Helios

60 years' experience of BMF stabilisation medication in FA

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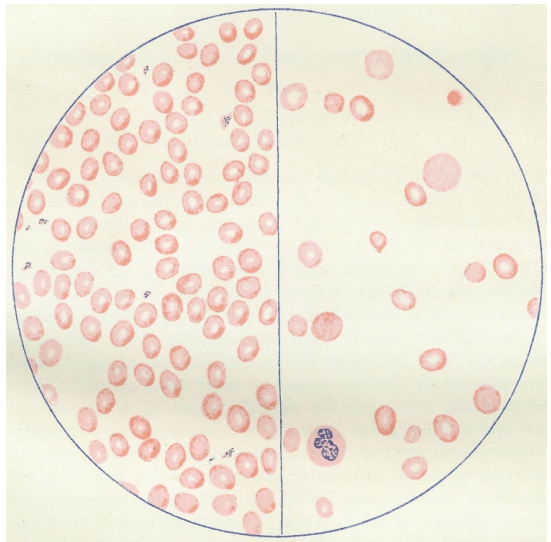
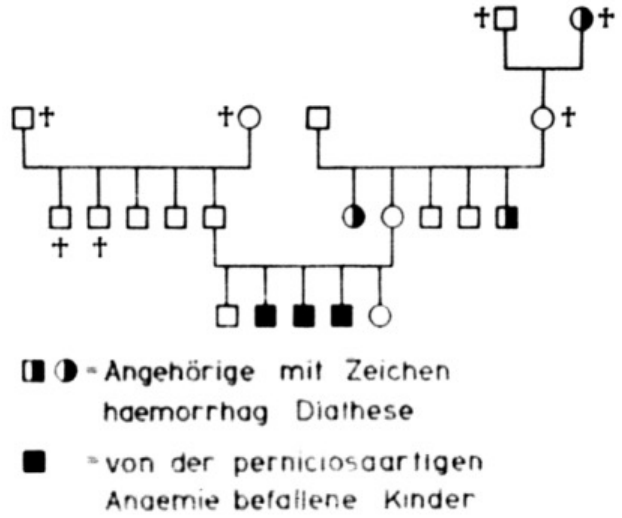
Krefeld and Düsseldorf, Germany

Familiäre infantile perniziosaartige Anämie (perniziöses Blutbild und Konstitution).

Von

Privatdozent G. FANCONI,
Oberarzt der Klinik.



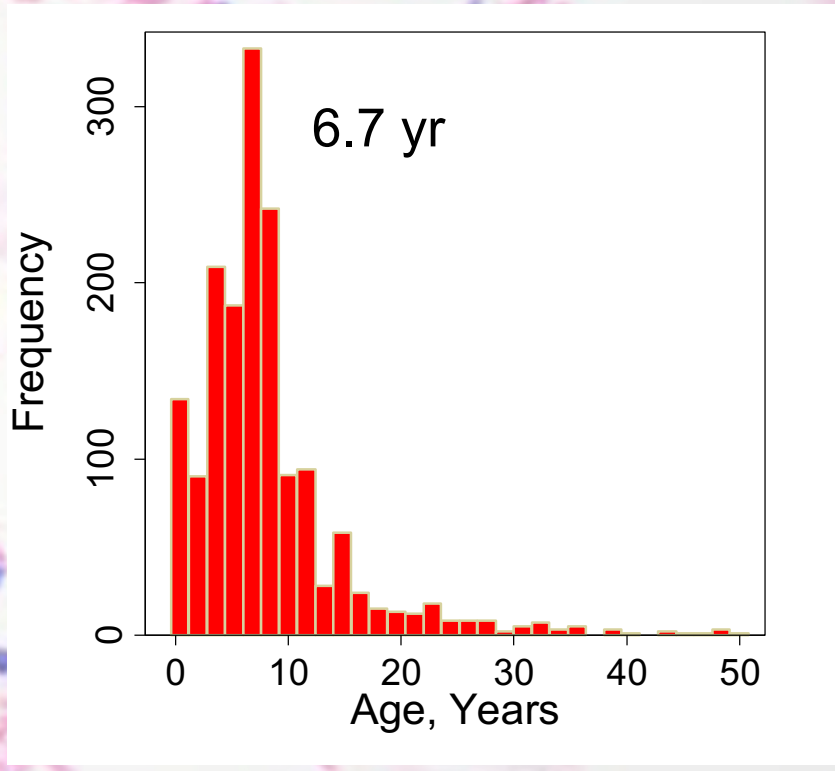


Fanconi 1927

Bone marrow failure in FA

Fanconi anemia is the **most common** cause of an inherited bone marrow failure syndrome!

	Mild	Moderate	Severe
Neutrophils	< 1,500/µl	< 1,000/µl	< 500/µl
Platelets	150,000 – 50,000/µl	< 50,000/µl	< 30,000/µl
Hemoglobin	≥ 8 g/dl	< 8 g/dl	< 8 g/dl



