derived medicinal products in the future of Europe

OPEN DISCUSSION - AVAILABILITY OF PDMPS AND TIMELY ACCESS TO THERAPIES

Musings of the Moderator

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Defining shortages

A shortage, in economic terms, is a condition *where the quantity of a product or service demanded is greater than the quantity supplied* at the market price.

Investopedia

“Shortage” vs “Scarcity”

- **Note that shortage should not be confused with the economics term "scarcity."**
- **Shortages are usually *temporary* and can be corrected while scarcities tend to be *systemic* and cannot be readily resolved.**

Immunoglobulin – Supply and demand

Factors affecting supply

- Availability of plasma
- Manufacturing capacity
- Production and final yield
- Company commercial interest
- Government intervention

Money

- In 2022, the Italian public health system paid **96.7 million Euros** which returned to the system
  - 72% of current usage of albumin
  - 64% of current usage of normal immunoglobulins
  - 75% of ATIII
  - 98% of pd FVIII
  - 87% of PCC
  - Etc etc

- The residual usage cost the system **205.6 million Euros**

How long are companies going to wear this?

Italian contract fractionation – yields obtained

Partnership of regions and fractionator	Price for fractionation, EUR/kg	Yield, g/kg		2015 demand, g		Plasma for fractionation in 2017, kg	Plasma needed for self-sufficiency, kg		Present % of self-sufficiency	
		albumin	Ig	albumin	Ig		albumin	Ig	albumin	Ig
NAIP (CSL Behring)	94.60	25.0	4.9	5,105,358	931,743	194,993	204,214	190,152	95	103
RIPP (Kedrion/ Grifols)	118.00	26.0	4.1	8,880,723	1,093,923	206,067	341,435	266,810	60	77
PLANET (Baxter/Baxalta)	99.85	25.3	5.0	11,984,644	1,416,880	181,536	473,701	283,376	47	64
ACCORDO (Kedrion old contract)	144.00	25.7	3.7	9,404,018	1,191,762	245,126	365,915	322,098	67	76
Italy				**35,374,743**	**4,634,308**	**827,720**	**1,377,893**	**1,162,000**	**66**	**77**

De Angelis V, Breda A Transfus Med Hemother (2019)

Commerce ?

The growing importance of achieving national self-sufficiency in immunoglobulin in Italy. The emergence of a national imperative

Albert Farrugia[1,3], Giuliano Grazzini[2,3], Isabella Quinti[4], Fabio Candura[3], Samantha Profili[3], Giancarlo M. Liumbruno[3]

It should be noted that manufacturers allocate their products to specific countries according to the price obtained in that market i.e. ***the product follows the price****. This results in higher priced markets receiving preferential allocation. Companies seek the highly priced US market and any products approved for this market will be drawn into it before any other markets are satisfied.*

Government ?

“Exports reduce the amount of immunoglobulin available to [American] patients. Blood and plasma donors provide a precious community resource with the expectation [their donations] will benefit their neighbours and countrymen, particularly in times of shortage. Yet exports of immunoglobulin made from US plasma held constant in 1997, at more than 20% of total production, even as domestic supplies fell by 10%. That is very troubling to many patients, and it is an issue that must be addressed by the

