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PERSPECTIVES IN THE TREATMENT OF RENAL ANAEMIA NEW CONCEPTS AND NEW DRUGS

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A b s t r a c t: There are several new erythropoiesis-stimulating agents that may potentially improve in the near future the management of anaemia in patients with chronic kidney disease.

Some of the new erythropoiesis-stimulating agents have been synthesised by modification of the aminoacide sequence of the erythropoietin (EPO) molecule and hyperglycosylation and therefore they have improved pharmacokinetics (darbopoietin or CERA) by prolongation of the serum elimination half-life compared to epoietins. These agents may be administered less frequently with better stabilisation of blood haemoglobin concentration.

There are promising attempts to overcome the paraenteral method of drug administration. Such non-peptide drugs acts as inhibitors of prolyl hydroxylase and the GATA-2 transcription factor enhancing the endogenous EPO synthesis.

Key words: darbepoietin alfa, CERA, EPO-mimetics, inhibitor of prolyl hydroxylase, synthetic erythropoietin peptides.

Introduction

The management of anaemia in patients with chronic kidney disease was revolutionised in the late eighties by the introduction of the recombinant human erythropoietin (rHuEPO) [1]. In the following 15 years a considerable number of clinical trials proved their efficacy and safety. A low haemoglobin

level has been identified as a risk factor for cardiovascular complications in patients with chronic kidney diseases (CKD) [2]. In the late eighties and nineties of the 20th century, when epoietins were introduced into clinical practice, almost all patients started treatment simultaneously with dialysis initiation. They already had cardiovascular complications enhanced by long-lasting anaemia at that time. Early correction of anaemia in CKD patients (before renal replacement therapy), when cardiovascular complications are less advanced, is crucial for the risk reduction of cardiac disease and mortality [3]. The recommended target haemoglobin (Hb) concentration in CKD patients is lower than in the general population and in the same range for men and for women, regardless of different physiological levels in both sexes. The target Hb in anaemia management guidelines has not changed very much since 1997 in Europe, USA and Australia. According to the European Best Practice Guidelines the lower Hb limit is >11 g/dl [4]. The new National Kidney Foundation guidelines for anaemia management in CKD recommend a similar lower Hb limit and pay attention to the upper Hb concentration, which should not be higher than 13 g/dl [5]. The results of the CREATE trial (Cardiovascular risk Reduction by Early Anaemia Treatment with Epoietin β) performed in non-dialysed CKD patients showed significant improvement of quality of life, without significant impact on mortality in patients with Hb concentration 13–15 g/dl [6]. In the other trial, CHOIR, the non-dialysed CKD patients treated with epoietin α with a target Hb of 13.5 g/dl showed increased risk of composite endpoint events (mortality, stroke, heart attack, hospitalisation) compared to patients with target Hb 11.3 g/dl [7]. The latter results are similar to the results in dialysis patients, in whom Hb normalisation increased mortality risk [8]. Currently there is inconclusive evidence for a specific upper Hb limit in CKD patients.

Endogenous EPO is predominantly produced in renal peritubular, fibroblast-like cells in response to oxygen demand [1]. Erythropoietin binding to the extracellular domain of the EPO receptor on the erythroid progenitor cells results in dimerisation of two monomers [9]. Stimulation of these receptors prevents apoptosis of burst-forming unit-erythroid (BFU-E), colony- forming unit-erythroid (CFU-E) and normoblasts, thus enhancing the erythropoiesis [9].

Commercially available tree isoforms of rHuEPO – epoietin-α (Eprex®, Procrit®), epoietin-β (NeoRecormon®) and epoietin-ϖ (Epomax®) are glycolproteins produced by Chinese hamster ovary cells (epoietin-α and epoietin-β) or baby hamster kidney cells (epoietin-ϖ) containing the EPO gene. Although these glycolproteins differ in their carbohydrate structures and pharmacokinetic activity profiles (epoietin beta has a slightly longer elimination half-life), the treatment efficacy and the route of administration (only paraenteral) are almost identical.

Further modification of the erythropoetic peptide structure by hyperglycosylation and changing of the aminoacids strain (darbepoietin epoietin) or

other modifications (Continuous Erythropoietin Receptor Activator – CERA and Synthetic Erythropoiesis Protein – SEP) have produced additional improvement to its pharmacokinetics.

The attempt to design proteins with greater than rHuEPO haemopoietic activity has resulted in the creation of dimeric fusion proteins (EPO-EPO) and finally synthetic polypeptides conjugated with polyethylene glycol (pegylation) such as Hematide (AF37702). The higher activity of these dimeric moieties is a consequence of the facilitation of EPO receptor dimerisation. However, all those modifications have not imposed the necessity of a paraenteral route for the administration of these compounds.

The 'hunt' for non-peptide erythropoietic agents – EPO-mimetics – did not produce any spectacular discovery.

Recently, quite a new approach has appeared – the enhancement of endogenous EPO synthesis by innovation of the prolyl hydroxylase and GATA-2 inhibitors. The efficiency of such management, even in the case of cirrhotic kidneys, has brought new hope for the procurement of an orally active drug in the future.

On the other hand, patents for a number of approved biopharmaceutical agents including epoietins have expired or will run out soon. The patents for epoietin-α expired in Europe in 2004 and biosimilar versions of this therapeutic agent (i.e. biosimilars) are likely to emerge onto the market soon [10]. The development of biosimilar proteins is more complicated than for conventional generic drugs. Biopharmaceuticals are heterogeneous proteins produced by different manufacturing processes. The pharmacodynamics and clinical effectiveness of such biopharmaceuticals is unclear. The change in the formulation of epoietins highlights the potential for an increased risk of immunogenicity and a higher occurrence of antibody mediated pure cell aplasia (PRCA). Therefore the approval of these agents requires more than the confirmation of pharmacokinetic bioequivalence. The regulatory requirements for the approval of biosimilars have not been yet fully established. Companies manufacturing biosimilar epoietins may obtain a product licence if a rigorous clinical trial programme is undertaken and postmarketing surveillance may be mandatory. Because of the above-mentioned problems some companies have abandoned their programmes of development of biosimilar epoietins. Biosimilar epoietins are already marketed in countries such as China, India, Korea and Cuba. The quality and biological activity of these products has been shown to be very variable [11].

Novel erythropoiesis stimulating peptide – NESP (Darbepoietin alfa)

Based on the knowledge that sialic acid residues in vivo are responsible for maintaining the biological activity of EPO, a new molecule containing not

three (as a native moiety of the human EPO), but five N-linked oligosaccharide chains (NESP), was synthesised [12, 13]. The original amino acid sequence of EPO was modified at 5 positions (Ala30Asn, His32Thr, Pro87Val, Trn88Asn and Pro90Thr) in order to attach additional oligosaccharides at asparagine residue positions 30 and 88 [12, 13]. Darbepoietin alfa binds to the EPO receptor in a manner indistinguishable from native EPO, to stimulate an intracellular signalling pathway. However, the pharmacokinetics of darbepoietin alfa is different. The glycoprotein clearance is slower and the serum elimination half-life is 3 times longer (25.3 vs 8.5 hrs in haemodialysis patients after intravenous injection) [12, 13]. The serum elimination half-life of darbepoietin alfa can be further prolonged to 48.4 hrs after subcutaneous injection [12] (Table 1).

Table 1 – Tabela 1

Serum half-life (hours) of epoietins, darbepoietin alfa and CERA administered intravenously and subcutaneously (13, 17, 19).
Серумски полуживот (часови) на администрираните епоиетини, дарбоиоетин алфа и CERA

	Intravenous	Subcutaneous
Epoietin alfa	6.8 ± 0.6	19.4 ± 2.5
Epoietin beta	8.8 ± 0.5	24.2 ± 2.6
Epoietin omega	not determined	not determined
Darbepoietin alfa	25.3 ± 2.2	48.8 ± 5.2
CERA	133 ± 10	137 ± 22

mean values ± SEM

Longer serum elimination half-life enables less frequent administration of darbepoietin alfa than epoietin. Darbepoietin alfa may be administered once a week or even every second week in the initial treatment of anaemia and once every 3–4 weeks for the maintaining of haemoglobin concentration [14].