Shimamura et Alter 2010

Treatment options of BMF in FA

	Mild	Moderate	Severe
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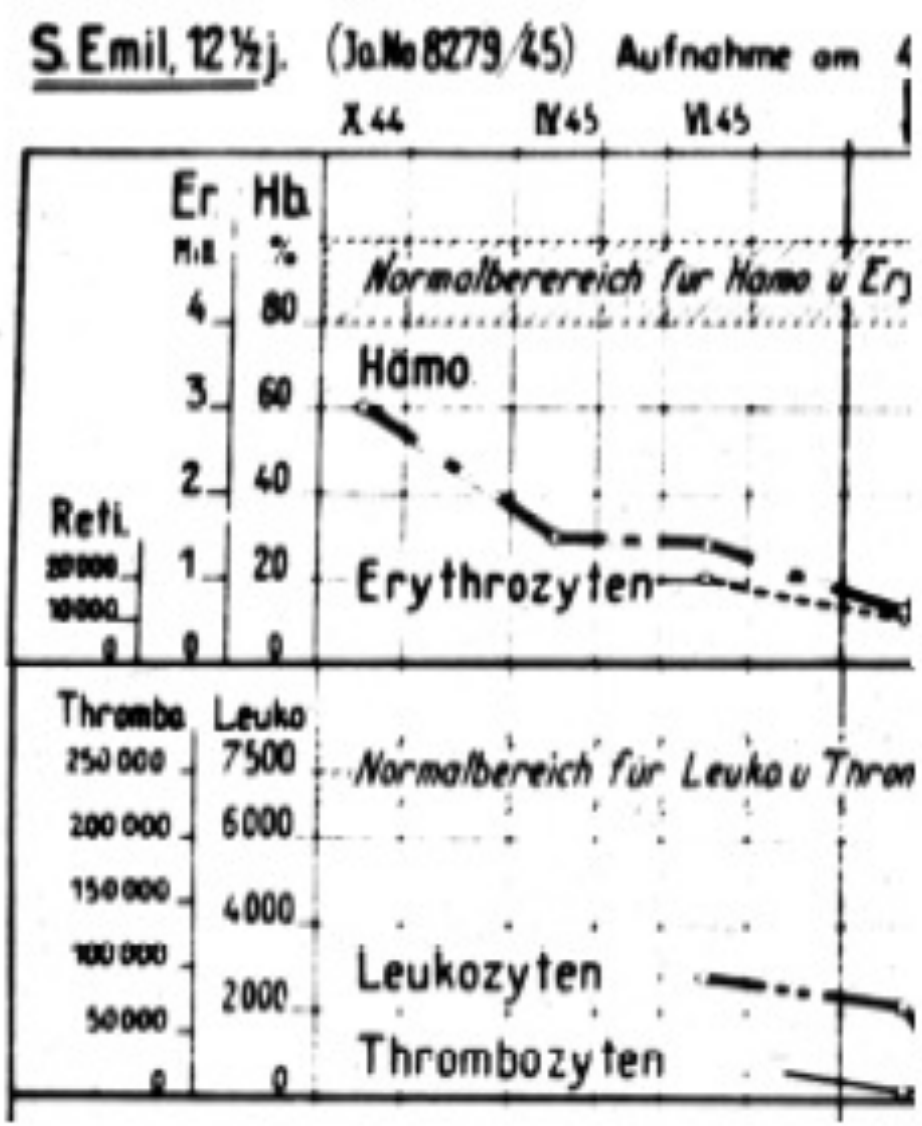
Platelets	150,000 – 50,000/µl	< 50,000/µl	< 30,000/µl
Hemoglobin	≥ 8 g/dl	< 8 g/dl	< 8 g/dl
	• Watch and wait • Medications? • Gene therapy	• Hematopoietic stem cell transplantation • Medications (Androgens, Elthrombopag) • Transfusions • Gene therapy?	

