HEART FAILURE TREATMENT IN PATIENTS WITH THALASSEMIA MAJOR

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ABSTRACT

The modern treatment of heart failure (HF) in patients with thalassemia is based on the prevention of cardiac impairment. Iron overload cardiomyopathy is the most serious and life-threatening complication of transfusion-dependent thalassemia, but due to its association with iron deposition it is reversible. Treatment includes chelation therapy and conventional medication for HF. Severely decompensated cases are treated in specialized centers.

Keywords: thalassemia major, heart failure

The modern treatment of heart failure (HF) in patients with thalassemia is based on the prevention of cardiac impairment. The aim is to keep pre-transfusion values of hemoglobin above 100 g/L, combined with appropriate chelation therapy targeting T2*> 20 ms (1,2). Deterioration of myocardial function may require specific treatment for HF, but may also indicate a need for intensified chelation therapy.

Treatment of acute and chronic HF in patients with thalassemia is different to other patients. On one hand, these are younger patients, on the other, they develop toxic cardiomyopathies as a result of iron overload, and therefore myocardial iron clearance is of primary importance for restoration of ventricular function rather than inotropic stimulation. And thirdly, these patients have a number of concomitant diseases that also require specific therapy (3).

Cardiac dysfunction usually occurs several years after myocardial iron deposition (4). Unfortunately, myocardial iron removal might take several years - 3 or more (5), and the beneficial effects of preventive chelation compared to therapeutic one has been repeatedly tested and confirmed (6).

Patients with T2*<6 ms have the greatest risk of developing symptomatic HF and should undergo intensive chelation therapy, even with preserved cardiac function (7).
Iron overload cardiomyopathy is the most serious and life-threatening complication of transfusion-dependent thalassemia, but due to its association with iron deposition it is reversible.

IRON CHELATORS: PRINCIPLES OF CHELATION THERAPY

The purpose of chelation therapy is to block the ability of iron ions to catalyze oxidative reactions in the cell by forming reactive oxygen species, to ensure adequate transport through cell membranes and excretion, without the possibility of return. This is accomplished by blocking the active electrochemical coordination regions, which are 6 (3). Depending on the number of coordination sites, iron ligands could be hexadentate, tridentate and bidentate. "Denticity" is a function of molecular weight and hexadentates have a higher molecular weight than tri- and bidentate molecules. Another important characteristic of chelators is their lipophilicity since diffusion through biological membranes, gastrointestinal resorption and cell penetration depend on it (8). Relevant to their effectiveness are selectivity and affinity for Fe3+ oxidation state since they reduce chelation of other important divalent cations. These include copper and zinc, while the effect on trivalent elements such as aluminum and gallium is negligible. Iron chelator affinity and stability of the ligand-metal complex is expressed through the value of pFe3+. This is a negative logarithm of the concentration of free Fe3+, measured in a solution of 10 μmol/L ligand and 1 μmol/L Fe3+ at pH 7.4. The higher the pFe3+ value, the greater the stability of the complex (3).

Three iron chelators are available.

Deferoxamine

Deferoxamine was the first approved iron chelator to be introduced into clinical use in the 1960s. It is a hexadentate ligand. Deferoxamine is not absorbed effectively by the gastrointestinal tract and must be administered parenterally, usually in subcutaneous infusions, due to its short half-life of about 20 minutes. When intensive chelation is needed, deferoxamine can be given as a continuous intravenous infusion. The most common deferoxamine side effects are local in-fusion-site reactions (induration, erythema, swelling, and itching). Serious adverse events have occurred, particularly in patients on higher deferoxamine doses relative to their iron burden. Ophthalmologic and audiological monitoring are recommended.

When administering the drug in standard subcutaneous infusions, iron is removed from the myocardium by about 1.1-2.2% per month (9), and continuous in-
Deferoxamine (Deferoxamine)

Deferoxamine is a bidentate ligand that binds to iron in 3:1 molar ratio (10). It is taken orally and is rapidly absorbed from the upper gastrointestinal tract. It is mainly metabolized to a glucuronide conjugate that lacks iron-binding capability. Given its relatively short plasma half-life of 1.5 to 2.5 hours, the drug is usually administered 3 times daily and is excreted in the urine. The most common adverse effects are gastrointestinal symptoms (nausea, vomiting, abdominal pain) and a transient increase of liver enzymes (10).

