Farmacologia clinica degli immmunosoppressori e degli anti-infettivi: interazioni e tossicità

Antonio D'Avolio

Laboratory of Clinical Pharmacology and Pharmacogenetics

Department of Medical Sciences, University of Turin, ASL TO2, Amedeo di Savoia Hospital, Turin, Italy

Web Site: www.tdm-torino.org ; e-mail: info@tdm-torino.org; UNI EN ISO 9001:2008; 13485:2012 CERTIFIED LABORATORY

Antonio D'Avolio
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from last 5 years to date

Drug Interactions

♦ ***Drug Interaction:***

- ***The pharmacologic or clinical response to the administration of a drug combination different from that anticipated from the known effects of the two agents when given alone***

- **May be harmful: toxicity, reduced efficacy**

- **May be beneficial: synergistic combinations, pharmacokinetic boosting, increased convenience, reduced toxicity, cost reduction**

Types of Drug Interactions

- **Pharmacodynamic**
  - **Related to the drug's effects in the body**
  - **One drug modulates the pharmacologic effect of another: <u>additive, synergistic, or antagonistic</u>**

- **Pharmacokinetic**
  - **What the body does with the drug**
  - **<u>One drug alters the concentration of another</u>**
  - ***Usually mediated by cytochrome P450 (CYP)***

Drug Interactions

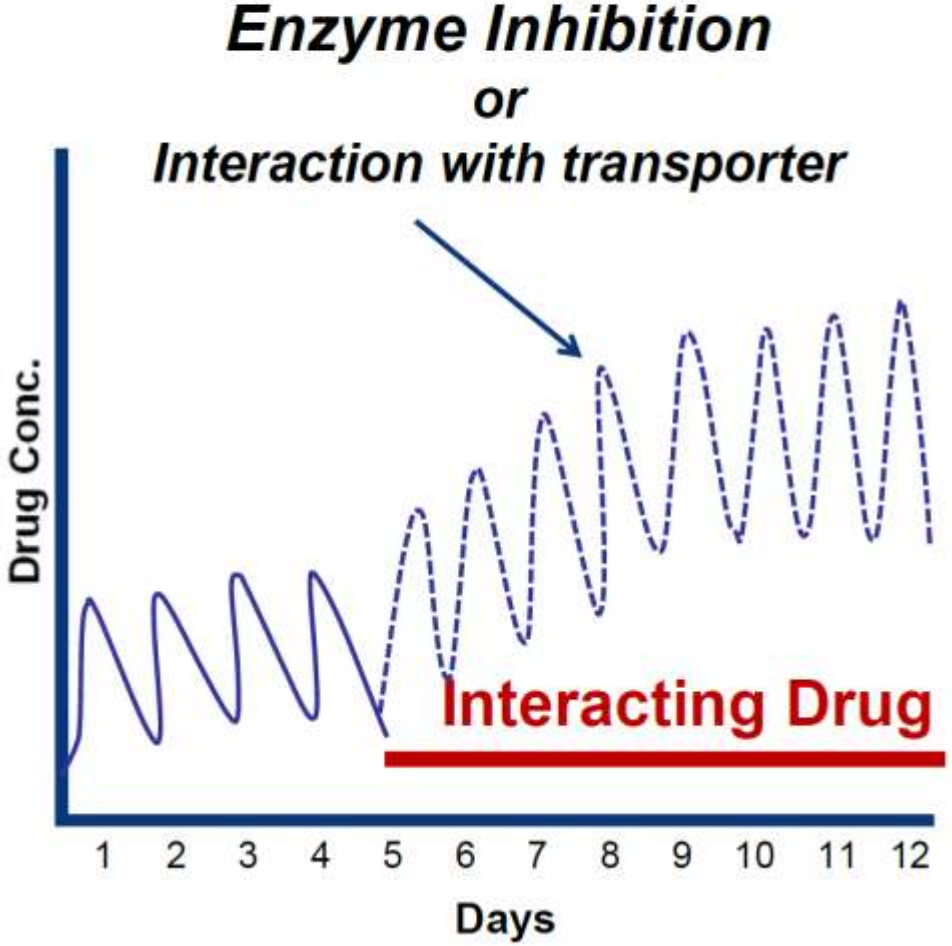
Absorption: food, chelation, G.I. motility, pH

Distribution: transport, protein binding

Metabolism: Phase I (CYP450), Phase II (conjugation)

Elimination: Renal (glomerular filtration); transport

Key Mechanisms of Drug Interactions: Alteration of steady state of a drug in the regimen



