Combination Immunosuppression in IBD

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Whether to use biologic treatment for inflammatory bowel disease as monotherapy or in combination with immunosuppressives has been a matter of debate in the last 2 decades. Combination therapy was not superior in any of the registration trials for Crohn's disease and ulcerative colitis for TNF antagonists, vedolizumab, or ustekinumab. It needs to be mentioned, though, that none of these trials were powered to detect such differences, and that many patients entered the trial after having failed conventional immunosuppressives.

Postmarketing studies revealed that patients on background immunosuppression have a lower risk of immunogenicity (often resulting in infusion/injection reactions) than patients on monotherapy. In the SONIC and UC-SUCCESS trials, superiority of the combination azathioprine-infliximab was demonstrated in Crohn's disease and ulcerative colitis, respectively. This trial design has not been used with any other biologic for IBD, so far. Meanwhile, it has also become clear that combination treatment with TNF antagonists is associated with increased toxicity, mainly infections, but also malignancy such as lymphoproliferative disease. This toxicity could perhaps be reduced by using lower doses of immunosuppressives, a strategy that has been shown to be equally potent in reducing immunogenicity. Additionally, combination treatment could be used for a limited period of time (12 months or even shorter) since most immunogenicity develops in the beginning of the biologic treatment. Patients who develop anti-drug-antibodies later on can often be rescued by reintroduction of thiopurines or methotrexate.

In summary, combination treatment is certainly beneficial with infliximab, at least in the first 12 months of treatment. With other TNF antagonists, vedolizumab, and ustekinumab, the available data do not offer clear guidance. In patients without increased risk of toxicity, and certainly in those with limited treatment options, it may be wise to offer combination treatment with all biologics for the time being and at least during the initiation phase.

Key Words: inflammatory bowel disease, immunosuppression, anti-tumor necrosis factor agents, biologic agents, immunomodulators, combination therapy

INTRODUCTION AND HISTORICAL BACKGROUND

Initial studies with the anti-TNF agent infliximab for Crohn's disease (CD) and ulcerative colitis (UC) did not demonstrate increased efficacy when this therapeutic antibody was combined with immunosuppressive agents, however in the Phase 3 study ACCENT-1 for CD, a trend towards greater efficacy of combination treatment was observed at week 30 ($P = 0.062$).[1,2]

It also became rapidly clear that after discontinuation and reinitiation of infliximab (IFX) treatment, patients on background immunosuppressive treatment experienced fewer infusion reactions and loss of response, a phenomenon that was explained by lower anti-IFX antibody formation.[3] It took until 2008, when the results of the SONIC trial were published, before it was demonstrated that combination treatment of IFX with the immunosuppressive azathioprine (AZA) led to superior clinical and endoscopic results compared to either monotherapy in CD.[4] Combination treatment was characterized by higher IFX serum concentrations and a lower immunogenicity risk. This finding was replicated in the UC-SUCCESS trial.[5] Subsequently, combination treatment has been recommended for all patients in whom IFX is started.

The observations for other biologics, which are more humanized than the chimera IFX, are less convincing. In the Phase 3 trials with adalimumab (ADL), golimumab (GOLI), certolizumab pegol (CZP), vedolizumab (VEDO), and ustekinumab (UST), no evidence was found for an additional benefit from combined immunosuppression, although none of these trials were powered to answer this question specifically.[6–14] SONIC-like programs were never performed for biologics other IFX.

For most biologics some retrospective data or cohort studies suggest benefit of combination immunosuppression,

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but presently the results do not appear strong enough to recommend combined treatment for all patients receiving nonIFX biologics.

MECHANISMS OF ACTION OF COMBINATION THERAPY

Several mechanisms have been proposed to explain the increased effectiveness of combined immunosuppressives and anti-TNF therapy (mainly IFX) compared with anti-TNF therapy alone. The best documented feature of combination therapy in this regard is the reduction in risk of immunogenicity, (ie, anti-drug antibody formation) with both the thiopurines and methotrexate (MTX). Presence of anti-drug antibodies against IFX has been associated with a 4-fold increase in drug clearance, most likely due to enhanced clearance of drug/anti-drug antibody immune complexes.[15] Rapid drug clearance results in low or undetectable circulating drug concentrations, which are associated with lower success rates for induction of remission and with loss of response.

