WEBINAR

Thursday 22 July 2021

IBD: IDENTIFIED UNCERTAINTIES IN OPTIMISING BIOLOGIC AND SMALL MOLECULE MEDICINES – THE LATEST EVIDENCE

TARGETED THERAPIES ALLIANCE

Helping consumers and health professionals make safe and wise therapeutic decisions about biological disease-modifying antirheumatic drugs (bDMARDs) and other specialised medicines. Funded by the Australian Government Department of Health through the Value in Prescribing bDMARDs Program Grant.

TARGETED THERAPIES ALLIANCE

University of South Australia

GESA Gastroenterological Society of Australia

NPS MEDICINEWISE

MEET THE PANEL

Prof Debra Rowett
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A/Prof Susan Connor
IBD Gastroenterologist

A/Prof Jakob Begum
IBD Gastroenterologist

Dr Karen Luetsch
Senior Research Fellow
& Pharmacist

Declarations of interest provided at end of slides

OUTLINE

The webinar will discuss:

- Choice of biologic for first and second-line biological therapy
- The use of biologics in combination with immunomodulators
- The use of therapeutic drug monitoring to optimise therapy
- When to consider dose-escalation and dose de-escalation of biological therapy.

BACKGROUND

- Evidence summaries developed on behalf of the Therapeutic Targeted Alliance.
- These underpin the design and delivery of services and resources for gastroenterologists and patients with inflammatory bowel disease.

ABBREVIATIONS

- Infliximab – IFX
- Adalimumab – ADA
- Golimumab – GOL
- Ustekinumab – UST
- Vedolizumab – VED
- Tofacitinib – TOF

- ACG – American College of Gastroenterology
- AGA – American Gastroenterological Association
- BSG – British Society of Gastroenterology
- ECCO – European Crohn's and Colitis Organisation
- GESA – Gastroenterological Society of Australia

LINE OF THERAPY – BIOLOGICS

- Where to start and move on to:
  - Evidence for first and second-line choices of biologics in moderate to severe ulcerative colitis and Crohn's disease
- Guideline recommendations on treatment choices and summary of pivotal RCTs
- Which, when, what and how:
  - Network meta-analyses establish infliximab as the most effective biologic, for other agents they are conflicting.

MODERATE TO SEVERE ULCERATIVE COLITIS – 1ST LINE BIOLOGIC / SMALL MOLECULE

Guidance: ECCO and AGA currently recommend IFX, VED.

- Efficacy for clinical remission calculated from pivotal RCTs, expressed as number needed to treat (NNT)*

	NNT induction	NNT maintenance
IFX	4	5
VED	6–7	3–4
GOL	8	5
TOF	10	4 (overall)
UST (not PBS)	10	5–6
ADA	12	10

*NNT calculated based on rates of clinical remission (defined as Mayo score ≤ 2, no sub-score > 1)
ACT I&II, GEMINI 1, VISIBLE, PURSUIT, OCTAVE, ULTRA, UNIFI

MODERATE TO SEVERE ULCERATIVE COLITIS – 2ND LINE BIOLOGIC / SMALL MOLECULE

Guidance: ECCO / AGA currently recommend

- Alternative TNF inhibitor agent, VED, TOF

Efficacy clinical remission in patients who (usually) were non-responsive to TNF inhibitors

	NNT induction	NNT maintenance
VED	7	3–4
TOF	8	4?

* NNT calculated based on rates of clinical remission (defined as Mayo score ≤ 2, no sub-score > 1) GEMINI, VISIBLE, OCTAVE

ULCERATIVE COLITIS – 2ND LINE BIOLOGIC / SMALL MOLECULE

If VED or TOF fail as the first biologics

- Sparse evidence to support any choice of second line agents
- IFX as potentially preferred option due to its general enhanced effectiveness
- IFX and ADA – no data from RCTs, moderate evidence from observational studies that IFX is effective after VED failure
- GOL – no data from RCTs, weak evidence from observational studies

MODERATE TO SEVERE LUMINAL CROHN'S DISEASE – 1ST LINE BIOLOGIC

Guidance:
ECCO recommends: IFX (in combination with IM), ADA
AGA recommends: IFX (in combination with IM), ADA, UST
Efficacy for clinical remission calculated from pivotal RCTs*

	NNT induction	NNT maintenance
IFX	5	5
ADA	4–6	4–5
UST	5	5–6
VED	10	5

*NNT calculated based on rates of clinical remission (defined as CDAI < 150) ACCENT I&II, GEMINI 2, CLASSIC, CHARM, UNITI

CROHN'S DISEASE – 2ND LINE BIOLOGICS – USUALLY AFTER TNF-INHIBITOR FAILURE

Efficacy for clinical remission*

- Little data on efficacy of biologics after failure of UST & VED as 1st line therapy.
- IFX recommended due to overall high efficacy.