Deferiprone (Deferiprone)

Deferiprone is a bidentate ligand that binds to iron in 3:1 molar ratio (10). It is taken orally and is rapidly absorbed from the upper gastrointestinal tract. It is mainly metabolized to a glucuronide conjugate that lacks iron-binding capability. Given its relatively short plasma half-life of 1.5 to 2.5 hours, the drug is usually administered 3 times daily and is excreted in the urine. The most common adverse effects are gastrointestinal symptoms (nausea, vomiting, abdominal pain) and a transient increase of liver enzymes (10). Arthropathy may occur, ranging from mild pain in 1 or more joints (usually knee) to severe arthritis, and low plasma zinc levels have been reported in a minority of patients, but the most serious adverse reaction is agranulocytosis - in about 1% of patients. A less severe form of neutropenia has been reported in 5% of patients. This necessitates monthly neutrophil control for the early detection of agranulocytosis. These are transient conditions occurring when therapy is discontinued.

Deferiprone monotherapy provides better cardioprotection and improves myocardial iron burden and survival compared to deferoxamine (11,12). Survival data are also verified by the European Medicines Agency. The daily dose of deferiprone is 93 mg/kg and it removes myocardial iron at a rate of 2.2% per month, which is about twice higher than deferoxamine. The decrease of deposits in the liver is not significant. Deferiprole treatment improves the left and right ventricular ejection fraction more significantly than deferoxamine (13). Deferiprole monotherapy is recommended in myocardial siderosis, decreased ejection fraction, or asymptomatic left ventricular dysfunction. It is also possible to combine both drugs (both administered daily), in severe myocardial siderosis.

A one-year prospective study comparing deferoxamine (DFO) monotherapy with DFO and deferiprone (DFP) combination therapy in TM patients with left ventricular ejection fraction (LVEF) ≤56% was conducted by the Thalassemia Clinical Research Network (TCRN) (14). All patients received DFO 50-60 mg/kg for 12-24h/day subcutaneously or i.v. 7 times a week combined with DFP 75 mg/kg/day (combination therapy arm) or placebo (DFO monotherapy arm). The endpoint of the study was LVEF assessed by magnetic resonance imaging (MRI).
Heart Failure Treatment in Patients with Thalassemia Major

Results: Out of the 104 screened patients, 20 were randomized. Improvement of LVEF was significant at the 6th and 12th month (p<0.04) for both arms of the study. Normalization of ventricular function was observed in 9 patients. In the combination therapy, EF increased from 49.9% to 55.2% (+5.3%; p<0.04; n=10) at 6 months and 58.3% at 12 months (+8.4%; p<0.04; n=7). In the DFO monotherapy, LVEF increased from 52.8% to 55.7% (+2.9%; p<0.04; n=6) at 6 months and 56.9% at 12 months (+4.1%; p<0.04; n=4). The change in EF did not reach a statistical difference between the two arms (p<0.89).

There was fatal deterioration of HF during follow-up in two patients in the monotherapy and one patient in the combination therapy arm. The initial intention was to recruit 86 participants in the study and achieve a 5% improvement in EF between the two treatment regimens. The study was terminated earlier because of slow patient recruitment. With 20 recruited patients and 80% statistical power, the 8.6% difference in EF was not achieved. Myocardial T2* was improved in both arms: in the combined therapy arm with 1.9±1.6 ms; p<0.04 and in the DFO arm with 1.9±1.4 ms; p<0.004, but with no difference between the two therapy regimens (p=0.65). Reduction of iron levels in liver (p<0.03) and ferritin values (p<0.001) was observed only in the combination therapy. The conclusion is that both mono- and combined therapy improve LVEF (14).