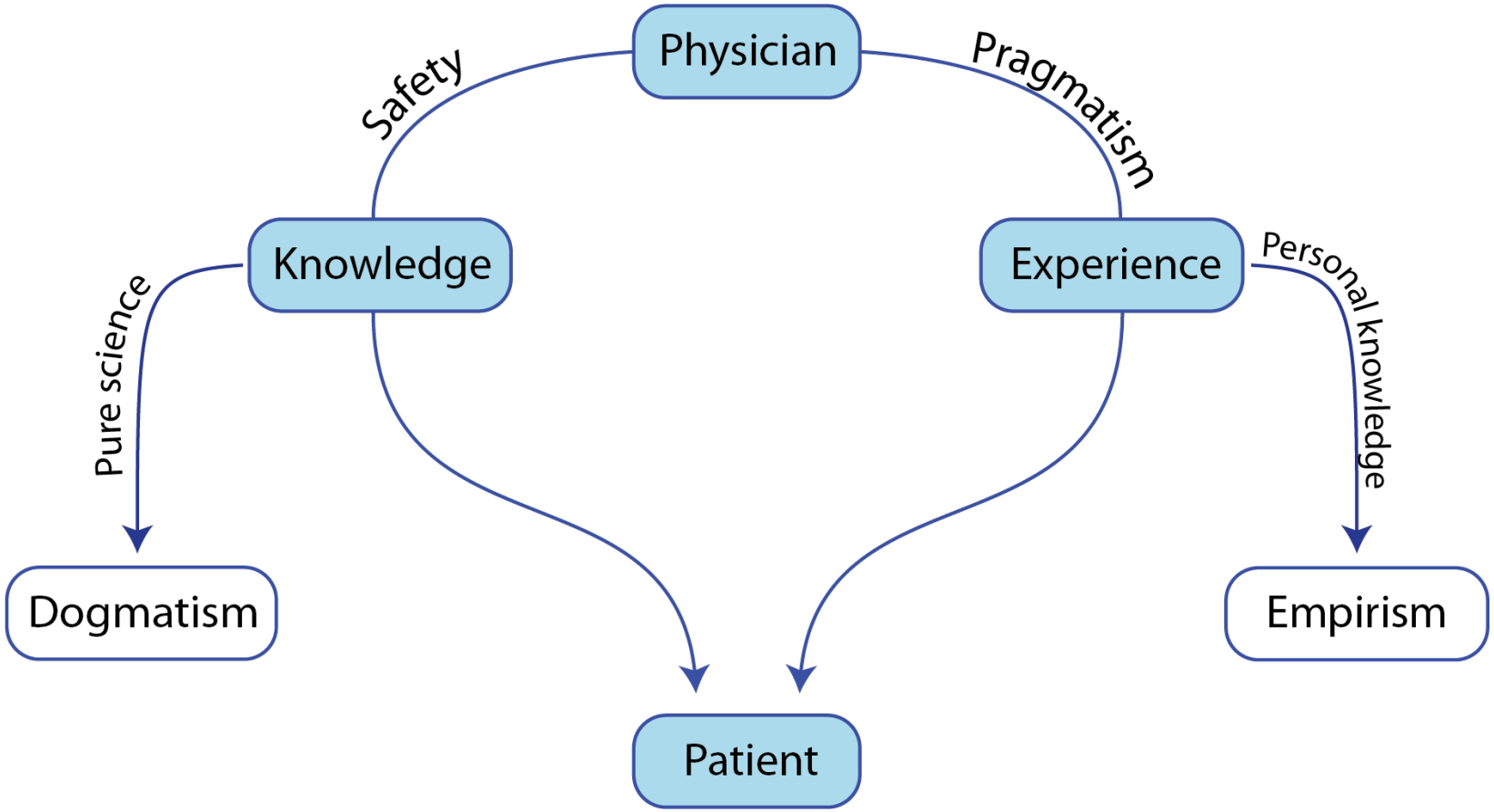
Treatment options of BMF in FA



Helios

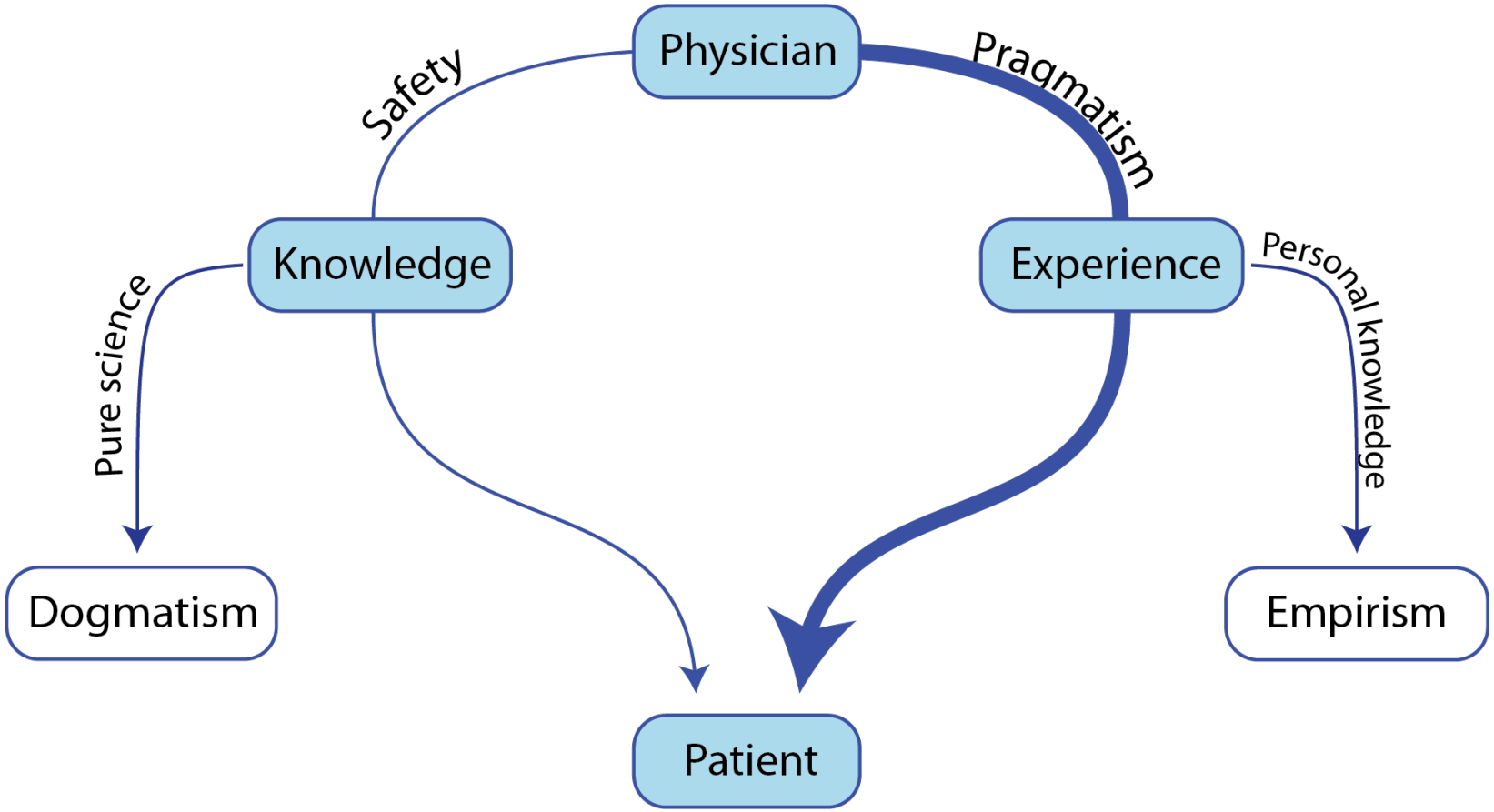
Fanconi 1967

Decision making in medicine



Labisch 2002

Decision making in medicine

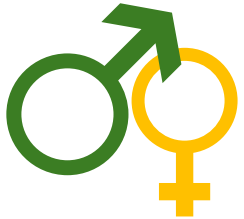


Labisch 2002

Rational for Androgens

Observation:

- Males have higher hemoglobin levels than females.



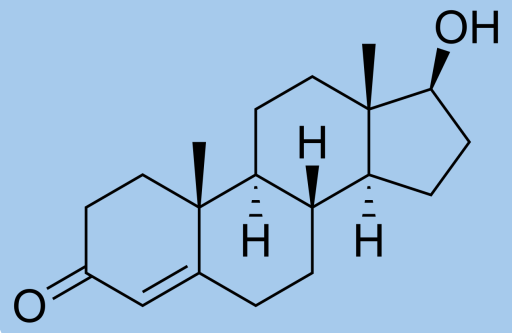
- Some FA individuals show improvement of blood counts during/after puberty

Testosterone-induced remission in aplastic anemia of both acquired and congenital types. Further observations in 24 cases.

