Do Immunomodulators Still Have a Place in the Treatment of IBD?

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Outline

- Intro to immunomodulators (IM) in IBD
- IM in combination with IFX and ADA
- IM in combination with other biologics
- Risks associated with IM use

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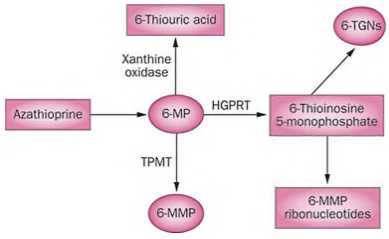
Immunomodulators

- Azathioprine (AZA), 6-mercaptopurine (6MP), methotrexate (MTX)
- First used in other autoimmune disorders (RA -1965)
- Efficacious in CD and UC (except MTX?) – first used in 1960s, prospective data - 1970s
- Effective steroid sparing agents, huge advance in treatment of IBD

Present et al. N Eng J Med1980;402-981–7
O'Donoghue et al. Lancet1978;ii:955–7
Rosenberg et al. Gastroenterology1975;69:96–9

Thiopurines

- Azathioprine, 6-mercaptopurine



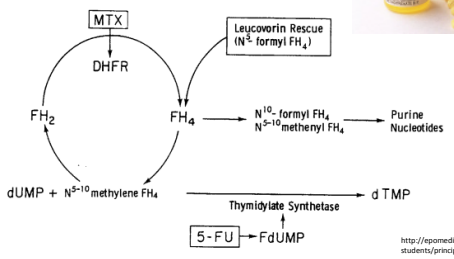
Typical dose:
AZA: 2-2.5 mg/kg
6MP: 1-1.5 mg/kg

Pharmacogenetics:
- TPMT
- NUDT15

Inflamm Bowel Dis. 2017 Sep;23(9):1592-1599

https://atlasofscience.org/prompt-resolution-of-essential-drug-intolerance/

Methotrexate



http://epomedicine.com/medical-students/principles-of-chemotherapy/

Methotrexate Monotherapy

- Monotherapy effective for CD
  - North American trial - 1995
  - 25 mg SC or IM for 12-16 wks
  - CSFR 39% vs 19% for placebo
- Limited evidence for PO MTX
  - Small trials, no clear benefit for induction
  - Cochrane Review 2014: only SC/IM is effective for induction therapy
  - Absorption of PO MTX can be limited by enteritis, and bioavailability peaks ~15 mg

Feagan et al, NEJM 1995;332(5):292-7
McDonal et al, Cochrane Database Syst Rev. 2014 Aug 6:8:CD003459

Methotrexate Monotherapy

- Monotherapy may not be effective for UC
  - Only few studies
  - 2 older RCTs, oral MTX 12.5-15 mg dose
  - No benefit for induction or maintenance
  - 2 recent trials of parenteral MTX:
    - METEOR
    - MERIT-UC

Oren et al, Gastroenterology 1996
Maté-Jiménez et al, Eur J Gastr Hepatology 2000

METEOR Trial (induction for UC)

- Multicenter European trial 2016
- 111 patients CS-dependent UC
- MTX 25 mg weekly SC/IM
- 1^0 endpoint: CSFR 16 wks:
  - 32% vs. 20% placebo; p=0.15
- 2^0 endpoint: Clinical remission 16 wks (minus endoscopy score):
  - 42% vs 24% placebo; p=0.04
- Trend toward increased rates of mucosal healing

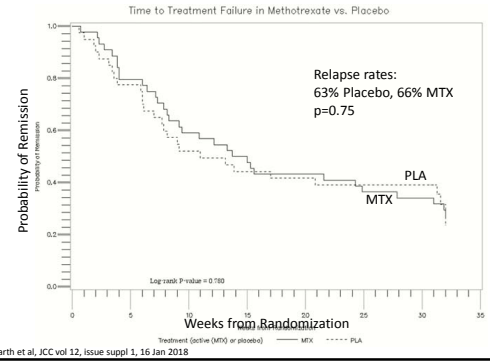
Carbonnel et al, Gastroenterology 2016

MERIT-UC Trial (maintenance for UC)

