Tandem use of Anti-TNF Agents in Patients with IBD who Fail First Line Anti-TNF Therapy: Real Life Lessons from a National Database.

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Abstract

Background: Inflammatory bowel disease (IBD) is a chronic relapsing and remitting inflammation of the bowel. Biologic therapy is safe and effective in IBD. Anti-TNF agents were the first biologics introduced for treatment of IBD. As more and more anti-TNF agents joined the market, treating physicians started using ant-TNF agents consecutively when the first agent failed. Data for this treatment choice is scanty and therefore we set out to evaluate tandem use of anti-TNF agents in IBD patients.

Method: The South African Gastroenterology Society (SAGES) established a national database for all IBD patients commenced on biologic therapy. We used this registry to evaluate the data for all patients who received consecutive anti-TNF agents. Demographic and clinical details as well as treatment outcomes for all patients were documented.

Results: Eight-seven (7.6%) of 1150 patients received consecutive anti-TNF agents. The Crohn's disease (CD) group had 42 (48%) patients and ulcerative colitis (UC) group 45 (52%). Gender distribution was equal with 45 (52%) male and 42 (48%) female patients. All patients failed the first anti-TNF agent over time, but better remission rates were obtained with consecutive anti-TNF agents. Patients treated with adalimumab during any stage of the study, had a higher rate of dose escalation compared to infliximab prior to switching to next anti-TNF agent. Similarly, side effects were also more significant with adalimumab, although few. Few patients required a switch to a third and further biologic agent. All patients remained in clinical remission over 4 years of the study.

Conclusion: It is reasonable to try a second anti-TNF agent when the first agent failed in IBD. Switching between different anti-TNF agents maintained clinical remission and avoided surgery and hospitalisation. This is a cost-effective strategy especially in resource constraint settings. Adalimumab is associated with higher rates of dose escalation and worse side-effect profile

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory diseases of the intestine with a relapsing and remitting course. Maintenance therapy in the form of immunomodulators and aminosalicylates are often required to prevent disease flares. Despite adequate doses of maintenance therapy, patients still experience flares requiring escalation of treatment with biological therapy[1, 2].

Anti-TNF agents (infliximab, adalimumab, golimumab and certolizumab) were the first to the market and have been extensively used for the treatment of inflammatory bowel disease (IBD) over the last 2 decades. Their mechanism of action is by blocking the binding of TNFα with its receptor, TNFR, and thus preventing the downstream inflammatory cascade[3]. Newer agents include ustekinumab, an IL-12 and IL-23 bocking agent, and vedolizumab, which is an anti-integrin. Tofacitinib, a Jak-Stat inhibitor, also known as a small molecule, have recently been launched following good clinical trial data[4].

Following failure of conventional therapy, consisting of corticosteroids and immunomodulators, most treatment guidelines currently recommend anti-TNF agents as first line biologic therapy in IBD. The efficacy of anti-TNF agents is well established[5]. Biosimilars for these drugs have become widely available and the cost of anti-TNF treatment have reduced considerably, making these drugs cost-effective alternatives[6]. However, anti-TNF therapy remains suboptimal for 2 main reasons among others: (i) primary non-response reported to be as high as 20–40% in clinical trial and 10–20% in real life cohorts; and (ii) secondary loss of response due to immunogenicity and increased anti-TNF clearance in 13–26% of patients in 12 months[7, 8].

Primary non-response is managed by switching to another class of biologic as it is argued that a second biologic of the same class will not be effective. A few years ago, however, another class of biologic was not readily available and treating physicians had to cycle patients through available anti-TNF agents to achieve clinical remission. Although newer classes of biologic agents for IBD have become available and treatment guidelines are recommending them, access to them are limited as healthcare funding agencies insist that a second anti-TNF agent be tried before switching. In addition, there are other barriers to drug access as discussed by Shajiva *et al*[9]. Therapeutic drug monitoring has simplified the process of choice of biologic use in IBD. In a patient with secondary loss of response with a normal therapeutic drug level, the patient is switched to another class of biologic. If the patient has a subtherapeutic drug level however, treatment with the same anti-TNF will be optimised by increasing the dose or reducing the dosing frequency[10].

Although newer biologic agents have become more widely available, they are expensive, and their use is still limited because of this. Despite having entered the era of personalised biologic therapy in IBD in 2021, anti-TNF agents are still being used in tandem when one agent fails. This is often driven by cost and healthcare funders. This is especially true in resource poor settings.

Consecutive use of anti-TNF agents in IBD is not based on solid scientific evidence as no controlled trials have addressed this question. The aim of this study is to assess the effectiveness of a second anti-TNF agent in patients with IBD who fail the first anti-TNF agent, for whatever reason.

