

Should Steroids still be the first choice for newly diagnosed ITP?

Swami Padmanabhan Iyer, MD

Leader, Early Drug Development Program in Oncology,
The Methodist Cancer Center,
Weill Cornell Medical College,
Houston, TX





Learning Objectives

Steroids are the first choice

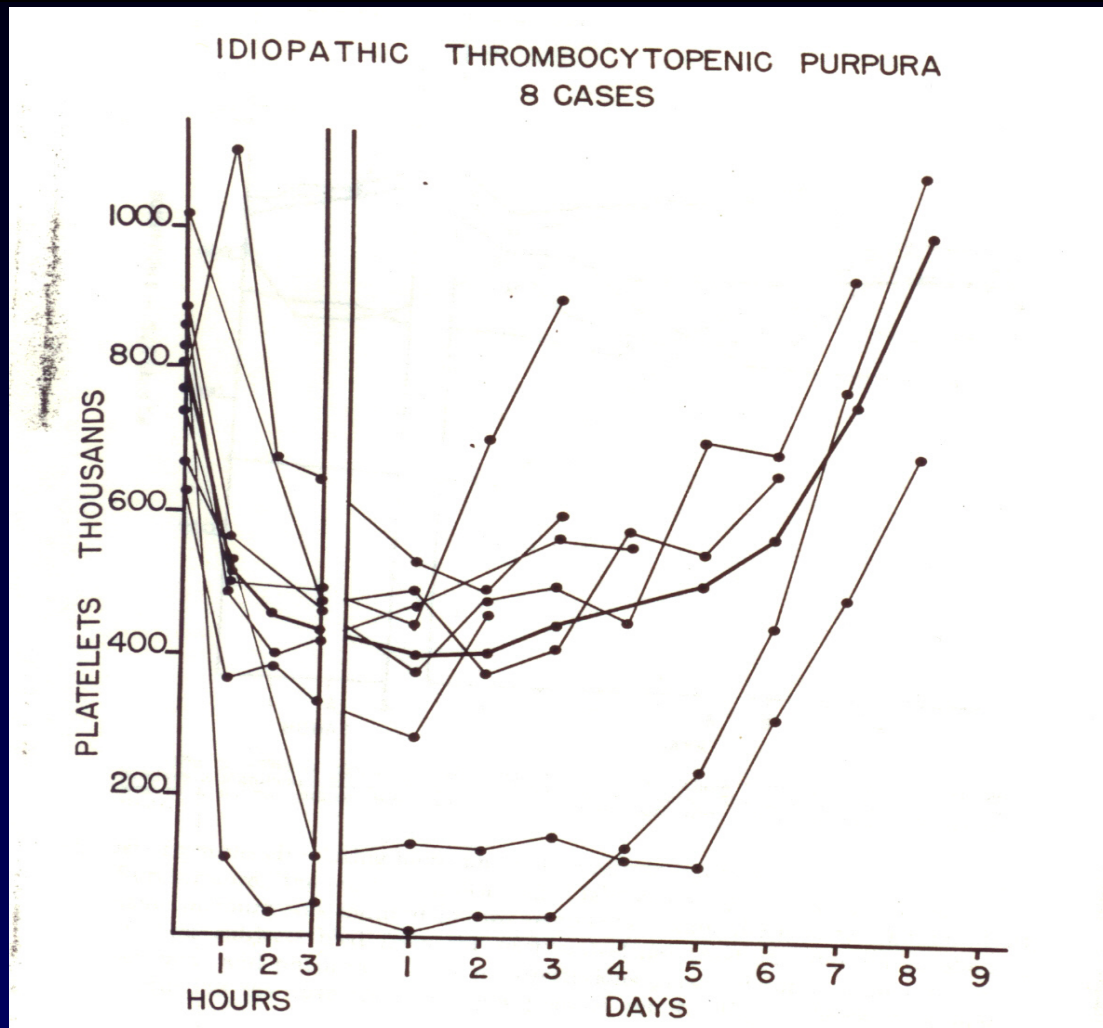
- **The newer understanding of pathophysiology of ITP suggests a systemic immune dysfunction that includes antibody production against platelets along with T cell dysfunction**

- **Understanding the historical therapeutic strategies for ITP with this new perspectives and relevant health risks and side effects**

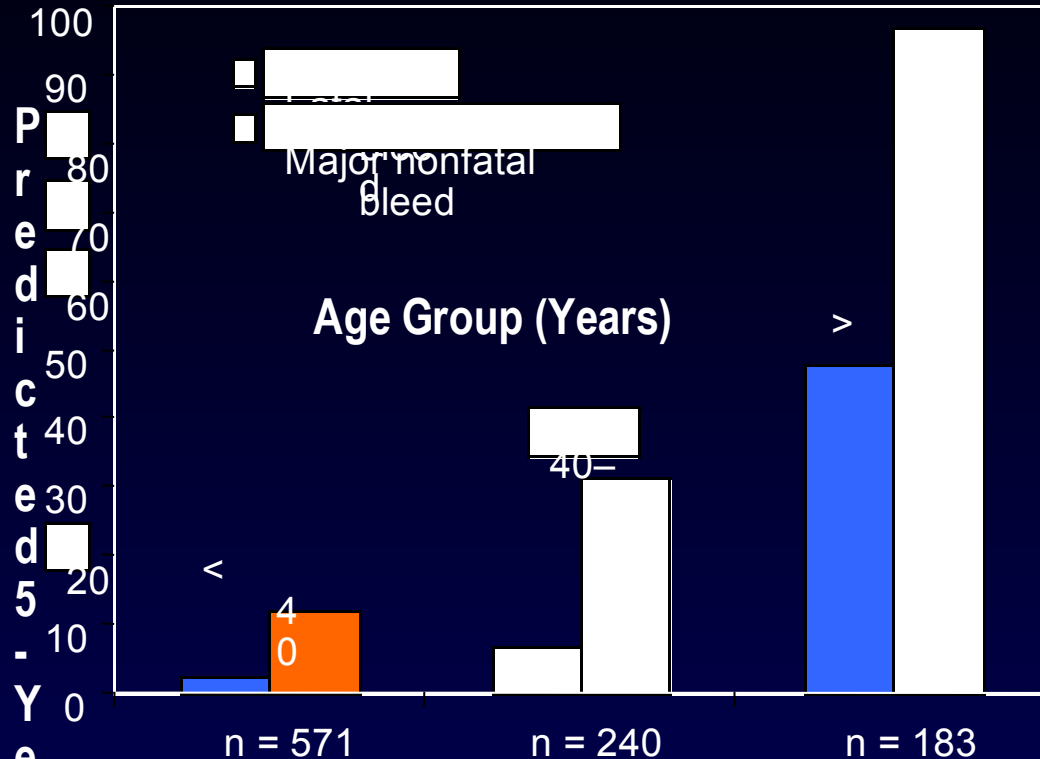
- **Place and role of TPO mimetics for ITP and their associated clinical evidence**

