



Introducing Patterns of Variability for Overcoming Compensatory Adaptation of the Immune System to Immunomodulatory Agents: A Novel Method for Improving Clinical Response to Anti-TNF Therapies

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Primary lack of response and secondary loss of response (LOR) are major obstacles to the use of anti-tumor necrosis factor (TNF)-based therapies in patients with rheumatoid arthritis or inflammatory bowel disease. Here, we review the mechanisms and methods for predicting LOR and the currently used methods for overcoming the ineffectiveness of anti-TNFs. The complex functions of TNF and anti-TNF antibodies, which can promote both pro- or anti-inflammatory actions, and the factors that affect the induction of immune tolerance to their effects are presented. The lack of rules and the continuous dynamics of the immune processes partly underlie the unpredictability of the response to anti-TNFs. Variability is inherent to biological systems, including immune processes, and intra/inter-patient variability has been described in the response to drugs. This variability is viewed as a compensatory adaptation mechanism of the immune system in response to drugs and may contribute to treatment LOR. Dose reductions and drug holidays have been tested in patients treated with anti-TNFs. Regular dose-based regimens may be incompatible with physiological variability, further contributing to treatment inefficacy. We present the concept of overcoming immune system adaptation to anti-TNFs by introducing patient-tailored patterns of variability to treatment regimens.

Keywords: anti-TNF, rheumatoid arthritis, inflammatory bowel disease, loss of response, variability

INTRODUCTION

Anti-tumor necrosis factor (TNF) monoclonal antibodies (mAbs) are the most common biological drugs used for treating inflammatory disorders. Since the introduction of biological therapies almost 2 decades ago, specifically, the anti-TNF α agents, major alterations of the natural history of rheumatoid arthritis (RA) and inflammatory bowel disease (IBD) have been observed (1, 2). Anti-TNF α agents both induce and maintain clinical remission, improve quality of life, decrease the need for surgery, and improve morbidity, coupled with decreasing the total RA- and IBD-related costs (3).

Despite major progress and the wide use of these drugs, only a portion of treated patients achieve long-term clinical remission. Some patients who receive anti-TNFs fail to respond (primary failure), and others have loss of response (LOR) following an initial response (secondary failure) (4). Both primary and secondary failure are major obstacles to the long-term use of anti-TNFs in RA and IBD. Better understanding of the mechanisms for the development of drug resistance may enable improved responses (5). In the present review, we discuss some of the potential mechanisms for the compensatory adaptation of the immune system toward anti-TNF-based drugs, focusing on potential methods for overcoming it.

PRIMARY AND SECONDARY NON-RESPONSIVENESS TO ANTI-TNF AGENTS IN RA AND IBD

It is currently estimated that only up to 60% of patients with RA achieve long-term response to anti-TNF drugs (6, 7). One-third of patients with RA show inadequate primary response these medications (8). In a study of 157 patients treated with various anti-TNF formulations, 21% of the patients achieved 1-year clinical remission, and 58% of patients had >1.2 reduction of disease activity score (DAS28). There was moderate response according to European League Against Rheumatism (EULAR) criteria in 46% of patients, and 35% of patients had a good response (9). Primary failure was attributed to disease heterogeneity in terms of the types of inflammatory mechanisms and subsets of cells involved (10, 11).

In RA, there is no consensus for the definition of secondary failure, when efficacy is lost over time despite a good initial response. Secondary failure is considered if there is an increase in DAS28 of >0.6 during the previous 6 months or an increase in EULAR response (5, 12, 13). The time to discontinuation of a biological drug, or drug survival, is affected by loss of efficacy, immunogenicity, adverse events, and/or poor adherence. Loss of efficacy is the major cause of treatment discontinuation, and occurs in 48% of patients; 34% of patients experience adverse events (14, 15). Anti-TNF drug survival in patients with RA is 47 months (14). The overall 10-year retention rate of first-line anti-TNF agents is 23% (5, 16).

Primary LOR in IBD is defined as failure to achieve clinical remission as evaluated by clinical scores, including the Crohn's disease activity index (CDAI) and Harvey-Bradshaw index (HBI), and laboratory remission as evaluated by serum inflammatory markers. The timeframe within which primary response or non-response is determined varies between trials (17, 18). Nonetheless, expert consensus and clinical trials indicate that primary non-response to anti-TNF drugs should not be assessed

