Risk of consecutive immunogenic failure in switchers of anti-tumor necrosis factor alpha among patients with inflammatory bowel diseases

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Abstract

Background: Evidence regarding the risk of immunogenicity in patients with inflammatory bowel disease (IBD) who switched anti-tumor necrosis factor alpha (anti-TNFα) therapies to a subsequent anti-TNFα (either infliximab or adalimumab) is conflicting. We aimed to assess the risk of consecutive immunogenicity to anti-TNFα in a large cohort of patients.

Methods: This was a multicenter retrospective study. Medical records of adult and pediatric IBD switchers who had pharmacokinetic data for both agents between 2014 and 2020 were retrieved. Data including age, sex, disease type, duration of therapies, and concomitant use of immunomodulators (IMMs) were recorded.

Results: Overall, 164 patients were included [52% female; 88% Crohn's disease; mean age = 24.4 ± 14.6 years; 108 (66%) switched from infliximab to adalimumab and 56 (34%) vice versa]; 120 (73.1%) patients switched due to an immunogenic failure. Among patients switching therapy from infliximab to adalimumab due to an immunogenic failure immunogenicity to infliximab was significantly associated with consecutive immunogenicity to adalimumab ($p = 0.026$). Forthy four out of 120 patients (36.6%) with an immunogenic failure to the first anti-TNFα started an IMM with the second anti-TNFα. This combination with IMM was not associated with reduction of consecutive immunogenicity ($p = 0.31$), but it was associated with longer drug retention ($p = 0.007$). Multivariate analysis demonstrated that older age at second anti-TNFα, adjusted to the chronology of therapy and sex, was associated with increased immunogenicity to the second anti-TNFα.

Conclusion: Patients with IBD who switch from infliximab to adalimumab following an immunogenic failure are at increased risk for consecutive immunogenicity to adalimumab. IMM use after a switch prolongs drug retention.

Keywords: adalimumab, antibodies, anti-TNF, immunomodulators, infliximab

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Introduction

Monoclonal antibodies against tumor necrosis factor alpha (TNFα) became the mainstay of treatment in adult and pediatric patients with moderate to severe inflammatory bowel disease (IBD), due to their established efficacy.[1] Nevertheless, primary or secondary treatment failures of anti-TNFα treatment are significant shortcomings hindering their efficacy[2] with reported loss of response (LOR) rate of up to 13% annually.[3,4] Immunogenicity, meaning the development of neutralizing antibodies against the drug (anti-drug antibodies, ADAs), is a leading cause for LOR to anti-TNFα, occurring in 8–60% and

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2–44% of patients treated with infliximab (IFX) and adalimumab (ADL), respectively.[5,6]

A combination of IFX and an immunomodulator (IMM) was consistently shown to be superior to IFX monotherapy in both adults and children, partially, *via* suppression of ADAs.[7–9] In contrast, the effect of adding IMM to ADL is more controversial with conflicting results, ranging from no benefit[10–12] to significant beneficial effect, mostly through suppression of immunogenicity.[13] Recently, it was shown that the HLA-DQA1*05 allele, carried by approximately 40% of Europeans, significantly increased the rate of immunogenicity of both IFX and ADL, regardless of combination treatment with an IMM.[14]

Primary and secondary failures to the first agent were shown to result in decreased efficacy of the second agent;[15] however, a switch in-class is still the recommended option when the cause of failure is immunogenicity.[16] There is scarce data suggesting that the risk for immunogenicity is increased in patients with IBD who switched to a second anti-TNF (switchers) following development of ADAs to the first anti-TNFα agents (consecutive immunogenicity).[17,18]

Here, we aimed to further investigate the impact of switch in-class between IFX and ADL (or vice versa) on the risk to develop consecutive immunogenicity.

Materials and methods

Design

This was a multicenter retrospective study conducted in three tertiary medical centers in Israel; two large IBD centers for adults – Rabin Medical Center (RMC) and Sheba Medical Center – and one pediatric center at the Schneider Children's Hospital.

