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A virtual clinic increases anti-TNF dose intensification success via a treat-to-target approach compared with standard outpatient care in Crohn's disease

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ABSTRACT

Background: Virtual clinics represent a novel model of care in inflammatory bowel disease. Their effectiveness in promoting quality use of biologic therapy and facilitating a treat-to-target approach is unknown.

Aim: To evaluate clinical and process-driven outcomes in a virtual clinic compared to standard outpatient care amongst patients receiving intensified anti-TNF therapy for secondary loss of response.

Methods: We performed a retrospective multi-centre, parallel, observational cohort study of Crohn's disease patients receiving intensified anti-TNF therapy for secondary loss of

response. Objective assessments of disease activity and anti-TNF trough levels at secondary loss of response and during subsequent 6-month semesters, were compared longitudinally between virtual clinic and standard outpatient care cohorts. The primary endpoint was treatment success, with appropriateness of dose intensification, tight disease monitoring and treatment de-escalation representing secondary outcomes.

Results: Of 149 patients with similar baseline characteristics, 69 were managed via a virtual clinic and 80 via standard outpatient care. There were higher rates of treatment success in the virtual clinic cohort (60.9 v 35.0%, $p<0.002$). Rates of appropriate dose intensification (82.6 vs 40.0%, $p<0.001$), biomarker remission (faecal calprotectin $p=0.002$), tight-disease monitoring (84.1 vs 28.8%, $p<0.001$) and treatment de-escalation (21.3 vs 10.0%, $p=0.027$) also favoured the virtual clinic cohort.

Conclusion: This study favoured a virtual clinic-led model-of-care over standard outpatient care in facilitating treatment success as part of an effective treat-to-target approach in Crohn's disease. A virtual clinic model-of-care also improved treatment outcomes and quality use of intensified anti-TNF therapy through processes that promoted appropriate dose intensification and tight-disease monitoring, while encouraging more frequent dose de-escalation.

INTRODUCTION

Despite the efficacy of anti-TNF therapy, up to 60% of initial responders develop secondary loss of response within the first 12 months.^{1,2} Therapeutic options to address secondary loss of response include the addition of glucocorticoids or immunomodulator therapy, intensifying or switching biologic agents, or surgery.^{3,4} Understanding the mechanism underlying secondary loss of response remains important in determining which of these treatment strategies is most appropriate.

The use of thiopurine metabolites and anti-TNF drug levels to support clinical decision-making in conjunction with objective markers of disease activity, as part of a treat-to-target

strategy reflects the modern treatment approach.⁵⁻¹⁶ Dose adaptation strategies that incorporate anti-TNF drug levels increase the likelihood of therapeutic success.^{8,17-19} Dose intensification represents an appropriate intervention to overcome pharmacokinetic failure characterised by objective loss of response associated with subtherapeutic anti-TNF trough levels.^{8,17-19} Conversely, dose intensification may not represent an effective treatment strategy in the setting of therapeutic drug levels given that loss of response may be driven by non-TNF pathways.^{17,18,20}

Whilst a treat-to-target approach is increasingly acknowledged as best practice in inflammatory bowel disease (IBD), clinical decision support tools available to facilitate this model are lacking.¹⁵ Virtual clinics have emerged as a novel model of care to facilitate decision support and care co-ordination. A small number of studies in IBD have concluded that virtual clinics are of benefit in coordinating multi-disciplinary clinical decision making using a range of objective assessments, including drug level monitoring.²¹⁻²³ Moreover, these studies have proposed that virtual clinics may improve capacity across outpatient services by reducing the number of patient visits, delivering a proactive approach to care, and reducing the cost associated with biologic therapies via increased rates of de-escalation. However, the mechanics and extent to which virtual clinics help improve the processes involved in the co-ordination of care and clinical outcomes, compared to standard outpatient-based care in IBD, remains unclear, and warrants further study.

