PEG-ASPARAGINASE DESENSITIZATION

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LEARNING OBJECTIVES

Describe **novel therapy alternatives** for patients with L-asparaginase hypersensitivity.

Understand **allergy test** in hypersensitivity to chemotherapy agents.

Highlight the importance of working in a **multidisciplinary team** to achieve an integrated care.

CONFLICT OF INTEREST DISCLOSE

I have no potential conflicts of interest to report.

PATIENT MEDICAL HISTORY

AGE: 12

GENDER: male

ALLERGIES: asparaginase

Sept 2022

Diagnosis: ALL-B High risk

Complete remission

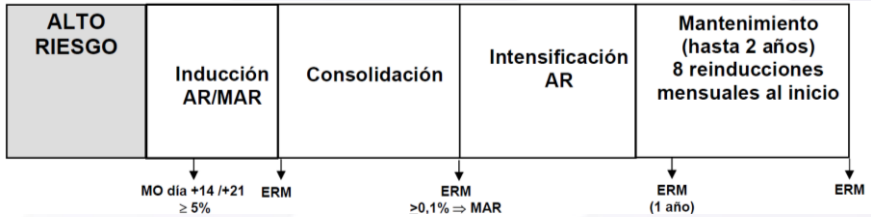
Late extramedullary relapse

April 2012 | May 2014 | July 2022

ALL TREATMENT

April 2012

LAL/SEHOP-PETHEMA 2005



LAL/SEHOP-PETHEMA 2005 HR	
INDUCTION	26/04/2012
CONSOLIDATION	12/06/2012
INTENSIFICATION	10/08/2012
MAINTENANCE	17/10/2012 - 01/05/2014

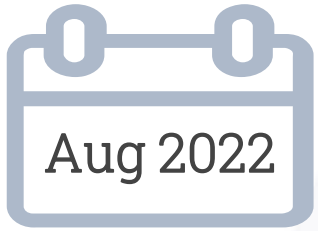
Phase	Admin date	Drug	Dose
Induction	14/05/12	Pegaspargase	2.500 UI/m^2
Intensification	10/08/12	Pegaspargase	2.500 UI/m^2
Maintenance	17/10/12	Asp E. Coli	10.000 UI/m^2
Maintenance	12/12/12	Asp E. Coli	10.000 UI/m^2
Maintenance	06/02/13	Asp E. Coli	10.000 UI/m^2
Maintenance	03/04/13	Asp Erwinia	20.000 UI/m^2

E. COLI ASPARAGINASE HIPERSENSITIVITY REACTION

Symptoms (06/02/13): 10 min after 3rd dose of asparaginase. Nausea, vomiting, urticaria, disappearing after administration of dexchlorpheniramine 2 mg, methylprednisolone 25 mg. No respiratory afection or angioedema. Symptoms reappear after 1h 30min, requiring hospitalization.

MAINTENANCE COMPLETED WITH ONE LAST DOSE OF ERWINIA ASPARAGINASE

ALL TREATMENT



LAL/SEHOP-PETHEMA 2015 FIRST RELAPSE
Standard risk

09/08/2022

Week.	1-4	5-8	9-12	13-15	16-18	19-21	22-24	25-27	28-131
	Induction	Cons. 1	Cons. 2	Cons. 3	Cons. 4	Cons. 5	Cons. 6	Cons. 7	Maintenance

19/09/2022

3rd GRADE IMMEDIATE HYPERSENSITIVITY REACTION AFTER ERWINIA ADMINISTRATION

Symptoms (19/09/22): tachycardia, generalized erythema, itching, lip angioedema, swallowing difficulties, dyspnea ($SatO_2$ < 85%), cough, abdominal pain, vomiting. Needs: corticosteroid therapy, epinephrine, antihistamines.

