



Defining response to TNF-inhibitors in rheumatoid arthritis: the negative impact of anti-TNF cycling and the need for a personalized medicine approach to identify primary non-responders

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Abstract

Current guidelines recommend treating rheumatoid arthritis (RA) patients to reach low disease activity or remission, however, most biologic-naive RA patients fail to reach treatment targets on their first biologic therapy. Approximately 90% of biologic-naive RA patients receive a tumor necrosis factor alpha inhibitor (anti-TNF) as their first biologic treatment, even though several alternative mechanism of action (MOA) therapies are approved as first-line options. After 3 months of therapy, patients may remain on anti-TNF therapy even if they fail to achieve the treatment target, mainly due to formulary structures. This means patients have to endure a second and even a third ineffective anti-TNF—called anti-TNF cycling—before changing MOA. This significantly delays patients from reaching their treatment targets. All anti-TNF drugs target the same molecular and inflammatory pathways; thus, it is not surprising that most patients who are primary non-responders to their initial anti-TNF therapy fail to achieve their treatment targets when cycled through alternative anti-TNFs. This suggests that primary non-responders should be switched to an alternative MOA therapy rather than enduring anti-TNF cycling. Avoiding anti-TNF cycling would prevent disease progression and improve quality of life for RA patients who are primary non-responders to anti-TNFs. The development of a personalized medicine approach to identify primary non-responders to anti-TNFs prior to treatment would allow significantly more patients to reach their treatment target by treating them with alternative MOA therapies as first-line therapies.

Keywords Anti-TNF cycling · Classifier · Personalized medicine · Rheumatoid arthritis · TNF inhibitors · Treat-to-target

Introduction: treatment target goals and the definition of response

Rheumatoid arthritis (RA) is a complex, chronic, autoimmune disease that leads to inappropriate inflammation and systemic tissue damage. RA can progress from painful inflammation of the joints to joint stiffness, joint destruction, loss of function, and, eventually, to permanent irreversible disability [1]. As RA progresses, it negatively affects the ability of patients to work and perform activities of daily living and household chores, leading to decreased quality and length of life [2].

The objective of treatment is to slow or even halt disease progression and improve the quality of life for RA patients.

The RA population is very heterogeneous and the development of disease symptoms depends on a variety of genetic (susceptibility genes, epigenetic modifications) and environmental factors (smoking, obesity, changes to the microbiome of the mouth and gut). Together, these factors elicit immune responses, leading to inappropriate and robust immune cell proliferation, differentiation, and autoantibody production, which stimulate and maintain the inflammatory cascade in the synovium [1]. This can occur through multiple molecular pathways that involve signaling through pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF- α) and interleukin-6 (IL-6) [1]. The variety of molecular inflammatory pathways activated in RA patients may determine each individual's response to treatment, as recently approved therapies for RA treatment are molecularly targeted. The advent of personalized [3] or precision [4] medicine (PM) for RA will

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make it possible to determine if an individual will respond to a specific targeted treatment, improving a clinician's ability to "treat-to-target" [5, 6], which is the primary goal of RA therapy. Treat-to-target is the foundation of the American College of Rheumatology (ACR) [7] and the European League Against Rheumatism (EULAR) [8], and their current guidelines for RA treatment define the target as achieving either remission or, if remission is not possible, achieving low disease activity (LDA). Remission is an extremely high bar for therapy targets and is achieved by only a very small proportion of RA patients. In the DREAM registry, 6% of patients achieved remission as defined by ACR and EULAR criteria, whereas 27% achieved Disease Activity Score (DAS28) < 2.6 which is a less stringent measure of remission as it allows for some residual disease activity [9]. Table 1 compares the specific cut-offs in the different disease activity scales for LDA and remission and summarizes these for the ACR and EULAR guidelines. Although it is achieved by only a small proportion of patients, there are substantiated structural and functional benefits to achieving remission compared to LDA [12], including delaying disease progression and improving quality of life. However, LDA remains the most realistic and achievable target for the majority of RA patients.

To follow the treat-to-target recommendations, it is necessary for a rheumatologist to measure the DAS, specify the DAS target to be met, and decide on a period of time to define the response to treatment for each patient. Therefore, standardizing the measurement of disease activity has been key to determining the efficacy of RA drugs and for clinicians to evaluate and follow the effect of treatment on their patients. The most commonly used measures in clinical care (Table 1) are the Clinical Disease Activity Index (CDAI) and DAS28 [7, 8]. For drug development, the ACR20, ACR50, and ACR70 were established as response criteria. The ACR number refers to the percentage of improvement in a standard set of measures (Table 2) [14]. ACR20 is the most widely used measure of response in RA clinical trials and accepted by the Food and Drug Administration (FDA) as the efficacy bar for

drug approval [10], despite not being routinely used in the clinic.