Method

The South African Gastroenterology Society (SAGES) has established an IBD registry in 2016. SAGES obtained ethics clearance (SAGES BIOL 001) from PharmaEthics to run this registry. The study was approved by the Human Ethics Research Committee (HREC) of PharmaEthics. Data from all patients starting a biologic or continuing an existing biologic are captured on this registry. The study was conducted according to stringent good clinical practice guidelines. The treating gastroenterologist as well as the patient signed informed consent to participate in this study.

Data was retrieved from the database from 2016 to 2020 for all patients receiving a consecutive anti-TNF agent when the first agent failed. Demographics details were obtained for all patients including age, gender, duration of disease and smoking history. Specific parameters about the disease including extent

of disease, duration of disease, severity, treatment history and anti-TNF agents use. Outcome for all patients was documented.

Escalating to biologic therapy followed a step-up approach. Patients were escalated to biologic therapy once they failed conventional induction and maintenance therapy. The decision to initiate biologic therapy and the choice of the biologic agent was solely that of the treating physician. Similarly, escalation of therapy or switching to another agent was at the sole discretion of the treating gastroenterologist. Loss of response was defined as having persistent symptoms with raised faecal calprotectin and disease activity score. Patients who experienced loss of response despite adequate drug levels were switched to another anti-TNF agent, while those with inadequate drug levels were dose optimised with escalation of the same agent.

Statistical analysis

Non-categorical data were calculated as median and interquartile range. Statistical comparisons were examined with Chi-square test (or Fisher-Freeman-Halton Exact tests) and one-way analysis of variance (ANOVA). Cox regression analysis was used for univariate and multivariate analysis to identify risk factors of significance. Pearson's Chi-square goodness-of-fit test was utilized to compare hypothetical assumptions to the dataset. Odds ratios were calculated to compare treatment groups. The results were considered significantly different at $p < 0.05$.

Results

The database had a total combined patient population of 1150 of which 583 (51%) were female. There were 764 (66.4%) patients with CD and 387 (33.6%) patients with UC. A total of 87 (7.6%) patients received consecutive anti-TNF agents, 42 with CD and 45 with UC.

The gender distribution of the entire group was equal with 45 (51.7%) male and 42 (48.3%) female patients. The majority of patients were started on and switched between infliximab and adalimumab. A small proportion of patients, all of them with ulcerative colitis, were on golimumab either as first or subsequent anti-TNF agent. For the entire group, as outlined in Table 1, infliximab was the first anti-TNF agent in 45 (51.7%) patients, adalimumab in 40 (46%) patients and golimumab in only 2 (2.3%) patients.

Table 1
Consecutive anti-TNF use in CD and UC for total study population.

		Infliximab	Adalimumab	Golimumab
First anti-TNF agent	CD 42	23	19	0
	UC 45	22	21	2
	Total 87	45 (51.7%)	40 (46%)	2 (2.3%)
Second anti-TNF agent	CD 42	19	23	0
	UC 45	20	21	4
	Total 87	39 (44.8%)	44 (50.6%)	4 (4.6%)

No significant difference was noted for infliximab vs adalimumab for the second anti-TNF agent used, although adalimumab was used slightly more (51% vs 45%) the second time around.

All patients failed the first anti-TNF agent. However, patients remained in clinical remission with the second anti-TNF agents, irrespective of which one, except for golimumab. A small minority of patients moved on to newer agents as 3rd and 4th biologic choices.

To understand specific disease-related dynamics of consecutive anti-TNF agent use in IBD, CD and UC are analysed separately below.

Crohn's disease:

Fourty two (5.5%) out of 764 received a consecutive anti-TNF agent. Of these, 24 (57%) were male. The majority, 34 (81%) were non-smokers of which 6 (14%) were ex-smokers and 8 (19%) were current smokers.

Demographic and clinical disease characteristics of all patients with CD are depicted in Table 2. From this group, 13 (31%) had previous surgery with 4 (30.8%) left with an end-ileostomy and 3 (23.1%) with permanent colostomy. Concomitant medications for all patients with CD showed that thirty-nine (92.9%) of 42 patients were started on an immunomodulator (IM), either azathioprine, 6-mercaptopurine or methotrexate. Of these, 6 (14.8%) discontinued IM altogether because of side-effects, intolerance, or failure to achieve clinical response and remained only on a biologic agent. A further 12 (28,6%) switched between the various IM's while 17 (40.4%) patients were started on an IM and remained on this therapy for the duration of the study. Three (7.1%) patients were never started on an IM and was commenced on a biologic agent from the outset.