NEXT DOSES OF ERWINIA DISCONTINUED

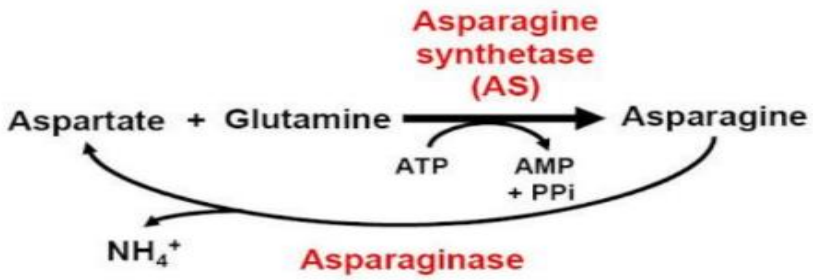
Phase	Admin date	Drug	Dose
Induction	11/08/22	Asp Erwinia	20.000 UI/m²/48 h (x6)
Induction	26/08/22	Asp Erwinia	20.000 UI/m²/48 h (x6)
Cons 1	19/09/22	Asp Erwinia	20.000 UI/m²/48 h

31/08

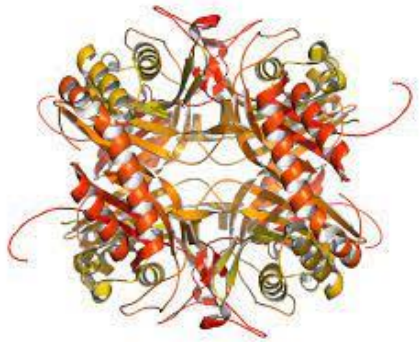
AAL*= 305 UI/l

AAL*= Asparaginase activity levels

ASPARAGINASE



Side-effect profile ✓
Hypersensitivity ✗
Silent inactivation ✗



- **First line therapy**.
- **Asparagina depletion**: essential part of ALL treatment.
- Bacterial origin → Specific ab → Hypersensitivity
- Incidence 30 % (re-exposure)
- Induction with PEGASPARGASA
- **Switching** in case of silent inactivation / hypersensitivity
- **Therapeutic drug monitoring** of EACH DOSE (Hospital de la Santa Creu i Sant Pau).

1000 UI/m²/dosis ⇄ 1 = 6 ⇄ 20.000 UI/m²/48 h

Pegaspargasa Oncaspar®

$t_{1/2}$ (5,5-7 d)

Day +7: AAL> 100 UI/l
Day +14: AAL> 20 UI/l

Erwinia Erwinase®

$t_{1/2}$ =16 h

Post-48 h: AAL> 20 UI/l

WHAT COULD WE DO NOW?

PHARMACY

ALLERGOLOGY

PEDIATRIC ONCOLOGY

DESENSITIZATION

NO TIME FOR ALLERGY SKIN TEST

05/10/22

- Administering slow increases of administration speed
- 16 steps (v)
- 4 infusion bags
- Saturate IgE receptors
- Avoiding granulocyte and mast cell degranulation.

1. 0,75 UI pegaspargasa / 250 ml NaCl 0,9%
2. 15 UI pegaspargasa / 250 ml NaCl 0,9%
3. 150 UI pegaspargasa / 250 ml NaCl 0,9%
4. 1488,16 UI pegaspargasa / 250 ml NaCl 0,9%

Desensitization protocol (Pegaspargasa)

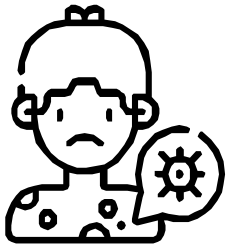
Dose: 1500 UI
$V_{infusion}$ max: 80 ml/h
t: 6,6 h

Premedication:

Cetirizine 10 mg
Famotidine 20 mg
ASA 300 mg
Montelukast 10 mg

PEGASPARGASE HYPERSENSITIVITY REACTION

Symptoms: 22/11/22 (2nd cycle) while administering 3rd infusion bag.
Abdominal pain, erythema, itching. Required: epinephrine, methylprednisolone, dexchlorpheniramine, famotidine, hydroxyzine



TESTING

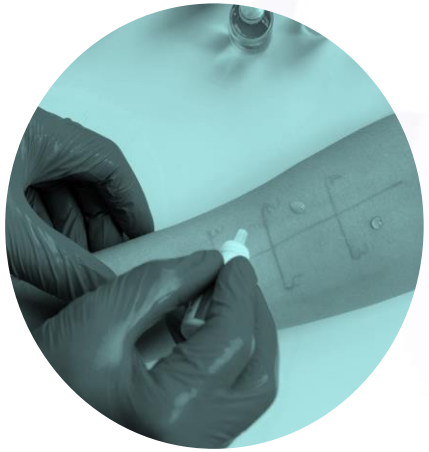
Skin allergy test

01/12/22 (day +9)

