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Role of L- glutamine and crizanlizumab in sickle cell anaemia painful crisis reduction: A review

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REVIEW

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ABSTRACT

Background
Patients with sickle cell disease, frequently suffer from intense painful episodes. Till recently hydroxyurea was the only available medical therapy that approved for reduction of painful episodes.

Aims
To summarize the available data from randomized controlled trials that aim to evaluate the efficacy of newly approved L-glutamine (alters redox state of red blood cells [RBCs]) and crizanlizumab ((anti-P-selectin)) on vaso-occlusive episodes in Sickle cell disease patients.

Methods
PubMed, Google Scholar, and EBSCO databases were systematically search for relevant articles. The terms L-glutamine, sickle cell disease, sickle cell anaemia, crizanlizumab and vaso-occlusive episodes were used.

Results
Out of Four-hundred seventy-two records, only three fulfilled the inclusion criteria. Two trials were aimed to evaluate the efficacy of L-glutamine therapy on the frequency of painful crises in sickle cell anaemia patients. Both studies showed that L-glutamine therapy significantly reduce the frequency of VOEs. Only one trial examined the ability of crizanlizumab on VOEs reduction, and showed crizanlizumab successful reduce the occurrence of VOEs.

Conclusion
Newer agent with different mechanism of action, such as L-glutamine, and crizanlizumab may consider if hydroxyurea not effective or not tolerable.

Key Words
Sickle cell disease, vaso-occlusive crises, pain, crizanlizumab, p-selectin, L-glutamine

What this study adds:

1. What is known about this subject?
Treatment options for reducing the occurrence of VOEs are limited. Till recently hydroxyurea was considered the only available medical to reduce the VOEs.

2. What new information is offered in this study?
L-glutamine and more recently crizanlizumab were

approved for VOEs reduction in patients suffering from recurrent VOEs.

3. What are the implications for research, policy, or practice?

For Sickle cell anaemia patients who develop multiple painful episodes despite adequate dose of hydroxyurea, L-glutamine or crizanlizumab could be considered as an alternative therapeutic strategy.

Background

Sickle cell disease (SCD) is a genetic abnormality inherited in autosomal recessive pattern characterized by the presence of abnormal haemoglobin structure due to substitution of glutamic acid to valine at the sixth amino acid position in the beta-chain haemoglobin protein.[1]

SCD patients suffered from recurrent intense painful events known as vaso-occlusive episodes (VOEs), which is in the most of the time required emergency department visit and hospitalization. VOEs usually presented by sudden, sever pain in the extremities, back and chest. Rarely VOEs may lead to stroke, hepatic or splenic sequestration. Furthermore, VOEs and it is associated long-term consequences considered the leading cause of death among SCD patients.[2,3]

While the acute management of VOEs contestant of pharmacological (NSAIDs, weak and strong opioid) and non-pharmacological (heat compressor) aiming to reduce and control the painful episodes. Little approaches that are available for reducing the risk of VOEs morbidity and mortality in sickle cell disease (SCD) and include regular red blood cell (RBC) transfusions, hydroxyurea therapy, and hematopoietic cell transplantation (HCT).[4]

The U.S. Food and Drug Administration (FDA) approved hydroxyurea to treat SCA.[5] hydroxyurea consider as a ribonucleotide reductase inhibitor that found to increase foetal haemoglobin (HbF) level and resulting in a significant reduction in VOEs frequency.[5]

In 2017, L-glutamine was the second drug approved by the U.S. FDA to treat SCD. Furthermore, in 2019, crizanlizumab a monoclonal antibody against P-selectin which inhibit the adhesion of sickle RBCs and leukocytes to endothelial cells by 90 per cent and 80 per cent, respectively, approved as an additional option to treat SCD patient who unresponsive o hydroxyurea, L-glutamine, or both.

The current study aimed to summarize the randomized controlled trials that assess the role of L-glutamine and crizanlizumab on VOEs in SCD patients.

Method

A systematic electronic search was conducted including the PubMed, Google Scholar, and EBSCO using the following terms in different combinations L-glutamine, sickle cell disease, sickle cell anaemia, crizanlizumab and vaso-occlusive episodes. A full text randomized controlled trials that available in English, aimed to assess the role of L-glutamine and crizanlizumab on VOEs in SCD patients were included. Studies published in abstract form only were excluded. The abstracts and full texts were screened independently by two authors (AI, AB). The authors extracted the data, and then the author's names, year and region of publication, the study type, period of study, and the result were reported. (Table 1) The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Chart was used in the current survey (Figure 1).

Results

The initial literature search resulted in 472 records, after duplicates were removed and applying the inclusion criteria records were further limited to three randomized control trials.