Patients

Medical records of adults and pediatric patients with IBD who were followed between 2014 and 2020 at the respective medical centers and who were treated with anti-TNFα agents and had pharmacokinetic (PK) data were reviewed. Patients who switched from one anti-TNFα to another and had a comprehensive clinical and PK data were assessed for consecutive immunogenicity – cohort of switchers. Drug levels and antibody measurements were performed based on the treating physician discretion. All adults and pediatric population were eligible. Rates of IFX and ADL ADAs were assessed from the lab databases – PK results (irrespective of indication).

PK analysis

Most PK tests were performed at the Sheba Gastroenterology Laboratory, Ramat Gan, Israel, and 29 tests were performed at the RMC lab.

PK analysis at both labs is performed by an enzyme-linked immunosorbent assay (ELISA). Of note, the Sheba lab uses a drug tolerant assay based on an anti-human lambda-chain detection on an ELISA platform, previously described elsewhere.[19,20] The RMC lab utilizes a commercial assay by Theradiag©, Beaubourg, France. Drug level values at both these labs are measured by the same units of micrograms per milliliter. However, ADA measurements for these assays are not similar, and these tests have different positive cutoffs and scale. For uniformity of assessment of immunogenicity, we have defined each test of ADA as either positive or negative according to the specific relevant assays' cutoffs: >2 micrograms per milliliter for the Sheba lab and >10 nanograms per milliliter for the RMC lab. In order to assess the impact of ADA titers, we calculated antibody ratio based on the level of antibodies at the first positive test based on the positive cutoff for the appropriate lab.

Description of variables and outcomes

Data including age, sex, disease type, duration of therapies, concomitant use of IMMs, and reason for discontinuation of the first anti-TNFα were recorded.

Immunogenic failure was defined as clinical LOR leading to drug discontinuation in the presence of anti-TNFα antibodies with no drug present.

Statistical analysis

Continuous variables were evaluated for normal distribution using histogram, Q–Q Plots, and Kolmogorov–Smirnov test, and reported as median (interquartile range, IQR) for non-normally distributed variables or mean (standard deviation, SD) for normally distributed variables. Categorical variables were reported as frequency and percentage. Similarity of characteristics at

baseline between the two groups (according to chronology of treatment) was assessed by using Mann–Whitney test or *t*-test for continuous variables, and chi-square test or Fisher's exact test for categorical variables. We used Kaplan–Meier curves to analyze the effect of first agent immunogenicity on second drug immunogenicity according to different variables. Cox regression analysis was used to assess variables associated with increased immunogenicity to the second anti-TNFα. All reported *p* values are two-sided. The *p* values <0.05 were considered significant. Data were analyzed using SPSS (IBM SPSS Statistics, Version 26.0, IBM Corp., Armonk, NY, USA).

Ethical considerations

The study was approved by the local institutional review board of each participating center, and the requirement for a documented informed consent was waived. The reporting of this study conforms to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement .

Results

Overall, 164 patients who switched between anti-TNFα agents – 52% male; 88% Crohn's disease; mean age = 24.4 ± 14.6 years, 61/164 patients ⩽17 years of age (A1) – were included in the analysis; 108 patients (66%) switched from IFX to ADL, and 56 (34%) from ADL to IFX. Median duration of disease from diagnosis to initiation of the first anti-TNFα was 18 months (IQR = 4–88 months), and from diagnosis to the second anti-TNFα was 49 months (IQR = 16–118 months). Patients' characteristics at baseline are depicted in Table 1. Immunogenic failure was present in 93/108 (86.1%) patients who had been on IFX first and in 27/56 (48.2%) patients who had ADL first. All other reasons for switching therapies are presented in Table 2. ADAs to the first and second anti-TNFα agents were present in 120/164 (73%) and 61/164 (37%) patients, respectively. An IMM was initiated in 38 (23%) and 55 (33%) patients with the first and second treatments, respectively; 44/120 patients (36.6%) who had an immunogenic failure to the first anti-TNFα started an IMM with the second anti-TNFα. Patients' disposition is depicted in Figure 1. Status of the second anti-TNFα therapy is presented in Supplementary Table 1.

When stratifying the cohort according to chronology (IFX to ADL, $n = 108$; ADL to IFX, $n = 56$), there were no significant differences in all variables at diagnosis between the two sub-cohorts (data not shown).

Consecutive immunogenicity

Kaplan–Meier analysis was used to assess the time dependent rate of ADAs development to the second anti-TNFα according to immunogenicity to the first anti-TNFα (Figure 2(a)). No significant difference was noted when analyzing the entire cohort, regardless of chronology of switch (IFX to ADL and vice versa; $p = 0.30$).

