

The efficacy of immunomodulators in the prevention and suppression of anti-drug antibodies to anti-tumor necrosis factor therapy in inflammatory bowel disease

Fotios S. Fousekis^a, Konstantinos Papamichael^b, Georgios Kourtis^c, Eleni N. Albani^d, Afroditi Orfanidou^e, Maria Saridi^f, Konstantinos H. Katsanos^a, Dimitrios K. Christodoulou^a

School of Health Sciences, University Hospital of Ioannina, Faculty of Medicine, University of Ioannina, Ioannina, Greece; Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA; "Sotiria" General Hospital, Athens, Greece; Laiko General Hospital, Medical School of National and Kapodistrian University of Athens, Greece; University of Patras, Greece; University of Patra, Greece; University of Thessaly, Greece

Abstract

The development of biological agents against tumor necrosis factor (TNF) has revolutionized the management of inflammatory bowel disease (IBD), frequently achieving induction and maintenance of remission in both ulcerative colitis and Crohn's disease. However, a loss of response due to the development of anti-drug antibodies (ADA) is seen annually in approximately 20% of IBD patients receiving anti-TNF therapy. Current evidence suggests that the use of immunomodulators (IMM), such as thiopurines (azathioprine and 6-mercaptopurine) or methotrexate, may prevent or suppress ADA formation. In this article, we present a comprehensive review of the available literature regarding the efficacy of IMM in the prevention and suppression of ADA development to anti-TNF therapy in patients with IBD.

Keywords anti-TNF, anti-drug antibodies, inflammatory bowel disease, thiopurines, methotrexate

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^aDepartment of Gastroenterology, School of Health Sciences, University Hospital of Ioannina, Faculty of Medicine, University of Ioannina, Ioannina, Greece (Fotios S. Fousekis, Konstantinos H. Katsanos, Dimitrios K. Christodoulou); ^bCenter for Inflammatory Bowel Diseases, Division of Gastroenterology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA (Konstantinos Papamichael); ^cDepartment of Department of Nursing, "Sotiria" General Hospital, Athens, Greece (Georgios Kourtis); ^dDepartment of Nursing, University of Patra, Patra, Greece (Eleni N. Albani); ^eAcademic Department of Gastroenterology, Laiko General Hospital, Medical School of National Kapodistrian University of Athens, Greece (Afroditi Orfanidou); ^fDepartment of Nursing, University of Thessaly, Lamia, Greece (Maria Saridi)

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Correspondence to: Dimitrios K. Christodoulou, MD, PhD, FEBGH, Professor of Gastroenterology, Department of Gastroenterology and Hepatology, School of Health Sciences, University Hospital of Ioannina, Faculty of Medicine, University of Ioannina, PO Box 1186, Ioannina 45110, Greece, e-mail: dchristodoulou@gmail.com

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Introduction

The use of biological agents that target tumor necrosis factor (TNF) has revolutionized the treatment of inflammatory bowel disease (IBD), offering induction and maintenance of disease remission for both Crohn's disease (CD) and ulcerative colitis (UC). Currently, there are 4 approved anti-TNF agents against IBD: infliximab, adalimumab, golimumab, and certolizumab pegol. Infliximab is a chimeric monoclonal anti-TNF antibody, while adalimumab is a humanized monoclonal antibody, and they can be used in both UC and CD. On the other hand, certolizumab pegol, a polyethylene glycol-conjugated Fab fragment of recombinant humanized monoclonal antibody, has been approved to treat only CD, while golimumab, a human anti-TNF IgG1, has been approved as a treatment for UC [1].

However, a significant proportion of IBD patients on anti-TNF treatment show a loss of response (LOR), requiring either dose intensification or switching to a different anti-TNF agent, or to an agent with a different mechanism of action. According to a meta-analysis, the estimated annual risk of LOR to anti-TNF agents is 20.9% per patient-year and the mean percentage of patients who lose response to infliximab, adalimumab and certolizumab pegol is 37.8%, 35.4% and 43.3%, respectively [2], while up to 40% of UC patients responding to golimumab will lose response

over time [3]. LOR can be mostly explained by subtherapeutic drug concentrations due to pharmacokinetic issues and the development of anti-drug antibodies (ADA), so called immunogenicity [4]. ADA may reduce the efficacy of anti-TNF agents via neutralization of the biological agent or acceleration of drug clearance [5]. The latter can also be induced by increased body weight and a high inflammatory burden, characterized by low albumin levels and elevated C-reactive protein (CRP) levels [6,7]. A recent systematic review demonstrated that ADA development is more frequent in patients receiving infliximab, and that the incidence of ADA formation varies from 0-65.3%. On the other hand, the incidence of ADA in patients receiving adalimumab, golimumab or certolizumab ranges between 0.3-38%, 0.4-2.9% and 3.3-25.3%, respectively [8].

