

Refractory Evans' Syndrome : Therapeutic Options

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Introduction

Some chronic immune-mediated hematological disorders in adults, such as autoimmune hemolytic anemia (AHA), idiopathic thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia with thrombocytopenia (Evans' syndrome) will achieve a prompt and last remission after corticosteroid treatment. Nevertheless, many patients will be resistant¹. They might be requiring high dose corticosteroid therapy or other modalities of treatment such as intravenous high-dose immunoglobulins (frequent but transient improvement),² suppression by chemotherapeutic drugs (about 50% response rate) and or splenectomy (50-70% complete or partial remissions). There are reports that have dealt with the beneficial effect of cyclosporin A in refractory cases³.

Physicians face therapeutic dilemmas when patients are resistant to known treatment in life-threatening conditions. We report a case of Evans' syndrome that was treated with combination of various medical therapies including high dose steroids, immunoglobulins, anabolic steroids, vitamin C and vincristine. Later cyclosporin was added when patient relapsed on tapering of steroids.

Case Report

BC 70 year old male had come with chief complaints of jaundice and pallor of 6 month duration. He had developed melena 8 days ago for which he had received 4 blood transfusion outside. Following melena, he developed orthopnea and edema feet for last 6 days. On examination, he had pallor, jaundice, bilateral pedal edema. There was no purpura. His pulse rate was 110 min, blood pressure 160/70mm Hg, and respiratory rate 16/minute. Cardiovascular examination revealed ejection systolic murmur at base. He had bilateral fine basal crepitations and 4cm firm splenomegaly. CNS examination was normal except that bilateral ankle reflexes were absent. Fundus examination showed background retinopathy. With this, working diagnosis of upper GI bleed, portal hypertension with congestive heart failure was made. Ryle's tube showed altered blood. 4 packed red blood cells were transfused slowly. Upper GI endoscopy showed large esophageal ulcer and multiple punctate hemorrhages in the fundus.

On investigations, complete hemogram showed hemoglobin 7.3gm%, total leukocyte count 8000/mm³, platelets 50000/mm³, reticulocyte count 40% and peripheral smear showed polychromasia, nucleated RBC's, spherocytes and reduced platelets. His biochemical parameters showed blood sugar 456mg%, S. Bilirubin T/D/I 5.6/1.2/4.4 mg%, SGOT/PT 40/44 IU, S. Protein 5.0/1.5/3.5 gm%, Urea 40mg%, Creatinine 1.2mg%, Na 140meq/L and K 4.4 meq/L. Blood gas analysis showed pH 7.26, pO₂ 86mm of hg pCO₂ 26mm of Hg and HCO₃ of 13.4 mmol/L. His coagulogram was within normal limits. Coombs test, both direct and indirect were strongly positive. Antibody subtyping showed it to be IgG (negative for IgM, IgA, C3, and C4). Antiplatelet antibodies were also strongly

positive. Plasma hemoglobin was 20mg%. Bone marrow examination showed erythroid hyperplasia with increase in megakaryocytes. Antinuclear factor was negative, while thyroid profile and prostate specific antigen were normal. Chest X-ray, electrocardiogram, ultrasound abdomen and echocardiogram were within normal limits.

With above findings diagnosis of idiopathic Evans' syndrome i.e. autoimmune hemolytic anemia (Warm-Antibody type) and thrombocytopenia, along with noninsulin dependent diabetes mellitus (NIDDM), essential Hypertension and esophageal ulcer was made. Patient was started on I/V hydrocortisone (100mg I/V 6 hourly) along with antacids, sucralfate and proton pump inhibitor. His diabetic hyperosmolar state was controlled with hydration, central venous pressure monitoring (10-12 cm of water) and insulin therapy. The sepsis was controlled adequately with I/V vancomycin, ceftazidime and amikacin. Congestive heart failure responded to blood transfusions, albumin, furosemide and oxygen.

At one week, GI bleed continued. Repeat upper GI endoscopy showed no active blood, while on colonoscopy, caecum and ascending colon showed multiple hemorrhagic spots with mild ooze of blood. Purpura had also appeared since platelet count remained low i.e. 30000-40000/mm³ along with low hemoglobin. Multiple platelets transfusions were given followed by single donor platelets. At 10th day, patient was started on intravenous immunoglobulins (.4gm/kg/day for 5 days). Even with this platelet showed no rise, however hemoglobin had shown significant rise of up to 10.0 gm%. From 3rd week, patient was started on Danazol 600mg/day along with vincristine (VCR) 2mg I/V every week for 3 doses. After third dose of VCR, platelet increased to 1.5 Lac/mm³. On tapering steroids 5mg every week, platelets count again fell to 50000/mm³ on 40mg prednisolone at 3½ months. This fall responded to single dose of VCR. After that VCR could not be repeated as, patient was showing signs of peripheral neuropathy. As platelets were showing fall, while lowering steroids, he was started on cyclosporine 5mg/kg/day in two divided doses for 6 days followed by 3 mg/kg/day. Cyclosporin levels at 2 weeks were 170ng/L. Steroids were tapered at 5 mg/week. The patient stabilized on prednisolone 10mg/day and cyclosporin in 3mg/kg/day with platelet count of 1.5 Lac/mm³ and hemoglobin of 12gm%.