Demonstration of a thrombocytopenic factor in the blood of patients with thrombocytopenic purpura

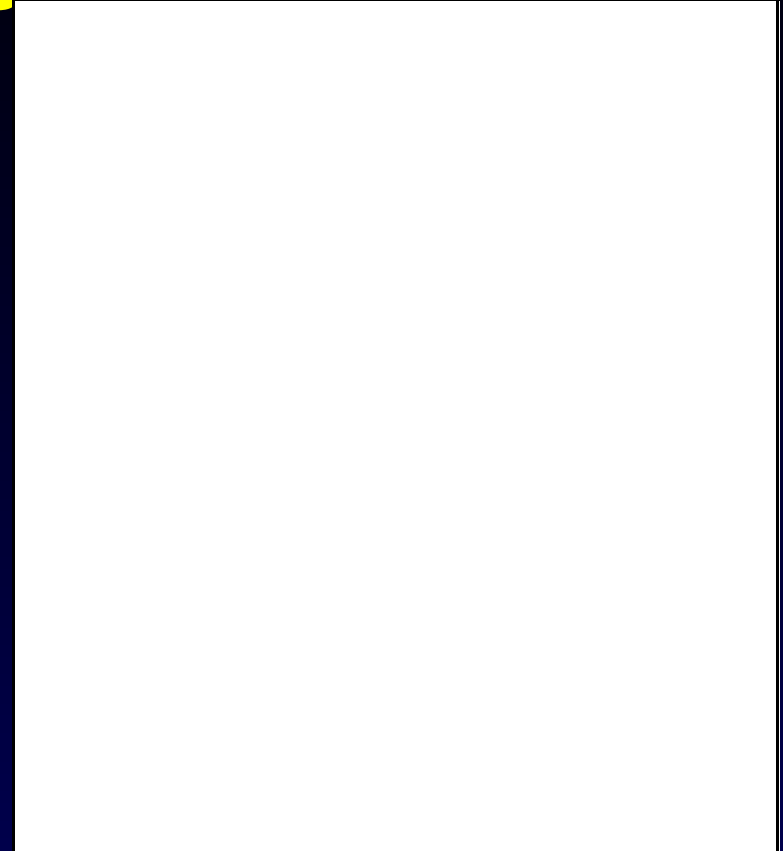
Harrington, Minnich, Hollingsworth, Moore



The Natural History of Adult ITP



- Review of 17 studies including 1817 ITP patients
- Fatal bleeding calculated as 1.6 – 3.9% per patient year
- Increased risk with higher age groups (>60)



Antiplatelet Antibodies in ITP

Fc portion available for
binding to Fc receptor →
on macrophages



Case Presentation

A 29-year-old male with significant past medical history of type 1 diabetes, in the past presents with petechiae which started a few days ago.

PE: petechiae on his buccal mucosa and posterior pharynx.

CBC: White blood cell count 5.9, hemoglobin 12.4, hematocrit 35.6, platelets 20,000, MCV 82.1. Pt. is Rh positive

bone marrow biopsy and flow cytometry: No significant immunophenotypic abnormalities. Cytogenetics 46XX.

How should this patient be treated?