Current treatment guidelines [7, 8] for RA (Fig. 1) recommend beginning treatment with a conventional synthetic (cs) disease modifying anti-rheumatic disease (DMARD) monotherapy such as hydroxychloroquine, leflunomide, methotrexate, or sulfasalazine. Methotrexate is the initial DMARD recommended for treating patients with early RA, defined as a disease duration of < 6 months [7]. Patients with early RA or RA flares may be given low-dose glucocorticoids (prednisone or equivalent ≤ 10 mg/day) for short periods (< 3 months) of time along with the csDMARD. If the goal of treatment is not met, the guidelines recommend switching to combination therapy with two or three csDMARDs or targeted therapies (anti-TNFs, non-TNF biologics, or non-biologic Janus kinase (JAK) inhibitors) with methotrexate, if possible [7, 8].

Following these recommendations, Smolen et al. [1] reported that approximately 25% of patients reached remission on initial DMARD monotherapy with methotrexate or glucocorticoids within 6 months and roughly another 25% achieve LDA. Similar results have been reported using either combination csDMARDs and glucocorticoids or anti-TNF therapy plus methotrexate [16]. In a non-inferiority trial for patients with sub-optimal response to methotrexate, likelihood of continuation of therapy after 1 year of follow-up for triple therapy was shown to be significantly more durable than for methotrexate-etanercept [17]. These results illustrate that not all patients require biologic therapy to achieve treatment targets; however, for those failing to reach LDA on csDMARDs and combination therapies, their disease activities were moderate to high. Those who were initiating a biologic therapy in recent pivotal [15, 18–20] and real-world [21] trials had a median DAS28 of 5.4 at baseline. To achieve a meaningful response compatible with ACR and EULAR targets, the required decrease in DAS28 would be > 2.2 to reach LDA (DAS < 3.2).

A recent observational study of insurance plan and Medicare data found that anti-TNF drugs were the first-line

Table 1 Comparison of common disease activity measures and the ACR and EULAR guidelines

Disease state	Common disease activity measures used and ACR guideline thresholds CDAI ^a	Disease activity measures as per EULAR guidelines DAS28-ESR ^a	DAS28-CRP ^b	DAS28-ESR ^c	DAS28-CRP ^c
Remission	≤ 2.8	< 2.6	0–< 2.4	≤ 2.6	< 2.4
Low	> 2.8–10.0	≥ 2.6 –< 3.2	2.4–< 2.9 ^a	> 2.6– ≤ 3.2	≥ 2.4 – ≤ 2.7
Moderate	> 10.0–22.0	≥ 3.2 – ≤ 5.1	2.9–4.6	> 3.2– ≤ 5.1	> 2.7 and ≤ 4.1
High	> 22.0	> 5.1	> 4.6	> 5.1	> 4.1

^a From Table 3 in [7]

^b There are conflicting recommendations for the cut-off for all DAS28-CRP categories as follows: remission < 2.3 [10] or 2.4 [11]; low disease activity 2.7 [10] or 2.9 [11] and high disease activity 4.1 for [10] or > 4.6 [11]

^c [12]

Table 2 Comparison of Disease Activity Score (DAS) response criteria in rheumatoid arthritis (RA)

Components	ACR response criteria ^a	CDAI ^b	DAS28 response/EULAR ^c
Measures	Developed to measure the effectiveness of arthritis medication in clinical trials Measures improvement in tender or swollen joint counts (TJC/SJC) and improvement in at least three of the following parameters: <ul style="list-style-type: none"> • patient assessment • physician assessment • pain scale • disability/functional questionnaire • acute phase reactant (ESR^d or CRP^e) 	Developed to assess RA activity TJC28 ^f SJC28 ^g PaGH ^h PrGH ⁱ	TJC28 SJC28 Acute phase reactant (ESR or CRP) PaGH
Computation	Measures percent improvement, comparing disease activity at two timepoints (baseline and post-baseline) Depends on baseline DAS to determine ACR level of response	CDAI score = TJC28 + SJC28 + PaGH + PrGH	$DAS28 = 0.56 \times \sqrt{(TJC28)} + 0.28 \times \sqrt{(SJC28)} + 0.70 \times \ln(ESR) + 0.014 \times GH$
Comments	ACR20: 20% improvement in TJC or SJC and a 20% improvement in at least three of the five criteria.		DAS28-ESR and DAS28-CRP are not equivalent. DAS28-CRP gives slightly lower scores. ^j

a*American College of Rheumatology (ACR) [13]

b† Clinical Disease Activity Index (CDAI) [14]

c‡ European League Against Rheumatism (EULAR) [15]

