CP-086

CD69 A>G (RS11052877) GENETIC POLYMORPHISM ON THE RESPONSE OF TOCILIZUMAB IN RHEUMATOID ARTHRITIS PATIENTS.

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Objectives: CD69 receptor is a C-lectine transmembrane protein expressed by T, B and Natural Killer (NK) cells. This receptor is involved on the production and regulation of these cells and are involved in Interleukin-6 (IL-6) production.

Interleukin 6 (IL-6) is a multifunctional glicoprotein involved in inmune response, inflammation and bone metabolism; IL-6 makes significant contributions to such autoimmune and inflammatory diseases as rheumatoid arthritis (RA).

→*The aim of this study is evaluate the role of CD69 A>G (rs11052877) genetic polymorphism on the response of Tocilizumab in RA patients.*

Methods: The CD69 A>G (rs11052877) genetic polymorphism was genotyped using predesigned **TaqMan®** genotyping assays technology and analyzed on a ViiA7® Real-time PCR system. Clinical response was evaluated **at 3, 6, 9 and 12 months** after the first infusion of the drug with the use of the 28-joint disease activity score criteria **(DAS28)** and good responders were classified **according to EULAR criteria**.

→EULAR good response was defined as a change of DAS28>1.2 and DAS28 ≤3.2.

RESULTS

CD69 A>G vs EULAR Good Response

		RESPONDERS NO n(%)	RESPONDERS YES n(%)	OR (95% C.I.)	P-value
3 months N=124	G/G	8 (11.9)	12 (21.1)	1.97 (0.74-5.21)	0.17
	A/G or A/A	59 (88.1)	45 (79)		
6 months N=142	G/G	6 (10.9)	16 (18.4)	1.84 (0.67-5.03)	0.22
	A/G or A/A	49 (89.1)	71 (81.6)		
9 months N=120	G/G	5 (12.8)	16 (19.8)	1.67 (0.56-4.96)	0.34
	A/G or A/A	34 (87.2)	65 (80.2)		
12 months N=139	G/G	2 (6.1)	18 (17)	3.17 (0.70-14.45)	0.09
	A/G or A/A	31 (93.9)	88 (83)		

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CONCLUSIONS:

These results show that CD69 A>G (rs11052877) genetic polymorphism by itself is not useful as a predictor of Tocilizumab response in R.A. patients but its influence should be further studied.

Genyo

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eahp european association of hospital pharmacists making the difference in medication

Evaluation of clinical, economic and organisational impacts of pharmacists' interventions on immunosuppressive therapy management among lung transplant outpatients

CP–109
ATC L04

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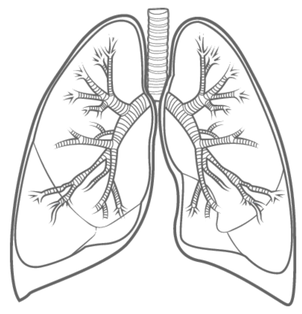
Background and purpose

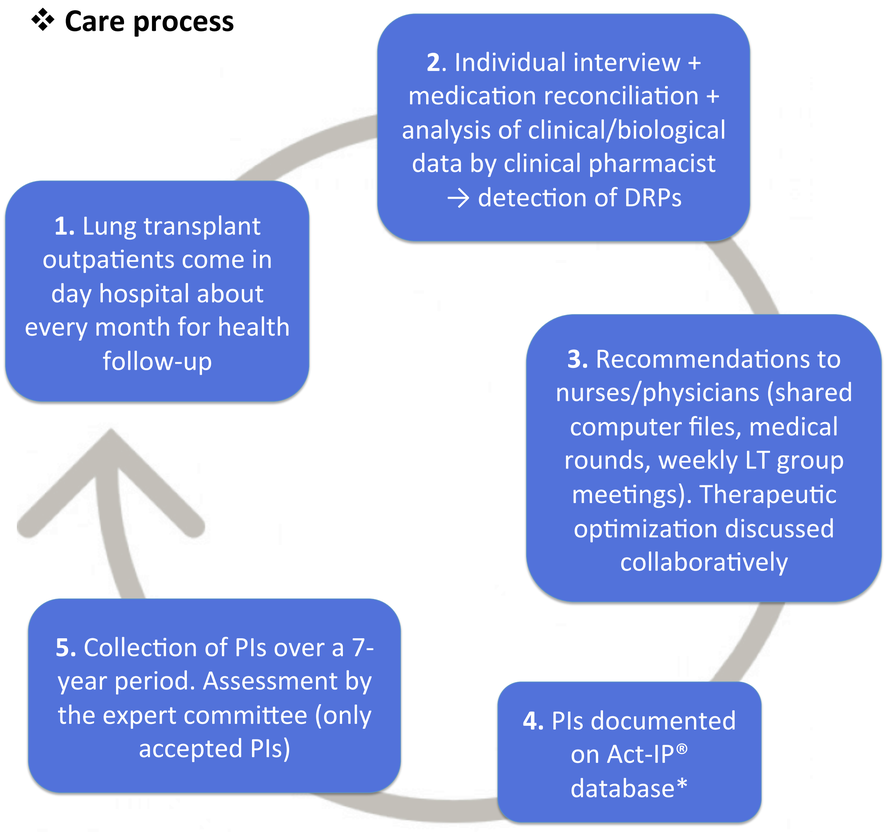
Lung transplant recipients require multidisciplinary care because of therapeutic management complexity, such as **life-long immunosuppressive therapy (1,2)**. Clinical pharmacists are able to detect **drug related problems (DRPs)** and provide recommendations to physicians for improving patient care. The potential significance of **pharmacists' interventions (PIs)** has never been studied by a multidimensional approach in **lung transplantation (LT) (3)**.