The extent of reduction in antidrug antibodies appears similar for the thiopurines and MTX.[4,5,16,17] The rate of antidrug antibody formation is lower with ADL than IFX and so the effect of suppression of anti-drug antibodies with immunosuppressives may be less pronounced with ADL combination therapy.[18] Combination immunosuppressive therapy leads, however, to less immunogenicity and higher ADLserum concentrations.[19,20] Of note, anti-drug antibody formation has been observed as early as 18 days after commencing IFX, leading to a greater chance of nonresponse, and so it seems advisable to commence immunosuppression as early as possible in combination with anti-TNF-alpha therapy.[15]

In addition to preventing immunogenicity, introduction of an immunosuppressant also has a high chance of reversing anti-drug antibody formation, with most cases reversing within 12 months using either a thiopurine or MTX.[21,22] One study also has shown a median increase in IFX trough concentrations of 2.84 mg/L with addition of a thiopurine or MTX to IFX.[22]

It has been postulated that the addition of immunosuppression to anti-TNF-alpha therapy may have benefits beyond altered immunogenicity or pharmacokinetics, resulting in treatment synergy. There are limited data to support this. However, in vitro studies have shown that anti-TNF drugs induce regulatory macrophages that assist in wound and mucosal healing and that AZA, when combined with IFX, further increases the number and wound-healing properties of these macrophages, which then also display stronger immunosuppressive properties.[23–26] This would support the possibility of synergy at the pharmacological level.

EFFICACY OF COMBINED IMMUNOSUPPRESSION

The efficacy of IFX combined with immunosuppressive agents has been studied extensively. The SONIC trial showed that combination therapy resulted in higher rates of corticosteroid-free clinical remission and mucosal healing (absence of ulcers) after 26 weeks of treatment in CD patients (56.8% vs 44.4%; $P = 0.02$ and 43.9% vs 30.1%; $P = 0.06$, respectively).[4] A recent posthoc analysis of this trial showed significantly higher rates of anti-drug antibodies in the monotherapy patients (36% vs 8%). The benefit of combination therapy seemed mainly driven by the effect of AZA on the pharmacokinetics and immunogenicity of IFX in those on combination therapy.[27]

Likewise, the UC-SUCCESS trial showed increased corticosteroid-free remission in UC patients on combination therapy after 16 weeks of treatment (39.7% vs 22.1%, $P = 0.017$), although in this trial the mucosal healing rates (assessed by local investigators) were not higher with combination than with monotherapy (62.8% vs 54.6%, $P = 0.295$ in combination vs monotherapy).[5] The superiority of IFX combination therapy in UC patients also was shown in a systematic review and meta-analysis.[27]

IFX combined with parenteral MTX was studied in the COMMIT trial for CD. After 50 weeks of treatment starting with an induction regimen of prednisone, no improved clinical efficacy was observed in the combination group compared to monotherapy, although patients receiving MTX had higher serum concentrations of IFX on average.[16] The corticosteroid induction treatment for up to 14 weeks may have affected the efficacy outcomes blurring the potential additional benefit of MTX. Also, unlike the SONIC trial, this trial had no endoscopic endpoint.

As stated above, the superiority of combination immunosuppression with ADL has been demonstrated less convincingly. The question has never been investigated in a prospective trial. The large Phase 3 trials with ADL for CD, CHARM, and ulcerative colitis, ULTRA, could not demonstrate an additional benefit of combined immunosuppression.[14,28] A recent systematic review and meta-analysis included 24 CD studies and showed no difference for induction of clinical remission (OR 0.86; 95% CI: 0.70–1.06; $P = 0.19$) and clinical response (OR 1.01; 95% CI: 0.62–1.65; $P = 0.96$) and also no differences for maintenance of clinical remission (OR 0.97; 95% CI: 0.79–1.14; $P = 0.75$) or response (OR 0.91; 95% CI: 0.54–1.54; $P = 0.74$).[19]

A few isolated studies, nonetheless, reported clinical benefit of combination treatment with immunosuppressives. Matsumoto et al showed no difference in clinical efficacy in CD patients on combination therapy versus monotherapy in a 52-week prospective trial (remission rates 68% vs 72%). However, endoscopic improvement (the secondary outcome defined as a decrease of SES-CD of at least 8 points from the baseline, or SES-CD ≤ 4) was more frequently attained in patients after 26 weeks of combination treatment [84.2%, n = 5 vs 63.8%, n = 58 ($P = 0.019$)].[20] Nevertheless, this endoscopic difference was not sustained after 52 weeks of treatment. Kariyawasam and colleagues conducted a retrospective study in 91 CD patients and found higher rates of induction

and maintenance of clinical response on combination treatment (83% vs 61%; $P = 0.02$ and 81% vs 60%; $P < 0.0001$, respectively), but they did not assess endoscopic outcomes.[29] Reenaers showed lower risk of ADL failure in the first semester of combination treatment (5% vs 10%; $P = 0.04$; OR 0.48) and fewer flares beyond 6 months of combination treatment in a retrospective dataset (14% vs 36%; $P = 0.02$; OR 0.31).[30] Finally, Cosnes showed longer anti-TNF survival in patients on combination treatment with similar effect for ADL and IFX [adjusted HR 2.17 (95% CI: 1.71–2.70)].[31]