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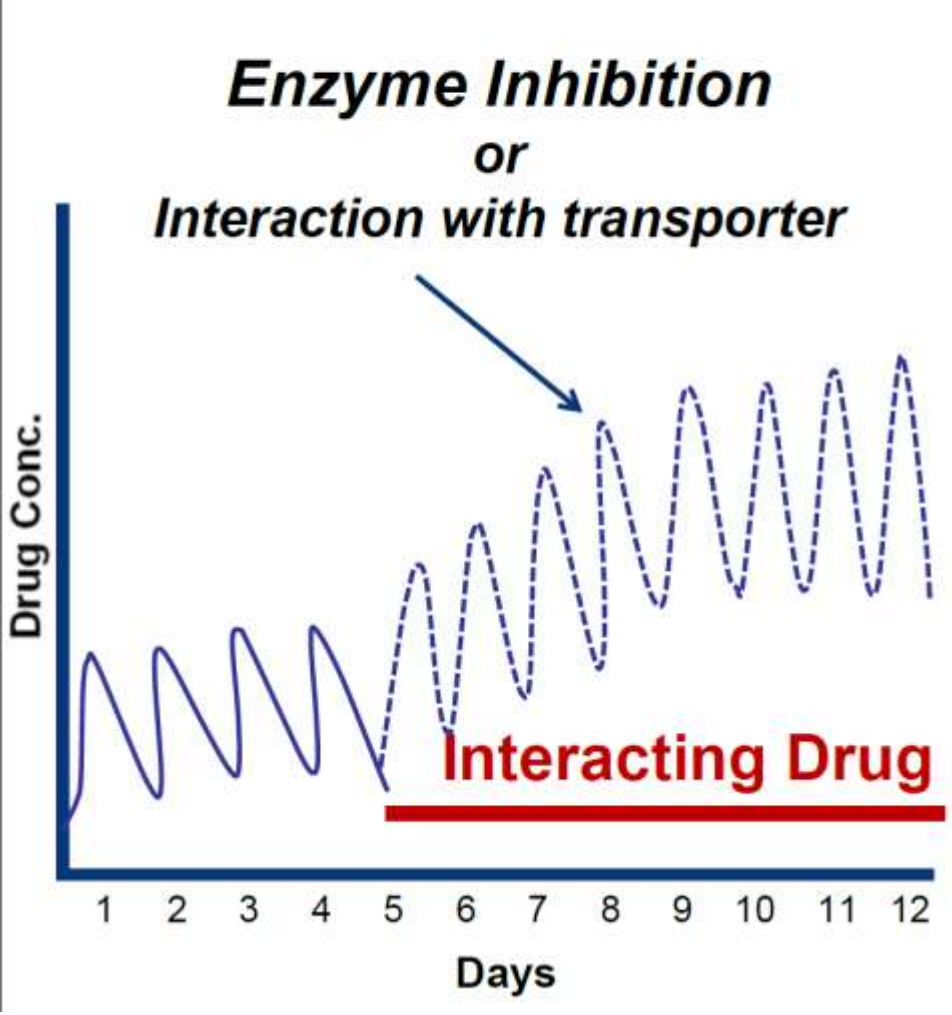
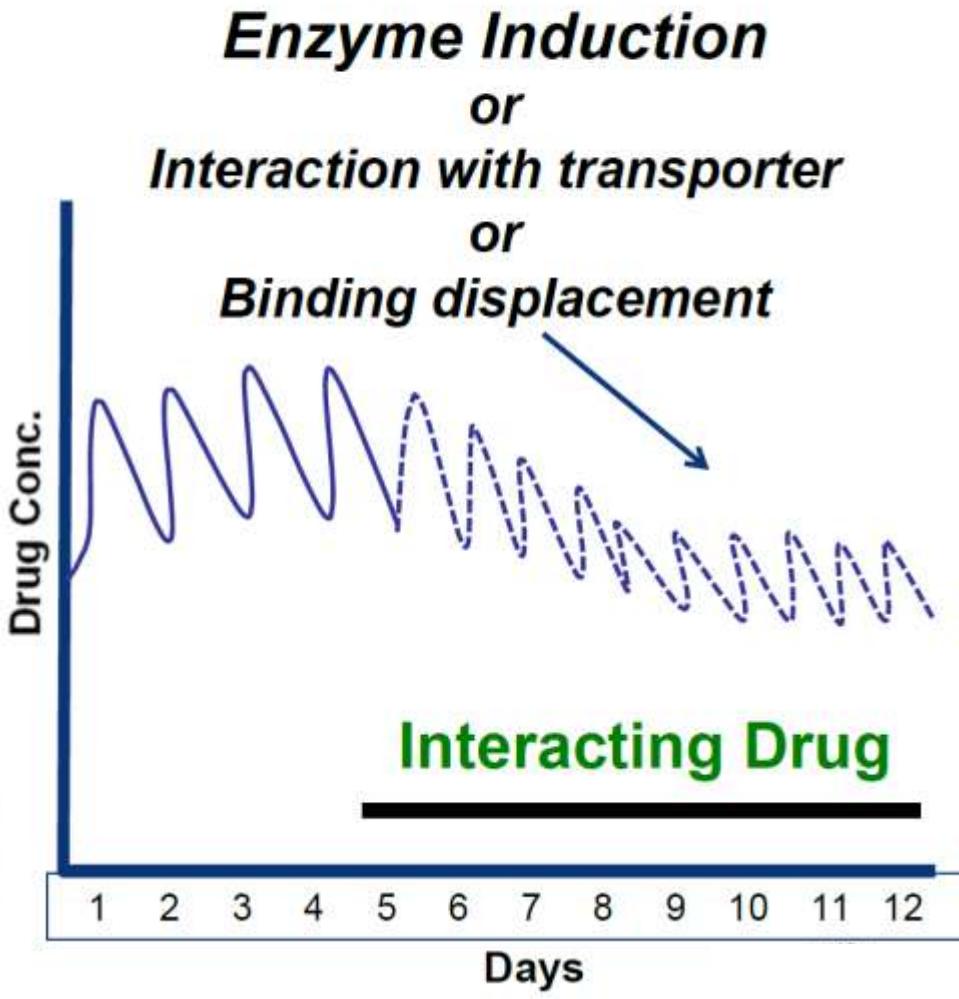
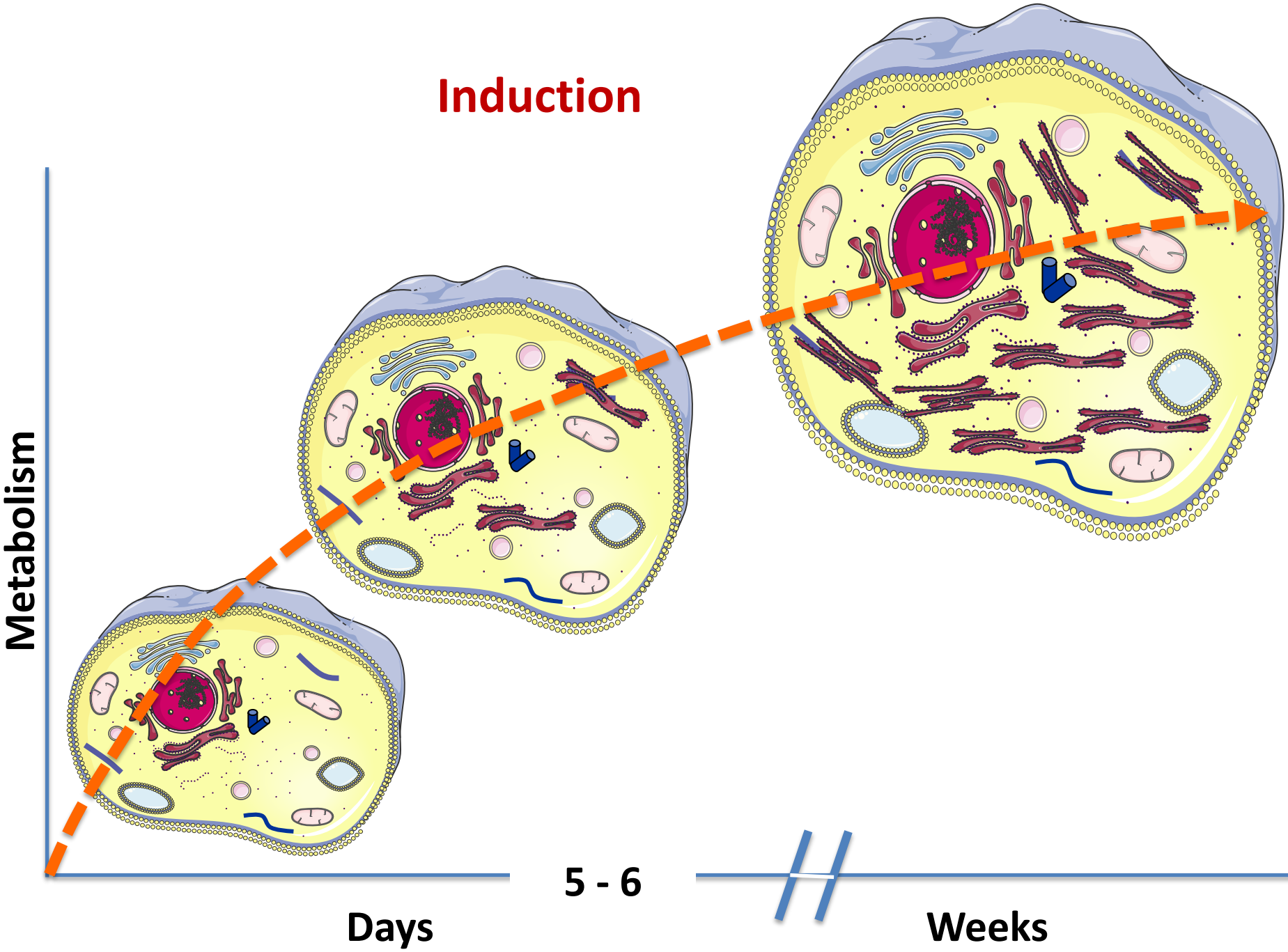
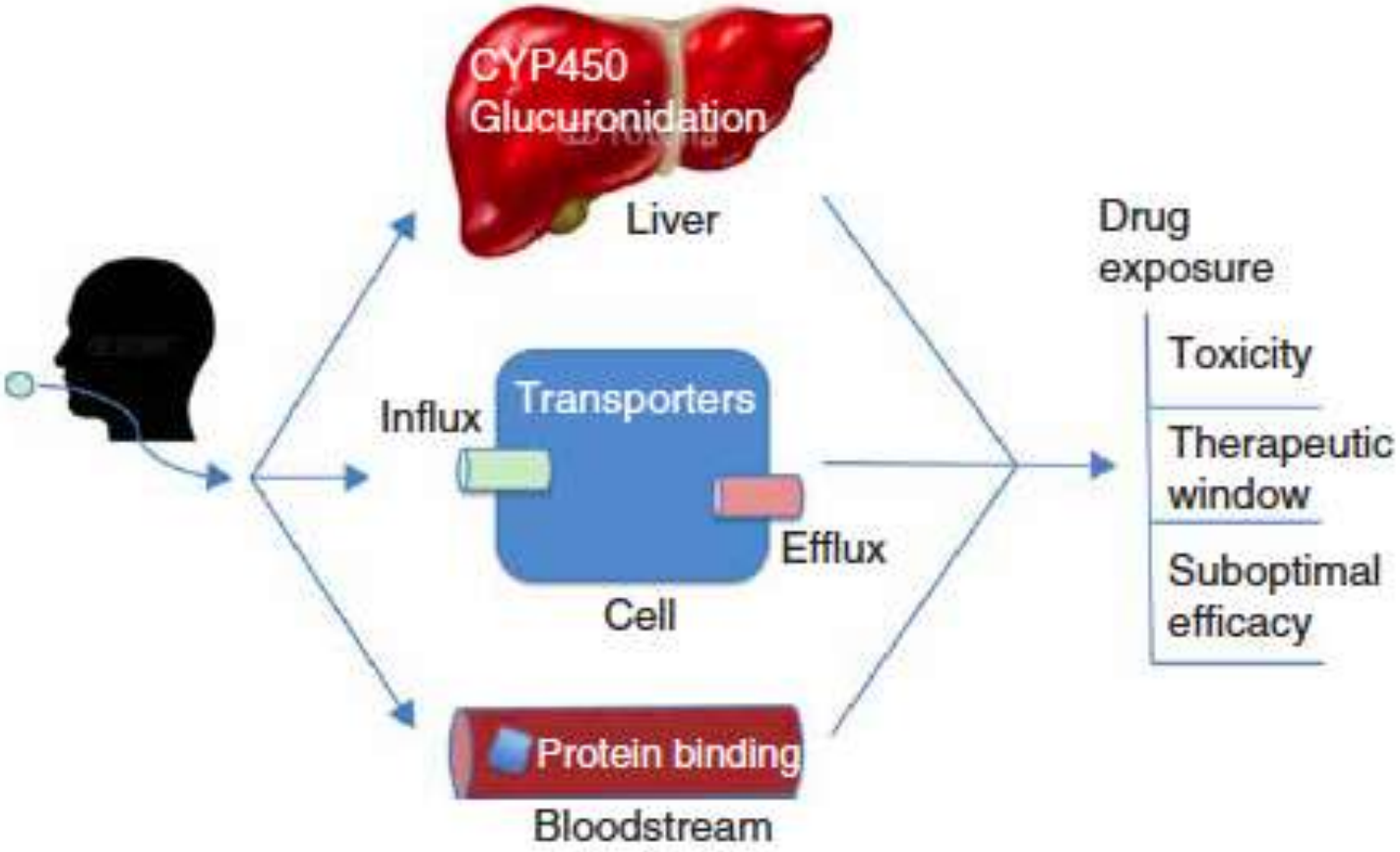