Prick test: 750 UI/ml

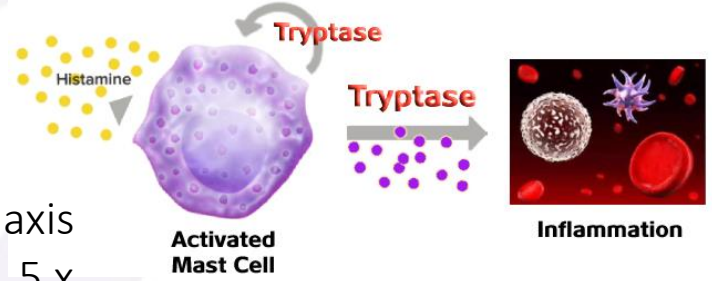
Intradermal test:

0,75 UI/ml; 7,5 UI/ml; 75 UI/ml; 750 UI/ml



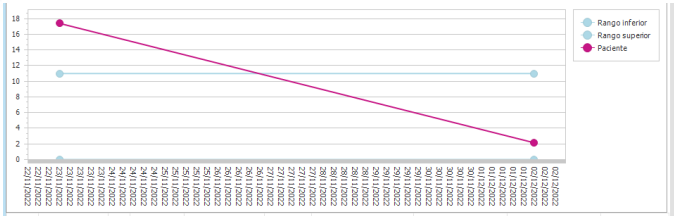
Tryptase

- Marker for mast cell activation.
- Serum levels after 30-120 min.
- Baseline: 2-3 weeks after anaphylaxis
- Tryptase levels greater than 2 x (1,5 x baseline) indicates type I HSR