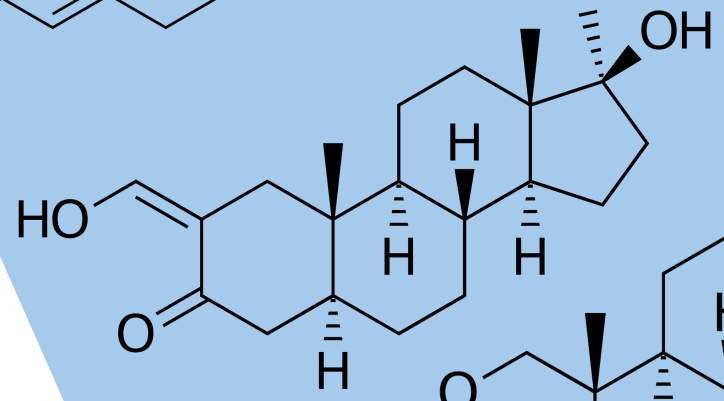
Shahidi et al 1961

Available drugs

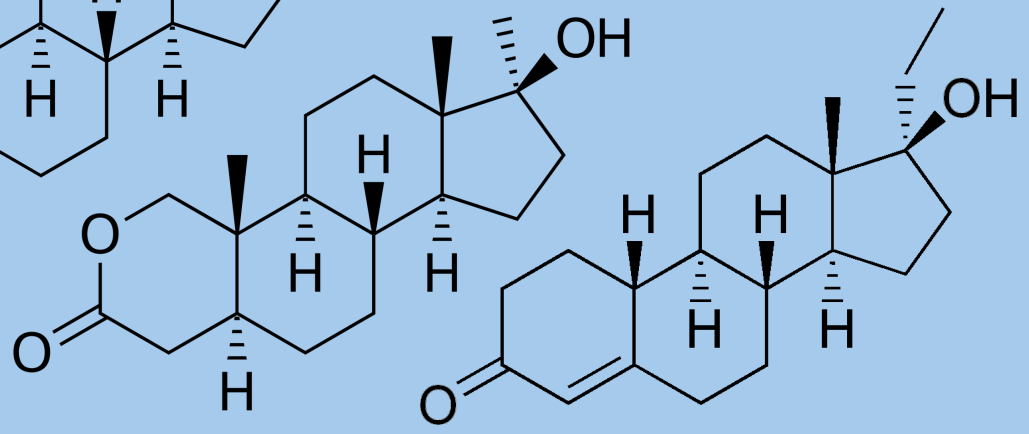
Testosterone



Oxymetholone

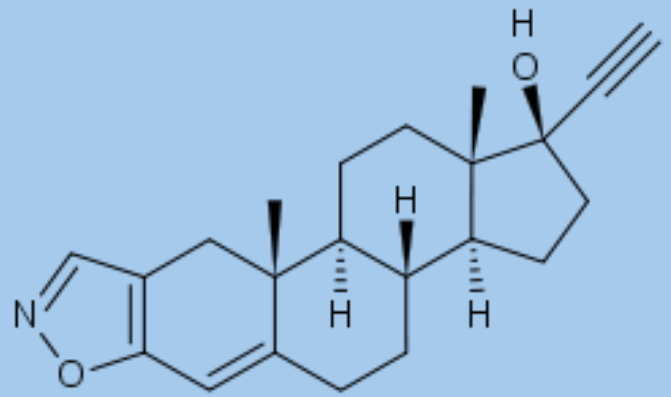


Oxandrolone



Nilevar

Danazol



Publications/clinical experiences

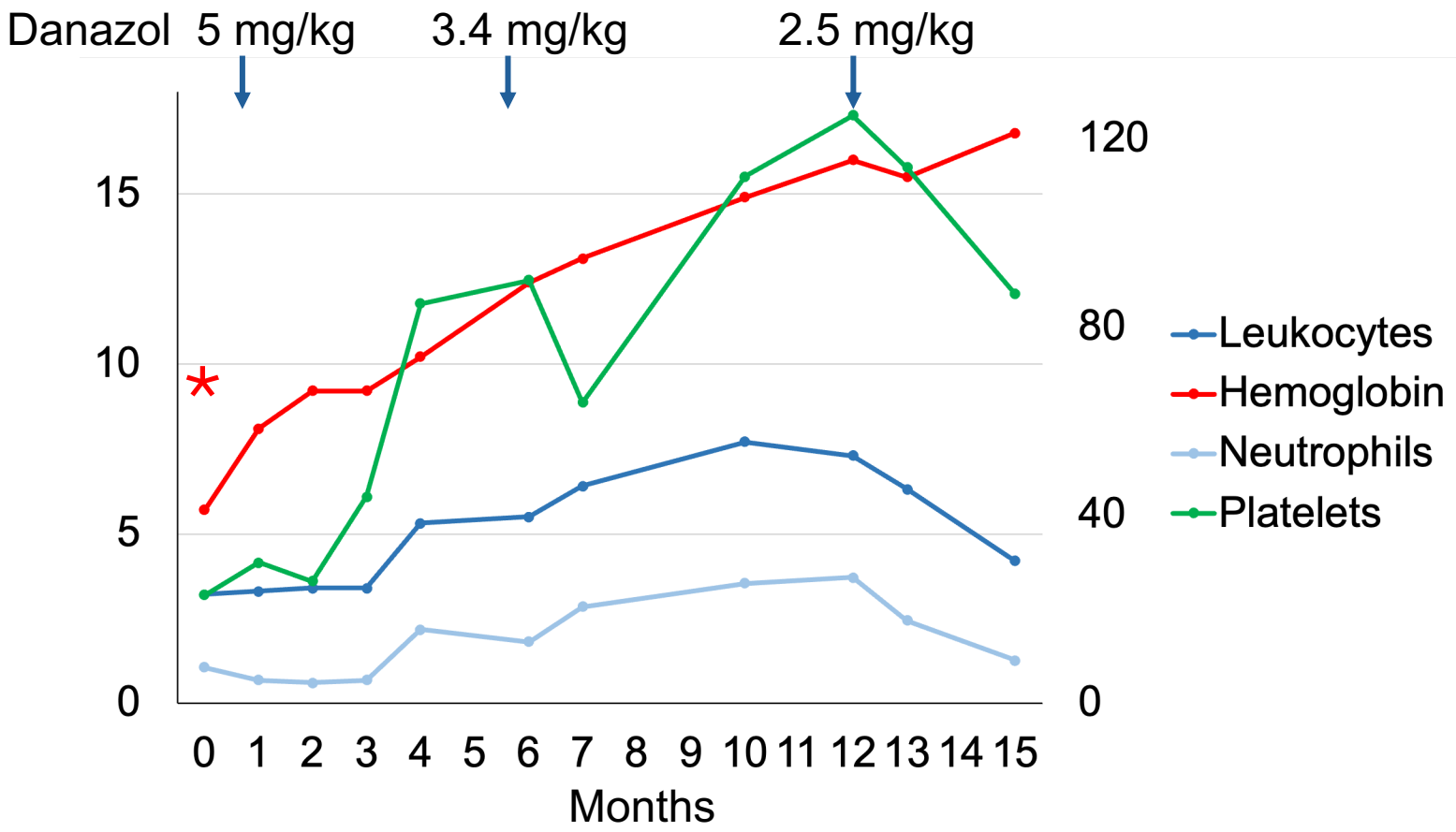
Hematological condition (n. of patients on androgen) [ref.]	Androgen	Dose	Study type	Age	Hematological outcome	Response criteria
FA (70), DKC (9) [37]	Norethandrolone (36%), Danazol (36%), Oxymetholone (19%), Nandrolone (3%), Other (6%)	NA	Retrospective registry-based	8 y (IQR: 6–12)	3-months CR in 8% 3 months PR in 29%	CR: normalization of Hb, PLT > 150 × 10^9/L, ANC > 1.5 × 109/L, PR: Transfusion independent; no longer meet criteria for severe disease
FA/DKC/ unclassifiable IBMFS (29) [44]	Danazol (15) Oxymetholone (9) Different Schedules (5)	Starting: 1 mg/kg d 0.68 mg/kg d	Retrospective registry based	6.8 (0.2–11)	Hematologic response in 16/29 (55%) mTTR: 1.9 mo (2.9–4.5)	Hb increase ≥2 g/dL from baseline and to ≥7 g/dL and transfusion-independence, PLT increase 2-fold from baseline and ≥ 20 × 10^9/L; ANC increase 2-fold from baseline and ≥ 0.5 × 10^9/L.
FA (9) [43]	Oxymetholone (9)	2.5–7 mg/kg d	Case series	6.9y	NA for oxymetholone alone	NA
FA (37) [42]	Oxymetholone (32) Danazol (3) Methenolone Enanthate (1) Norethandrolone (1)	Median starting dose of oxymetholone of 2 mg/kg d	Retrospective series	8.8 y (3.8–21.5)	Hb response in 25/37 (68%), mTTR 14 w; PLT response in 21/37 (57%), mTTR 11.5 w; ANC response in 13/27 (48%), mTTR 12 w	Hb: rise >2.0 g/dL; PLT: 2-fold increase above baseline, to >30 × 10^9/L; ANC: 2-fold increase from baseline and > 0.75 × 10^9/L
FA (9) Front-line [39]	Oxandrolone (9)	Starting daily dose 0.1 mg/kg (males) or 0.0625 mg/kg (females)	Prospective single arm phase 1/2	9 y (6–12)	PLT response in 4/6 (66%) Hb response in 7/9 (79%) TTR for Hb: 9.3 w (3.1–12.8)	Hb increase of >2 g/dL for 8-week and transfusion-independent. PLT: 2-fold increase from baseline and to >30 × 10^9/L. ANC: 2-fold increase from baseline and 0.75 × 10^9/L
FA (8) Front-line [45]	Danazol (8)	4.8 mg/kg d (range 2.9–7.7)	Retrospective series	12 y (3–21)	PLT or Hb improvement in 7/8 (88%)	NA
FA (17) [38]	NA	NA	Retrospective series	NA	Hb response in 12/17 (71%)	Hb increase by 2 g/dL or to a normal value