Two randomized control trials, evaluated the efficacy of oral L-glutamine therapy on the frequency of painful crises in sickle cell anaemia patients.[6]

The first study was a phase II randomized, double-blind, placebo-controlled, parallel-group, multi-center study. The study includes sickle cell (HbS/S) or sickle- thalassemia (HbS/β0-) patients who aged five years or more with at least two painful crises in the last one year. Study participants were randomly assigned into treatment arm (oral L-glutamine at 0.3g/kg) or placebo arm. A 58 per cent reduction of painful crisis was observed among L-glutamine arm.[7]

The second study, a phase 3 trial, randomized, placebo-controlled, double-blind, multi-center trial. The study includes sickle cell (HbS/S) or sickle- thalassemia (HbS/β0-) patients who aged five years or more with at least two painful crises in the last one year. Study participants were randomly assigned into treatment arm (oral L-glutamine at 0.3g/kg) or placebo arm. A 17.9 per cent reduction of painful crisis was observed among L-glutamine arm.[8]

The efficacy of crizanlizumab were evaluated in a randomized, double-blind, placebo-controlled phase II study. Over 52 weeks the trial evaluated 198 patients with sickle cell anaemia. Study participant randomly assigned to:

A)- high-dose crizanlizumab (5mg/kg)

B)- low-dose crizanlizumab (2.5mg/kg)

C)- placebo

At the end of the trial period, a significant reduction in painful crisis (1.63 events versus 2.98 events) was observed in high-dose crizanlizumab group.[9]

Discussion

Individuals with sickle cell anaemia at increased risk of multiple acute and chronic complication, contributed to vessels vaso-occlusion and haemolysis that associated with reduced life-expectance.[10]

The current treatment opiates that affect the disease outcome are limited, allogeneic hematopoietic stem cell transplantation consider the only curative therapy, it is restricted to the availability of suitable donor.[11]

As a result of limited curative therapy of SCD, trials focused on therapies that reduce VOEs and prevent the disease complication. Three medication proven to be effective in reducing VOEs in individuals suffering from sickle cell anaemia.

A) Hydroxyurea:

Since 1998, hydroxyurea was the corner stone medical therapy that approved to use in SCD patients who are older than 2 years of age. Hydroxyurea effectively reduce the frequency of VOEs, acute chest syndrome and increase the level of foetal haemoglobin (HbF). In a randomized, double-blind, placebo-controlled trial, that include 299 patients. Study show a lower rate of VOEs among hydroxyurea group compared with placebo group (2.5 events versus 4.5 events).[12]

B) L-glutamine:

Two trials met the inclusion criteria for this review, both studies showed the superiority of L- glutamine in reduction of VOEs compared with placebo.[7,8] With regard to adverse events, L-glutamine appear to be safe, data from pilot study report that no significant adverse effect were reported among the patient treated with L-glutamine verses placebo.[13] Furthermore, in the randomized trial conducted in 2014, and reports no difference in safety profile between groups.[7] More recently, in 2018, another trial was conducted and state that, more adverse event such as extremities, back pain and nausea were more reported among the placebo group.[8]

C) Crizanlizumab:

In SUSTAIN trial, crizanlizumab proven to be effective in preventing VOEs, with low occurrence of medication related adverse events.[9]

Conclusion

If medical therapy is indicated for patients with sickle cell anaemia, hydroxyurea consider the first choice due to it is proven efficacy in reducing the frequency of the painful episodes, hospitalization and possible stroke as well as the huge accumulative safety date. Newer agent with different mechanism of action, such as L-glutamine (alters redox state of red blood cells [RBCs]), and crizanlizumab (anti-P-selectin) may consider if hydroxyurea not effective or not tolerable.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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None

Table 1: RCTs that evaluated the role of L- glutamine and Crizanlizumab

	Author–Year	Methods	Results
1	Niihara et al.[7] 2014	Study design: Phase II randomized trail Treatment regimen: Oral L-glutamine at 0.3g/kg or placebo twice daily Follow-up duration: 12 months Primary endpoint: Frequency of painful crises	Study Participants: Eighty-one patients. Result: Reduction in painful crisis in L-glutamine group compared to placebo (p=0.060) Conclusion: L-glutamine treatment was efficacious in reducing the frequency of painful crises
2	Niihara et al.[8] 2018	Study design: Phase 3 randomized, placebo-controlled, double-blind trials Treatment regimen: Oral L-glutamine at 0.3g/kg or placebo Follow-up duration: 12 months Primary endpoint: Frequency of painful crises	Study Participants: Two-hundred and thirty patients Result: Reduction in painful crisis in L-glutamine group compared to placebo (P=0.005). Conclusion: The number of pain crises over 48 weeks was lower among those who received oral therapy with l-glutamine
3	Ataga et al.[9] 2017	Study design: Phase II randomized trail Treatment regimen: low-dose crizanlizumab (2.5mg per kilogram of body weight), high-dose crizanlizumab (5.0mg per kilogram), or placebo Follow-up duration: 52 weeks Primary endpoint: Frequency of painful crises	Study Participants: Hundred Ninety-Eight patients Result: Reduction in painful crisis in high-dose crizanlizumab group compared to placebo (P=0.01) Conclusion: Crizanlizumab therapy resulted in a significantly lower rate of sickle cell–related pain crises than placebo

Figure 1: Flow diagram through the different phases of the systematic review (PRISMA flowchart)