Primum non nocere
First do no harm: Adverse effects of IBD therapy & how to prevent them

Tariq Ahmad, Exeter, UK
Symposium Sanct Gallen 2018

Adverse drug reactions (ADRs)

• ADRs kill 197 000 EU citizens annually, at a cost of €79 billion
• 6.5% of UK hospital admissions due to ADRs
• Annual UK cost £1 billion
• Incidence is increasing
• 70% ADRs possibly or definitely avoidable

Frequency of ADRs leading to drug withdrawal in IBD

Swiss IBD cohort: 3138 patients median disease duration 12 years

Most common ADRs leading to drug withdrawal in the Swiss IBD cohort

<table>
<thead>
<tr>
<th>Drug</th>
<th>ADR</th>
<th>% of total ADR withdrawal events</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-ASA</td>
<td>Nausea, diarrhoea</td>
<td>24.6%</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>Renal hypertension</td>
<td>16.7%</td>
</tr>
<tr>
<td>Mercaptopurine</td>
<td>Leucopaenia, GI intolerance</td>
<td>12.5%</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>GI intolerance</td>
<td>19.0%</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>GI intolerance</td>
<td>27.6%</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Adverse skin reaction</td>
<td>15.6%</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Adverse skin reaction</td>
<td>15.1%</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Cushingoid features</td>
<td>17.9%</td>
</tr>
<tr>
<td>Other steroids</td>
<td>Cushingoid features</td>
<td>22.2%</td>
</tr>
</tbody>
</table>

Consequences of ADRs in IBD

• Increased morbidity and mortality.
• Increased time with active disease.
• Increased rates of polypharmacy.
• Loss of confidence in prescriber.
• Decreased adherence.
• Increased healthcare costs.

Reducing the burden of ADRs

Preventative strategies
Personalised prescribing
Early detection & management
Reducing ADRs

Preventative strategies → Personalised prescribing → Early detection & management

Screening and vaccination for OI

Vaccination uptake could be improved

Self reported vaccination rates and adult, childhood and travel vaccines

Reasons for non-uptake
- Uncertainty about indications
- Concerns regarding vaccine safety

Herpes Zoster vaccination
Live-attenuated (LAV) & (adjuvant recombinant vaccine (ARV))

- At diagnosis or >50yrs?
- 3-4 weeks before or 4 weeks after immunosuppressive withdrawal
  - LAV appears safe in patients taking anti-TNF, Pred <20mg

Tofacitinib and risk of HZ
- 4/100 vs. 0.7/100 patient-yrs, 94% non-serious
- Risk groups: Elderly, Asians
- LAV and ARV vaccines not studied in IBD patients

Negative screening and risk of TB in patients treated with anti-TNF

- 44 patients: TST-ve (25), IGRA-ve (12), TST & IGRA –ve (7)
- 30 (68%) treated with immunomodulators / steroids at screening (Screen at diagnosis)
- Pulmonary TB - 25 [57%] patients; 40 [91%] ≥ 1 extrapulmonary location (CXR follow-up may not suffice)
- Median time from anti-TNF treatment to TB diagnosis 14.5 months (IQR: 4.9-43.3) (maintain vigilance)
- 14 7incident cases of TB (keep testing in high risk groups, inc healthcare workers and travellers to endemic areas)

Reducing ADRs

Preventative strategies → Personalised prescribing → Early detection & management
Pharmacogenetics (PGx)

- The study of variations in DNA sequence as related to drug response
  - Efficacy
  - Side effects
  - Dose
- 20-30% of ADR could be avoided by PGx testing

20-30% of ADR could be avoided by PGx testing

Ingelman-Sundberg J int Med 2001

Identifying genetic markers of ADRs

Case Definition and Phenotype Standardization in Drug-Induced Liver Injury

Strict case definitions

Large cohorts / linked EHR

Sequencing

5ASA induced nephrotoxicity

- 151 / 210 patients “definite” or “probable”
- Male predominance
- Median time to onset of renal injury 3.0 years
- Interstitial nephritis is the most common histological abnormality
- Only 30% of patients demonstrate full recovery after drug withdrawal
- 9.3% patients dialysis or transplantation

Heap et al JCC 2015

HLA-DRB1*0301 predisposes to 5ASA induced nephrotoxicity

rs3135356 OR 3.1, P=4x10^{-9}

No clinical utility

Thiopurine induced pancreatitis

- Within 3 months of starting a thiopurine:
  - Acute severe abdominal pain
  - ≥ 3 fold rise in lipase or amylase
  - Thiopurine implicated and drug withdrawn
- 335 / 441 patients passed adjudication
- Median thiopurine exposure 23.8 days
- 70% hospitalised, mean stay 5.7 days

Heap Nature Genetics 2014

HLA-DRB1*0701 predisposes to thiopurine pancreatitis

Rs2647087 OR 2.59, P=2x10^{-16}

Replication OR 2.21, P=4x10^{-6}

• Heterozygote risk 2.5x, homozygote risk 5x
• 7.7% IBD population are HLA-DRB1*0701 homozygotes and have a 17% risk of pancreatitis
• NNG - 76 patients to prevent 1 case of pancreatitis

Heap Nature Genetics 2014
Exome wide association study UK caucasians
328 cases vs. 633 thiopurine tolerant controls