In conclusion, data regarding ADL combination therapy are conflicting and most studies that showed clinical benefit used a retrospective design. Therefore, adequate prospective studies that are properly powered are needed to clarify this issue.

The effect of combination therapy with the anti-TNF agents GOLI and CZP is unknown. The PURSUIT trials (GOLI in UC) and PRECISE trials (CZP in CD) did not report data on clinical efficacy of combination therapy.[6,7,11,13] To our knowledge no other studies on combination therapy with these agents have been conducted.

The efficacy of VEDO combination therapy also remains uncertain. The Gemini I and II trials showed no clinical benefit of VEDO combined with immunosuppressive agents in CD and UC, but the trials were not designed to answer this question.[9,10] Following these Phase 3 trials, several postmarketing cohort studies equally did not show beneficial outcomes of VEDO combination therapy in either CD or UC when compared to monotherapy.[32–34] One multicenter cohort study showed different results indicating superior clinical efficacy after 54 weeks of VEDO treatment with an immunosuppressant in CD, with an odds ratio of 8.33 (95% CI 2.15–32.26).[35] This was a retrospective study, however, and only patients that responded to 14 weeks of induction treatment were included in this analysis. Therefore, it is difficult to draw firm conclusions based on this study.

Currently, there is no evidence supporting superiority of UST combination therapy. The UNITI trials did not show better outcomes for patients on background immunosuppressive therapy treated with UST, but these trials were evidently not powered to address this question.[36] Battat et al showed equivalent corticosteroid-free and endoscopic remission for UST monotherapy and combination therapy after 26 weeks of treatment in 62 CD patients.[37] However, the study was not designed, and was underpowered, to assess this outcome.

Long-term outcomes of combination therapy are relatively unknown. It is not clear what the effect of combination treatment is on outcomes such as surgery and disease behavior over many years. However, it is to be expected that adequate control of inflammation leads to better long-term outcomes. This is reflected by the fact that the number of hospitalizations and surgeries have diminished since the introduction of biologic agents.[38]

EFFECT OF IMMUNOSUPPRESSION ON WITHDRAWAL OF BIOLOGICS

The timing of anti-TNF treatment withdrawal in IBD patients in remission has been a matter of discussion. According to the STORI trial, approximately 50% of patients with CD previously treated with >1 year of IFX in combination with an antimetabolite experienced a relapse within 18 months after discontinuation of IFX (with continued immunosuppression).[39] Risk factors for relapse included male sex, the absence of previous surgical resection, and elevated inflammatory biomarkers. Importantly, relapsing patients on continued immunosuppressives were successfully re-treated with IFX after a median drug-holiday of 6.6 months. None of the patients experienced a significant infusion reaction, as followed-up to the third re-treatment infusion. Although the follow-up is limited and preinfusion corticosteroid prophylaxis was applied, median IFX trough levels were not significantly different between the baseline and third retreatment infusions. Additionally, no increase in the formation of anti-drug antibodies was detected in these patients with sustained antimetabolite treatment.

The IMID (immunosuppression withdrawal in Crohn's disease) study evaluated whether continued treatment with immunosuppressives beyond 6 months of combination treatment offered benefit over scheduled IFX monotherapy in patients with CD in stable remission.[40] There was no significant difference in the proportion of patients requiring dose intensification of IFX or stopping IFX therapy among patients on IFX monotherapy or continued combined immunosuppression. However, discontinued immunosuppression was associated with lowering of median IFX concentrations, which correlated with elevated serum CRP levels and clinical scores.

Additionally, an open-label randomized trial recently showed that in IBD patients with durable remission on combination therapy, dose reduction of AZA to 1–1.25 mg/kg/day was as effective as treatment at full dose in terms of clinical relapse after 1 year.[41] Median IFX trough levels dropped significantly in the IFX monotherapy group compared to the combination treatment or reduced AZA dose groups.