Table 2
Demographic and clinical details of patients with CD. n = 42

Male (%)	24 (57%)
Median age in years	42.5 (IQR 22)
Smoking history:	
• Never	28 (67%):
• Previously	6 (14%):
• Current	8 (19%)
Disease duration (median) in years	8 (IQR 8.75)
Disease characteristics:	
Age distribution:	
• A1	9 (21%)
• A2	22 (52%)
• A3	8 (19%)
• A4 +	3 (6%)
Location:	
• L1	13 (31%)
• L2	11 (26%)
• L3	18 (43%)
Behaviour	
• B1	20 (48%)
• B2	7 (17%)
• B3	4 (10%)
Perianal disease	11 (26%)
Fistula	13 (31%)
Previous surgery	13 (31%)
Concomitant medication	
• Immunomodulator	21 (62%)
• Aminosalicylates	2 (6%)
• Combination	11 (32%)

Male (%)	24 (57%)
Time to first biologic (median) in years	3 (IQR 6)
Corticosteroids at time of starting biologic	10 (29%)

Ulcerative colitis:

Fourty-five (12%) of 386 patients received tandem anti-TNF agents. Of these, 24 (53%) were female. The majority, 37 (82%) were non-smokers of which 5 (11%) were ex-smokers and 7 (16%) were current smokers. The smoking status of 1 (2%) patient was unknown.

Demographic and clinical disease characteristics for all patients with UC are depicted in Table 3. None of the patients in this group had any surgery. Concomitant medications for patients with UC showed that all patients except 1 (2%) started on maintenance therapy in the form of an IM, 5-ASA or both.

Table 3
Demographic and clinical details of patients with UC. n = 45

Male (%)	21 (47%)
Median age in years	45 (IQR 24)
Smoking history:	
• Never	32 (71%)
• Previously	5 (11%)
• Current	7 (16%)
Disease duration (median) in years	6 (IQR 5.25)
Disease extent:	
• E1	0 (0%)
• E2	16 (42%)
• E3	21 (55%)
Concomitant medication:	
• Immunomodulator	6 (17%)
• Aminosalicylates	11 (31%)
• Combination	19 (53%)
Time to biologic (median) in years	2 (IQR 5)
Corticosteroids at time of initiation of biologic	16 (42%)

Crohn's disease:

First anti-TNF agent: Standard induction doses were used for both agents in all patients. Infliximab was the first anti-TNF agent used in 23 (54.7%) patients and adalimumab for the rest. Twenty-eight (66.7%) patients remained on standard maintenance therapy until they switched to the second anti-TNF agent – secondary loss of response with normal drug level. During the maintenance phase of the first biologic agent, 4 (17.4%) patients on infliximab had to escalate therapy to a double dose regime, while 10 (55.6%) patients on adalimumab had to escalate therapy to weekly dosing - secondary loss of response with low drug level.

Loss of response was the main reason for switching from the first to the second anti-TNF agent. Thirty-five (83.3%) had secondary loss of response, while 4 (9.5%) had primary loss of response and 3 (7.1%) had side effects. Twenty-six (61.9%) patients switched to the second anti-TNF agent within 2 years of initiation and 36 (85.7%) within 4 years of commencement of therapy (Fig. 1).

Second anti-TNF agent: All 42 patients who started initially on an anti-TNF agent were switched to a second anti-TNF agent. All 23 (54.7%) patients who initially received infliximab were changed to adalimumab and 19 (45.2%) patients first on adalimumab were switched to infliximab. All patients received standard induction therapy regimens with the second anti-TNF agent.

Two (4.7%) patients, 1 on infliximab and 1 one adalimumab, failed induction therapy with the second anti-TNF agent and was escalated to newer molecules with a different mechanism of action. The majority, 25 (59.5%) remained on standard therapy on the second ani-TNF agent. Of the patients on infliximab, 5 (27.8%) patients had to escalate treatment further either to a double dose regime or reduced dosing frequency. For adalimumab, 10 (43.5%) patients had to escalate treatment to weekly dosing.

Thirty-three (82.5%) continued with the second anti-TNF agent and remained in remission. Of the 15 (23.8%) patients who required dose escalation on the second anti-TNF agent, 12 (80.0%) remained on the escalated dose and remain in clinical remission.

Patients with CD started on adalimumab as first anti-TNF agent had a 3-fold (55% vs 17%) increased risk to escalate therapy compared to infliximab {OR = 5.28, 95% CI [1.29, 21.51], p < 0.05}. Once switched to a second anti-TNF agent, patients on adalimumab had a 2-fold risk (43% vs 27%) of dose escalation compared to infliximab {OR = 4.25, 95% CI [1.09, 16.61], p < 0.05}.

Third and more biologic agents: Seven (17.5%) patients required a switch to yet another biologic agent. Loss of response was the indication in all but 1 (2.5%) patient who developed side-effects. Figure 2 gives graphic representation of the treatment algorithm in CD for all drugs.