Bosi et al 2023

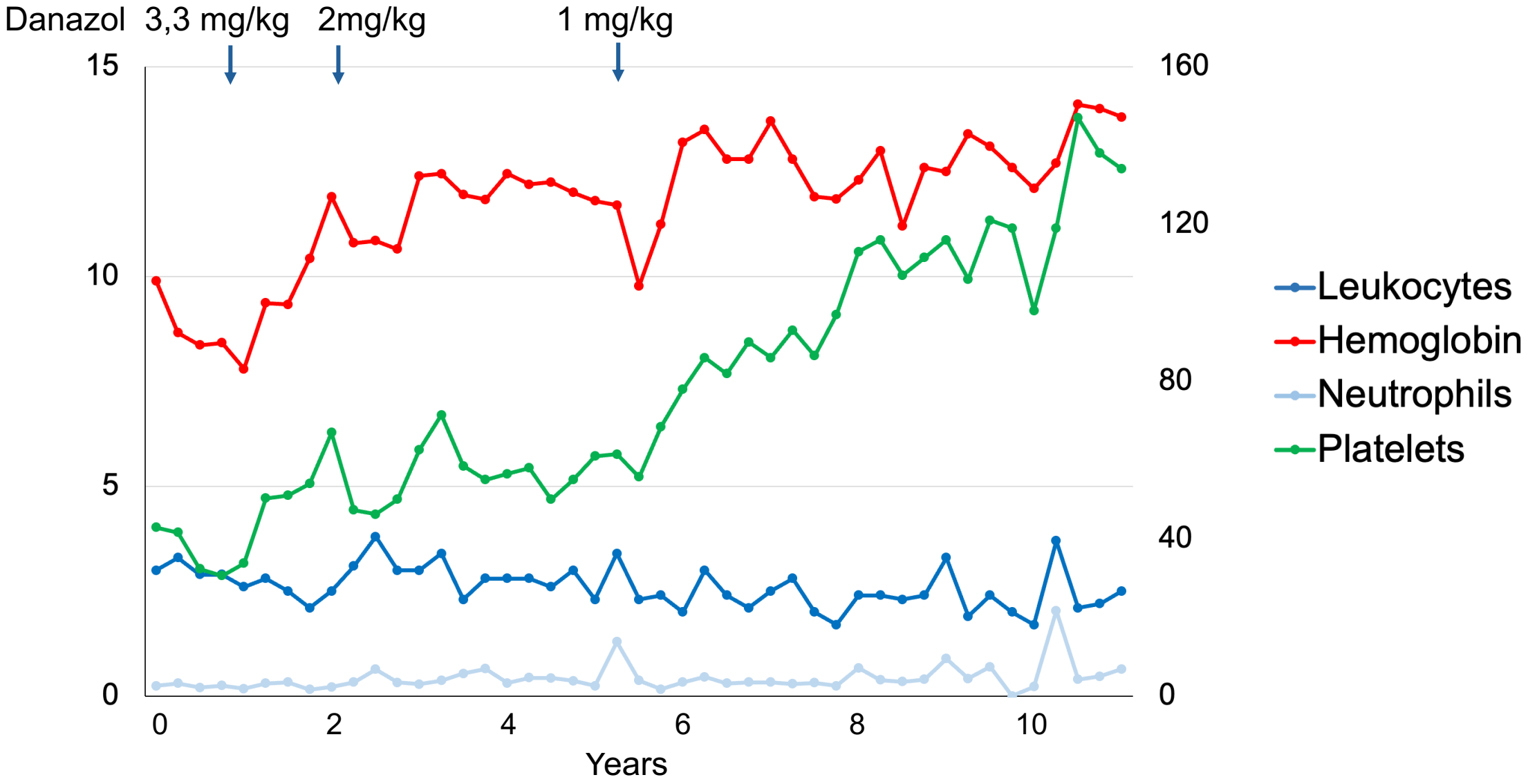
Response

As low and short as possible!