EFFECT OF COMBINED IMMUNOSUPPRESSION ON IMMUNOGENICITY AND SERUM CONCENTRATIONS OF BIOLOGIC DRUG

Many studies have shown a significant reduction in IFX anti-drug antibody formation with combination therapy versus IFX monotherapy in patients on maintenance treatment.[1,4,5,16,42,43] The degree of reduction in anti-drug-antibodies appears similar for the thiopurines and MTX, although no head-to-head studies have been performed specifically addressing this question.[4,5,16,17] Reduction of immunogenicity results in higher IFX serum concentrations. On the other hand, the reduction in immunogenicity also could be explained by a boost in IFX serum concentrations caused by immunosuppressives.

As an example, in the SONIC study, week 30 median trough IFX concentrations were 1.6 mg/L for IFX monotherapy vs. 3.5 mg/L for combination with AZA, and patients with higher trough concentrations had a higher chance of remission.[4] As mentioned above, a recent prospective trial conducted by Roblin et al. showed that lower doses of AZA were equally effective in maintaining adequate IFX concentrations and preventing antibody formation as full AZA doses.[41]

The rate of antidrug antibody formation is lower in patients treated with ADL when compared to IFX.[12,44–46] Although ADL combination immunosuppressant therapy has generally not been shown to be more effective, it leads to less immunogenicity and higher ADL trough concentrations.[19,20,47] A systematic review showed that the presence of anti-drug-antibodies was associated with a significant reduction in concentrations of IFX and ADL (−7.07, 95%CI -5.25 -8.9).[47] It is unclear why ADL combination therapy is not as effective as IFX combination therapy. Other factors such as tissue concentrations may be of relevance here. Since ADL appears to be less immunogenic than IFX, reduction of antibody formation to ADL could be less important.

A posthoc analysis of the PURSUIT trials showed a small increase in GOLI serum concentrations in patients receiving combination treatment with 50 mg GOLI every 4 weeks but not in patients receiving 100 mg every 4 weeks, but this did not influence clinical treatment efficacy.[48] The Precise I and II trials showed a small difference in the development of antibodies against CZP in mono versus combination therapy.[11,13] The influence of immunogenicity on treatment efficacy and drug serum concentrations was not reported, but it is to be expected that lower antibody formation results in higher CZP serum concentrations. Concomitant immunosuppressive treatment also resulted in lower immunogenicity to VEDO in the GEMINI I and II trials.[9,10] The immunogenicity of UST appears to be very low.[36,37] The effect of combination therapy on the immunogenicity of UST has not been studied and remains unknown.

SAFETY OF COMBINATION THERAPY

There are 2 areas of particular interest when discussing the safety of combination treatment: the risk of infections and malignancy. Safety data for combination treatment is derived from pooled posthoc analysis of registration trials, from dedicated trials on combination treatment, and from registries with long-term outcomes.

Data on the safety of combination treatment with biologic drugs derived from individual registration trials is limited by the relatively low number of events and short-term follow-up. However, a pooled analysis of sponsor-initiated trials on IFX in IBD, (mainly based on results from the ACCENT I, ACCENT II, SONIC, and ACT I and II studies) resulted in 1713 IFX-treated patients (and 406 placebo-treated patients) with or without concomitant immunosuppressives.[49] There was no increased incidence of infections, serious infections, or malignancy with IFX monotherapy when compared to placebo. Immunosuppression in patients with UC was associated with a higher incidence of infections [120.07 (95% CI 110.66, 130.08)/100 patient-years vs 92.47 (84.54, 100.94)/100 patient-years]. The most common serious infections in IFX-treated patients were pneumonia, cellulitis, abdominal abscess, and perirectal abscess. Additionally, among placebo-treated patients with CD, those on immunosuppressives had a higher incidence of malignancy compared to no immunosuppressive treatment [1.84 (0.22, 6.66)/100 patient-years vs 0.00 (0.00, 0.00)/100 patient-years].[49]

Clinical registries play an important role in evaluating medication safety. They include larger numbers of patients with a long follow-up period compared to randomized trials and represent real-life practice. The Crohn's Therapy, Resource, Evaluation, and Assessment Tool (TREAT) Registry was a US-based prospective registry that was designed to examine the safety of CD medications, including IFX. The registry included 6273 patients with CD who were followed up for a median duration exceeding 6 years. In an exposure-based analysis, the use of immunosuppressives alone (OR 4.19; 95% CI 0.58– 30.37; $P = 0.16$) or in combination with IFX (OR 3.33; 95% CI 0.46–24.06; $P = 0.23$) was associated with a numerically greater risk of malignancy than treatment with IFX alone (OR 1.96; 95% CI 0.23–17.02; $P = 0.54$), however, this was not statistically significant.[50]