The aim of this study was to compare clinical and process-driven outcomes using a virtual clinic led model of care relative to standard outpatient IBD care, for the management of intensified anti-TNF therapy to address secondary loss of response in patients with Crohn's disease. The primary endpoint was treatment success, with appropriateness of dose intensification, rates of tight disease monitoring and treatment de-escalation representing secondary outcomes.

METHODS

Study design and setting

This retrospective multi-centre observational parallel cohort study included consecutive adult patients with confirmed Crohn's disease, based on standardised clinical, endoscopic, histological and radiological criteria, who were referred for virtual clinic assessment or underwent infliximab or adalimumab dose intensification for secondary loss of response as

part of standard outpatient IBD care between January 2013 and December 2018.²⁴ Patients were managed across three tertiary IBD centres within a 15-kilometre radius in Melbourne, Australia. All centres were similarly resourced and practiced a similar model of IBD care, with comparable socio-economic and local environmental factors. Patients at Austin Health and Eastern Health were managed through standard outpatient IBD care, while patients at Alfred Health were managed via a virtual clinic.

Prior to loss of response, all patients were treated with standard infliximab (5 mg/kg week 0, 2 and 6 and then 5 mg/kg 8-weekly) or adalimumab (160 and 80mg at week 0 and 2 and then 40mg every other week) dosing regimens. Dose intensification was defined as either shortening the interval (for infliximab, 5mg/kg 6 or 4 weekly, or for adalimumab, 40mg weekly), or increasing the dose whilst maintaining the same interval (for infliximab, 10mg/kg 8-weekly) after induction, defined as after week 14. The study was approved by the research ethics committees of each participating health service.

Intervention group

Dose intensified patients at Alfred Health were managed through a virtual clinic. In brief, patients in the standard IBD outpatient clinic with suspected secondary loss of response were referred to the virtual clinic for baseline investigations, including anti-TNF trough levels, to confirm objective disease activity and appropriateness of dose intensification. Baseline investigations included anti-TNF trough levels, C-reactive protein (CRP), faecal calprotectin, colonoscopy, intestinal ultrasound and/or cross-sectional imaging, where appropriate. The virtual clinic convened on a 4-weekly basis and was attended by IBD gastroenterologists, IBD nurse specialists, a pharmacist and an administrative assistant. Approved patients underwent dose intensified anti-TNF therapy for 6 months and subsequently underwent non-invasive disease re-assessment according to a pre-defined protocol (Figure 1) as part of a treat-to-target model. Patients with objectively verified biomarker response continued intensified therapy and underwent 6 monthly review within the virtual clinic, with subsequent management decisions made based on the results of protocolised non-invasive disease assessment. The results of initial and subsequent investigations across the virtual clinic cohort were prospectively collected and entered into an IBD database. Anti-TNF dose de-escalation was routinely considered and documented at every virtual clinic review. Patients for whom dose intensification was deemed inappropriate (owing to lack of objective disease activity to account for clinical loss of response) were managed back to standard care. This article is protected by copyright. All rights reserved

response, or anti-TNF levels deemed unlikely to benefit from dose intensification) were referred back to the standard IBD outpatient clinic for subsequent management. Virtual clinic patients were also seen in the outpatient clinic 6-monthly in keeping with local anti-TNF prescribing requirements, with more frequent review as needed.

Control Group

The standard outpatient care cohort comprised two parallel cohorts of patients managed at Austin Health and Eastern Health outpatient IBD clinics who had undergone dose intensification for secondary loss of response. The decision to undertake dose intensification, together with the duration of intensified therapy, was at the discretion of the treating clinician. Outpatient clinical review was undertaken at least every 6 months in keeping with local anti-TNF prescribing requirements, with more frequent review as needed. The timing and nature of investigations used to evaluate disease activity and/or response before and after anti-TNF dose intensification including CRP, faecal calprotectin, radiologic assessment and endoscopy, were also determined by the treating doctor and were not protocolised.