prior to 14 weeks of infliximab (IFX) therapy or prior to 12 weeks of adalimumab (ADM) therapy (19). Moreover, in the clinical practice of some experts, patients are considered to have primary non-response after 6 months of anti-TNF treatment without evidence of remission. Secondary LOR in IBD is defined by lost or attenuated clinical and endoscopic response over time to anti-TNFs after an initial response to anti-TNFs. To confirm the diagnosis of secondary LOR, the patient must fulfill two conditions: develop reappearance of the clinical symptoms associated with disease exacerbation, and that the symptoms are mediated by inflammatory disease exacerbation of the underlying IBD (20). Primary failure of anti-TNF induction therapy occurs in up to 40% of patients with IBD in clinical trials and in 10–20% of patients in clinical series (21). Secondary LOR was reported in 25–61% of patients on anti-TNF maintenance therapy (22–24). A recent controlled study showed that >50% of patients with CD treated with IFX and ADM developed LOR (24). Additional trials have reported secondary LOR in 23–46% of patients 12 months after drug initiation. A review of 86 trials on patients with CD reported LOR incidence of 8–71%. The incidence of LOR with a median follow-up of 1-year was 33%. The rate of LOR in patients treated with IFX, ADM, and certolizumab pegol was 33, 30, and 41%, respectively. Overall, the mean percentage of LOR to anti-TNFs was 38%, with an annual rate of 20% per patient-year (25).

Taken together, both primary and secondary failure remain major obstacles to achieving a prolonged, sustainable effect of anti-TNFs in both RA and IBD.

DIFFICULTIES IN PREDICTING LOR TO ANTI-TNFs IN RA AND IBD PREVENT THERAPY GUIDANCE IN THE MAJORITY OF PATIENTS

Identifying the causes and biomarkers for predicting efficacy and for anticipating the development of primary or secondary LOR is an unmet need. It may also provide a means for selecting newer lines of therapy and minimizing adverse effects and cost. The causes of secondary loss of efficacy are not fully understood.

In patients with IBD, the underlying mechanisms of loss of effect include longer disease duration, smoking, and several genetic mutations (21). The data are still limited, and data on the role of these measurements in guiding therapy are conflicting (21). Those mechanisms are classified into several domains:

- (i) **Drug factors:** Immunogenicity is defined by the formation of ADAbs in the setting of low biological drug levels. Both primary and secondary LOR are attributed to ADAbs. ADAbs neutralize the anti-TNF drug connecting to the Fab segment of the protein, or may bind solely to the anti-TNF molecule, promoting the formation of immune complexes leading to increased drug clearance through the reticuloendothelial system. ADAbs or sub-therapeutic trough concentrations explain LOR in only a proportion of patients with IBD, as many patients experience disease exacerbation with LOR in the setting

Abbreviations: mAbs, monoclonal antibodies; RA, rheumatoid arthritis; IBD, inflammatory bowel disease; DAS, disease activity score; EULAR, European League Against Rheumatism; ETA, etanercept; IFX, infliximab; ADM, adalimumab; LOR, loss of response; ADAbs, anti-drug antibodies; SNPs, single-nucleotide polymorphisms; GWAS, genome-wide association study; MTX, methotrexate; CD, Crohn's disease; ED, elemental diet; tmTNF, transmembrane tumor necrosis factor; TNFR, TNF receptor; FcRn, neonatal Fc receptor; AS, ankylosing spondylitis.

of therapeutic drug concentrations and the absence of ADAbs (26). Combo-therapy with immunosuppressive and immunomodulatory drugs aimed at suppressing the reaction of antibody formation has not been consistently shown to improve treatment durability or efficacy in all studies. Additionally, less immunogenic humanized anti-TNF therapies have similar rates of LOR as the chimeric IFX (20, 27). The current evidence supporting the routine estimation of ADAbs or serum trough levels during anti-TNF therapy is limited; however, they are suggested as guidance for changing between therapeutic biologics in secondary failure (5).

- (ii) Pharmacokinetic failure is defined by decreased levels of the drug with typically absent or low anti-drug antibodies (ADAbs). The pathogenesis is secondary to accelerated non-immune drug degradation via tissue or systemic circulation. The three main mechanisms underlying pharmacokinetic failure are proteolytic catabolism within the reticuloendothelial system, mAb binding to Fc gamma receptors, and degradation in lysosomes by binding to membrane-bound TNF (28–30).
- (iii) Autoantibodies: The presence of autoantibodies, including antinuclear antibodies (ANA) and antibodies against double-stranded DNA (anti-dsDNA), may contribute to LOR. Higher levels of these autoantibodies may interact with the anti-TNFs, reducing their efficacy (31).
- (iv) Genes and proteins expression: Alteration of the expression of the apolipoprotein (*APO*) genes, mainly *APO4*, which produces a protein with antioxidant ability, has been associated with LOR (32, 33). In patients with IBD, LOR cannot be attributed directly to pathways that bypass the action or induce resistance to anti-TNF therapy. An RNA microarray study showed that patients with LOR had elevated colonic expression of the pro-inflammatory chemokines CXCL20, CXCL9 (C-X-C motif chemokine ligand 9), and CXCL10. Patients with continued inflammation had elevated MMP3 (matrix metalloproteinase 3), MMP1, and MMP12. Patients with LOR had dysregulated cysteine and methionine metabolism pathways, implying alterations in the oxidative stress burden (32).
- (v) Patients and disease phenotypes: Factors predictive of longer time to failure include obesity, smoking, higher baseline serum albumin, male sex, and thiopurine co-therapy. Higher baseline fecal calprotectin is associated with shorter time to failure (21, 34, 35). Elevated body mass index (BMI) is associated with poorer response to IFX and correlates with higher drug levels, but not a higher response rate, suggesting that circulating drug levels do not correlate with tissue levels (36).
- (vi) Fibrostenotic disease behavior has been associated with both primary and secondary LOR, and in those cases, surgical resection is more appropriate than biological therapy. Lower response rates have been described in fibrostenotic disease (37). Severe inflammatory activity has been associated with lower efficacy of anti-TNFs due to non-immune clearance of the drug, accounting for

