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DAPSONE AS A SECOND LINE THERAPY IN CHRONIC IMMUNE THROMBOCYTOPENIC PURPURA IN ECONOMICALLY LESS PRIVILEGED POPULACE: THREE YEAR DATA ANALYSIS OF A TERTIARY CARE HEMATOLOGY CENTRE OF NORTH INDIA

ALEEM JAN[1], MUBARAK NAQASH [2], ARSHAD HASSAN[3] & AFSHAN ATTA [4]

[1]Department of Cl. Hematology, SKIMS, India

[2]Department of Medicine SKIMS Medical college, India

[3]Department of ImmunoHaematology SKIMS Srinagar, India

[4]Department of Pathology ASCOMS Medical College Jammu, India

ABSTRACT

Introduction

Chronic immune thrombocytopenic purpura is an auto-immune disorder characterized by persistent thrombocytopenia in which patients immune system reacts with a platelet auto antigen or antigens resulting in thrombocytopenia due to immune mediated platelet destruction and or suppression of platelet production. ITP affects both children and adults. The estimated incidence is 100 cases per one million persons per year, with almost equal proportion of children and adults.

Materials & Methods

71 cases of Chronic ITP fulfilling inclusion and exclusion criteria were included in the study. Records were taken in tabulated form with name, age, sex, residence, marital status, age at diagnosis. Relevant investigations like CBC, MPV, manual Platelet count, ANA, TSH, H.pylori, Anti-HCV, HIV, and G6PD were done in cases where Dapsone was planned. Dapsone was used at a dose of 1-2 mg/kg/d for a minimum of three months after G6PD assay was negative.

Results

Number of cases analyzed was seventy one. Median age was 27.8 years with M: F percentage of 26.8 % and 73.2% respectively. Percentage of response was Fair (19.3%), Good (66.3%), Excellent (4.4%) and Poor (10%). Average time to response was 3.2 months. All responders were able to abandon other ITP related treatment. Average duration of treatment was 1.62 years. The mean post treatment platelet count in responders was 30,000-1.9 L/cu mm. Side effects in form of allergy, Rash, including Steven Johnson syndrome was seen in 4(5.06%) cases. Spleenectomy was done in 10 patients (14%).

Conclusions

Categorization of response to Dapsone was seen as good (66.3%), Fair (19.3%), Excellent (4.4%) and Poor (10%), with no long term haemolysis. Hence, suggesting Dapsone as safe second line drug for Chronic ITP.

KEYWORDS: ITP, TPO, G6PD, MPV, HCV

INTRODUCTION

Immune thrombocytopenia (ITP) is characterized by isolated thrombocytopenia more often than not occurring without any specific precipitant. An auto immune disorder characterized by persistent thrombocytopenia in which patients immune system reacts with a platelet auto antigen or antigens resulting in thrombocytopenia due to immune mediated platelet destruction and or suppression of platelet production. ITP affects both children and adults. The estimated incidence is 100 cases per one million persons per year, with almost equal proportion of children and adults (1, 2, 3). Peak age in children is 2-4 years, with equal affliction of boys and girls. Disease is self limiting in children with spontaneous recovery occurring in several weeks to months with doctrine of "First does no harm "(4). On the contarary in adults, disease is more common in women, insidious in onset and chronic in course.

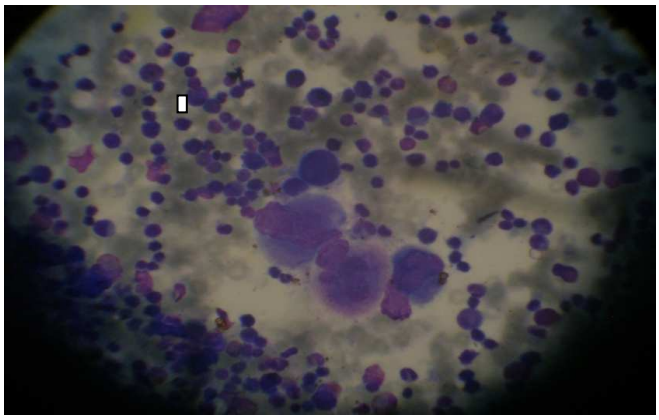
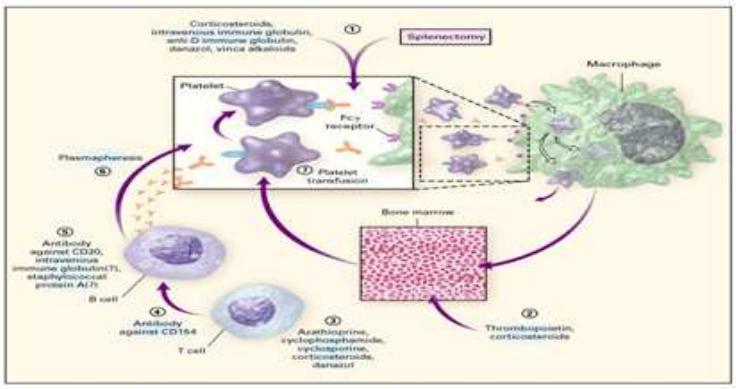


