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The clinical impact of therapeutic drug monitoring in inflammatory bowel disease — a critical literature review and meta-analysis

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Objective

- A critical literature review and meta-analysis was undertaken in order to investigate if therapeutic drug monitoring (TDM) may play a role to improve clinical outcomes in inflammatory bowel disease (IBD) patients with respect to symptoms-based management [1].

Methods

- MEDLINE, EMBASE and Cochrane database were searched up to 1 February 2019 for comparisons of proactive/reactive TDM with empiric care (see right box).
- Inclusion criteria are: (1) follow-up ≥16 weeks, (2) comparative i.e. with vs w/o TDM or pre vs post TDM studies, (3) ≥30 patients per arm in observational studies. Both pediatric and adult IBD populations were included, with no restrictions for TDM assay.
- One of the following outcomes had to be reported: clinical remission/response/relapse, endoscopic remission/response, surgery, hospitalization, drug discontinuation, immunomodulators/steroids concomitant therapy, and adverse events.
- Search results are combined to eliminate duplicate records with the software tool EndNote or by manual check.
- Previews review and meta-analyses on the subject were use to integrate the core database with any new relevant record.
- Two review authors independently screened title and abstract of all publications and full text of all papers identified as potentially fulfilling inclusion/exclusion criteria were reviewed to finalize the decision on inclusion. Any doubt regarding the inclusion was discussed until consensus was reached.
- Clinical benefit of TDM was estimated in terms of odds ratio (OR) using RevMan 5.3. Effect estimates were pooled separately for RCT, observational studies and congress abstracts (to take into different designs) using a random-effect model in case of heterogeneity>50% [2].

Box – Search strings used for each database

Medline (both simple and using Mesh terms) and Cochrane

("inflammatory bowel disease" OR "Crohn's disease" OR "ulcerative colitis") AND "therapeutic drug monitoring" AND (ustekinumab OR vedolizumab OR interleukin OR biologic OR infliximab OR adalimumab OR "anti-tumour necrosis factor")

Embase

('inflammatory bowel disease'/exp OR 'inflammatory bowel disease' OR 'crohn disease'/exp OR 'crohn disease' OR 'ulcerative colitis'/exp OR 'ulcerative colitis') AND ('therapeutic drug monitoring'/exp OR 'therapeutic drug monitoring') AND ('ustekinumab'/exp OR ustekinumab OR 'vedolizumab'/exp OR vedolizumab OR 'interleukin'/exp OR interleukin OR 'biologic'/exp OR biologic OR 'infliximab'/exp OR infliximab OR 'adalimumab'/exp OR adalimumab OR 'anti-tumour necrosis factor') + filters: 'human'/de AND ('article'/it OR 'article in press'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'review'/it)

Results

- 12 papers were selected: 3 RCTs [3-5], 6 observational studies [6-11] and 3 conference abstracts [12-14] (Figure 1).
- A total of 2,243 patients were enrolled in the analysis: mean age 34 years, 49% female, 73% Crohn's disease (Table I).
- TDM is associated with superior clinical response rate (Figure 2), however subgroup analysis excluding low quality studies (conference abstracts) highlights residual uncertainty on results. In contrast, reduction of relapse/treatment failure rates results more evident (Figure 3).
- There is also evidence of better clinical remission rate in TDM group although the significance threshold was not reached (Figure 4).
- Almost 4 out of 10 patients are in pharmacodynamics failure (PF) i.e. failing treatment despite adequate serum drug levels and absence or low anti-TNFa antibodies; such patients could be better treated swapping to a different mechanism of action (e.g. interleukin inhibitors) instead of switching within anti-TNFa class (Table II).
- Probably due to better disease management, discontinuation rate is lower in TDM group; favorable outcomes related to hospitalization and IBD related surgery rates are observed. Results for all included outcomes are detailed in Table III.

Table I. Baseline characteristics of included studies;