both primary and secondary LOR (38, 39). The proposed underlying mechanism for this is fecal loss of anti-TNFs through the ulcerated and sloughed colonic mucosa (40).

- (vii) Treatment factors: The dosing regimen is important for primary non-response. Remission at 4 weeks in patients receiving ADM was associated with a higher drug dose (41). A similar study on IFX (ACCENT 1) reported a lower primary non-response rate in patients who received a higher dose of the drug (17).
- (viii) Combo-therapy: A previous study (SONIC) showed that early co-treatment of IFX with immune modulators (azathioprine) vs. monotherapy had a higher response rate, accompanied by a significantly higher rate of mucosal healing. However, no similar data have been reported for ADM (42).
- (ix) Oxidative stress can dysregulate the cysteine and methionine pathways in patients with IBD with LOR. Both pathways are important for producing nicotinamide adenine dinucleotide phosphate (NADPH) and S-adenosylmethionine (SAM), which regulate oxidative stress by producing oxidative stress protein scavengers (32).

In patients with RA, most biomarkers used have insufficiently strong predictive value for predicting treatment response in individual patients with RA (43). Many baseline disease characteristics fail to predict the outcome, suggesting that drug metabolism or receptor adaptation may be contributing factors (44).

- (i) Genotypes: Patients with RA with a TNF-308 G/G genotype, human immunoglobulin (Ig) allotypes in the IgG1 heavy chain (G1m1 and G1m17), and HLA (human leukocyte antigen)-DRB1 locus have better response (45–47). Five tagging single-nucleotide polymorphisms (SNPs) in the TNFRSF1B (TNF receptor superfamily member 1B) gene were studied in 1412 patients with RA, and the authors reported that carriers of the rs3397C/C, rs1061622G/G, and rs1061631A/A genotypes have increased risk for worse response to anti-TNFs. However, the association with specific SNPs only reached marginal significance and was not confirmed in a meta-analysis. Overall, these data do not support a major effect of TNFRSF1B variants in determining the response to anti-TNF drugs (48). SNPs in the steroid hormone-related genes showed significant correlation of CYP3A4 (cytochrome P450 family 3 subfamily A member 4) rs11773597 and CYP2C9 rs1799853, with changes in DAS28 after the administration of anti-TNFs. A model comprising eight steroid hormone-related variants predicted drug response (49). A review of all studies reporting associations between genetic variants in RA identified 25 SNPs as being associated with anti-TNF response. These were mapped to genes involved in T cell function, nuclear factor kappa B (NFκB), and the TNF signaling pathways (50). A genome-wide association study (GWAS) conducted in 372 patients with RA showed an association between the MED15 (mediator complex subunit 15) gene and the response to ETA (51). The impact of dose

titration based on pharmacoeconomics in clinical practice remains questionable (52).

- (ii) Anti-drug antibodies: Most anti-TNF agents induce a certain degree of immunity, and ADABs may limit drug survival (5, 53). It is unclear whether these antibodies are a major cause of the loss of anti-TNF clinical efficacy (5, 54). IFX is a chimeric mAb and is more immunogenic, but ADABs also bind to the idiotype of the fully human mAb ADM. Etanercept (ETA) is associated with reduced immunogenicity (55). ADABs were detected in the sera of 7–53 and 1–31% of IFX- and ADM-treated patients with RA, respectively, and were suggested to correlate with decreased response and increased adverse events (56, 57). The detection of ADABs is confounded by the detection method used, high serum concentrations of rheumatoid factor, and the presence of the drug itself (58). In some studies, ADABs were associated with reduced clinical response in RA, suggesting that monitoring drug levels may aid in optimizing the dosing regimen (59–61).
- (iii) Patients and disease phenotypes: In a study where 42% of patients stopped therapy, increased likelihood of discontinuation was associated with higher physician global scores and RA Disease Activity Index scores 6 months prior to stopping the TNF inhibitor, and a higher number of TNF inhibitors used previously. There was a lower percentage of ETA discontinuation than IFX and ADM (62). A study of 299 patients with RA reported that age, female sex, and high values of both disease activity and disability were predictors of non-response (63).
- (iv) Immune background: The presence of rheumatoid factor or anti-cyclic citrullinated peptide antibodies was associated with reduced response (64). Baseline serum levels of interleukin-6 (IL-6) predicted depletion of the drug and were suggested as a biomarker of treatment failure (65). Serum calprotectin had moderate predictive value for clinical response to anti-TNFs (66).