Deferasirox

Deferasirox is an orally active tridentate chelator that binds iron in a 2:1 molar ratio. Single oral doses of deferasirox are absorbed rapidly, achieving peak plasma levels within 1 to 3 hours after administration; with a mean elimination half-life of 8 to 16 hours, plasma levels are maintained within a therapeutic range over 24 hours, which supports once-daily administration (15). Feces are the main route of excretion. It is available in the form of dispersible tablets, adverse effects are rare: mild transient gastrointestinal discomfort (nausea, vomiting, diarrhea, abdominal pain), diffuse maculopapular rash, elevation of ALT and creatinine levels (15). These side effects usually do not require discontinuation of therapy. Safety data on long-term is the same as short-term data. (16). Mild elevations in serum creatinine levels occur in ~33% of patients, but some may have higher levels. Although the changes in serum creatinine are usually nonprogressive, deferasirox is contraindicated in patients with creatinine clearance <40 mL/min or serum creatinine greater than twice the normal threshold (17). Several cases of Fanconi syndrome (441) have also been reported. Auditory and ocular toxicities occur in ~1% of patients.
Deferasirox monotherapy can be applied in confirmed iron overload in the myocardium with preserved cardiac function (18,19,20,21). However, no changes in LVEF were reported. Myocardial iron clearance is between 1.3 and 1.5% per month and is comparable to that of deferoxamine. The efficacy of deferasirox for myocardial iron removal at an average daily dose of 36.7 mg/kg is the same as that of deferoxamine. Deferasirox is not recommended as a first-line drug in T2* values <6 ms and in patients with reduced EF. Deferasirox can be used as a monotherapy in myocardial siderosis, but not in the abovementioned cases.

The lack of increase in EF increase was also confirmed in the CORDELIA study (22). In the prospective HYPERION study from 2015, the combination of deferasirox and deferoxamine was evaluated in patients with severe myocardial siderosis, where T2* was 5-10 ms, and LVEF ≥56%, followed by deferoxamine monotherapy on reaching T2*>10 cm. The mean dose of deferasirox was 30.5 mg/kg, and for deferoxamine 36.3 mg/kg/day. The EF remained stable for 24 months of follow-up.

The three chelating drugs are presented in Table 1 with their main characteristics: application, dosage and adverse effects.

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA approved</th>
<th>EMA approved</th>
<th>Route</th>
<th>Dosage mg/kg/day</th>
<th>Frequency</th>
<th>Excretion</th>
<th>Adverse effects</th>
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<tbody>
<tr>
<td>Deferoxamine</td>
<td>Yes</td>
<td>Yes</td>
<td>SC (i.v. in HF)</td>
<td>20-50</td>
<td>8- to 14-h infusion for 5-7 d/wk</td>
<td>60% urine 40% feces</td>
<td>sensoneural deafness, visual disturbance, skeletal abnormalities, growth retardation</td>
</tr>
<tr>
<td>Deferiprone</td>
<td>Yes</td>
<td>Yes</td>
<td>Oral</td>
<td>75-100</td>
<td>x3/d</td>
<td>75-90% in urine</td>
<td>agranulocytosis, gastrointestinal disorders, arthropathy</td>
</tr>
<tr>
<td>Deferasirox</td>
<td>Yes</td>
<td>Yes</td>
<td>Oral</td>
<td>20-40</td>
<td>x1/d</td>
<td>90% in feces</td>
<td>rash, GI disorders, rise in creatinine</td>
</tr>
</tbody>
</table>

COMBINED DRUG TREATMENT

The combination of deferoxamine and deferiprone is successful and both drugs are taken together. When the drugs are combined, a synergistic effect on improving iron clearance (23) is reported; there is also improvement in LVEF and reversal of myocardial siderosis (24,25). Even in severe iron burden of T2*<8 ms, combination therapy led to a rise in T2* by 3.3% per month, in T2* 8-20 ms, the rise was 4.2% per month compared to only 2.2% in monotherapy. The
right ventricular function also improves as a result of combination therapy (26). When switching from deferoxamine monotherapy to combination therapy, better results were reported in severe myocardial iron overload (27).