IWG Definitions in ITP

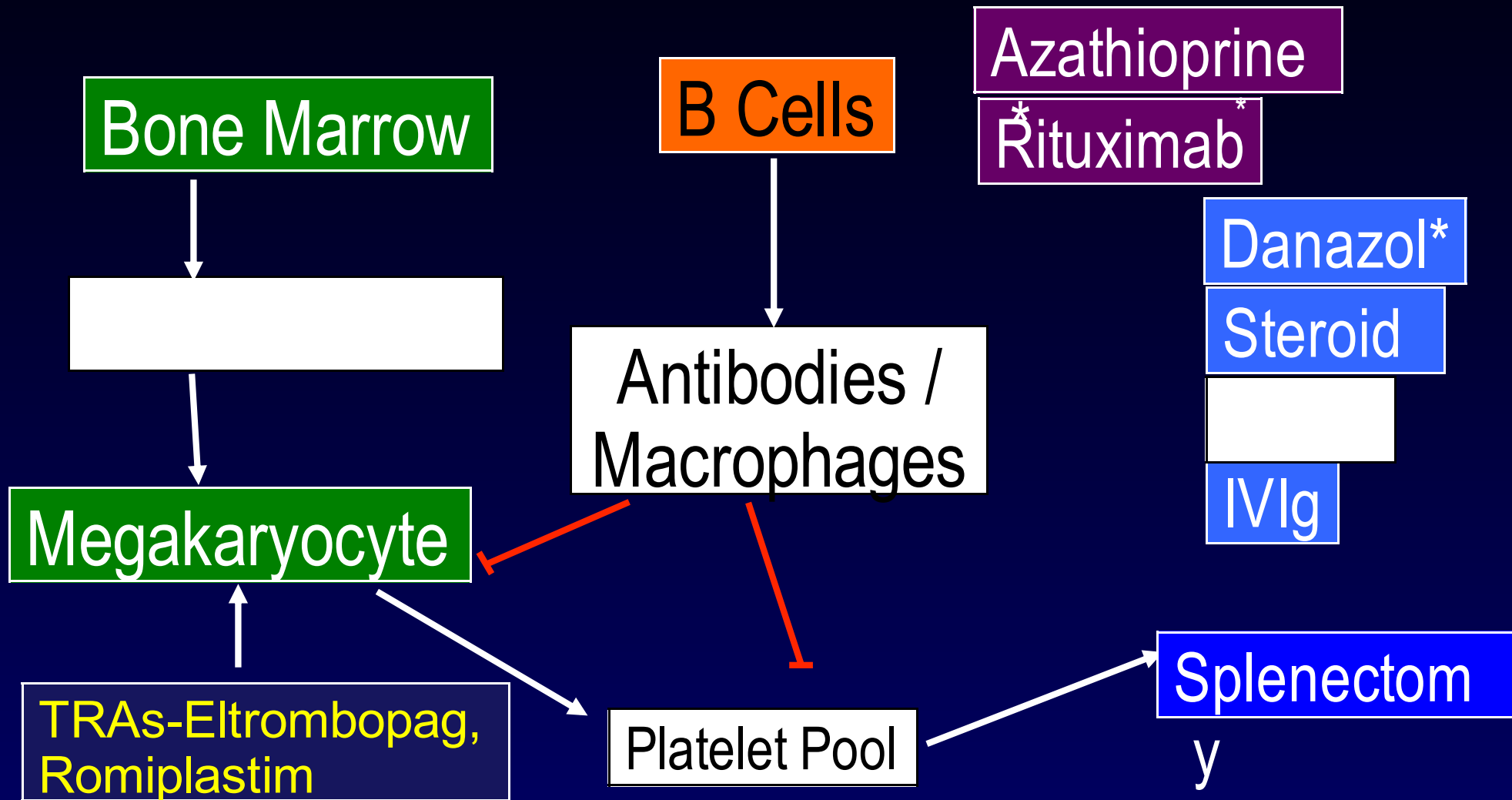
Primary ITP definitions:

- **Severe** : Where there is clinically relevant bleeding irrespective of platelet count
- **Refractory**: Failed splenectomy or relapsed AND severe ITP or risk of bleeding

Secondary ITP: other conditions can be causally found on investigations.

Who Should be Treated: Risk/Benefit Analysis

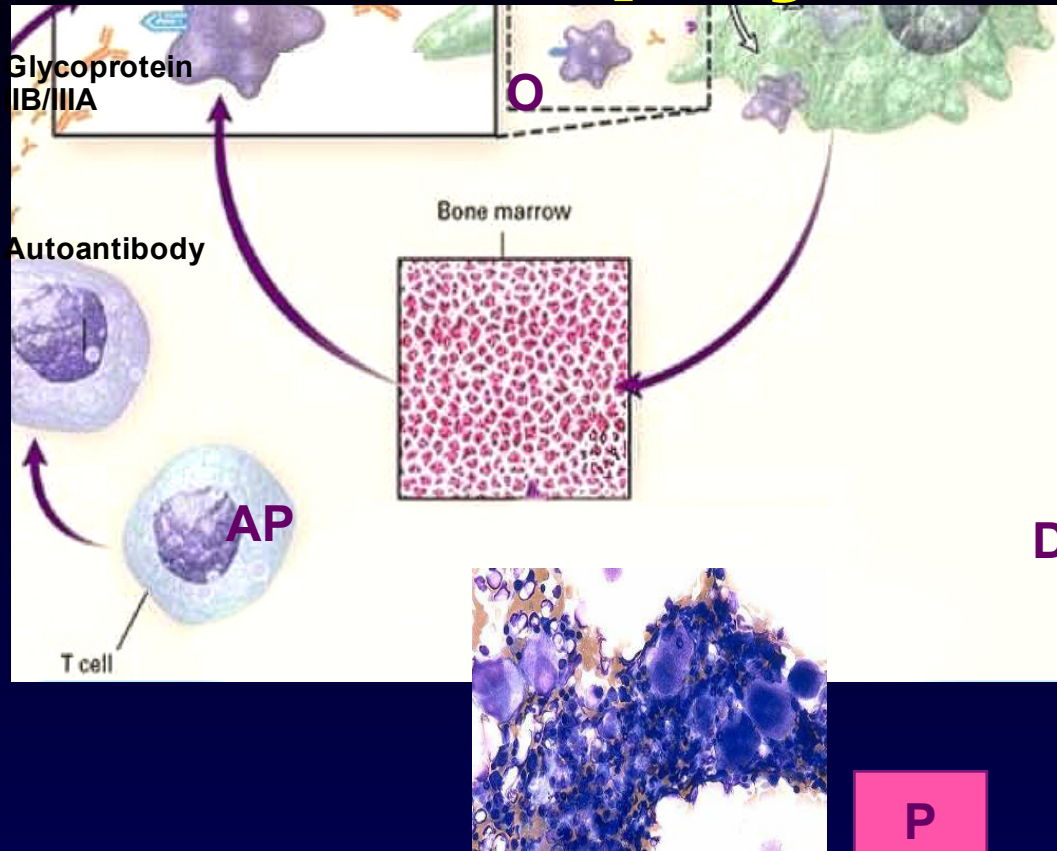
Mechanisms of Common Treatments Used to Treat Adult Chronic ITP



