Short Research Article

High-sensitivity C-Reactive Protein Levels at Presentation and Its Association with Platelet Recovery in Newly Diagnosed Immune Thrombocytopenia in Children

Abstract:

Background: Immune Thrombocytopenia (ITP) is an acquired immune mediated platelet destruction aided by the inflammatory marker high sensitivity C-Reactive Protein (hs-CRP). Higher CRP levels at presentation co-relate with retarded platelet (PLT) recovery as proposed by various studies.

Objective: To determine the quantitative level of CRP at presentation and during therapy and correlate the levels with platelet count to assess platelet recovery and be able to identify the non-responders based on the CRP level at presentation in newly diagnosed ITP.

Study design: Prospective observational study (duration: 1year 11months)

Participants: 30 cases of newly diagnosed ITP (<18 years) after excluding secondary ITP causes.

Method: Complete blood count, peripheral blood smear and other routine tests were done at presentation. Follow up involved platelet count and hs-CRP level estimation between Day 21-28 and Day 35-42 of diagnosis with treatment and assessing the trend of CRP with platelet count changes.

Outcomes: All patients presented with platelet count <10000/µL. On assessment of response to therapy, total 86.6% (n=26) of children showed complete response to treatment, 3 children showed partial response and 1 did not show response thereby requiring multi-drug therapy.

Results: 53.3% (n=16) cases belonged to age group 5-12 years and 53.3% (n=16) of cases were females. Mean CRP levels at presentation was 2.98 among 0-5 years old children, 2.38 (± 2.48) and 3.05 (± 2.90) in children who belonged to the age groups 5 – 12 years and 13 - 18 years respectively. CRP level among complete responders on three occasions were 2.6 (Day 1), 1.74 (Day 28) and 1.25 (Day 42) (p=0.17) and in the non-responder were 5.1 (Day 1), 5 (Day 28) against platelet count of 8000/microL and 13000/microL respectively. 92.9% cases (13/14) treated with IVIG showed complete response as compared to 80.0% (12/15) cases with oral steroid and one with Anti D.

Conclusion: Children with higher CRP at presentation and during follow up showed no/ lack of response to treatment making it a useful prognostic marker to predict the response to treatment. IVIG may lead to the faster recovery of platelet counts as compared to steroids.

Keywords:

Immune thrombocytopenia (ITP), C-reactive protein (CRP), children, Intravenous immunoglobulin (IVIG), steroid

INTRODUCTION

Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by accelerated platelet (PLT) destruction due to anti-platelet antibodies that accelerate platelet phagocytosis via the reticuloendothelial system (RES).[1] In most cases, the condition recovers within weeks to months. A peripheral blood platelet count of $<100 \times 10^9$/L in the absence of other causes or disorders that may be associated with thrombocytopenia can be defined as Primary ITP.[2]

Thrombocytopenia occurs as Fc receptor-mediated antibody-coated platelets are cleared more rapidly from the circulation (often in the spleen) by macrophages than they can be replaced by compensatory platelet production in the bone marrow. The exact antigenic target for most anti-platelet antibodies, in the majority of cases of acute ITP in childhood, remains undetermined (Fig.1).[2] Recently, a role for inflammatory acute-phase reactant C-reactive protein (CRP) has also been implied in ITP pathogenesis through a series of elegant studies on adults done by Kapur et al.[3,4] It acts by enhancing IgG-mediated respiratory burst and phagocytosis of platelets in vitro and in vivo.

ITP can be now clinically classified into 3 broad phases according to the Vicenza International Consensus Conference (October 2007), which are[5,6]:-

Newly diagnosed ITP	From diagnosis to 3 months (previously known as acute ITP until 6 months from diagnosis)
Persistent ITP	3-12 months after diagnosis
Chronic ITP	More than 12 months after diagnosis (previously defined as more than 6 months after diagnosis)
Refractory ITP	If patient is at risk of or displays bleeding despite splenectomy
Severe ITP	Presence of bleeding that requires treatment or treatment escalation

