Abstract:-
We retrospectively analysed 20 patients of ITP who were treated with dapsone. 14(70%) of them showed a response and 9(45%) showed a Complete Response. The median interval between diagnosis of ITP and dapsone therapy was 25.15 months. The mean pre-treatment platelet count was 15,250 ± 6810.83 /cumm. The average time for response was 30.35 days (range 11-60 days) and the average duration of treatment with dapsone in responders was 9.92 months (range 4-30). The mean post-treatment platelet count in responders was 1,18,142.85±49726.19/cumm. Side effects requiring discontinuation of therapy were observed in three (15%) patients. Thus the study suggests that dapsone is a safe and effective second-line agent for steroid-dependent or refractory ITP patients

Background
ITP is an acquired autoimmune disease characterized by thrombocytopenia with increased platelet destruction, impaired megakaryocyte maturation with reduced platelet production with variable severity of bleeding. Oral prednisone remains the standard first-line treatment. However, despite the high initial therapeutic efficacy, in many cases, steroids tapering or withdrawal is followed by a drop in platelet count and the need for additional treatment. Children usually have acute ITP, with 70% experiencing a permanent recovery. In contrast, more than 50% of the adults have the chronic form.

About a third of children and half of adults with ITP remain steroid dependent or non-responsive. Treatment options for these patients include therapy with pulse dexamethasone, azathioprine, cyclosporine, danazol, or vincristine, with response
rates between 10% and 30% or splenectomy to which about 70% of these patients respond.

Splenectomy remains the best curative treatment for chronic symptomatic ITP and platelet counts <30 x 10⁹/L after failure of the first-line treatments. Rituximab is probably the single most effective agent, as well as the least toxic, when splenectomy fails: the short-term response rate is 50% and the sustained-response rate more than 30%.

Cytotoxic or other immunosuppressive agents like azathioprine, cyclosporine A, vincristine should be reserved for patients with severe disease refractory to both splenectomy and rituximab. Thrombopoietin receptor agonists are a new class of drugs for which promising results have been reported, but more data regarding long-term safety are needed. Treatment is generally indicated for symptomatic patients, that is, those with active bleeding or very low platelet count (usually < 20–30 x 10⁹/L).

The best treatment for patients with chronic ITP in whom splenectomy is ineffective or contra-indicated is a difficult challenge, as the treatment options are inconsistently and usually transiently effective; and their side-effects are sometimes severe. Dapsone is an antibacterial sulphonamide with anti-inflammatory property, which has shown therapeutic activity in patients with immune thrombocytopenia. Its antimicrobial effect against leprosy, pneumocystis jiroveci pneumonia in AIDS, toxoplasmosis, and malaria is well known. It is also recognized to have activity in a number of non-infectious inflammatory diseases of the 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 myeloperoxidase, inhibition of lysosomal enzymes, chemotaxis, 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 sex, age, platelet count, or duration of ITP and even persistence of response after dapsone discontinuation has been registered in some patients.

**Material and Methods**

This was a retrospective analysis of patients treated in the Haematology department of Victoria Hospital, under Bangalore Medical College and Research Institute from February 2010 to December 2013.

The diagnosis of ITP was based on the presence of thrombocytopenia with normal or increased megakaryocytes in a morphologically normal marrow. Patients with secondary causes for thrombocytopenia like systemic lupus erythematosus, human immunodeficiency virus, lymph proliferative disorder and drugs were excluded. Dapsone was used at a dose of 1–2 mg/kg/d (50-150mg per day) for at least 3 months. It was stopped earlier in case of any side effects. All
patients had failed initial therapy with prednisolone (1–1.5 mg/kg/d) for at least 4 wks. or were heavily steroid dependent before dapsone was initiated. All the patients were screened for glucose-6-phosphate-dehydrogenase deficiency. Complete response (CR) was considered when the platelet count was ≥ 100 × 10⁹/L. Response (R) was defined as a platelet count ≥ 30 but < 100 × 10⁹/L and a doubling from baseline.

20 patients (16 adults and 4 children) with idiopathic thrombocytopenic purpura (ITP) and a platelet count of <50 × 10⁹/L were treated with dapsone at a dose of 1-2 mg/kg/d (50–150 mg per day). The mean age of patients was 28.55 years (8–65 yrs.). 2 patients with 4 months history of disease, which was steroid refractory, had severe bleeding and could not afford other modalities of treatment and hence given dapsone. 5 patients had bleeding episodes of varying severity.

The number of prior therapies before starting dapsone ranged between 1-3 (mean of 1.85). All had received oral prednisolone, 9 had received pulse dexamethasone therapy and 1 had got rituximab therapy. Two patients had undergone splenectomy. 4 were steroid refractory and 16 were steroid dependent. In the 2 patients with severe unresponsive thrombocytopenia, with platelet counts that were constantly about 5×10⁹/L, dapsone was combined with low-dose steroid treatment.

The median interval between diagnosis of ITP and dapsone therapy was 25.15 months (range 4–84 months), being 23.07 months in responders and 30 months in non-responders. Response (platelet count ≥ 30 × 10⁹/L) and complete response (CR; platelet count ≥ 100 × 10⁹/L) were 70% (14/20) and 45% (9/20), respectively. All responders were able to interrupt any other specific anti-ITP treatment.