The treatment of renal anaemia with darbepoietin alfa is equally effective as with epoietin [15]. The drug was introduced into clinical practice in 2002. There is still not enough information concerning the cost ratio over the currently used epoietins [15].

It is worth stressing that, until now, no case of antibody-mediated PRCA associated with darbepoietin alfa treatment has been reported.

Synthetic Erythropoiesis Protein (SEP)

Kochendoerfer *et al*. have described a 166-aminoacid polypeptide of similar sequence to EPO, which differs strikingly in the number and type of

polymers attached to the main chain [16]. Two precisely-constructed branched peptides were designed to bear negative charges and give optimal potency and prolonged duration of action in vivo [16]. The biological activity of SEP is superior to epoietin alfa. The serum half-life is almost twice as high, not, however as long or even as for darbepoietin alfa [16]. This fact limits at least its above-mentioned SEP applicability in the future.

Continuous Erythropoietin Receptor Activator (CERA)

CERA is an innovative erythropoietic agent (synthetic polypeptide conjugated with methoxy-polyethylene glycolsuccinimidyl-butanoic acid), which has currently entered preclinical (phase III) studies in renal anaemia. Four placebo-controlled phase I studies demonstrated a dose-dependent erythropoietic response of CERA with a prolonged serum half-life [17]. After both intravenous and subcutaneous injections, serum elimination half-lives exceed 130 hrs [18] (Table 1). This unique feature suggests that CERA may be administered at longer than darbepoietin intervals. It has already been proved that the mean increase of haemoglobin level is similar in patients receiving CERA once a week and every third week [19].

The results of larger studies with CERA in dialysis patients should be available this year.

Dimeric fusion peptides

The binding of native EPO to its receptor results in dimerisation, which is required to trigger the biological response [20]. This finding initiated a search for dimeric fusion peptides providing two polypeptide fragments with high affinity domains for EPO receptor and a linker peptide [21].

Dimeric EPO-EPO protein with 6-aminoacid linker obtained by DNA recombination technique provided a new protein with a pharmacokinetics similar to EPO monomer (weaker binding affinity) and 3–4 times higher biological activity [22].

It has been demonstrated that the length or – even more importantly – the structure of the linker may influence the activity of dimeric fusion protein. When the linker was too long, the activity of such a protein was similar to the monomer [21].

Another dimeric fusion protein was composed of GM-CSF and EPO [23]. The idea of that invention was based on the fact that burst-forming unit-erythrocyte (BFU-E) requires stimulation by GM-CSF (a granulocyte/monocyte

colony stimulating factor) or interleukin 3 (IL-3) for further differentiation to the next erythrocyte precursor – a colony forming unit-erythrocyte (CFU-E). During this transformation, the erythrocyte progenitor enables EPO receptors to synthesise – a target for the second part of this fusion protein. It is important to stress that GM-CSF – EPO fusion protein is more effective than a mixture of GM-CSF and EPO at the induction of erythroid differentiation [23].

A particularly interesting novel fusion protein contains EPO and an Fc fragment of human immunoglobulin G. This Fc fragment enables transport of such fusion protein across the epithelial cells barrier of the upper and central airways by binding to the specific receptors (FcRn). By this mechanism the EPO-Fc fusion molecule can be delivered to the human body in aerosol form. The phase I clinical study demonstrated a dose-dependent increase of serum concentration of EPO-Fc fusion protein and an increase in the reticulocyte count [24].