Baseline tryptase: 2,2 ug/l

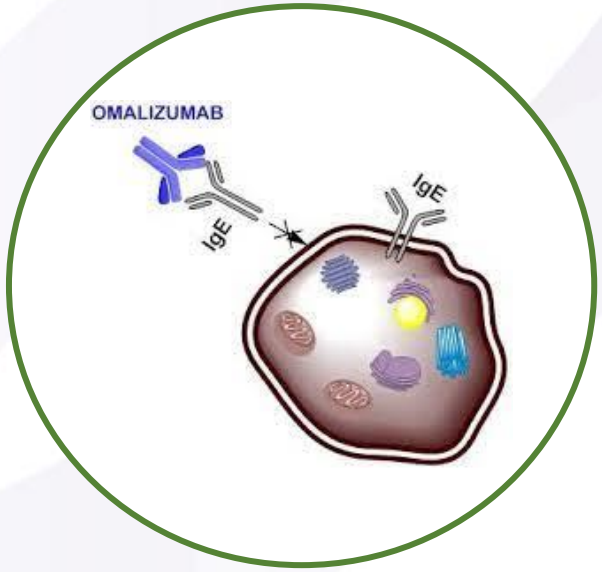
Tryptase*: 17,4 ug/l

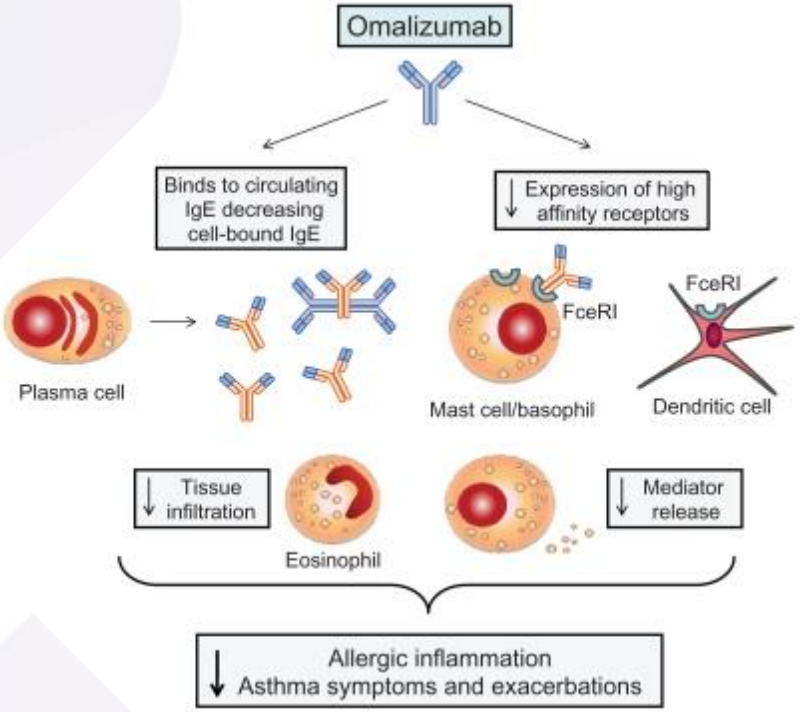


#	Nº Petición	E	Resultado	Rango referencia	Muestra	Fecha toma/extracción	Activación	Validación	Entrega
	01544580		2,2 µg/L	0,0 - 11	SUERO	02/12/2022 0:00:00	02/12/2022 8:53:37	06/12/2022 17:25	02/12/2022
	01638250	↑	17,4 µg/L	0,0 - 11	SUERO	23/11/2022 0:00:00	23/11/2022 8:43:25	24/11/2022 10:16	23/11/2022

OMALIZUMAB

- Anti-IgE recombinant humanized monoclonal antibody.
- Also used in protocols for chemotherapy desensitization (platinum, taxanes).
- Different dose regimen recommended.





- FIRST DESENSITIZATION CYCLE WITH OMALIZUMAB: 600 mg sc on day -14; 300 mg sc on day -1.
- NEXT DESENSITIZATIONS: 300 mg sc days -1.

Bumbacea RS, Ali S, Corcea SL, et al. Omalizumab for successful chemotherapy desensitisation: What we know so far. *Clin Transl Allergy*. 2021;11(10):e12086. Published 2021 Dec 13. doi:10.1002/clt2.12086

ASPARAGINASE ADMINISTERED DOSES

LAL/SEHOP -PETHEMA 2005 (HR)

Phase	Admin day	Drug	Dose
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Intensification	10/08/12	Pegaspargase	2.500 UI/m^2
Maintenance	17/10/12	Asp E. Coli	10.000 UI/m^2
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LAL/SEHOP -PETHEMA 2015 FIRST RELAPSE (SR)

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Induction	26/08/22	Asp Erwinia	20.000 UI/m^2/48 h (x6)
Cons 1	19/09/22	Asp Erwinia	20.000 UI/m^2/48 h (x6
Cons 1	05/10/22	Pegaspargase desens	1.000 UI/m^2
Cons 3	22/11/22	Pegaspargase desens	1.000 UI/m^2
Cons 4	20/12/22	Pegaspargase desens + OMALI	1.000 UI/m^2
Cons 5	09/01/23	Pegaspargase desens + OMALI	1.000 UI/m^2
Cons 6	31/01/23	Pegaspargase desens + OMALI	1.000 UI/m^2

31/08 — AAL= 305 UI/l

05/10 — AAL (+7)= 777 UI/l

22/11 — AAL (+7)= 528 UI/l
AAL (+14)= 440 UI/l

20/12 — AAL (+7)= 499 UI/l
AAL (+14)= <5 UI/l

09/01 — AAL (+7)= 399 UI/l
AAL (+14)= 310 UI/l

CURRENT SITUATION

- LAL/SEHOP-PETHEMA 2015 RE: Consolidation 7
- Peg-asparraginasa desensitization regimen following the protocol, with extra premedication:
  - Cetirizine 10 mg
  - Famotidine 20 mg
  - ASA 300 mg
  - Montelukast 10 mg
  - Omalizumab 900 mg (600 mg on the previous week to the first desensitization administering omalizumab, followed by 300 mg on the day before each desensitization).

GREAT TOLERANCE TO L-ASPARAGINASE

TO CONCLUDE

Pharmacy validation of prescriptions in onco-hematological patients is critical. Not only allows it to detect and **to avoid prescription errors**, but it enables the pharmacist **to get involved in patient's care**.

Desensitization is an alternative for ALL patients suffering from hypersensitivity to both asparaginase types. The **off-label use of omalizumab**, as part of the premedication helps to achieve a successful chemotherapy desensitization.

Pharmacists play a very important role as a nexus between professionals in hospitals to **work together**.

Thank you very much!

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