In switchers from IFX to ADL, immunogenicity to IFX was significantly associated with higher rates of consecutive immunogenicity to ADL (Figure 2(b); $p = 0.026$). In contrast, switchers from ADL to IFX did not demonstrate increased rates of consecutive immunogenicity (Figure 2(c); $p = 0.29$).

Among the 120 patients who developed ADAs to the first anti-TNFα, 44 (36.6%) initiated an IMM with the second anti-TNFα. Combination therapy of an IMM with the second agent was not associated with reduction of consecutive immunogenicity (Figure 3(a); $p = 0.31$). Analysis of the effect of IMM according to the chronology did not yield significant differences (Figure 3(b) and (c)). Survival analysis of time to second anti-TNFα cessation according to the addition of IMM demonstrated a significant beneficial effect of combination therapy on second anti-TNFα retention in the entire cohort (Figure 4(a); $p = 0.007$) and also when stratifying the cohort according to the chronology (Figure 4(b) and (c); IFX to ADL, $p = 0.045$; ADL to IFX, $p = 0.05$).

Variables associated with consecutive immunogenicity

Associated risk factors for consecutive immunogenicity by univariate analysis is presented in Supplementary Table 2; the chronology of treatment ($p = 0.008$; IFX to ADL > ADL to IFX), sex ($p = 0.028$; females > males), and age at second anti-TNFα ($p = 0.005$; older > younger) were associated with increased immunogenicity to the second anti-TNFα. In contrast, type of diagnosis, time to first anti-TNFα, and duration of first anti-TNFα therapy were not associated with immunogenicity to the second anti-TNFα.

Table 1. Patients' characteristics ($N = 164$).

Disease type, CD, *n* (%)	145 (88.4)
Male, *n* (%)	85 (51.8)
Age at diagnosis (median, IQR)	19.8 years (14.2–30.6)
Time from diagnosis to onset of 1st anti-TNFα therapy (median, IQR)	18 months (4–88)
Duration of 1st anti-TNFα therapy (median, IQR)	10 months (5–19)
Time from diagnosis to onset of 2nd anti-TNFα therapy (median, IQR)	49 months (16–118)
Duration of 2nd anti-TNFα therapy (median, IQR)	15 months (7–34.8)
Chronology of treatment, IFX 1st therapy, *n* (%)	108 (65.9)

anti-TNFα, anti-tumor necrosis factor alpha; CD, Crohn's disease; IFX, infliximab; IQR, interquartile range.

Table 2. Reasons for discontinuation of the first anti-TNFα.

	1st anti-TNFα	
	IFX, $n = 108$	**ADL, $n = 56$**
Primary non-response, *n* (%)	1 (0.9)	10 (17.8)
Immunogenic secondary failure, *n* (%)	93 (86.1)	27 (48.2)
Non-immunogenic secondary failure, *n* (%)	10 (9.2)	16 (28.6)
Drug levels 0–4.9 mcg/ml	8	10
Drug levels 5–10 mcg/ml	1	1
Drug levels >10 mcg/ml	1	5
Adverse events, *n* (%)	4 (3.7)	3 (5.3)

ADL, adalimumab; anti-TNFα, anti-tumor necrosis factor alpha; IFX, infliximab.

After adjustment to sex and chronology of treatment, multivariate analysis demonstrated that only age at second anti-TNFα remained significant ($p = 0.009$). Stratification to three groups according to age at second anti-TNFα (0–17, 17–40, >40) demonstrated a clear separation between age groups with significant increased immunogenicity in patients older than 40 (Figure 5; $p = 0.04$). In contrast, age at onset of the first anti-TNFα agent was not associated with ADA development against this agent ($p = 0.14$).

Finally, no significant association was seen between the titer of ADAs in patients who developed ADAs to the first anti-TNFα and immunogenicity to the second anti-TNFα ($p = 0.61$). Similarly, stratification according to the chronology and different thresholds to ADA titers did not yield any significant association (data not shown).