Purpose: To assess the **clinical, economic and organisational impacts** of PIs on immunosuppressive therapy management among lung transplant outpatients.

Population and methods

❖ **Care process**



* French Society of Clinical Pharmacy's tool (SFPC): patient's features, description of the DRP and the PI according to the SFPC classification

❖ **Retrospective analysis** of PIs from 1st January 2009 to 31th December 2015
❖ Study population: 234 lung transplant patients followed at Grenoble University Hospital
❖ PIs impact evaluation: ▪ **Expert committee**: 1 pneumologist, 1 pharmacovigilant, 1 clinical pharmacist
▪ Tool: « **CLEO** » **scale** (4)

	Score	Impact	Definition: the clinical impact is evaluated according to the most likely case expected
CLINICAL IMPACT	-1C	Nuisible	The PI can lead to adverse outcomes on clinical status, knowledge, satisfaction, patient adherence and/or quality of life of the patient
	0C	Nul	The PI can have no influence on the patient regarding the clinical status, knowledge, satisfaction, patient adherence and/or quality of life of the patient
	1C	Minor	The PI can improve knowledge, satisfaction, medication adherence and/or quality of life OR the PI can prevent damage that does not require monitoring/treatment
	2C	Moderate	The PI can prevent harm that requires further monitoring/treatment, but does not lead or do not extend a hospital stay of the patient
	3C	Major	The PI can prevent harm which causes or lengthens a hospital stay OR causes permanent disability or handicap
	4C	Vital	The PI can prevent an accident that causes a potentially intensive care or death of the patient
	ND	Non-determined	The available information does not determine the clinical impact
ECONOMIC IMPACT	-1E	Increase of cost	The PI increases the cost of the drug treatment of the patient
	0E	No change	The PI does not change the cost of the drug treatment of the patient
	1E	Decrease of cost	The PI saves the cost of the drug treatment of the patient
	ND	Non-determined	The available information does not allow to determine the economic impact
ORGANI-SATIONAL IMPACT	-1O	Desfavorable	The PI reduces the quality of care process
	0O	Null	The PI does not change the quality of care process
	1O	Favorable	The PI increases the quality of care process
	ND	Non-determined	The available information does not identify the organisational impact

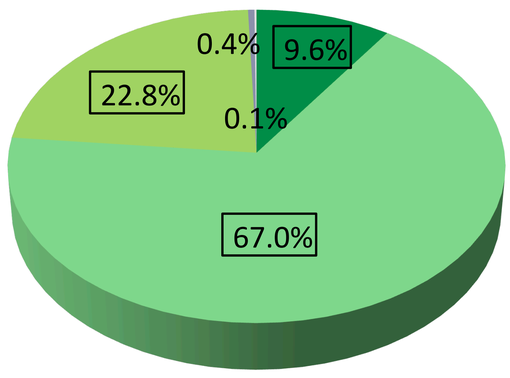
Results

➢ Overall, 1568 PIs performed, including 713 (45.5%) related to immunosuppressive drugs. Among PIs related to immunosuppressants (IS):
- Physician acceptance rate of PIs: **94% (N=670)**
- IS involved in PIs: **tacrolimus (58.5%)**, everolimus (26.5%), glucocorticoids (8.0%), mycophenolic acid (5.0%), ciclosporin (1.0%), azathioprine (1.0%)

Example:

Drug 1	Drug 2	Cli.	Eco.	Org.	Problem	Intervention
Tacrolimus 2mg/day	Voriconazole 400mg/day	**3C**	**1E**	**0O**	Voriconazole for pulmonary aspergillosis: strong enzymatic inhibitor of CYP 450 3A4 leading to ↗ of tacrolimus residual level to 20.3µg/L (target: 5-10µg/L)	Decrease tacrolimus dosage to 1mg/day + drug monitoring Day +7

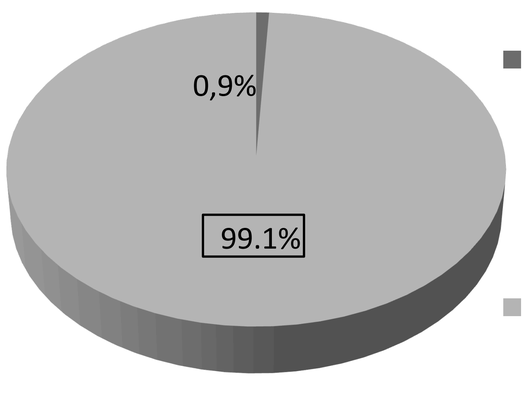
❖ Clinical impact



N=670

- 3C ⟶ Drug-drug interactions between IS and antifungals (56.0%), supratherapeutic dosage (25.0%)
- 2C ⟶ Supratherapeutic dosage (32.7%), subtherapeutic dosage (42.1%), adverse drug reaction (11.6%)
- 1C ⟶ Supratherapeutic dosage (41.2%), drug monitoring (17.0%), adverse drug reaction (14.4%)
- 0C ⟶ Dose adjustment without any impact
- ND ⟶ Lack of information

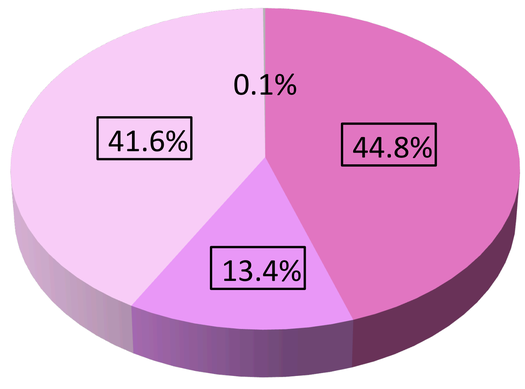
❖ Organisational impact



N=670

- -1O ⟶ Immunosuppressant « area under curve » monitoring
- 0O ⟶ No organisational impact on quality of care process from health care providers' viewpoint