Immunoglobulin – Supply and demand

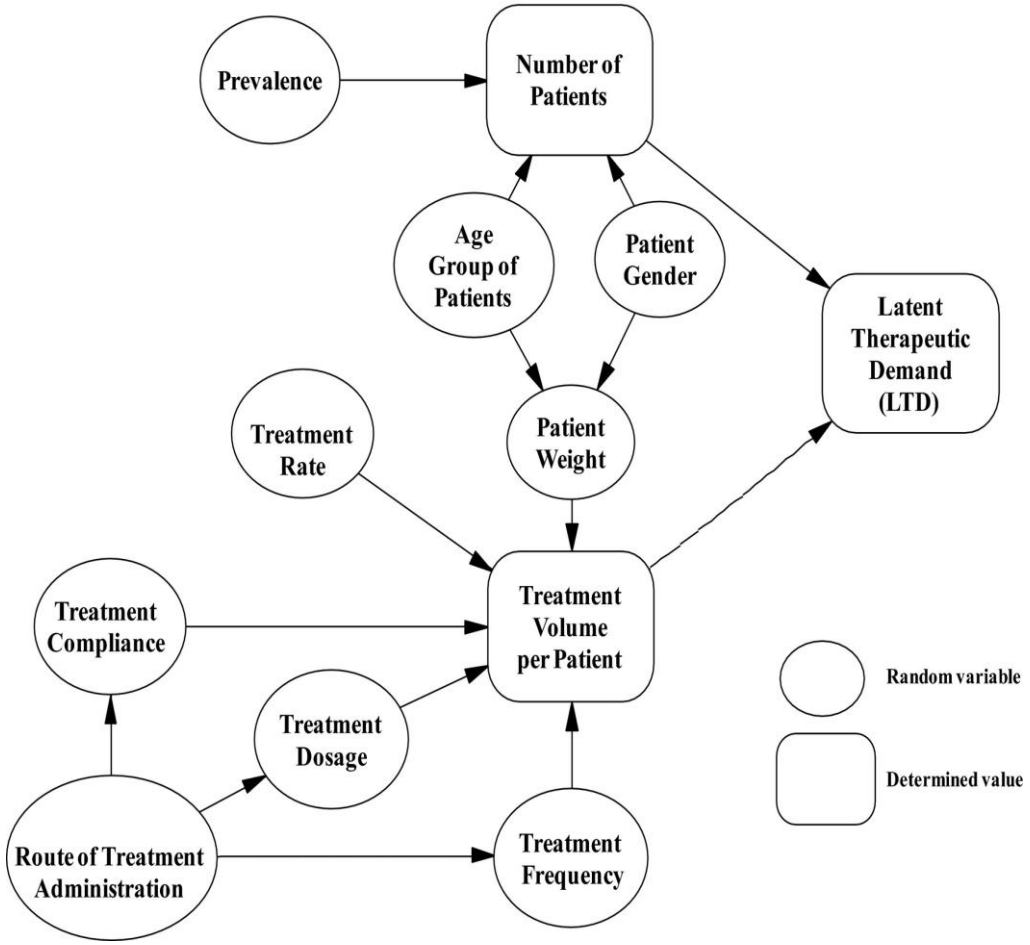
Factors affecting demand

- Diagnostic provision
- Status of health care
- Alternative therapies

The concept of Latent Therapeutic Demand

- *Usage* approaches *sufficiency* as supply approaches the *latent therapeutic demand*

- We define Latent Therapeutic Demand (LTD) as *the underlying demand that represents how physicians would prescribe treatment and how patients would comply with the prescribed treatment if ample supplies were available and affordable, and access to therapy was unencumbered by issues other than evidence-based clinical need, such as*