The mean pre-treatment platelet count was 15,250 ± 6810.83 /cumm (5000-30000/cumm). The average time for response was 30.35 days (range 11-60 days) and the average duration of treatment with dapsone in responders was 9.92 months (range 4-30). The mean post-treatment platelet count in responders was 1,18,142.85±49726.19/cumm (30000-1.9L/cumm).

Side effects requiring discontinuation of therapy were observed in three (15%) patients. Dapsone-induced haemolysis was usually moderate and necessitated treatment withdrawal in only two patients (1 child and 1 adult) in whom mild haemolytic anaemia occurred 15 days to 1 month after starting therapy. One patient discontinued therapy due to elevated liver transaminases (three times normal value). Three patients (15%) did show any response and hence treatment was discontinued. Dapsone-related adverse events were mild and promptly reversed by treatment withdrawal. Thus the results of our study suggest that dapsone is a safe and effective second-line agent for steroid-dependent or refractory ITP patients. Because of its well-known safety profile and low cost compared to other potential second-line treatments for ITP, a trial course of dapsone should be viewed as an attractive option before splenectomy in steroid-dependent of refractory patient ITP patients.
We are still following up the patients regularly to assess the long term response, optimal dose and duration of therapy. The numbers of children in our study were very less and hence not a representative sample.

**Discussion**

Our study confirms the results of previous published data (Durand² et al 1991, Godeau⁴ et al 1993, Hernandez³ et al 1995, S.Damodar⁶ et al 2005, Francesco Zaja¹ et al 2012) which showed similar results, that dapsone is an effective, safe, affordable and valuable second-line drug in the management of ITP. In countries, where patients have to spend on medical expenses from their savings, it is an extremely important second-line alternative. It gives safe platelet counts in over half the patients and the effect is maintained for a prolonged period. However, patients are known to relapse when dapsone is stopped, and the risk–benefit ratio of dapsone and splenectomy should therefore be carefully considered in young, especially child bearing age- group patients. Dapsone may be valuable for patients who have contra-indications or resistance to splenectomy. The inherent risks of surgery and sepsis after splenectomy without a guarantee of success justify the search for strategies aimed to avoid splenectomy. Studies involving more of older patients with longer duration of illness have shown lower response rates (see table). S.Damodar⁶ et al have reported 63.3% response rates on 90 patients (55 adults and 35 children).

Several immune suppressive agents such as azathioprine, cyclosporine-A, mycophenolate mofetil , cytotoxic drugs like cyclophosphamide or vincristine and hormonal agent like danazol have shown response in 30–50% of patients with ITP, but their administration is frequently associated with side effects⁹⁻¹⁵. Dapsone appears to have similar, if not higher, therapeutic activity and a much more favourable safety profile.

In this last decade, several studies indicated the therapeutic activity of rituximab 375 mg/mg given weekly for 4 weeks, with 60 and 40% short-term R and CR rates, respectively. Factors in favour of rituximab are the curative purpose, the relative short-term period of therapy, the good compliance of the patients. However, rituximab is expensive, may worsen immune suppression and, although rare, can cause progressive multifocal Leucoencephalopathy in some. Furthermore, nearly 20–40% of adult patients experience subsequent relapse in the first 2 years and those who achieve and maintain a long-term effect at 5 years is reported to be around 20 and 40%¹⁶⁻¹⁸.

Romiplostim and eltrombopag are two thrombopoietin mimetics now available for clinical use that stimulate megakaryocyte proliferation and overcome the inadequately increased platelet production occurring in most patients with ITP. These agents showed very good activity in nearly 80% of patients with ITP¹⁹⁻²⁰ but have a palliative activity and necessitate continuous indefinite administration. At present, there are still some concern and perplexities regarding the possible long-term effect, secondary to the chronic proliferative pressure of megakaryocytes and stem cells. In addition, safety concerns in terms of increased bone marrow reticulin formation and
of an increased risk of thromboembolism await for the results of currently ongoing long-term studies. Their cost is prohibitive.

In contrast, dapsone has a good, satisfactory profile. It is contraindicated in patients with G6PD deficiency. Haemolytic anaemia and an increase of methemoglobin are the main reported side effects. It is however important to monitor carefully, especially during the first month, for anaemia, haemolysis, methemoglobinemia related cyanosis, hepatitis, lung diseases and pneumonia. Most patients achieve a response as early as one month and maintain it for a long time. The mechanism by which dapsone induces a platelet count increment is unknown. One postulated mechanism is based on competitive inhibition of the reticulo-endothelial system; haemolysis induced by dapsone might be responsible for the platelet response by replacing the destruction of antibody-coated platelets by red blood cell phagocytosis.

**Conclusion**

Thus dapsone is an effective, inexpensive and well-tolerated treatment for ITP and could be considered for patients who previously failed first line treatment and/or a relatively recent diagnosis of ITP. The excellent toxicity profile, its cheap cost and efficacy makes it an attractive second -line armamentarium in the management protocol of ITP. A better comprehension of ITP pathophysiology and of dapsone mechanism of action will allow in the future a better and rational integration of this agent into the treatment algorithm of primary ITP.
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<th>Our study</th>
<th>Francesco Zaja et al</th>
<th>Godeau et al</th>
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<tr>
<td>Patients</td>
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References:


