THROMBOPOIETIC AGENTS IN THE TREATMENT OF THROMBOCYTOPENIA

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Thrombopoietic Agents

- Clinical case presentation
- Introduction to thrombopoietin
- Development of thrombopoietic agents
- Clinical Indications
- Eltrombopag use in aplastic anemia
- Future uses

Case patient

- 33 yo F G8P8 admitted at 28 wga with concern for severe aplastic anemia and platelet refractoriness
- Treated with prednisone and intermittent RBC and platelet transfusions for presumed ITP
- Emergent CS due to seizures
- Small SAH on head CT
- Neurosurgery goal platelets >100,000 then > 80,000 then > 50,000 then >30,000

Case patient

- Received crossmatched platelets
- Treated with IVIG
- HLA-matched platelets
- Bone marrow biopsy 6/3/15 and 6/19/15

Platelet Count

Date/time	Platelet Count (x10^3/µL	Transfusion
5/31/15 20:25	8,000	
6/01/15 01:01		2 apheresis
6/01/15 06:05	9,000	
6/08/15 01:20	14,000	
6/08/15 11:29		3 apheresis
6/08/15 15:00	5,000	
6/11/15 21:23	56,000	
6/12/15 01:01		1 crossmatched apheresis
6/12/15 03:49	91,000	
6/19/15 04:45	14,000	
6/20/15 00:12		1 HLA matched apheresis
6/20/15 02:53	28,000	

HLA Antibodies

Hospital: Vanderbilt Med Ctr (Heart PRE XP) - 3627 Physician: Patient Category: Heart

Recipient Name:	Recip #	SS#	MR#/Other ID	DOB	Race	Gender	Genotype	ABO
		###-##-			Unknown	Female	ac	O

PRA Results - HLA Class I Antibody/Specificity - Last 6 months for Recipient:

Serum # SER 2015 9908 Serum Date: 6/9/2015 Serum Status: H Order Date: 6/10/2015 Final Reviewer: doc

Test Code/Test Name: 138 / HLA Class I Antibody ID- Luminex Single Antigen panel Final Review Date: 6/12/2015

Class I PRA Specificity: anti-A 1, 3, 11, 23, 24, 25, 26, 32, 34, 36, 43, 66, , , , , , , ; anti-B 7, 8, 13, 18, 27, 35, 41, 42, 45, 47, 48, 49, 50, 51, 52, 53, 54, 55 ; anti-CW 2, 15, , , , , , ,

Class I % = 99 MICA: DTT= Report Comments: also B56,57,58,59,60,61,62,63,64,65,67,73,77,78,81,82; watch A80, B71,72; Cw5,6,17,18

PRA Results - HLA Class II Antibody/Specificity - Last 6 months for Recipient:

Serum # SER 2015 9908 Serum Date: 6/9/2015 Serum Status: H Order Date: 6/10/2015 Final Reviewer: doc

Test Code/Test Name: 139 / HLA Class II Antibody ID- Luminex Single Antigen panel Final Review Date: 6/12/2015

Class II PRA Specificity: anti-DR 7, , , , , , , , , , , , , , , , , , ; anti-DQ , , , , , , , , ; anti-DRW , ,

Class II % 24 DP: Report Comments: watch DR9,16

PRA Results - Class I Class II Flow Antibody Screen - Last 6 months for Recipient:

Serum # SER 2015 9908 Serum Date: 6/9/2015 Serum Status: H Order Date: 6/10/2015 Final Reviewer: doc

Test Code/Test Name: 32 / HLA Class I and Class II antibody screen - Flow c Final Review Date: 6/12/2015

Class I % Positive **Class II %** Positive Report Comments:

Bone Marrow Biopsies

Accession #: H15-2275
Collection Date: 6/3/2015 13:00

Diagnosis:
BONE MARROW - PERIPHERAL BLOOD SMEAR, ASPIRATE SMEAR, PARTICLE PREPARATION, BIOPSY, AND FLOW CYTOMETRY: MARKEDLY HYPOCELLULAR MARROW (<10% CELLULAR) WITH TRILINEAGE HYPOPLASIA

Impression: This is a markedly hypocellular marrow exhibiting trilineage hypoplasia. In the proper clinical context, these findings are supportive of a diagnosis of aplastic anemia. There is no definitive morphologic dysplasia, although the specimen is suboptimal for this evaluation due to the absence of an aspirate smear.