Four (57.1%) patients who were in the standard dosing group required further escalation: 3 (42.9%) patients were on adalimumab and 1(14.3%) patient was on infliximab. Two patients were escalated to ustekinumab and 2 to vedolizumab.

Of the 3 patients in the previously escalated group, 1 (14.3%) patient on infliximab was further escalated to ustekinumab. The other 2 (28.6%) patients already on higher dose of adalimumab were escalated to

double dose infliximab. One of them reached clinical remission on this regimen and remained on that for the duration of the study. The other patient also received double dose infliximab for a short while, but never went into clinical remission and subsequently received vedolizumab, followed by ustekinumab and appeared to have achieved remission finally.

At the end of 4 years, 40 (95.2%) patients remained on anti-TNF therapy without requiring hospitalisation or surgery. Two (4.8%) patients failed therapy, dropped out and was lost to follow-up.

Ulcerative colitis:

First anti-TNF agent: Standard induction doses were used for all patients who required treatment escalation to a biologic agent. Infliximab was the first biologic agent used in 22 (48.9%) patients in this group with UC and 21 (46.7%) receiving adalimumab. Two (4.4%) patients received golimumab as standard induction therapy. In the maintenance phase, 22 (48.9%) patients remained on standard dose with 12 (26.7%) on infliximab, 9 (20%) on adalimumab and 1 (2.2%) on golimumab. Treatment escalation was required in 22 (48.9%) patients with 12 (26.7%) on adalimumab and 10 (22.2%) on infliximab.

Induction therapy failed in 2 (4.4%) patients, 1 was started on adalimumab and another started on golimumab. They were both immediately switched to infliximab. Loss of response was the main reason for switching to the second anti-TNF agent for the rest of the group. Thirty-seven (82.2%) patients experienced secondary loss or response, while 6 (13.3%) developed serious adverse events; 1 developed pulmonary tuberculosis, 2 developed pneumonitis, 1 developed intractable arthralgia and 2 developed serious infusion reactions. One (2.6%) patient was switched from infliximab to adalimumab for convenience of administration.

Second anti-TNF agent: All 45 patients started on the first anti-TNF agent were switched to a second anti-TNF agent. The majority, 42 (93.3%) patients switched within 2 years of commencing biological therapy with 10 (22.2%) switching withing the same year (Fig. 3). All patients who were switched received standard dose induction therapy with the second anti-TNF agent.

Of the 22 (48.9%) patients who started off with infliximab as initial biologic agent, 21 (46.7%) were switched to adalimumab and 1 (2.2%) was switched to golimumab. Twenty-one (46.7%) patients commenced on adalimumab first off were switched to infliximab (18 patients 40%), golimumab (2 patients 4.4%) and vedolizumab 1 patient (2.2%). Both patients (4.4%) initially started on golimumab were switched to infliximab. The majority of patients, 29 (64.4%) remained on standard maintenance dose during this phase of their treatment. Of the 16 (35.6%) patients whose treatment was escalated, 12 (26.7%) patients were on adalimumab and 4 (8.8%) patients on infliximab.

Two patients died during this second anti-TNF phase: 1 from a myocardial infarction and 1 from complications of a haematological malignancy. Both were on infliximab at the time, but this was not considered a drug-related serious adverse event. Two (5.3%) patients, both on adalimumab, discontinued anti-TNF therapy and was lost to follow-up.

Thirty-one (68.9%) patients remained on the second biologic for the duration of the study, 24 (77.4%) patients were on standard dose maintenance therapy, while 7 (22.6%) remained on an escalated anti-TNF dose/dosing schedule.

There was no increased risk of dose escalation for patients with UC started on either adalimumab or infliximab (27% vs 22%) as a first anti-TNF agent {OR = 1.60, 95% CI [0.48, 5.34], p > 0.05}. However, once switched to a second anti-TNF, patients on adalimumab had a 3-fold (27% vs 9%) risk of dose escalation compared to infliximab {OR = 5.33, 95% CI [1.32, 21.53], p < 0.05}.

Third and further biologic agents: Fourteen (31.1%) patients experienced secondary loss of response and were switched to yet another biologic agent. Three of these patients were switched to a fourth biologic agent for the same reason. Figure 4 gives a graphic representation of the treatment algorithm in UC. Of these patients, 5 (41.7%) (3 infliximab and 2 adalimumab) were on standard dose maintenance therapy with adequate drug levels. Nine (64.3%) patients were already on escalated doses with 5 (55.6%) on weekly dosing with adalimumab and 4 (44.4%) patients on escalated dosing schedules of infliximab.