Discussion

In this retrospective cohort, we have shown that immunogenicity to IFX was significantly associated with higher rates of consecutive immunogenicity to ADL ($p = 0.026$), unlike patients switching from ADL to IFX. We have also shown that concomitant IMM given with the subsequent anti-TNFα was associated with longer drug retention ($p = 0.007$), but it did not reduce the rate of consecutive immunogenicity. Finally, we were able to show that older age at the start of the second anti-TNFα was significantly associated with increased consecutive immunogenicity.

Our findings of a clear association between immunogenicity to IFX as a first-line anti-TNFα therapy and higher rates of consecutive immunogenicity to ADL have been previously shown by others;[17,18] Frederickson and colleagues showed that patients with previous IFX-ADA were significantly more prone to develop ADL-ADA (33%) than those without (0%) (odds ratio estimated = 11, $p = 0.04$).[17] This susceptibility to develop ADA might be attributed to a genetic trait, as was recently shown in the PANTS (Personalizing Anti-TNF Therapy in Crohn's Disease) trial.[14] Nonetheless, in our cohort, switching from ADL to IFX was not associated with higher rates of consecutive immunogenicity. Possible explanations might include higher thresholds to develop ADA to ADL compared with ADA to IFX and of course a small cohort.

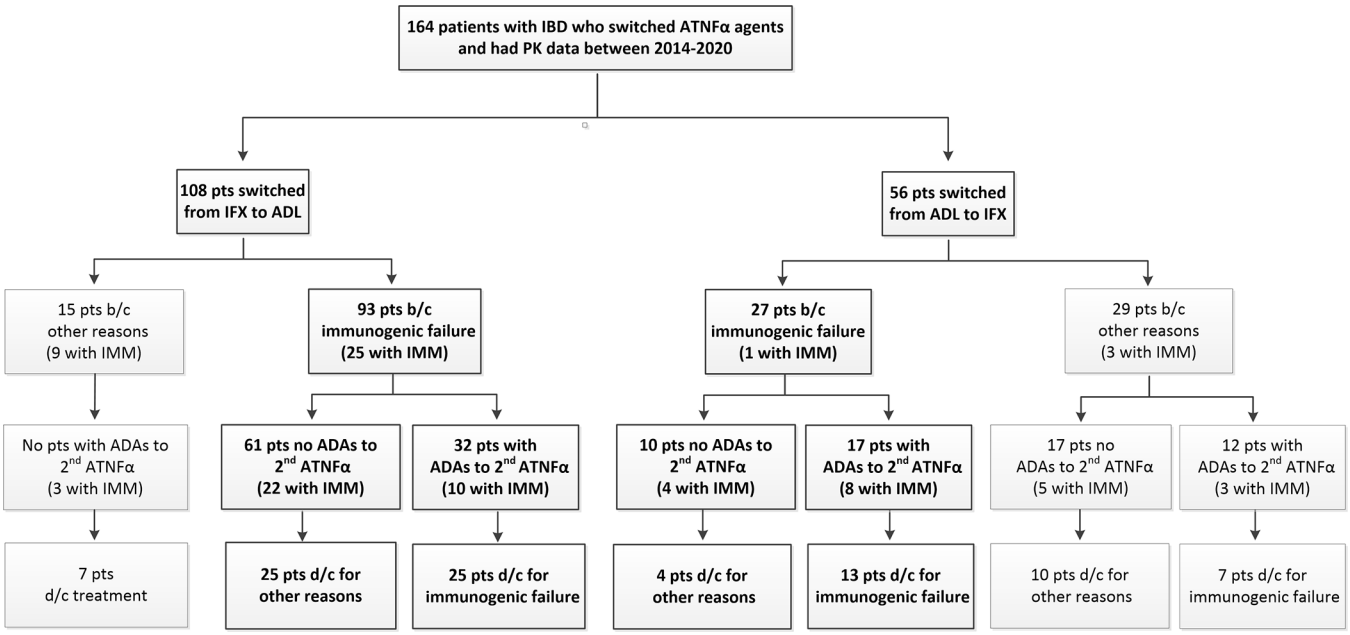


Figure 1. Patients' disposition.