Data collection and laboratory methods

Patient demographics, including Montreal disease classification, smoking status, prior surgical history, prior anti-TNF treatment exposure and use of concomitant immunomodulator therapy were collected from the electronic medical record and/or prospectively maintained IBD databases at participating centres. In addition, data including anti-TNF drug levels and objective measures of disease activity including CRP, endoscopic activity, imaging reports and faecal calprotectin at 6, 12, 18 and 24 months following dose intensification, were collected where available. Information pertaining to adverse drug events, number of outpatient appointments, accident and emergency presentations, unplanned IBD-related surgery and IBD-related admissions were also recorded.

Anti-TNF trough levels were evaluated using a drug sensitive Matriks ELISA assay, with the 'therapeutic range' defined as 3-7µg/ml and 5-8µg/ml for infliximab and adalimumab respectively. Sub-therapeutic levels were defined as those below the therapeutic range. Anti-bodies to anti-TNF were measured in the setting of undetectable drug levels, and were reported qualitatively as positive or negative. Faecal calprotectin, serum CRP and other laboratory testing was performed as per the local laboratory's usual practise.

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Study definitions

Complex disease was defined as stricturing (Montreal B2), penetrating (Montreal B3) or perianal Crohn's disease. Maintenance anti-TNF dosing was defined as 8-weekly infliximab or fortnightly adalimumab following induction dosing and prior to dose intensification. Time to secondary loss of response was defined as the duration from the date of commencement through to the date of dose intensification of the same anti-TNF agent. Objective evidence of active Crohn's disease was defined as one or more of faecal calprotectin $\geq 150\mu\text{g/ml}$, CRP $\geq 5\text{mg/L}$, and/or documented inflammation on intestinal ultrasound, cross-sectional imaging or endoscopy reports. Dose intensification was defined as appropriate if there was both objective evidence of disease activity *plus* anti-TNF levels at or below the lower limit of the therapeutic range (see above) demonstrated prior to anti-TNF dose intensification.

Treatment success following dose intensification was defined as achieved when two consecutive 6-month semesters occurred during which objective disease assessment was undertaken with no evidence of active disease demonstrated. Tight monitoring post intensification was defined as having been undertaken when both objective assessment of disease activity and anti-TNF trough levels were evaluated across all consecutive eligible semesters of follow-up. However, if inactive disease was objectively confirmed in the preceding semester, anti-TNF trough levels were not mandatory in the following semester within these criteria. Treatment escalation failure following dose intensification was defined as the occurrence of one or more of: the need to switch, or discontinue, intensified biologic therapy; recommencement of corticosteroids, and/or IBD-related abdominal surgery. Time to treatment escalation failure was defined as the time from the date of commencing dose intensification until the date of treatment escalation failure.

Statistical analysis

Data assessed descriptively and according to Shapiro-Wilk tests were found to be non-parametric; thus, medians are presented throughout [with minimum and maximum ranges]. Continuous data were compared with Mann-Whitney tests, and proportions were expressed as percentages and compared using two-sided Fisher's exact tests. Continuous data were kept in original form where possible.

Further bivariate analyses were performed, including Kaplan-Meier survival curves to

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compare the proportion achieving treatment success and time to objectively assessed disease remission following dose intensification through to end of follow-up across both cohorts with differences assessed by log-rank tests. Subsequently, Cox multivariable regression analysis was performed, incorporating statistically significant (and those trending towards significant, $p < 0.10$) variables associated with time to treatment success in bivariate analyses, plus factors putatively important in anti-TNF treatment success, including age at time of intensification, sex, disease behaviour and extent, time to commencement of anti-TNF from diagnosis, time since diagnosis, concurrent immunomodulation, markers of inflammatory activity and serum albumin. A forced entry model was used, with the final model selected on the basis of the Omnibus test of goodness of fit. P-values < 0.05 were considered statistically significant.