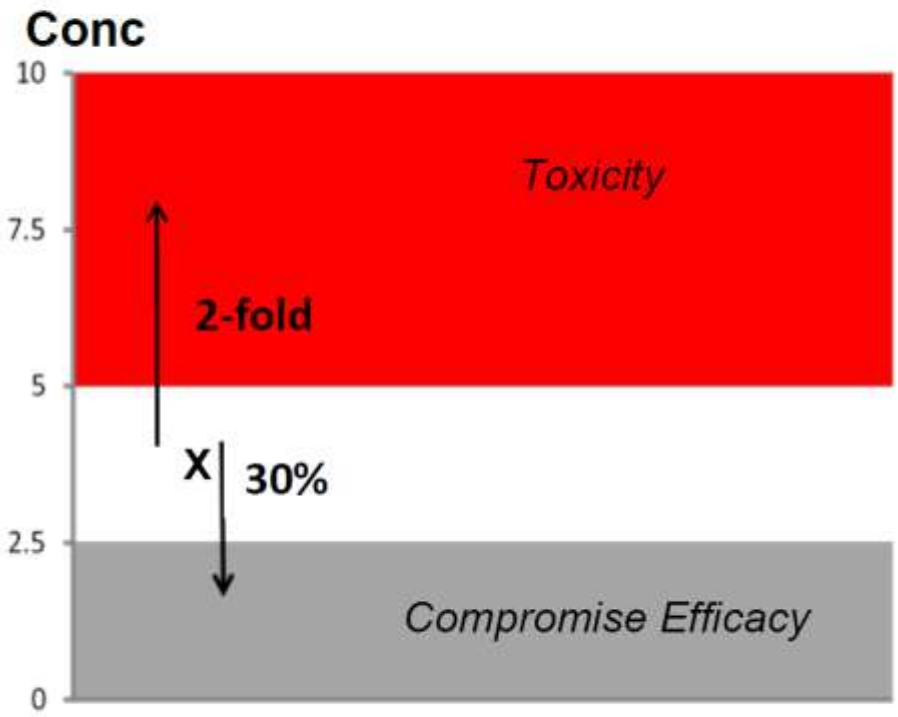
Induction



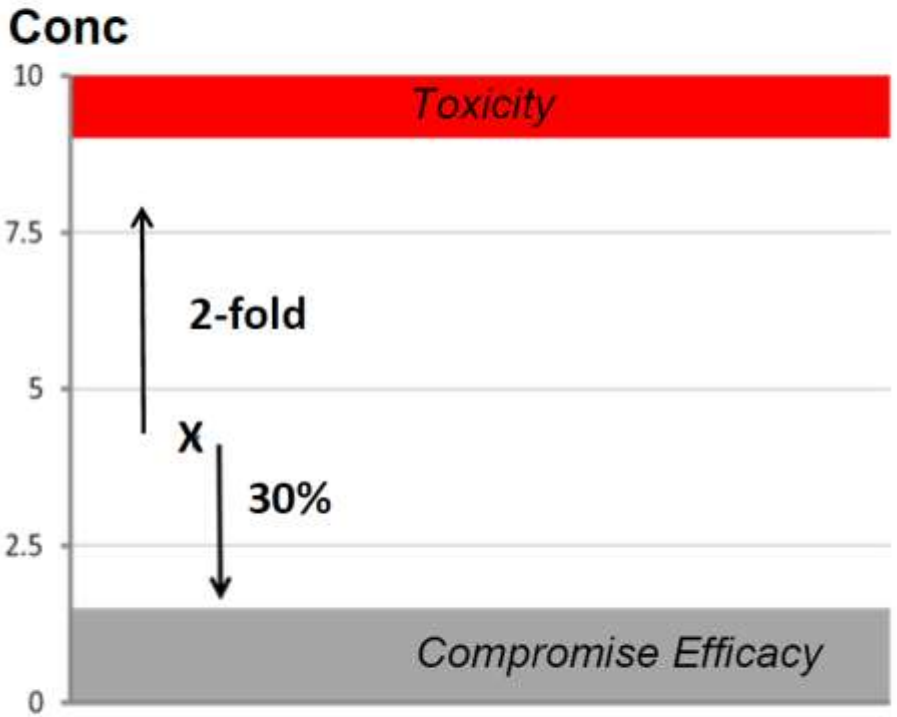
Mechanisms of drug-drug interactions



The importance of the Therapeutic Window



Narrow Therapeutic Window



Wide Therapeutic Window

Interazioni per i farmaci immunosoppressori delle malattie reumatiche?

- Tiopurine
- Methotrexate
- Glucocorticoidi

- AC Monoclonali…

(poche interazioni farmacologiche)

- Abatacept
- Etanercept
- ….altri….

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REVIEW

IMPORTANT DRUG INTERACTIONS IN PATIENTS WITH RHEUMATIC DISORDERS: INTERACTIONS OF GLUCOCORTICOIDS, IMMUNOSUPPRESSANTS AND ANTIMALARIAL DRUGS

L. Hromadkova[1], T. Soukup[2] and J. Vlcek[1]

[1]Department of Social and Clinical Pharmacy, Faculty of Pharmacy, Charles University in Prague, [2]Second Department of Internal Medicine, University Hospital and Faculty of Medicine, Charles University in Prague, Prague, Czech Republic

Table I. *Parameters and levels of severity used in the evaluation (derived from 3, 4).*

Severity of drug interactions[1]

Level	*Definition*
Minor	Small changes in pharmacokinetic parameters (C_{max} increased by < 25% or decreased by < 20%, AUC modified by < 25%, any change at a significance level of < 0.05).
Mild	Small changes in pharmacokinetic parameters at a significance level of < 0.01 or cases with greater changes where modification of the interval between drugs results in a significant reduction of the changes.
Moderate	Considerable changes in pharmacokinetic parameters (C_{max} increased by 25-99%, C_{max} decreased by 20-49%, AUC increased by 25-199%, AUC decreased by 25-59%).
Severe	Great changes in pharmacokinetic parameters (above the ranges given for moderate interactions) requiring one/both drug dosage adjustment in most patients to prevent adverse events or toxicity.
Very severe	Great changes in pharmacokinetic parameters associated with adverse events, toxicity and hospitalization and/or death or considered as contraindication.

Documentation quality

Type/level	*Definition*
Manufacturer's information	Company documentation, the manufacturer considers a given combination of drugs as contraindicated or severe.
Case reports	A single case or a set of a maximum of three cases reported in the literature.
Good	Targeted trial with less than six subjects or a report of at least four cases with closely similar outcomes.
Very good	Targeted trial with at least six healthy volunteers or patients.

Drug interaction onset

Type	*Definition*
Rapid	Clinical symptoms observed within 24 hours from drug administration.
Delayed	Clinical symptoms not expected within 24 hours from drug administration.

Interaction assessment scale

Score	*Definition*
1	Minimal changes, dosage adjustment not needed.
2	Small changes, dosage adjustment not needed, modification of the interval between drugs may be needed
3	Moderate changes, some patients may need dosage adjustment based on clinical or laboratory results
4	Great changes, most patients need dosage adjustment based on clinical or laboratory results.
5	Coadministration associated with a high risk, benefit needs to be considered with caution.

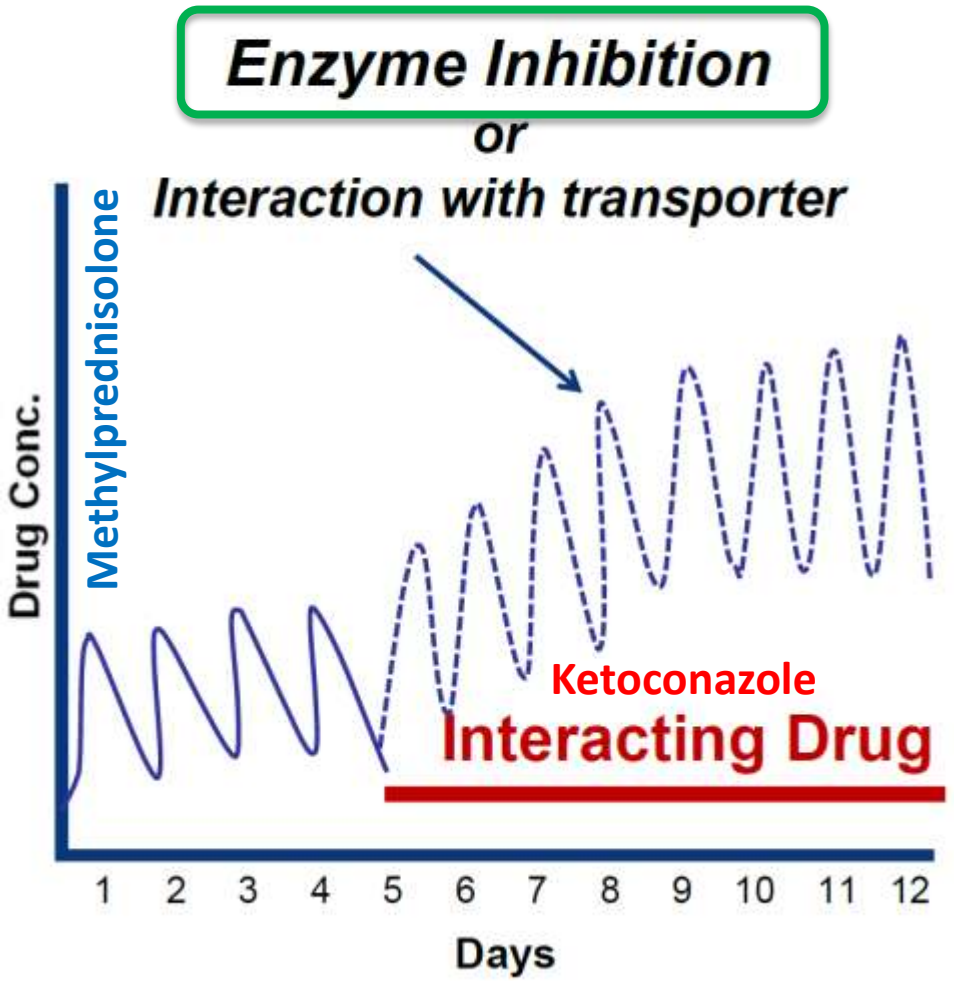
[1]For all levels of drug interactions (except for minor) pharmacodynamic parameters are presented if indicated by primary authors.
AUC, area under the curve; C_{max}, maximum concentration.