Current data suggest that the combination of biological agents with immunomodulators (IMM), such as thiopurines and methotrexate, may prevent (Table 1) [9-18] or reduce (Table 2)

[19-23] ADA development, leading to maintenance of remission. Azathioprine and 6-mercaptopurine are the most frequently used thiopurines in IBD and they are considered suitable for maintenance of remission for both UC and CD [24,25]. Furthermore, methotrexate, a folate antagonist, may be used alone or as a combination therapy for the maintenance of remission in patients with CD [26], while it does not seem to have any role in UC [27]. The purpose of this review is to present and analyze the role of IMM in the prevention and suppression of ADA development in patients with IBD receiving anti-TNF therapy.

Literature search

We performed an in-depth review of the literature in PubMed to identify articles about the use of thiopurines in

Table 1 Major studies regarding prevention of ADA to anti-TNF therapy using combination therapy with an IMM

Anti-TNF agent	Study design	IBD type	Number of patients on monotherapy or combination therapy with an IMM	Outcomes (follow up)	Study (year) [Ref.]
IFX	Prospective	CD	IFX, n=366 IFX+MTX/THP, n=587	HR 0.39; 95% CI:0.32-0.46 for ADA on combination therapy	Kennedy, <i>et al</i> (2019) [9]
IFX	Retrospective	CD/ UC	IFX, n=139 IFX+MTX/6-MP, n=84	ADA: 20.1% ADA: 9.5%	Chi, <i>et al</i> (2018) [10]
IFX	Retrospective	CD	IFX, n=93 IFX+THP (past THP responders), n=52 IFX+THP (past THP failures), n=34 IFX+THP (de-novo combination), n=28	ADA: 46.6% (1y) ADA: 19.3% (1y) ADA: 16.1% (1y) ADA: 21.9% (1y)	Bar-Yoseph, <i>et al</i> (2017) [11]
IFX	RCT	CD	IFX, n=63 IFX+MTX, n=63	ADA: 20% (w50) ADA: 4% (w50)	Feagan, <i>et al</i> (2014) [12]
IFX	Prospective	CD	IFX, n=59 AZA+IFX, n=65	ADA: 71% (w4) ADA: 48% (w4)	Vermeire, <i>et al</i> (2007) [13]
ADM	Prospective	CD	ADM, n=344 ADM+THP, n=311	HR 0.44; 95% CI: 0.31-0.64 for ADA on combination therapy	Kennedy, <i>et al</i> (2019) [9]
ADM	Retrospective	CD/ UC	ADM, n=67 ADM+THP, n=31	ADA: 28% ADA: 26%	Holmstrom, <i>et al</i> (2018) [14]
ADM	RCT	CD	ADM, n=85 ADM+AZA, n=91	ADA: 13.2% (w26) ADA: 4% (w26)	Matsumoto, <i>et al</i> (2016) [15]
GOL	RCT	UC	GOL, n=719 GOL+THP/MTX, n=345	ADA: 3.5% (w54) ADA: 1.5% (w54)	Adedokun, <i>et al</i> (2017) [16]
CZP	RCT	CD	CZP ^a , n=94 CZP+IMM, n=55	ADA ^b : 78% ADA ^b : 19%	Sandborn, <i>et al</i> (2017) [17]
CZP	RCT	CD	CZP (for 6w), n=407 CZP+MTX/6-MP (for 6w), n=261 CZP (for 26w), n=126 CZP+MTX/6-MP (for 26w), n=87	ADA: 1% (w6) ADA: 0% (w6) ADA: 12% (w26) ADA: 2% (w26)	Schreiber, <i>et al</i> (2007) [18]

^aWithout IMM for ≥ 90 days, ^bPersistent ADA

ADA, anti-drug antibodies; RCT, randomized controlled trial; CD, Crohn's disease; UC, ulcerative colitis; IFX, infliximab; ADM, adalimumab; GOL, golimumab; CZP, certolizumab pegol; AZA, azathioprine; IMM, immunomodulators; MTX, methotrexate; 6-MP, 6-mercaptopurine; THP, thiopurines; HR, hazard ratio; w, week; y, year