In comparison, ENCORE was a European 5-year prospective safety registry, that included 2960 IFX-naive CD patients treated with IFX or conventional therapy.[51] The most common serious infections were abscess, pneumonia, peritonitis, and sepsis, but incidence rates were not different in the IFX and AZA/6-MP combination treatment group compared with the infliximab monotherapy group [25.4/1000 patient-years (95% CI 20.4, 31.4) vs. 39.1/1000 patient-years (20.2, 68.3)]. IFX was associated with an increased rate of benign haematological conditions. However, 45/46 of these incidents were reported in patients on combination therapy. Lymphoproliferative disorders and malignancy were reported in 49/1541 IFX-treated patients. The rates per 1000 patient-years exposure in patients with and without AZA/6-MP combination were 7.0 (95% CI 5.1, 9.3) and 14.5 (6.6, 27.5), respectively.

In a pooled analysis of 1594 patients with CD who participated in clinical trials of ADL (CLASSIC I and II, CHARM, GAIN, EXTEND, and ADHERE) giving a total of 3050 patient-years of exposure, 44% were receiving concomitant immunosuppressives (563 with thiopurines and 131 with MTX). There were 44 malignancies reported in 34 patients (2.1%), 12 events on ADL monotherapy and 32 events on combination treatment. Compared with the general population, patients receiving ADL monotherapy did not have an increased incidence of nonmelanoma skin cancer (NMSC) or other cancers. In contrast, those receiving combination therapy had a greater than expected incidence of malignancies other than

TABLE 1: Benefits and Harms of Combination Treatment in IBD and Recommendations for Practice

we	Benefits	Harms	Recommendations
IFX	-Lower immunogenicity -Higher serum concentrations -Increased efficacy -Reverse antibody formation -No increased infection risk	-Small increase in malignancy risk with thiopurines	-At least 1 year of treatment -Lower IM doses may suffice
ADL	-Lower immunogenicity -Higher serum concentrations -Increased efficacy questionable -Reverse antibody formation -No increased infection risk	-Small increase in malignancy risk with thiopurines	-Questionable
GOLI	-Slightly higher serum concentrations	-Unknown	-Questionable
CZP	-Slightly lower immunogenicity	-Unknown	-Questionable
VEDO	-Unknown	-Unknown	-Questionable
UST	-Unknown	-Unknown	-Questionable

IFX = infliximab; ADL = adalimumab; GOLI = golimumab; CZP = certolizumab pegol; VEDO = vedolizumab; UST = ustekinumab; IM = immunosuppresive

NMSC (standardized incidence ratio, 3.04; 95% CI 1.66–5.10) and of NMSC (standardized incidence ratio, 4.59; 95% CI 2.51–7.70). Compared with patients receiving ADL monotherapy, patients receiving combination therapy had an increased risk of malignancy for types other than NMSC (relative risk, 2.82; 95% CI 1.07–7.44) and also for NMSC (relative risk, 3.46; 95% CI 1.08–11.06).[52]

The PYRAMID registry analysed long-term safety of ADL in patients with CD, which also included subgroup analysis on serious infections and malignancy in patients with ADL monotherapy compared to combination treatment.[53] Of 5061 patients enrolled, 2444 completed the 6-year follow-up, which resulted in a cumulative ADL exposure of 16,680.4 patient-years. There were 24.2% of patients who received concomitant immunosuppressives and an additional 11.6% of patients who received both corticosteroids and immunosuppressives at baseline. There was a significant difference in the incidence of treatment-emergent malignancies between the ADL monotherapy and ADL and thiopurine combination therapy groups (1.9 vs. 3.1%, $P = 0.014$). Nine of the 10 patients diagnosed with lymphoma received concomitant immunosuppressive treatment. Additionally, there was a significant difference in the incidence of treatment-emergent serious infections when comparing ADL monotherapy and combination therapy groups (9.6 vs. 12.7%, $P = 0.007$).