The combined therapy with deferoxamine and deferasipron is well accepted and is being applied successfully in all centers around the world, especially in cases of moderate and severe myocardial iron burden and in suppressed LVEF. It is recommended to use it in these particular cases (3). No increase in adverse effects has been reported in combination therapy (28).

The efficacy and safety DFO and DFX combination therapy have also been evaluated in smaller scale studies (29,30). In one of these pilot trials, DFX 20-30 mg/kg/d and DFO 35-50 mg/kg for 3-7 d/wk were administered for one year to 22 patients with iron burden. Significant improvement in liver iron concentration (31%; \( p<0.001 \)) and ferritin was reported; in all 6 patients with pathological myocardial iron burden, the value of T2*; \( p<0.031 \) improved. Non-transferrin bound iron and labile plasma-iron values were also assessed and their values were also significantly reduced: \( p<0.004 \) and \( p<0.006 \), respectively. Thus, DFX and DFO combination therapy reduces myocardial iron concentrations and provides excellent control over toxic free plasma iron values.

**SEQUENTIAL DRUG TREATMENT**

Sequential drug treatment with alternating administration of deferoxamine and deferasipron on consecutive days (not on the same day) is the method of choice in mild myocardial siderosis. This alternating administration also provides good cardioprotection comparable to deferasipron monotherapy (31).

**PROGNOSTIC SIGNIFICANCE OF CHELATION THERAPY**

A retrospective study of 315 patients with TM in the UK (Pennell 2011, 32) demonstrated the prognostic significance of chelation therapy in terms of developing HF. Patients were divided into two groups: the first with EF 56-62% (considered reduced in patients with TM) and the second with EF 63-70%. EF was evaluated by MRI. The results showed that in the 315 patients who had a total of 754 magnetic resonance tests for the retrospective analysis period, an increase of even 1% compared to baseline EF resulted in a statistically significant reduction in the risk of future development of HF for both groups: EF 56-62%; RR 0.818; \( p<0.001 \) and EF 63-70%; RR 0.893; \( p<0.001 \). These data strongly demonstrate that even a slight
ното лечение с дефероксамин (DFO) и деферасирокс (DFX) е също оценявана в неголеми студии (29,30). В едното от тези пилотни изпитвания на 22 пациенти с желязно обременяване е прилаган DFX 20-30 мг/кг дневно и DFO 35-50 мг/кг за 3 до 7 дни/една година. Отчетено е сигнификантно подобрение в чернодробната желязна концентрация с 31%, p<0,001 и феритина; при всички 6 пациенти с патологично желязно миокардино отлагане се подобрява стойността на T2*, р<0,031. Оценена е и стойността на нетрансферени свързаното желязо и лабилното плазмено желязо, които също значимо се понижават, p=0,004 и p=0,006 съответно. Така комбинираната терапия DFX и DFO намалява миокардните желязни концентрации и осигурява отличен контрол върху токсичното свободно плазмено желязо.

СЕКВЕНЦИАЛНО МЕДИКАМЕНТОЗНО ЛЕЧЕНИЕ
Секвенциалното медикаментозно лечение с редуване на приема дефероксамин и деферипрон в последователни дни, но не в едни и същи ден, е средство на избор при лека миокардна сидероза. Този алтерниращ метод също осигурява добра кардиопротекция, сравнима с монотерапията с деферипрон (31).

ПРОГНОСТИЧНО ЗНАЧЕНИЕ НА ХЕЛАТОРНОТО ЛЕЧЕНИЕ
Ретроспективно проучване на 315 пациенти с ТМ в Обединеното кралство (Pennell 2011, 32) доказва прогностичното значение на хелаторното лечение по отношение на развитието на сърдечна недостатъчност. Пациентите са разделени на две групи, едната е с ФИ 56-62%, която е счита на за понижена при пациенти с ТМ, и втората с ФИ 63-70%. ФИ е оценявана с ЯМР. Резултатите показват, че при тези 315 пациенти, на които са проведени общо 754 магнитно-резонансни изследвания за периода на ретроспективен анализ, увеличението дори с 1% на ФИ от изходното ниво води до статистически значимо намаление на риска от бъдещо развитие на СН и за двете разделени по стойност на ФИ групи: ФИ 56-62%, RR 0,818, p < 0,001 и EF 63-70%, RR 0,893 p = 0,001. Тези данни категорично демонстрират, че и лекото покачване на ФИ при лечението с железни хелатори за миокардна сидероза води до подобряване на прогнозата на пациентите с ТМ, намалявайки риска от бъдещо развитие на СН. Подобряването на ФИ с 2,6% до 3,1%, което е отчитано и в други проучвания, се увеличение в LVEF в iron chelator therapy for myocardial siderosis leads to improved prognosis in TM patients, reducing the risk of future HF development. Improvement of EF by 2.6% to 3.1% (also reported in other studies) was followed by a reduction in risk for HF by 25.5% to 46.6% over a 12-month period.