- Not everyone response to androgenic medication.
- First improvement of blood counts generally after three months
- Red lineage mostly the first responses



Long-term response



Side effects of Danazol

20 years with Danazol

Increase of LDL, decrease of HDL

Transaminitis (mild liver dysfunction)

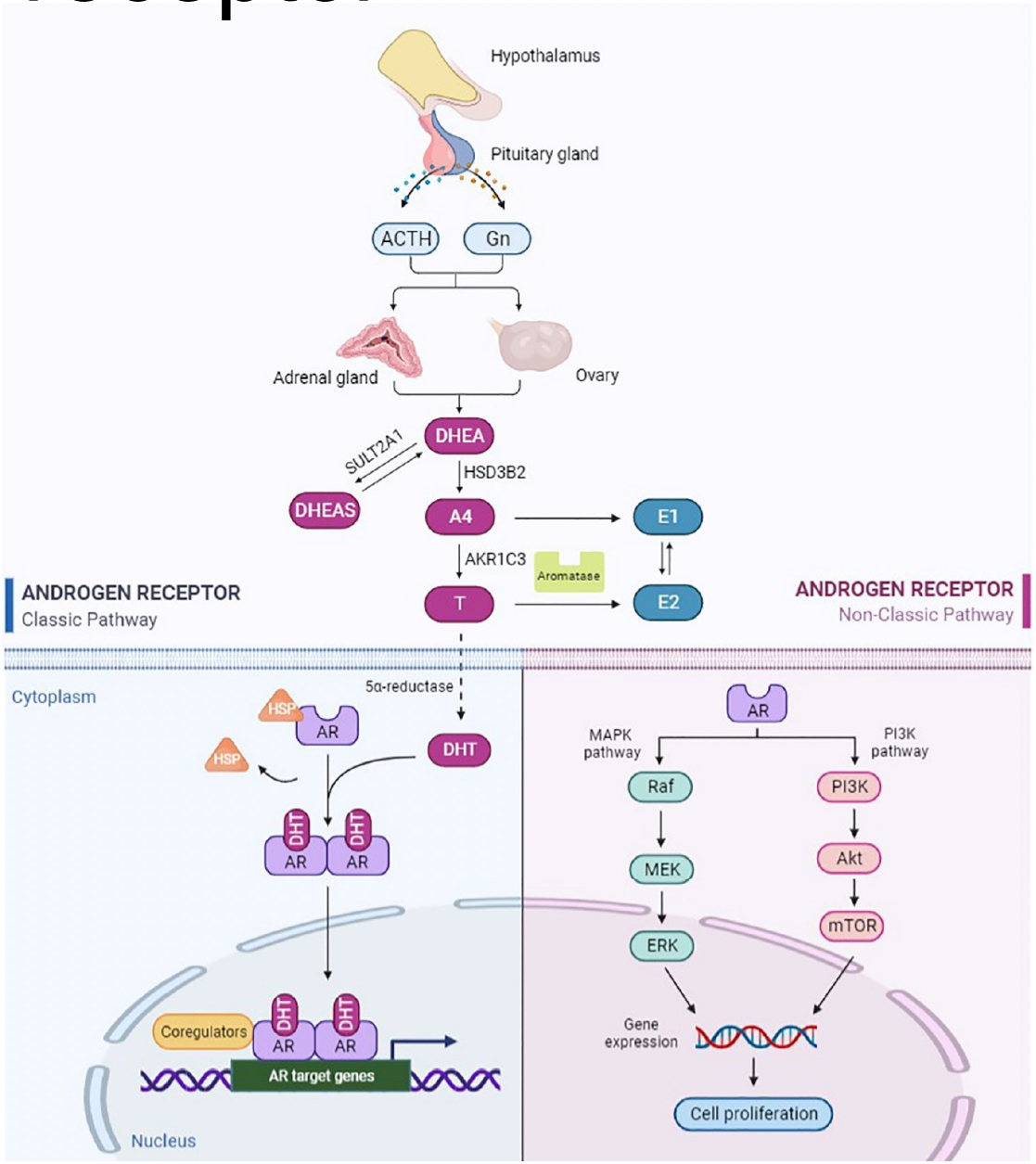
Deepening of voice, acne

Menstrual irregularities

Correlate to dose (mg/kg body weight) and length of the treatment

Ashfaq et al 2024

The androgen receptor



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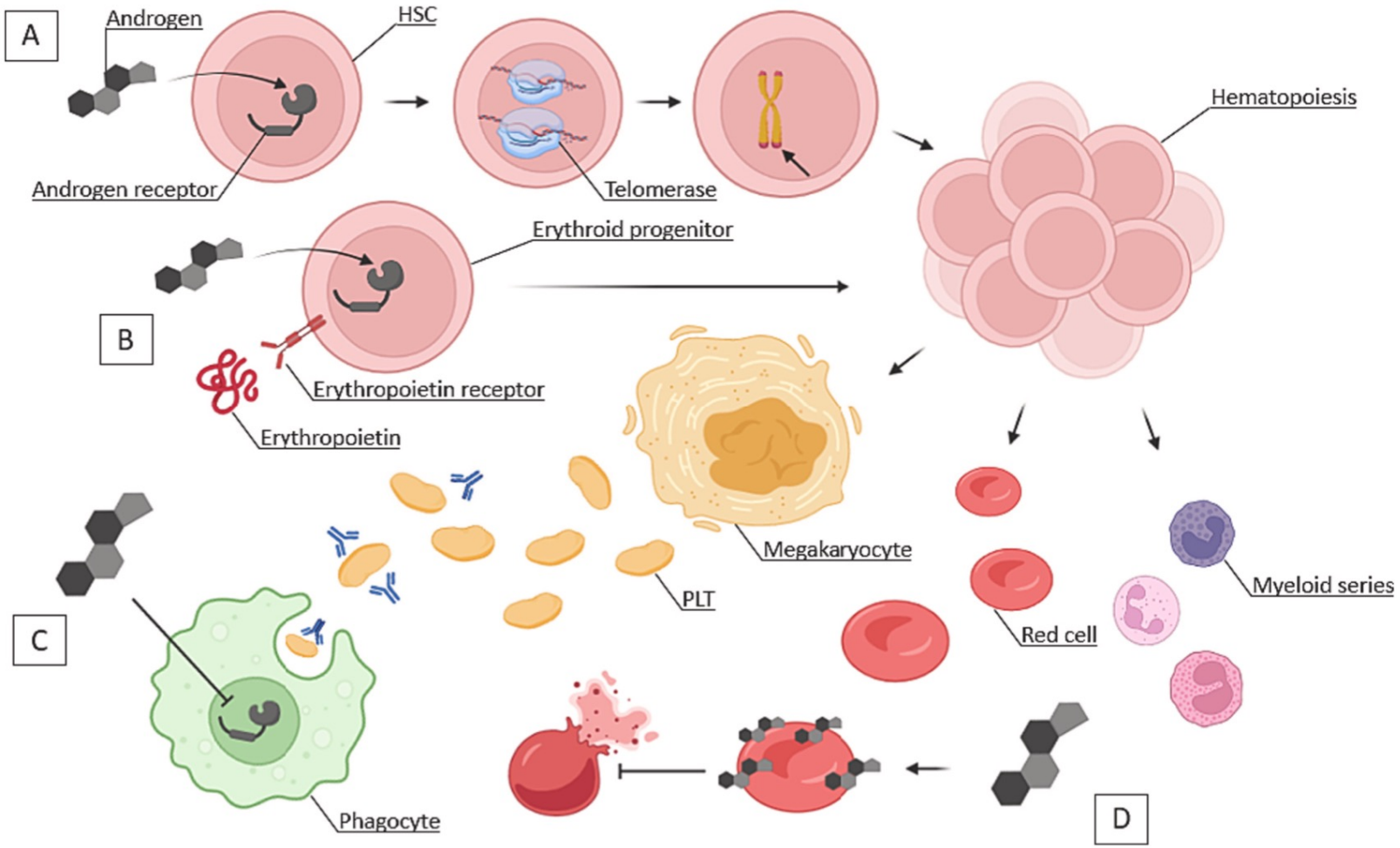
Lv et al 2022