Overall, the currently available tests do not provide a valid tool for therapy guidance in terms of predicting primary and secondary failure.

CURRENT METHODS FOR OVERCOMING INEFFECTIVENESS OF ANTI-TNFs IN RA AND IBD FAIL TO OVERCOME LOR IN THE MAJORITY OF PATIENTS

In RA, concomitant administration of immunosuppressive agents is commonly used for improving response rates to anti-TNFs. Improved results were noted in patients treated with methotrexate (MTX) in combination with anti-TNFs. The synergy between anti-TNF and MTX is not fully understood and can only be partially explained by suppression of ADAB formation and increased trough concentrations (5, 67–69).

Switching between different anti-TNF formulations is another commonly suggested method for improved response in RA and has been successful in some studies (70, 71). The improved response following switching is attributed to differences

in structure, immunological action, immunogenicity, and pharmacokinetics (72). Switching was beneficial in secondary lack of effectiveness [defined as loss of ACR50 (American College of Rheumatology response criteria—50% improvement)] in 479 patients with RA. In these patients, the disease activity parameters improved from baseline upon use of IFX or ADM, but had increased prior to the switch. Switching from ETA to ADM restored the response achieved with the first drug. Several activity parameters that had improved from baseline upon use of ETA were maintained but were not improved further after switching to ADM. When switching due to adverse events, the second agent achieved a similar degree of response to that of the first agent (73). In a study of 356 patients with RA, 38 switched from IFX/ADM to ETA, 26 from ETA to IFX/ADM, and eight from one mAb (IFX/ADM) to another. Switches occurred due to primary failure (36.1%), escape (33.3%), or intolerance (30.6%). More switchers responded to the second anti-TNF regardless of molecules switched. The second anti-TNF had longer survival with the switch from a mAb to a soluble receptor than vice versa (74). Taken together these data support the notion that LOR may be improved by a switching strategy.

In a study of 99 patients with RA, switching took place if no reduction >0.6 in the initial DAS28 occurred after 12–24 weeks (inadequate response) or if a severe adverse event was reported. Switching was performed in 39% of patients. The retention of the first agent was 60%, and the mean time to switching was 14 months. After switching, there was a tendency toward decreased DAS28, and 43% of patients had good/moderate EULAR response; however, there was a low likelihood of remission and no significant improvement in functional capacity (75). In a trial of 300 patients with RA with persistent disease activity [DAS28–erythrocyte sedimentation rate (DAS28-ESR) ≥ 3.2] and insufficient response to anti-TNF therapy, patients were randomly assigned to receive a non-TNF targeted biologic agent or to switch to another anti-TNF. Within 6 months, 69% of patients in the non-TNF group and 52% in the second anti-TNF group achieved good or moderate EULAR response, and the non-TNF group had lower DAS28-ESR than the second anti-TNF group. At weeks 24 and 52, more patients in the non-TNF group vs. the second anti-TNF group showed low disease activity. The data suggest that a non-TNF biologic agent is more effective than a second anti-TNF for achieving good or moderate response at 24 weeks (8).

Several of these methods are also being used for overcoming LOR in patients with IBD. In CD, dose-optimization strategies for IFX using induction doses at 0, 2, and 6 weeks, followed by maintenance administration every 8 weeks, conferred better protection against ADAB formation (76). A randomized, controlled study of 69 patients with CD with secondary IFX failure showed that using an algorithm based on combined IFX and IFX antibody measurements reduced the average treatment cost per patient without negative effects on efficacy (77).

Re-induction is an effective strategy in LOR (35). Dose intensification was proposed as a means of overcoming LOR in IBD. Dose intensification with a median follow-up of 1 year was needed in 38% of patients for IFX, 36% for ADM, and 2% for certolizumab pegol. A mean 23% of patients needed anti-TNF dose escalation, with an annual risk of 18% (25).

Following dose escalation for ADM-treated patients with CD, a clinical response was observed in 79 and 61% of patients at 3 months and 12 months, respectively (78). Compared with empirical adjustment, an algorithm for dose intensification and therapeutic drug monitoring of IFX trough levels and ADAb assays resulted in fewer dose escalations, i.e., 45 vs. 71%, without loss of efficacy (79).

Dose intensification of anti-TNFs is mainly used in the setting of secondary LOR, where there is a sub-therapeutic level of the drug and low/undetectable ADAb levels. It can be performed by either shortening the interval frequency or increasing the dosage. The efficacy of this strategy has been proven even without drug monitoring (80, 81). However, further studies have shown that drug level monitoring during dose intensification is more cost-effective and may reflect the recapturing response for anti-TNFs in patients who achieve an increment in drug level following dose intensification (82, 83). Implementing dose intensification in the presence of ADABs has not been established. Dose intensification of IFX in the presence of ADABs was associated with a paradoxical decreased response (84). Low ADA levels with detectable ADABs were associated with drug failure (26). Patients with IFX ADABs were more likely to fail dose intensification (82). Higher ADAb levels identify patients who do not respond to increased drug dosage (85). ADABs are associated with lower ADA serum levels and a lower likelihood of remission. However, patients have experienced loss of ADABs to ADA following dose escalation (86). IFX intensification in secondary LOR improved the clinical response while decreasing ADABs irrespective of the levels of serum IFX and ADABs (87). Increased serum IFX levels after dose intensification were associated with improved clinical outcomes and undetectable IFX ADABs (88). Recent treatment algorithms suggest that dose intensification may overcome low ADAb levels (30, 80, 82, 89, 90).