RESULTS

Baseline patient and disease characteristics

Of 149 patients who underwent anti-TNF dose intensification, 94 (63.1%) were treated with infliximab and 55 (36.9%) with adalimumab. 69 patients were managed via the virtual clinic and 80 patients via standard outpatient care. Adalimumab and infliximab use were similar between virtual clinic and standard outpatient care groups ($p = 0.867$). Patient and disease characteristics between both cohorts were comparable (Table 1). The median time to anti-TNF dose intensification to address secondary loss of response across the virtual clinic and standard outpatient care cohorts was 1.9 and 2.4 years respectively ($p = 0.374$).

Comparison of clinical and treatment-based outcomes between the virtual clinic and standard outpatient care cohorts

Comparison of anti-TNF treatment success and failure between virtual clinic and standard outpatient care groups

Anti-TNF treatment success (absence of active disease on objective disease assessment, across two consecutive 6 month semesters) occurred more frequently in the virtual clinic cohort (60.9 v 35.0%, $p = 0.002$) (Figure 2). Furthermore, management via the virtual clinic was associated with shorter time to treatment success (log rank test, $p < 0.001$) (Figure 3),

and was the strongest, independent predictor of treatment success when accounting for other potential confounders in Cox regression analysis (OR 4.67, 95% CI 2.44-8.92, $p<0.001$).

There were also higher proportions of CRP and calprotectin normalisation achieved (log rank tests, $p=0.061$ and $p=0.002$ respectively), reflective of objective biomarker remission in the virtual clinic relative to the standard outpatient care group over the duration of study follow-up (Figure 4).

Overall, rates of anti-TNF treatment escalation failure were comparable across both groups (46.4 v 35.0%, $p=0.182$). Moreover, there were no differences in rates of treatment failure (48.5 v 38.2%, $p=0.732$) and treatment de-escalation (17.0 v 16.8%, $p=1.000$) when stratified by infliximab and adalimumab respectively.

Comparison of other clinical and treatment related outcomes between virtual clinic and standard outpatient care groups

Considering other clinical outcomes between the two groups, a similar proportion of virtual clinic and standard outpatient care patients underwent surgical resection within the follow-up period (4.3 v 8.8% respectively, $p=0.341$). Rates of anti-TNF discontinuation (for any reason) were comparable across virtual clinic and standard outpatient care cohorts (30.4 v 18.8%, $p=0.125$). There were similarly high proportions of immunomodulator co-therapy at commencement of anti-TNF intensification (87.0 vs 87.5% respectively, $p=1.000$), and at final assessment prior to end of study follow-up (71.3 v 60.0%, $p=0.858$) across virtual clinic and standard outpatient care cohorts. Finally, there were no differences in rates of adverse drug reactions ($p=0.329$), recommencement of steroids ($p=1.000$), IBD related admissions or number of outpatient visits ($p=0.807$) over the duration of follow-up across both cohorts.

A higher proportion of virtual clinic patients had de-escalation of anti-TNF therapy back to baseline dosing (24.6 vs 10.0%, $p=0.027$). The decision to de-escalate intensified anti-TNF therapy was also more frequently based on objectively assessed inactive disease in the virtual clinic cohort (82.3 vs 25.0%, $p<0.001$) within the follow-up period.

Comparison of process-based indicators of quality use of medicines between the virtual clinic and standard outpatient care cohorts

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Assessment of secondary loss of response prior to dose intensification

Appropriate dose intensification was more frequent in the virtual clinic cohort (82.6 vs 40.0%, $p < 0.001$, Figure 5), while dose intensification in the absence of objective disease or assessment of anti-TNF trough levels was more common in the standard outpatient care cohort (0.0 v 10.0%, $p = 0.008$).

Assessment of anti-TNF trough levels at secondary loss of response was performed more frequently (93.0 vs 65.0%, $p < 0.001$) across the virtual clinic managed cohort, with a higher proportion of virtual clinic patients demonstrating sub-therapeutic drug levels (84.0 vs 43.0%, $p = 0.028$). Rates of detectable antidrug antibodies prior to dose intensification were similar across both cohorts (7.2 v 3.8%, $p = 0.472$).