Table II. *Overview of clinically significant drug interactions.*

	Interacting drug	Manifestation	Documentation	Onset	Severity	Score
Glucocorticoids	Warfarin	↑ INR	Very good	Delayed	Severe	4
	Fluoroquinolones	Tendon rupture	Very good	Delayed	Moderate	3
	Azole antifungals	↑ GC AE	Very good	Delayed	Moderate	4
Methotrexate	Co-trimoxazole	MTX toxicity	Good	Delayed	Severe	4
	PPIs	MTX toxicity	Very good	Rapid	Severe	4
	Amiodarone	Hepatotoxicity	Case reports	Delayed	Severe	4
	Hepatotoxic drugs	Hepatotoxicity	Case reports	Delayed	Severe	4-5
	Nephrotoxic drugs	Nephrotoxicity	Product information	Delayed	Moderate-severe	3
Leflunomide	Warfarin	↑ INR	Case reports	Delayed	Severe	4
	Cholestyramine, activated carbon	↓ Efficacy of LEF	Product information	Rapid	Severe	4
Azathioprine	Allopurinol	AZA toxicity	Very good	Deleayed	Severe	5
	Warfarin	↓ INR	Good	Delayed	Severe	4
	ACE inhibitors	Myelosuppression	Good	Delayed	Moderate-severe	3
Ciclosporin	CYP3A4 inhibitors	↑ Ciclosporin toxicity	Very good	Delayed	Moderate-very severe	3-4
	CYP3A4 inducers	↓ Efficacy of ciclosporin	Very good	Delayed	Moderate-very severe	3-4
	Statins	Statin toxicity	Very good	Delayed	Very severe	4-5
Antimalarial drugs	Digoxin	Digoxin toxicity	Case reports	Delayed	Moderate	2
Cyclophosphamide	Allopurinol	Myelosuppresion	Very good	Delayed	Moderate	2
Sulfasalazine	Digoxin	↓ Digoxin BAV	Good	Rapid	Moderate	3
Penicillamine	Fe, Al, Mg salts	↓ Penicillamine BAV	Very good	Delayed	Severe	2

ACE, angiotensin-converting enzyme; AE, adverse events; AZA, azathioprine; BAV, bioavailability; GC, glucocorticoids; INR, international normalized ratio; LEF, leflunomide; MTX, methotrexate; PPIs, proton pump inhibitors

Key Mechanisms of Drug Interactions: Alteration of steady state of a drug in the regimen



Azole antifungals

Glucocorticosteroid therapy is one of the risk factors for systemic mycosis; therefore, coadministration with azole antifungals is likely. Inhibition of the CYP3A4 isoenzyme with azole antifungals may result in elevated plasma levels of glucocorticosteroids and thus a higher risk of adverse effects (myopathy, altered glucose tolerance, Cushing's syndrome symptoms, neuropsychiatric reactions, water/electrolyte imbalance, hypertension)

THOMSON REUTERS – Drugs of Today 2012, 48(8)

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	Amiodarone	Hepatotoxicity	Case reports	Delayed	Severe	4
	Hepatotoxic drugs	Hepatotoxicity	Case reports	Delayed	Severe	4-5
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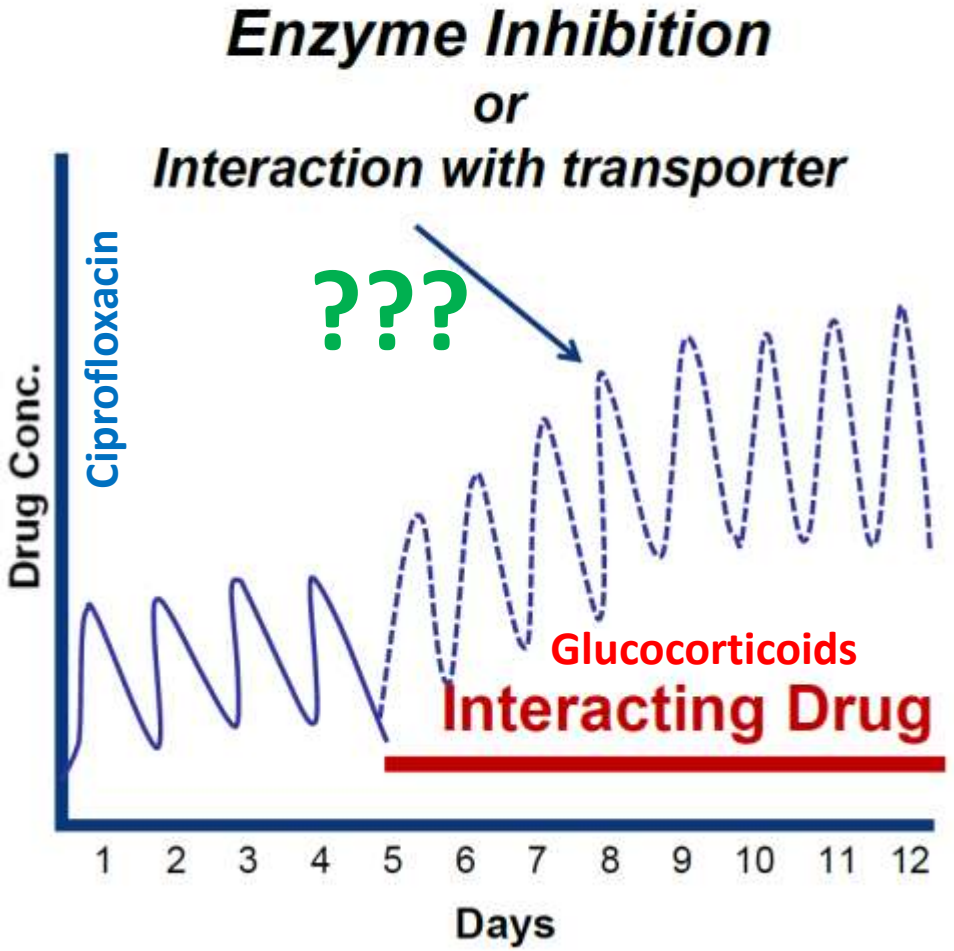

Fluoroquinolones

Glucocorticosteroids and fluoroquinolones can both cause enthesopathy, and their combination is supposed to raise the risk of tendon rupture. The actual mechanism remains unclear. It is recommended that these antibiotics should be avoided by the concomitant use of glucocorticosteroids in patients complaining of pain, inflammation or tendon rupture. Strenuous physical exercise should be avoided while on fluoroquinolones particularly by patients above 60 years of age.

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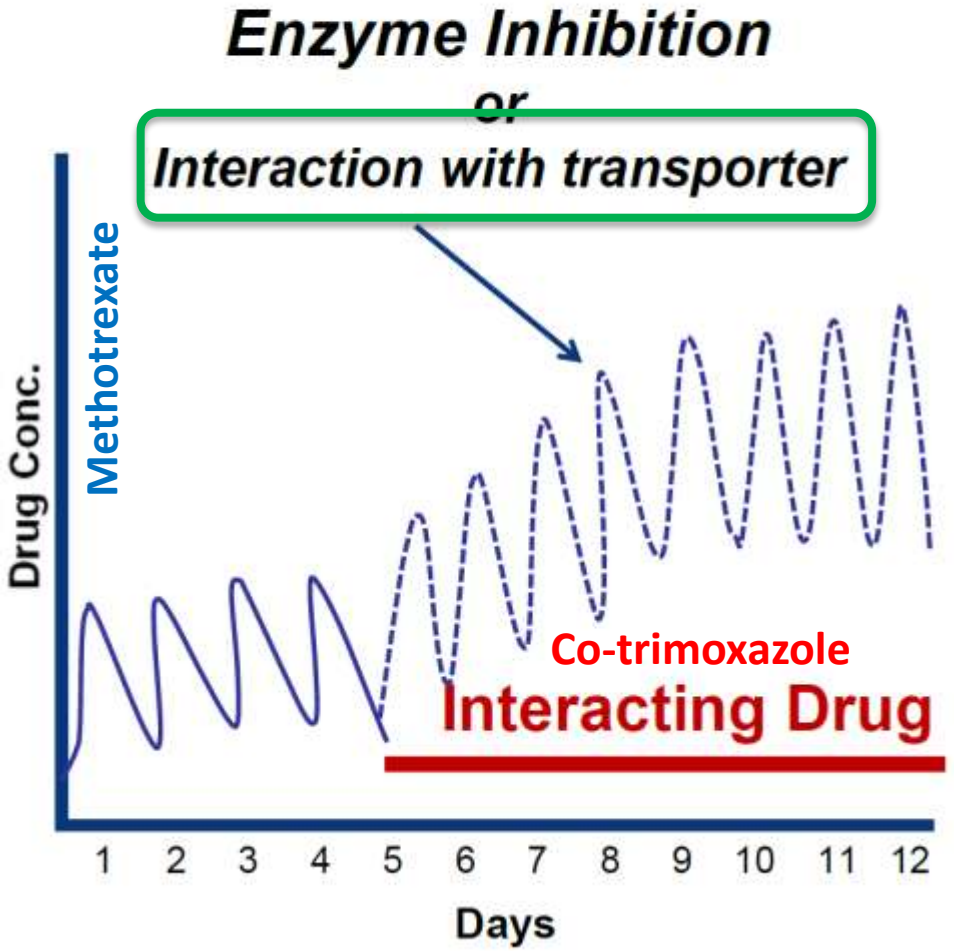

Co-trimoxazole

The pharmacodynamic interaction is based on a synergistic antifolate effect. Nevertheless, altered pharmacokinetics of methotrexate has also been reported. This is likely the result of a reduction of methotrexate tubular elimination or displacement from protein binding.
It is recommended to avoid this coadministration.
Methotrexate should be discontinued when infections need to be treated with co-trimoxazole. Otherwise, hematological abnormalities and nephrotoxicity need to be carefully monitored.

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Methrotexate and other hepatotoxic drugs

Additive hepatotoxic effects are likely when methotrexate is coadministered with other hepatotoxic drugs (**rifampicin**, bosentan, nimesulide, leflunomide, azathioprine, sulfasalazine, **ketoconazole**, **itraconazole, isoniazid, anthracyclines** and acitretin). Methotrexate coadministration with acitretin is even contraindicated.

Methotrexate and nephrotoxic drugs

Pharmacodynamic interactions potentiating methotrexate nephrotoxicity can be supposed when methotrexate is coadministered with potentially nephrotoxic drugs (**amphotericin B**, **amikacin**, cyclooxygenase inhibitors, ciclosporin, platinum-based chemotherapy drugs, gentamicin, meloxicam, naproxen, gold sodium thiomalate, tacrolimus, **teicoplanin** and **vancomycin**). Increased caution should be exercised, and nephrotoxicity and plasma levels of creatinine and urea should be monitored.