Several studies suggested that combining immunomodulatory agents with anti-TNFs is can be used in IBD. The addition of immune modulators has mainly been implicated in immunogenicity-mediated primary LOR, which is defined by the inability of anti-TNFs to bind to the TNF molecules, resulting in increased immune-mediated drug clearance (80). Concomitant combo-therapy with an immunomodulator is used to prevent immunogenicity. Adding thiopurine or MTX as an immune modulator starting together upon the initiation of anti-TNF has been associated with decreased ADABs formation (91) and can improve the clinical and histological outcomes, coupled with increased rates of steroid-free remission and decreased need for switching (19, 42, 92, 93). Notably, no difference in adverse effects, including infection and malignancy, were noted when combo-therapy was used as compared to biological monotherapy in one study (94).

Additional trials raised concern about the long term efficacy and safety of a combination therapy. Up to 45% of IBD patients who experienced LOR during a follow-up period of up to 8.5 years were followed using combination therapy with an immunomodulatory drug (59%) or monotherapy (40%). The median time to LOR was not different between groups. The data suggest that patients treated with anti-TNF monotherapy have similar LOR rates as patients on anti-TNF combination

therapy (95). Switching to another anti-TNF may aid 50% of patients with IBD. Switching from ADM to IFX was beneficial in patients with LOR and in patients with undetectable ADM trough levels. The majority of patients required IFX therapy intensification during their first year of treatment (96). Recent trials have raised safety concerns, including comorbid malignant diseases such as lymphoma, with the concomitant use of other immunosuppressive drugs or increased dosages (97). A concomitant elemental diet (ED) with ADM in patients with CD showed that the ED group had a higher cumulative non-ADA LOR rate. ED reduced ADA LOR in IFX-intolerant or -refractory patients than in anti-TNF α -naïve patients. The ED group had lower serum TNF α levels (98).

None of the measures used for overcoming LOR are personalized, nor do they fit the dynamic type of the compensatory adaptations to anti-TNF therapy, which may change over time between patients and in the same patient. While they provide a solution for some patients, none can provide a prolonged response for the majority of patients.

THE PARADOXICAL FUNCTION AND TOLERANCE TOWARD ANTI-TNF ANTIBODIES ARE UNPREDICTABLE AND DYNAMIC OVER TIME

The mechanisms of action of both TNF and anti-TNF mAbs are not fully elucidated. The complex responses of the immune system to anti-TNFs, impact both their short- and long-term clinical effects. Many of these effects are dynamic and may occur over time, and vary between patients and in the same patient, making them irregular and difficult to predict.

Humans may develop tolerance of anti-TNFs, improving the response by reducing ADAb levels. Alterations of treatment regimens, where IFX is administered at week 0, 2, 6, and 14, and every 8 weeks thereafter, was associated with higher trough levels reducing ADAb development (99), supporting high-dose tolerance, which is induced by the high antigenic load (5, 100).

Both linear and non-linear eliminations have been reported for anti-TNF mAbs depending on the amount of the target antigen, immune reactions to the antibody, and patient demographics (28). Their clearance demonstrated non-linear kinetics due to receptor loss following repeated doses, which was proposed to be associated with disease severity (28, 29). Due to their molecular size, mAb distribution to tissues is slow, and their distribution volumes are low. Anti-TNFs are metabolized by phagocytes or by their target cells to peptides and amino acids, and are protected from degradation by binding to the neonatal Fc receptor (FcRn), which explains their long elimination half-lives.

TNF exerts both pro-inflammatory and immune-suppressive effects. Lower or higher TNF production characterizes many autoimmune diseases. TNF blocking in autoimmune and chronic inflammatory diseases is associated with unpredictable outcomes (101). Treatment timing and duration can alter this unpredictability. Both IFX, ETA, and ADM neutralize soluble TNF and bind to transmembrane TNF (tmTNF). They are dual-function and can act as antagonists by blocking TNF interactions

with the TNF receptors TNFR1 and TNFR2, or initiate a reverse signaling cascade leading to apoptosis, cell activation, or cytokine suppression (55).