Table 1- Different phases of Immune thrombocytopenia

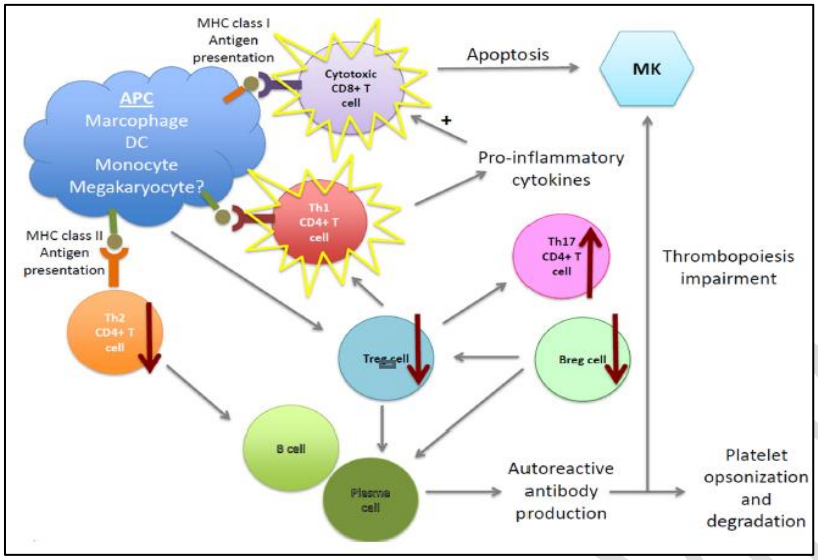

Fig.1: Summary of the cellular pathogenic mechanisms in immune thrombocytopenia

Clonal proliferation of plasma cells, cytotoxic CD8+, helper CD4+ T cells and Th17 cells, decreased expression of regulatory B & T cells and impaired plasmacytoid dendritic cells in ITP [7-13] (Zufferey et.al.)

Most patients with no bleeding or mild bleeding with skin manifestations can be treated with observation alone regardless of platelet count. The decision to treat should involve a discussion with the patient/ parents and consideration of the severity of bleeding, anticipated surgical procedures, medication side effects, and health-related quality of life.[5,6] In such a case, first-line therapy includes a trial of oral steroid (Prednisolone, 2-4 mg/kg PO daily for 4-7 days (max.120mg/day), intravenous immunoglobulin (0.8-1 g/kg per dose iv) or Anti-D (50-75 µg/kg per dose iv).[5,6] If previous treatment with oral corticosteroids, intravenous immunoglobulins (IVIG), or anti-D has been unsuccessful, subsequent treatment may include a more potent immunosuppression (Methyl Prednisolone, high dose Dexamethasone pulse therapy, Rituximab), thrombopoietin receptor agonists (Eltrombopag or Romiplostim) or splenectomy (after 12 months of age) for improved quality of life despite conventional treatment but with the associated risk of potentially serious complications (Fig 2).[5,6,7]

