Sažetak sa skupa

Mogućnosti liječenja dekompenziranog srčanog zatajivanja

Meeting abstract

Therapeutic options in decompensated heart failure

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Unatoč napretku u dijagnostici i farmakološkom liječenju, prognoza zatajivanja srca i dalje ostaje ozbiljna. Izbor lijekova za dekompenzirano srčano zatajivanje se promijenio u zadnjih nekoliko desetljeća, novi lijekovi su neuspješni u važnim istraživanjima (npr. levosimendan) ili se povezuju s disfunkcijom bubrega ili potencijalno povećavaju stopu smrtnosti (npr. nesiritid). Stoga postoji potreba za novim terapijskim opcijama u liječenju dekompenziranog srčanog zatajivanja.

Rezultati velikih studija su pokazali da velike nade i očekivanja polagane u antagoniste endotelina, antagoniste TNFα, inhibitore vazopeptidaze i metaloproteinaze, kao i aktivatore CERCA nisu ispunjene.

Natriuretski peptidi, npr. ularitide, inhibitori renina (aliskiren), antagonisti adenozin A1-receptora (rolofylline, SLV320) i modulatori topive gvanilat ciklaze (sGC) su tvari u koje se polažu nove nade.

Naglasak ovog sažetka bit će antagonisti adenozinskih A1-receptora (SLV320) i aktivatori sGC (cinaciguat).

Antagonist adenozin A1-receptora (SLV320)

Dekompenzirano srčano zatajivanje često je povezano s poremećajem funkcije bubrega. Nekoliko studija tijekom posljednjih godina utvrdilo je povezanost između lošeg ishoda (pobol, smrtnost) i prisutnog kongestivnog srčanog zatajivanja i bubrežne insuficijencije. Aktivirani tubuloglomerularni povratni mehanizam (TGF) se čini važnim patogenetskim čimbenikom koji doprinosi disfunkciji bubrega kod pacijenata sa srčanim zatajivanjem. TGF je bar djelomično posredovan preko adenozin A1-receptora što dovodi do vazokonstrikcije Vas afference i smanjenja glomerularne filtracije (GFR).

SLV320 je selektivni antagonist adenozin A1-receptora razvijen od strane Solvay Pharmaceuticals u svrhu terapije pacijenata sa srčanim zatajivanjem i oštećenom funkcijom

Despite advances in diagnosis and pharmacological therapy the prognosis of heart failure remains serious. Drug choice for decompensated heart failure has changed little for several decades, with novel agents failing in pivotal studies (e.g. levosimendan) or being associated with kidney dysfunction and, potentially, increased mortality rates (e.g. nesiritide). Thus, there is a unmet need for new therapy options in treating decompensated heart failure.

The great hopes and expectations placed in endothelin antagonists, TNFα antagonists, vasopeptidase and metalloproteinase inhibitors as well as CERCA activators could not be fulfilled as was shown by results of large-scale studies.

Natriuretic peptides, e.g. ularitide, renin inhibitors (aliskiren), adenosine A1-receptor antagonists (rolofylline, SLV320) and modulators of soluble guanylate cyclises (sGC) are substances on which our new hopes are now pinned.

Focus of this presentation will be adenosine A1-receptor antagonists (SLV320) und sGC activators (cinaciguat).

Adenosine A1 receptor antagonist (SLV320)

Decompensated heart failure is frequently associated with impaired renal function. In recent years, several mortality studies have shown that patients with congestive heart failure and renal insufficiency are characterized by a poor outcome with respect to morbidity and mortality. The activated tubuloglomerular feed back mechanism (TGF) seems so be an important pathogenetic factor contributing to renal failure in heart failure patients. TGF is at least partially mediated via the adenosine A1-receptor leading to vasoconstriction of Vas afference and a decrease of the glomerular filtration rate (GFR).

SLV320 is a selective adenosine A1 receptor antagonist developed by Solvay Pharmaceuticals for the therapy of patients with heart failure and impaired renal function. The

bubrega. Kardiorenalni učinci SLV320 su istraživani na 111 pacijenata sa srčanim zatajivanjem stupnja NYHA II i III uspoređujući s placebom i 40 mg fursemida. Hemodinamske varijable su procijenjene desnom kateterizacijom srca pomoću Swan Ganz termodilucijskog katetera u trajanju od 24 sata.

SLV320 je pokazao trend smanjenja tlaka punjenja lijevog i desnog ventikula, a bez znatne promjene drugih hemodinamskih varijabli. Fursemid je doveo do najjačeg smanjenja PCWP-a, PAP-a i RAP-a uz znatno povećanje SVR-a u usporedbi s placebom i SLV320, dok je SLV320 bio neutralan s obzirom na ukupni periferni otpor.

