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Opsežno kliničko iskustvo primjene klopidogrela u liječenju akutnog koronarnog sindroma

Extensive clinical experience with clopidogrel in the treatment of acute coronary syndrome

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SAŽETAK: *Akutni koronarni sindrom (AKS) predstavlja veliki problem sustava zdravstvene skrbi obzirom da je godinama uzrok velikog broja hospitalizacija. Kako AKS može biti s po život opasno stanje, potrebna je pravodobna odluka o farmakološkom liječenju, kao i strategijama revaskularizacije. Postoje čvrsti dokazi o učinkovitosti i dobroj podnošljivosti klopidogrela, antitrombocitnog lijeka za sekundarnu prevenciju ishemijskih događaja kod pacijenata s različitim kardiovaskularnim bolestima, uključujući i one s AKS. Dokazi o učinkovitosti i sigurnosti postoje i za antitrombocitni lijek Zyllt® (Krkin klopidogrel), a temelje se na rezultatima mnogih studija sigurnosti i učinkovitosti koje su provedene nakon odobrenja lijeka. Ove studije donijele su važne rezultate i opsežnu bazu podataka koja nije dostupna niti za jedan drugi generički klopidogrel. Visoka učinkovitost i dobra sigurnost, kao i prihvatljiva cijena, Krkinog klopdogrela mogli bi bez sumnje doprinijeti boljem pridržavanju terapije kod više pacijenata s AKS.*

KLJUČNE RIJEČI: *akutni koronarni sindrom, sekundarna prevencija, klopidogrel.*

SUMMARY: *Acute coronary syndrome (ACS) is a major problem for healthcare systems, as it is the cause of a large number of hospitalisations every year. Moreover, as ACS may be a life-threatening condition, timely decisions on pharmacological management as well as coronary revascularisation strategies are needed. Clopidogrel has a strong evidence base supporting its use as an effective and well tolerated antiplatelet agent for the secondary prevention of ischemic events in patients with various cardiovascular conditions, including those with ACS. An evidence base demonstrating the efficacy and safety of antiplatelet therapy has also been established for Zyllt® (Krka's clopidogrel) in many post-authorisation safety and efficacy studies. The studies yielded important results and an extensive data base, which is not available for any other generic clopidogrel. The high efficacy and good safety as well as the reasonable price of Krka's clopidogrel could undoubtedly contribute to a better compliance with the treatment in more patients with ACS.*

KEYWORDS: *acute coronary syndrome, secondary prevention, clopidogrel.*

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Kardiovaskularne bolesti su trenutno vodeći uzrok smrti u industrijaliziranim zemljama. Među njima prevladava koronarna bolest srca (KBS) koja se klinički manifestira kao nijema ishemija, stabilna angina pektoris, nestabilna angina, infarkt miokarda, srčano zatajivanje i iznenadna smrt.[1] Pacijenti s bolovima u prsnom košu odgovorni za velik broj akutnih hospitalizacija diljem Europe pa stoga akutni koronarni sindrom (AKS) predstavlja značajan problem za zdravstveni sustav.[1,2] Budući da AKS može biti uzrokom i smrtnog ishoda, potrebna je pravovremena odluka o farmakološkom liječenju, kao i strategiji revaskularizacije.[1]

Aktivacija trombocita i kasnija agregacija imaju dominantnu ulogu u širenju arterijske tromboze te posljedično predstavljaju ključne terapijske ciljeve liječenja AKS. Kako bi se smanjio rizik od akutnih ishemijskih komplikacija i povratnih aterotrombotskih događaja, antitrombocitnu bi terapiju, čim se ustanovi dijagnoza AKS, trebalo započeti što je ranije moguće.[1] Vezanje ADP na trombocitne P2Y12 receptore ima važnu ulogu u aktivaciji i agregaciji trombocita. Antagonisti P2Y12 receptora (primjerice klopidogrel) predstavljaju glavni terapijski alat za liječenje AKS.[1] Čvrsti dokazi pozicioniraju klopidogrel kao učinkovit i dobro podnošljiv antitrombocitni lijek u sekundarnoj prevenciji