Table 2 Studies regarding suppression of ADA to anti-TNF therapy using combination therapy with an IMM

Anti-TNF agent	Study design	IBD type	No. of patients (IMM)	Outcomes	Study (year) [Ref.]
IFX	Retrospective	CD	n=13, (AZA)	Decrease of ADA levels, [mean, (IQR)], [320 (200-600) to 60 (10-500) (P=0.01)] and elevation of IFX concentration [0.015 (0.01-0.02) to 0.9 (0.01-2.7) µg/mL (P=0.01)]. Clinical remission was achieved in 54% of patients	Peyrin-Biroulet, <i>et al</i> (2016) [19]
IFX	Retrospective	CD/UC	n=5, (THP/MTX)	Suppression of ADA levels, elevation of IFX trough concentrations and restoration of clinical response in all patients	Ben-Horin, <i>et al</i> (2013) [20]
ADM	Retrospective	CD/UC	n=23, (THP/MTX)	48% of patients achieved elimination of ADA	Ungar, <i>et al</i> (2017) [21]
IFX/ADM	Retrospective	CD	n=30, (AZA/MTX)	87% decrease of median ADA levels	Colman, <i>et al</i> (2021) [22]
IFX/ADM	Retrospective	CD/UC	n=17 (THP/MTX)	76% of patients achieved undetectable ADA	Strik, <i>et al</i> (2017) [23]

ADA, anti-drug antibodies; CD, Crohn's disease; UC, ulcerative colitis; IFX, infliximab; ADM, adalimumab; AZA, azathioprine; MTX, methotrexate; 6-MP, 6-Mercaptopurine; THP, thiopurines; IQR, interquartile range; IMM, immunomodulator

the prevention and suppression of ADA in IBD, using the following search string: (“thiopurines” OR “azathioprine” OR “6-mercaptopurine” OR “methotrexate”) AND (“anti-drug antibodies”) AND (“inflammatory bowel disease”) AND (“anti-TNF” OR “infliximab” OR “adalimumab” OR “certolizumab pegol” OR “golimumab”). The references of relevant papers were also checked, while only articles in English were reviewed.

Prevention of ADA to anti-TNF therapy

Several studies have suggested that using either thiopurines or methotrexate in IBD patients on anti-TNF therapy may prevent ADA formation (Table 1) [9-18]. The concomitant use of thiopurines seems to contribute to the prevention of ADA development in patients treated with infliximab. In a multicenter cohort study, the prevalence of ADA was lower in the group of patients on combination therapy (infliximab plus azathioprine) compared to patients receiving infliximab monotherapy (46% vs. 73%; P<0.001) [13]. Regarding the impact of azathioprine dose on immunogenicity, a retrospective study including patients with IBD receiving either infliximab or adalimumab combination therapy with azathioprine—group 1 (dose of azathioprine <1 mg/kg), group 2 (dose of azathioprine ≥1 and <2 mg/kg), and group 3 (dose of azathioprine ≥2 mg/kg)—found that there were no differences in trough concentrations, ADA, CRP and fecal calprotectin among the groups [28]. Along similar lines, a randomized clinical trial (RCT) demonstrated that the reduction in azathioprine dosage from 2-2.5 mg/kg/day to 1-1.25 mg/kg/day did not significantly affect infliximab trough concentrations and ADA development [29]. The same study showed that the optimal 6-thioguanine (6-TGN) level to predict unfavorable IFX pharmacokinetics was <105

pmol/8.10⁸ red blood count (RBC). Consequently, it seems that the effect of azathioprine on ADA development and infliximab trough concentrations may not be dose-dependent, at least when 6-TGN levels are ≥105 pmol/8.10⁸ RBC.