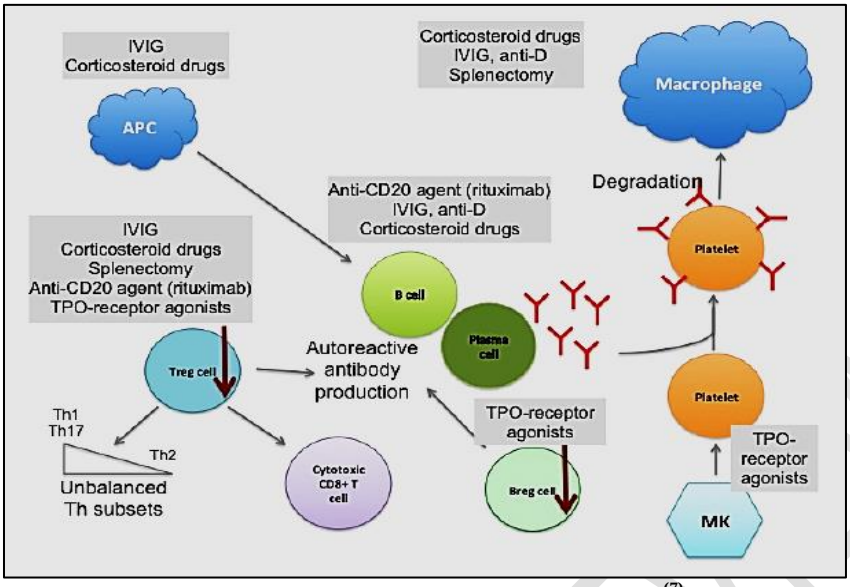

Fig.2: Therapeutic mechanisms of current ITP treatments.[7](Zufferey et.al.)
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Terminology	Criteria
Complete response (CR)	A platelet count ≥ 100 x 10^9/L measured on 2 occasions > 7 days apart and the absence of bleeding
Response (R)	A platelet count ≥ 30 x 10^9/L and a greater than 2-fold increase in platelet count from baseline measured on 2 occasions > 7 days apart in the absence of bleeding
No response (NR)	A platelet count < 30 x 10^9/L or a less than 2-fold increase in platelet count
Loss of complete response	A platelet count < 100 x 10^9/L measured on 2 occasions more than a day apart and/or the presence of bleeding
Loss of response	A platelet count < 30 x 10^9/L or a less than 2-fold increase in platelet count from baseline or the presence of bleeding. Platelet count must be measured on 2 occasions more than a day apart

Response to treatment in ITP is assessed as:- [6]

Table 2- Response to treatment in ITP

Role of CRP in ITP

C-reactive protein, a major acute-phase protein, belongs to the pentraxin family and is a known ligand for Fc receptors responsible for apoptosis. It is significantly up regulated during infections (from 0.05 to 500 mg/L), but may also be present in healthy sera at a lower concentration (0.8 mg/L in healthy volunteers).[4,14] The de novo hepatic synthesis starts very rapidly after a single stimulus with serum concentrations rising above 5 mg/L by about 6 hours and peaking around 48 hours. The plasma half-life of CRP is about 19 hours and is constant under all conditions of health and disease.[15] To detect lower levels of CRP (0.3 to 1.0 mg/L), high-sensitivity CRP (hs-CRP) methods are recommended (reported in mg/dL) as the usual CRP detection tests are less precise.

Kapur et.al. revealed an intriguing direct correlation between CRP concentrations and antibody-mediated phagocytic activity against platelets.[3,4] The postulated mechanism is that, on binding of antiplatelet antibodies, platelet oxidation occurs and results in exposure of platelet membrane phosphorylcholine, to which CRP binds in a calcium-dependent manner and boosts the phagocytic uptake and degradation of opsonized platelets via phagocytic Fc receptors.[4] From a prognostic perspective, patients with elevated CRP levels at diagnosis took longer to normalize their platelet counts after 3 months. This remarkable finding could perhaps be used to determine which children with newly diagnosed ITP are in need of treatment.[3,4] Kishore et.al., in their study on adults, highlighted that the definitive CRP levels on Day 1 (before initiation of treatment), can predict response to the treatment.[16]

Hence this study was taken with the aim to correlate the CRP levels with platelet counts in newly diagnosed ITP patients and predict platelet recovery with identification of non-responders based on the CRP level at presentation.

METHODS

Sample collection and Duration: Pediatric cases (below the age of 18 years) of newly diagnosed ITP were included in this prospective observational study over 1 year and 11 months.

Inclusion criteria: All children with newly diagnosed ITP up to the age of 18 years.
Exclusion criteria: Secondary ITP due to other diseases -

a) Infections (Human Immunodeficiency Virus (HIV), Hepatitis C Virus (HCV), Epstein Barr virus (EBV), Cytomegalovirus (CMV), Helicobacter pylori
b) Autoimmune disorders like lupus, Evans syndrome, Sjögren's syndrome, antiphospholipid syndrome
c) Hematologic malignancies
d) Primary immune deficiency [common variable immune deficiency (CVID), autoimmune lymphoproliferative syndrome (ALPS)]
e) Drug exposure/vaccination

After obtaining approval from the Institutional Ethics Committee, all patients satisfying the inclusion criteria are enrolled in the study and informed written consent was obtained. Necessary evaluation with detailed history (isolated bleeding symptoms consistent with thrombocytopenia without other symptoms or history of chronic intake of drugs) and physical examination (absence of hepatosplenomegaly, lymphadenopathy, pallor or stigmata of congenital conditions, well-looking child) was done.