Data are limited with regard to the safety of combination treatment of immunosuppressives with VEDO and UST. In the GEMINI 1 and II studies, 19 (17%) and 16 (17%) patients treated with VEDO received concomitant immunosuppressive or glucocorticoids and immunosuppressives at baseline, respectively.[9,10] A pooled analysis of 6 VEDO trials including 2830 patients with 4811 patient-years of VEDO exposure indicated that baseline immunosuppressive use was not associated with serious infections in either CD or UC.[54] In the maintenance trial of UST, 35%, 39%, and 33% of patients in the placebo, 90 mg UST every 12 weeks, and 90 mg UST every 8 weeks groups received stable doses of concomitant immunosuppressives, respectively, including overall 1281 patients.[36] During 1 year of treatment, 3 opportunistic infections occurred, including 1 case of Listeria meningitis (under UST and prednisolone treatment) and 2 cases of esophageal candidiasis (1 with UST treatment and 1 with UST, MTX and prednisolone combination therapy). There were 8 NMSC events occurring in 5 patients, 2 of whom were receiving placebo and 3 receiving UST maintanence treatment. Of the 5 patients with NMSC 3 were currently using or had previously used immunosuppressants.

The SECURE registry was established to evaluate safety outcomes in patients with CD treated with CZP . However, no results are yet available from the interim analysis that compares CZP monotherapy with combination treatment.[55]

A systematic review and meta-analysis including 11,702 persons with immune-mediated diseases (RA, IBD, and psoriasis) and a prior diagnosis of cancer found that rates of cancer recurrence were similar among individuals who received no immunosuppression (37.5 per 1000 person-years), anti-TNF therapy (33.8 per 1000 person-years), immunosuppressive therapy (33.8 per 1000 person-years), or combination treatment (54.5 per 1000 person-years; $P > 0.1$ for all), although recurrence was numerically higher in the latter group.[56] A subgroup analysis of new and recurrent cancers separately, type of immunosuppressive therapy, or immune-mediated disease showed similar results, with no increase in risk. However, prolonged treatment with thiopurines appears to be associated with a small increase in risk of lymphoma.[57] Additionally, the ongoing I-CARE project aims to evaluate prospectively the presence and

the extent of safety concerns (cancers, especially lymphoma, and serious infection risks) for anti-TNF monotherapy or combination treatment among IBD patients (NCT02377258).

In conclusion, risk of serious infections has been shown to be increased with combination immunosuppressive treatment in comparison to monotherapy.[49,58] The rate of malignancy with thiopurine therapy has been reported to be 2- to 5-fold higher for both lymphoproliferative disorders and NMSC and has also been associated with increased risk of overall cancer compared with IBD patients not treated with thiopurines.[59–61] There is no current evidence to clearly indicate increased risk of malignancy with anti-TNF monotherapy or with combination MTX.[62] The increased risk of cancer with thiopurine and anti-TNF combination therapy is a safety risk in IBD. Based on current evidence, the relative contribution of thiopurines to risk may be more important than that of anti-TNF drugs.[63] Combining immunosuppressives with VEDO or UST seems to be safe, although prospective data specifically addressing this topic are not currently available.

RECOMMENDATIONS FOR CLINICAL PRACTICE

Combination treatment is pivotal for successful monoclonal antibody treatment in IBD. Benefits and harms of combination treatment and recommendations for clinical practice are summarized in table 1. In patients starting on IFX, it should currently be recommended that the IFX be combined with thiopurines (and if not tolerated, with MTX) for at least 1 year. In combination treatment, it is probable that lower doses of immunosuppressives suffice compared to monotherapy doses of immunosuppressives. It remains to be confirmed if immunosuppressives can be completely abandoned in the presence of higher serum concentrations of monoclonal drugs. Safety and (potential) toxicity, mainly associated with thiopurines in combination with anti-TNF, has to be balanced against the clinical benefit with combination treatment. For instance, the small risk of lymphoma associated with prolonged thiopurine treatment could be considered when deciding to continue combination treatment beyond 1 year.

Immunosuppressives also play a role in the management of immunogenicity. Multiple studies have demonstrated that adding or switching immunosuppressives when anti-drug antibodies appear is often a successful intervention, with suppression of antidrug antibodies and increase of monoclonal drug concentrations, with recapture of clinical benefit.

Finally, immunosuppressives appear to have a beneficial effect when patients stop anti-TNF treatment. Patients who continue immunosuppressives have a significantly lower risk of relapse. It remains to be seen if the initiation of an immunosuppressive when the biologic drug is discontinued can maintain remission.

Combination treatment with VEDO and UST warrants further exploration. Although the immunogenicity of these agents is lower than that of IFX, initial combination with an immunosuppressive for a number of months may be beneficial.

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