1. Cines DB, McMillan R. *Annu Rev Med.* 2005;56:425-442.

2. George JN, et al. *Blood.* 1996;88:3-40.

Pathophysiology of ITP



AP

O

Platelet Opsonization

D

↑ Platelet Destruction

P

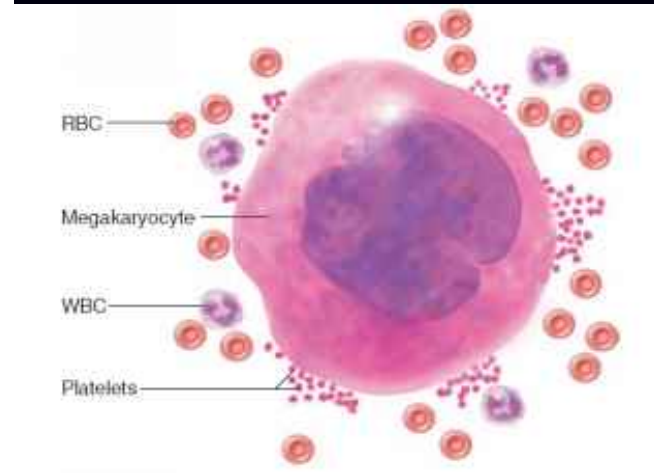
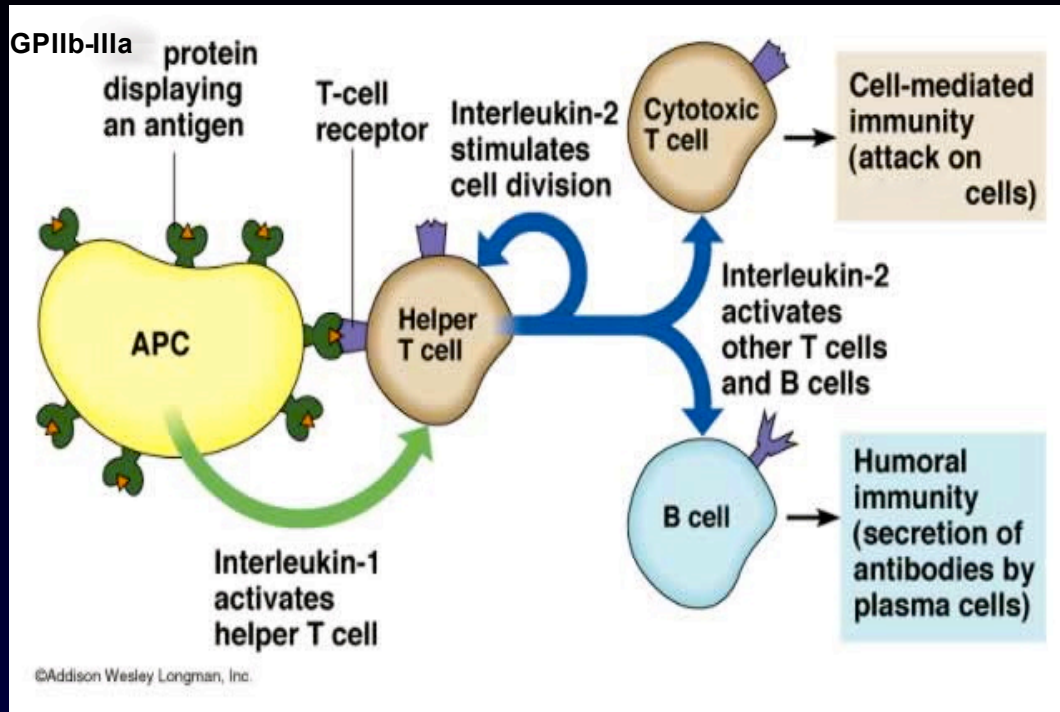
TC

TC

P

- ITP is an autoimmune disorder arising from the production of autoantibodies to platelet glycoproteins
- Leading to destruction of platelets by the reticulo-endothelial system
- Resulting in thrombocytopenia and associated clinical sequelae, bruising and bleeding

ITP- a rebel mutiny



MAIN CAST:

The villain or the Bully- B cell clones producing antibody missiles at the insistence of T cells

The Protagonist- Platelets and Megakaryocytes, Innocent Bystanders affected by the anti GPIIb-IIIa

(Daily Bread- Thrombopoietin)

Battleground or the Alley- Spleen

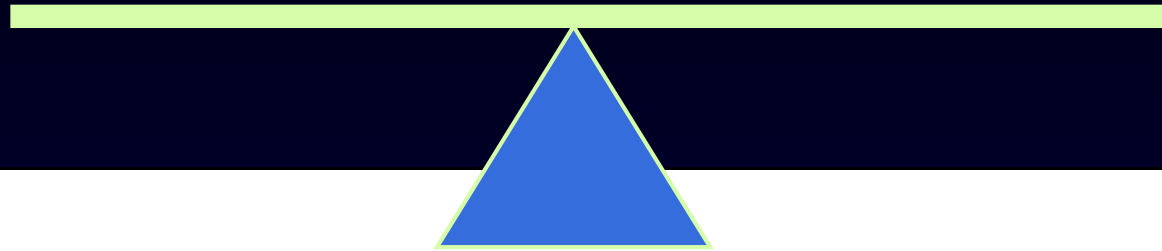
Mastermind- CD4 and their facilitators- Dendritic Cells