Indeed, the PANTS trial reported lower of immunogenicity to ADL *versus* IFX.[13]

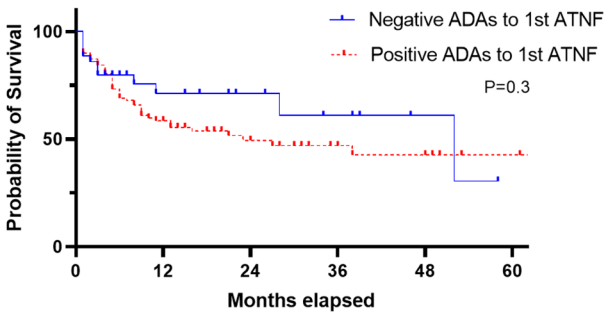
In our study, combination therapy with an IMM was not found to be associated with reduced rate of consecutive immunogenicity. On one hand, this might be in line with the findings in the PANTS trial who demonstrated that carriage of 1 or more HLA-DQA1*05 alleles confer an almost twofold risk of immunogenicity to anti-TNFα therapy irrespective of concomitant immunomodulatory use.[14] On the other hand, this is in contrast to the findings reported by Roblin *et al.*[21] who showed that combination therapy with IMM (azathioprine at 2–2.5 mg/kg) was significantly associated with reduced PK failure after an anti-TNF switch.

Most studies have shown the value of the addition of an IMM in reducing the risk of immunogenicity with IFX and improving efficacy.[7,8,13,22,23] However, data on combination of IMMs and ADL are more conflicting, on one hand questioning the impact on efficacy[12] while on the other hand demonstrating mitigation of immunogenicity.[13] In addition, previous studies have demonstrated that the addition of IMM, when antibodies against anti-TNFα occurred, was able to suppress their presence in some patients.[24,25] However, these studies did not assess whether the addition of an IMM at the time of the switch to another anti-TNFα in patients in whom antibodies to a first anti-TNFα occurred would be useful in decreasing immunogenicity. Differences in outcome could be attributed to several factors, including the methodology of antibody measurement after switching and methodology of assay used for ADAs and IMM dosing. It may be also possible that the number needed to treat for establishing the benefit of combination therapy for preventing ADA formation is high (especially for ADL) and that our study was not powered to demonstrate such difference.

Importantly, while concomitant IMM was not associated with reduced rate of antibody development in our study, longer survival of drug therapy was seen in patients on combination therapy. This prolonged survival was previously reported in several cohorts[23,26] and could be associated with higher drug trough levels, with a synergistic anti-inflammatory effect of the two drugs or due to the duration of follow up – that was insufficient to demonstrate the clinical effect of immunogenicity (a lag between onset of clinical LOR and the appearance of ADA).

We also found that older age is associated with a higher risk for consecutive immunogenicity. The impact of age on ADA development is

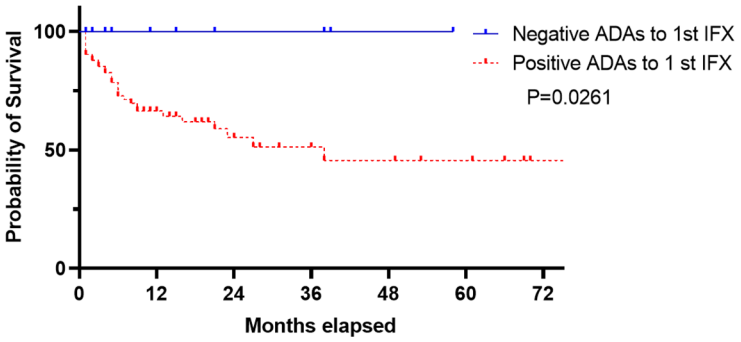
(a)



Number at risk:

Months	0	12	24	36	48	60
Positive ADAs to 1st ATNF	120	41	21	12	9	5
Negative ADAs to 1st ATNF	44	17	11	6	3	1

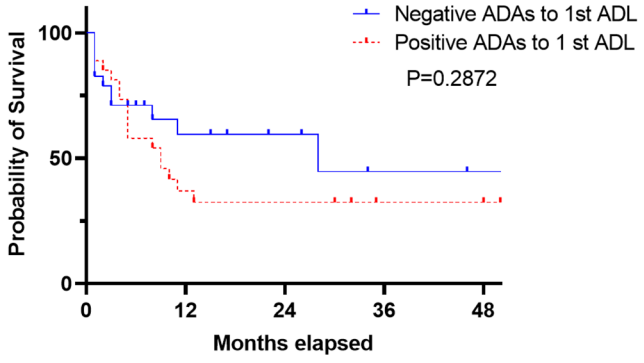
(b)



