MEASURING IMMUNOSUPPRESSIVE DRUGS – WHY, HOW, WHAT DOES IT MEAN?

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LISTEN GROUP

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An NHS partnership with SYNLAB

AGENDA

1. Immune system overview
2. Preventing rejection
3. Monitoring
4. Measuring
5. Interpretation
6. Future

1. The Immune System

Protects the body from damage and infection caused by 'invaders'

Made up of white blood cells (leukocytes), special proteins e.g. CRP, complement, interferons

Innate system

- **Non-specific response, never changes, acts quickly**
- **Inflammation occurs to attract more immune cells**

Adaptive system

- **Highly specific, changes over time, slower to develop initially, memory**
- **Targets 'non-self'**
- **T cells, B cells, antibodies**

Transplantation

- Our immune system protects us against foreign bodies
- It sees donor organs as 'foreign' because it does not match the 'self' exactly
- The organ is therefore targeted to be got rid of
- → REJECTION

Organ Rejection

- The strength of the immune response to a transplant somewhat depends on the organ
  - Bowel > heart / lung > kidney > liver
- Rejection can be rapid (1 to 2 weeks: acute), or long-term (chronic)
- Helper T cells induce the attack on the donor organ and damage it
- In the liver, damage is caused to the blood vessels, liver cells, and the biliary tree
- Seen in deranged LFTs
  - Increased AST / ALT, bilirubin, gamma GT

2. Preventing Rejection - Immunosuppressive Agents

Used to alter the immune response, esp. adaptive

a) Broad-acting

- Steroids

b) Targeted agents

- Tacrolimus, ciclosporin, sirolimus (also everolimus, MMF)

The good bit:

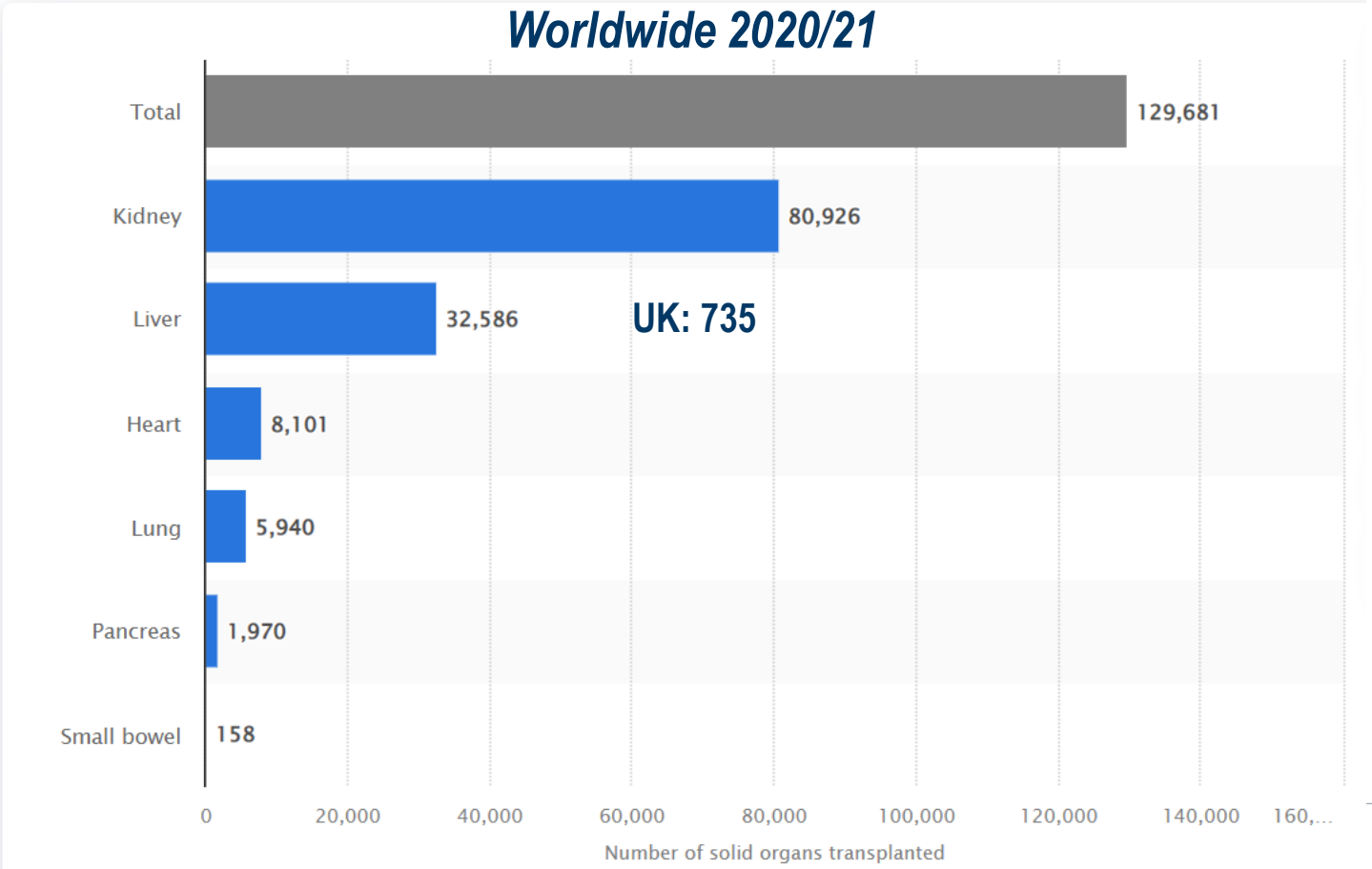
- Reduce chances of organ rejection
- Improves graft survival and health