Similarly, assessments of objective disease prior to anti-TNF dose intensification were more frequently undertaken across the virtual clinic cohort (96.0 v 76.0%, $p < 0.001$). Faecal calprotectin (55.1 v 26.3%, $p < 0.001$) was more commonly used across the virtual clinic cohort, while endoscopic assessment (21.7 v 46.3%, $p = 0.002$) was undertaken more frequently across the standard outpatient care cohort. Serum CRP was used as the single objective marker of disease activity at secondary loss of response more commonly in the standard outpatient care cohort (2.9 v 15.0%, $p = 0.012$).

Monitoring of disease and anti-TNF trough levels after dose intensification

As described above (see Supplementary Figure), a per-patient, consecutive, semester-based analysis was conducted from dose intensification with a median duration of follow-up of 1.9 [0.2, 2.0] and 1.5 [0.2, 2.0] years for the standard outpatient care and virtual clinic cohorts, respectively ($p = 0.427$). Overall, objective monitoring following dose intensification was more stringently performed in the virtual clinic cohort, with no objective assessment of disease activity undertaken in 58.6% of standard outpatient care and 2.3% of virtual clinic semesters of follow-up, respectively ($p < 0.001$). Similarly, anti-TNF trough levels were more frequently assessed within 12 months of objectively confirmed disease activity across the virtual clinic versus standard outpatient care cohorts ($p < 0.001$). Tight monitoring (objective disease assessment and anti-TNF trough levels measured during each semester) was performed in 84.1% of virtual clinic and 28.8% of standard outpatient care cases, respectively ($p < 0.001$, Figure 3).

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Treatment decisions undertaken post anti-TNF intensification

Immediately prior to anti-TNF treatment escalation failure, assessment of objective disease activity ($p=0.006$) and anti-TNF trough levels ($p<0.001$) were undertaken more frequently across the virtual clinic cohort. Similarly, in cases where biologic switching was undertaken in response to anti-TNF escalation failure, virtual clinic patients were more likely to have had objective inflammation ($p=0.020$) and assessment of anti-TNF trough levels ($p=0.004$) compared to the standard outpatient care cohort.

Relationship of treatment outcomes with process-based outcomes and other clinical outcome measures (irrespective of cohort grouping)

There was no difference in the proportion achieving treatment success between those who had appropriate versus inappropriate anti-TNF escalation (45.5 vs 47.4%, $p=1.000$) across the combined patient cohort, even when stratified by standard outpatient care versus virtual clinic model of care.

Patients who underwent tight monitoring had higher rates of treatment success (63.0 vs 27.9% $p<0.001$). Furthermore, the tight monitoring group achieved treatment success, CRP normalisation and calprotectin normalisation faster than those who did not undergo tight monitoring post intensification (median 0.99 vs 1.5y ($p<0.001$), 0.59 vs 1.1y ($p=0.027$), 1.0 vs 1.3y ($p=0.011$), respectively).

Finally, those who achieved and maintained therapeutic anti-TNF drug levels post-dose intensification achieved a higher rate of treatment success (71.0 vs 23.8%, $p<0.001$) and higher rates of CRP and/or calprotectin normalisation (56.5 vs 28.6%, $p=0.046$) within the follow-up period.

Factors associated with anti-TNF treatment escalation success over follow-up period

A Cox multivariable regression analysis was performed to assess factors associated with treatment escalation success in the overall cohort. The variable with the largest effect size was virtual clinic grouping (compared to standard outpatient care, OR 4.67, 95% CI [2.44, 8.92], $p<0.001$). Other variables associated with treatment success included older age,

shorter duration from Crohn's diagnosis to anti-TNF commencement, non-stricturing, non-penetrating phenotype and higher serum albumin (each $p < 0.05$, see Table 2).