	NNT induction	NNT maintenance
ADA (after IFX)	7	5–7?
UST	7	7
VED (w10)	10	7

* NNT calculated based on rates of clinical remission (defined as CDAI < 150) ACCENT I&II, GEMINI, EXTEND, UNITI, CERTIFI

DISCUSSION

FISTULISING CROHN'S DISEASE

1st line biologic therapy (guideline recommendations)

- IFX or ADA in combination with immunomodulator

2nd line therapy

- No evidence to establish preferred treatment
- ADA after IFX failure or UST after TNF inhibitor failure seem reasonable approaches

SPECIAL SITUATIONS / COMORBIDITIES

Extraintestinal manifestations of IBD

- 1st line biologic therapy (guideline recommendation)
  - IFX, followed by ADA (possibly as IM combination therapy)

Pregnancy and breastfeeding – only if benefit outweigh risk:

- 1st line biologic therapy – as most experience
  - IFX and ADA
- 2nd line therapy
  - Alternative TNF inhibitor and possibly VED and UST

COMBINATION THERAPY YES, NO OR MAYBE?

- RCTs testing the efficacy and safety of biologics in combination with immunomodulators have only been conducted with IFX and ADA.
- In all efficacy trials a proportion of patients were taking concomitant immunomodulators.
- Evidence for efficacy of reduced thiopurine doses in combination with IFX is emerging.

Yes	No	Maybe
IFX – both UC (thiopurine) & CD (thiopurine or MTX)	Tofacitinib	12 months with all bDMARDs

COMBINATION THERAPY YES, NO OR MAYBE?

Uncertainties

- For all biologics, combination therapy for a 12 months period could be considered to optimise chances of success in high-risk patients.
- Combination IM therapy with ADA increases drug serum levels and reduces formation of anti-drug antibodies – may increase durability over time.
- For UST, it may be beneficial to add an IM if patients are slow to respond to treatment.

DISCUSSION

BIOLOGIC DOSE ESCALATION & DE-ESCALATION

- Approximately a third of patients prescribed IFX or ADA, doses may have to be escalated to achieve or re-induce/ maintain remission.
  - Escalation for IFX is generally achieved by increasing the dose from 5 mg/kg to 10 mg/kg every 8 weeks
  - for ADA by shortening the dose interval from 40 mg every two weeks to 40 mg every week.
- Very little data on dose escalation of other biologics.

BIOLOGIC DE-ESCALATION AFTER DOSE ESCALATION

- Evidence on dose de-escalation after a dose escalation is limited to mostly observational studies.
  - varying parameters guiding or determining de-escalation strategies and success
- Combining evidence from observational studies on dose de-escalation with the few RCTs on TDM based dosing and monitoring of faecal calprotectin permit the following conclusions.

BIOLOGIC DOSE ESCALATION & DE-ESCALATION

- Approximately two thirds of patients will not relapse when dose de-escalation occurs after previous dose escalation when:
  - Deep remission for twelve months
  - Serum drug levels are maintained within recommended therapeutic ranges
  - Faecal calprotectin is within normal range before and after de-escalation
- After failed de-escalation, 10–20 % of patients will not regain remission with successive dose escalation.

Interpret within the context of lacking control groups and the ‘usual’ relapse rates or LOR over time in patients treated with TNF inhibitors.

TDM FOR BIOLOGICS – DRUG SERUM LEVELS & ANTI-DRUG ANTIBODIES

- Therapeutic drug monitoring – usually defined as monitoring serum drug levels and anti-drug antibodies.

- In practice, anti-drug antibodies are often only measured if serum drug levels are low or undetectable.

TDM FOR BIOLOGICS – DRUG SERUM LEVELS

- Serum drug levels which constitute a therapeutic range have only been established for IFX and ADA

- Minimum therapeutic serum levels or therapeutic ranges for other biologics are still exploratory
  - GOL – levels suggested based on PURSUIT
  - UST and VED – only observational studies linking levels to treatment success