- 84 patients who achieved steroid-free response at 16 weeks using MTX 25 mg IM/SC
- Patients also given 2.4 g mesalamine
- 32 wk maintenance period, placebo vs. MTX
- Prelim results (presented at ECCO 2018):

Herfarth et al, JCC vol 12, issue suppl 1, 16 Jan 2018

MERIT-UC Results



Herfarth et al, JCC vol 12, issue suppl 1, 16 Jan 2018

Take home points

- AZA/6MP are effective induction and maintenance therapies for CD and UC
- MTX effective for induction and maintenance of CD, data does not fully support use in UC

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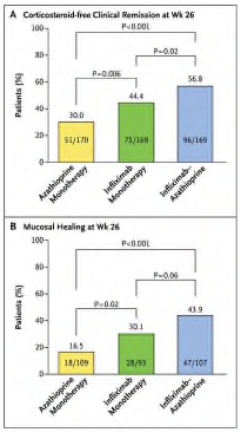
IM plus Infliximab

- SONIC trial:
  - Naïve CD patients
  - AZA, IFX, or combination therapy
  - Increased rates of MH and CSFR in combination group
  - Lower rate of immunogenicity in combo group (0.9% vs 14.6%)
  - Higher trough IFX levels in combo group (3.5 ug/mL vs. 1.6 ug/mL)

Colombel et al, NEJM 2010

SONIC RESULTS



Colombel et al, NEJM 2010

UC-SUCCESS

- Similar design to SONIC - 2014
- 239 UC patients, randomized to 3 groups
- CSFR rates:
  - AZA: 23.7%
  - IFX: 22.1%
  - AZA+IFX: 39.7%
- Lower immunogenicity rate in combo group (3% vs. 19% in IFX monotherapy)

Panaccione et al, Gastroenterology 2014; 146(2):392-400

Combination therapy with ADA

- Some retrospective studies have suggested benefit of combo Rx
- Studied in only one RCT – 2016
- 85 CD patients randomized to ADA vs ADA+AZA
- Open label design
- AZA dose 25-100 mg
- CSFR at wk 26: 71.8 vs 68.1% (p=0.63)

Matsumoto et al, JCC 2016

What is the role of IM in combo RX with anti-TNF?

- What is the mechanism?
  - Enhance anti-TNF activity (reducing immunogenicity, boosting drug level)
  - Independent anti-inflammatory effect?
- Post-hoc analysis of SONIC…

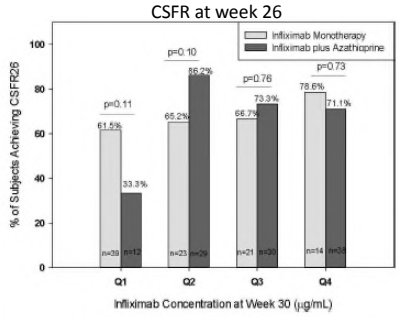
Post-hoc analysis from SONIC

- 206 patients with IFX levels at wk 30
- Separated in quartiles based on IFX level
  Q1: <0.84, Q2: 0.84-2.35, Q3: 2.36-5.02, Q4: >5.02
- Compared compared AZA + IFX group with IFX monotherapy group
- CSFR26 and MH26

Colombel et al, Gastroenterology 2017;152(5) suppl 1:S37-38

Post-hoc analysis from SONIC

CSFR at week 26

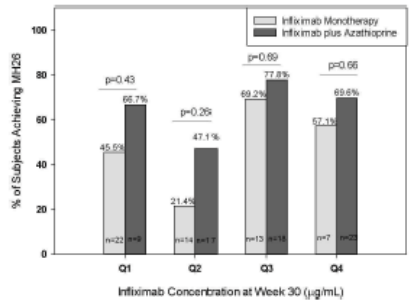


Q1: <0.84 µg/mL; Q2: 0.84 µg/mL to <2.36 µg/mL; Q3: 2.36 µg/mL to <5.02 µg/mL; Q4: ≥5.02 µg/mL