Complete blood count with special emphasis on platelet distribution width, mean platelet volume and immature platelet fraction was analyzed on *Sysmex Xn-1000 Analyser*. Identified platelets on peripheral blood smear should be normal to large-sized with normal red and white blood cell morphology.

Additional Evaluation (HIV, HCV, HbsAg, immunoglobulins assay (IgG, IgA, IgM, IgE), ESR, LDH, ANA and anti-double stranded DNA) followed by bone marrow aspiration and biopsy and in selected cases clinical exome sequencing was also done to rule out causes of secondary thrombocytopenia/ inherited thrombocytopenic syndromes.

CRP estimation (hs-CRP) at presentation using Roche Cobas 6000 analyser (Normal levels: 0.3 to 1 mg/dL). At follow-up, the platelet count and CRP levels between Day 21-28 (3rd to 4th week of treatment initiation) and between Day 35-42 (between 5th to 6th week) were determined along with assessing the trend of CRP with platelet count changes. Response to treatment in ITP based on platelet count was based on the definitions highlighted above.[5,6]

STATISTICAL METHODS AND DATA ANALYSIS

Considering that the difference is around 15% between the patients who showed a response with negative CRP and do not show any response with positive CRP, power as 80% with a 5% level of significance the estimated sample size was 30. Collected data was entered in Microsoft Excel and all the statistical analyses were performed by using 10.0 version of statistical software SPSS.

$$n = \frac{\sigma_d{}^2 (Z_\beta + Z_{\alpha/2})^2}{\text{difference}^2}$$

Where:

n = sample size

σ = standard deviation of the within pair difference = 30%

difference = clinically meaningful difference = 15%

Zβ = corresponds to power (0.84 = 80% power)

Zα/2 = corresponds to two-tailed significance level (1.96 for α = 0.05)

Descriptive Analysis:

Continuous variables were summarized by using summary statistics (number of observations, mean, and standard deviation with range). Categorical values like age and gender were estimated by using frequencies and percentages as per rapid tests.

Tests of significance:

In this study, CRP levels were compared as per age group by using an analysis of variance. Average CRP levels were compared at presentation and during follow-up by using student t test. The association between types of treatment with response in terms of platelet count recovery was compared by using Chi-square test. All values were reported two-sided and all the statistical tests were interpreted at a 5% level of significance level. *p* value less than 0.05 was taken as level of significance.

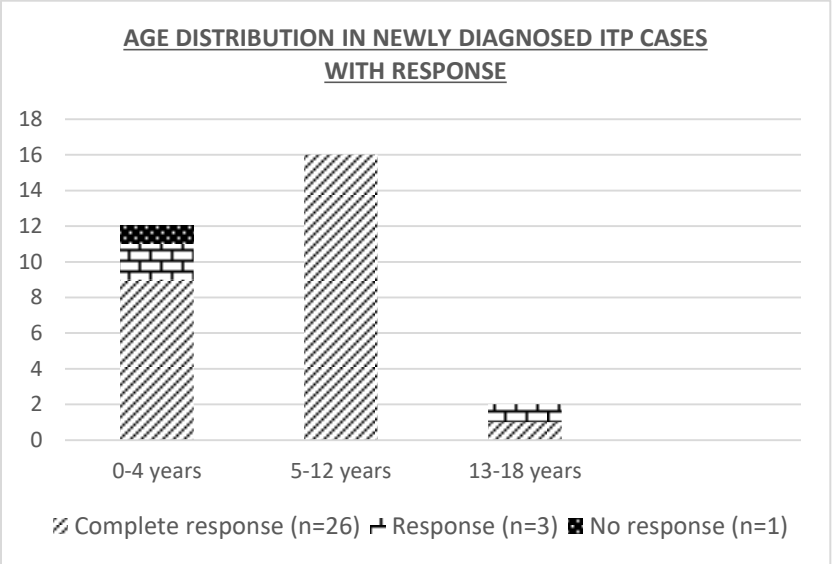
RESULTS

Our study included 30 newly diagnosed ITP cases who presented with acute onset of bruises, petechiae, ecchymosis with a platelet count of <10000 without significant bleeding. All the cases were distributed according to the age, gender, treatment given, response to the treatment given and CRP level compared with platelet recovery. Amongst them, 53.3% (n=16) of cases belonged to age group 5-12 years, followed by 40.0% (n=12) to the 0-4 years age group and 6.7% (n=2) to the 13-18 years age group with male-female ratio of 1:1.4.