Number at risk:

Months	0	12	24	36	48	60	72
Positive ADAs to 1st IFX	93	33	15	10	7	5	2
Negative ADAs to 1st IFX	15	6	4	3	2	1	0

(c)

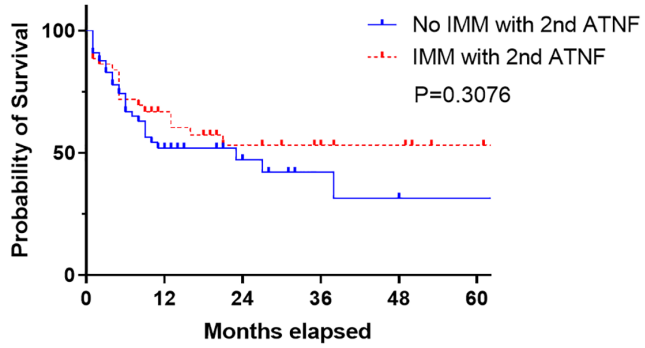


Number at risk:

Months	0	12	24	36	48
Positive ADAs to 1st ADL	27	9	8	3	2
Negative ADAs to 1st ADL	29	11	5	3	2

Figure 2. Kaplan–Meier analysis of consecutive immunogenicity according to ADA development to the first anti-TNFα: (a) analysis of the entire cohort, (b) patients who switched from infliximab to adalimumab, and (c) patients who switched from adalimumab to infliximab.

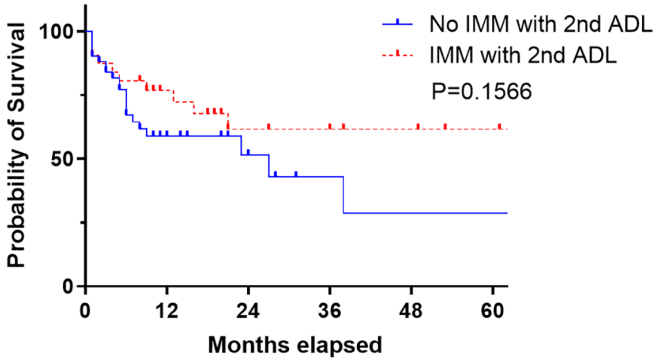
(a)



Number at risk:

Months	0	12	24	36	48	60
No IMM W 2nd ATNF	76	20	10	4	3	3
IMM W 2nd ATNF	44	22	14	8	6	3

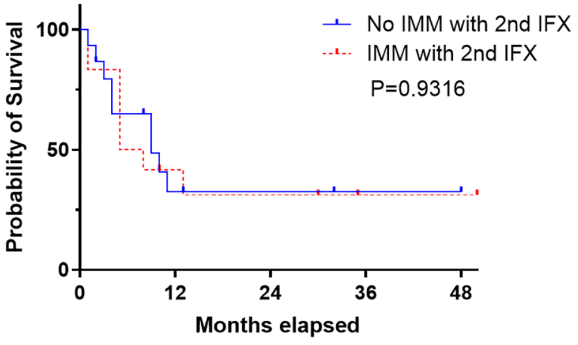
(b)



Number at risk:

Months	0	12	24	36	48	60
No IMM W 2nd ADL	61	16	7	3	3	3
IMM W 2nd ADL	32	18	11	7	5	3

(c)

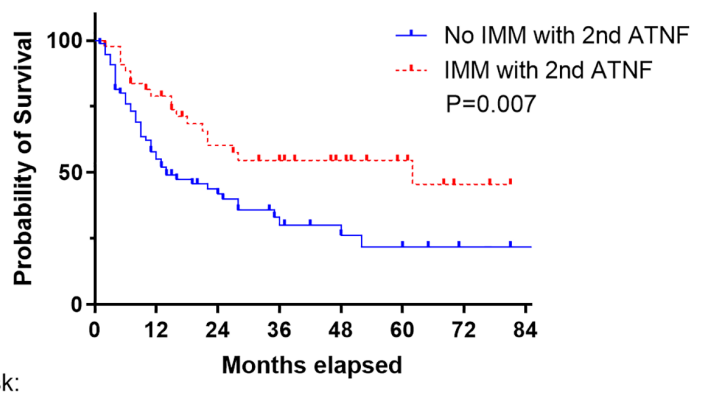


Number at risk:

Months	0	12	24	36	48	60
No IMM W 2nd IFX	15	4	4	3	1	0
IMM W 2nd IFX	12	4	4	2	1	1

Figure 3. Kaplan–Meier analysis of consecutive immunogenicity in patients who developed ADAs to the first anti-TNFα according to immunomodulatory use with the second anti-TNFα: (a) analysis of the entire cohort, (b) patients who switched from infliximab to adalimumab, and (c) patients who switched from adalimumab to infliximab.

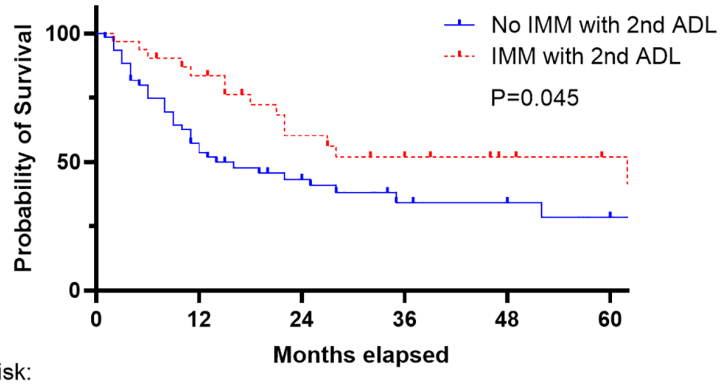
(a)



Number at risk:

Months	0	12	24	36	48	60	72	84
No IMM W 2nd ATNF	76	40	23	11	8	5	3	2
IMM W 2nd ATNF	44	33	24	17	12	8	4	1

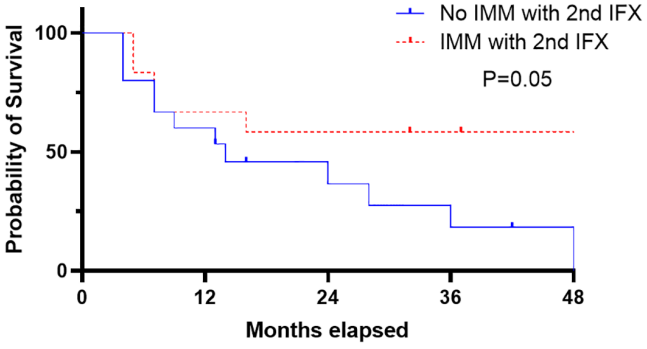
(b)



Number at risk:

Months	0	12	24	36	48	60
No IMM W 2nd ADL	61	31	19	10	7	5
IMM W 2nd ADL	32	25	17	11	8	6

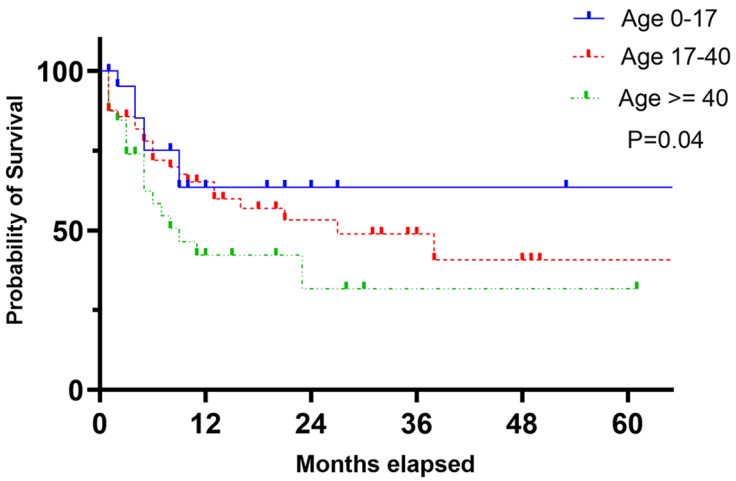
(c)



Number at risk:

Months	0	12	24	36	48
No IMM W 2nd IFX	15	9	5	3	1
IMM W 2nd IFX	12	10	8	7	4

Figure 4. Kaplan–Meier analysis of second anti-TNFα cessation in patients who developed ADAs to the first anti-TNFα according to immunomodulatory use with the second anti-TNFα: (a) analysis of the entire cohort, (b) patients who switched from infliximab to adalimumab, and (c) patients who switched from adalimumab to infliximab.



