Prevention and Identification of Infectious Complications in IBD Patients

Iyad Issa MD
Chief Medical Officer, RHUH
Part time consultant, CMC

THE FIRST
Inflammatory Bowel Disease Day
of The Lebanese Society of Gastroenterology
• Most IBD patients (excluding mild phenotypes) end up with treatment with either thiopurines or “biologic agents” (anti-TNF alpha or anti-integrins)

• The common knowledge is that these medications increase the risk of side effects and notably infections and malignancy

• However, available data may be conflicting as some has shown no increase in risk

• Which Rx carries worse risk for infections? type? location? risk factors?
• Anti-TNFs versus thiopurines?
• Combination Rx worse?
• What about the newer anti-integrins?
Biologic options for IBD

**TNF ANTAGONISTS**
- INFLIXIMAB (since 2002 for CD, since 2005 for UC)
- ADALIMUMAB (since 2008 for CD, since 2012 for UC)
- CERTOLIZUMAB PEGOL (since 2008 for CD, not approved for UC)
- GOLIMUMAB (since 2013 for UC, not approved for CD)

**ANTI-INTEGRINS**
- NATALIZUMAB (since 2008 for CD, not approved for UC)
- VEDOLIZUMAB (since 2014 for CD and UC)

**IL-12/IL-23 ANTAGONISTS**
- USTEKINUMAB (since 2016 for CD, not approved for UC)
Do biologics cause infections?

- Numerous “network meta-analysis” were conducted in recent years in an attempt to quantify and compare the magnitude of infectious risk imparted by the biologic agents used in IBD.

- Three meta-analyses were conducted to compare the overall safety profiles, including infectious risk, of biologic agents in relation to placebo in CD (10 RCTs), UC (7 RCTs), and overall IBD (16 RCTs).

- Overall, the authors found no evidence of an increased rate of infection among any of the biologic therapies in all 3 analyses.

- This is consistent with the findings published in an AGA technical review. In fact, there was no increase in any adverse events with biologic therapies compared with placebo.

Do biologics cause infections?

- Recent meta-analysis, 14 long term (>52 weeks), P C DB trials of maintenance Rx on biologic mono therapy.
  - 8 RCTs in CD
    - 6 anti-TNF (IFX, ADA, CZM) = 2013 patients
    - 2 anti-integrin (NZM, VDM) = 883 patients
  - 6 RCTs in UC
    - 5 anti-TNF (IFX, ADA, GOL) = 1832 patients
    - 1 anti-integrin (VDM) = 373 patients

Shah ED, Inflamm Bowel Dis. 2017;23:570-577
Do biologics cause infections?

No increased risk of **SERIOUS** or **OPPORTUNISTIC** infections between biologic Rx and placebo


<table>
<thead>
<tr>
<th>THERAPY</th>
<th>CD</th>
<th>UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled anti-TNF Rx</td>
<td>1.12</td>
<td>1.16* (NNH=18.3)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>0.81</td>
<td>1.19</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>1.18</td>
<td>1.14</td>
</tr>
<tr>
<td>Certolizumab</td>
<td>2.94</td>
<td></td>
</tr>
<tr>
<td>Golimumab</td>
<td></td>
<td>1.38* (NNH=9.3)</td>
</tr>
<tr>
<td>Pooled anti-integrin Rx</td>
<td>1.10</td>
<td>1.02</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>1.09</td>
<td>1.02</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>1.11</td>
<td></td>
</tr>
</tbody>
</table>
Do biologics cause infections?

49 RPCTs = 14,950 participants

Primary outcomes:
- Serious infections
- Opportunistic infections
- TB
- Any infection

Disease duration 4.7 - 12.4 yrs
F/U time 1 - 24 months

Infections = 4698
Serious infections = 310
Opportunistic infections = 79
TB = 10

Do biologics cause infections?