Internal Police- Regulatory T cells

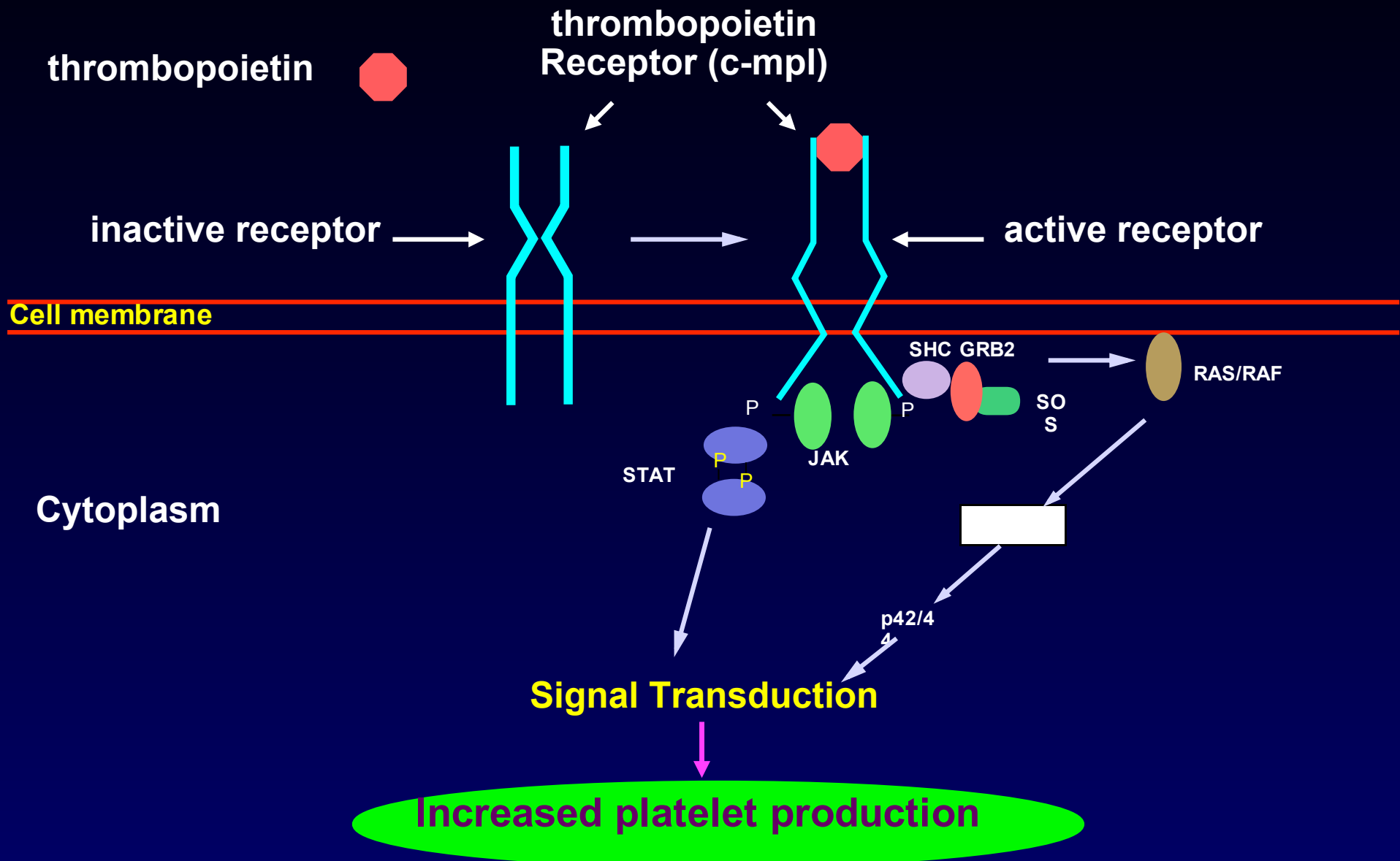
T cells in ITP

Helper T cells

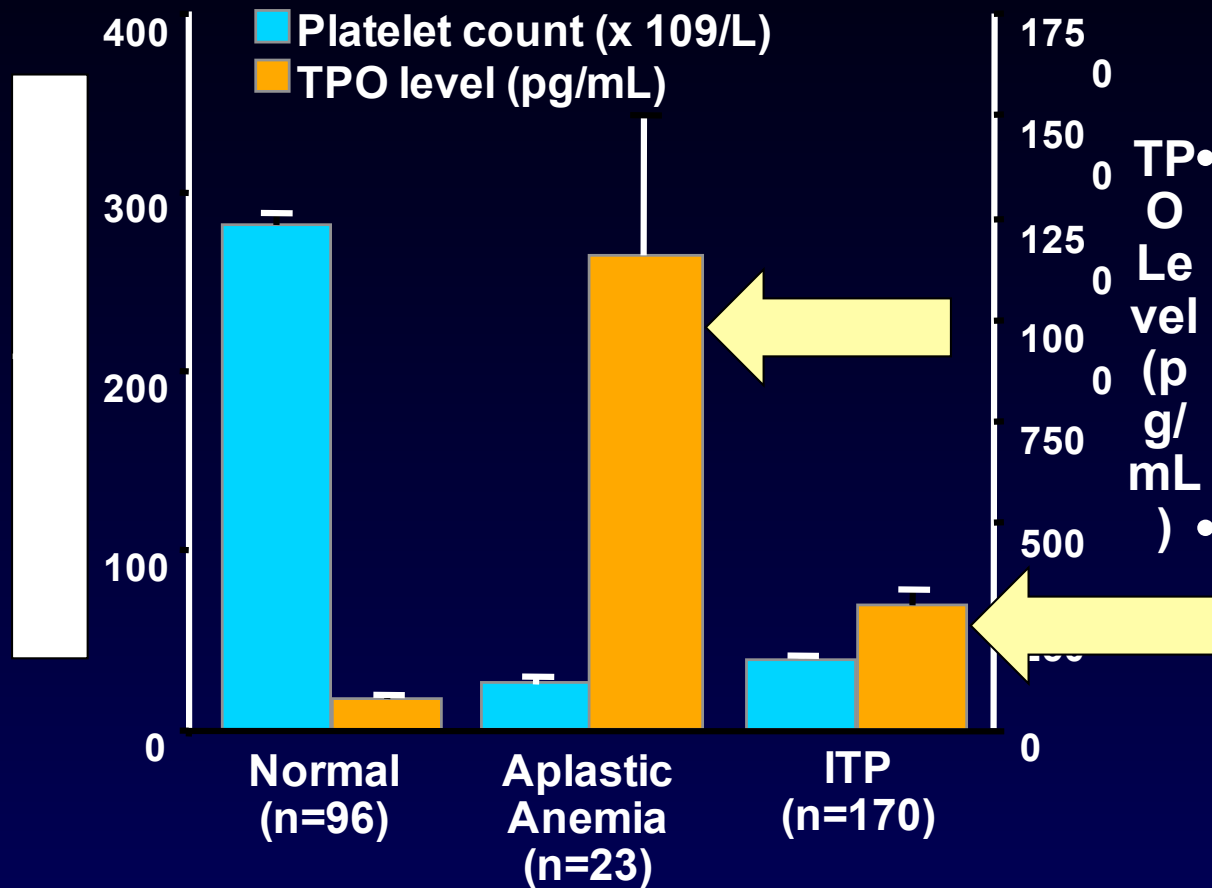
Regulatory
T cells



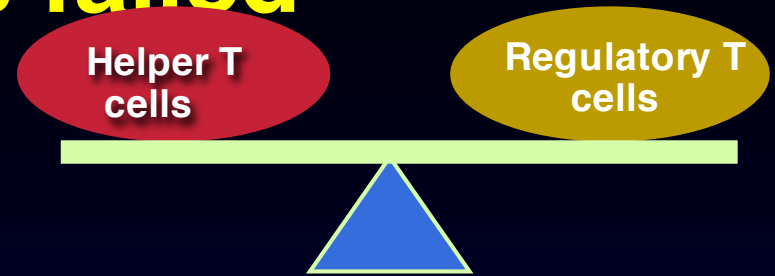
Thrombopoietin (TPO) and Megakaryocytes



ITP: Inadequate Platelet Production



“Steroids as first strike when Diplomacy has failed”



Battle for immune restoration- goal of restoring balance between the dysfunctional CD4 and T regs cells- B cells become polyclonal, DCs do not recognize GPIIb-IIIa antibodies and the ITP is cured.

Steroids- wound the instigators, puts them on the run- Best if Quick and short-

Steroids taper-U.N. withdraws pressure.. Internal force which is the T regulatory cells now asks the Helper T cells to behave. Local order is restored.