Besides thiopurines, methotrexate may also prevent the development of ADA against infliximab. A double-blind, placebo-controlled RCT demonstrated that CD patients on combination therapy compared to those receiving infliximab monotherapy had a lower risk of ADA development (4% vs. 20%, P=0.01) and higher median serum trough infliximab concentrations (6.35 mg/mL vs. 3.75 mg/mL, P=0.08) [12]. Moreover, the prospective PANTS (Personalising Anti-TNF Therapy in Crohn's Disease) study found that infliximab combination therapy with an IMM (methotrexate or thiopurines) decreased the risk of developing ADA (hazard ratio [HR] 0.39, 95% confidence interval [CI] 0.32-0.46; P<0.001) [9]. In a cross-sectional analysis of 233 pediatric and young adult patients with IBD, those receiving combination therapy of infliximab with 6-mercaptopurine or methotrexate compared to those receiving infliximab alone had a lower rate (9.5% vs. 20%, respectively) and a lower risk of detectable ADA (odds ratio [OR] 0.3, 95%CI 0.1-0.7; P<0.01). In addition, patients on combination therapy had higher infliximab concentrations than those on infliximab monotherapy (17.00±1.33 µg/mL vs. 13.18±1.26 µg/mL; P<0.001) [10].

In contrast to infliximab, there are conflicting data regarding the use of thiopurines in IBD patients on adalimumab and their efficacy in increasing adalimumab serum concentrations, prevention of ADA and improvement of clinical outcomes [30]. A multicenter, open-labeled RCT showed that there was only a trend towards a lower rate of ADA formation in patients on adalimumab combination therapy with azathioprine compared to adalimumab monotherapy at week 26 (4% vs. 13%; P=0.078), while clinical efficacy and adalimumab trough concentrations

were similar between the 2 groups [15]. A meta-analysis demonstrated that combination adalimumab therapy with azathioprine is associated with less ADA formation (OR 0.24, 95%CI 0.07-0.82; $P=0.02$), although there was no statistically significant difference between combination therapy and monotherapy regarding the induction and maintenance of remission [31]. A recent study analyzing the interaction between thiopurine metabolites, adalimumab and ADA in previously infliximab-treated IBD patients, demonstrated that combination therapy is not associated with prevention of ADA, and that the levels of thiopurine metabolites are not associated with ADA development [14]. However, the prospective PANTS study found that adalimumab combination therapy with IMM (methotrexate or thiopurines) reduced the risk of developing ADA (HR 0.44, 95%CI 0.31-0.64; $P<0.001$) [9]. In one RCT, IBD patients in corticosteroid-free clinical remission for at least 6 months on adalimumab and thiopurines were randomized into 2 subgroups: withdrawal or continuation of thiopurines. After 52 weeks, there was no statistically significant difference in ADA positivity between the 2 groups (20% vs. 10%, respectively; $P=0.437$) [32].

In contrast to infliximab and adalimumab, there are limited data regarding the impact of IMM on the development of ADA against certolizumab pegol and golimumab. An analysis of results from the phase 2/3 PURSUIT RCTs demonstrated only a numerically lower incidence of ADA against golimumab in patients receiving golimumab and IMM compared to those on golimumab monotherapy (1.5% vs. 3.5%) [16]. A population PK model, using data from the PURSUIT (Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment) RCTs, showed that anti-golimumab antibodies increased drug clearance by 24.3% and that the impact of ADAs on golimumab concentration was more notable at higher ADA levels ($\geq 1:100$) [34]. One RCT demonstrated that the incidence of ADA was lower in patients receiving certolizumab and IMM compared to certolizumab monotherapy during both induction (0% vs. 1%) and maintenance therapy (2% vs. 12%) [18].

Prevention of ADA in patients with prior anti-TNF failure due to immunogenicity

It is worth mentioning that IBD patients with ADA to a prior anti-TNF agent seem to be more likely to develop ADA to a subsequent anti-TNF [35-37]. A recent retrospective case-control study including 5828 patients with IBD showed that patients who developed ADA to infliximab and switched from infliximab to adalimumab had a higher risk of developing ADA against adalimumab (OR 2.82, 95%CI 2.35-3.38; $P<0.001$). The same applied for patients who developed ADA to adalimumab and had to switch from adalimumab to infliximab: they had a higher risk of developing ADA against infliximab (HR 3.43, 95%CI 2.81-4.2; $P<0.001$) [35]. One RCT showed that the addition of azathioprine to the switch of anti-TNF agent in patients with IBD in clinical relapse with undetectable anti-TNF trough concentrations and ADA is associated with lower rates of clinical failure compared to anti-TNF monotherapy [36]. In

addition, combination therapy decreased the pharmacokinetic failure significantly (undetectable trough concentrations of infliximab or adalimumab and high ADA levels) compared to anti-TNF monotherapy (adalimumab and azathioprine: HR 0.12, 95%CI 0.03-0.40; $P<0.001$; infliximab and azathioprine: HR 0.16, 95%CI 0.06-0.37; $P<0.001$) [36]. Thus, it is recommended to add an IMM to a subsequent anti-TNF therapy when considering switching within drug class in case of LOR to a first anti-TNF agent due to immunogenicity [37].