The mean CRP levels of patients at presentation among these categories was determined and compared with platelet counts during follow up by day 21-28 (3-4 weeks) and day 35-42 (5-6 weeks) of treatment.

All the boys showed complete response to the treatment whereas 18.75% (n=3) of girls showed partial response and 6.25% (n=1) of girls showed no response to the treatment.

Graph 1: PROFILE OF AGE DISTRIBUTION IN NEWLY DIAGNOSED ITP CASES WITH RESPECT TO TREATMENT OUTCOME

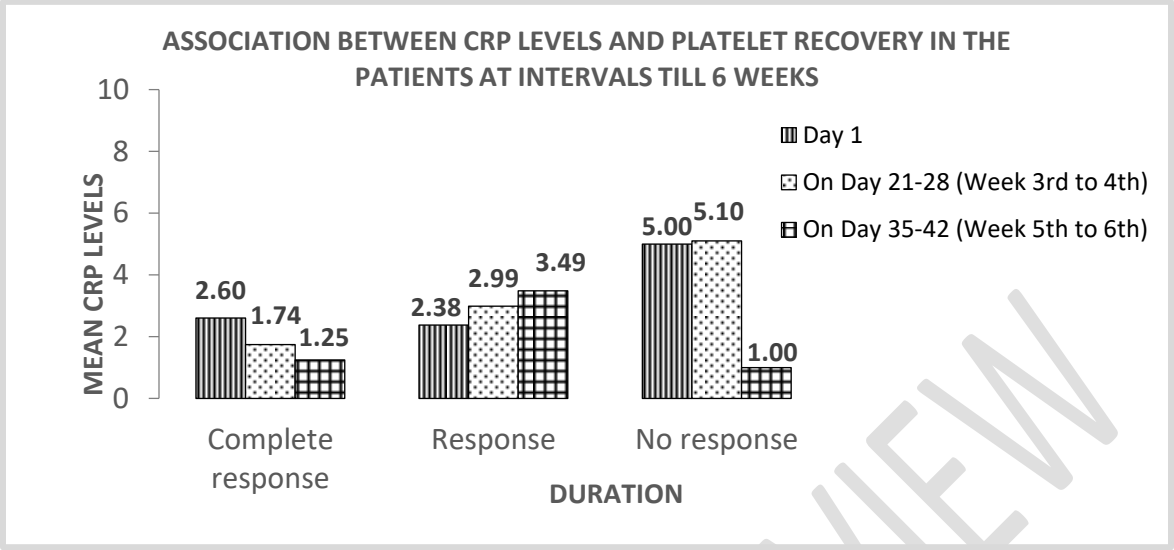


- *Graph 1* depicts that 75% (n=9) of <5 years old children showed complete response to treatment while 8.3% (n=1) showed no response and 16.6% (n=2) showed only partial response to the treatment.
- All the children (n=16) between 5 to 12 years of age showed complete response to treatment.
- 50% of children (n=1 out of 2) above 13 years showed complete response to treatment given.

Table 3: ASSOCIATION OF CRP LEVELS WITH PLATELET RECOVERY IN THE PATIENTS AT GIVEN INTERVALS TILL 6 WEEKS

Duration	Mean CRP level (mg/dl) ($\overline{X} \pm SD$)		
	Complete response (N=26)	Response (N=03)	No response (N=01)
Day 1	2.60 ± 2.82	2.38 ± 2.35	5.00 ± 0.00
Day 21-28 (Week 3rd to 4th)	1.74 ± 0.97	2.99 ± 0.82	5.10 ± 0.00
Day 35-42 (Week 5th to 6th)	1.25 ± 0.53	3.49 ± 4.25	1.00 ± 0.00 p = 0.017
Mean difference (Day 1 – Day 21-28) (p value)	-0.86 ± 2.20 p =(0.057)	0.61 ± 1.82 (0.620) NS	0.10 ± 0.00 (-)
Mean difference (Day 1 – Day 35-42) (p value)	*-1.35 ± 2.70 (p=0.017)	1.11 ± 5.79 p=(0.771) NS	-4.00 ± 0.00 (-)
By Student 't' Test	NS=Not Significant	*Significant	