EPO-mimetics and haematopoietic cell phosphatase (HCP) inhibitors

The search for small molecules with EPO mimetic properties focuses on two different approaches (Fig 1). The main 'hunt' concerns the small moieties enabling the cause of the dimerisation of EPO receptors. The alternative way targets the intracellular signalling pathway – enzymes, such as haematopoietic cell phosphatase (HCP) [25].

The first approach led to the discovery of peptides called EPO-mimetics. One of these EMP1 (EPO mimetic peptide 1) is a small (20-aminoacid) cyclic peptide, containing some conservative amino acid residues of native EPO structure [21]. EMP1 shows a similar binding affinity to an EPO receptor and activates an intracellular pathway like a native EPO [26, 27]. However, even after EMP1dimerisation, its activity – both in vitro and in vivo conditions – remains much lower [26]. This diminished EMP1 dimer activity is not related to its lower binding affinity, which suggests that a natural ligand activates the EPO receptor in multiple ways. This complex interaction between EPO and EPO receptor dampens our zeal for the rapid invention of small non-peptide orally delivered EPO-mimetics.

The second approach targets the intracellular signal transduction of the EPO receptor [25]. After the EPO receptor dimerisation, JAK2 protein undergoes autophosphorylation and subsequently phosphorytates the EPO receptor and STAT protein, which translocate to the nucleus and activate the transcription of the target genes [20]. Dephosphorylation of JAK2 protein by the haematopoietic cell phosphatase (HCP) is a negative regulator of the EPO receptor signalling (Figure 1) [20]. Thus, the inhibition of the HCP could augment the receptor

stimulation [25]. A number of HCP inhibitors were tested [25]. No data concerning their efficacy are available.

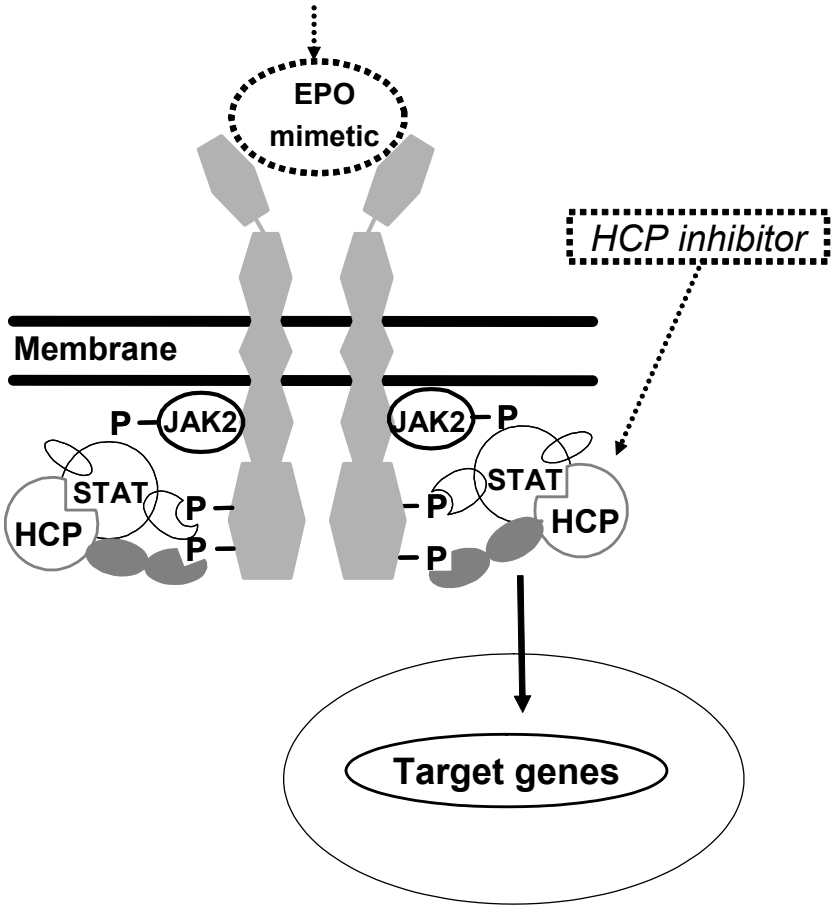

Figure 1 – Schematic depiction of EPO receptor signal transduction with mechanisms of EPO-mimetic and haematopoietic cell phosphatase (HCP) inhibitor action (Modified based on 34).