Study	Patient population	Design	Follow-up	N	Age	Female	% CD
D'Haens 2018	Anti-TNFα naive in MAIN after IND	RCT	54 weeks	82 TDM 40 control	30 (23-46) TDM 29 (22-40) Control	54% TDM 68% control	100% TDM 100% control
Steenholdt 2015	IFX MAIN therapy experienced LOR	RCT	12 weeks, 20 weeks	33 TDM 36 control	**36** (19 to 81) TDM **37** (19 to 63) Control	61% TDM 61% control	100% TDM 100% control
Vande Casteele 2015	Responders patient in MAIN therapy with IFX	RCT	1 year	128 TDM 123 control	41 (30-50) TDM 42 (32-48) Control	48% TDM 42% control	71% TDM 67% control
Guidi 2018	IFX MAIN therapy for ≥4 months experienced LOR	P-L-C	12 weeks	96 TDM 52 control	**39**±18 TDM **43**±7 control	47% TDM 54% control	58% TDM 54% control
Kelly 2017	Active IBD	R-O-C	Median 12 months	128 TDM 143 control	26 (21-36) TDM 28 (21-41) Control	51% TDM 50% control	58% TDM 54% control
Papamichael 2017	IFX MAIN therapy	MC-R-C	Median 2.4 years	130 TDM 134 control	31 (23-43) TDM 31 (25-46) Control	40% TDM 44% control	68% TDM 58% control
Papamichael 2019	ADA MAIN therapy	MC-R-C	Median 3.1 years (4-4.8)	53 TDM 329 control	31 (23-38) TDM* 38 (26-51) Control*	49% TDM 51% control	77% TDM 82% control
Restellini 2018	Patient with LOR to ADA	R-C	12 months	56 TDM 48 control	30 (18 to 83) TDM 36 (18 to 75) Control	43% TDM 46% control	100% TDM 100% control
Vaughn 2014	Patients receiving IFX for IBD	CR	5 years	48 TDM 78 control	35 (29-43) TDM 35 (26-50) Control	31% TDM 42% control	79% TDM 67% control
Bernardo 2017	Patients receiving IFX or ADA for IBD	NA	48 weeks	117 TDM 101 control	**29** (7 to 65) TDM NR control	45% TDM NR control	84% TDM NR control
Mulgund 2017	Pediatric patients with IBD treated with IFX or ADA	R-O-C with PSM	52 weeks	81 TDM 81 control	NR	NR	NR
Perinbasekar 2017	Patients with IBD treated with IFX or ADA	NA	1 year	79 TDM 81 control	34 (NR) TDM 28 (NR) Control	57% TDM 60% control	72% TDM 77% control

#age is presented as median or mean (in bold) and standard deviation (±), IQR (if spaced by "-") or range (if spaced by "to"); *Calculated as sum of age at diagnosis and disease duration (assuming a normal distribution); CD: Crohn disease; MAIN: maintenance; IND: induction; RCT: randomized clinical trial; MC: multicenter; R: retrospective; P: prospective; C: cohort; O: observational; CR: chart review; L: longitudinal

Figure 1. PRISMA flowchart depicting study selection

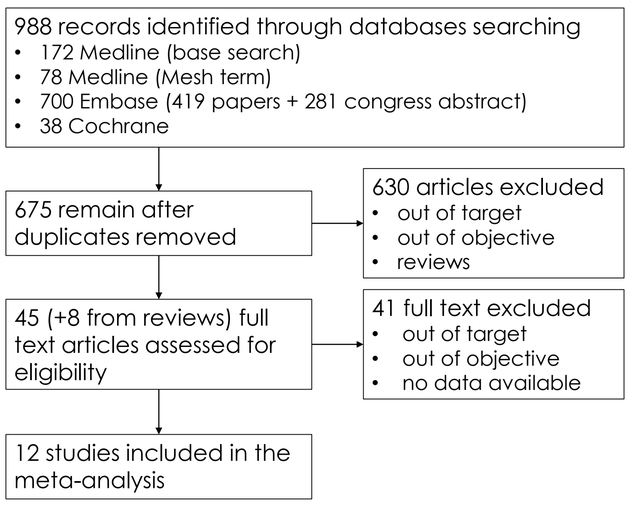


Table II. Estimated pharmacodynamics failure rate according to selected papers

Study	N	in PF
Guidi 2018	148	55 (37.2%)
Papamichael 2017	130	13 (10.0%)
Papamichael 2019	40	22 (55.0%)
Steenholdt 2015	69	48 (69.6%)
Vaughn 2014	48	25 (52.1%)
Estimated PF (95% CI)	**37.4% (23–68%)**	

Table III. Summary of meta-analysis results (comparison TDM vs control)

Outcome	Studies	Patients	OR (95% CI)
Clinical remission	9	1299	1.225 (0.963–1.558)
Clinical response	5	814	2.066 (1.488–2.869)
Relapse/failure	4	1115	0.284 (0.106–0.756)
Endoscopic response	4	412	1.605 (0.798–3.228)
Ulceration free	2	244	0.719 (0.415–1.244)
AB detected	5	961	0.384 (0.137–1.079)
Discontinuation	10	1664	0.505 (0.27–0.941)
Dose escalation	4	741	1.811 (0.475–6.902)
Dose intensification	4	741	1.811 (0.475; 6.902)
IMM/steroids	2	535	0.367 (0.159–0.848)
Hospitalizations	3	753	0.472 (0.226–0.983)
IBD related surgery	6	1446	0.461 (0.305–0.695)
SAE >grade 3	4	763	0.266 (0.041–1.703)