TREATMENT OF MYOCARDIAL SIDEROsis WITHOUT CARDIAC DYSFUNCTION
The importance of chelation therapy is determined by the fact that even in preserved cardiac function with an estimated iron accumulation of T2*<6 msec the risk of developing HF within one year is 47%, and the relative risk compared to patients with T2*> 10 ms is 270 (7). Therefore, also in T2* <6 msec, the treatment is the same as in manifest cardiac failure. Only 1 in 80 TM cases with T2*<10 msec develop HF for a follow-up period of about 10 years (33), therefore these patients are usually treated more conservatively. T2* measurements mainly provide information on insoluble iron in the form of inert hemosiderin that is in equilibrium with toxic labile iron (3). By maintaining a constant chelator level in the circulation for 24 h, continuous free iron binding is ensured and the risk of progression to HF decreases regardless of T2* levels. In the absence of a chelator, labile plasma iron concentrations increase rapidly and the use of short-term acting chelators is associated with increased cardiac risk (34,35).

Deferoxamine, deferasirox and deferiprone remove the iron from the myocardium when given in adequate doses and in good co-operation by patients. Each drug has advantages and disadvantages to be assessed in the particular patient (3).

TREATMENT OF SEVERE DECOMPENSATED HF IN TM PATIENTS
This is a severe, life-threatening condition that should be treated in specialized centers by detoxification with chelation therapy.

The steps of the treatment of severe decompensated HF in TM are stated the Cardiovascular Function and Treatment in B-Thalassemia Major: A Consensus Statement from the American Heart Association (3) and in the Guidelines for the Management of Transfusion-Dependent Thalassaemia of the Thalassemia International Federation (1). These are:

• immediate start of chelation therapy with a 24-hour continuous i.v. infusion of deferoxamine 50mg/kg;
• continuous electrocardiographic and hemody-
последва от намаляване на риска за СН с 25,5% до 46,6% за период от 12 месеца.

**ЛЕЧЕНИЕ НА МИОКАРДНА СИДЕРОЗА БЕЗ СЪРДЕЧНА ДИСФУНКЦИЯ**

Важността от хелаторното лечение се определя от това, че дори и при запазена сърдечна функция, при установено желязо натрупване с T2*<6 мсек, рискът от развитие на СН в рамките на една година е 47%, а релативният риск в сравнение с пациенти с T2*>10 мсек е 270 (342). Затова и при T2*<6 лечението се провежда както при манифестна СН. Само 1 на 80 случая с TM и T2*>10 мсек развиват СН за проследения период от около 10 години (33) и затова тези пациенти обикновено се лекуват по-консервативно.

Измерването на T2* дава информация главно за неразтворимото желязо под формата на инертен хемосидерин, който е в равновесие с токсичното лабилно желязо (3). При поддържане на постоянно ниво хелатор в циркулацията за цялото денонционно се осигурява непрекъснато свързване на своебодното желязо и рискът от прогресия към СН се намалява, независимо от нивата на T2*. При липса на хелатор концентрациите на лабилното плазмено желязо нарастват много бързо и приложението на краткодействащи хелатори е свързано с повишен сърдечен риск (34,35).

Дефероксамин, деферасирокс и деферипрон извеждат желязото от миокарда, когато се дават в адекватни дози и при добро сътрудничество от пациентите. Всеки медикамент има предимства и недостатъци, които трябва да се оценят при конкретния пациент (165).