❖ Economic impact



N=670

- 1E ⟶ Dose decrease or drug discontinuation due to supratherapeutic dosage, adverse drug reaction, infectious disease or no indication (antifungals)
- 0E ⟶ Usual drug monitoring (32.2%), drug switch with same cost (52.2%)
- -1E ⟶ Dose increase (74.9%), adding of drug monitoring (24.4%)
- ND ⟶ Lack of information

Discussion - Conclusion

To our knowledge, this is the first study assessing not only clinical, but also economic and organisational-related dimensions of PIs in LT. We used a validated tool (CLEO) to assess potential significance of PIs. Our structured pharmacist collaborative care program underlines that clinical pharmacist has a key role in lung transplant patients' management, as 10% of his PIs have a major clinical impact. His intervention is largely relevant (94% of PIs accepted), in order to optimize immunosuppressive therapy management and improve patient care.

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Patients

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EVALUATION OF THE CLINICAL SIGNIFICANCE AND VALUE OF A CLINICAL PHARMACY SERVICE AT A TEACHING HOSPITAL

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Background

Clinical pharmacy services (CPS) have been shown to provide significant clinical benefits on patient care. The paucity of literature reports within the Austrian healthcare system highlights that studies showing the evidence for CPS are urgently needed.

Purpose

To assess the clinical significance and value of the CPS by determining the number, type and clinical significance of identified drug-related problems (DRPs), the acceptance rate of suggested interventions and their benefit to inpatient care.

Methods

Two-phase mixed method:

1) Prospective descriptive study of number and type of identified DRPs, suggested interventions and their acceptance rate based on a validated classification-system[1]
2) Independent expert panel rating of the clinical significance of identified DRPs and the clinical value of suggested interventions based on a reliable rating-method[2]

Setting:

455-bed teaching hospital in Vienna; CPS across two surgical, two trauma, one cardiology and two internal medicine wards.

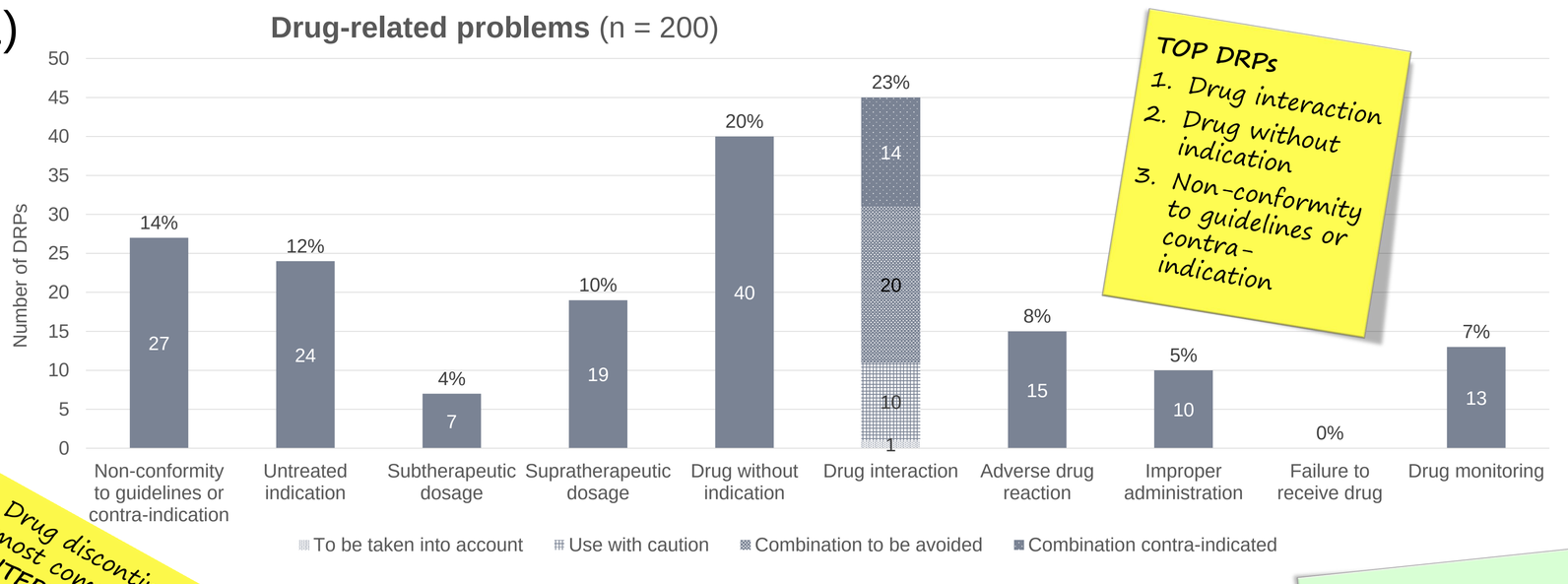
Sampling:

- All patients receiving the CPS during a 4-week data collection period
- Expert panel assessment carried out on randomly selected representative sample (confidence-level 95%)