AB: antibody, IMM: immunomodulators, SAE: serious adverse events, OR: odds ratio, CI: confidence interval

Figure 2. Effect of algorithmic dose management on clinical response

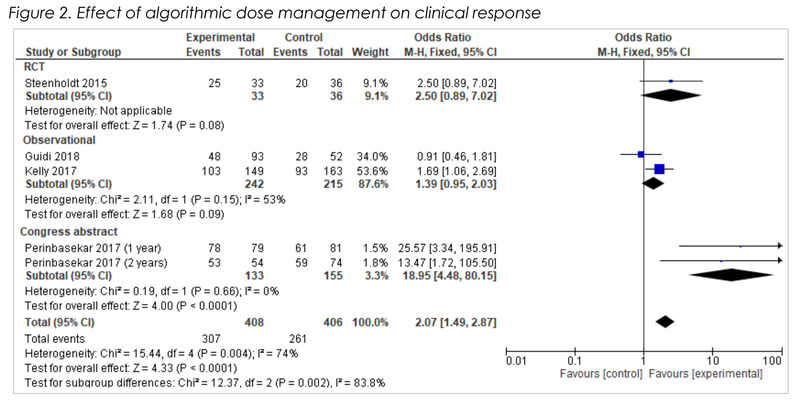


Figure 3. Effect of algorithmic dose management on relapse/treatment failure

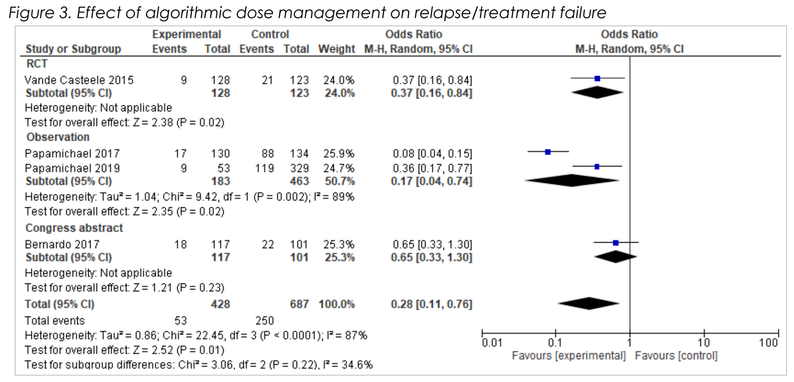
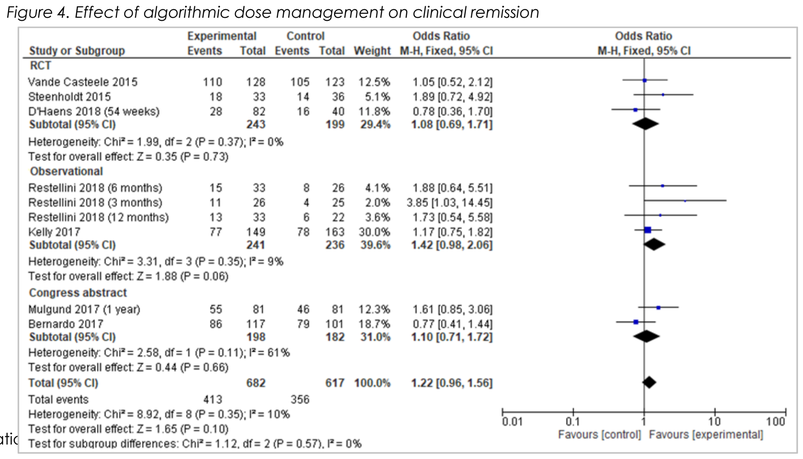


Figure 4. Effect of algorithmic dose management on clinical remission



Conclusions

TDM based management of dose escalation have not completely demonstrated to be an effective option (particularly in experimental studies). Nevertheless, results from the present analysis suggest that TDM approach may play in the future a role as efficient patient management solution. Conclusion from RCTs using TDM approach are not exhaustive, but pose a question for further investigation.

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ISPOR Copenhagen 2019

The present work was funded by Janssen-Cilag Italy

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