**Serious infections**
- Rx grp: 2.4%
- Plb grp: 2.1%
No difference between CD & UC
No difference between meds

**Opportunistic infections**
- Rx grp: 0.6%
- Plb grp: 1.1%
OR = 1.90
NNH = 194
No difference between CD & UC

**Any infection**
- Rx grp: 33.6%
- Plb grp: 30.8%
OR = 1.19
NNH = 26
No difference between CD & UC

CONCLUSIONS:

Overall, we detected a significant increase in the odds of developing any infection among patients receiving biologics.

The occurrence of opportunistic infections (including TB) was significantly higher among patients allocated to biologic treatment group.

Serious infections were not increased in patients treated with biologics.
Do biologics cause infections?

Infection risk of biologics vs thiopurines vs anti-inflammatory vs antibiotics vs corticosteroids

- 38 RCTs
- No increased risk of infection in any group compared to the other
- No increased risk of mono therapy vs combination therapy!

NB: wide CI

CONFUSING??
NMAs or cohorts??

- NMAs:
  - Exclusively include data from RCTs
  - Study a select grp of patients
  - Excluding patients with risk for infections
  - RCTs not powered to study differences in adverse events
  - Generalizability issues

*In these instances cohorts maybe a better fit to answer these questions!*
Do TNF antagonists cause infections?

Cohorts

• The European National Crohn’s Observational Registry (ENCORE)
  ★ Prospective comparison in CD patients receiving IFX vs conventional therapy
  ★ 5 years analysis = IFX associated w increased risk of SERIOUS infections (HR=1.64, 1.17-2.31) but decreased mortality (RR=0.39, 0.17-0.88)
  

• Therapy, Resource, Evaluation, and Assessment Tool (TREAT) registry
  ★ Prospective comparison in CD patients receiving IFX vs conventional therapy
  ★ 5.2 years analysis = IFX associated w increased risk of SERIOUS infections (HR1.43, 1.11-1.84)

  Lichtenstein GR, Am J Gastroenterol. 2012;107:1409-1422

• Adalimumab registry (PYRAMID)

• Certolizumab pegol registry (SECURE)

Biologics & infection risk: bottom line!

• Variable results between cohorts and pooled analyses!

• Determination of overall risk difficult

• Similar pooled RCTs data in RA showed an increased risk for infections

• Nonetheless an association is highly suspected

• Absence of head-head studies

Singh JA, Lancet 2015;386:258-265

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Risk of serious infections with biologic therapy in patients with inflammatory bowel disease: Summary of available data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Individual RCTs</td>
</tr>
<tr>
<td>TNF antagonists</td>
<td>No association</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>No association</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>No association</td>
</tr>
</tbody>
</table>

RCT, randomized controlled trial; RA, rheumatoid arthritis.
Accepted Manuscript

Risk of Serious and Opportunistic Infections Associated With Treatment of Inflammatory Bowel Diseases

Julien Kirchgesner, Magali Lemaitre, Fabrice Carrat, Mahmoud Zureik, MD; Franck Carbonnel, Rosemary Dray-Spira

PII: S0016-5085(18)30445-1
DOI: 10.1053/j.gastro.2018.04.012
Reference: YGAST 61840

To appear in: Gastroenterology
Accepted Date: 6 April 2018
The aim of this prospective population-based study was to compare the risks of **serious** and **opportunistic** infections between thiopurine monotherapy, anti-TNF monotherapy, and combination therapy in a large sample of patients with IBD.

This cohort study was based on the French National Health Insurance database (Système National d'Information Inter-Régimes de l'Assurance Maladie, SNIIRAM), which covers 95% of the French population with different insurance schemes based on employment situation.