Graph 2: CO-RELATION BETWEEN CRP LEVELS AND PLATELET RECOVERY OF THE PATIENTS AT THE GIVEN INTERVALS TILL 6 WEEKS



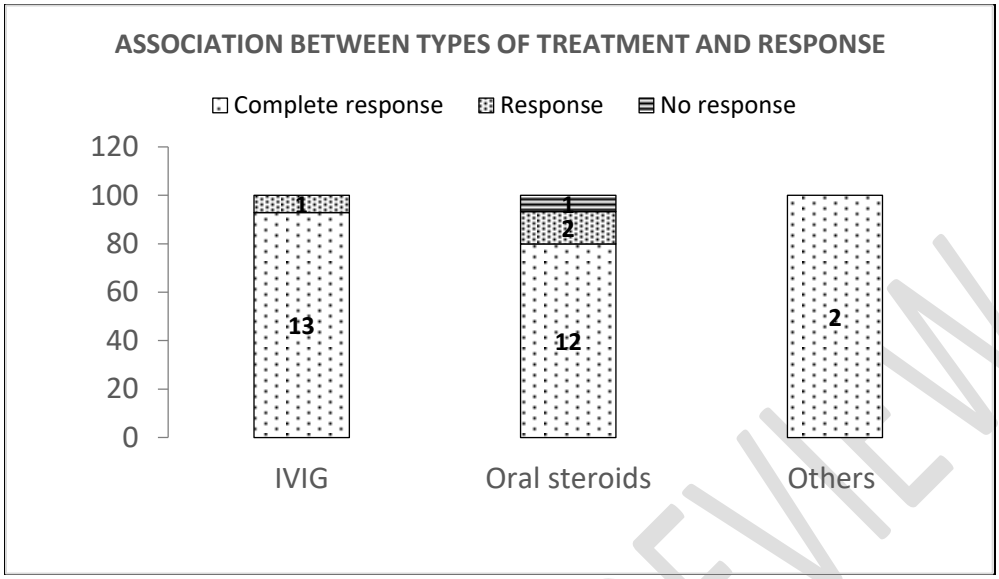
- *Table 3 and Graph 2* highlight the co-relation between CRP levels and platelet recovery in the patients at given intervals till 6 weeks of therapy.

- Total 26 out of 30 children (86.6%) showed complete response to treatment (platelet count >100000/microL). Out of the remaining, 3 children showed response (platelet count 30000-100000/microL without bleeding) and only 1 did not respond (platelet count<30000/microL) to the treatment given and had to be taken on second line agent, after which she attained response.

Table 4: ASSOCIATION BETWEEN TYPES OF TREATMENT AND RESPONSE

Treatment	No. of cases	Response assessment based on platelet count on recovery					
		Complete response		Response		No response	
		No.	%	No.	%	No.	%
IVIG	14	13	92.9	01	07.1	-	-
Oral steroids	15	12	80.0	02	13.3	01	06.7
Others • Anti D • Methylprednisolone	02	02	100.0	-	-	-	-
Chi Square test	p = 0.501, Not Significant						

Graph 3: ASSOCIATION BETWEEN TYPES OF TREATMENT AND RESPONSE (based on platelet count)



- *Table 4 and Graph 3* suggests that 92.9% (13/14) cases who received IVIG showed complete response as compared to 80.0% (12/15) cases who received oral steroids.
- Both the cases (including the non-responder escalated on second line therapy) received other forms of treatment (Anti D globulin/ intravenous Methylprednisolone) showed complete response. However, the relationship of treatment given with platelet recovery did not show any statistical significance (*p* value: 0.501).