Collateral damage- reviewed in terms of diabetes, infections and loss of the daily raw material supply- TPO

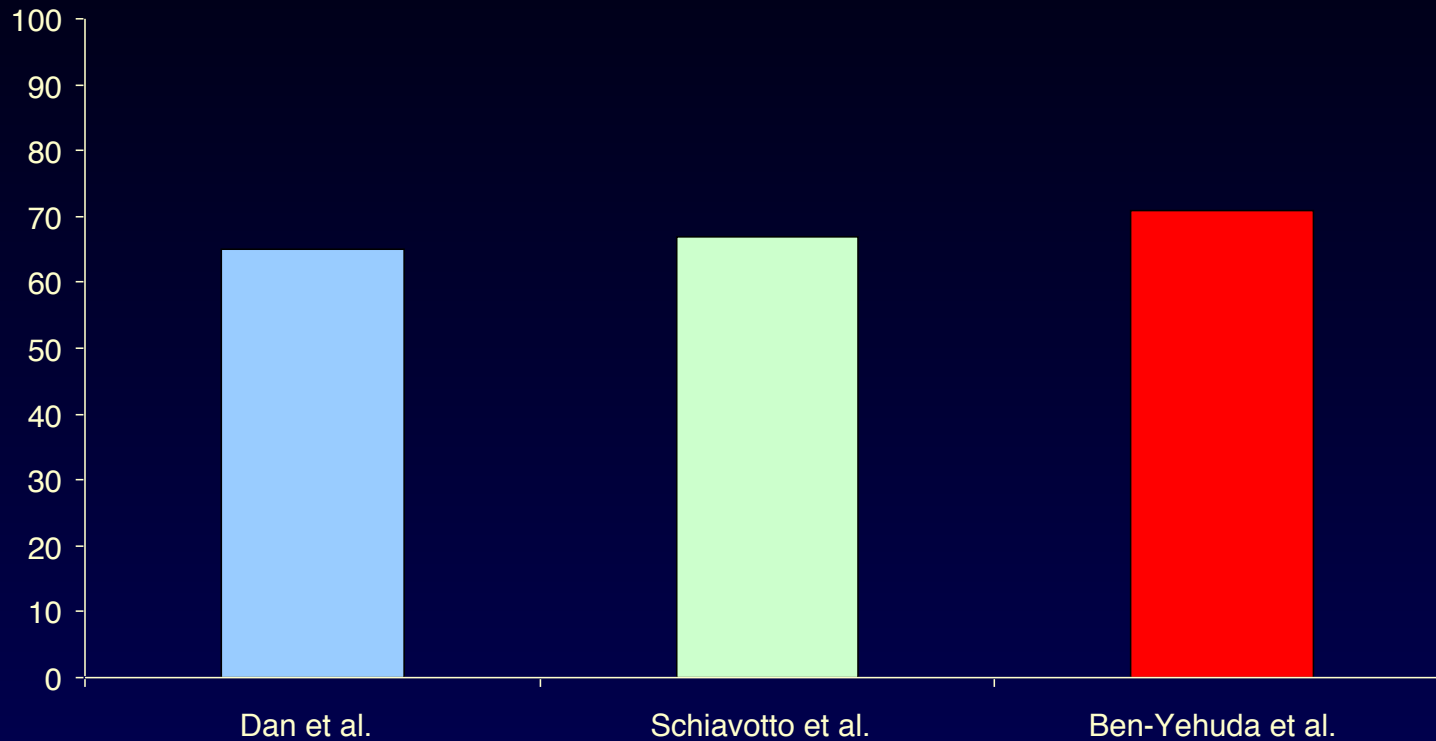
Rebuilding- An exercise that needs replenishment of TPO

Other strategies are:

Rituximab- CD20 guided missile targeting the Clonal B cells

Calcectam - Eliminate the battlefield

Response to Corticosteroids in Chronic ITP



- Median time to platelet count > 100,000/mcl was 7 to 10 days
- Only 13 to 17% of patients achieved long-term unmaintained remissions

Dan K, et al. *International J Hematol.* 1992;55:287-292.
Schiavotto C, et al. *Haematologica.* 1993;78(suppl II):22-28.
Ben-Yehuda D, et al. *Acta Haematol.* 1994; 91:1-6.

Corticosteroids- Which one to use and how long?