Cardiovascular diseases are currently the leading cause of death in industrialised countries. Among these, coronary artery disease (CAD) is the most prevalent manifestation, clinically presented as silent ischemia, stable angina pectoris, unstable angina, myocardial infarction, heart failure, and sudden death.[1] Patients with chest pain represent a substantial proportion of all acute medical hospitalisations in Europe and, therefore, acute coronary syndrome (ACS) represents a huge problem for the healthcare system.[1,2] As ACS may be a life-threatening condition, timely decisions on pharmacological management as well as coronary revascularisation strategies are needed.[1]

Platelet activation and subsequent aggregation play a dominant role in the propagation of arterial thrombosis and, consequently, are the key therapeutic targets in the management of ACS. Antiplatelet therapy should be instituted as early as possible when the diagnosis of ACS is made, in order to reduce the risk of both acute ischemic complications and recurrent atherothrombotic events.[1] ADP binding to the platelet P2Y12 receptor plays an important role in platelet activation and aggregation. The antagonists of the P2Y12 receptor (such as clopidogrel) are major therapeutic tools in ACS.[1] Clopidogrel has a strong evidence base supporting its use as an effective and well tolerated antiplatelet agent for the secondary prevention of ischemic

ishemijskih događaja kod pacijenata s različitim kardiovaskularnim bolestima, uključujući i one s AKS.

Krkin klopidogrel (Zyllt®), uz šestogodišnju prisutnost na međunarodnom tržištu, s više od 850.000 do sada uspješno liječenih pacijenata[3] uz učinkovitost i sigurnost dokazanu u studijama sigurnosti i učinkovitosti nakon autorizacije, također omogućava liječenje na dobro utemeljenim kliničkim dokazima.[4-9]

Terapijska ekvivalentnost Krkinog klopidogrela također je, pored studije bioekvivalentnosti, dokazana u izravnoj usporedbi između originalnog i Krkinog klopidogrela.[4] U toj su studiji pacijenti s nestabilnom anginom i infarktom miokarda bez elevacije ST-segmenta randomizirani na dvije skupine: uz acetilsalicilnu kiselinu (ASK), pacijenti su primali ili originalni ili Krkin klopidogrel. Analizirana je učestalost ozbiljnih koronarnih događaja (primarni ishod) i sigurnost (sekundarna procjena) tijekom 150 dana praćenja. Rezultati nisu dokazali statistički značajne razlike u terapijskoj učinkovitosti i sigurnosti između dva lijeka. Ovo je u skladu sa zaključcima objavljene meta-analize studija učinkovitosti i sigurnosti originalnog klopidogrela i njegovih generičkih oblika.[10]

U poznatoj studiji CAPRIE dugotrajna primjena klopidogrela bila je povezana s blagom no statistički važnom prednosti u odnosu na ASK u smanjenju učestalosti nepovoljnih kardiovaskularnih ishoda u pacijenata s ustanovljenom kardiovaskularnom bolesti.[11] U kliničkoj studiji s uključenim pacijentima s KBS nakon operacije aortokoronarnog premoštenja, primjena Krkinog klopidogrela je rezultirala povoljnijom kliničkom kardiovaskularnom prognozom u odnosu na uporabu ASK.[5] U svih pacijenata liječenih klopidogrelom, o ADP ovisna agregacija trombocita bila je značajno smanjena, a laboratorijska rezistencija nije bila registrirana. Tijekom razdoblja praćenja nisu zabilježeni slučajevi nestabilne angine, akutnog infarkta miokarda ili smrtnih ishoda te nije registrirano ni značajnih ni manjih krvarenja ili alergijskih reakcija na klopidogrel. Slabija antitrombocitna aktivnost ASK, prisutnost rezistencije na ASK u nekih pacijenata uz povezanost s nepovoljnim koronarnim epizodama potiče primjenu potentnijih antitrombocitnih lijekova, poput klopidogrela, kao i njegovu kombinaciju s ASK, naročito kod visokorizičnih pacijenata.[5]