DISCUSSION

This was a prospective study at a tertiary private hospital which included 30 children aged 0-18 years of acute ITP with mean platelet count <10000/μL at presentation. The overall incidence of ITP among the females (53.3%) was marginally higher than in males and majority belonged to 5-13 years age group. ***Glanz J et.al.***[18] determined that children whose illness was diagnosed at 10 years of age or more had an approximate fivefold risk for progressing to chronic disease when compared with children who presented at 2 years or lesser of age.[18]

All the ITP patients were subjected to various first-line treatment modalities available and the treatment outcome was assessed based on the platelet counts at given time intervals. At presentation, hs-CRP level among poor responders was higher than the mean levels of the other groups, indicating the poorer treatment outcomes in the groups. In contrast, the mean hs-CRP levels showed a falling trend from Day 1 to Day 42 (2.60 → 1.74 → 1.25mg/dL) among complete responders (p-value = 0.017). It co-related with a marked increase in platelet count as observed in prior studies.[3,4,16] The child who showed no response to treatment had higher CRP level at presentation (Day 1=5.1; PLT=8000) and during follow-up (Day 28=5; PLT=13000). She required IVIG (0.8g/kg) at presentation followed by MPS (30mg/kg/day x 3 days) after 4 weeks due to loss of sustained response. Thus, the high hs-CRP at

presentation also could help us in determining the prognosis. Additionally, it was observed that those who showed some response (PLT< 100000 but >double the baseline) had rising CRP levels (2.38 → 2.99 → 3.49) during follow-up with poor platelet increment.

Rama et.al.[16] conducted a maiden study in 2017 to assess a correlation between CRP levels and response to treatment in newly diagnosed ITP adult patients and suggested that elevated CRP levels had a direct correlation with the severity and late recovery of thrombocytopenia to steroid treatment. The rise in the CRP levels in that cohort not responding to treatment is much higher than that in our pediatric population. In our study, the sensitivity and specificity of using CRP as a tool at presentation to predict treatment response in acute ITP could not be assessed on Receiver Operating Characteristic (ROC) curves due to insufficient number of non-responders (n=1).

Association between different types of Treatment and Response can also be deciphered from Graph 3. Although the association between IVIG and better response to treatment was not statistically significant in our study, yet it cannot be deferred that IVIG administration helps in rapid normalization of platelet counts as compared to steroids. A randomized trial by ***Rosthøj S et al.*** on Danish ITP study group also revealed that IVIG had induced greater and sustained platelet responses as compared to Methylprednisolone pulse therapy until 6 months follow-up.[19] Furthermore, ***Celik M.et.al***.[20], through their study on 60 Turkish newly diagnosed ITP children, also indicated that platelet counts at day 7 were observed to be higher in the IVIG group than in the methylprednisolone group.[20]

These studies help to strengthen the findings of ***Kapur et.al.***[4] who in their study concluded that IVIG leads to significant decrease in CRP levels, causing increase in platelet numbers, and clinically decreased severity of bleeding. In a similar clinical trial, ***TIKI study NTR1563***[21], children with newly diagnosed ITP (below 20×10^9 platelets/L) were randomized to the observation arm, or to those receiving 0.8 g/kg IVIG and followed in time. It showed that those individuals who had normalized their number of platelets after 1 week from diagnosis also had significantly lower CRP levels at diagnosis compared with those with thrombocytopenia (below 100×10^9/L). The trial concluded that slow platelet count recovery is associated with increased CRP levels at diagnosis and treatment with IVIG resulting in fall in CRP levels accompanied by decreased clinical bleeding severity and faster normalization of platelet counts.

Although our finding is not statistically significant ($p = 0.50$), due to the small sample size, yet the observation cannot be ignored.

Future studies may expand these fascinating observations and further investigate CRP effects on IgG-mediated phagocytosis in other diseases such as those associated with anti-red blood cell antibodies. The diagnostic potential of CRP in these disorders should be validated and perhaps targeting CRP decline, either directly or via oxidation inhibitors, may be a promising therapeutic approach atleast in patients with IgG antiplatelet antibodies.

CONCLUSION

Patients with ITP who had higher hs-CRP levels at presentation took longer time to normalise their platelet counts highlighting the role of CRP (Day 1) in predicting response to treatment. These patients showed no response to treatment till 6 weeks of follow-up when compared to complete responders with lower CRP. Hence CRP assessed at the time of presentation may be used as a prognostic marker to predict the response to treatment and to decide upon the need for intervention, although administration of the type of treatment does not significantly alter the course and outcome of the disease.

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