comprises three sequential dose groups (0.3 or 0.5 or 0.7 mg/kg) with a 3 : 1 ratio of sotatercept or placebo (six individuals in the sotatercept arm and two in the placebo arm). The primary outcome measures will be pharmacokinetic parameters (C_{max}, PK-AUC 28d, T1/2,z; time frame up to 309 days). The purpose of the second trial (NCT01999582) is to determine the optimal route of administration, dose level and safety of IV and SC dosing of sotatercept for maintaining [Hb] in hemodialysis patients switched from conventional ESAs.

As of May 2, 2018, no study results were posted on ClinicalTrials.gov for these two studies on CKD patients (https://clinicaltrials.gov). Thus, it seems unlikely that ActRII ligand traps will put the recombinant ESAs out of the market in nephrology in the near future.

Anemias in association with malignancies (solid tumors, myelodysplastic syndrome and multiple myeloma) and others

Sotatercept was reported to be effective in cases of advanced and metastatic solid tumors [15]. Of even greater interest are patients suffering from MDS because these do not usually present with an Epo deficiency, but are anemic due to their ineffective erythropoiesis. Recently, an open-label, multicenter, dose-ranging, phase II trial was performed to establish a safe and effective dose of sotatercept for the treatment of anemia in patients with lower risk MDS in whom previous ESA treatment had failed [16▪]. The most commonly reported adverse events were fatigue in 19 (26%) of 74 patients and peripheral edema in 18 (24%) of 74 patients under sotatercept therapy. Grade 3–4 treatment-emergent adverse events (TEAEs) were reported in 25 (34%) of 74 patients; four (5%) patients had grade 3–4 TEAEs (mostly lipase increase and anemia), which each occurred in three (4%) of 74 patients [16▪]. Seventeen (23%) of 74 patients had at least one serious TEAE, and one patient died from a treatment-emergent subdural hematoma due to a fall [16▪].

A phase IIa study has evaluated the safety and tolerability of sotatercept and its effects on bone metabolism and hematopoiesis in newly diagnosed and relapsed multiple myeloma patients, who received concomitant melphalan, prednisolone and thalidomide (MPT; NCT00747123) [17]. Patients were randomized (4 : 1) for four 28 day cycles of sotatercept (0.1, 0.3 or 0.5 mg/kg) or placebo. Thirty patients were enrolled; six received placebo and 24 received sotatercept. Grade $\geq$3 adverse events were reported in 17% of patients receiving placebo and 58% receiving sotatercept. Grade 4 adverse events in sotatercept-treated patients were neutropenia, granulocytopenia and atrial fibrillation (one patient each). In patients without bisphosphonate use, anabolic improvements in bone mineral density and in bone formation relative to placebo occurred. Six patients (20%) treated with sotatercept reported a reduction in bone pain, as assessed by the Visual Analog Scale [17]. Increases in [Hb] and the duration of the increases were higher in the sotatercept-treated patients, with a trend suggesting a dose-related effect. In conclusion, multiple doses of sotatercept and MPT were considered safe and generally well tolerated in multiple myeloma patients [17].

In summary, clinical trials with sotatercept have included treatment of anemia due to CKD (NCT01146574 and NCT01999582; recruitment status on May 2, 2018: completed, no results posted),

solid tumors (NCT01190644, terminated because the isotope needed to conduct RBC/plasma volume analysis as the primary endpoint was no longer available from manufacturer), multiple myeloma (NCT00747123, completed, no results posted; NCT01562405, recruiting patients), myeloproliferative neoplasm (MPN)-associated myelofibrosis and anemia (NCT01712308, recruiting patients), low-risk or intermediate- risk MDS or nonproliferative chronic myelomonocytic leukemia (CMML) (NCT01736683, active, not recruiting patients), transfusion-dependent Diamond Blackfan anemia (NCT01464164, recruiting patients) and β-thalassemia (NCT01571635, active, not recruiting patients).

Luspatercept

Furthermore, studies have been initiated with the second TGFß ligand trap, luspatercept (ACE-536), an Act-RIIB fusion protein that does not bind activin A but binds other TGFβ-like proteins. Luspatercept was tested initially in a phase I trial in healthy postmenopausal women (NCT01432717, recruitment status on May 2, 2018: completed, no results posted) and recently in phase II/(III) clinical trials for the treatment of MDS (NCT01749514, recruiting patients; NCT02268383, recruiting patients; NCT02631070; active, not recruiting patients), MPN-associated myelofibrosis and anemia with and without RBC transfusion dependence (NCT03194542; recruiting patients) and β-thalassemia (NCT01749540; completed, no results posted; NCT02268409, active, not recruiting patients, NCT02604433, active, not recruiting patients; NCT02626689, completed, no results posted; NCT03342404, recruiting patients).