Clinical validity interaction with NUDT15 and TPMT

<table>
<thead>
<tr>
<th>NUDT15 genotype</th>
<th>ref/ref</th>
<th>ref/variant</th>
<th>variant/variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPMT haplotype</td>
<td>unknown</td>
<td>ref/ref</td>
<td>ref/variant</td>
</tr>
<tr>
<td>ref/ref</td>
<td>6.0%</td>
<td>5.2%</td>
<td>54.6%</td>
</tr>
<tr>
<td>ref/variant</td>
<td>12.1%</td>
<td>11.0%</td>
<td>73.1%</td>
</tr>
<tr>
<td>variant/variant</td>
<td>77.6%</td>
<td>77.2%</td>
<td>98.7%</td>
</tr>
</tbody>
</table>

Number needed to NUDT15 genotype = 100 patients
Pre-treatment genotyping for NUDT15 should reduce the number of TIM cases by 13%

HLA-B*5801 and severe cutaneous adverse reaction (SCAR) to Allopurinol

- Mortality from SCAR ~ 25%
- HLA-B*5801 associated with SCAR in all populations
- Han Chinese:
  - HLA-B*5801 carriage 20%
  - SCAR OR 165, PPV 2% NPV 100%
- Not cost effective as stand alone PGx test in European populations

PDGFD and corticosteroid induced adrenal suppression

GWAS of steroid induced adrenal suppression
low-dose short synacthen test: peak cortisol < 350 nmol/L
- 499 paediatric patients with asthma treated with inhaled CS
- Replicated in paediatric asthma (n=81) and adult COPD (n=78) cohorts
- Risk of adrenal suppression mt/mt
  - Children asthma 5.89 (2.97–11.68)
  - Adults COPD 2.41 (1.10–5.28)

Zineh Pharmacogenomics 2011; Ko BMJ 2015

Exome wide association study UK caucasians
328 cases vs. 633 thiopurine tolerant controls

Novel 6bp in in-frame deletion
AGGAGTC/A => p.Gly17_Val18del
5.8% cases vs 0.2% controls; OR = 38.2; P value = 1.3 × 10⁻⁸

Any coding NUDT15 variant
10.3% TIM cases vs. 0.8% controls; OR = 14.5; P = 3.3 × 10⁻¹²

Clinical validity interaction with NUDT15 and TPMT

NUDT15

phenotype

Wild-type TIM cases

Cases TPMT and/or NUDT15 variants

P value

Lowest neutrophil count (<10⁹/L) median (IQR)

1.0 (0.7–1.2) 0.8 (0.4–1.1)

P = 2.0 × 10⁻⁶

Hospitalisation n(%)

16.5% (38/231) 39.8% (39/98)

P = 4.8 × 10⁻⁶

Infections n(%)

16.5% (38/231) 21.4% (21/98)

P = 0.282 (ns)

GCSF n(%)

5.4% (12/231) 19.4% (19/98)

P = 5.1 × 10⁻⁵

Zineh Pharmacogenomics 2011; Ko BMJ 2015

PDGFD and corticosteroid induced adrenal suppression

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low-dose short synacthen test: peak cortisol < 350 nmol/L


499 paediatric patients with asthma treated with inhaled CS
Replicated in paediatric asthma (n=81) and adult COPD (n=78) cohorts
Risk of adrenal suppression mt/mt
  - Children asthma 5.89 (2.97–11.68)
  - Adults COPD 2.41 (1.10–5.28)
Reducing the risks of combination therapy

Annual risk per patient

<table>
<thead>
<tr>
<th>Age</th>
<th>Unexposed</th>
<th>Thiopurine Mono</th>
<th>Anti-TNF Mono</th>
<th>Combo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>128,285</td>
<td>47,483</td>
<td>26,355</td>
<td>12,023</td>
</tr>
<tr>
<td>Serious infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤65</td>
<td>1/159</td>
<td>1/105</td>
<td>1/56</td>
<td>1/46</td>
</tr>
<tr>
<td>≥65</td>
<td>1/43</td>
<td>1/37</td>
<td>1/19</td>
<td>1/20</td>
</tr>
<tr>
<td>Opportunistic infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤65</td>
<td>1/2500</td>
<td>1/625</td>
<td>1/526</td>
<td>1/250</td>
</tr>
<tr>
<td>≥65</td>
<td>1/1000</td>
<td>1/370</td>
<td>1/169</td>
<td>1/119</td>
</tr>
<tr>
<td>Lymphoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>1/3846</td>
<td>1/1852</td>
<td>1/2439</td>
<td>1/1053</td>
</tr>
</tbody>
</table>

3 month mortality rate: Serious infection 3.9%, opportunistic infection 3.0%

Kirchgesner et al Gastroenterology 2018; Lemaitre et al JAMA 2017

HLA-DQA1*05 and time to antibody development

<table>
<thead>
<tr>
<th>Chr.</th>
<th>Top variant</th>
<th>Minor Allele Frequency</th>
<th>Hazard ratio</th>
<th>P-value</th>
<th>Replication</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>rs2097432</td>
<td>20%</td>
<td>1.68</td>
<td>4.2×10⁻¹³</td>
<td>7.84×10⁻⁴</td>
</tr>
<tr>
<td>11</td>
<td>rs1272102</td>
<td>6%</td>
<td>0.46</td>
<td>4.76×10⁻⁸</td>
<td>0.49</td>
</tr>
</tbody>
</table>
Evolution of ADAs by genotype & immunomodulator (ADA titre ≥10AU/ml at any time)

Accelerating the time to clinical implementation

Reducing ADRs

The impact of delayed recognition of ADRs

Summary

• ADRs are a major cause of morbidity and mortality and a huge burden for healthcare systems
• Clinical and research focus on screening and vaccination strategies is required to reduce the burden of serious and opportunistic infections
• Pharmacogenetic research has identified promising predictive biomarkers of ADRs. Overcoming the barriers to implementation is a research priority.
• Greater awareness and earlier detection is required to reduce the morbidity and costs of ADRs.