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Esempi di interazioni con farmaci antivirali (anti-HIV e anti-HCV) per i pazienti con patologie reumatiche ed infezione da HIV e/o HCV

Da:

www.**hiv**-drug**interactions**.org

www.hep-**druginteractions**.org/

University of Liverpool

Interactions with Entry & Integrase Inhibitors

Charts revised September 2016. Full information available at www.hiv-druginteractions.org

	DTG	E/C/F/ TAF	E/C/F/ TDF	MVC	RAL
Immunosuppressants					
Azathioprine	◆	◆	◆	◆	◆
Ciclosporin	◆	■	■	■	◆
Mycophenolate	◆	◆	■	◆	◆
Sirolimus	◆	■	■	◆	◆
Tacrolimus	◆	■	■	◆	◆
Prednisolone	◆	■	■	◆	◆
Methotrexate	◆	◆	■	◆	◆
Sulfasalazine	◆	◆	◆	◆	◆

Coadministration has not been studied but may increase prednisolone concentrations. Careful monitoring of adverse effects is recommended when prednisolone is coadministered with elvitegravir/cobicistat. Emtricitabine and tenofovir alafenamide are unlikely to interact with prednisolone.

Key to abbreviat

DTG	Dol
E/C/F/TAF	Elvi Ten
E/C/F/TDF	Elvi Ten
MVC	Maraviroc (Celsentri®, Selzentry®)
RAL	Raltegravir (Isentress®)

he interaction is available at

ot been studied; an
etabolic profiles of the drugs.

	nistered
	close monitoring, of administration
◆/◇	No clinically significant interaction expected
✦/✧	There are no clear data, actual or theoretical, to indicate whether an interaction will occur

Interactions with Entry & Integrase Inhibitors

Charts revised September 2016. Full information available at www.hiv-druginteractions.org

	DTG	E/C/F/ TAF	E/C/F/ TDF	MVC	RAL
Immunosuppressants					
Azathioprine	◆	◆	◆	◆	◆
Ciclosporin	◆	■	■	■	◆
Mycophenolate	◆	◆	■	◆	◆
Sirolimus	◆	■	■	◆	◆
Tacrolimus	◆	■	■	◆	◆
Prednisolone	◆	■	■	◆	◆
Methotrexate	◆	◆	■	◆	◆
Sulfasalazine	◆	◆	◆	◆	◆

Coadministration has not been studied. Methotrexate is predominantly eliminated via the kidneys, including active tubular secretion (OAT1, OAT3 mediate methotrexate transport in the kidney whereas MRP4 and BCRP mediate methotrexate efflux in the urine). A clinically significant interaction with elvitegravir, cobicistat or emtricitabine is unlikely. In theory, there is potential for competition for active renal transport mechanisms if tenofovir-DF and methotrexate are coadministered. However, the results of a clinical study evaluating the co-administration of high-dose of intravenous methotrexate with different NRTI, including tenofovir, showed that methotrexate half-life was not prolonged. However, since methotrexate and tenofovir may both cause tubular toxicity, the use of tenofovir-DF should be avoided with concurrent or recent use of a nephrotoxic medicinal product. If coadministration is unavoidable, renal function should be monitored weekly. Note, some methotrexate product labels contraindicate its use or advise caution in immunodeficiency and some contraindicate its use in HIV infection.

Interactions with Protease Inhibitors

Charts revised September 2016. Full information available at www.hiv-druginteractions.org

	ATV	Cobi	DRV	FPV	IDV	LPV	NFV	RTV	SQV	TPV
Immunosuppressants										
Azathioprine	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Ciclosporin	■	■	■	■	■	■	■	■	■	■
Mycophenolate	■	◆	■	■	■	■	■	■	■	■
Sirolimus	■	■	■	■	■	■	■	■	■	■
Tacrolimus	■	■	■	■	■	■	■	■	■	■
Methylprednisolone	■	■	■	■	■	■	■	■	■	■
Prednisolone	■	■	■	■	■	■	■	■	■	■
Methotrexate	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Sulfasalazine	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆

Coadministration has not been studied. Prednisone is converted to the active metabolite prednisolone by 11-B-hydroxydehydrogenase. Prednisolone is then metabolized by CYP3A4. Coadministration **could** potentially increase prednisolone concentrations thus increasing the risk of steroid related toxicity. Careful monitoring for adverse effects is recommended.

Interactions with NNRTIs

Charts revised September 2016. Full information available at www.hiv-druginteractions.org

	DLV	EFV	ETV	NVP	RPV
Immunosuppressants					
Azathioprine	◆	◆	◆	◆	◆
Ciclosporin	■	■	■	■	■
Mycophenolate	■	■	◆	■	◆
Sirolimus	■	■	■	■	◆
Tacrolimus	■	■	■	■	■
Methylprednisolone	■	■	■	■	◆
Prednisolone	■	■	■	■	◆
Methotrexate	◆	◆	◆	◆	◆
Sulfasalazine	◆	◆	◆	◆	◆

Prednisone is converted to the active metabolite prednisolone by 11-B-hydroxydehydrogenase. Prednisolone is then metabolized by CYP3A4. Pharmacokinetics of prednisolone were determined following administration of prednisone (20 mg single dose) in three groups of ten HIV+ subjects receiving either lopinavir/ritonavir or efavirenz or no antiretrovirals. Prednisolone AUC was significantly lower (40% decrease) in the presence of efavirenz versus lopinavir/ritonavir and was higher in the subjects taking lopinavir/ritonavir than in subjects on no antiretrovirals, but this was not significant. Prednisolone concentrations may fluctuate widely when patients on efavirenz switch to lopinavir/ritonavir or vice versa.

Interactions with NRTIs

	ABC	ddI	FTC	F/TAF	3TC	d4T	TDF	ZDV
Immunosuppressants								
Azathioprine	◆	■	◆	◆	◆	◆	◆	■
Ciclosporin	◆	◆	◆	■	◆	◆	■	◆
Mycophenolate	■	◆	◆	◆	◆	◆	■	■
Sirolimus	◆	◆	◆	◆	◆	◆	■	◆
Tacrolimus	◆	◆	◆	◆	◆	◆	■	◆
Methylprednisolone	◆	◆	◆	◆	◆	◆	◆	◆
Prednisolone	◆	◆	◆	◆	◆	◆	◆	◆
→ Methotrexate	◆	■	◆	◆	◆	■	■	■
Sulfasalazine	◆	◆	◆	◆	◆	◆	◆	■

Coadministration has not been studied. Methotrexate is predominantly eliminated via the kidneys, including active tubular secretion (OAT1, OAT3 mediate methotrexate transport in the kidney whereas MRP4 and BCRP mediate methotrexate efflux in the urine). In theory, there is potential for competition for active renal transport mechanisms if tenofovir-DF and methotrexate are coadministered. However, the results of a clinical study evaluating the co-administration of high-dose of intravenous methotrexate with different NRTI, including tenofovir, showed that methotrexate half-life was not prolonged. However, since methotrexate and tenofovir may both cause tubular toxicity, the use of tenofovir-DF should be avoided with concurrent or recent use of a nephrotoxic medicinal product. If coadministration is unavoidable, renal function should be monitored weekly. Note, some methotrexate product labels contraindicate its use or advise caution in immunodeficiency and some contraindicate its use in HIV infection.

HCV Directly Acting Antivirals & RBV

Charts revised September 2016. Full information available at www.hep-druginteractions.org

	BOC	DCV	EBR/ GZR	LED/ SOF	OBV/ PTV/r	OBV/ PTV/r +DSV	SMV	SOF	TVR	VEL/ SOF	RBV
Immunosuppressants											
Azathioprine	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	■
Basilixumab	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Ciclosporin	■	◆	●	◆	■	■	●	◆	■	◆	
Eculizumab	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Etanercept	■	■	■	■	■	■	■	■	■	■	■
Fingolimod	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Mycophenolate	◆	◆	◆	◆	■	■	◆	◆	◆	◆	◆
Sirolimus	■	◆	■	◆	■	■	■	◆	■	◆	
Tacrolimus	■	◆	■	◆	■	■	■	◆	■	◆	
Methylprednisolone	■	◆	◆	◆	■	■	■	◆	■	◆	
Prednisone	■	◆	◆	◆	■	■	■	◆	■	◆	
Methotrexate	■	■	■	◆	◆	◆	◆	◆	■	■	■
Sulfasalazine	◆	◆	◆	◆	■	■	◆	◆	◆	◆	◆

Coadministration has not been studied but based on metabolism and clearance an interaction is unlikely. However there have been reports of worsening of hepatitis C in patients receiving etanercept. Use with caution and monitor closely for worsening of HCV.

Un ruolo per il Therapeutic Drug Monitoring?

TDM, Quando?