U nedavno objavljenoj kliničkoj studiji (CURRENT-OASIS) potvrđeno je da udarna doza od 600 mg klopidogrela ima brže djelovanje i potentniji inhibitorni učinak naspram doze od 300 mg.[12]

Učinkovitost i sigurnost Krkinog klopidogrela u udarnoj dozi od 600 mg analizirana je u pacijenata s KBS koji su bili podvrgnuti postupku perkutane transluminalne koronarne angioplastike (PTCA) koji su liječeni primjenom ASK kao temeljnom antitrombocitnom terapijom. Studija je pokazala statistički značajno smanjenje agregacije trombocita. Kasna tromboza stenta je nastupila u 2% slučajeva, 6 i 8 mjeseci nakon PTCA kod pacijenata koji se nisu pridržavali režima trajne dvostruke antitrombocitne terapije s ASK i klopidogrelom. Ova studija je potvrdila da je kombinirana antitrombocitna terapija primjenom ASK (75-100 mg) i klopidogrela (udarna doza od 600 mg dva sata prije PTCA i daljnja primjena 75 mg) učinkovita u prevenciji akutne/subakutne tromboze stenta.[6]

events in patients with various cardiovascular conditions, including those with ACS.

Krka's clopidogrel (Zyllt®), which has been present on the international market for more than 6 years, with more than 850,000 patients[3] successfully treated so far, and with the efficacy and safety proven in post-authorisation safety and efficacy studies, also provides a therapy based on well-established clinical evidence.[4-9]

The therapeutic equivalence of Krka's clopidogrel was, in addition to a bioequivalence study, also proven in direct head to head comparison between the originator's and Krka's clopidogrel.[4] In this study, patients with unstable angina and non ST-segment elevation myocardial infarction were randomly assigned to two treatment groups: in addition to the aspirin, patients received either the originator's or Krka's clopidogrel. The frequency of serious coronary events (primary end point) and safety (secondary evaluation) during 150 days of the observation were analysed. The results showed no statistically significant differences in the therapeutic efficacy and safety between the medicines. They were in compliance with the conclusions from the published meta-analysis of studies on the efficacy and safety of the originator's clopidogrel and its generic form.[10]

In the well-known study performed with clopidogrel, the CAPRIE study, long-term administration of clopidogrel was associated with a modest but statistically significant advantage over aspirin in reducing adverse cardiovascular outcomes in patients with established cardiovascular disease.[11] In the clinical study conducted in patients with CAD after coronary artery bypass graft surgery, the use of Krka's clopidogrel resulted in a more favourable clinical cardiovascular prognosis compared with the use of aspirin.[5] In all patients treated with clopidogrel, ADP-dependent platelet aggregation was significantly decreased and no laboratory resistance was observed. During the follow up period, no cases of unstable angina, acute myocardial infarction, or death were registered and there were no major or minor hemorrhages or allergic reactions to clopidogrel. The weaker antiplatelet activity of aspirin, the presence of aspirin resistance in some patients, and its association with unfavourable coronary events increasingly stimulate the use of more potent antiplatelet agents, such as clopidogrel, as well as its combination with aspirin, especially in high-risk patients.[5]

In a recently released clinical trial (CURRENT-OASIS), a 600 mg loading dose of clopidogrel was confirmed to have a more rapid onset of action and more potent inhibitory effect than the 300 mg dose.[12]

The efficacy and safety of Krka's clopidogrel in a single loading dose of 600 mg were studied in patients with CAD undergoing percutaneous transluminal coronary angioplasty (PTCA) that received aspirin as a basic antiplatelet therapy. The study showed a statistically significant decrease of platelet-induced aggregation. Late stent thrombosis occurred in 2% of cases 6 and 8 months after PTCA in patients not adhering to the regimen of permanent dual antiplatelet therapy with aspirin and clopidogrel. This study confirmed that combined antiplatelet therapy with aspirin (75-100 mg) and clopidogrel (loading dose of 600 mg two hours before PTCA and further therapy with 75 mg) is effective in prevention of acute/subacute stent thromboses.[6]