Discussion

Steroids are the mainstay of therapy for Evans' syndrome. Therapeutic response to oral prednisolone (1-2 mg/kg/day) is seen in 1-2 weeks. If no response is seen in 3-4 weeks, or in case of life threatening emergencies other options are looked for. High dose methyl prednisolone (HDMP) in doses of 20mg/kg for 3 days produces faster response in 3-5 days. HDMP needs to be followed up with oral steroids. Intravenous immunoglobulin (IVIg) are the fastest means of increasing platelets. Platelet counts rises in 24-48 hours. Response rate is 60-80%; however response only lasts a week or more². At present the recommended indications of IVIg are acute life threatening emergencies or preoperative period. Other drugs used include Danazol 600-800/day, however it produces slow therapeutic response (weeks to months). the

major benefit of Danazol is that it sustains partial remission and allows lower doses of steroids. *Cytotoxic immunosuppressants* (azathiaprine, cyclophosphamide) have been used in refractory cytopenias⁴. The major indications being disease of months duration and contraindication for splenectomy in patients unresponsive to steroids. The disadvantage is that therapeutic response is slow to achieve (2-4 months), response rate is about 50% and associated side effects are well known. Vincristine has important role in refractory conditions as it achieves therapeutic response within several days. However, response lasts only a few days to weeks, as happened in our patients.

Various treatment modalities have been suggested for Evans' syndrome. In view of high relapse rate after splenectomy, medical treatment with multiagents i.e., IVIG, steroids, vincristine, Danazol and possibly cyclosporin has been advocated⁵. There have been reports in literature regarding the efficacy of cyclosporin in refractory Evans' syndrome. Cyclosporin appears as a salvage treatment in life threatening resistant autoimmune hematological diseases^{2,5}. Splenectomy was not considered in our patient because of lack of families consent and well known disadvantages like high relapse rate, procedure related morbidity and mortality and overwhelming

postsplenectomy infection (OPSI).

Hence Evans' syndrome unresponsive to steroids can be a challenging proposition. Situation becomes more complex, when IVIG fails to produce platelet rise. At this stage multiagent treatment modalities need to be used in such life threatening situations.

References

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Drug Profile

Alfuzosin

Alfuzosin is a selective alpha 1 adrenoreceptor antagonist. It distributes preferentially in the prostate compared to plasma and decreases the prostatic smooth muscle tone.

Mechanism of Action : The symptoms associated with benign prostatic hyperplasia (BPH) such as urinary frequency, nocturia, weak stream, hesitancy and incomplete emptying are related to two components, anatomical (static) and functional (dynamic). The smooth muscle tone is regulated by Alpha(x) - adrenergic receptors. Alfuzosin exhibits selectivity for alpha adrenergic receptors in the lower urinary tract. Blockade of these adrenoreceptors can cause smooth muscle in the bladder neck and prostate to relax, resulting in an improvement in urine flow and a reduction in symptoms of BPH. It is a selective antagonist of post-synaptic alpha adrenoreceptors, which are located in prostate, bladder neck, prostate capsule and prostate urethra.

Pharmacokinetics : Absolute bioavailability of Alfuzosin 10mg under basal conditions is 49%. Following multiple dosing of 10mg Alfuzosin lead to maximum concentration is 9 hours. It is moderately bound to human plasma proteins (82 to 90%). It undergoes extensive metabolism by the liver; it is metabolized by three metabolic pathways: oxidation, O-demethylation, and N-dealkylation CYP3A4 is the principal hepatic enzyme isoform involved in its metabolism. It is excreted 69% in feces and only 11% of the administered dose is excreted unchanged in urine. Half life is 10 hours. The extent of absorption is 50% under fasting conditions' therefore, alfuzosin should be taken immediately following a meal.

Indications : It is indicated for the treatment of the signs and

symptoms of benign prostatic hyperplasia.

Dosage and administration : Recommended dose is 10mg daily to be taken immediately after the same meal each day.

Precautions : (i) Carcinoma of the prostate and BPH cause many of the same symptoms. These two diseases frequently coexist. Therefore patients thought to have BPH should be examined prior to starting therapy with alfuzosin to rule out the presence of carcinoma of prostate. (ii) **Drug Interactions :** Pharmacokinetic and pharmacodynamic interactions between alfuzosin and other alpha blockers have not been determined. However' interactions may be expected and alfuzosin should not be used in combination with other alpha blockers. (iii) **Coronary insufficiency :** If symptoms of angina pectoris appear or worsen' alfuzosin should be discontinued. (iv) **Hepatic insufficiency :** It should not be given to patients with moderate or severe hepatic insufficiency. (v) **Renal insufficiency :** Systemic exposure increases by approximately 50% in patients with renal insufficiency. (vi) Patients with congenital or acquired Qt prolongation. Worsen with 40mg dose. (vii) Postural hypotension with or without symptoms (e.g. dizziness) may develop within a few hours following administration of extended-release alfuzosin.

Adverse Reactions : Dizziness-5.7% URT infection-3%, headache-3.0%, fatigue-2.7%, rarely abdominal pain, dyspepsia constipation nausea. impotence, bronchitis, sinusitis, pharyngitis rashes and tachycardia.

Compiled by Dr. P. Chattree

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