Original Article

Combined and alternative iron chelator drugs in treatment of thalassemia major

Bijan Keikhaei

ABSTRACT

Objective: To assess the efficacy and safety of the sequential deferoxamine (DFO) and deferasirox/Osveral (OSV) [(Seq OSV/DFO)] protocol and combinations of Deferroxamine/ Deferiprone (Com DFO/DEF) in thalassemia major (TM) patients.

Methodology: A total of 148 male and 142 female patients of thalassemia major (TM) were enrolled in these studies. Out of 290 patients sixty two (31 male, 31 female) aged 6 to 30 years (mean: 18.5) entered into Seq OSV/DFO study and 228 TM (117 male, 111 female) aging 2 through 36 years (mean: 17) were eligible for Com DFO/DEF trial. Seq OSV/DFO was a regimen consisted of four days Osveral followed by three days deferoxamine and Com DFO/DEF was a protocol of DEF seven days a week, along with DFO of a minimum of two to four nights per week. The duration of trial was six months. The efficacy was determined by comparison of pre and post treatment ferritin and safety was assessed by frequency of adverse drugs reaction (ADR).

Results: For both regimens serum ferritin declined significantly and compliance response was excellent. During trials 33.8% and 21% of patients experienced at least one ADR for combination and sequential respectively.

Conclusion: Deferoxamine (DFO) /deferasirox (OSV) and Deferroxamine/Deferiprone(DEF) are acceptable regimens with high efficacy, low toxicity and excellent compliances.

KEY WORDS: Deferroxamine, Deferiprone, Deferasirox, Combination, Sequential, Thalassemia Major.

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INTRODUCTION

Iron overload is an inevitable problem in thalassemia major(TM) patients. Every unit of packed blood cell contains 200-250 mg iron.[1] The body has no active mechanism to excrete iron accumulation. Iron overload can cause tissue damage and sequelae such as heart failure, liver disease, endocrine disturbances and eventual death.[2] There have been established evidences that iron chelator drugs reduce tissue damage caused by excess iron and improve life expectancy in TM patients.[3]

These patients require a continuous ion chelator drugs. The goal treatment of TM is to reduce total iron burden and iron cells. By decreasing iron in these pools, one aims to minimize tissue damage especially in key organs such as heart and liver to result. Saving the critical tissue cells from toxic labile iron effects improves organ function, reduces morbidity and prolongs survival.

High efficacy and compliance, low adverse effects and cost, providing 24- hour drug coverage and reduction of gap free iron chelators should be added to the aforementioned items. [4] In recent years multiple different iron chelators such as monotheray, combined and alternative sequential regimens which

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incorporated all described therapeutic goals have been proposed.[5-6]

This study demonstrated that both combinations of Deferroxamine/Deferiprone (Com DFO/DEF) and alternating sequential of Deferasirox (Osveral)/ Deferroxamine (Seq OSV/DFO) have a similar significant effect in decreasing of serum ferritin.Com DFO/DEF is a familiar regimen to most clinicians, but SeqOSV/DFO is the first trial which applied in TM patient to date.

METHODOLOGY

These trials were performed in Research Center for Thalassemia and Hemoglobinopathy at Shafa Hospital affiliated to Ahvaz Joundishapur University of Medical Science. The studies were approved by the local Research Review Board of Ahvaz Joundishapur University of Medical Science.

After taking written informed consent from patients or their parents a total of 228 TM (117 male, 111 female) aging 2 through 36 years (mean: 17) enrolled in Com DFO/DEF study. Simultaneously in another study 62 patients (31 male, 31 female) aged 6 to 30 years (mean: 18.5) entered into Seq OSV/DFO study. All patients were treated in a mean total daily dose of DEF 67 mg/kg(range 50-80) seven days a week, along with DFO 40 mg/kg(range 30-50) of a minimum of two to four nights per week for Com DFO/DEF and a mean total daily dose of OSV 23 mg/kg (range 17.2-30) 4 days a week (Saturday until Tuesday), single dose at least half an hour before breakfast followed by DFO 50 mg/kg(range 30-55)/ over 12 hours subcutaneously for three next days (Wednesday until Friday).

For everybody Cell Blood Count (CBC), serum ferritin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), Blood Urea Nitrogen (BUN), Creatinine, urinalysis, visual, auditory examination and echocardiography were done initially and repeated periodically. Compliance with drugs was assessed by pill counts and diary cards. The efficacy of both regimens was estimated by comparison of serum ferritin in pre and post-treatment. The duration of treatment was six months. DEF and OSV were prepared by an Iranian pharmaceutical company Avicenna and Osve respectively. DFO was manufactured by Novartis pharma. After collecting data, statistical analysis was performed by SPSS 16.0.2. Values were presented as means ± 2 SD. Differences were considered significant at $P < 0.05$.

RESULTS

Out of all patients 38(16.6%) of combination and 7(6.3%) of sequential therapy discontinued treatment for medical and personal reasons. For Com DFO/ DEF the results were as follow: Mean serum ferritin concentration declined significantly ($p < 0.005$) from 2564.69ng/ml (range 750-6000) to 2050.44 ng /ml (range 250-5500).Compliance response was acceptable (93%).

During trial 33.8% of patients experienced at least one general adverse drug reaction (ADR) (Table-I). These events occurred mainly in the first weeks of therapy and were mild /moderate in severity. Hematologic side effects were minimal. Agranulocytosis [Absolute Neutrophil Count [(ANC) less than $0.1*10^9$/L] occurred in only two patients (0.87%) and leucopenia (ANC<$1.5*10^9$/L) in five patients (2.19%). There was no episode of thrombocytopenia. Fluctuation in liver enzyme (ALT) was significant. The mean difference between ALT before and after treatment was significant ($p < 0.005$). There was significant correlation between initial serum ferritin and ALT post treatment ($p < 0.005$). Elevated ALT occurred mostly in heavily iron overloaded. The results of SeqDFO/ OSV were as below:

Mean serum ferritin concentration declined significantly ($P < 0.005$) from 3590 ng/ml (range 1200-7200) to 2563 ng /ml (range 750-5800). Compliance response was acceptable (95%). During trial 13 of patients (21%) experienced at least one general ADR (Table-II). These events occurred mainly in the first weeks of therapy and were mild in severity. Increased liver enzymes were seen in 16 to18 percent of patients. Most increase was in two to five times of normal level. In contrast the initial increased liver

Table-I: Side effects of combination deferroxamine /deferiprone regimen.

Adverse effect	*Frequency*	*Percent*
Skin rash	4	1.8
Nausea,Vomiting	37	16.2
Anorexia	7	3.1
Bone pain, Arthralgia,Arthritis	24	10.5
Abdominal pain	5	2.2

Table-II: Side effects of sequential Osveral /deferroxamine regimen

Adverse effect	*Frequency*	*Percent*
Rising Creatinine	13	21
Elevated ALT	11	17.7
Elevated AST	10	16
Headache, Skin rash, Abdominal pain, Diarrhea, Anorexia, Proteinuria	1 - 2	1 - 3

enzymes levels were decreased after starting treatment in 17% and 27% of patients for ALT and AST respectively.

Side effects such as headache, proteinuria, diarrhea, anorexia, skin rash and abdominal pain were seen in one to three percent of patients. The most significant adverse effect of the protocol was elevated serum Creatinine. It occurred in 21%of patients. All creatinine rising were in the normal range. DFO infusion was not associated with abscess at the site of infusion and allergic reactions.

DISCUSSION

Monotherapy with DFO needs an electronic pump for slow infusion over 8-12 hours, five to seven nights per week. This approach of therapy profoundly impact on patients' compliance, meaning that a lot of TM patients abandon treatment and don't gain benefits of therapy.[7]

The other iron chelator drug as DEF has a half-life of 3–4 hours and, like DFO is unable to provide 24-hour chelation coverage; Thus, all therapeutic goals are not possible with monotherapy such as DFO and DEF as these have a short half life (20-30 minutes for the former and 3-4 hours for the latter) and plasma levels decline rapidly after consumption.[7]

Deferasirox is a potent oral iron chelator with a long half life so it can be used as monotherapy and thus it is not recommended in combination therapy. Deferasirox can provide constant gap-free chelation coverage with a single daily dose.[4-5] As well deferasirox has an efficient and selective role on specific organs such as heart and liver.[5,8-9] Deferasirox might produce an acceptable 24 hours iron chelator coverage. But its efficacy on the heavily iron overload is questionable and may not achieve a negative iron balance in all patients at highest recommended dose and increased dosage may accompany with high side effects. Most clinicians visit some patients with an increasing serum ferritin despite the use of the currently highest recommended dose of deferasirox. Probable reasons for the low efficacy of deferasirox might include inadequate drug dosage due to clinicians fear in increasing dosage, low compliance and simply a big iron burden in excess of chelator capacity should be considered. For these reasons, none of iron chelator drugs can provide all therapeutic goals in TM patients based on the monotherapy approaching, however, deferasirox partially covers some therapeutic goals.[10-11]

Combination therapy first practiced in TM by Anderson and Wonke et al in a few patients. They used combination DFO / DEF and proposed several potential advantages with this regimen.[12] Drugs with different properties and mechanisms may access different iron pools. The molecule of DEF is small and can easily enter into cells and is able to transfer iron into plasma for DFO chelation.[13]

Combination DFO/DEF as an intensified chelator is a good approach therapy to reach a high level of iron excretion that cannot be achieved by either drug alone without extra side effects and with higher efficacy and compliance.[14-15]

In present Com DFO/DEF study ferritin significantly decreased with high compliance and low toxicity. Overall gastrointestinal symptoms occurred in 21.5% of patients (nausea and vomiting 16.2, anorexia 3.1, abdominal pain 2.2); where as in Cohen's et al study these symptoms were reported in 33% of cases.[16]

These events were mild to moderate in intensity and resolved without discontinuation of therapy in most patients. Severe to gravid vomiting can be relieved with escalating drug approach. Joint and bone pain occurred in 10.5% of patients. This adverse effect reported in 3.9 to 20% of other studies.[13,17]

The results of Com DFO/DEF study are in agreement with reported studies by Tanner et al, Zareifar et al. and Wonke et al.[13,18,19] Tanner et al. showed that the combination DFO/DEF compared with deferoxamine / placebo was significantly effective in heart function and ferritin level.[13]

Baseline serum ALT was normal in 69.7% of patients in Com DFO/DEF, after treatment decreased to 57%. DEF can cause raised ALT levels. Most rises are asymptomatic and transient and may not need to be interrupted the treatment.[20]

Agranulocytosis a life threatening drug reaction in com DFO/DEF study luckily occurred in 0.87% of patients. This finding is in concordance with the other studies.[16-18]

Alternating sequential therapy is a common clinical practice in TM patients. The advantages of this approach of therapy are:

* Reducing the number of DFO infusion.
* It is a practical regimen.
* The compliance of this approach therapy is high particularly for patients with a poor compliance of DFO therapy alone.

Two drugs with different biochemical properties can reach to more iron pools and achieving longer therapeutic chelation coverage. This approach of therapy is a flexible regimen ,which would allow the clinicians reduce the nightly DFO injections and increase the oral doses with high efficacy and low

toxicity ,because the free of oral iron chelator days to allow the physicians to provide a wide therapeutic index for oral iron chelator.

The effectiveness of the alternating use of deferiprone and DFO was initially reported by Aydinok et al in a small non-controlled clinical study.[21]

In a study of SeqDFO/OSV serum ferritin decreased significantly. This regimen was associated with minimal adverse effect. The major serious side effect of this regimen was Creatinine rising which occurred in 21% of patients. All Creatinine rising were in normal limits. In monotherapy approach this adverse drug reaction is high.[22] Sequential DFO / OSV is a new protocol to date with advantages of more time iron chelator coverage, acceptable efficacy and compliance and lower side effects. The alternating use of both chelator is effective in heavily iron loaded and most importantly, support clinicians who need to give patients a period of time in which injected chelation can be interrupted and replaced with maximum dose of oral chelation and a deferasirox-free period may be sufficient to prevent the occurrence of major side effects. The only disadvantage of this regimen might put the patients in some times of gap free iron chelator.

This regimen is not reported to date but the first combination of deferoxamine/deferasirox was reported by Lal et al. They found good results in safety and efficacy in TM patients.[23]

CONCLUSION

The results of this study show that combination and sequential therapy of iron chelator drugs have a significant reduction in serum ferritin with considerable compliance and no serious toxicity.

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