International Journal of Internal Medicine 2015, 4(1): 14-16
DOI: 10.5923/j.ijim.20150401.03

Methotrexate as a Promising Treatment for Immune Thrombocytopenia

Mohamed N. Al-Alfy[1,*], Ahmed Hamdy[2]

[1]Internal Medicine Department, Faculty of Medicine, Al-Azhar University, Egypt
[2]Egyptian Ministry of Health

Abstract Immune thrombocytopenia either primary or secondary to other diseases may be life threatening especially in cases resistant to the usual treatment regimens. I present here several, among many others, life-threatened ITP patients with failed treatment modalities and a very narrow time window. At this point, we started to use "Methotrexate" as a new treatment modality, not mentioned in the literature before, with excellent results as regard lifesaving and as a complete replacement to other treatments. We are optimistically waiting for the results of a current study to determine the exact efficacy of such modality with very promising results.

Keywords ITP, Methotrexate, Thrombocytopenia, Systemic lupus erythematosus

Key Messages:

- Immune thrombocytopenia can be life threatening especially when it is resistant to the usual lines of treatment.
- Now we have a novel line of treatment using an existing drug used clinically in other diseases with promising results saving many young lives.

1. Introduction

The most difficult problem a physician encounters is the management of patients with idiopathic thrombocytopenic purpura (ITP), who have persistent severe thrombocytopenia after failure of initial treatment with glucocorticoids and splenectomy. Most of the patients refractory to corticosteroids and splenectomy will become refractory to other available agents, such as intravenous immunoglobulin (IVIg), danazol or chemotherapy [1]. We present here a series of cases, five female patients have presented with intractable Immune thrombocytopenia with brisk bleeding threatening their lives. Four of them were diagnosed as having immune thrombocytopenia (ITP) with failed usual treatment modalities, so an astonishing idea made us use Methotrexate as a rapid solution for the situation resulting in marvellous results saving the girls' lives. The fifth case was diagnosed to have systemic lupus erythematosus (SLE) with thrombocytopenia in a very narrow time window to receive another treatment line with also a life threatening bleeding, so we tried the same Methotrexate modality to save her life with a rapid response making a time to make splenectomy safely. It is to be mentioned that using this drug in such cases is not mentioned in literature before among other immunosuppressant drugs.

* Corresponding author:
mnalfy@yahoo.com (Mohamed N. Al-Alfy)
Published online at http://journal.sapub.org/ijim

2. Case Description

A 26-year-old Egyptian female patient presented to the ER at Sayed Galal Al- Azhar university hospital because of intractable vaginal bleeding, also there was a history of recurrent attacks of epistaxis. examination revealed extensive petechiae and ecchymotic patches, significant pallor and scar of splenectomy with no other physical findings of clinical significance. Detailed history and revising her present and old reports assured a previous diagnosis of chronic idiopathic thrombocytopenic purpura for which the first line therapy (corticosteroids) had failed. Therefore, they went to the second line (splenectomy), she responded well for the splenectomy and remained in a state of remission (about 8 years) until 10 days ago when she started to bleed again. Our emergency investigations confirmed the previous diagnosis, (the platelets was severely reduced less than 5,000/mcL), we tried to save the life of the patient by the all lines of treatment that we have, essentially and firstly by IV pulse steroids. However, the IVIgG was not available urgently at that time, it was a hard time, but the most awesome thing we have faced was the failure of all the lines we have used, so we went into blind alley.

It was just hunch to use the methotrxate injection in a dose of 12.5 mg, perhaps the strong thing that pushed us to respond to our hunch and to give a drug not previously used

in this aspect is the fact that we have nothing to do for this poor life-threatened young patient. Of course after obtaining a written consent, however, it was a huge delight, as we saw the marvelous response clinically (stoppage of bleeding) and laboratory (raising the platelets nearly touching the lower limit). However, with subsequent weekly injections by the same dose, the platelets number goes within the normal range.

This good response encouraged us to use it for other three young girls (under the age of 18 year) with chronic ITP, corticosteroid resistant and unfit for urgent splenectomy, which showed also marvellous response.

Lastly a case of already diagnosed and treated SLE female patient 51- year-old showed so much encroachment on the platelets that led to extensive bleeding tendency, and the platelets number approaching the dangerous levels (below 5.000/mcL) with also failure of the IV pulse corticosteroids and other traditional lines. There was a decision had been taken for urgent splenectomy if she responded to IVIgG. We had succeeded with difficulty to convince them to use the methotrexate injection trial while they were preparing the IVIgG that was not available at that time. They were astonished by dramatic platelets rising up to 122.000/mcL within days of the first injection.

However, we must emphasize that all the patients remained in a nearly normal state either clinically or laboratory as long as they were continued on the weekly injection dose (12.5 mg) and surprising prolonged remission we have shown in a current expanded study with promising results, We shall send you when it becomes available for publishing.

3. Discussion

Immune thrombocytopenic purpura (ITP), also termed idiopathic thrombocytopenic purpura, is an acquired disorder in which there is immune destruction of the platelets and possibly inhibition of platelets release from the megakaryocyte. In children, it is usually an acute disease, most commonly following an infection and with self-limited course, in adults it usually runs a more chronic course [2, 3].