Results

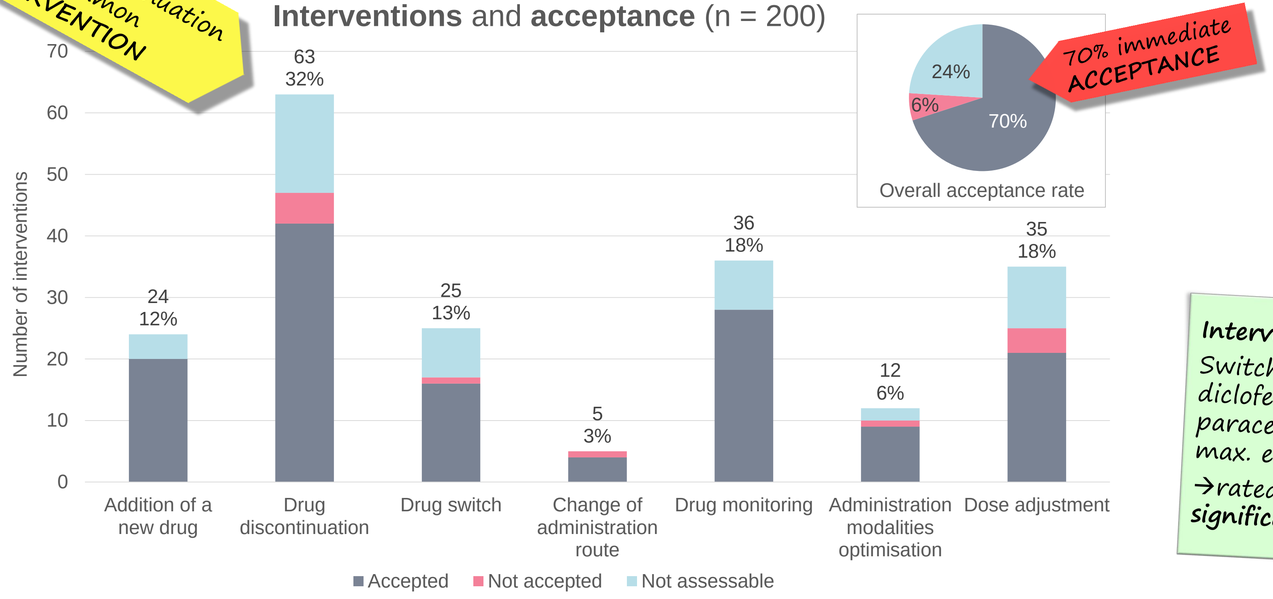
- 250 medication reviews in 162 patients (54% ♀)
- 200 DRPs, on average 1.2 (± 1.8) DRPs/patient
- 54% of patients at least one DRP
- Patients with DRPs: in average on 11.2 (± 4.0) drugs

1)



TOP DRPs
1. Drug interaction
2. Drug without indication
3. Non-conformity to guidelines or contra-indication

Drug discontinuation most common INTERVENTION

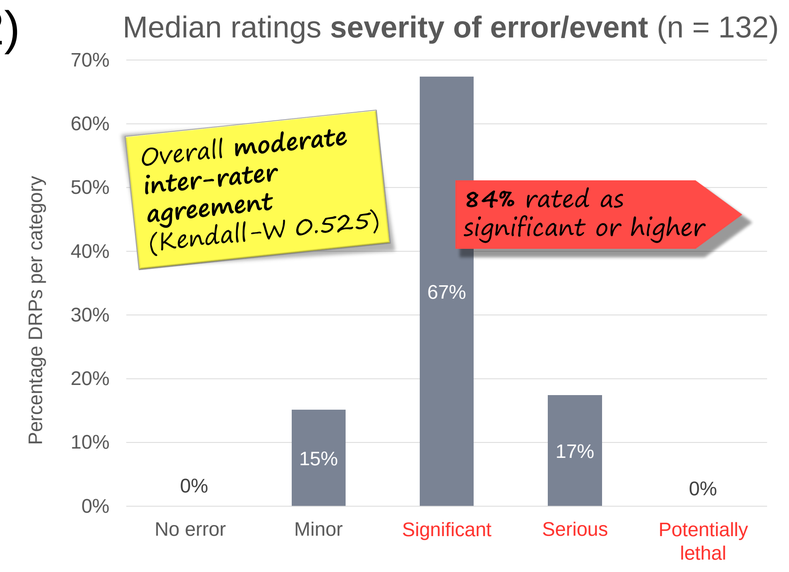


70% immediate ACCEPTANCE

DRP #102
71 years, ♀ patient with recent hip fracture;
on 3 antidepressant drugs + on lithium;
receives diclofenac 75mg i.v. → elevated lithium levels
→rated as **serious**

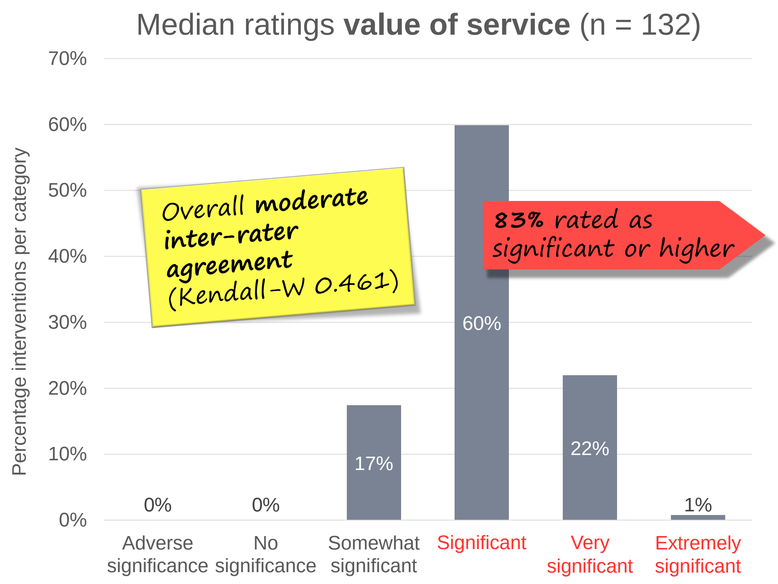
Intervention #102
Switch from diclofenac to paracetamol 1g max. every 6h
→rated as **very significant**