DISCUSSION

This study has demonstrated the benefit of adopting a virtual clinic led treat-to-target approach compared to standard outpatient care in the management of dose-intensified anti-TNF therapy for secondary loss of response in Crohn's disease. The virtual clinic led model of care not only improved clinical outcomes, normalised objective markers of disease activity more frequently and shortened the time to treatment success relative to standard outpatient care, but was also found to be an independent predictor of treatment success. The virtual clinic was also associated with more appropriate dose intensification, tighter disease control and more frequent treatment de-escalation than standard outpatient care alone.

The virtual clinic facilitated a standardised approach to secondary loss of response and evaluation of response following dose intensification using objective markers and anti-TNF trough levels to maintain tight control of disease. Management via the virtual clinic was accordingly associated with more frequent and rapid achievement of treatment success and biomarker normalisation than standard outpatient care. This was also associated with a longer median time to treatment escalation failure, defined as the need for surgery and/or biologic discontinuation across the virtual clinic cohort. Although it is difficult to discern what might have contributed to the success of the virtual clinic relative to standard outpatient care in relation to improving clinical outcomes, a few factors warrant consideration. The virtual clinic provided a multidisciplinary forum to support challenging therapeutic decisions via consensus rather than the traditional approach of decision making by a single clinician. Multidisciplinary team involvement with engagement of pharmacist, nursing and administrative support within the virtual clinic also provided the operational support to execute and monitor the outcomes of these decisions. Taken together, these observations suggest that the virtual clinic performs better than standard outpatient care as a model of care to optimally co-ordinate the use of anti-TNF trough levels and objective markers of disease activity in order to improve clinical outcomes and defer treatment failure.

In addition to the decision making undertaken within the virtual clinic, a key aspect to the virtual clinic-led model of care was the proactive scheduling of disease reassessment following dose intensification to evaluate the outcome of the therapeutic intervention. This study indicates that virtual clinic driven processes are associated with a more consistent approach to disease reassessment following dose intensification, thereby facilitating a treat-to-target management approach to help achieve tight control. Such a tight-control approach has recently been found by the CALM study to achieve superior outcomes compared to symptom-based monitoring alone.²⁵

Despite the therapeutic success of anti-TNF dose intensification in addressing secondary loss of response, evidence-based guidelines regarding de-escalation are lacking. The virtual clinic promoted active decision making informed by objective markers of disease activity, thereby minimising exposure to futile therapies or the risks associated with unnecessary immunosuppression. This was reflected by higher rates of treatment de-intensification back to baseline dosing intervals across the virtual clinic cohort relative to standard outpatient care. This study highlights the value of the virtual clinic as a model of care that is a gatekeeper to anti-TNF dose intensification, plus addresses the 'set and forget' mentality following dose intensification by facilitating more frequent consideration of anti-TNF de-intensification, which is associated with reduced exposure to drug toxicity and potential cost savings.^{23,26}

The virtual clinic led model of care provides an example of how clinical outcomes can be improved by optimising current anti-TNF treatment algorithms in lieu of switching to newer and perhaps more expensive treatments. Moreover, cost-efficiencies driven by the introduction of biosimilar medications re-inforce the need to optimise anti-TNF use prior to switching to potentially more expensive biologic alternatives. Recent studies have also demonstrated that tight disease control based on a treat-to-target approach was both clinically and cost effective over 48 weeks in adalimumab-treated patients with early Crohn's disease.^{13,25} Although potential cost and resource savings were not assessed as part of this study, differences in favour of the virtual clinic cohort across rates of appropriate dose intensification ($p<0.001$) and anti-TNF de-escalation ($p=0.027$) suggest these savings would likely have been substantial. However, to truly appreciate the imputable cost saving associated with anti-TNF dose de-escalation back to baseline intervals, healthcare costs

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associated with relapse must also be considered. It was difficult to assess the rates of adverse events and health-care utilisation (IBD related admission(s) and/or outpatient visit(s)) between the two cohorts owing to variability in reporting and documentation; however, we acknowledge that further analysis of the pharmacoeconomic impact of the virtual clinic intervention is warranted. We further postulate that the lack of difference in healthcare utilisation and adverse events between the virtual clinic led model of care and standard care may have related to insufficient duration of clinical follow-up which may have been overcome by a longer study duration.