A paradoxical expansion of T helper 1 (TH1) and TH17 pro-inflammatory lymphocytes following IFX treatment may be another mechanism of LOR in some patients (102). Anti-TNF therapy is associated with drug-induced anti-dsDNA production and with the development of the manifestations of lupus and neuroinflammatory diseases (103). In patients with multiple sclerosis, anti-TNF treatment was associated with immune activation and disease exacerbation (104). The heterogeneity of TNFR usage during immunosuppression vs. the inflammatory tissue damage may underlie some of these findings. It implies that the effect of anti-TNF at receptor level is of greater relevance in human chronic inflammatory and autoimmune conditions (101). These paradoxical effects are unpredictable and dynamic over time.

Tolerance to TNF has been described at receptor level. Soluble TNFR1 (sTNFR1) is an endogenous mechanism for reducing serum TNF. Endotoxin tolerance via lipopolysaccharide (LPS)-preconditioning downregulates pro-inflammatory cytokine production. Tolerance mechanisms upregulates TNFR1, which binds and clears TNF while reversing the TNF-to-sTNFR1 ratio (105, 106). tmTNF is transiently expressed on the surface of LPS-stimulated monocytes, macrophages, and dendritic cells, and can be enhanced following treatment with a TNF inhibitor (107).

Repetitive administration of low doses of human TNF to mice induces tolerance to the effects of mouse TNF via post-receptor mechanisms (108). No differences in pharmacokinetic parameters were noted in tolerant vs. control mice. There was an antibody response to human TNF, but the antibodies did not neutralize the mouse TNF. The tolerance did not protect mice against lethality induced by TNF. When tolerance was induced in athymic nude mice, which lack an antibody response, there were no effects on the levels of soluble receptors or receptor binding in the tolerant vs. control groups (108).

Overall these complexities further contribute to long term loss of effects of these drugs.

VARIABILITY IS INHERENT TO BIOLOGICAL SYSTEMS AND COMPRISES MARKED INTRA/INTER-PATIENT VARIABILITY IN RESPONSE TO DRUGS

Both intra- and inter-subject biological variability (BV) in biological and immune systems has been described at cellular organelle level, as well as at whole-organ level (109–115). This inherent variability is difficult to overcome. Lymphocyte subpopulation phenotype variability has been described when tested as biomarkers of immune-associated disorders. The antibody response toward pathogens includes expansion of antigen-specific B cells that is based on stochastic competition between competing cell fates, or deterministic cell fate decisions that execute a predictable program (116). Variability was noted for both cell proliferation and death decisions and evolved from heterogeneity in founder cells. The data imply that a small

number of genetically identical founders are associated with the majority of the responses. A high rate of variability in the generation of CD4+ T regulatory cells (Tregs) is a major obstacle for cell therapy of immune-mediated disorders (117). An *ex vivo* cytokine release test, measured after stimulation of whole blood with various stimuli, showed high intra-group and inter-individual variability. The median coefficient of variation of the repeated tests was 29 and 52% for IL-1 β and IL-8, respectively. Upon stimulation with endotoxin, a confidence interval of 60–140 and 70–271% was calculated for IL-1 β and IL-8, respectively (118).

The inter- and intra-individual variability described in the response toward drugs has been attributed partly to pharmacogenomics- and pharmacodynamics-based drug metabolism, and drug responsiveness (119–122). However, there is heterogeneity between individual cells in their response to drugs (123). Complex physicochemical determinants of drug-target interactions in a cell have been described and are not defined by simple diffusion and intrinsic chemical reactions. The non-specific interactions of drugs and macromolecules in cells are beyond “simple” pharmacodynamics, affect drug function, and are difficult to control for. Non-specific interactions greatly slow the incorporation kinetics of DNA-binding drugs and have been attributed to anomalous drug diffusion in cells (123). Differential cell compartment effects affect intracellular drug kinetics variability (123). There is marked intra-patient variability in drug serum levels between days, suggesting additional underlying mechanisms (122, 124).

The inherent variability in biological systems evolves along a trajectory associated with the body's response to multiple internal and external triggers, and are aimed at reaching a newer steady state. These systems function under unpredictable conditions, are highly dynamic, and are therefore difficult to alter. Each exogenous trigger, e.g., anti-TNF antibodies, induces a compensatory adaptation mechanism that may lead to a paradoxical response, tolerance, and a new steady state.

DOSE ALTERATIONS AND INTRODUCING VARIABILITY INTO ANTI-TNF THERAPIES IS ASSOCIATED WITH IMPROVED RESPONSE

The high rate of LOR to anti-TNFs, along with their complicated mechanism of action at receptor/post-receptor level, has led to additional approaches for overcoming LOR. Both anti-TNF dosage escalations and reductions are used in the real-world setting. Intermittent dosing with drug holidays has clinical benefits while minimizing drug exposure and potential adverse effects (125).

Anti-TNF re-induction following a drug holiday has been suggested as a means of overcoming LOR. The outcome of this approach depends on the circumstances during which the drug holiday is commenced (21). Dose modifications compared to basal dose have been described in 7% of patients on ETA, 30% of patients receiving ADM, and 21% of patients on IFX. ADM and IFX have been associated with higher risk of dose

escalation relative to ETA, and dose reductions are similar among all anti-TNFs (126).