Seven patients on adalimumab were switched to a third biologic as follows: 2 patients each to infliximab, vedolizumab and ustekinumab and a single patient switching to golimumab. Seven patients on infliximab were switched as follows: 4 patients to vedolizumab, 2 patients to golimumab and 1 patient to adalimumab. A further 3 patients were switched to a fourth biologic: 2 patients started on golimumab were switched to infliximab and ustekinumab respectively and 1 patient on adalimumab were changed to vedolizumab.

Of the three (21.4%) patients who required a fourth biological agent, 1 was switched from golimumab to high dose infliximab, 1 from adalimumab to vedolizumab and 1 from golimumab to ustekinumab. All three remained in clinical remission.

At the end of 4 years, 34 (89.5%) patients remained on a biologic agent and never required hospitalization or surgery.

Risk factor prediction:

These are patients with aggressive disease at high risk of disease progression and need for escalation of therapy. We assessed the usual risk factors (age, gender, smoking status, disease extent and concomitant medication use) associated with worse outcome in IBD for significance of response to anti-TNF therapy. The Fisher-Freeman-Halton Exact tests, ANOVA, and Cox regression analysis all failed to clearly identify any risk-factor to failing a specific biologic treatment, in either UC or CD.

Pearson's Chi-squared goodness-of-fit tests, with a Yate's correction, was run to assess the impact of escalating maintenance doses to achieve clinical remission. While the p-values show that escalation of the maintenance dose does not have an impact on the patient's likelihood to move on to another biologic, the numbers do suggest that further data should be collected. For CD, the results are significant, and for

IBD the results are very close for significance (just one patient would need to gain remission for the results to give p = 0.0381). As we discuss below, a major limitation of this study is the relatively small sample size. Over time, with more data collection, this question can be re-evaluated.

The same goodness-of-fit tests were also run to evaluate likelihood to achieve remission on a consecutive anti-TNF agent. The analysis suggests that switching treatments has a statistically significant impact (p < 0.001) on a patient's likelihood to maintain therapy and remain in clinical remission.

Discussion

Switching from one anti-TNF agent to another when the first agent fails in patients with IBD appears counterintuitive. This study has however shown that this strategy is useful, effective and cost saving. It is not a widespread clinical strategy as < 10% of all the patients in this registry was treated this way.

In the early days, anti-TNF agents were the only biologics available for the treatment of IBD, and if one agent failed, it was common practice to cycle patients through the available anti-TNF agents to achieve clinical remission. Currently, although a number of new agents in a different class and mechanism of action is available, healthcare funders make it compulsory that for a patient to migrate to the newer class agent, they should have failed one, or sometimes more anti-TNF agents. This is clearly driven by cost.

Although the total number of patients in this study is small, valuable insights were gleaned from this data. The majority of these patients with aggressive disease, for both CD and UC, have remained on a biologic agent, albeit a different one over time, and remained in clinical remission.

In CD, patients started on adalimumab as first anti-TNF agent had a significant risk of dose escalation compared to infliximab. Similarly, patients have a statistically significant risk of dose escalation if switched to adalimumab as a second anti-TNF agent, compared to infliximab.

There was no significantly increased risk of dose escalation for patients with UC started on either adalimumab or infliximab as a first anti-TNF agent. However, patients switched to adalimumab as second anti-TNF in UC, had a significant increased risk of dose escalation compared to infliximab.

Lessons from this study showed that tandem use of consecutive anti-TNF agents is a reasonable clinical approach. Data from this study suggest that it makes no difference which anti-TNF agent is started first for both CD and UC. It showed that all anti-TNF agents used eventually failed over time. However, patients on adalimumab have a greater risk of dose escalation before loss of response.

During active inflammation, as seen in IBD, activated macrophages and T-lymphocytes release TNFα, which will bind the TNF receptors 1 and 2. This leads to the activation of NF-κβ which sets off an inflammatory cascade where a myriad of cytokines is produced that fuels the inflammation. This is known as the classical TNFα pathway and is linked to acute, rapid activation of inflammation. The alternative pathway is activated by lymphotoxin-β (LTβ), CD40 ligand, B-cell activating factor and receptor-activated NF-κB ligand (RANKL). This pathway is associated with chronic progressive IBD[11].

Although the different anti-TNF agents interrupt the blockade of TNFα – TNFR, it is not clear whether the different anti-TNF agents have similar clinical efficacy. As there are differences in the molecular constructs of the different anti-TNF agents as well as the dose used and the route of administration differs, effectiveness may differ. Moreover, in a recent electron microscopy study, it was found that adalimumab and infliximab bind to different areas of the TNFR[12, 13]. The affinity and degree to which the anti-TNF engage with the receptor will eventually determine the clinical efficacy of the relevant anti-TNF agent. However, this theory is untested. Furthermore, evidence suggests that the efficacy of the anti-TNF agents is not solely due to TNFα neutralisation, but through a Fc mediated anti-inflammatory mechanism[14].