The not-so-good bit:

- Notable side effects including infection, malignancy, renal dysfunction, diabetes

Transplant Numbers

There are many thousands of liver transplants performed every year:



3. Why Monitor Immunosuppressants?

There are large differences between individuals due to:

- **Genetics**
  - Absorption of drugs
  - Removal of drugs (metabolism)
- **Environmental factors**
  - Condition of the transplant
  - Health issues, diet, lifestyle
  - Other drugs may interfere with absorption / metabolism

Why monitor?

- The therapeutic 'window' (target concentration range) is narrow
- Not only that, but the strength of immune suppression required changes with time after transplant
- Need a balance between too little (rejection) and too much (infection, malignancy, toxicity)
- Dose is individualised based on concentration measurements

Why monitor all the time?

- New drugs added
  - MMF or sirolimus
  - Transfer to generic version of drug
  - Change of formulation, e.g. twice daily Prograf to once daily Advagraf
- Health status or treatment might change (new drugs, change in environment)

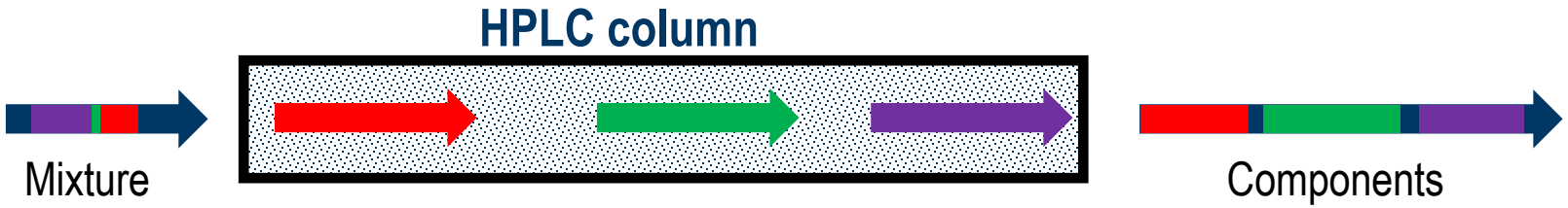
4. Measuring Immunosuppressive Drugs

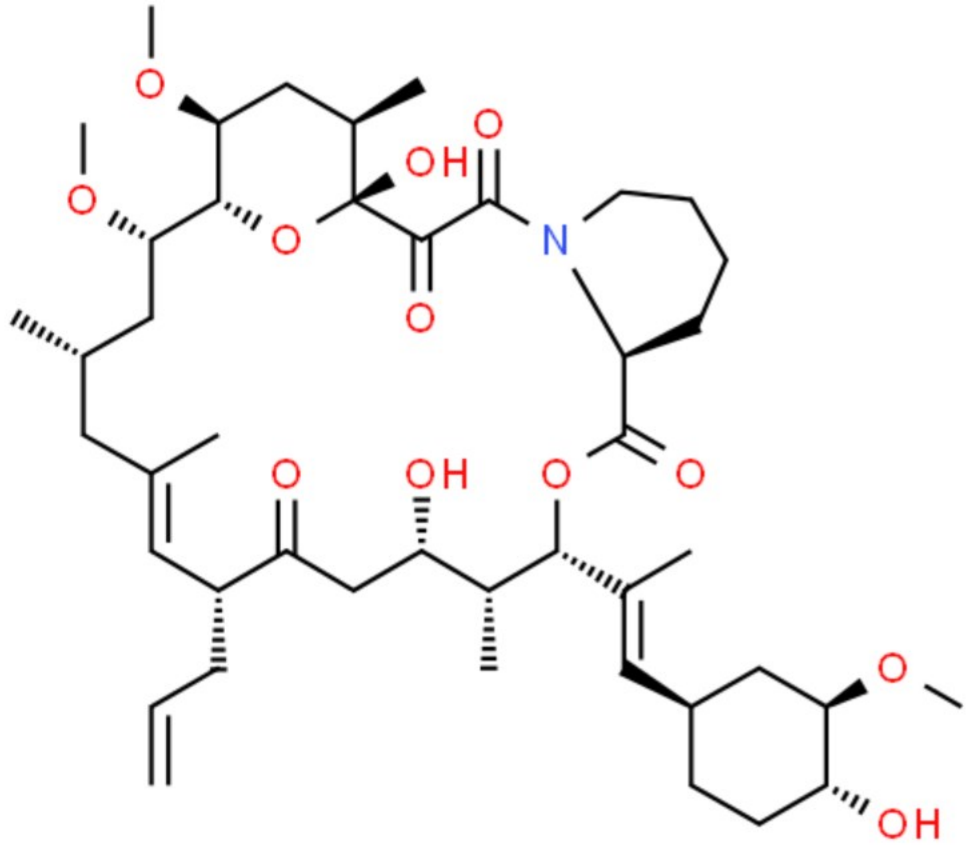
What happens to your sample?

- Makes its way to the Drug Monitoring Lab, Liver Unit
- Sample is mixed, and a small portion taken for analysis
- Remove the bits that might interfere
- Separate the drug(s) from other components (chromatography)
- Measure the amount of drug in the sample (mass spectrometry)
- Interpret the result and advise clinician

How is it measured?