Dexamethasone



Efficacy reduced if used late



More potent and toxic than prednisone



Very useful when used early? Curative?



do not have predictive markers for responders

High dose Dex vs. Prednisolone

Untreated ITP patients, age >15 with platelets $\leq 30K$ (N = 151)

High Dose Dexamethasone 40mg/d for 4 days n-(76)*

Prednisolone 1 mg/kg/day for 2-4 weeks, then tapered, n-(75)

Assess response 6 weeks

* Second course give if platelet count $\leq 30 \times 10^9/L$ in 6 months if the platelet count was $\geq 30K$ at Day 14

Early use of Dexamethasone



Initial Rx with Dexamethasone

Study	N	Initial Response	Sustained Response
Cheng '03	125	84.8%	42.4% (6 mo)
Borst '04	36	83%	59% (31 mo)
Mazzuconi'07	37	89.2%	67.6% (26 mo)
Mazzuconi'07	90	85.6%	74.4% (8 mo)

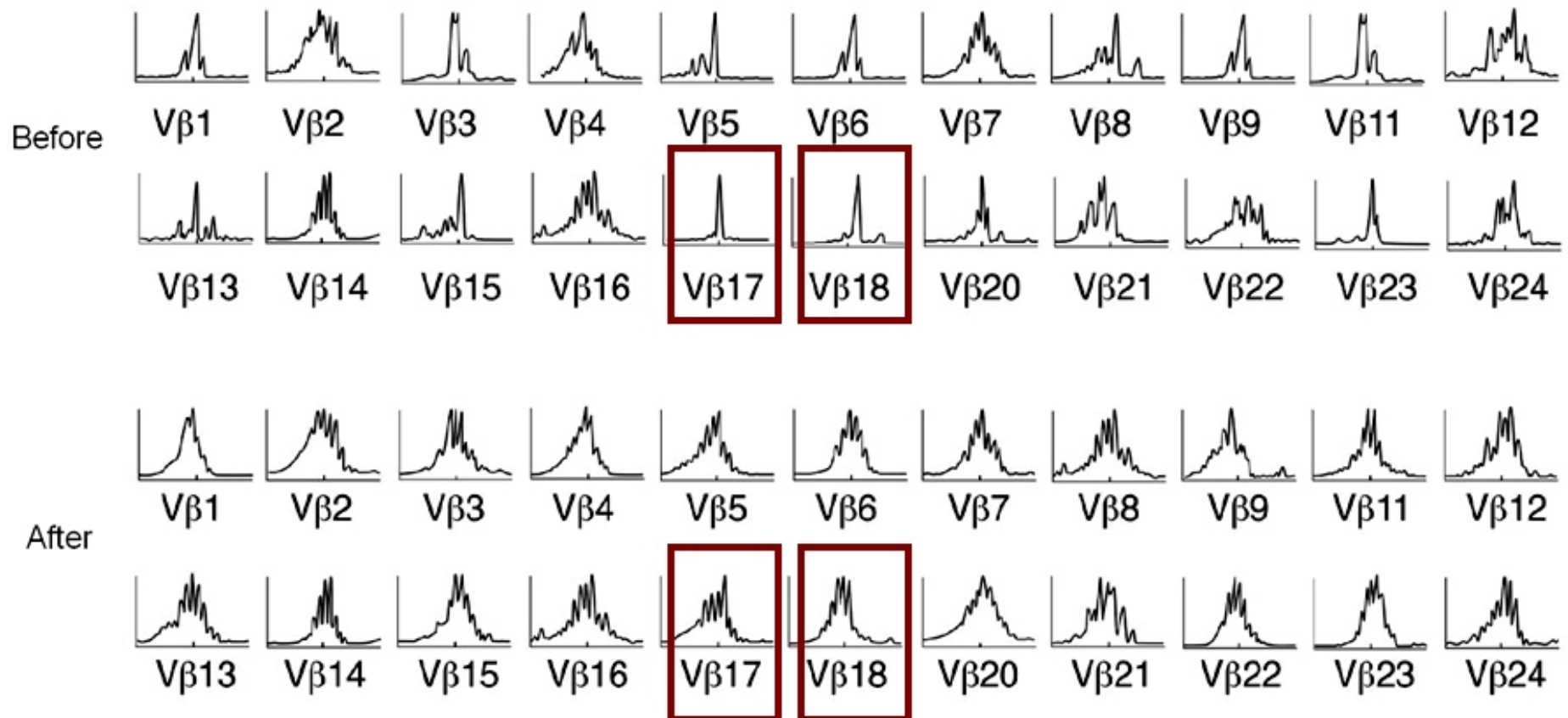
Alternative first-line treatments



Response to Rituximab

	Low dose	Standard dose
Patients	28	57
Dose	100 mg x 4	375 mg/m² x 4
CR	12 (43%) (>100,000)	18 (32%) (>150,000)
CCR	9 (32%) (11 months)	16 (28%) (17 months)
Time to response	44 days	21-56 days

Oligoclonal T cells turn to polyclonal after successful rituximab treatment



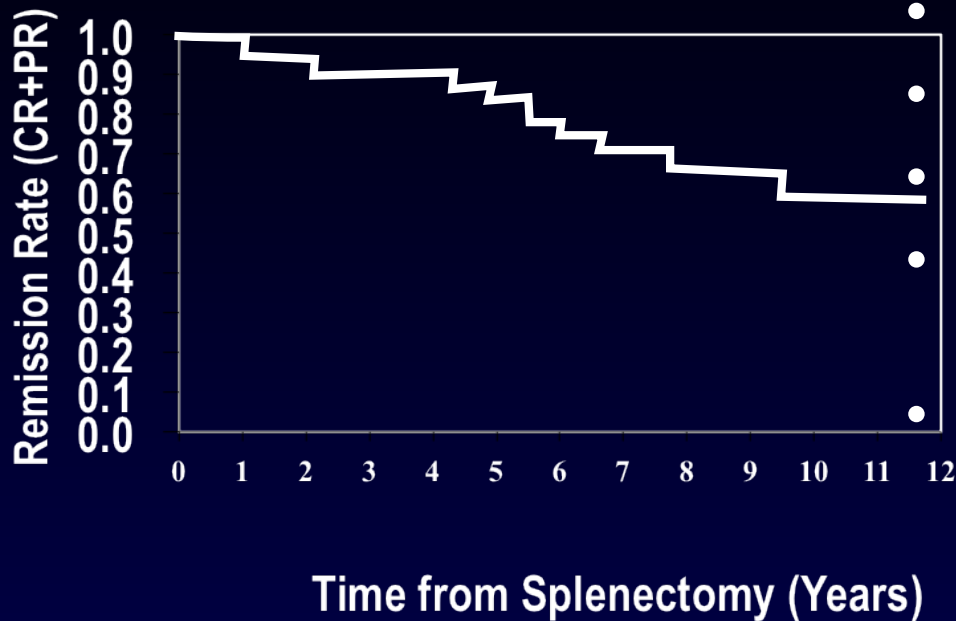
- **No cures, but retreatment similar responses.**
- **Long term rates are “disappointingly low” $\leq 25\%$.**
 - **No affect on Ig Levels**
 - **? B cell depletion as guide**
- **Potential complications and Cost**