Suppression of ADA to anti-TNF therapy

As mentioned above, LOR to anti-TNF therapy due to immunogenicity is a frequent issue of IBD management and switching to another agent appears to be a common strategy. However, treatment optimization (dose escalation and/or addition of an IMM) can also be an option in case of low-titer ADA, as current data suggest that these can be suppressed or even eliminated, leading to elevation of serum anti-TNF trough concentrations, restoration of clinical response and salvage of the current anti-TNF biological agent [38-40]. Preliminary data suggest that the addition of an IMM may contribute to ADA suppression and recapture of anti-TNF response (Table 2) [19-23]. In 2013, a retrospective analysis of IBD patients documented for the first time that the administration of IMM in 5 IBD patients with LOR and ADA against infliximab was associated with suppression of ADA levels, elevation of infliximab trough concentrations and restoration of clinical response in all patients. Three of 5 patients received thiopurines and 2 patients received methotrexate [20]. Similarly, another retrospective study demonstrated the suppression of ADA in IBD patients with LOR to infliximab or adalimumab after the addition of IMM [23]. Six of 10 patients on anti-TNF monotherapy receiving thiopurine and all (7/7) patients receiving methotrexate achieved clinical remission, undetectable ADA and elevation of drug concentrations [23]. A recent retrospective study, which included pediatric IBD patients with ADA against adalimumab or infliximab, reported that addition of an IMM is associated with suppression of ADA, an increased likelihood of steroid-free clinical remission and anti-TNF durability [22]. In this study, patients on combination therapy exhibited an 87% decrease in ADA levels and a median increase of 7.2 $\mu\text{g/mL}$ of anti-TNF drug concentrations [22]. Furthermore, in another multicenter retrospective study, 14 IBD patients on adalimumab monotherapy, LOR and ADA development received thiopurine as salvage therapy. Restoration of clinical response and elimination of ADA were achieved in half of the patients. The median time to sero-reversal was 5 months [21].

Thus, the addition of IMM in IBD patients with ADA to infliximab or adalimumab and undetectable or sub-therapeutic drug concentrations appears to be an effective strategy to overcome immunogenicity before switching to another agent. However, a limitation of the aforementioned studies is the very small sample size and the retrospective design. Moreover, data regarding the role of IMM for suppression or elimination of ADA in IBD patients receiving golimumab or certolizumab pegol are missing.

Biosimilars

Current data suggest that infliximab and adalimumab biosimilars share immunodominant epitopes and exhibit similar immunogenicity with the originators [41-43]. Switching from infliximab originator to biosimilar, both single and multiple switches, does not seem to raise any efficacy and safety issues or immunogenicity concerns [44,45]. However, due to cross-immunogenicity, switching from an originator to a biosimilar or *vice versa* when the one or the other fails due to ADA formation should not be recommended [46,47].

Mechanisms of IMM to prevent or suppress immunogenicity of anti-TNF therapy

The mechanisms of action of IMM to prevent or suppress immunogenicity of anti-TNF agents have not been fully clarified. It has been suggested that methotrexate and thiopurines may reduce T-cell proliferation and cause attenuation of memory B cell and CD-4 T cells, reducing anti-TNF immunogenicity and eliminating ADA formation [48,49]. However, further studies are warranted.

Discussion

Despite extensive research into the treatment of IBD, treatment options remain relatively limited, at least for some IBD phenotypes, such as perianal fistulizing CD and acute severe UC, where infliximab is the cornerstone treatment. Thus, also taking into account the chronicity of the disease, it may be prudent to try to maintain the initially used biologic before switching to an alternative therapy.

In recent years, measurement of drug concentrations and ADA levels, so called therapeutic drug monitoring (TDM), has contributed to efficiently optimizing anti-TNF therapy. Several medical societies and TDM expert groups recommend reactive TDM to better explain the cause of lack or loss of response, while some also suggest proactive TDM with dose adaptation to a target drug concentration in patients with quiescent disease at post-induction, and at least once during maintenance therapy, to improve the efficacy of anti-TNFs [50]. Regarding reactive TDM, Yanai *et al* showed that patients with LOR and no or low-titer ADA compared to those with high-titer ADA against adalimumab (>4 µg/mL) or infliximab (>9 µg/mL) had a longer duration of response following dose intensification [51]. Regarding proactive TDM, a large retrospective study found that proactive TDM compared to empiric dose optimization and/or reactive TDM of infliximab was associated with better therapeutic outcomes, including a lower risk of ADA development [52]. TDM, with emphasis on measuring ADA, should also be performed after reinitiation of infliximab following a drug holiday, as ADA developed early (1-3 weeks) after re-exposure to infliximab has been associated with (severe) infusion reactions [53,54].