- Liquid chromatography separates the mixture





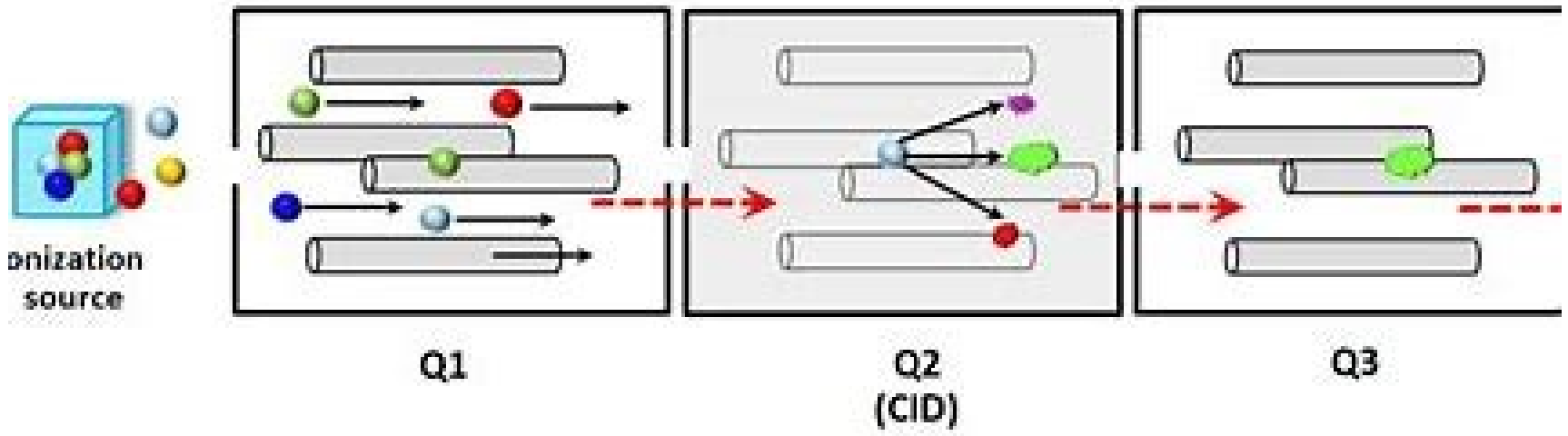
Tacrolimus has a mass of 804

Ciclosporin 1203

Sirolimus 914

MPA 320

- **Use mass spectrometry to measure the drug by 'weighing' it**



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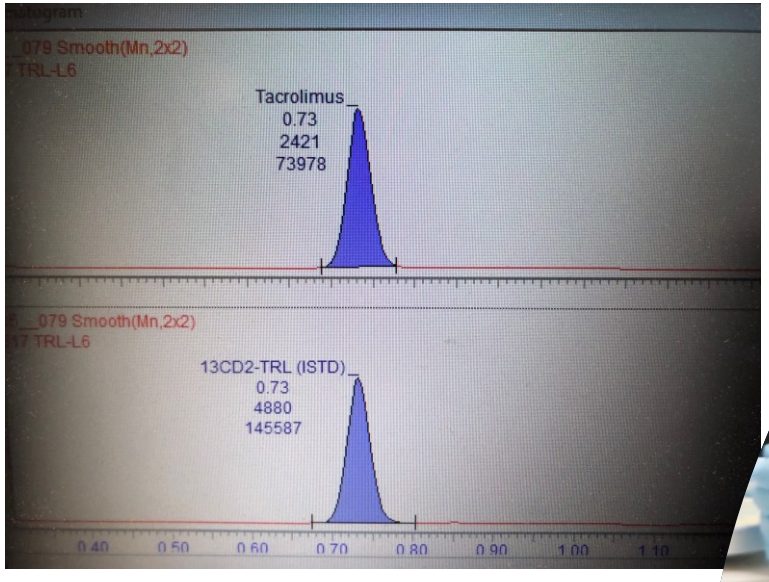

5. What do the results mean?

- Typically lower concentrations used in liver transplant
- Concentration highest immediately post-transplant, then tends to be lowered over time
- Might be reduced if side effects, or increased if rejection episode
- Individualised dose and concentration based on clinical background and drug concentrations

	Suggested target range LC-MS/MS
Tacrolimus	1 – 12 µg/L
Ciclosporin	>40 µg/L
Sirolimus	3 – 15 µg/L
MPA	1 – 3 mg/L

- Note that these are 'suggested' ranges, and could actually be lower or higher
- You can help by:
  - Making sure the sample is pre-dose
  - Remember when you last took the dose, and tell the care team
  - Tell if you are taking herbal remedies or any other drugs

6. The Future

- Automation of the analysis

- New immunosuppressive agents?
- Tolerance, especially in liver
- Gene manipulation

Thank you