Dose reduction schedules of anti-TNF as maintenance therapy in patients with spondylarthritis are used in clinical practice (127). Dose reduction implemented empirically for several years has improved treatment efficiency in RA (128). In a study of 153 patients, 45% received a lower dose after achieving remission or low activity at standard doses, and maintained good disease control. Dose titration of anti-TNF in RA by 67% of patients was not associated with a change in DAS28, and no patient dropped out because of disease worsening (129). An anti-TNF dose-tapering strategy was evaluated in patients with ankylosing spondylitis (AS). In the reduced dosing group, the median dose of anti-TNF corresponded to 0.67 of the initiated dose, and was 0.5 at 12 months. Up to 79% of patients did not require return to standard dosing

regimen. Patients that had received reduced or standard dosing had similar mean change per year in the Bath AS Activity Index, C-reactive protein, Health Assessment Questionnaire Disability Index, Bath AS Functional Index, and quality-adjusted life-year (130).

In a prospective trial, 80 patients with CD and ulcerative colitis (UC) in clinical remission receiving IFX maintenance treatment were randomized to receive IFX dosing guided by a pharmacokinetic model, aiming to maintain a drug level using a (de-)escalation dashboard or to continue regular dosing. There was loss of clinical response in 36% of controls vs. only 13% of patients in the intervention group. In the intervention group, 50% had dose reduction while 35% had dose escalation. The clinical and laboratory benefits were achieved irrespective of the lack of change in drug level, and with narrowed dose range variability (131). The results support the premise that even