Quando è utile fare il TDM:

- **Quando il range terapeutico è *ristretto*: il livello di concentrazione terapeutico è molto vicino a quello tossico.**
- **Quando l'insuccesso della terapia si associa a *conseguenze significative* (es. rigetto di un organo nel caso del monitoraggio di farmaci immunosoppressivi, usati in pazienti trapiantati) oppure ad *effetti tossici gravi*.**
- **Se c'è *variabilità cinetica tra gli individui*: c'è una diversa biodisponibilità da paziente a paziente (es. con farmaci molto variabili come la ciclosporina e la digossina); o variabilità dovuta a fattori genetici**
- **Per prendere *decisioni terapeutiche* o consolidarne la validità (PK/PD: Cmax/MIC Ratio; AUC/MIC Ratio; T>MIC)**
- **Per verificare la *compliance dei pazienti al trattamento*, ovvero il grado in cui un paziente segue le raccomandazioni cliniche del medico: in questo caso si verifica se il paziente assume il farmaco, eseguendo un dosaggio sul sangue venoso (importante per terapie prolungate nel tempo: HIV, HCV, TBC, ecc…)**
- **In caso di *inefficacia* della terapia o di effetti collaterali o tossici.**
- **Quando si *modifica il dosaggio* per valutare se, una volta raggiunto lo steady state, si sia ancora nel range terapeutico.**
- **Quando la *risposta terapeutica non può essere verificata*: ovvero in quei casi, in cui un trattamento farmacologico serve a prevenire un determinato evento (es. nelle terapie antiepilettiche, dove si deve prevenire l'evento, non si può verificare se il farmaco sta facendo effetto o meno, fino a che il paziente subisce una crisi epilettica).**
- **Quando i pazienti sono in condizioni fisiologiche (es. gravidanza) oppure patologiche (es. insufficienza renale o epatica) tali da *poter modificare la cinetica del farmaco in maniera non prevedibile*.**
- **Studiare, valutare e gestire le interazioni tra i farmaci co-somministrati**

Therapeutic Drug Monitoring Rational

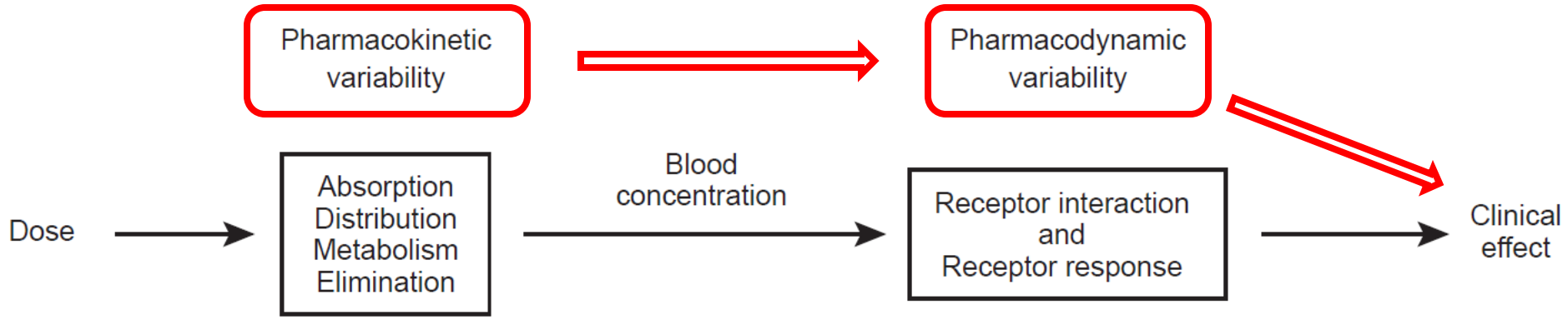


Figure 1 Pharmacokinetics and pharmacodynamics contribute to variability in the relationship between drug dose and response.

Best practice in therapeutic drug monitoring

Annette S. Gross
Department of Clinical Pharmacology, Royal North Shore Hospital, St Leonards NSW 2065, Australia

 Br J Clin Pharmacol, **52**, 5S–10S

Limitazioni al TDM

Diversi fattori limitano l'uso routinario del TDM:

• l'assenza di studi prospettici che mostrano l'utilità del TDM nel migliorare gli outcomes clinici.

• l'assenza di un range terapeutico definito, o cut-off di attività (con non molte eccezioni).

• la mancanza di esperti per aiutare ad interpretare i dati, e applicarli modificando il regime terapeutico.

• costi elevati per la spedizione ai (pochi) centri qualificati (con know-how e certificazioni).

• la velocità di refertazione (assenza di automazione [se non si usano sistemi immuno-enzimatici], con poche eccezioni).

La giustificazione all'uso del TDM per gli immunosoppressori

BioDrugs. 2000 Dec;14(6):355-69.

Drug concentration monitoring of immunosuppressive agents: focus on tacrolimus, mycophenolate mofetil and sirolimus.

Tsunoda SM[1], Aweeka FT.

Author information

Abstract

Several new immunosuppressive agents have recently been approved for use in solid organ transplantation. Many of these agents have narrow therapeutic ranges, which necessitates drug concentration monitoring in order to optimise efficacy, minimise toxicity and individualise dosages. Some of the lessons learned with the clinical use of the revolutionary agent cyclosporin have been applied to the newer agents tacrolimus and sirolimus. The agent mycophenolate mofetil has been in clinical use without widespread drug concentration monitoring; however, recent data suggest that therapeutic monitoring may improve clinical outcomes, especially in certain high risk subsets of patients. This review focuses on the literature published to date on drug concentration monitoring of the newer immunosuppressive agents - tacrolimus, mycophenolate mofetil and sirolimus. In addition, pertinent aspects of the clinical pharmacokinetics and metabolism of each agent are reviewed.

the new immunosuppressive agents **tacrolimus, sirolimus and MMF have significant clinical roles in solid organ transplantation, but they have narrow therapeutic ranges and numerous toxicities**. Strategies to individualise dosages and optimise treatment with these agents are therefore particularly important. ***In this respect, TDM can be used,*** along with clinical monitoring of patients, and together with an awareness of the pharmacokinetic profiles of specific agents, to optimise treatment outcomes.

(*Drug Ther Perspect*. 2001)

Studi osservazionali, ma non prospettici…

Un ruolo per il Therapeutic Drug Monitoring?

RHEUMATOLOGY

Rheumatology 2014;53:988–997
doi:10.1093/rheumatology/ket355
Advance Access publication 5 November 2013

Review

Therapeutic drug monitoring in rheumatic diseases: utile or futile?

Lisa K. Stamp[1,2] and Murray Barclay[1,3]

Monitoring drug concentrations in the treatment of rheumatic diseases could produce improved outcomes.

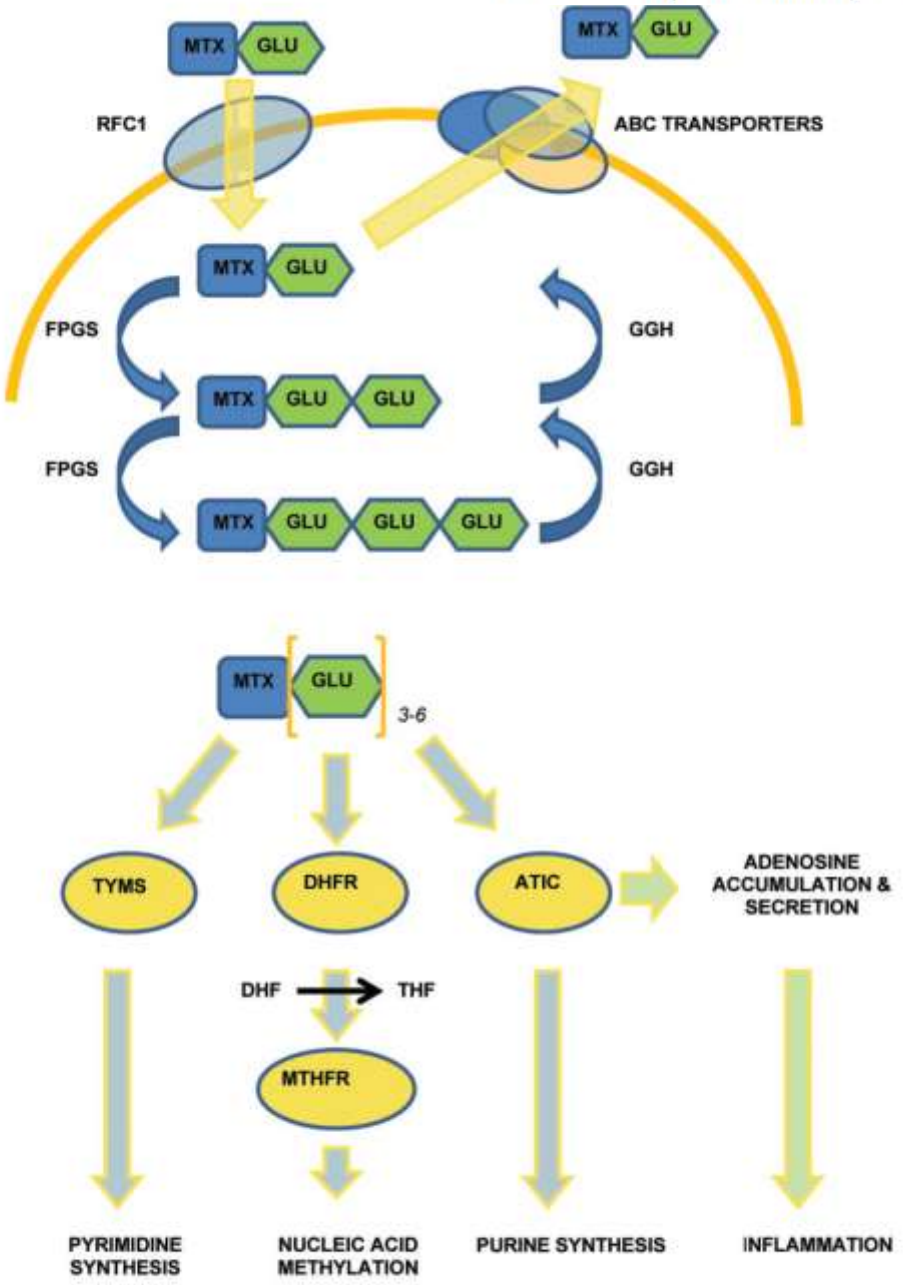
MTX polyglutamates: pharmacology

Once absorbed, MTX is taken up rapidly from the plasma into a variety of cells. Intracellularly, up to four additional glutamate (GLU) moieties are added to MTX by folylpolyglutamate synthetase. Terminal MTX GLUs are removed by g-glutamyl hydrolase, returning MTX to its monoglutamate form, which is rapidly transported out of the cell by multidrug resistance proteins (Fig. 1). **The long-chain MTX polyglutamates (MTXGlu3-5) are thought to be responsible for most of the anti-inflammatory effects of MTX.** They inhibit several important intracellular enzymes, including dihydrofolate reductase, resulting in decreased DNA methylation, and thymidylate synthase, interfering with DNA synthesis, and 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase, which ultimately inhibits production of proinflammatory cytokines including TNF-a, IFN-g and IL-1 (Fig. 1).