2)



Overall **moderate inter-rater agreement** (Kendall-W 0.525)

84% rated as significant or higher



Overall **moderate inter-rater agreement** (Kendall-W 0.461)

83% rated as significant or higher

Conclusion

The expert panel assessed the CPS to be of great clinical significance and of high clinical value to inpatient care. The prevalence of identified DRPs and the high rate of accepted interventions reflect the contribution of the service to the reduction and prevention of adverse drug events, treatment failure and the achievement of therapy goals. This suggests that the CPS is a valuable contribution to improve patient safety and patient care.

Acknowledgements

Many thanks to the expert panel members for their invaluable contribution!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DEVELOPING AN INTERACTIVE TOOL TO EDUCATE PATIENTS ON GOOD MANAGEMENT OF DRUGS

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Purpose

- To develop an interactive educational tool focusing on general information on drugs specifically for patients
- To evaluate this tool by a panel of participants

Conclusion

- ✓ Creation and validation of the educational tool
- ✓ Significant improvement of the knowledge and the degree of certitude
- ✓ Very good satisfaction of the participants

Background

Involving the patient in his drug therapy is essential and contributes to improve his empowerment. Currently, there are few reliable educational tools addressing general information on the good management of drugs by patients.

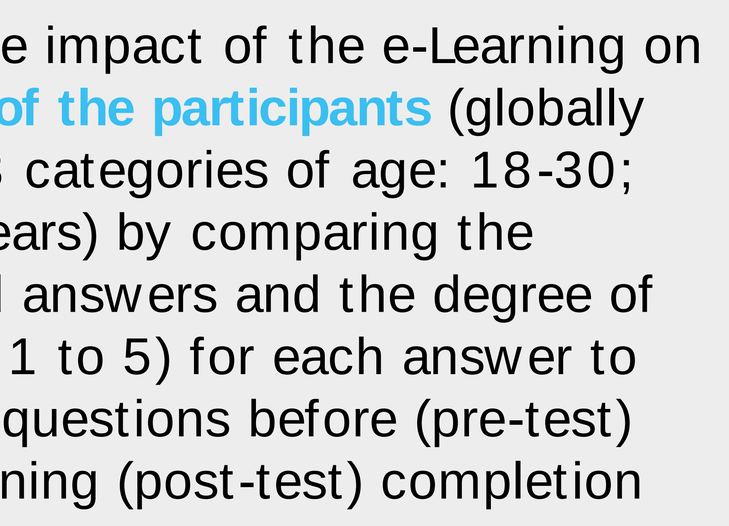
Methods

- Identification of **patients'needs**: focus groups with patients and healthcare professionals (2 sessions of 2 hours)
- Creation of the interactive educational tool into an **e-Learning format** (Software Articulate® Storyline 1)
- Evaluation of the impact of the e-Learning on the **knowledge of the participants** (globally and divided in 3 categories of age: 18-30; 31-65; > 65 years) by comparing the number of good answers and the degree of certitude (scale 1 to 5) for each answer to multiple choice questions before (pre-test) and after e-Learning (post-test) completion
- **Satisfaction evaluation** through a standardized questionnaire

e-Learning development

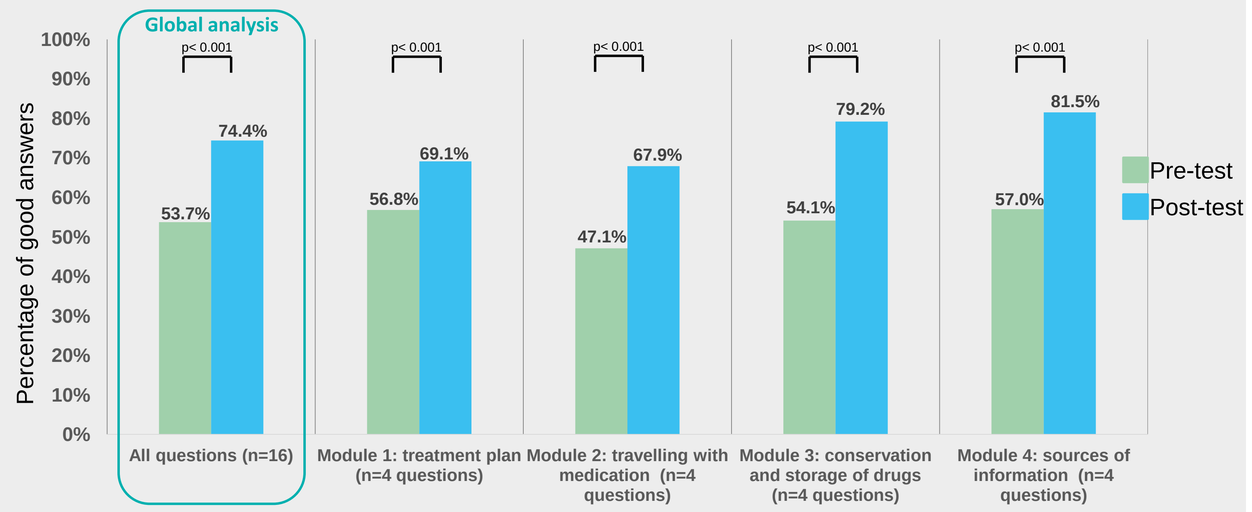
Selection of 4 topics to develop in the form of learning modules:

- Module 1: treatment plan
- Module 2: traveling with medication
- Module 3: conservation and storage of drugs
- Module 4: sources of information



e-Learning evaluation

- 77 participants (43% female, 57% male)
- Significant improvement of the knowledge



Percentage of good answers before and after e-Learning (n = 77 participants)

- Significant improvement of the degree of certitude: 3.84 (pre-test) and 4.75 (post-test) (p< 0.001)
- Global satisfaction of the participants:

	Category of age			
	18-30 years (n=27)	**31 -65 years (n=34)**	**> 65 years (n=16)**	**Total**
Satisfied	34.6%	25.7%	31.3%	29.9%
Very satisfied	65.4%	74.3%	68.8%	70.1%

- Specific satisfaction of the participants:

	Category of age			
	18-30 years (n=27)	**31-65 years (n=34)**	**> 65 years (n=16)**	**Total**
Are you satisfied with the claritiy of this e-Learning lesson ?				
Satisfied	30.8%	5.7%	18.8%	**16.9%**
Very satisfied	69.2%	94.3%	81.3%	**83.1%**
Are you satisfied with the quality of this e-Learning lesson?				
Satisfied	26.9%	25.7%	25.0%	**26.0%**
Very satisfied	73.1%	74.3%	75.0%	**74.0%**
Are you satisfied with the usefullness of this e-Learning lesson in your daily life ?				
Not satisfied	7.7%	0%	0%	**2.6%**
Satisfied	42.3%	32.4%	25.0%	**34.2%**
Very satisfied	50.0%	67.6%	75.0%	**63.2%**

- No significant impact of the age on the improvement of the knowledge nor on the satisfaction

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eahp european association of hospital pharmacists
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No conflict of interest
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INFLUENCE OF CYTARABINE METABOLIC PATHWAY POLYMORPHISMS IN EFFECTIVENESS OF ACUTE MYELOID LEUKAEMIA INDUCTION TREATMENT

PKP-003

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BACKGROUND

✗ **Cytarabine** is considered the **most effective** chemotherapeutic agent in **acute myeloid leukemia** (AML) treatment.

PURPOSE

✗ Several studies suggest that single nucleotide polymorphisms (**SNPs**) in genes involving **metabolic pathway of cytarabine** could **influence in treatment outcomes**, although their clinical relevance remains undetermined.

METHODS

Patients: 225 adults at initial diagnosis from AML, induction with idarubicin plus cytarabine

SNPs: *DCK*:rs2306744, rs11544786, rs4694362; *CDA*:rs2072671, rs3215400, rs532545, rs602950; *NT5C2*:rs11598702; *RRM1*:rs9937; *NME1*:rs2302254

Technique: Sequenom® mass spectrometry–based multiplex genotyping assay

Efficacy: complete remission (CR) vs. partial remission (PR)/resistance (deaths excluded); overall survival (OS), event-free survival (EFS), disease-free survival (DFS) and relapse-free survival (RFS) at 5 years

Statics: linear and logistic regression adjusting for age, gender, ECOG, leukocyte and platelet count, hemoglobin, creatinine, bilirubin, albumin and LDH level at diagnosis (R® 3.1.2)

RESULTS

Patients: median age 51.1 years (range 16-78 years)

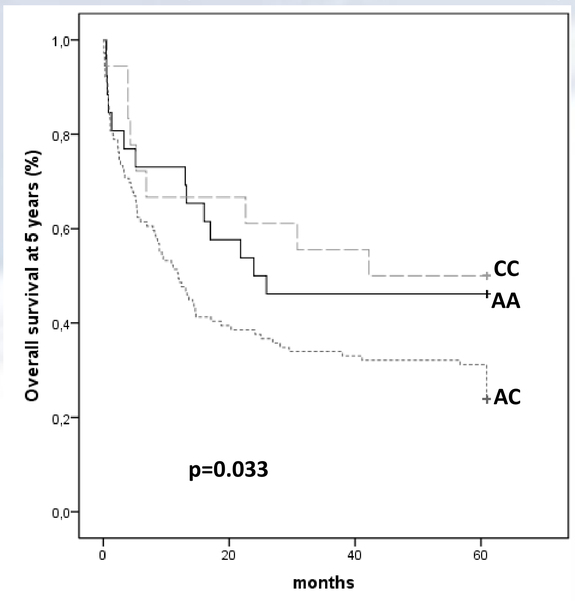
Effectiveness: significant associations were summarized in tables 1-2

TABLE 1. Associations between metabolic Ara C SNPs and efficacy variables.

Variable	Gene/SNP	Genotypes	CR n (%)	non-CR n (%)	OR (95%CI)	P-value
CR	*DCK* rs2306744	GG	116 (56.6)	89 (43.4)	1	
		GA	15 (83.3)	3 (16.7)	6.2 (1.3-30.2)	0.024
CR	*CDA* rs602950	TT	46 (57.5)	34 (42.5)	1	
		TC	58 (53.7)	50 (46.3)	ND	NS
		CC	27 (75.0)	9 (25.0)	3.0 (1.02-8.8)	0.045

ND: not determined; NS: non-significant; HR: hazard ratio; OR: odds ratio;

FIGURES 1 & 2. Kaplan-Meier curve of OS at 5 years for AML patients by rs2072671 & rs602950