Potential mechanisms of action



Helios

Bosi et al 2023

Potential mechanisms of action

Stem Cell Reports
Article

ISSCR

OPEN ACCESS

Oxymetholone Therapy of Fanconi Anemia Suppresses Osteopontin Transcription and Induces Hematopoietic Stem Cell Cycling

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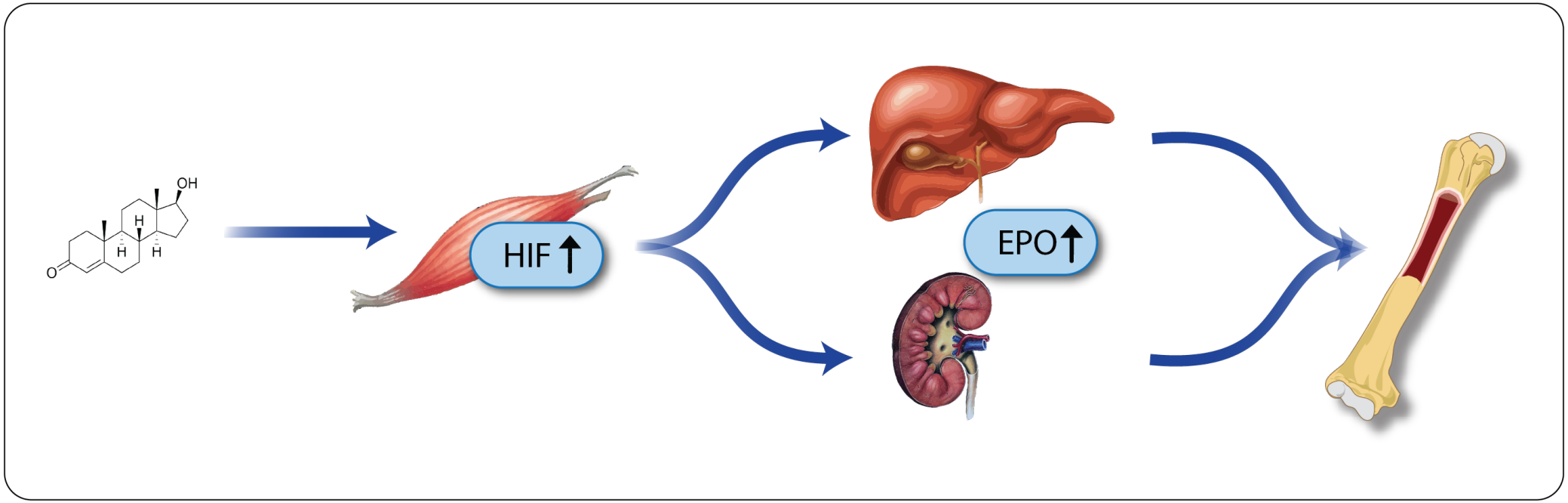
Hypothesis of indirect effects via HIF

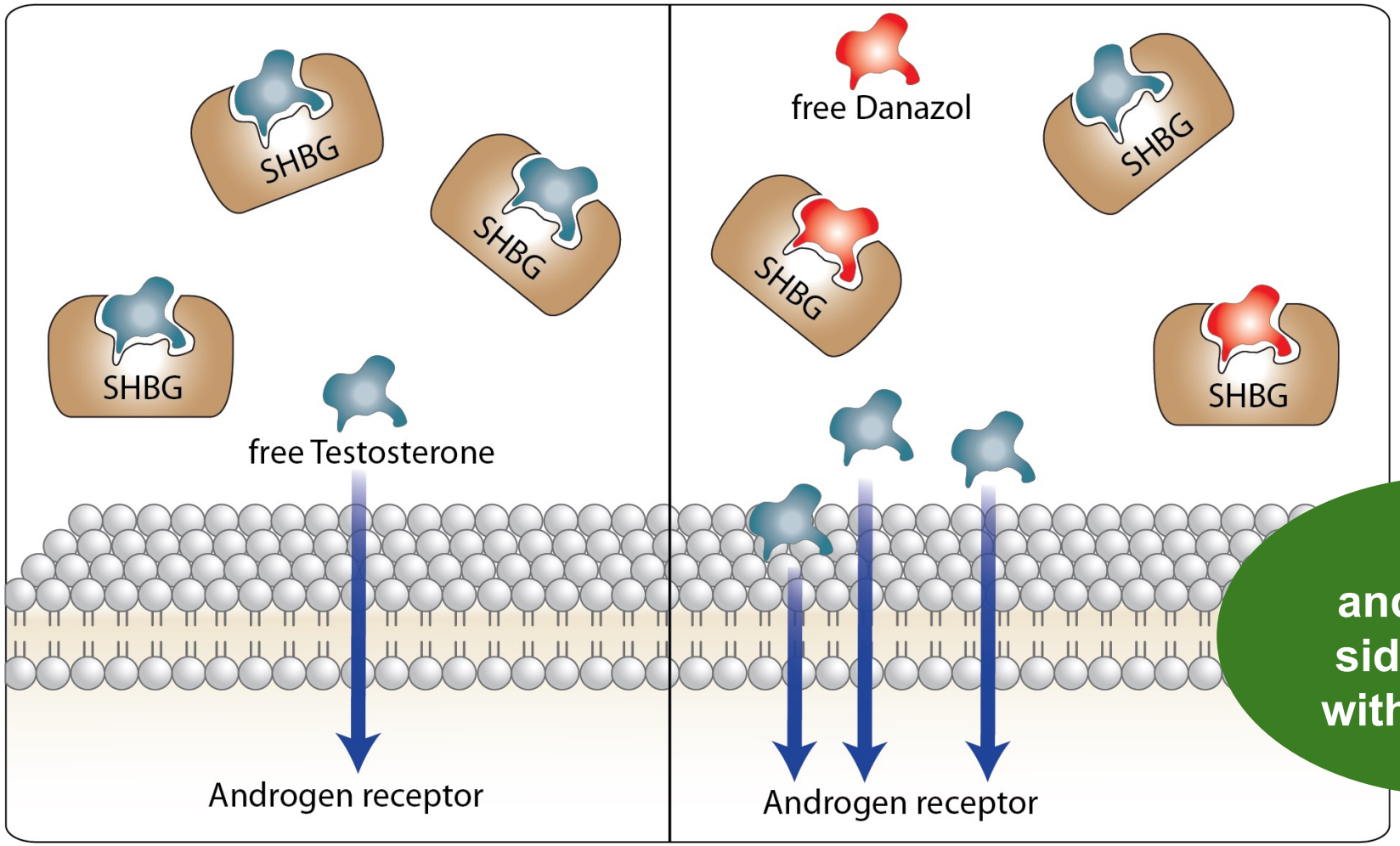
Rational: First improvement of blood counts generally after three months