Plasma MTX concentrations have not been correlated with disease activity, a finding that is not surprising given that MTX has a short plasma half-life of elimination (6 h) and is rapidly taken up into cells. RBC MTX polyglutamates have a long elimination half-life (weeks) and are thus a potential candidate for monitoring MTX therapy. However, so far evidence does not strongly support a clinically useful relationship between MTX polyglutamate concentrations and disease activity or adverse effects in RA. **White blood cells (WBCs) have a critical role in driving the inflammatory process through their production of proinflammatory cytokines.**

FIG. 1 MTX metabolism and mechanism of action.

Lisa K. Stamp and Murray Barclay



RFC-1: reduced folate carrier; FPGS: folylpolyglutamate synthetase; GGH: γ-glutamyl hydrolase; TYMS: thymidylate synthase; ATIC: amino-imidazole carboxamidoribonucleotide (AICAR) transformylase; DHFR: dihydrofolate reductase; MTHFR: 5,10-methylenetetrahydrofolate reductase.

Anti-TNF therapy in RA

- Biologic therapies have revolutionized the lives of many patients with rheumatic diseases. For patients with active early RA and poor prognostic features, TNF inhibitors are now recommended as first-line treatment.
- However, as seen with most non-biologic DMARDs, there is considerable variation in the clinical response to treatment with anti-TNF therapy.
- Biologic therapies, including anti-TNF therapy, are expensive, and more cost-effective use of these drugs would benefit both patients and health care systems.
- In IBD, there have been at least 20 studies with anti-TNF trough drug concentrations and/or anti-drug antibodies assessed in relation to disease activity and adverse effects.
- In a systematic review of these studies, it was concluded that **there was a close relationship between trough drug concentrations and maintenance of response, with cut-off concentration values of between 3 and 7.2 mg/ml depending on the individual study.**
- **It was also concluded that the presence of anti-TNF drug antibodies increased drug clearance.**

- **The authors suggest that TDM of anti-TNF drug concentrations and antibody titres may prove useful in IBD.**

Lisa K. Stamp and Murray Barclay

Current clinical role for measuring oxypurinol

Plasma oxypurinol measurement may be most useful in those patients where SU fails to decline as expected with allopurinol therapy.

In this setting, **low plasma oxypurinol (<20 mmol/l) will help identify non-compliant patients so further efforts at educating the patient as to the importance of compliance can be undertaken.** Whether TDM provides any clinical benefit in this setting is arguable, particularly when there is no association between elevated drug concentrations and adverse drug effects. Thus the pragmatic clinical approach is to ensure compliance and then continue to dose escalate allopurinol until the target SU is achieved, adverse effects occur or the maximum dose of 900 mg/day is reached irrespective of oxypurinol concentration. Further safety studies of allopurinol at doses above the CrCL-based dose are awaited.

AZA

- The thiopurines AZA and 6-mercaptopurine are used in a variety of inflammatory diseases.
- **In IBD, it has become common to use TDM by monitoring the concentrations of the thiopurine metabolites 6-thioguanine nucleotide (6-TGN) and 6-methylmercaptopurine (6-MMP).**
- There is evidence for increased drug response with 6-TGN concentrations >235 pmol/8x10^8 RBCs. Furthermore, 6-TGN concentrations >450 pmol/8x10^8 RBCs have been associated with an increased risk of myelotoxicity.
- Therefore a therapeutic range of 235-450 pmol/8x10^8 RBCs is used.
- 6-MMP concentrations >5700 pmol/8x10^8 RBCs have been associated with hepatotoxicity and dose regimens are altered so as not to exceed this threshold.

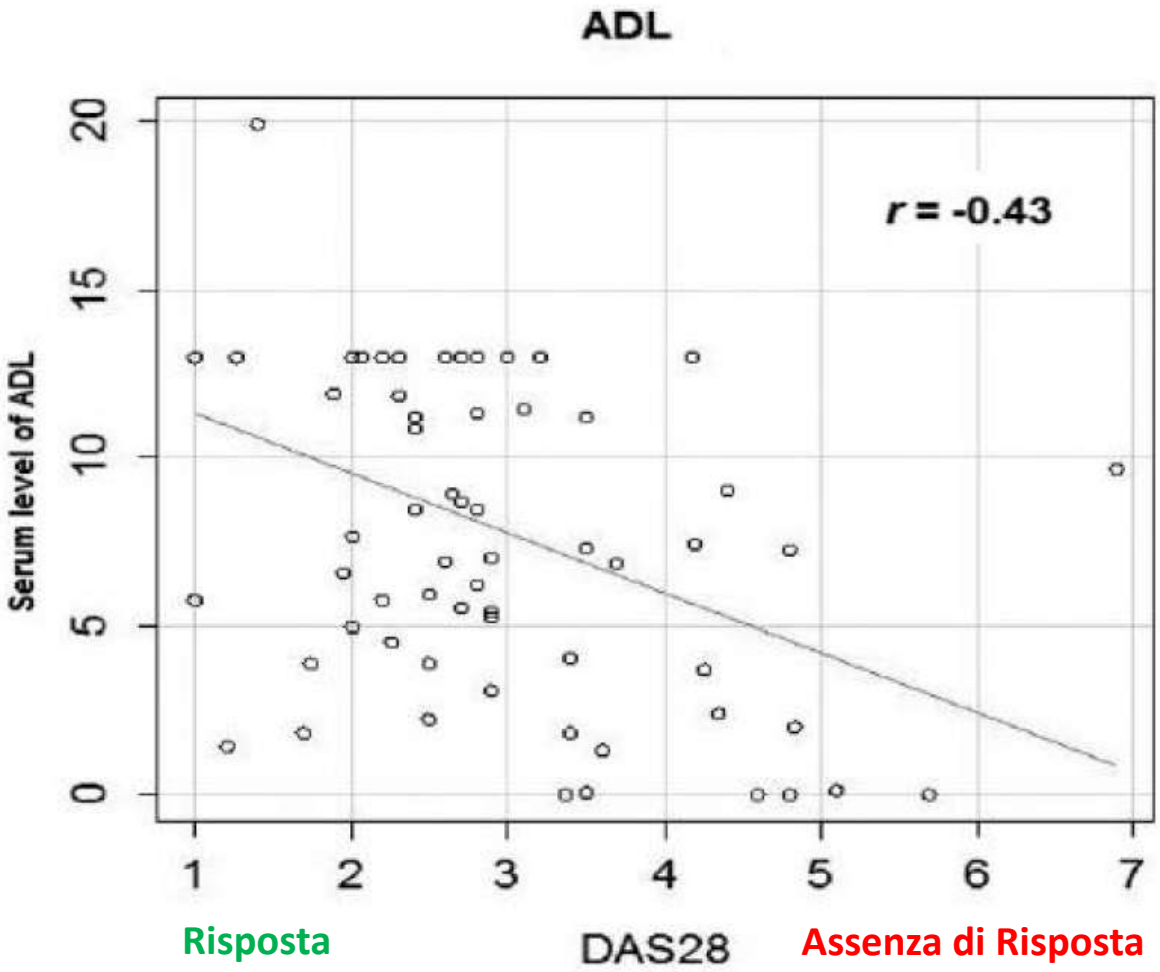
- Despite the evidence in IBD, there is a paucity of data in inflammatory rheumatic disease. **Only small studies of patients with inflammatory rheumatic diseases, including RA, SLE, myositis and polyarteritis nodosa, have been undertaken and no association has been observed between 6-TGN concentrations and hepatotoxicity or myelotoxicity or disease activity.**

- **These data suggest there is currently no role for the measurement of AZA or mercaptopurine metabolites**, but this is somewhat surprising given the data in IBD.
- The apparent lack of utility of thiopurine metabolites in rheumatic diseases may reflect study design and low patient numbers. However, there is the potential for larger prospective studies to address this.

Lisa K. Stamp and Murray Barclay

Clinical relevance of monitoring serum levels of adalimumab in patients with rheumatoid arthritis in daily practice

J. Rosas[1], F. Llinares-Tello[2], I. de la Torre[3], C. Santos-Ramírez[4], J.M. Senabre-Gallego[1], L. Valor[3], X. Barber-Vallés[5], D. Hernández-Flórez[3], G. Santos-Soler[1], E. Salas-Heredia[1], L. Carreño[3], and the AIRE-MB Group



Clinical and Experimental Rheumatology 2014; **32**: 942-948.