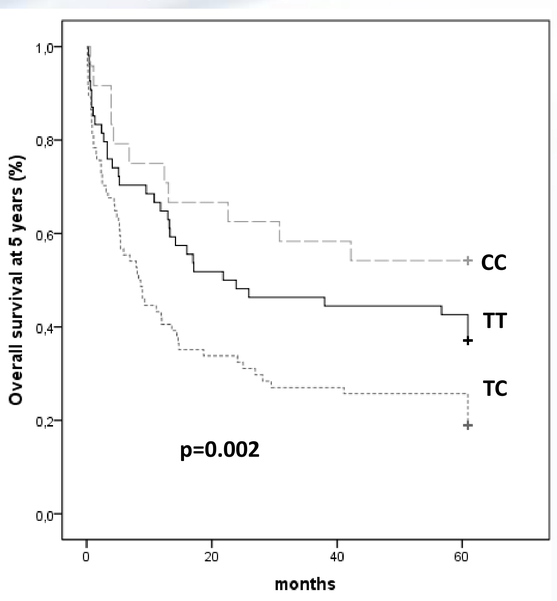


TABLE 2. Associations between metabolic Ara C SNPs and survival rates.

Variable	Gene/SNP	Genotypes	Non-event n (%)	Event n (%)	HR (95%CI)	P-value
OS at 5 years (FIGURE 1)	*CDA* rs2072671	AA	12 (46.2)	14 (53.8)	1	
		AC	26 (23.9)	83 (76.1)	2.2 (1.2-4.1)	0.015
		CC	9 (50.0)	9 (50.0)	ND	NS
EFS at 5 years	*CDA* rs2072671	AA	11 (42.3)	15 (57.7)	1	
		AC	17 (15.6)	92 (84.4)	1.9 (1.01-3.4)	0.045
		CC	9 (50.0)	9 (50.0)	ND	NS
DFS at 5 years	*CDA* rs2072671	AA	11 (73.3)	4 (26.7)	1	
		AC	17 (30.9)	38 (69.1)	3.8 (1.2-12.4)	0.027
		CC	9 (75.0)	3 (25.0)	ND	NS
RFS at 5 years	*CDA* rs2072671	AA	11 (84.6)	2 (15.4)	1	
		AC	17 (44.7)	21 (55.3)	9.1 (1.2-68.6)	0.032
		CC	9 (90.0)	1 (10.0)	ND	NS
DFS at 5 years	*CDA* rs3215400	DEL/DEL	16 (59.3)	11 (40.7)	1	
		DEL/C	12 (30.8)	27 (69.2)	2.9 (1.4-6.3)	0.006
		CC	9 (56.3)	7 (43.7)	ND	NS
RFS at 5 years	*CDA* rs3215400	DEL/DEL	16 (72.7)	6 (28.3)	1	
		DEL/C	12 (48.0)	13 (52.0)	3.3 (1.1-9.9)	0.033
		CC	9 (64.3)	5 (35.7)	ND	NS
OS at 5 years (FIGURE 2)	*CDA* rs602950	TT	20 (37.0)	34 (63.0)	1	
		TC	14 (18.9)	60 (81.1)	1.7 (1.03-2.6)	0.039
		CC	13 (54.2)	11 (45.8)	ND	NS
EFS at 5 years	*CDA* rs602950	TT	13 (24.1)	41 (75.9)	1	
		TC	11 (14.9)	63 (85.1)	ND	NS
		CC	13 (54.2)	11 (45.8)	0.4 (0.2-0.8)	0.014
OS at 5 years	*RRM1* rs9937	AA	16 (44.4)	20 (55.6)	1	
		AG	14 (21.5)	51 (78.5)	2.0 (1.1-3.5)	0.021
		GG	17 (32.7)	35 (67.3)	ND	NS
RFS at 5 years	*RRM1* rs9937	AA	12 (75.0)	4 (25.0)	1	
		AG	11 (47.8)	12 (52.2)	3.8 (1.02-14.3)	0.047
		GG	14 (63.6)	8 (36.4)	ND	NS

CONCLUSION

- Influence in **Ara C efficacy of *DCK*, *CDA* and *RRM1* polymorphisms** in AML adult patients, previously suggested in other studies.
- **Novel associations** between SNPs in metabolic Ara C genes were detected.
- Further studies with larger population are needed to validate these associations, which could be **useful biomarkers in clinical practice**.

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RELATION BETWEEN CLINICAL REMISSION AND TROUGH INFLIXIMAB LEVELS IN CHILDREN WITH INFLAMMATORY BOWEL DISEASE

PKP-009

A03 - Drugs for functional gastrointestinal disorders

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Introduction and objectives

Depending on individual therapeutic response, infliximab (IFX) dosage and infusion interval may be adjusted

→ **Loss of efficiency can be observed as well as sometimes a decrease of trough infliximab levels**

OBJECTIVES

To correlate trough infliximab concentrations with clinical remission in Intestinal Bowel Disease (IBD) children/adolescents and determine an IFX threshold associated with clinical remission

Study design

Inclusion

- Retrospective records between February 2011 and July 2013
- Children/adolescents < 18 years with **Crohn Disease** (CD), **Ulcerative Colitis** (UC) or **Indeterminate Colitis** (IC)
- Treated with at least three IFX perfusions = maintenance phase with results of trough IFX levels

Evaluation

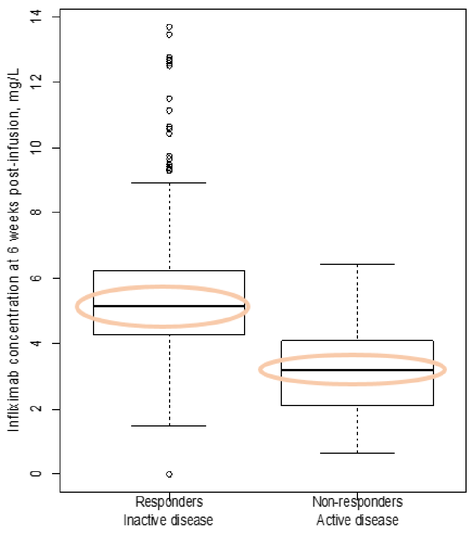
Two scores used to calculate clinical activity of disease :