Myelodysplastic syndromes

Similar to sotatercept, luspatercept therapy is particularly promising in patients in whom ESA treatment has failed. Platzbecker *et al.* [18▪] have reported results of a multicenter, open-label, dose-finding phase II study, with long-term extension, of luspatercept for the treatment of anemia in patients with lower risk MDS (PACE-MDS; NCT01749514). Fifty-eight anemic patients (baseline [Hb] < 100 g/l) with MDS were enrolled in the 12 week base study. Patients received luspatercept SC once every 21 days at doses ranging from 0.125 to 1.75 mg/kg b.w. for five doses (over a maximum of 12 weeks). Three grade 3 TEAEs occurred in one patient each (2%): myalgia, increased blast cell count and general physical health deterioration [18▪]. Encouraging response rates were also observed with luspatercept in MDS patients presenting with ring sideroblasts in the bone marrow [19].

The clinical studies with sotatercept and luspatercept in clonal hematopoietic disorders including MDS have been reported in more detail elsewhere [19,20].

β-Thalassemia

Apart from other novel treatment options in thalassemia, a recent review delineates outcomes with luspatercept (NCT01749540/Extension NCT02268409) and sotatercept (NCT01571635) in transfusion dependent (TDT) and nontransfusion dependent (NTDT) patients with ß-thalassemia [21]. In the multicenter, open-label, dose-finding study to evaluate luspatercept in adults with TDT or NTDT, 83% of transfusion-dependent patients had a reduction in transfusion burden at least 33% (67% of transfusion-dependent patients showed a reduction $\geq$50%) over any 12-week period during the study, compared to baseline. Among the NTDT patients, 78 and 56% had an increase in [Hb] at least 10 and at least 15 g/l. In both TDT and NTDT, a reduction of liver iron concentration was observed. Similar results were obtained with sotatercept. Both drugs are administered SC every 3 weeks. Reportedly, the therapy was generally well tolerated. Adverse events were in the majority of cases mild to moderate, including bone pain, myalgia, arthralgia, headache, asthenia, and musculoskeletal pain [21]. Note that the multicenter, double-blind, randomized, placebo controlled phase III study (BELIEVE) to determine the efficacy and safety of luspatercept and best supportive care (BSC) versus placebo and BSC in adults who require regular RBC transfusion due to β-thalassemia (NCT02604433) is ongoing.

Mechanism of action of the ActRII ligand traps

The mechanisms underlying the alleged beneficial effects of sotatercept and luspatercept on RBC production are still poorly understood. In-vitro studies suggest that the stimulatory activity of sotatercept is mediated by cellular or soluble factors present within the bone marrow microenvironment [22]. As the drugs act as TGFß ligand traps and promote late erythroid precursors, their action is distinct from that of ESAs which signal through the Epo receptor. Animal studies with the murine sotatercept analog RAP-011 (extracellular domain of human ActRIIA linked to the Fc portion of murine IgG_{2a}) have provided evidence that GDF11 inactivation is the primary mechanism of action [23]. ActRIIA-Fc can pull down activin C, activin E, BMP10 and GDF11 (BMP11) from human serum

and activin B, activin C, activin E, inhibin alfa-subunit, GDF8 and GDF11 from mouse serum. Reportedly, ActRIIA-Fc does not bind TGFß-1, TGFß-2 or TGFß-3 [13]. Actually, GDF11 binds to ActRIIA and impedes terminal erythroid maturation. GDF11 is abundant in the sera of patients with MDS and β-thalassemia. Thus, ActRIIA ligand traps are believed to rescue GDF11/Activin A-induced inhibition of late-stage erythropoiesis [24,25].

Effects of the ActRII ligand traps on hepcidin expression

Sotatercept can inhibit hepcidin gene transcription in the liver [22]. In hepcidin gene transgenic mice, the murine sotatercept analog RAP-011 increased [Hb] but prevented depletion of splenic iron stores. Hence, the compound could be useful for anemias characterized by increased hepcidin expression and iron-restricted erythropoiesis [26]. CKD patients often present with elevated levels of circulating hepcidin. Lowering hepcidin would be beneficial in CKD patients, but to the author's knowledge no studies have been performed with ActRII ligand traps along these lines.

Beneficial effects of the ActRII ligand traps on renal tissue

TGFß signaling can drive fibrosis in renal disease. In order to assess whether alterations in TGFβ superfamily receptor function are involved in the pathogenesis of the CKD-mineral bone disorder, effects of the murine ActRII ligand trap RAP-011 on CKD-stimulated atherosclerotic calcification and renal αklotho levels were recently investigated in a mouse model [27]. The ActRIIA ligand trap reversed CKD-induced vascular smooth muscle dedifferentiation as assessed by smooth muscle 22α protein levels, osteoblastic transition and decreased atherosclerotic vascular calcification. The application of RAP-011 increased αklotho expression in the kidneys, whereas it decreased renal Wnt (portmanteau of Wingless and Integration) activation and circulating Dickkopf 1 (Dkk1) levels. In summary, vascular calcification, renal fibrosis and proteinuria were lowered by the ActRIIA ligand trap. Hence, ActRIIA signaling may be a potential therapeutic target in CKD [27].