Slika 1 ‡ [ematsko prika`uvawe na signalnata transdukcija na EPO receptorot so mehanizmi na EPO-mimetskata i hematopoetska akcija na inhibitorot na kleto~nata fosfataza

Pegylated Peptide-Based Erythropoiesis-Stimulating Agent

Hematide (AF37702) developed by Affymax is a synthetic dimeric polypeptide linked to polyethylene glycol [28]. In contrast to dimeric fusion

peptides, its aminoacid sequence is unrelated to that of EPO. Thus, antibodies do not cross-react with rHuEPO and AF37702. Regardless of this modification, the binding affinity to the erythropoietin receptor is maintained. The erythropoietic activity and efficacy of AF37702 have been confirmed in in vitro and in vivo studies [28]. Pharmacokinetic data showed an extended serum elimination half-life in comparison with epoietin alfa, (58.4 hrs) [28].

AF37702 may be especially useful in patients with previous PRCA as neutralisation antibodies against rhuEPO do not cross-react with its moiety [28].

Inhibition of Hypoxia-Inducible Factor (HIF) prolyl 4-hydroxylase

Endogenous EPO production is stimulated by hypoxia. It is currently believed that a key element of the oxygen sensing mechanism is the Hypoxia Inducible Factor (HIF) [29]. HIFα is a cytosolic transcriptional factor constitutively produced in the majority of cells (29). In normoxic conditions, HIFα is rapidly degradated [30]. As shown in figure 2, this process is mediated by the von Hippel-Lindau tumour suppressor protein, which enables ubiquitination and degradation of HIFα by targetting it to the proteosome [31]. After cell exposure to hypoxia, a stabilisation of HIFα is observed with subsequent dimerization with HIFß (29). HIF complex mediates the transcriptional response to hypoxia including enhancement of EPO synthesis [29, 32].

The mechanism of oxygen dependent HIF degradation is regulated by hydroxylation of HIF proline residues [33]. This modification is carried out by HIF-specific prolyl hydroxylase [34]. Recently it has been found that quite similarly to hypoxia, FG-2216 (manufactured by FibroGen) inhibits prolyl hydroxylase leading to HIF stabilization and induction of EPO synthesis not only by the kidney, but also in the liver [35].

It is worth stressing that FG-2216 shows high bioavailability after oral administration (over 75%) [35]. It is also characterised by high efficacy. In animals, an elevation up to 300-fold of plasma EPO concentration was observed after oral FG-2216 administration [36]. Also, after the bilateral nephrectomy, an increase of plasma EPO concentration was observed [36].

In healthy human subjects, FG-2216 given orally in a dose of 10mg/kg or higher twice a week, effectively induced endogenous EPO synthesis [35]. Also in predialysis patients with chronic kidney disease a dose of 6mg/kg of FG-2216 weekly resulted in a 1g/dl increase of haemoglobin concentration after 3 weeks therapy [37].