**ЛЕЧЕНИЕ НА ОСТРО ДЕКОМПЕНСИРАНА СН ПРИ ПАЦИЕНТИ С ТМ**

Това е тежко животозастрашаващо състояние, което трябва да се лекува в специализирани центрове с детоксикараща хелаторна терапия. Същите, които трябва да се следят, са дадени в Консенсусния документ за лечение на сърдечно-съдовите нарушения при пациенти с таласемия майор на Американска кардиологична асоциация (3) и от Ръководството за трансфузия на Международната федерация по таласемия (1) и включват:

- незабавно започване на хелаторна терапия с 24-часова продължителна непрекъсната интравенозна инфузия с дефероксамин 50 мг/кг;
- непрекъснато електрокардиографско и хемодинамично мониториране;
- емерgency ехокардиография при пациенти в болничната койка за потвърждение на диагнозата и изключване на други причини за сердечен кризис, като прикоренемия, перикардна екссудация;
- интравенозна инфузия на амидарон 75 мг/кг;
- поддържане на адекватно дихателно и мозъчно аеробно заснемане, изключване на агресивна инотропна терапия, което има неблагоприятен ефект за тялото, понеже съществува риск от прогресия към СН;
- възможно намаляване на артериалното налягане при пациенти с нормалниили ниски сърдечни налягания, като се избегва корекция на нивото на артериално налягане при пациенти с нормални или ниски сърдечни налягания;
- диуретика трябва да се прилагат с предпазване, в минимални дози за да се поддържа адекватна плазмена концентрация на натриевата и останалите електролити;
- корекция на електролитните и метаболитните нарушения, като може да бъде включена инфузия на магнезий за профилактика на хипертрофна аритмия;
- поддържане на строго контрол на гликемията, като инсулин-плюсен успешно контролиране на метаболитните нарушения в стабилен пациент;
- негативно влияние на адреналния стрес, като възможно приложение на глюкокортикостероиди (хидрокортизон);
- корекция на калиемния, магнезийния и витаминния дефицит, както и възможно включване на витаминна терапия;
- стабилизация на хемоглобина със съвместими гранулени трансфузии, като при необходимост е възможно използване на трансфузии с гемодинамично нормален хемоглобин, измерен с индекс T2*;
- когато се установява или изключва кардиомегалия и съвместим със следния по T2* нормален хемоглобин, изследване със сцинтиграфия на миокарда в ранното време за потвърждение на диагнозата посредством хелатора със специфична квантов маркировка.
• heart transplantation is the last option since iron burden cardiomyopathies are completely reversible. Prolonged maintenance of vital organs is required in order for chelation therapy to work. Clinical stabilization of patients is expected within two weeks or up to a month after the initiation of continuous chelation therapy with clinical improvement preceding myocardial iron removal. Deferasirox has not been studied in HF and is not recommended in renal dysfunction. Prolonged deferoxamine intravenous infusion requires careful maintenance of the venous route, anticoagulation and sterility. After management of the acute moment, a 24-hour subcutaneous infusion may be initiated.

**CONVENTIONAL HF TREATMENT**

Therapeutic regimens for HF treatment with decreased EF have proven efficacy in reducing mortality and hospitalizations for HF and are presented in the current recommendations. These beneficial results have not been tested in TM patients, but it is widely accepted that major drug classes of ACE inhibitors, ARBs, beta blockers and mineral-corticoid antagonists should be also used in patients with thalassemia and myocardial dysfunction. The most frequent precaution when prescribing is low blood pressure, therefore it is always recommended to start with low doses and titrate slowly (1).

In a study by Derchi (36) including patients with a mean age of 26, 102 (19.5%) out of 524 TM patients have been prescribed cardiac therapy. The most commonly prescribed group of medications were: ACE inhibitors - 81 (15.5%), followed by diuretics - 39 (7.4%), beta blockers - 24 (4.6%), antiarrhythmics 16 (3.1%), and digoxin - only 8 patients (1.5%).