**Outcomes**
Study outcome was any serious infection
Serious infections were classified according to infection sites
Opportunistic infections were classified according to pathogens

Head-head study on infection risk

190,694 patients

- Rx naive: 55%
- Thiopurines: 25%
- Biologics: 14%
- Combination: 6%

Per 1000 py

<table>
<thead>
<tr>
<th></th>
<th>Serious Infections</th>
<th>Opportunistic Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>9.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Rx naive</td>
<td>8.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Thiopurines</td>
<td>10.5</td>
<td>*</td>
</tr>
<tr>
<td>Biologics</td>
<td>*</td>
<td>1.7</td>
</tr>
<tr>
<td>Combination</td>
<td>22.4</td>
<td>4.1</td>
</tr>
</tbody>
</table>

CONCLUSION:

1. These findings show that the various immunosuppressive-based IBD treatment regimens have heterogeneous risk profiles regarding the risks of serious and opportunistic infections.

2. Combination therapy exposes to higher risks of serious and opportunistic infections than anti-TNF monotherapy.

3. Anti-TNF monotherapy shows higher risks of serious infections, and opportunistic bacterial infections than thiopurine monotherapy.
Risk factors for infections

Still subject to debate
Risk factors for infections

- Single centre case-control analysis
- Specific risk factors for infections among IBD patients (100 cases - 200 controls)

Risk Factors: Combination Rx & Older age

- IFX: 4.4
- Steroids: 3.3
- AZA: 3.8
- MTX: 1.3
- Mesalamine: 1.1

Toruner M, Gastroenterol 2008;134:929-936
Risk factors for infections

- TREAT registry (6273 patients)
- Univariate analysis

- Nationwide Inpatient Sample (NIS)
- 67216 adm for inf vs 169224 adm


Risk factors for infections

What about serum concentration and dose of TNF antagonists??

- TAXIT trial
- Concentration based IFX dosing vs Clinically based dosing

Meta-analysis in RA patients

- Std dose & Hi dose biologics = increased infection risk
- Low dose biologics = no infection risk


## Risk factors for infections: Bottom Line

<table>
<thead>
<tr>
<th>Potential Risk Factor</th>
<th>Reported Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination therapy</td>
<td>OR = 2.9-14.5</td>
</tr>
<tr>
<td>Steroids</td>
<td>HR = 1.57</td>
</tr>
<tr>
<td>Narcotic analgesics</td>
<td>HR = 1.98</td>
</tr>
<tr>
<td>Old age</td>
<td>OR = 1.20</td>
</tr>
<tr>
<td>Diabetes</td>
<td>OR = 2.74</td>
</tr>
<tr>
<td>Disease severity</td>
<td>HR = 2.24</td>
</tr>
<tr>
<td>Disease duration (&gt;5 years)</td>
<td>HR = 1.42</td>
</tr>
</tbody>
</table>
Types of infections

- Retrospective analysis
- 100 IBD patients

764 opportunistic infections

<table>
<thead>
<tr>
<th>Category Name</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida Albicans</td>
<td>26%</td>
</tr>
<tr>
<td>Herpes Simplex</td>
<td>18%</td>
</tr>
<tr>
<td>CMV</td>
<td>12%</td>
</tr>
<tr>
<td>EBV</td>
<td>8%</td>
</tr>
<tr>
<td>Other</td>
<td>8%</td>
</tr>
<tr>
<td>Viruses</td>
<td>39%</td>
</tr>
<tr>
<td>Bacteria</td>
<td>24%</td>
</tr>
<tr>
<td>Mycobacteria</td>
<td>25%</td>
</tr>
<tr>
<td>Other</td>
<td>12%</td>
</tr>
</tbody>
</table>


Location of infections

- **TREAT registry**
  - Pneumonia: 0.24 cases per 100 years
  - Cellulitis: 0.15 cases per 100 years
  - Abd abscess: 0.11 cases per 100 years
  - Perirectal abscess: 0.11 cases per 100 years

- **ENCORE registry**
  - Abscess
  - Pneumonia
  - Peritonitis
  - Sepsis

- **NIS registry** (mortality related to):
  - Sepsis
  - Pneumonia
  - C Diff infection


8561 serious infections

- Skin: 17%
- GI tract: 23%
- Lung: 24%
- Urinary: 14%
- Other: 22%

- 07% sepsis
- 03% ENT
- 03% musculoskeletal
- 09% other

Kirchgesner J, Gastroenterology (2018)
Management of infections

Lack of definitive RCT data on risk and rates of infections makes creating evidence based guidelines difficult.