Colombel et al, Gastroenterology 2017;152(5)suppl 1:S37-38

Post-hoc analysis from SONIC

Mucosal healing at week 26



Colombel et al, Gastroenterology 2017;152(5) suppl 1:S37-38

Take home points

- AZA plus IFX: superior to IFX monotherapy for naïve CD and UC patients – SONIC and SUCCESS
- For patients failing IM therapy, benefit of continuing IM when "stepping up" to biologic is unclear
- Benefit of combination therapy with ADA is suggested by observational data, but lone RCT did not show clear benefit in CD
- Mechanism of IM benefit in combo Rx unknown
  - Reduce immunogenicity?
  - Increase biologic concentration?
  - Independent anti-inflammatory effect(s)?

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Combination Therapy: Other Biologics

- Certolizumab, Golimumab – little data
- Lower immunogenicity rates for these at baseline
  - IFX 25.3%
  - ADA 14.1%
  - CZP 6.9%
  - GOL 3.8%
- Vedolizumab – little data
  - Post-hoc analysis from GEMINI 1 trial showed no benefit for combination therapy (but AZA was discontinued at 6 weeks)
  - Several observational studies show no benefit
  - Immunogenicity rate in GEMINI trial – 4%
  - No conclusive evidence
- Ustekinumab – little data
  - UNITI trial pharmacokinetic data show no effect of concomitant IM on drug level or immunogenicity
  - Immunogenicity rate: 2.3%

Thomas et al. BioDrugs. 2015;29(4):241-58

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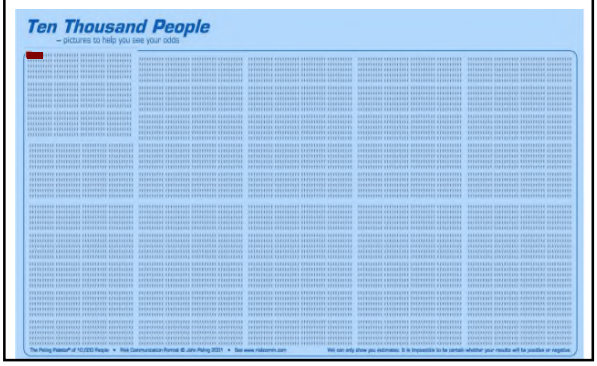
Risks of IM use

- Most significant risks: opportunistic infections and malignancy
- 2009 meta-analysis of 26 trials (9 RCTs) of CD patients:
  - Non-Hodgkin's lymphoma incidence rates
  - SEER database: 2 in 10,000 pt-years
  - IM alone: 4 in 10,000
  - Combination with anti-TNF: 6 in 10,000

Siegel et al Clin Gastro Hep. 2009

Lymphoma Risk: thiopurines, anti-TNF



Risks of IM use

- 2013 – FDA Adverse Reporting System
  - T-cell lymphoma increased by IM or combo
- 2012 – pooled analysis of 10 trials of IFX-treated IBD pts
  - Infection and malignancy signal for IM, not IFX
- 2011 – Kaiser IBD registry (>16,000 pts)
  - Lymphoma signal for IM and combo
- TREAT registry – large prospective cohort of CD pts
  - No statistically significant associations with infection/malignancy for IM or anti-TNF
  - Numerical trends for IM and combo

Herrinton Am J Gastro 2011 Lichtenstein Am J Gastro 2014
Lichtenstein Am J Gastro 2012

Risks of IM use

- Most recent data: French nationwide cohort study
- 189,289 patients:
  - Small but statistically significant increase in lymphoma rate in thiopurine, anti-TNF, or combination therapy
  - Risk of combo therapy > either drug alone

Lemaitre et al JAMA 2017

Take home points

- IM therapy increases risks of malignancy and opportunistic infection
- Most data suggests that IM risk >> anti-TNF
- Risks/benefits of IM use must be discussed with patients

Summary

- IM are effective treatments for IBD (MTX for UC??)
- Combination therapy (AZA+IFX) is superior in naïve patients
- Data is sparse for combination therapy with other biologics – treatment decisions should be individualized
- Risks of IM use may outweigh benefit in some, but not all, patients

Thank you!