Does the Evidence Support the Use of Mycophenolate Mofetil Therapeutic Drug Monitoring in Clinical Practice? A Systematic Review

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Mycophenolate Mofetil (MMF)
- Less variability in pharmacokinetic profile
- Fixed doses
  - 2-3 gm/day in divided doses
- Steroids
  - 7-8MPA-gluconolactone (MPG)
- Cyclosporine
- Low albumin renal failure
- Antibiotics

Factors affecting MPA pharmacokinetics

Therapeutic Drug Monitor (TDM)
- Inconvenient, costly
- Pharmacokinetic parameters vs. clinical outcome
  - Previous review (till 2005) → no clear evidence
  - Systematically search and current evidence

Materials and Methods
- Database
  - Ovid Medline and Embase
  - Cochrane Central Registry of Controlled Trials
  - Transplant Library from the Centre for Evidence in Transplantation
  - Clinical trial registries
- Key words: MMF, transplantation, TDM strategies
  - AUC monitoring, single-point sampling strategies (SPSS), multiple-point limited sampling strategies (LSS)
- Inclusion: solid organ transplantation, MMF
- Outcomes:
  - Acute rejection (AR), toxicity
Question:

- Is there a relationship between pharmacokinetic parameters (SPSS, LSS, or AUC) and clinical outcomes?
- Dose monitoring using these strategies (SPSS, LSS or AUC) improve clinical outcomes?

Results-AUC

- 8 retrospective (all KT), 2 prospective (1KT, 1HT)
- Total MAP AUC\(_{0-12h}\) vs. AR
  - Takahashi (1995): AUC > 40 mg/L/hr → low AR rate (22)
  - AR → low AUC (10, 23, 28)
  - Kuypers (2003), 100 FK-506-based regimen
    - No relationship in AR and diarrhea (29)
- Total MAP AUC\(_{0-12h}\) vs. adverse effects
  - Leukocytopenia, anemia, infection (22, 29, 31, 32)
  - GI effects (-): (10, 25, 29)
  - GI effects (+): (31, 32)
  - Weber (1999): free MAP AUC → adverse effects (26)

Results-SPSS

- Majority: trough level
  - Poor correlation with full AUC
- Post-dose 6-8hr
  - Best correlation
    - Cyclosporine, concurrent medical conditions
  - 26 studies (17KT, 7HT, 2LT)
  - 23 studies: SPSS MPA level vs. AR and adverse effects
    - Varies in AR rate
    - No relationship in adverse effects in majority (9, 23, 25, 29, 31, 33, 43, 44)
Results-LSS

- 2-3 times-points within 2hr post-dose
  - Regression analysis
    - Timing of sampling is critical
  - Bayesian approach
    - Population data
      - Demographic features, clinical features
    - Strict timing of sampling is not required
    - Specialized computer software
    - Adequate set of population data
    - MMF is not clearly defined in pharmacokinetic model

Results-LSS

- 6 studies (5KT, 1HT)
  - 4 retrospective (44, 57, 68, 69)
    - Various sampling times
    - AR → low estimated AUC
    - No relationship in adverse effect (57, 68)
  - 2 randomized controlled
    - International multicenter Fixed Dose versus Concentration Control (FDCC) (70, 71)
    - APOMYGRE from France (72)

Results-LSS

- FDCC, 901 KT, regression analysis
  - Fixed dose (1 g bid)
  - Concentration-controlled (AUC: 30-60 mg/L.hr)
    - Adjust at D3, D10, M1, M3, M6, M12
    - No difference in rejection, treatment failure, adverse effects at 12 mo
  - APOMYGRE, 137 KT, Bayesian model
    - Fixed dose (2 g/day)
    - 70% under dose by D14
    - Concentration-controlled (AUC:40 mg/L.hr)
    - Adjust at D7, D14, M1, M3, M6, M12
    - Treatment failure: 47.7% vs. 29.2%, p=0.03
    - Acute rejection: 30.7% vs. 12.3%, p=0.01
    - No difference in adverse effects

Results-LSS

- APOMYGRE
  - More homogenous patient population
  - Only cyclosporine as CNI
  - Stricter dose adjustment from computer
  - Long-term benefits remain to be determined
Discussion

- Current evidence for TDM of MMF is sparse
  - Full MPA AUC vs. acute rejection: good relationship
  - Full MPA AUC vs. adverse effects: no clear relationship
  - Fixed vs. concentration-controlled dose
    - Only one randomized trial (35, 36)
    - No clinical advantage
  - HT → KT?, LT?
  - 12h monitoring: unsuitable for clinical practice
  - SPSS: poor correlation
  - LSS (Bayesian model)
    - Potential to improve outcome
    - Need long-term follow-up

- Enteric-coated mycophenolate sodium (EC-MPS)
  - Bioequivalence to MMF
  - Delayed absorption
    - Higher, more variable trough level → affect SPSS, LSS
    - No study now

- Pharmacodynamic monitoring
  - Better reflect clinical outcome
  - MPA → inosine 5-monophosphate dehydrogenase (IMPDH)
    - High IMPDH → high rejection rate
    - Technically challenging, expensive, time-consuming