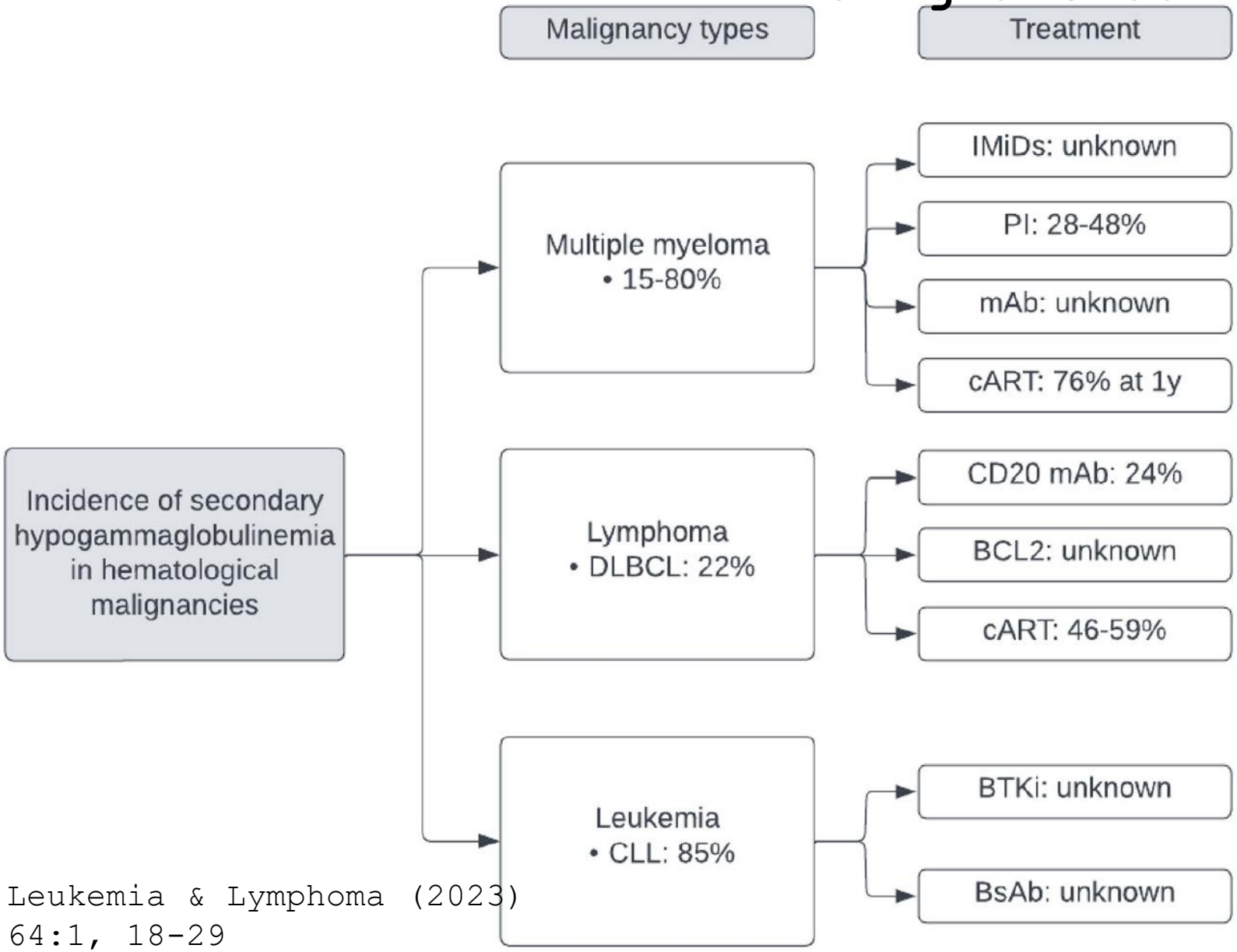
- Stonebraker JS, Farrugia A, Gathmann B, Orange JS. Modeling primary immunodeficiency disease epidemiology and its treatment to estimate latent therapeutic demand for immunoglobulin. J Clin Immunol. 2014 Feb;34(2):233-44.
- Stonebraker, J.S., Hajjar, J. and Orange, J.S. (2018), Latent therapeutic demand model for the immunoglobulin replacement therapy of primary immune deficiency disorders in the USA. Vox Sang, 113: 430-440.
- Farrugia A, Bansal M, Marjanovic I. Estimation of the latent therapeutic demand for immunoglobulin therapies in autoimmune neuropathies in the United States. Vox Sang. 2022

Latent therapeutic demand for IG in the USA
PIDs and neuropathies

Condition	Mean LTD immunoglobulin g/10^3 population
Common variable immune deficiency (CVID)	65.4 ± 73.6
X-linked agammaglobulinemia (XLA)	25.5 ± 27.6
Severe combined immune deficiency (SCID)	13.4 ± 13.5
Wiskott–Aldrich syndrome (WAS)	0.5 ± 0.4
hyper IGM syndrome (HIGM)	0.3 ± 0.3
Chronic inflammatory demyelinating polyneuropathy (CIDP)	83.05 ± 24.5
Guillain–Barré syndrome (GBS)	6.1 ± 3.2
Multifocal motor neuropathy (MMN)	36.1 ± 25.5
Total mean immunoglobulin consumption	230.35

Vox Sang. 2022;117:208–219

Incidence of secondary hypogammaglobulinemia in hematological malignancies



Leukemia & Lymphoma (2023) 64:1, 18-29

Area	Grade of evidence
IBW-based dosing	Moderate, from retrospective multicentre analysis
Duration of IG replacement therapy	Low
Cessation rules for	Low

Disruptive technology

CNS Drugs (2023) 37:467–473
https://doi.org/10.1007/s40263-023-01000-z

ADIS DRUG Q&A

Efgartigimod Alfa in Generalised Myasthenia Gravis: A Profile of Its Use

Young-A Heo[1]