Accession #: H15-2540
Collection Date: 6/19/2015 12:00

Diagnosis:
BONE MARROW BIOPSY, ASPIRATE SMEAR, FLOW CYTOMETRY, AND PERIPHERAL BLOOD: MILDLY HYPERCELLULAR MARROW WITH TRILINEAGE HEMATOPOIESIS; NO SIGNIFICANT DYSPLASIA OR INCREASE IN BLASTS (SEE IMPRESSION).

Impression: In contrast to this patient's recent marrow biopsy (H15-2275, 6/3/15), this specimen is mildly hypercellular, with a full range of trilineage maturation. The peripheral blood still demonstrates cytopenias, but overall these results are most consistent with marrow recovery from a transient aplastic insult, with a lag in peripheral blood counts. However, other possibilities cannot be completely discounted, including significant peripheral destruction of blood elements or heterogeneous marrow cellularity. Recommend correlation with trending counts.

Case patient, cont

- Due to recovering bone marrow, the decision was made to hold off on immunosuppression
- Patient discharged 6/22, plan to follow-up in clinic 6/26
- Considering treatment with eltrombopag
- No additional HLA-matched platelets reserved at this time

Eltrombopag (Promacta)

Pricing: US

Tablets (Promacta Oral)

12.5 mg (30): $3482.64

25 mg (30): $3482.64

50 mg (30): $6803.29

75 mg (30): $10204.94

Severe aplastic anemia: Oral: **Note:** Use the lowest dose to achieve and maintain hematologic response. Hematologic response may take up to 16 weeks and requires dose titration. Discontinue therapy if hematologic response is not achieved after 16 weeks of treatment, for excessive platelet responses or for liver function abnormalities. Consider discontinuing if new cytogenetic abnormalities are observed.

Initial: 50 mg once daily (25 mg once daily for patients of East-Asian ethnicity); dose should be titrated based on platelet response. Maximum dose: 150 mg once daily.

Dosage adjustment based on platelet response:

Platelet count <50,000/mm^3 (≥2 weeks after treatment initiation or a dose increase): Increase daily dose by 50 mg (if taking 25 mg once daily, increase dose to 50 mg once daily prior to increasing the dose amount by 50 mg daily); maximum: 150 mg once daily

Platelet count ≥200,000/mm^3 and ≤400,000/mm^3 (at any time): Reduce daily dose by 50 mg; reassess in 2 weeks

Platelet count >400,000/mm^3: Withhold dose for 1 week; when platelet count <150,000/mm^3, resume with the daily dose reduced by 50 mg

Platelet count >400,000/mm^3 after 2 weeks at the lowest dose: Discontinue treatment

http://www.uptodate.com.proxy.library.vanderbilt.edu/contents/eltrombopag-drug-information?source=search_result&search=eltrombopag&selectedTitle=1%7E17

Introduction

- Thrombopoietin
  - Cytokine synthesized in liver
  - Regulates proliferation and maturation of megakaryocytes and platelet production along with IL-3, IL-6, IL-11, and stem cell factor
  - Increases number of erythroid and myeloid progenitors
  - Consists of 353 amino acids (first 153 similar to erythropoietin)

Wormann B. Clinical Indications for Thrombopoietin and Thrombopoietin-Receptor Agonists. Transfus Med Hemother 2013; 40:319-325
Kuter DJ. What is the potential for thrombopoietic agents in acute leukemia. Best Practice and Research Clinical Haematology 24 (2011) 553-558

Introduction

- Benefits of thrombopoietic agents
  - Reduce risk for bleeding
  - Prevent severe thrombocytopenia
  - Reduce platelet transfusions
    - U.S. ~1,500,000 units per year
    - Risk for alloimmunization
    - Risk for transmission of infectious agents

Wormann B. Clinical Indications for Thrombopoietin and Thrombopoietin-Receptor Agonists. Transfus Med Hemother 2013; 40:319-325

Development of Thrombopoietic Agents

- First generation
  - Full-length recombinant heavily glycosylated human TPO (rhTPO) synthesized in Chinese hamster ovary cells
  - Megakaryocyte growth and differentiation factor (MDGF)- truncated non-glycosylated form produced in *E. coli*
- Clinical trials for first generation thrombopoietic growth factors stopped in 2001
  - Pegylated recombinant human MDGF study- 13 people developed antibodies that cross-reacted with endogenous TPO causing prolonged thrombocytopenia

Wormann B. Clinical Indications for Thrombopoietin and Thrombopoietin-Receptor Agonists. Transfus Med Hemother 2013; 40:319-325