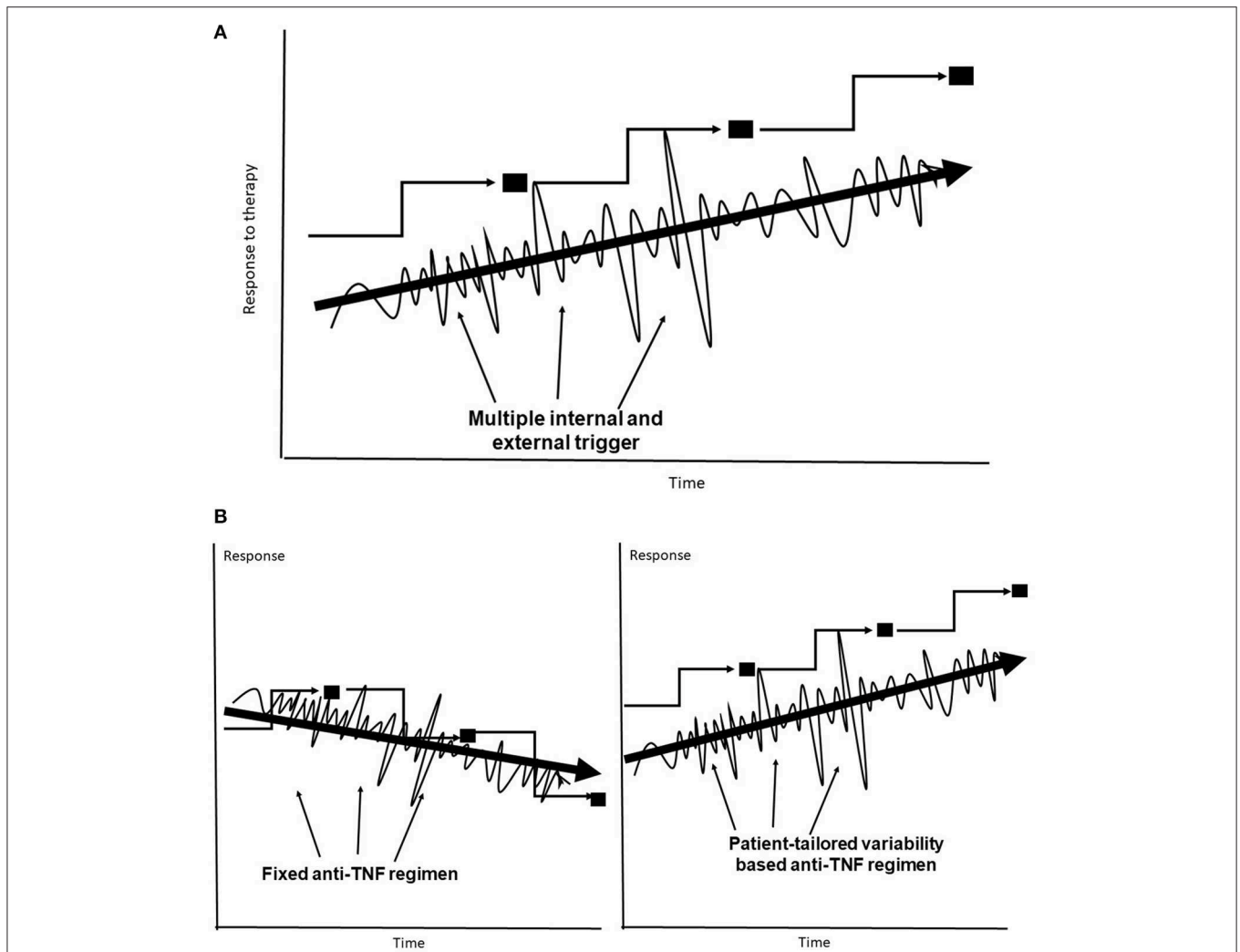


FIGURE 1 | (A) The body’s trajectory of compensatory adaptation in response to multiple internal and external triggers uses variability to reach a new steady state. **(B)** Fixed dosing may sometimes jeopardize the response to anti-TNF-based therapies, leading to lower steady states. Subject-tailored patterns of variability are introduced into anti-TNF administration along the trajectory for achieving an improved steady state.

simple dose alterations are associated with significant clinical improvement compared with regular fixed dosing.

OVERCOMING IMMUNE SYSTEM ADAPTATION TO ANTI-TNFs BY INTRODUCING PATIENT-TAILORED PATTERNS INTO TREATMENT REGIMENS

The unpredictability of the response to anti-TNF-based therapies, high LOR rate, and paradoxical activation of the immune system, along with empirical real-world data on the beneficial effects of drug holidays and dose reductions, supports evaluating BV as a method for overcoming LOR. Part of this inter- and intra-patient irregular behavior is viewed as normal adaptation attempts of the immune system in response to triggers such as the administration of anti-TNF.

Many biological systems lack fixed rules that remain constant over time. These systems are dynamic in both health and disease, as they are required to continuously respond to ongoing internal and external triggers in an attempt to reach a new steady state (132–135). The lack of rules in biological systems (132, 133), and the continuous dynamics of the immune processes (134, 135), along with the lack of understanding of some of existing rules, while responding to trigger(s) may underlie part of the unpredictability of the response to anti-TNFs. It has been proposed that the optimal state in variability is a U shape between a chaotic pattern of variability in a steady state and full predictability in a normal biological system (109, 110, 136–139). The body functions along a trajectory that implements variability patterns in an attempt to identify the optimal response to different triggers, including those by anti-TNF therapies. This behavior has an inherent variability that may not necessarily move toward a better point, makes mistakes, and can result in LOR (Figure 1).

The adaptation of the immune system may occur within a short time of drug administration, leading to primary failure, or following longer treatment periods, resulting in partial or complete loss of efficacy. The adaptation may manifest as immune tolerance in terms of lack of response to changes induced by the mAb at TNFR or post-receptor level. The inherent heterogeneity of the immune system response may result from the gradual accumulation of small amounts of intrinsic noise, which occur, for example, during cell differentiation (116).

Anti-TNF dosing using regular fixed regimens may not be compatible with the physiological variability in the immune system and may further contribute to LOR (140, 141). Fixed regimens may be incompatible with the random nature of the trajectories associated with the immune system, which both underlie inflammation and the compensatory mechanism for

anti-TNFs. It has been proposed that, for various systems, the dynamic properties of the system may be associated with its evolution into a structure that optimizes their function (142). Therefore, even if there are rules, they may change constantly over time.

Interdependency between different network properties, which is applicable to many immune processes, many of which behave randomly, can be quantified. The dynamic systems theory suggests that biological systems are self-organized according to environmental, biochemical, and morphological constraints to find the most balanced state (143). It has been proposed that a patient-tailored variable regimen can overcome this adaptation, thereby improving the short- and long-term responses to anti-TNFs.

It has been proposed that the system's degree of variability requires augmentation to improve anti-TNF efficacy. Introducing greater variability into the system follows the same trajectory used by the body in its response to the triggers induced by the drug itself. This is expected to improve the response to anti-TNF mAbs under conditions of unpredictability (Figure 1). The development of a new platform for anti-TNF therapy is proposed in stages. In the first stage, patients with LOR may benefit from introducing variability in dosages and administration times, including variable drug holidays within a pre-determined range with regulatory approval. In the second stage, patient-tailored algorithms based on quantifying variability signatures that are directly or indirectly related to the underlying chronic inflammatory state and to the response to the anti-TNFs, including patients' variability patterns, will be applied.

In summary, the complexity of the immune response to anti-TNF mAbs induces compensatory adaptation at several cellular levels that jeopardize the response, resulting in primary or secondary failure. Introducing patient-tailored variability to drug administration may provide a method for reducing the LOR in such patients. The results of ongoing studies implementing these concepts using patient-tailored-based algorithms will shed light on some of the mechanisms involved in immune adaptation to anti-TNFs and may provide a means of improving the response to these drugs.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Conflict of Interest: YI is the founder of Oberon Sciences and is a consultant for Teva, ENZO, Protalix, Betalin Therapeutics, Immuron, SciM, Natural Shield, Oberon Sciences, Tiziana Pharma, Plantylight, and Exalenz Bioscience.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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