Intravenous efgartigimod alfa (also known as efgartigimod alfa-fcab in the USA; Vyvgart ®) is the ***first neonatal Fc receptor antagonist approved*** in several countries worldwide, including the USA and EU for the treatment of generalised myasthenia gravis (gMG) in adults who are anti-acetylcholine receptor (AChR) antibody positive, and in Japan for the treatment of gMG regardless of antibody status. In the double-blind, placebo-controlled phase 3 ADAPT trial in patients with gMG, efgartigimod alfa significantly and rapidly reduced disease burden and improved muscle strength and quality of life compared with placebo. ***The clinical benefits of efgartigimod alfa were durable and reproducible.*** Furthermore, in an interim analysis of the ongoing open-label phase 3 ADAPT+ extension trial,

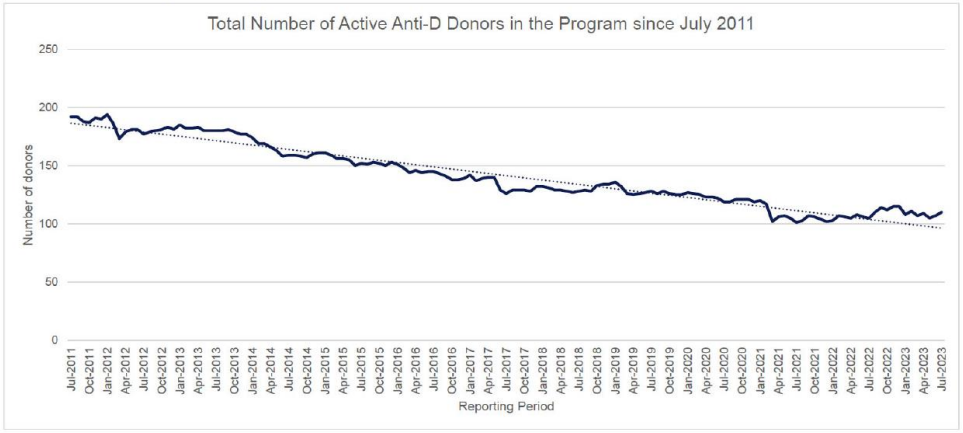
The most important plasma product

Present situation at Sanquin

- 2020: Decision to stop collection of anti-D plasma because
  - Sanquin Plasma Products did not continue specific IgG plasmaproducts
  - Extra costs for optimization of program
  - No market for relatively small batch of Dutch anti-D plasma

Challenge | Anti-D Supply decline of donor

5.2. National summary of Rh Program active donors since July 2011



Anti-D shortage – US authorities

bulin Shortages

an College of Obstetricians and Gynecol

Rho(D) Immune Globulin Shortages

Practice Advisory | March 2024

This Practice Advisory was developed by the American College of Obstetricians and Gynecologists.

The U.S. Food and Drug Administration, American Society of Health-System Pharmacists (ASHP), and Association for the Advancement of Blood & Biotherapies are reporting Rho(D) immune globulin (RhIg) shortages [1] [2] [3]. If a preferred brand of RhIg (eg, RhoGAM) is not available, an equivalent product (eg, HyperRHO S/D, Rhophylac) may be substituted [2] [4]. According to ASHP, shortage of RhoGAM (manufactured by Kedrion) is the main reason for the supply issues and other manufacturers (eg, Grifols and CSL Behring) have available supply [2].

The American College of Obstetricians and Gynecologists will continue to actively monitor the situation and update this Practice Advisory with additional information as needed. For more information on RhIg prophylaxis, see the following ACOG guidance documents:

REGULATORY UPDATE: FDA ANNOUNCES SHORTAGES OF RHO(D) IMMUNE GLOBULIN

February 14, 2024

The Food and Drug Administration recently issued **information about current shortages** of several products that are regulated by its Center for Biologics Evaluation and Research (CBER), some of which have relevance to the blood and biotherapies community.

Of particular note, FDA reported that there is currently a shortage of Rho(D) Immune Globulin. According to FDA, this shortage is caused by "a reduction of supply due to increase in demand."

AABB contacted Kedrion Biopharma Inc., a manufacturer of Rho(D) Immune Globulin. The company shared a letter it has sent to medical professionals and relevant organizations. "Due to various external factors beyond our control affecting the entire US anti-D plasma market, coupled with m
you that we anticipate not having the usual supply to meet demand ir
added that its "commitment to transparent communication and proac

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