Development of Thrombopoietic Agents

- Second generation- thrombopoietin receptor agonists which mimic TPO, lack sequence homology to endogenous TPO
  - Romiplostim (Nplate®; Amgen GmbH, Munich, Germany)
    - "peptibody"- 4 peptides coupled by glycine bridges to heavy chain fragment of IgG, binds and induces dimerization of receptor
    - Adverse effects- HA, nausea, arthralgia, thromboemboli
    - Reports of increased reticulin deposition in BM, reversible when drug was discontinued
    - Administered SQ, once weekly
    - Peak response ~day 15

Wormann B. Clinical Indications for Thrombopoietin and Thrombopoietin-Receptor Agonists. Transfus Med Hemother 2013; 40:319-325

Development of Thrombopoietic Agents

- Second generation, cont.
  - Eltrombopag (Revolade®, Promacta®; GlaxoSmithKline GmbH, Munich, Germany)
    - Non-peptide molecule binds c-mpl receptor on hematopoietic stem cells at transmembrane and juxtamembrane domains of TPO receptor (does not compete for binding with TPO)
    - Adverse effects- HA, N/V, thromboemboli, ↑ALT and bilirubin
    - Administered orally
    - Can also increase RBC and neutrophil counts
    - Peak response ~day 15-16

Wormann B. Clinical Indications for Thrombopoietin and Thrombopoietin-Receptor Agonists. Transfus Med Hemother 2013; 40:319-325
Desmond R, Townsley D et al. Eltrombopag in Aplastic Anemia. Sem in Hemat, Vol 52, No1, January 2015, pp 31-37

Clinical Indications of Eltrombopag

- Severe aplastic anemia
  - if insufficient response to immunosuppressive therapy
- ITP
  - if failed treatment with corticosteroids, immune globulin or splenectomy
- Chronic liver disease
  - used to reach target platelet count to initiate and maintain interferon therapy

Wormann B. Clinical Indications for Thrombopoietin and Thrombopoietin-Receptor Agonists. Transfus Med Hemother 2013; 40:319-325

http://www.uptodate.com.proxy.library.vanderbilt.edu/contents/eltrombopag-drug-information?source=search_result&search=eltrombopag&selectedTitle=1%7E17

Aplastic Anemia

- Severe aplastic anemia diagnosis
  - Hypocellular bone marrow
  - MDS ruled out
  - 2 of 3 of the following:
    - Absolute neutrophil count < 500/μL
    - Absolute reticulocyte count <60,000/μL
    - Platelet count <20,000/μL

Desmond R, Townsley D et al. Eltrombopag in Aplastic Anemia. Sem in Hemat, Vol 52, No1, January 2015, pp 31-37

Aplastic Anemia

- Aplastic anemia treatment
  - Allogeneic SCT- definitive, potentially curative
  - 2/3 patients respond to immunosuppressive therapy with horse anti-thymocyte globulin and cyclosporine
    - 30-40% relapse- cyclosporine, rabbit ATG, alemtuzumab
  - Non-responders- long-term transfusion dependence

Desmond R, Townsley D et al. Eltrombopag in Aplastic Anemia. Sem in Hemat, Vol 52, No1, January 2015, pp 31-37

Aplastic Anemia

- Eltrombopag treatment for refractory aplastic anemia
  - 43 pts w/SAA refractory to at least 1 course of IST for at least 6 months, platelet count <30,000/μL
  - Escalating dose- started at 50 mg, increased by 25 mg every 2 weeks to maximum 150 mg
  - Primary endpoint- hematologic response at 3-4 months
  - 17/43 (40%) had hematologic response

Desmond R, Townsley D et al. Eltrombopag in Aplastic Anemia. Sem in Hemat, Vol 52, No1, January 2015, pp 31-37

Aplastic Anemia

- Eltrombopag treatment for refractory aplastic anemia, cont.
  - Well-tolerated, some had reversible transaminitis
  - No increase in reticulin staining in bone marrow
  - 6 patients had drug withdrawn, maintained stable counts and normocellular marrow at median 24 months
  - 8 of 43 (19%) developed new cytogenetic abnormalities
    - chromosome 7, 13q deletion, trisomy 21
    - ? Stimulation of dormant clones by eltrombopag
    - SAA has baseline risk of clonal marrow dysfunction (15%)
  - 2 of 8 (5%) had dysplastic changes on bone marrow

Desmond R, Townsley D et al. Eltrombopag in Aplastic Anemia. Sem in Hemat, Vol 52, No1, January 2015, pp 31-37

Future Uses

- MDS
- Chemotherapy-induced thrombocytopenia
- Other hereditary and acquired bone marrow failure diseases
- Treatment with IST in newly diagnosed SAA
- Moderate aplastic anemia

Questions

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