ITP is secondary if it is associated with an underlying disorder: autoimmune disorders particularly SLE and infections such as HIV and hepatitis-C [4], the treatment of ITP utilizes drugs that decrease reticuloendothelial uptake of the antibody bound platelets, decrease antibody production and/or increase platelets production [5]. Initial treatment in patients without significant bleeding symptoms: severe thrombocytopenia (less than 5.000/mcL), signs of bleeding such as retinal hemorrhage or large oral mucosal hemorrhage can be instituted as outpatient using single agent, traditionally, this has been prednisone at 1mg/kg. For patients with severe ITP and/or symptoms of bleeding, hospital admission and combined modality therapy is given using high dose glucocorticoids with IVIgG or anti-Rho (D) therapy and as needed additional immunosuppressive agents [6, 7]. Splenectomy has been used for patients who relapse after glucocorticoids are tapered; it remains an important treatment option [8] Splenectomy, which produces a long-lasting response in a majority of patients, is still commonly used for those who do not have long-term responses to steroid therapy and it should remain the gold standard therapy. However, splenectomy is an invasive procedure with some patients relapsing even after several years. Very rare cases of life-threatening or lethal infections may also occur at any time after splenectomy and thus physicians and patients are increasingly reluctant to advise or agree to this treatment approach [9]. Other treatments have been evaluated to prevent or delay splenectomy, including high-dose dexamethasone, intermittent anti-D immunoglobulin infusions, and rituximab. There have been few randomized, placebo-controlled studies of these approaches, and they cannot currently be recommended as their efficacy and safety remain unclear [10], Thrombopoietin receptor agonists are currently under clinical investigation for the treatment of ITP and may represent an alternative treatment option in the future [11]. However, methotrexate not considered previously as a drug for treatment of immune mediated thrombocytopenia that gave a marvelous response in the refractory cases, case1 (failure of corticosteroids ,others as well as splenectomy) and prevent splenectomy after failure of corticosteroids and other therapeutic modalities in the other three cases, lastly it saved the life of the 5th case (systemic lupus erythematosus patient) after failure of all available therapeutic modalities and gives good chance to do safe splenectomy as her treating team was decided.

4. Conclusions

It is a great challenge to face a case of refractory immune thrombocytopenia to the usual lines of treatment as we faced in our cases, we can summarize the treatment lines widely used into: first line therapy consists of oral corticosteroids, second line is the splenectomy and third line for those who fail splenectomy a wide range of other therapies [12], methotrexate not one of them. We used methotrexate in this difficult situations and it succeeded to be the life boat for those patients, we used it in primary cases as well as in secondary ITP to other disease(SLE) and waiting for the promising results of using it as a first line therapy.

Lastly, methotexate is well-known, cheap, frequently used drug (in other indications) and had saved the life of many patients and we are waiting to save more and more, worldwide and to compete and replace the other lines.

REFERENCES

[1] Pasa S, Altintas A, Cil T, Danis R, Ayyildiz O. The efficacy of rituximab in patients with splenectomized refractory

chronic idiopathic thrombocythopenic purpura. *J Thromb Thrombolysis*. Mar 3 2008; [Medline]

[2] Barbara Knole: Disorders of platelets and vessel wall at Harrison's principles of internal medicine 18th Edition 2012 (Page 968).

[3] Aster RH et al: Drug-induced immune thrombocytopenia: Pathogenesis, diagnosis and management. J Throm Haemost 7:911,2009.

[4] Diz-Küçükkaya R, et al. Antiphospholipid antibodies and antiphospho-lipid syndrome in patients presenting with immune thrombocytopenic purpura: a prospective cohort study. *Blood*. 2001;98(6):1760–1764.

[5] Arnold DM, Kelton JG. Current options for the treatment of idiopathic thrombocytopenic purpura. *Semin Hematol*. Oct 2007;44(4 Suppl 5):S12-23. [Medline]

[6] Landaw SA, George JN. Approach to the adult patient with thrombocytopenia [subscription required]. UpToDate. http://www.uptodate.com/contents/approach-to-the-adult-patient-with-thrombocytopenia. Accessed November 28, 2011

[7] Rodeghiero F First-line therapies for immune thrombocytopenic purpura: re-evaluating the need to treat Eur J Haematol Suppl. 2008; (69):19-26 (ISSN: 0902-4506)

[8] Kahn MJ, McCrae KR. Splenectomy in immune thrombocytopenic purpura: recent controversies and long-term outcomes. *Curr Hematol Rep*. Sep 2004; 3(5): 317-23. [Medline]

[9] McMillan R, Durette C. Long-term outcomes in adults with chronic ITP after splenectomy failure. *Blood*. Aug 15 2004;104(4):956-60. [Medline]. Newland A. Emerging strategies to treat chronic immune thrombocytopenic purpura. *Eur J Haematol Suppl*. Feb 2008;27-33. [Medline]

[10] Rodeghiero F. First-line therapies for immune thrombocytopenic purpura: re-evaluating the need to treat. *Eur J Haematol Suppl*. Feb 2008;19-26. [Medline]

[11] Khellaf M, Charles-Nelson A, Fain O, Terriou L, Viallard JF, Cheze S, et al. Safety and efficacy of rituximab in adult immune thrombocytopenia: results from a prospective registry including 248 patients. *Blood*. Nov 20 2014; 124(22): 3228-36. [Medline].

[12] Bussel JB: Traditional and new approaches to the management of immune thrombocytopenia: Issue of when and who to treat. Hematol Oncol Clin, North Am 23:1329.2009.