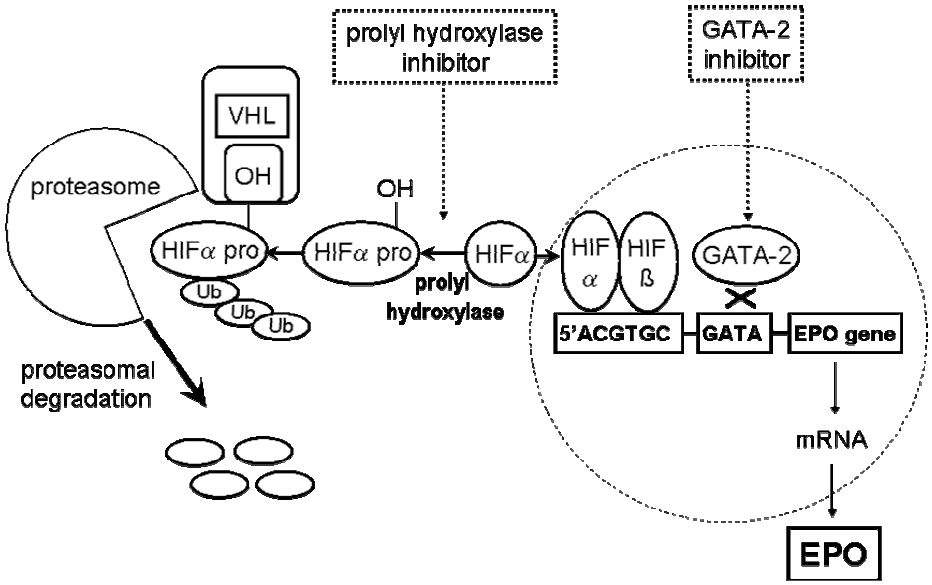

Figure 2 – The mechanism of stimulation of EPO synthesis by inhibitors of prolyl hydroxylase and GATA-2
Slika 2 ‡ Mehanizam na stimulacija na sintezata na EPO preku inhibicija na prolil hidroksilazata i GATA-2

GATA-2 inhibitors

The GATA-2 transcription factor suppresses erythropoietin gene transcription by binding to the highly conservative GATA motif in the promoter region, that also includes the hypoxic response element – HIF-1 binding sequence [38]. Inhibitors of transcriptional factor GATA-2 stimulate erythropoietin gene transcription, quite similarly to the prolyl hydroxylase inhibitors. Both intraperitoneal injections of K-7174 and oral administration of K-11706 (GATA-2 specific inhibitors) in animal models improved erythropoietin secretion and erythropoiesis suppressed by IL-1β or TNF-α [39, 40]. These studies raised the possibility that GATA-2 inhibitors might also in future be suitable for treating patients with refractory renal anaemia in inflammatory states.

Conclusion

There are several new erythropoiesis-stimulating agents that may in the near future potentially improve the management of anaemia in patients with

chronic kidney disease. The new agents will be administered less frequently with better stabilisation of blood haemoglobin concentration. There are also promising attempts to overcome the paraenteral method of drug administration. Additionally, there is a real chance that the new compounds will be much more cost-effective than the currently-used epoietins. This fact will certainly improve the management of anaemia, the quality of life and hopefully also the survival of patients with chronic kidney diseases.

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Резиме

ПЕРСПЕКТИВИ ВО ТРЕТМАНОТ НА РЕНАЛНАТА АНЕМИЈА: НОВИ КОНЦЕПТИ И НОВИ ЛЕКОВИ

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Има неколку нови стимулирачки агенси на еритропоезата кои можат во блиска иднина потенцијално да го подобрат лекувањето на анемијата кај пациентите со хронична бубрежна болест.

Некои од овие нови стимулирачки агенси на еритропоезата биле синтетизирани преку модификација на аминокиселинската секвенца на EPO молекулата и хипергликозилација и поради тоа имаат подобрена фармакокинетика (Дарбо-поетин или CERA) преку пролонгирањето на полуживотот на серумската елимина-

ција споредено со епоиетините. Овие агенси можат да бидат администрирани поретко и да покажуваат подобра стабилизација во концентрацијата на хемоглобинот.

Има некои ветувачки обиди да се надмине парентералниот начин на употреба. Таквите не-пептидни лекови делуваат како инхибитори на пролил хидроксилазата и GATA-2 транскрипцискиот фактор на тој начин зголемувајќи ја ендогената синтеза на EPO.

Клучни зборови: дарбепоиетин алфа, CERA, EPO-миметици, инхибитор на пролил хидроксилаза, пептиди на синтетички еритропоетин.