Cistatin C, visoko-osjetljivi marker bubrežne funkcije (GFR), se znatno snizio nakon SLV320 IV, dok je fursemid doveo do povećanja cistatina C što govori za poboljšanje funkcije bubrega nakon SLV320 i pogoršanje funkcije bubrega nakon fursemida. Fursemid i placebo nisu pokazali kontraučinke na adenozin A1-receptore, dok se inhibicija adenozin A1-receptora povećala sa povećanjem koncentracije SLV320.

Zaključno, antagonist adenozin A1-receptora SLV320 bi mogao poboljšati funkciju bubrega u usporedbi s fursemidom i istodobno stimulirati natriurezu i diurezu. Stoga bi, SLV320, kao antagonist adenozin A1-receptora, mogao predstavljati novu terapijsku mogućnost za liječenje pacijenata s kongestivnim zatajivanjem srca.

Modulatori gvanilat ciklaze (cinaciguat)

Ciklički gvanozin monofosfat (cGMP) je drugi glasnik nekoliko signalnih putova kardiovaskularnog sustava koji se temelje na gvanilat ciklazi. Razlikujemo dvije vrste gvanilat ciklaze: u obliku čestica (pGC) koje se aktiviraju natriuretskim peptidima i u topivom obliku (sCG) koji se aktivira preko dušičnog oksida i cinaciguata (BAY 58-2667), novog aktivatora sGC neovisnog o dušičnom oksidu i krvno neovisnog.

Važne razloge za buduću kliničku učinkovitost daje njegova mogućnost aktiviranja sGC u za dušični oksid nereaktivnom feričnom obliku ili stanju bez krvi. Klinički i hemodinamički učinci različitih doza (50-400 μg/sat) istraživani na pacijentima s akutnim dekompenziranim zatajivanjem srca. Prvi klinički rezultati su demonstrirali terapijski potencijal cinaciguata sa klinički značajnim smanjenjem tlaka punjenja lijevog i desnog ventrikula, smanjenje sistematskog vaskularnog otpora i uzastopno povećanje srčanog učinka.

Unatoč ograničenim kliničkim podacima o cinaciguatu kod dekompenziranog zatajivanja srca, preliminarni rezultati u ovoj skupini pacijenata pokazuju značajne hemodinamske dobrobiti s poboljšanjem kliničke slike. Stoga bi cinaciguat mogao biti koristan kod pacijenata s akutnim dekompenziranim zatajivanjem srca, poglavito jer ta skupina moguće ima oblik oksidiziranog sCG ili haem-free sCG koji se ne aktivira primjenom tradicionalne nitratne terapije.

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cardiorenal effects of SLV320 were studied in 111 patients with heart failure NYHA class II and III in comparison to placebo and 40 mg furosemide. Hemodynamic parameters were assessed by right heart catheterization using a Swan Ganz thermodilution catheter for 24 hours.

SLV320 showed a trend to a decrease of left and right ventricular filling pressures without significant alteration of other hemodynamic parameters. Furosemide led to the greatest decrease in PCWP, PAP and RAP with a significant increase in SVR compared to placebo and SLV320, whereas SLV320 was neutral with respect to total peripheral resistance.

Cystatin C, a high-sensitive marker for renal function (GFR), significantly decreased after SLV320 IV, whereas furosemide led to an increase of cystatin C suggesting an improvement of renal function after SLV320 and a deterioration of renal function after furosemide. Furosemide and placebo showed no antagonistic effect on adenosine A1 receptors whereas the adenosine A1-receptor inhibition increased with increasing SLV320 concentration.

In conclusion, the adenosine A1-receptor antagonist SLV320 might improve kidney function compared to furosemide while simultaneously promoting dose-depending natriuresis and diuresis. Thus, SLV320, as an adenosine A1-receptor antagonist, might represent a new therapeutic option for the treatment of patients with congestive heart failure.

Modulators of guanylate cyclase (cinaciguat)

Cyclic guanosine monophoshate (cGMP) is the second messenger of several important signalling pathways based on distinct guanulate cyclases in the cardiovascular system. Two types of guanulate cyclases can be differentiated: the particulate form (pGC) which is activated by natriuretic peptides and the soluble form (sGC) which is activated by NO and by cinaciguat (BAY 58-2667), a novel NO- and haem-independent sGC activator.

A strong rationale for future clinical effectiveness is provided by its ability to activate sGC in its NO-unresponsive oxidized ferric or haem-free state. The clinical and hemodynamic effects were investigated in patients with acute decompensated heart failure in different dosages (50-400 μg/hour). The first clinical results demonstrated the therapeutic potential of cinaciguat with a clinically relevant decrease in left and right ventricular filling pressure, a decrease in systemic vascular resistance and consecutive increase in cardiac output.

Despite limited clinical data of cinaciguat in decompensated heart failure, preliminary results in this patient group show substantial hemodynamic benefit and clinical improvement. Thus, cinaciguat may be useful in patients with acute decompensated heart failure, especially as this group may have oxidized or haem-free sCG which cannot be activated by traditional organic nitrate therapies.