ECCO consensus guidelines in 2009:

“IBD patients should be considered immunosuppressed if they are malnourished or receiving an immunosuppressant associated with increased infection risk (TNF antagonists, corticosteroids, thiopurines, calcineurin inhibitors and other biologics)”. 

Rahier JF, J Crohns Colitis. 2009;3:47-91
Management of infections: Viral

Focus on prevention prior to therapy initiation

- **Live vaccines**: 4 weeks prior to starting immunosuppression
- **Inactive vaccines**: 2 weeks prior to Rx
- **Varicella Zoster**: vaccine 3 weeks pre-Rx
- **Influenza & HPV**: as per local recommendations
- **HBV seronegative** = vaccine (follow up serology)
- **HBV seropositive** = nucleoside analog 2 months prior to Rx
- **R/O CMV colitis prior to uptitrating immunomodulators**
Management of infections: Bacterial

Recommended management is to treat the infection as per professional guidelines and hold concomitant immunomodulator therapy until the active infection resolves.

• **Prevention:**
  - patients on anti-TNF should receive the PCV13 vaccine
  - PPSV23 vaccine 8 wks later (Strep pneumoniae)
  - PPSV23 again at the 5 years mark

• **TB:**
  - Should be ruled out prior to therapy
  - Latent TB treated as per local guidelines (Isoniazid for 9 months)
  - Active TB should be treated fully prior to initiation

Rubin LG, Clin Infect Dis. 2014;58:e44-e100
Management of infections: Bacterial

- **Salmonella sp, Listeria monocytogenes, Legionella pneumophila, Nocardia sp:**
  - Immunomodulator discontinuation
  - Early pathogen rule out
  - Future risk-factor avoidance
    - ✓ *Salmonella*: raw eggs, unpasteurized cheese, uncooked meat
    - ✓ *Listeria*: Unpasteurized cheese, uncooked meat, raw vegetables
  - Legionella: stop Rx indefinitely

- **Clostridium Difficile:** not clear whether withholding immunotherapy,
  ECCO 2009 guidelines do not recommend withholding therapy for lack of evidence
Management of infections: Fungal or parasitic

• No vaccination available

• Current recommendations: exposure avoidance
## Management of infections: ECCO 2009

<table>
<thead>
<tr>
<th>ECCO recommendation</th>
<th>Pathogens</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccination</td>
<td>HBV, Influenza (annually), HPV, VZV, Strep pneumoniae Vaccinations prior to travel to endemic areas</td>
<td>Vaccination should ideally be prior to initiation therapy. Live vaccines contraindicated in patients receiving therapy</td>
</tr>
<tr>
<td>Screening prior to IM therapy</td>
<td>HIV, HBV, HPV, VZV</td>
<td>Annual cervical cancer screening</td>
</tr>
<tr>
<td>Chemoprophylaxis</td>
<td><em>Pneumocystis jirovecii</em></td>
<td>If 3 IM agents used and 1 is either an anti-TNF or a calcineurin inhibitor</td>
</tr>
<tr>
<td>Stop IM during active infection</td>
<td><em>Listeria monocytogenes, Salmonella sp, Legionella pneumophilia, S pneumoniae, M tuberculosis</em></td>
<td>IM therapy should be stopped until active infection resolves</td>
</tr>
<tr>
<td>Stop IM indefinitely</td>
<td><em>Nocardia sp</em></td>
<td></td>
</tr>
</tbody>
</table>

THANK YOU!

Iyad Issa MD
Chief Medical Officer, RHUH
Part time consultant, CMC