Figure 1: BMA

ITP is termed secondary if it is associated with underlying causes like Systemic lupus erythromatosis, HCV, HIV. Association of Helicobacter pylori in Japanese studies and our own observation is holding ground with each passing day.



pathogenesis

Figure 2

Since our patients bear their health care cost from their own pocket and also ASH (American society of Hematology) or BCSH (British committee on standards in Hematology)guidelines have also mentioned its limitations in applicability of these on basis of regional, cultural, ethnic and socioeconomic considerations (5), an out of box solution holds the key.

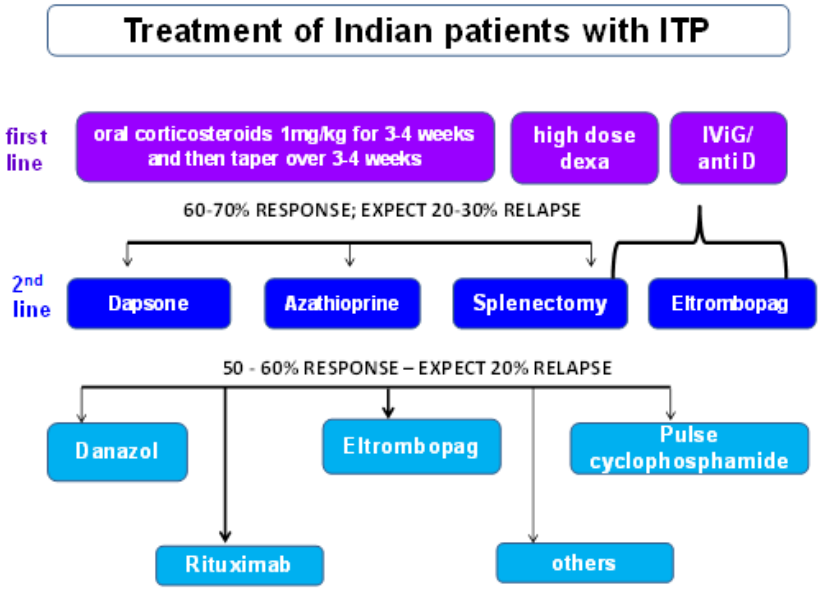


Figure 3

Methyl prednisolone 20-30mg/kg for 3 days or 1 gram daily followed by oral prednisolone remains the first line of treatment. Nonetheless, despite initial response in many cases, steroid tappering or withdrawal is followed by drop in platelet count and need for additional treatment, which include I/V Immunoglobulins, anti D if patient is Rh positive, Haemoglobulin >11 g/dl and intact spleen.

Pulse Dexamethasone, azathioprine, danazole, Vincristine are also used with a response rate of 10-30% however spleenectomy to which more than 70% respond is finding favor. Eltrombopeg, an oral TPO agent holds promise but has cost limitation. Rituximab (anti CD 20) 100mg/m2 with or without dexamethasone weekly, four doses as a bridge to spleenectomy or when it fails is perhaps still standard of care.

Dapsone is an antibacterial sulphonamide with anti-inflammatory property which has shown therapeutic activity in patients with chronic ITP. Its antimicrobial effect against leprosy, pneumocystis jerovi, pneumonia in AIDS, toxoplasmosis and malaria is well known. It is also recognised to have activity in a number of noninfectious inflammatory diseases of skin as dermatitis herpetiformis and blistering disorders. The anti-inflammatory effect of Dapsone though not fully understood appears to be targeted against neutrophils with interference of MPO, inhibition of lysosomal enzymes, chemo taxis and integrin mediated adherence function. Numerous studies highlighted the therapeutic activity of Dapsone as salvage therapy in primary ITP with 40-60% overall response rate and 15-50% CR rate. The response to Dapsone was unaffected by pre-treatment characteristics such as age, sex, platelet count, duration of ITP. Even persistence of response after discontinuation of Dapsone is reported.