We acknowledge that there are limitations to this study. Firstly, given the non-randomised and uncontrolled study design, it is possible that the observed differences in outcomes are due to differences in the patient population between the two cohorts. This is unlikely; all participating centres represented tertiary IBD hospitals operating within a small geographical area, with comparable service and clinician capability, adhering to local anti-TNF prescribing guidelines. Further, we found no difference in baseline patient or disease characteristics. Outside of the protocolised approach to objective disease assessment and review in the virtual clinic cohort, we do not anticipate any key differences between the two groups in the approach to managing secondary loss of response. Moreover, despite comparable rates of anti-TNF escalation failure across both cohorts, a proactive approach towards both disease assessment and anti-TNF trough levels may have elicited a higher rate of precocious failures in the virtual clinic cohort, reflective of lead-time bias; thereby achieving treatment success across the virtual clinic cohort relative to standard outpatient care was perhaps inherently more difficult based on the study definitions. Rates of treatment failure such as IBD-related abdominal surgery, anti-TNF discontinuation and switching, may not have been directly related to the virtual clinic approach, but rather related to other disease or patient-related factors including medication non-adherence, disease phenotype and co-therapy. While this study was successful in evaluating clinical and process-driven outcomes, it did not examine patient reported outcomes or undertake formal pharmacoeconomic comparison across cohorts.

Despite these limitations, our study represents the first multi-centre comparison of a virtual clinic model relative to standard clinical practice across a 'real-world' cohort of IBD patients. It is one of the few studies to have concurrently evaluated the utility of a virtual clinic for the administration of both infliximab and adalimumab. This study also illustrates the value

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of virtual clinic driven processes in augmenting traditional models of outpatient IBD care, thereby reproducing a 'real-world' treat-to-target strategy to address secondary loss of response in Crohn's disease. Moreover, the model of IBD care, including access to, and prescription of anti-TNF therapy in Australia, is comparable to other health jurisdictions, suggesting that the virtual clinic led model described is generalisable and amenable to implementation into existing IBD models-of-care.

CONCLUSION

Our study provides evidence across three domains that favours a virtual clinic led model of care over standard outpatient based IBD care to facilitate a treat-to-target approach to Crohn's disease management. First, virtual clinics help promote quality use of biologics by ensuring more appropriate anti-TNF dose intensification to address secondary loss of response based on objective markers and anti-TNF trough levels. Secondly, virtual clinic driven processes facilitate care-coordination via a more consistent, protocolised approach to disease reassessment following dose intensification that also improved clinical outcomes and treatment success. Finally, a virtual clinic also addresses the set and forget mentality following dose intensification by facilitating more frequent consideration of anti-TNF de-intensification back to baseline dosing intervals. A virtual clinic led model of care that facilitates these processes geared towards tight control is reflective of the modern IBD treat-to-target management approach and is associated with improved clinical outcomes. It is also important to evaluate the pharmacoeconomic impact of appropriate dose intensification and timely biologic de-escalation as part of a virtual clinic led model of care, particularly given that this "virtual" model readily lends itself to aspects of IBD care beyond just secondary loss of response in Crohn's disease. Future studies should also examine whether the clinical and process-driven advantages proffered by the virtual clinic model of care translate into improved patient-reported outcomes such as quality of life, satisfaction and disability.