Patients with UC treated with adalimumab had increased risk of hospitalization and serious adverse events compared to infliximab according to a study by Singh *et al*[15]. Our study has also shown, albeit to a smaller size, that adalimumab is associated with more serious adverse events compared to infliximab. Another study by Penaccione *et al* showed that patients with Crohn's disease who developed loss of response to infliximab, did well and remain in clinical remission with adalimumab treatment for over 96 weeks[16]. A recent study from Rundquist *et al* from a Swedish registry showed that a second line anti-TNF agent (infliximab and adalimumab) has similar clinical efficacy as vedolizumab, when the first agent failed[17].

The biggest limitation of this study is its retrospective nature, but databases lend themselves to these analyses. However, the benefit of this is that it allows evaluation of real-life decision making. The small number of patients in this study makes meaningful interrogation of the data difficult, but patient input onto the database is ongoing and results can be updated in future.

Conclusion

Despite a lack of clarity on factors indicating success of a particular anti-TNF agent, from a clinical standpoint, it is a reasonable approach to try a second ant-TNF agent when the first agent failed in IBD. Clearly, this must be a decision driven by patient profile and other disease specific risk factors. With the cost of anti-TNF therapy falling and biosimilars becoming more readily available, this treatment strategy is especially useful in resource constraint settings.

Declarations

Ethics approval and consent to participate:

Ethics approval was obtained from PharmaEthics and both the patient and the treating physician signed informed consent. The study was conducted within the regulatory framework as set out by PharmaEthics.

Consent for publication:

NA.

Availability of data and materials:

The dataset generated and analysed is with the corresponding author and will be made available on reasonable request. Data provided will de anonymised in keeping with 'protection of personal information' laws in South Africa.

Competing interest:

None

Funding:

None

Authors' contributions:

EF: Design the concept, wrote manuscript, drafted tables and figures

AT: Did all statistical analysis, drafted tables and figures

SG: Co-wrote manuscript and double checked statistical analysis

WdV: Co-wrote manuscript, critical analysis of draft

All authors reviewed and accepted the manuscript

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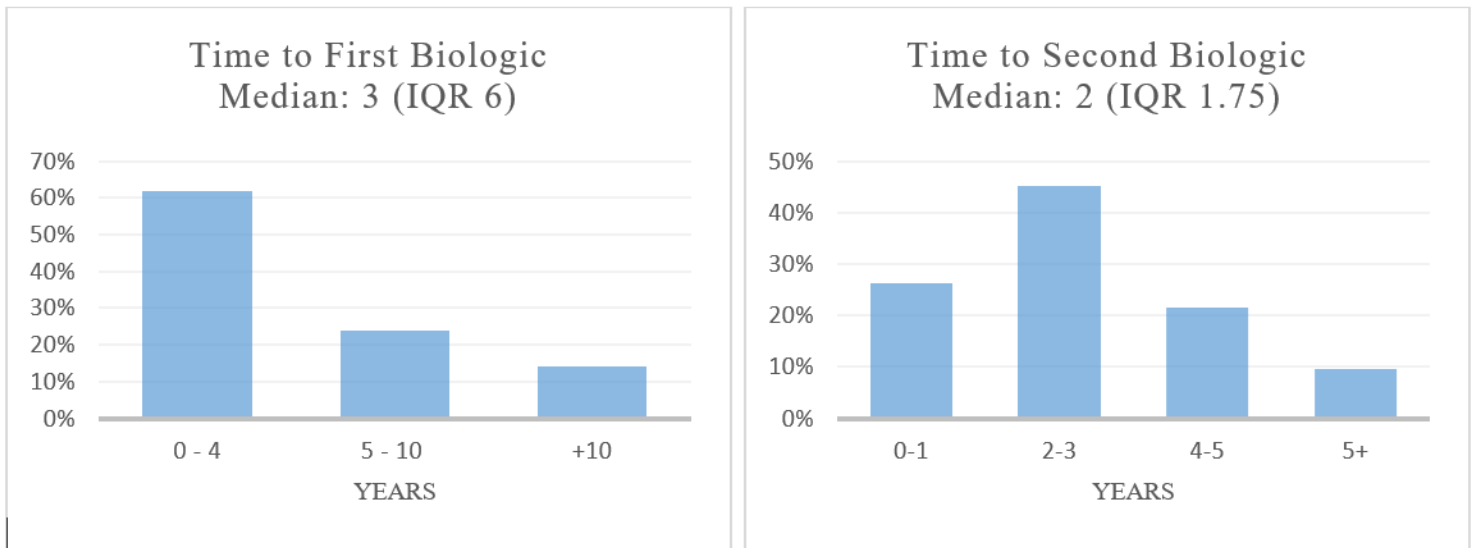
Figures