Dexamethasone vs. Dex + Rituximab as Initial Treatment

**Sustained response: Platelet counts at
6 months, no treatment after 30 days**

> 50,000		> 100,000		> 150,000	
Dex	Dex Rtx	Dex	Dex Rtx	Dex	Dex Rtx
36%	63%	33%	53%	25%	43%

Splenectomy: Long-Term Outcome in 56 Adults With ITP



- Surgical complications
 - Laparoscopy
 - Death 0.2%, complications 10%
- Late complications (rare)
 - Sepsis
 - Thromboembolic, cardiovascular

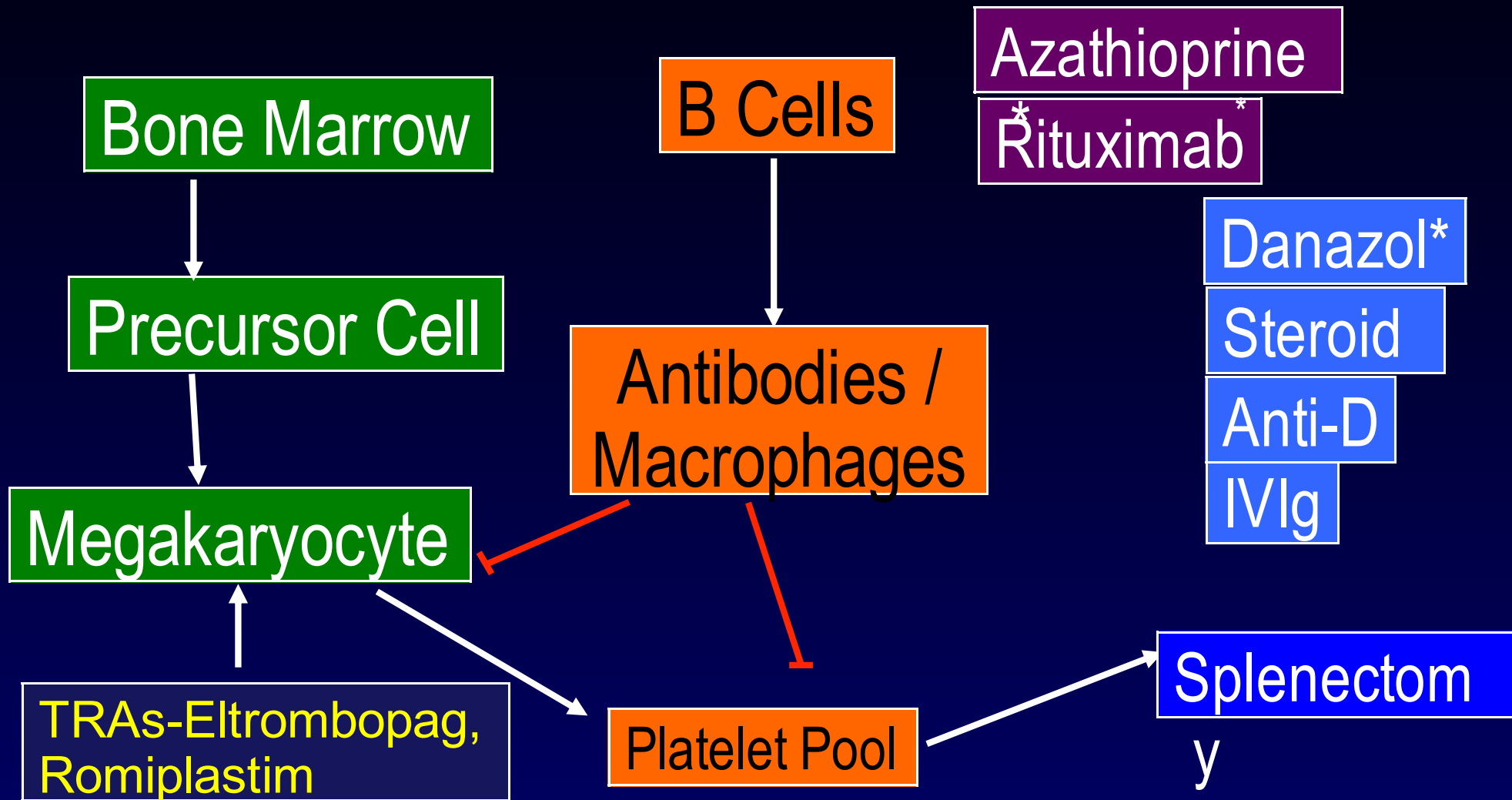
- Early response rate ~80%
- Responses usually rapid
- 15% relapse rate in 1st yr
- Defer up to 12 months for spontaneous remission
- Immunize with pneumococcal, Hib, meningococcal vaccine
- **REMEMBER: Recent Rituxan can impair this response**

How should this patient be treated?



ITP Summary

Mechanisms of Common Treatments Used to Treat Adult Chronic ITP



1. Cines DB, McMillan R. *Annu Rev Med.* 2005;56:425-442.

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For the newly Diagnosed ITP: Steroids and Beyond

Thank you