The concomitant use of IMM seems to be an effective strategy for the prevention and suppression of ADA against anti-TNF therapy and can lead to higher drug concentrations and better therapeutic outcomes. The mechanisms underlying the favorable impact of IMM on clinical outcomes are still not well understood. Besides their positive impact on anti-TNF drug pharmacokinetics, it may be also an “add-on” effect, although in a *post hoc* analysis of the SONIC (Study of Biologic and Immunomodulator Naïve Patients in Crohn’s Disease) RCT, stratification of infliximab concentrations displayed comparable outcomes within each concentration quartile, irrespective of concomitant azathioprine [55].

However, there may be safety concerns regarding combination therapy, including an increased risk of infections and

Table 3 Possible risks of anti-TNF combination therapy with an IMM in IBD

Outcome	Study design	Drug type	Risk of anti-TNF combination therapy with an IMM ^a	Study (year) [Ref.]
Serious infection	Retrospective Meta-analysis (12 RCTs)	IFX/ADM	HR 1.23; 95% CI:1.05-1.45	Kirchgesner, <i>et al</i> (2018) [56] Chen, <i>et al</i> (2021) [57]
		IFX/ADM	RR 1.20; 95% CI:0.83-1.73	
Opportunistic infection	Retrospective Meta-analysis (12 RCTs)	IFX/ADM	HR 1.96; 95% CI:1.32-2.91	Kirchgesner, <i>et al</i> (2018) [56] Chen, <i>et al</i> (2021) [57]
		IFX/ADM	RR 1.13; 95% CI:0.94-1.36	
Tuberculosis	Systematic review (40 RCTs) ^b	IFX/ADM/ CZP	OR 13.3; 95% CI:3.7-100	Lorenzetti, <i>et al</i> (2014) [58]
COVID-19	Retrospective	IFX/ADM/ CZP/GOL	aOR 4.01; 95% CI:1.65-9.78	Ungaro, <i>et al</i> (2021) [59]
Lymphoma	Retrospective	IFX/ADM	aHR 6.11; 95% CI:3.46-10.8	Lemaitre, <i>et al</i> (2017) [60]
NMSC	Meta-analysis (6 RCTs) ^c	ADM	RR 2.82; 95% CI:1.07-7.44	Osterman, <i>et al</i> (2013) [61]
Malignancies other than NMSC	Meta-analysis (6 RCTs) ^c	ADM	RR 3.46; 95% CI:1.08-11.06	Osterman, <i>et al</i> (2013) [61]

^aThiopurines/methotrexate; ^bIncluding also rheumatologic diseases; ^cCrohn’s disease

IBD, inflammatory bowel disease; Ahr, adjusted Hazard ratio; NMSC, non-melanoma skin cancer; aOR, adjusted odds ratio; CI, confidence interval; RR, relative risk; RCT, randomized clinical trial; TNF, tumor necrosis factor; IMM, immunomodulator; IFX, infliximab; ADM, adalimumab; CZP, certolizumab pegol; GOL, golimumab

malignancies [56-61] (Table 3). Consequently, an individualized risk-benefit assessment based on disease severity and extent, history of prior anti-TNF failure, the pharmacokinetic profile, and possibly the patient's genetic background, should be considered for determining the optimal therapy. Regarding the latter, a genome-wide association study of the PANTS study showed that the HLA-DQA1*05 allele increased the risk of development of ADA against infliximab and adalimumab, and that this was attenuated by the use of a concomitant IMM [62].

Concluding remarks

Current data suggest that IMM can prevent immunogenicity against anti-TNF therapy, leading to improved drug pharmacokinetics and therapeutic outcomes. In addition, preliminary data suggest that IMM can reduce or eliminate ADA against infliximab or adalimumab in patients with IBD and immunogenicity issues. However, given the safety concerns of combination therapy, an individualized risk-benefit assessment is essential for defining the most suitable treatment for each patient.

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