Number at risk:

Months	0	12	24	36	48	60
ADAs to 2nd ATNF Age 0-17	22	9	6	5	5	4
ADAs to 2nd ATNF Age 17-40	64	26	16	7	4	2
ADAs to 2nd ATNF Age >=40	33	8	4	2	2	1

Figure 5. Kaplan–Meier analysis of the association of age at second anti-TNFα initiation and consecutive immunogenicity.

sparsely reported. It may be assumed that differences in immune system activity during aging could result in decreased immune response as was demonstrated in patients with IBD receiving hepatitis B vaccination, for example.[27] Nevertheless, lower prevalence of ADAs to IFX was reposted for pediatric patients with IBD than for adults,[28,29] but later studies of pediatric populations and older populations failed to show that age plays a significant role in immunogenicity.[30,31] Larger population-based studies are required to consolidate the impact of age on immunogenicity of biologic agents in patients with IBD.

Limitations to our study include its retrospective nature with its inherent risk of bias and a relatively small group of patients. There were no scheduled repeated PK studies, and patients were sampled based on discretion of the treating physician. Only a small absolute number of patients were treated with IMM. We also did not have data regarding specific disease phenotype and location for most patients.

Conclusion

We have found an increased risk for the development of ADA to ADL following an immunogenic failure of therapy with IFX. Patients receiving IMM therapy following an the switch to a subsequent anti-TNFα had significantly longer drug persistence.

Hence, we recommend that patients who were failed by the first anti-TNFα therapy due to antibodies should receive IMM therapy when switching to a subsequent anti-TNFα and that therapeutic drug monitoring is used for early detection of consecutive immunogenicity.

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Author contributions

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Bella Ungar: Resources; Writing – review & editing.
Uri Kopylov: Resources; Writing – review & editing.

Tali Sharar Fischler: Visualization; Writing – review & editing.
Irit Avni Biron: Resources; Writing – review & editing.
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Raanan Shamir Resources; Writing – review & editing.
Iris Dotan: Resources; Writing – review & editing.
Shira Amir: Data curation; Project administration; Supervision; Validation; Writing – review & editing.
Amit Assa: Conceptualization; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Conflict of interest statement

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: H.Y.: Consultation and lectures fees from Abbvie, Janssen, Neopharm Ltd., Pfizer, and Takeda, and research grants from Pfizer. R.S.: Research grants from Abbvie. A.A.: Consultation and lectures fees from Abbvie and Takeda, and research grants from Abbvie and Janssen. M.M. and S.A. have no financial conflicts of interest to declare. B.U.: Consultation and lectures fees from Abbvie, Takeda, Janssen, and Neopharm Ltd. U.K.: Consulting fees from Abbvie, Jannsen, Takeda, MSD, Pfizer, and Medtronic; honoraria for lectures from Abbvie, Jannsen, Takeda, MSD, Pfizer, and Medtronic; leadership or fiduciary role from Takeda; and research grants from Takeda, Jannsen, and Medtronic. I.G.: Research grants from Pfizer, and travel grants from ECCO and IOIBD. I.D.: Institutional research grants from Altman and Pfizer; consulting fees from Arena, Gilead, Cambridge Healthcare, Wild bio, Food industries organization, and Integra Holdings; honoraria for lectures from Janssen, Abbvie, Takeda, Pfizer, Genentech/Roche, Arena, Neopharm Ltd., Celltrion, Rafa Laboratories, Ferring, Falk Pharma, Nestle, Celgene/BMS, and Abbott; and participation on a Data Safety Monitoring Board or Advisory Board from spare consortium Janssen, Abbvie, Takeda, Pfizer, Genentech/Roche, Arena, Neopharm Ltd., Gilead, Galapagos, Celltrion, Sublimity, Wild bio, Athos therapeutics, Food industries organization, Celgene/BMS, and Abbott. TSF, IAB, JEO and TTP report no conflicts of interest

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Supplemental material

Supplemental material for this article is available online.

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