Furthermore, the role of TGFß was studied in mice with experimental polycystic kidney disease (PKD) as a model for human autosomal-dominant PKD [28]. Mice with PKD had increased expression of activin ligands. Treatment with a soluble activin receptor IIB fusion protein (sActRIIB-Fc, produced in house) inhibited cyst formation in three distinct mouse models of PKD. The slower onset of PKD by sActRIIB-Fc treatment was associated with reduced SMAD2 expression, reduced SMAD2 phosphorylation, reduced SMAD2/3 target gene expression and reduced collagen deposition, which is in line with the concept of the ability of sActRIIB-Fc to sequester activin ligands that are increased in PKD. Clearly, sActRIIB-Fc can sequester other ligands of the TGFß superfamily, such as myostatin, GDF11, and, with lower efficiencies, a number of BMPs as well. However, activin signaling is considered a key pathway in PKD and a possible target for therapy [28].

CONCLUSION

Sotatercept (ACE-011) and luspatercept (ACE-536) are recombinant products that act as activin type-II receptor (ActRII) ligand traps which bind TGFß family members. The active substances consist of the extracellular domain of ActRII linked to the human IgG_1-F_c domain. The compounds were originally developed to treat postmenopausal osteoporosis. Unexpectedly, they proved to stimulate RBC production, thus increasing [Hb] and Hct in nonanemic women. In contrast to Epo, which acts mainly on CFU-Es, ActRII ligand traps stimulate late erythroid precursors. The novel compounds increase RBC numbers more rapidly than ESA, and without detectable changes in blood leukocytes and platelets. In addition, the ActRII ligand traps exert anabolic effects in bone that may be beneficial in anemic individuals, including CKD patients. However, the results of the clinical trials with sotatercept in CKD patients have not been disclosed, to the author's knowledge. The drugs are presently undergoing clinical trials for the treatment of anemias of various other causes, including those of MDS, multiple myeloma and ß-thalassemia.

For the treatment of renal anemia and chemotherapy-associated anemia, the established recombinant ESAs (rhEpo, epoetin; darbepoetin) are effective and well tolerated. With respect to these indications, ActRII ligand traps are unlikely to enter clinical routine in the near future. Recombinant ESAs, including the biosimilar epoetins and the long-acting analogs, will likely remain the mainstay of the antianemia therapy. Still, ActRII ligand traps (sotatercept and luspatercept) may provide an add-on for the established therapies. In particular, they may become useful for treating ineffective erythropoiesis in MDS and thalassemia, where ESAs are generally not effective.

Immunogenicity is a major issue with peptidic medicines. The immunogenicity of ActRII ligand traps still needs to be carefully investigated,

especially as they are foreign proteins. Note that recombinant ESAs are rarely immunogenic [5]. Because of the limited number of participants and the relatively short period of treatment, the current clinical trials cannot provide information of the effects of the drugs in all situations. Here, a lesson has been learned from the clinical use of the Epo-mimetic peptide peginesatide, which was approved for the routine treatment of anemic CKD patients in the United States in 2012, but recalled in 2013 because of prevalent cases of acute severe anaphylactoid reactions and associated fatalities [29▪]. Subsequent research has shown that the adverse events were not caused by the drug substance, but by the drug product that contained phenol when formulated in multiuse vials [30].

The precise mechanism of the erythropoietic action of sotatercept and luspatercept still needs to be identified. Evidence suggests that the drugs act predominantly as GDF11 antagonists [13]. In addition, it will be of interest to study effects of ActRII ligand traps on the synthesis of the hormone erythroferrone, as this is produced by erythroid precursors [31]. Erythroferrone inhibits hepcidin expression in the liver, thereby promoting the availability of iron required for the synthesis of Hb. Apart from the stimulation of RBC production, the physical consequences of the inhibition of the action of GDF11 and related TGFß proteins are unknown. Remember that the level of circulating GDF11 declines with age and exogenous treatment with GDF11 can reverse age-related effects including reducing cardiac hypertrophy, improving skeletal muscle regeneration and promoting neurogenesis [32▪▪].

Experimental studies in murine models of kidney diseases have provided evidence of beneficial effects of ActRII ligand traps on renal tissue. ActRIIA ligand trapping increases renal αklotho expression and reduces CKD-associated calcification, renal fibrosis and proteinuria. Thus, the ActRIIA signaling pathway may be a potential therapeutic target in CKD [27]. Members of the TGFß superfamily of proteins are also involved in PKD. Here, soluble ActRIIB fusion protein may inhibit cyst formation by means of reduced SMAD2/3 activity [28].

Acknowledgements

None.

Financial support and sponsorship

The author has received financial support from pharmaceutical companies producing/and or marketing recombinant ESAs for advisory tasks and lectures.

Conflicts of interest

There are no conflicts of interest.

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