HIF: Hypoxia induced factor, EPO: Erythropoietin

Hypothesis of indirect effects via SHBG

Rational: Best response of Danazol observed, if individuals are at start around the age of 10 years



SHBG: Sex hormone-binding globulin

Velleuer unpublished

Positive risk profile of androgenic medication

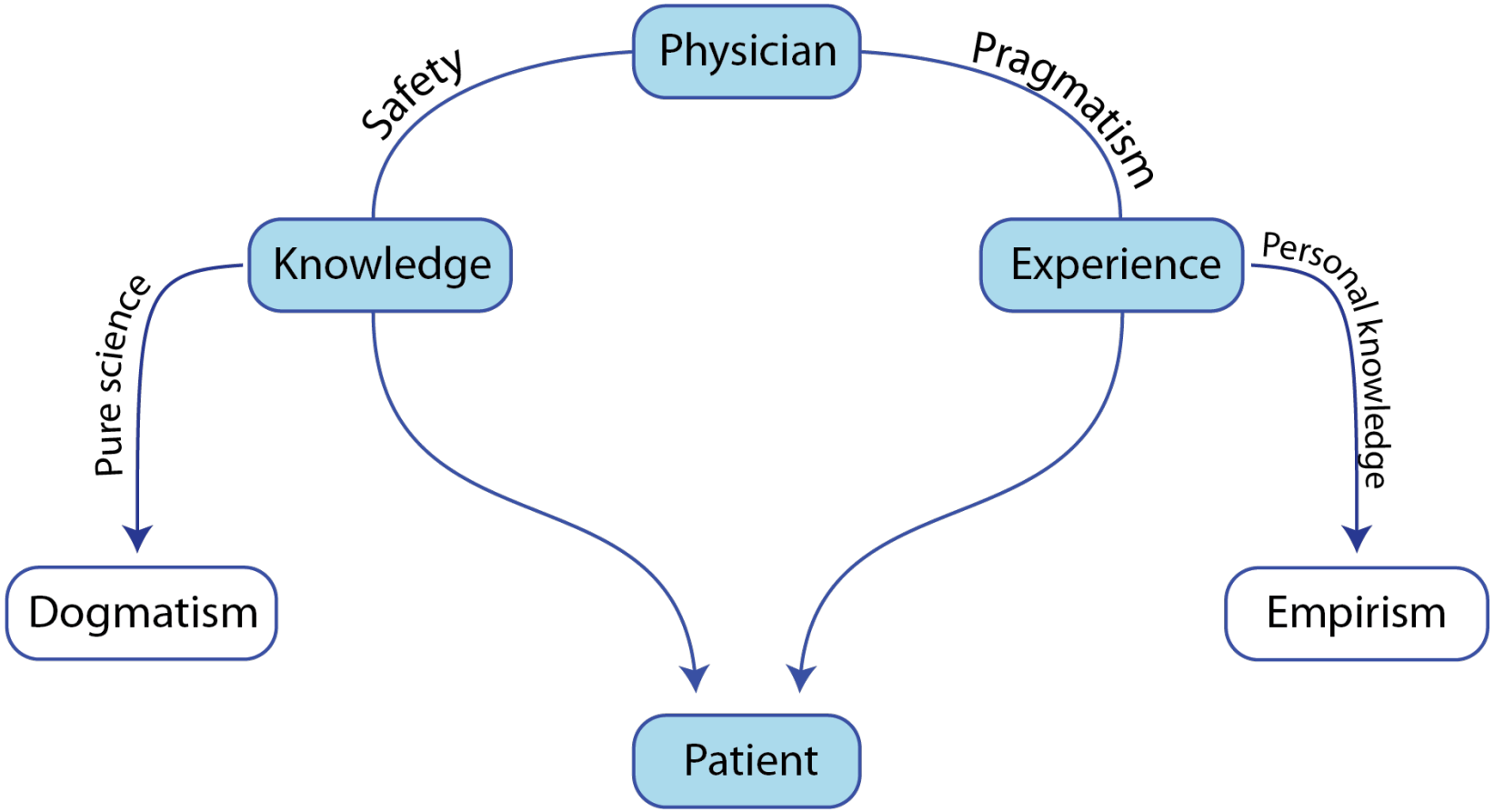
Advantages

- Many years of experience
- No short term and manageable long-term risks/side effects
- The profile of the side effects is well described and depends on the dose (mg/kg body weight) and the length of the therapy
- No negative impact on HSCT outcome

Risks

- They do not eliminate the risk for leukemia
- If FA individuals need a HSCT, they are older

Decision making in medicine



Labisch 2002

Thank you!

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