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Figure 1. Flow chart depicting virtual clinic model of care for management of secondary loss of response to anti-TNF therapy in Crohn's disease

Baseline patient characteristics			
Patients	80	69	
Male	45 (56%)	38 (55%)	1.000
Age (median, years)	43.7 [18,81]	40.5 [23,81]	0.367
Smoker	27 (34%)	19 (28%)	0.478
Prior biologic exposure	19 (24%)	25 (36%)	0.108

Disease duration at biologic initiation (median, years)	6.1 [0,41]	10.8 [0,36]	0.345
Crohn's disease characteristics			
Complex disease (Montreal classification B2, B3, p)*	60 (75%)	54 (78%)	0.701
Perianal disease	28 (35%)	31 (45%)	0.242
Prior Crohn's related abdominal surgery	38 (48%)	31 (45%)	0.869
IBD therapy at intensification			
Adalimumab	29 (36%)	26 (38%)	0.867
Infliximab	51 (64%)	43 (62%)	0.867
8-weekly 10mg/kg	2 (3%)	1 (1%)	1.000
6-weekly 5mg/kg	39 (49%)	38 (55%)	0.512
4-weekly 5mg/kg	10 (13%)	4 (6%)	0.260
Immunomodulator co-therapy	70 (88%)	60 (87%)	1.000
Thiopurine	45 (56%)	45 (65%)	0.315
Methotrexate	25 (31%)	15 (22%)	0.201
Steroids at intensification	17 (21%)	7 (10%)	0.077

Table 1. Baseline patient, disease and treatment characteristics across virtual clinic and standard outpatient care cohorts

*Complex disease refers to stricturing (B2), penetrating (B3) or perianal (p) Crohn's disease

Figure 2. Comparison of treatment and process-driven outcomes between virtual clinic and standard outpatient care cohorts

Table 2. Cox multivariable regression analysis of factors associated with probability of anti-TNF escalation success over time

Virtual clinic (vs Standard outpatient care)	4.67 [2.44, 8.92]	<0.001
Strictureing or penetrating phenotype	0.45 [0.22, 0.94]	0.034
Perianal fistulising disease phenotype	1.47 [0.84, 2.60]	0.181
Serum albumin at baseline* (per 1g/L increase)	1.08 [1.01, 1.16]	0.024
Serum C-Reactive Protein at baseline (per 1mg/ml increase)	0.99 [0.98, 1.01]	0.560
Age at baseline (per year increase)	1.04 [1.02, 1.07]	0.001
Male sex	0.76 [0.46, 1.27]	0.294
Duration from diagnosis to baseline ≥ 5 years	1.54 [0.65, 3.64]	0.327
Duration from diagnosis to start of anti-TNF (per year increase)	0.96 [0.92, 0.99]	0.006
*baseline = at/ just prior date of anti-TNF escalation		
Final model shown Omnibus test $\chi^2=33.0$, $p<0.001$		

Figure 3. Kaplan Meier survival analysis comparing virtual clinic and standard outpatient

care groups in terms of time to anti-TNF escalation success

Figure 4. Kaplan Meier survival analyses comparing virtual clinic and standard outpatient care groups in terms of time to objectively assessed disease remission via

- A) Serum C-Reactive Protein (CRP) normalisation**
- B) Faecal calprotectin normalisation**

Figure 5. Appropriate versus inappropriate anti-TNF escalation in the virtual clinic and standard outpatient care cohorts based on assessments of objective disease activity and anti-TNF trough levels prior to dose intensification

Standard outpatient clinical review

Identified to require anti-TNF dose intensification to address secondary loss of response

Referred to virtual clinic for assessment

Baseline investigations to confirm objective secondary loss of response AND
Anti-TNF trough levels to determine suitability for anti-TNF dose intensification

Anti-TNF dose intensification deemed
APPROPRIATE

Standardised 6-monthly non-invasive disease reassessment prior to scheduled virtual clinic:
(a) Faecal Calprotectin
(b) C-reactive protein
(c) Anti-TNF trough level
(+/- Endoscopy / Imaging if required)

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6-monthly virtual clinic review

Anti-TNF dose intensification deemed
NOT APPROPRIATE

Return to standard outpatient care to
consider alternate management strategy

A)

B)

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