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**Table 2. Drugs used for treatment of myocardial dysfunction and HF in TM patients (1)**

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Dosage</th>
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<tbody>
<tr>
<td>ACE inhibitor</td>
<td>ramipril</td>
<td>1.25-10 mg/x1 daily</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>enalapril</td>
<td>2.25-20 mg/x2 daily</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>captopril</td>
<td>6.25-50 mg/x3 daily</td>
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<tr>
<td>ACE inhibitor</td>
<td>lizinopril</td>
<td>2.5-40 mg/x1 daily</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>perindopril</td>
<td>2-16 mg/x1 daily</td>
</tr>
<tr>
<td>ARBs</td>
<td>lozartan</td>
<td>25-150 mg/x1 daily</td>
</tr>
<tr>
<td>ARBs</td>
<td>valsatran</td>
<td>20-160 mg/x2 daily</td>
</tr>
<tr>
<td>ARBs</td>
<td>candesatran</td>
<td>4-32 mg/x1 daily</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>bizoprolol</td>
<td>1.25-10 mg/x1 daily</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>carvedilol</td>
<td>3.125-50 mg/x2 daily</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>spironolactone</td>
<td>12.5-50 mg/x2 daily</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>eplerenone</td>
<td>25-50 mg/x1 daily</td>
</tr>
</tbody>
</table>
Heart Failure Treatment in Patients with Thalassemia Major

The recommended drugs for the treatment of myocardial dysfunction and HF in TM from the Guidelines for the Management of Transfusion Dependent Thalassaemia are presented in Table 2.

FUTURE THERAPEUTIC OPTIONS
The clarification of the role of L-type calcium channels in the development of myocardial iron burden was followed by the initiation of clinical trials to evaluate the effectiveness of calcium blockers in addition to chelation therapy. A small study demonstrated the benefit of using amiodipine with standard chelation therapy (37). A small cohort of 15 TM patients was divided into two groups: amiodipine was added to the first and placebo to the second in combination with chelation therapy. T2* values were studied at baseline, at the 6th and 12th months. In the amiodipine group, T2* of the heart increased significantly in the 6th month - from 217±7.2 ms to 28.2±7.9 ms; p=0.007 and at 12 months further to 28.3±8.0 ms; p=0.03. No change was observed in the control group but there was a difference in the T2* values between the two groups at 6 months: 28.2±7.9 and 24.7±7.8 ms; p=0.03. The conclusion is that amiodipine, added to standard chelating therapy, may be a new strategy in the prevention of organ damage from iron burden, especially in tissues where the entry of iron ions is associated with calcium channels, as is in the heart (37). Currently, the second and third phase of two other trials are being conducted: AmloThal, NCT01395199 and AMIT, NCT02065492 and the results are expected soon.

Nowadays, cardiac damages in hemoglobinopathies are characterized by a startling paradox. Among the patients with various hemoglobin defects, those with the highest quality of life and best monitored vascular status are the ones with the worst defects. Patients with transfusion-dependent thalassemia visit specialized centers and have access to all recommended diagnostic and therapeutic strategies, so our attention should be directed to non-transfusion-dependent thalassemia. It is necessary to implement strategies for early intervention and prevention of cardiovascular complications in these patients.

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Amlodipine in the Prevention

REFERENCES


Heart Failure Treatment in Patients with Thalassemia Major

and Treatment of Iron Overload in Patients With Thalassemia Major (AmloThal, NCT01395199) и Amlodipine for Myocardial Iron in Thalassemia (AMIT, NCT02065492), чиито резултати се очакват. В днешно време сърдечните увреждания при хемоглобинопатии се характеризират със стряскащ парадокс. Сред пациентите с различни хемоглобинови дефекти тези, които са с най-високо качество на живот и най-дobre проследяван сърдечно-съдов статус, са тези с най-тежките дефекти. Пациентите с трансфузионно зависима таласемия посещават специализирани центрове и имат достъп до всички препоръчани диагностични и терапевтични стратегии, което обръща вниманието ни към нетрансфузионно зависимата таласемия. Необходимо внедряване на стратегии за ранно обхващане и превентиране на сърдечно-съдовите усложнения при тези пациенти.

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