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Table 1: Serum half-life (hours) of epoietins, darbepoietin alfa and CERA administered intravenously and subcutaneously (13, 17, 19).
Табела 1: Серумски полуживот (часови) на администрираните епоиетини, дарбопоетин алфа и ЦЕРА

	Intravenous	subcutaneous
Epoietin alfa	6.8 ± 0.6	19.4 ± 2.5
Epoietin beta	8.8 ± 0.5	24.2 ± 2.6
Epoietin omega	not determined	not determined
Darbepoietin alfa	25.3 ± 2.2	48.8 ± 5.2
CERA	133 ± 10	137 ± 22

mean values ± SEM

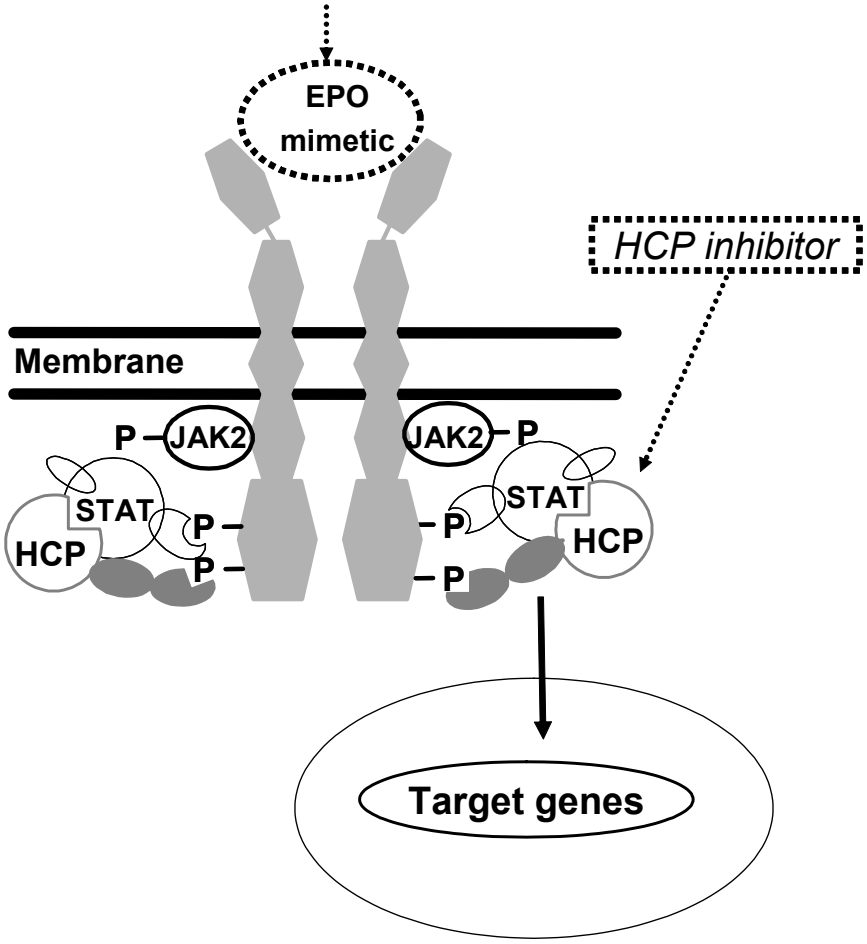

Fig 1.
Schematic depiction of EPO receptor signal transduction with mechanisms of EPO-mimetic and haematopoietic cell phosphatase (HCP) inhibitor action (Modified based on 34).