Figure 1
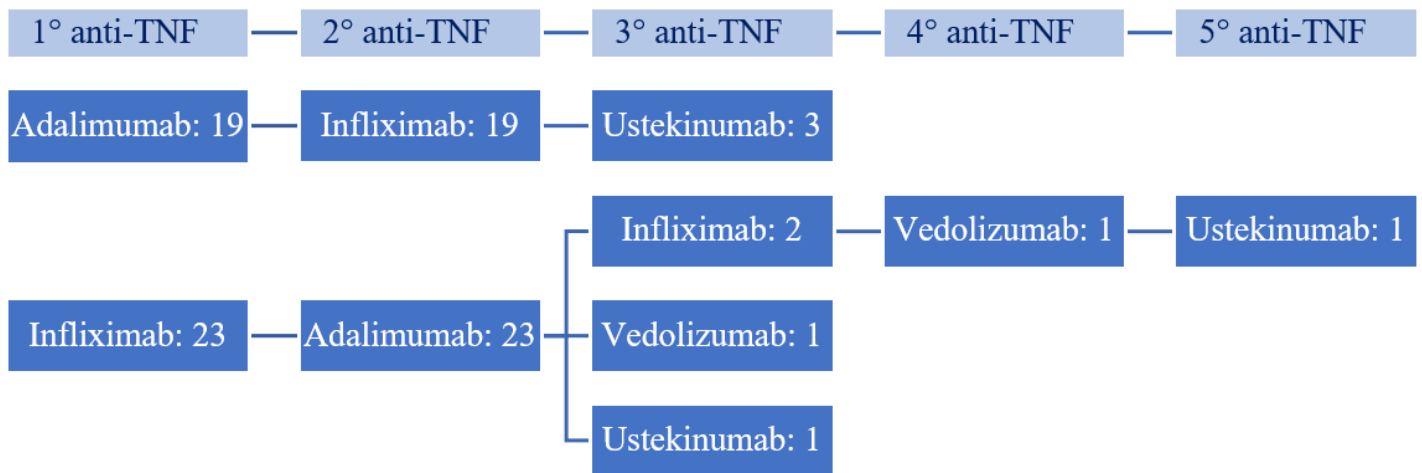
Time to biologic agent for CD

Figure 2

Diagrammatic representation of the biologics used for patients with CD

Time to First Biologic
Median: 2 (IQR 5)

Time to Second Biologic
Median: 1 (IQR 1)