TDM FOR BIOLOGICS

- Drug serum levels to achieve clinical response / remission

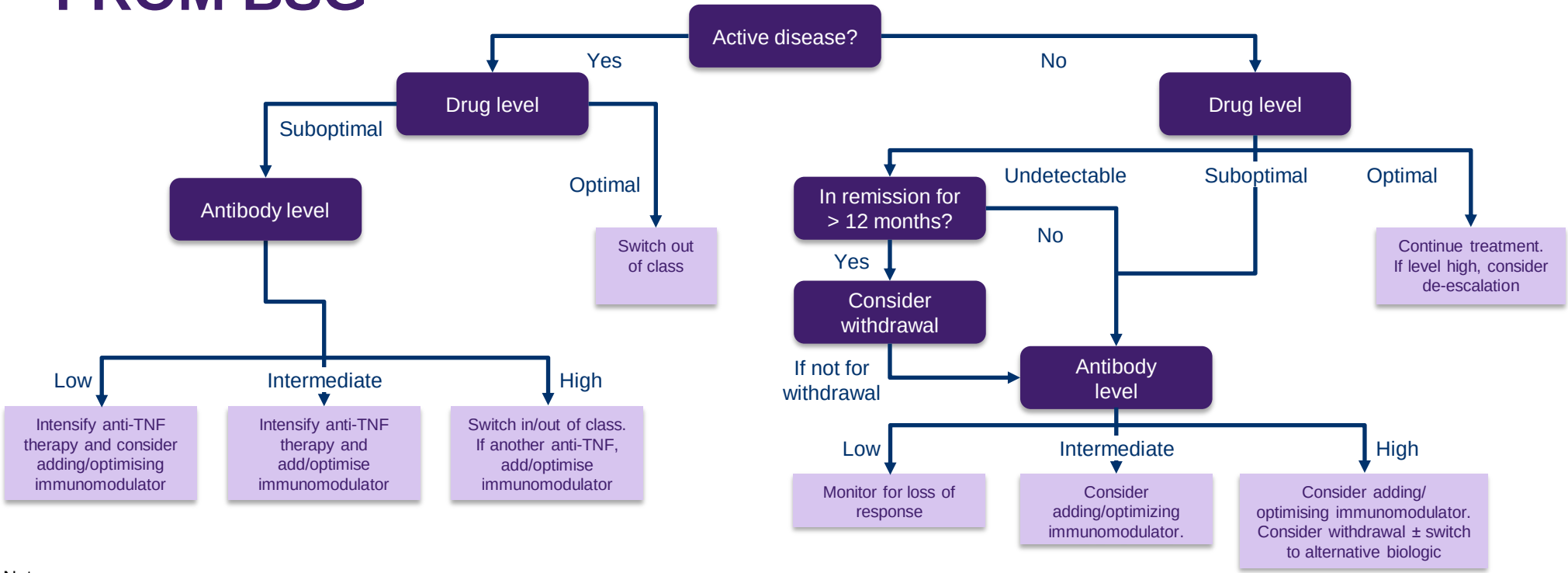
	After induction, response achieved	Active disease under treatment	Maintenance remission	
Guidelines				
AGA		IFX ≥ 5 µg/mL ADA ≥ 7.5 µg/mL GOL lack of evidence		
AGA technical review	IFX ≥ 3–5 µg/mL ADA ≥ 5 µg/mL GOL ≥ 2.5 µg/mL	IFX ≥ 7 µg/mL ADA ≥ 7.5 µg/mL GOL ≥ 1.4 µg/mL		GOL – based mainly on PURSUIT
ACG				Endorses AGA levels
Australian GESA	IFX 3–8 µg/mL ADA 5–12 µg/mL			
BSG	Optimal drug levels for IFX and ADA are not defined, depend on the assay used and clinical context			ECCO also does not have a statement on drug levels

TDM WITH BIOLOGICS – DRUG SERUM LEVELS & ANTI-DRUG ANTIBODIES

When to monitor:

- Reactive monitoring (strong evidence for supporting decision making, indirect evidence for clinical outcomes)
  - Secondary or primary LOR
- Proactive monitoring (may support clinical decision making, no evidence for influence on clinical outcome)
  - After induction
  - During maintenance
  - Step-down from combination or escalated biologic therapy

DECISIONS TO SWITCH – EXAMPLE FROM BSG



Notes:

- 'Optimal' drug levels for infliximab and adalimumab are not defined, depend on the assay used and clinical context
- After dose optimisation, the regular use of therapeutic drug monitoring in patients in remission is not currently recommended and further evidence of cost-effectiveness is awaited

https://www.bsg.org.uk/clinical-resource/bsg-consensus-guidelines-on-the-management-of-inflammatory-bowel-disease-in-adults/

DISCUSSION

QUESTIONS

RESOURCES

- **GESA** gesa.org.au
  - Australian Guidelines for General Practitioners and Physicians: Inflammatory Bowel Disease 4th Edition (updated 2018)
  - **Fact sheet for gastroenterologists:** Pregnancy, Fertility and Inflammatory Bowel Disease
  - Medication (Pregnancy, Fertility and Inflammatory Bowel Disease)
- **Crohn's & Colitis Australia** gutsmart.com.au
  - **GutSmart:** Online education platform for health professionals
- **NPS MedicineWise** nps.org.au/bdmards
  - **Action plan:** Thiopurines for inflammatory bowel disease
  - **Action plan:** Low-dose methotrexate for Crohn disease

DISCLOSURES

Susan Connor

- Received honoraria for Advisory Board participation, speaker fees, educational support and/or research support for Liverpool Hospital, South-Western Sydney Local Health District (SWSLHD) Academic Unit or the IBD charity “Crohn’s Colitis Cure” from: Abbvie, Aspen, BMS, Celgene, Celltrion, Chiesi, DrFalk, Ferring, Fresenius Kabi, Gilead, Janssen, MSD, Novartis, Pfizer, Takeda, Vifor

Jakob Begun

- Received honoraria, research grants or consulting fees from Abbvie, Janssen, Takeda, Pfizer, Ferring, Bristol Myers Squibb, Gilead, Tillott’s, Sandoz, Chiesi, Celltrion, Microba, Antara, Research Review, NHMRC, US Department of Defence, The Gutsy Foundation, The Gastroenterological Society of Australia, Viertel Foundation, and The Mater Foundation

DISCLOSURES

Debra Rowett and **Karen Luetsch**

- No disclosures to declare

THANK YOU