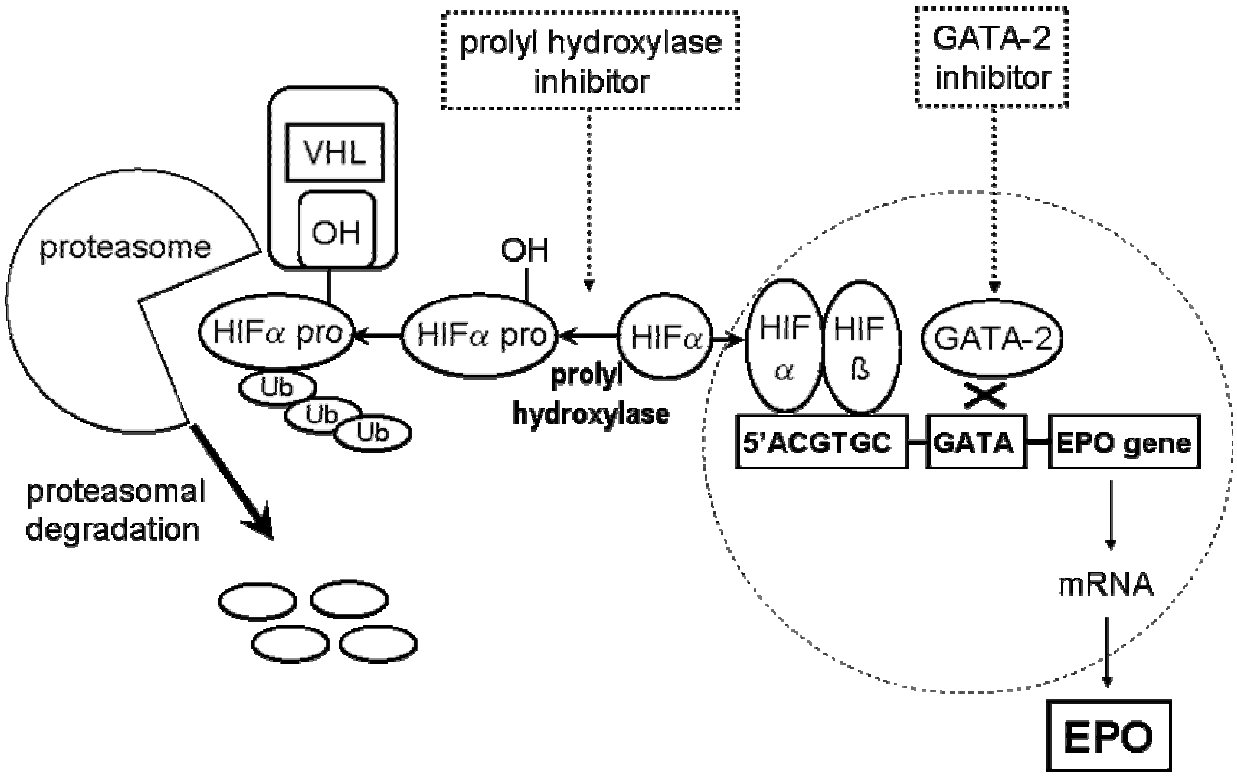

Fig 2.
The mechanism of stimulation of EPO synthesis by inhibitors of prolyl hydroxylase and GATA-2.

Резиме

Перспективи во третманот на реналната анемија: нови концепти и нови лекови

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Има неколку нови стимулирачки агенси на еритропоезата кои можат во блиска иднина потенцијално да го подобрат лекувањето на анемијата кај пациентите со хронична бубрежна болест.

Некои од ови нови стимулирачки агенси на еритропоезата биле синтетизирани преку модификација на аминокиселинската секвенца на ЕПО молекулата и хипергликозилација и поради тоа имаат подобрена фармакокинетика (Дарбопоетин или ЦЕРА) преку пролонгирањето на полуживотот на серумската елиминација споредено со епоиетините. Овие агенси можат да бидат администрирани поретко и да покажуваат подобра стабилизација во концентрацијата на хемоглобинот.

Има некои ветувачки обиди да се надмине парентералниот начин на употреба. Таквите не-пептидни лекови делуваат како инхибитори на пролил хидроксилазата и ГАТА-2 транскрипцискиот фактор на тој начин зголемувајќи ја ендогената синтеза на ЕПО.

Клучни зборови: дарбепоиетин алфа, ЦЕРА, ЕПО-миметици, инхибитор на пролил хидроксилаза, пептиди на синтетички еритропоетин.

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