Dapsone in a dose of 1-2mg/kg/d is an effective inexpensive, well tolerated treatment modality for Chronic ITP. Overall response rate of 61.8% has been observed in an Indian study (6, 7) in 55 adults and 80% in another (7) on 46 non spleenectomised adults. It was given for at least six months and median response was observed in 3.8 months. G6PD deficient patients are prone to haemolysis by this drug; therefore G6PD assay is mandatory before starting Dapsone even though prevalence of G6PD deficient populace is < 1% (8). Skin rash and iron overload after prolonged use is also observed.

MATERIAL AND METHODS

A study in our outpatient department on newly diagnosed and follow-up patients of ITP was conducted from September 2012 to August 2015. Records were taken in tabulated form with name, age, sex, residence, marital status, age at diagnosis. Relevant investigations like CBC, MPV, and manual Platelet count, ANA, TSH, H.pylori, Anti-HCV, HIV, and G6PD in cases where Dapsone was planned. Macro thrombocytopenia or Himalayan platelet syndrome and secondary causes were exclusion criteria for this study. Methylprednisolone (20-30mg/kg x3 days) followed by oral prednisolone was used as primary medication and definitions of acute (up to 3 months), persistent (3-9 months) and chronic beyond one year were strictly followed. Duration of treatment, time for adding second medication, response, duration of response and last follow up was recorded. Dapsone was used at a dose of 1-2 mg/kg/d for a minimum of three months after G6PD assay was negative. Dapsone was introduced while tappering steroids. Platelet count $\geq$ 100 $x10^9$ / ^{L} were considered as complete Response (CR) Which was further defined and categorized as excellent and good depending on platelet count of $\geq$150 $x10^9$. Response (R) was entertained only if there was doubling in platelet count from baseline or a count of $\geq$ 30 but < 100 $x10^9$. Response was further refined as Fair when no wet or dry purpura was noticed. Other modalities of treatment were thought of in no responders which were spleenectomy in majority of cases. In two pediatric cases of common variable immunodeficiency (CVID) three weekly I/V Ig have got them in remission and safe platelet count.

RESULTS

Number of analyzed cases strictly available as per criteria laid was seventy one. Median age was 27.8 years with M: F percentage of 26.8 % and 73.2% respectively. Percentage of response as Fair (19.3%), Good (66.3%), Excellent (4.4%) Poor (10%). Average time to response was 3.2 months. All responders were able to abandon other ITP related treatment. Average duration of treatment 1.62 years. The mean post treatment platelet count in responders was 30,000-1.9 L/cu mm. Side effects in form of allergy, Rash, including Steven Johnson syndrome was seen in 4(5.06%) cases, out of which Dapsone was abandoned in two. Spleenectomy was done in 10 patients (14%).

DISCUSSIONS

Ever since someone goes into Chronic form of ITP, exacerbations of wet and dry purpura sometimes critical thrombocytopenia is worrisome and there has always been an Endeavour to keep platelet count in safe range. There are prescribed guidelines and medications to accomplish the same (1, 3, 9), however, financial constraints limit their use.

Eltrombopeg, an oral thrombopiotic agent operating through CMPAL thereby causing megakaryocytic proliferation and resultant rise in platelet count in almost 80% of cases of Chronic ITP, preferably anti HCV positive cases (10, 11). There are concerns about long term use causing chronic proliferation of megakaryocytes and stem cells. Risk of thromboembolism and increase in bone marrow reticulin are a concern.

Several immune suppressants like Azathioprine or cytotoxic drugs like cyclophsphamide, Vincristine or anabolic drugs like Danazol though relatively cheap with a response rate of 30-50% in ITP (12) yet their side effects limit their use. As a parallel to that, Dapsone has almost similar therapeutic activity with a relatively safe side effect profile as second line medication for chronic ITP and our study compares well with results of similar and identical published data (13, 14, 15, 6) in highlighting its role.

CONCLUSIONS

Dapsone is safe affordable effective second line drug for Chronic ITP. Being encouraged by relatively negligible prevalence of G6PD deficiency in our population, a contraindication for Dapsone use, We at our centre use Dapsone as a preferred second line drug with fair degree of confidence.

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