Trenutne Europske smjernice za zbrinjavanje AKS ukazuju na to da terapijske strategije za liječenje AKS moraju obratiti pažnju na zahtjeve akutne faze kao i dugoročnog liječenja. Dugoročno liječenje AKS podrazumijeva promjenu životnog stila i farmakološko liječenje, što također uključuje antitrombocitnu terapiju i terapiju hipolipemicima.[1] U skladu s ovom preporukom je provedena studija kako bi se ustanovila farmakodinamika i klinička učinkovitost Krkinih lijekova (klopidogrel i atorvastatin) kod pacijenata s AKS i hiperlipidemijom. Pacijenti su podijeljeni u tri skupine: skupina I. na monoterapiji klopidogrelom, skupina II. na kombinaciji klopidogrela i atorvastatina te skupina III. na monoterapiji atorvastatinom. Liječeni su lipidogram u krvi, inducirana agregacija trombocita i aktivnost citokrom P-450 3A4 izoenzima. Rezultati su pokazali da klopidogrel nije utjecao na lipidogram, no znatno je smanjio induciranu agregaciju trombocita. Njegova učinkovitost je također dokazana i u kombinaciji s atorvastatinom, usprkos smanjenoj aktivnosti citokrom P-450 3A4 izoenzima. Učinak atorvastatina na sniženje lipida je zapažen i kod monoterapije i kod kombinacije s klopidogrelom. Studija je dokazala visoku učinkovitost antitrombocitnog lijeka klopidogrela i hipolipemika atorvastatina, što otvara mogućnost za njihovu češću primjenu u kardiološkoj praksi, posebice kod liječenja pacijenata s AKS.[7]

Nekoliko studija provedenih s Krkinim klopidogrelom je rezultiralo važnim rezultatima te opsežnoj bazi podataka, koja nije dostupna niti za jedan drugi generički klopidogrel. Visoka učinkovitost, dobra sigurnost, kao i prihvatljiva cijena ovog generičkog klopdogrela bez sumnje bi mogli doprinijeti boljem pridržavanju terapije kod više pacijenata s AKS koji se podvrgavaju postupcima revaskularizacije.

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The current European guidelines for the treatment of ACS imply that treatment strategies for ACS need to address the requirements for the acute phase as well as for long-term treatment. Long-term management of ACS implies lifestyle changes and pharmacological treatment, which also includes antiplatelet and lipid lowering therapy.[1] In line with this recommendation, a study was conducted to establish the pharmacodynamics and clinical efficacy of Krka's drugs (clopidogrel and atorvastatin) in patients with ACS and hyperlipidemia. Patients were divided in three groups: group I received clopidogrel monotherapy, group II a combination of clopidogrel and atorvastatin, and group III atorvastatin monotherapy. The blood lipid profile, induced platelet aggregation, and activity of cytochrome P-450 3A4 isoenzyme were measured. The results showed that clopidogrel did not affect the blood lipid profile, but it significantly reduced the induced platelet aggregation. Its efficacy was also demonstrated in combination with atorvastatin, despite reduced activity of cytochrome P-450 3A4 isoenzyme. The lipid lowering effect of atorvastatin was observed both in monotherapy and in its combination with clopidogrel. The study demonstrated a high efficacy of the antiplatelet agent clopidogrel and the lipid-lowering agent atorvastatin, which opens a window for their wide use in the cardiologic practice, in particular in the management of ACS patients.[7]

Several studies performed with Krka's clopidogrel yielded important results and an extensive data base, which is not available for any other generic clopidogrel. The high efficacy and good safety as well as the reasonable price of this generic clopidogrel could undoubtedly contribute to a better compliance with the treatment in more patients with ACS undergoing revascularisation procedures.

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