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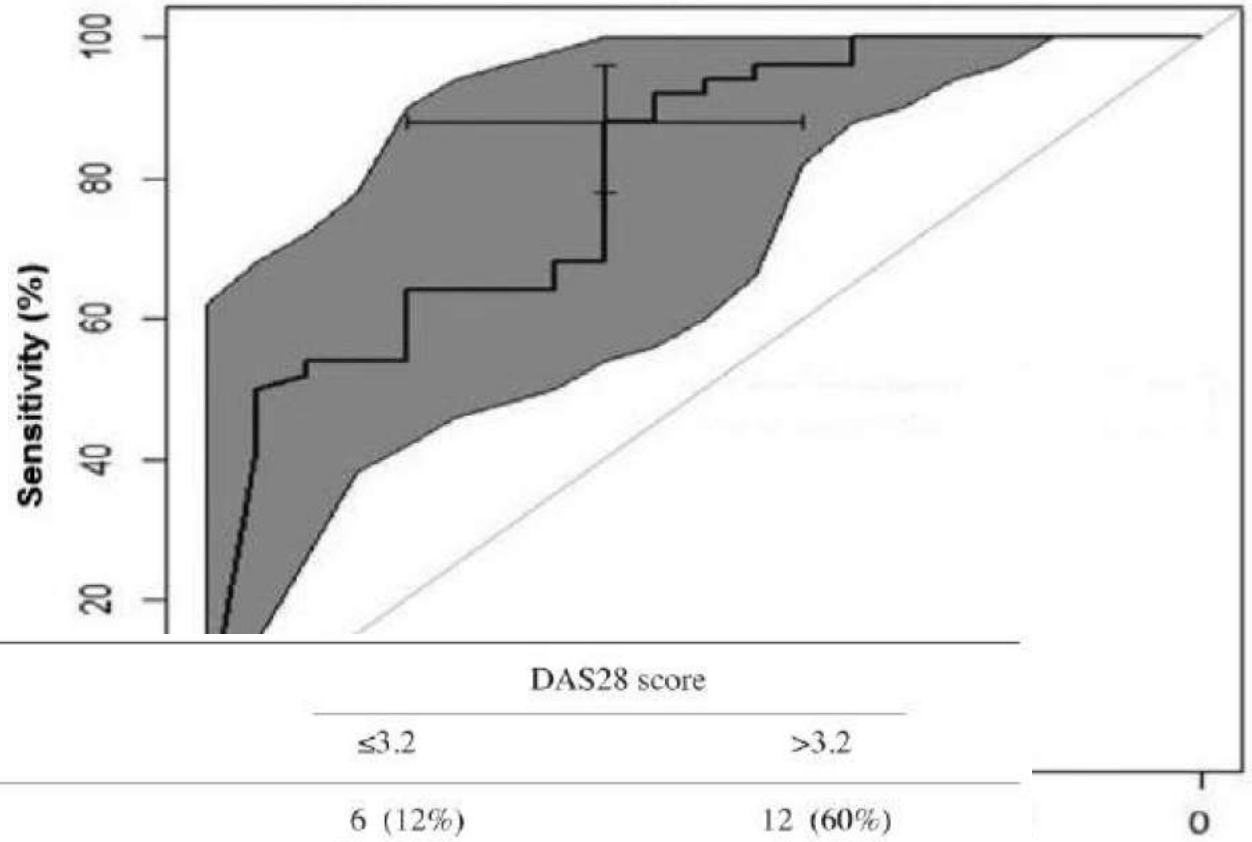

Serum levels of ADL	DAS28 score ≤3.2	DAS28 score >3.2
≤4.3 mg/L	6 (12%)	12 (60%)
>4.3 mg/L	44 (88%)	8 40%)

Fig. 2. ROC curve: cut-off of the serum level of ADL for DAS28 score of low disease activity (≤3.2); ADL: adalimumab.

Clinical and Experimental Rheumatology 2014; **32**: 942-948.

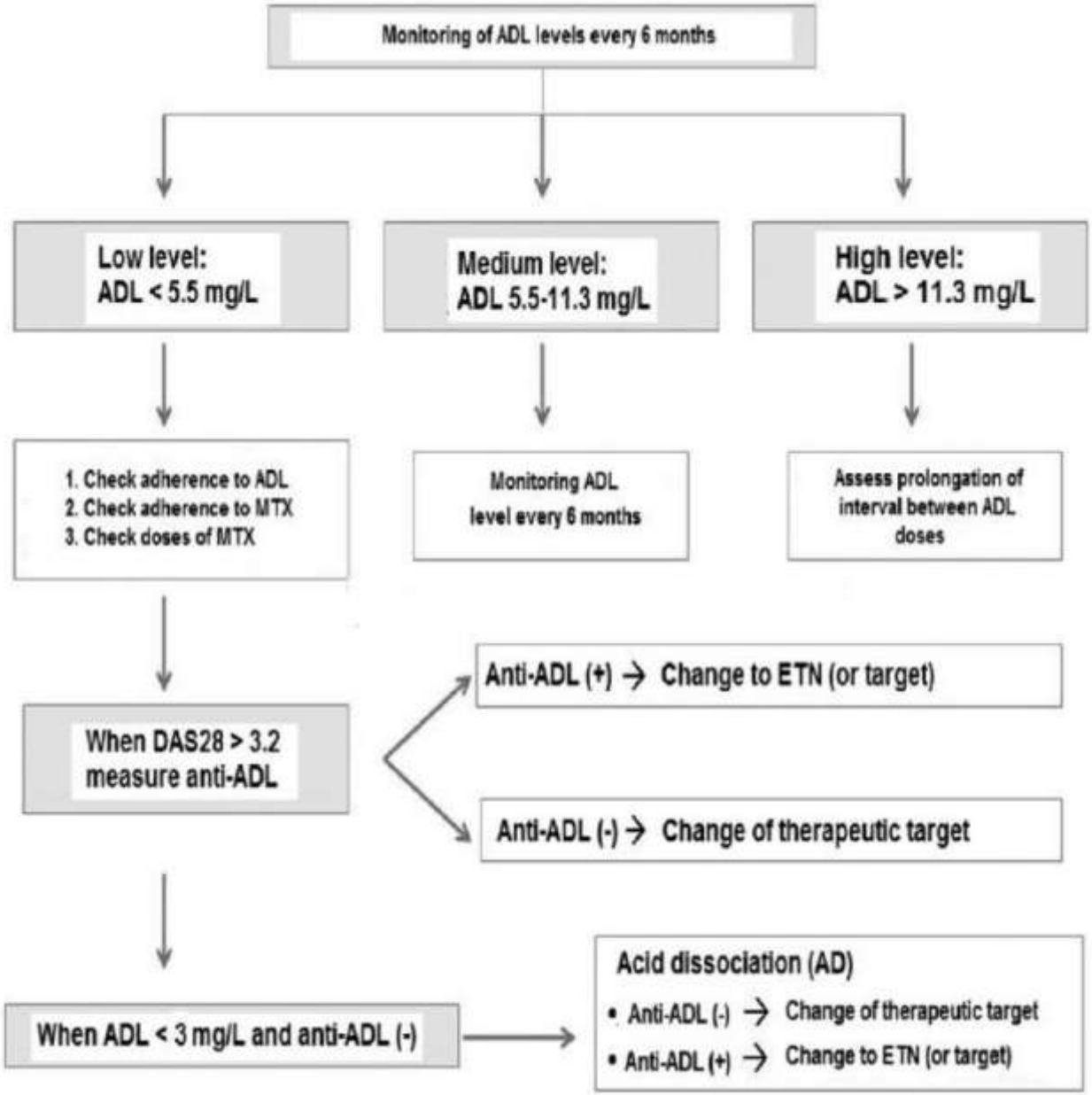

Fig. 4. Treatment algorithm based on monitoring of serum ADL levels and the presence of positive or negative anti-ADL antibodies (ADL: adalimumab; MTX: methotrexate; ETN: etanercept).

Letter to the Editor

Francisca Llinares-Tello*, José Rosas-Gómez de Salazar, José Miguel Senabre-Gallego, Gregorio Santos-Soler, Carlos Santos-Ramírez, Esteban Salas-Heredia, Juan Molina-García and the AIRE-MB Group[a]

Analytical and clinical evaluation of a new immunoassay for therapeutic drug monitoring of etanercept

Table 1 Mean serum levels of ETN and DAS28 or BASDAI in patients included in the clinical validation study.

Diagnostic			ETN 50 mg/7 days	ETN 50 mg/10 days	ETN 50 mg/14 days
RA (p=0.03)[a]	Responders (41 patients treated during 4.5±3.2 years)	ETN concentration (mg/L) (DAS28)	**6.1±2.8** (1.7±0.7)	**2.5±0.9** (1.5±0.6)	**2.1±1.1** (2.0±0.9)
	Non-responders (4 patients treated during 3.2±3.0 years)	ETN concentration (mg/L) (DAS28)	**3.2±2.4** (3.5±0.2)	–	–
AS (p=0.09)[a]	Responders (28 patients treated during 2.2±2.2 years)	ETN concentration (mg/L) (BASDAI)	**4.8±2.1** (2.0±1.0)	**3.1±1.1** (2.0±0.6)	**1.2±0.5** (2.1±0.9)
	Non-responders (8 patients treated during 1.8±1.6 years)	ETN concentration (mg/L) (BASDAI)	**3.8±1.9** (5.6±1.2)	–	–

[a]Statistical significance between responders and non-responders ETN levels.

Conclusioni ?

http://www.torrinomedica.it/farmaci/Interazioni/CercaInterazioni.asp#axzz48oOjJ2UQ

http://www.hiv-druginteractions.org/checker

http://www.hep-druginteractions.org/checker

https://www.micromedexsolutions.com/home/dispatch

…facile gestione delle interazioni…. ???

	HIV Drug Interactions	TRUVEN HEALTH ANALYTICS MICROMEDEX® SOLUTIONS	HIV Drug Interactions	TRUVEN HEALTH ANALYTICS MICROMEDEX® SOLUTIONS
	Cobicistat (with ATV or DRV)	Cobicistat (with ATV or DRV)	Ritonavir	Ritonavir
Atovaquone	◆	✓	■	Minor
Bupropion	◆	✓	■	Major
Dacarbazine	◆	✓	■	✓
Efavirenz	●	✓	■	Contraindicated
Gemfibrozil	◆	✓	■	✓
Metformin	■	✓	◆	✓
Nevirapine	●	Major	◆	✓
Olanzapine	◆	✓	■	Moderate
Omeprazole	■	✓	◆	Major
Pantoprazole	■	✓	◆	✓
Ranitidine	■	✓	◆	✓
Sulfadiazine	◆	✓	■	✓

● Do Not Coadminister ■ Potential Interaction ◆ No Interaction Expected ◇ No Clear Data

○ Do Not Coadminister □ Potential Interaction ◆ No Interaction Expected ◇ No Clear Data

Attenzione alle possibili mancate corrispondenze e/o segnalazioni!!!

Conclusioni

- **Interazioni farmacologiche sono (possono essere) un problema importante (tenere sempre presente la possibilità/probabilità)**

- **Aiuto ai clinici da linee guida e siti specializzati**

- **Collaborazione tra le diverse figure professionali con nozioni specifiche (Reumatologi, Infettivologi, Farmacologi, Farmacisti, ecc…)**

- **Il TDM può essere utile in molti casi (nonostante l'assenza di studi clinici prospettici).**

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Jessica Cusato
Amedeo De Nicolò
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