Harvey Bradshow Index → CD
Pediatric Ulcerative Colitis Activity Index →UC/IC

Analysis by ANOVA test (repeated measures) and logistic regression

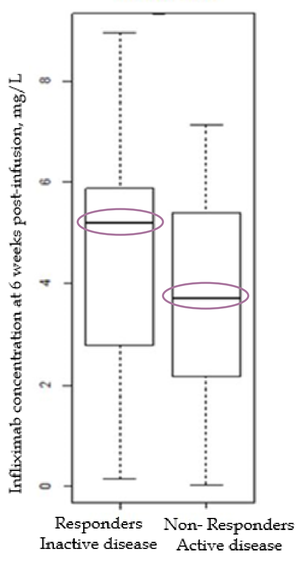
Results

Infliximab serum level 6 weeks after infusion in CD



55 patients included CD

Infliximab serum level 6 weeks after infusion in UC and IC



12 patients included UC & IC

Integral part of therapeutic decision in the clinical service

553 infusions analyzed for CD

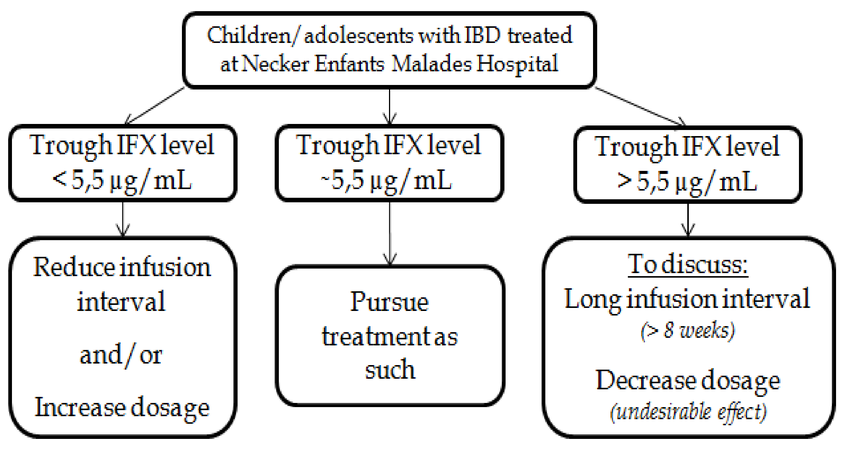
Anova p=10^{-4}

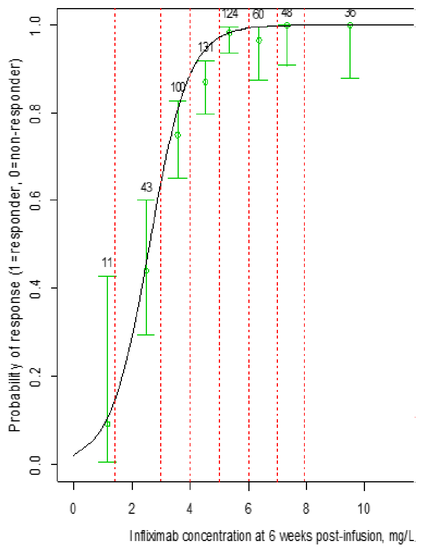
Responders =	Non-responders =
HB < 4	HB ≥ 4
IFX trough level **5,5 µg/mL**	IFX trough level **3,1 µg/mL**

168 infusions analyzed for UC and IC

Anova p=10^{-4}

Responders=	Non-responders=
PUCAI < 10	PUCAI ≥ 10
IFX trough level **5,2 µg/mL**	IFX trough level **3,7 µg/mL**

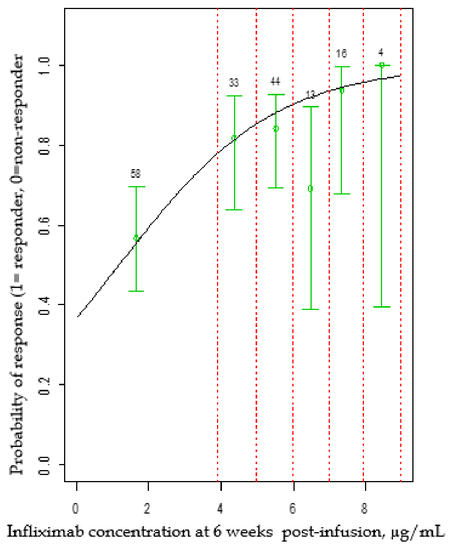




Equation of the probability of responding according to the concentration at 6 weeks C6w:

Logit (p=R)=3,860+(1,480*C6w)+1,25

Probability of success is near 100% when IFX trough level is 5,5 µg/mL.



Equation of the probability of responding according to the concentration at 6 weeks C6w:

Logit (p=R)=-0,546+(0,464*C6w)+1,32

Probability of success is near 100% when IFX trough level is 5,5 µg/mL.

Conclusion

- **There is a relation between trough IFX level and disease activity/ clinical remission in IBD children.**
- **A target trough IFX level** is highlighted**: 5,5 µg/mL.**
- The target has an interest in clinical practice for gastroenterology departments: it is **a decision-making factor linked to the activity of the disease** allowing a therapeutic follow-up and a reaching of the target rate during the treatment.
- Prospective studies are necessary to confirm our results.