Figure 3
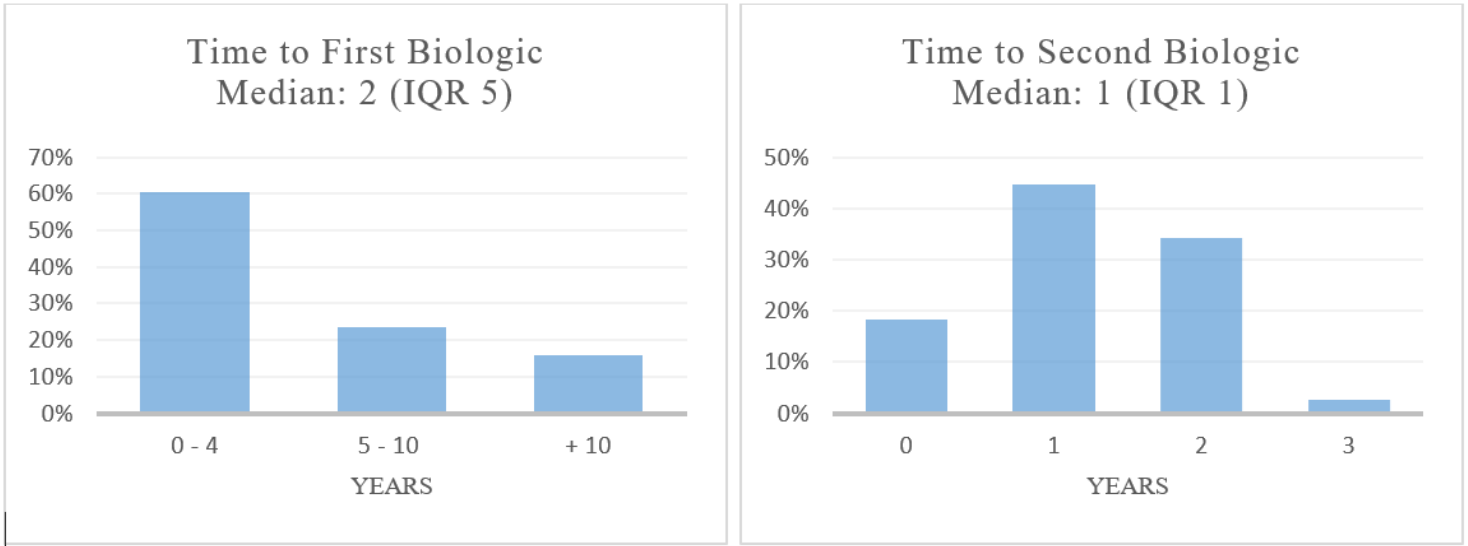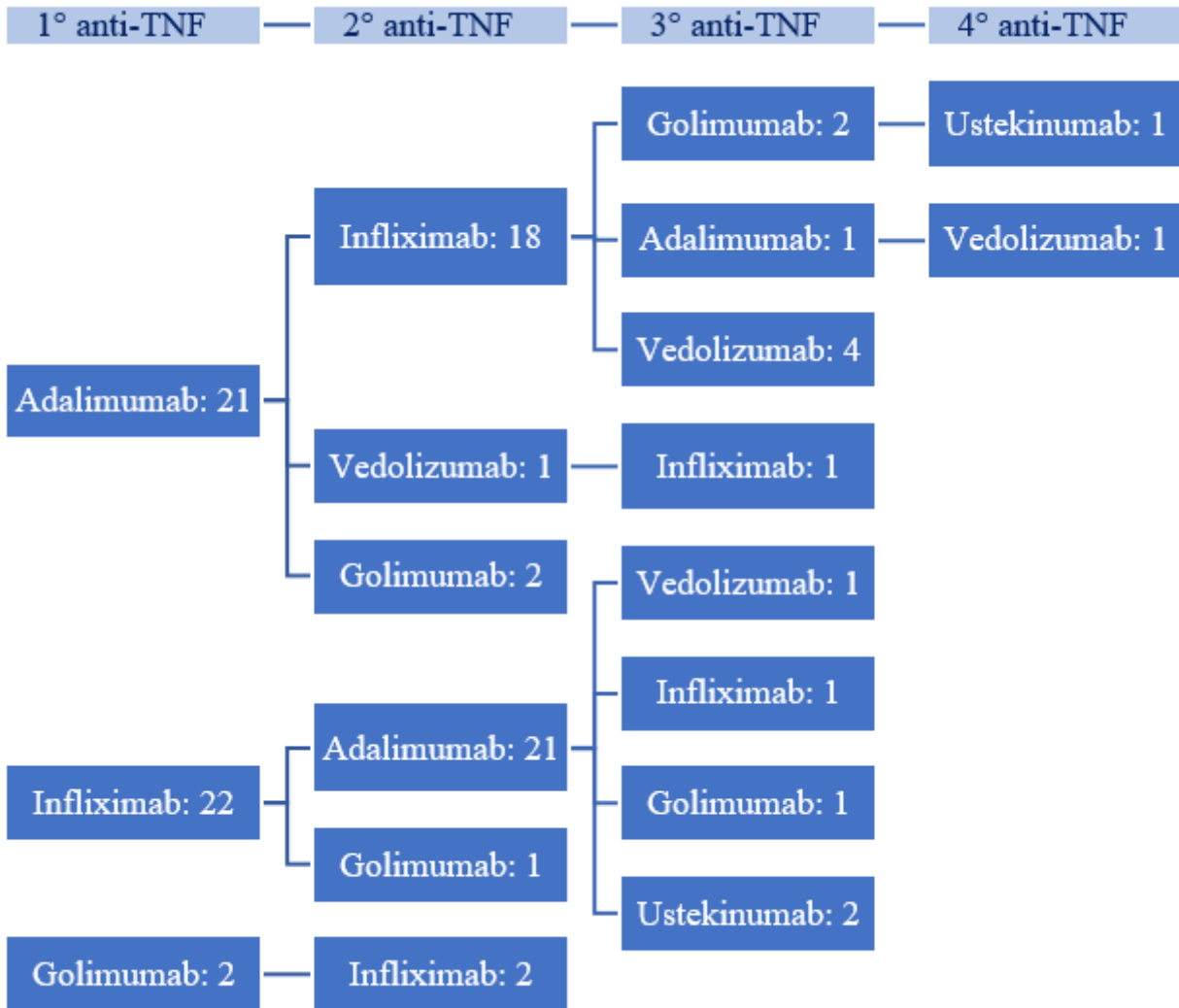
Time to biologic agent in UC

Figure 4

Diagrammatic representation of biologic agents used for patients with UC.