d ESR is erythrocyte sedimentation rate

e CRP is C-reactive protein

f TJC28 is the number of tender joints

g SJC28 is the number of swollen joints

h PaGH is the patient global health assessment

i PrGH is the care provider global health assessment

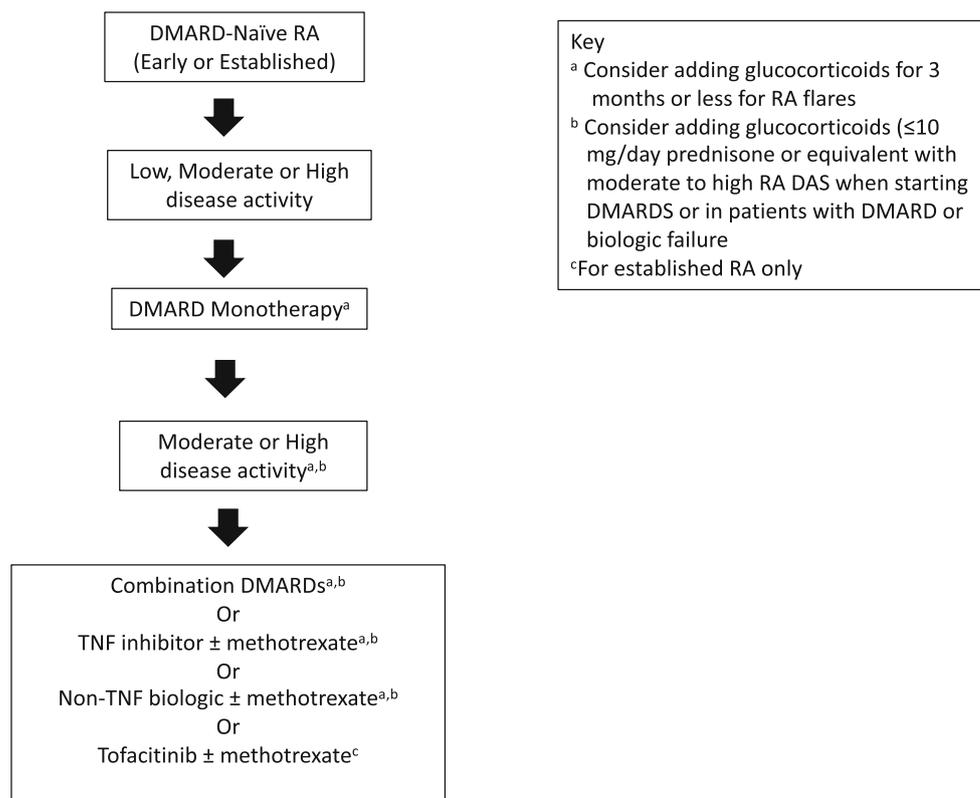
j [13]

treatment in 96% of patients who fail methotrexate therapy [22]. In pivotal trials, between 25 and 42% of anti-TNF-treated patients achieved ACR50 (Table 3) [47]. Drug trials typically enroll patients with moderate to severe disease activity and report the percentage of subjects who achieved ACR20, ACR50, or ACR70. In terms of achieving clinically meaningful change in disease activity, it is unlikely that an ACR20 response would be sufficient. Rather, patients realistically need to achieve at least an ACR50 to reach DAS scores compatible with remission, and close to ACR50 to reach LDA. ACR50 is therefore a better indicator of meaningful clinical progress and response than ACR20 and is more relevant to achieving treatment targets [48–50]. Patients who do not reach their treatment targets [50] are forced to cycle through multiple anti-TNF drugs while their disease has time to progress. A recent study compares the consistency of Boolean, CDAI, and SDAI regarding their stringency, power, and face value in assessing patients reaching remission. It finds that these three measures are roughly comparable when assessing remission, with Boolean being the most stringent and requiring the largest sample size for statistical power. However, CDAI is the most practical and preferred choice in clinical practice [51].

The goal of this paper is to review current use of anti-TNF drugs and their impact on clinically meaningful responses, discuss alignment with ACR's treat to target guidelines for RA, and propose a future alternative approach that allows more patients to reach their treatment targets using a PM approach.

Anti-TNF and alternative approved targeted therapies

In the late 1990s, anti-TNF therapies revolutionized RA treatment because significant numbers of patients achieved LDA for the first time. The first anti-TNF biologic to be tested in RA patients was infliximab (Remicade®, Janssen Biotech Inc., Horsham, PA) [11, 52]. Infliximab is a chimeric mouse-human monoclonal antibody that binds to soluble and membrane-bound TNF- α and blocks TNF- α signaling. With infliximab therapy, inflammation was reduced through down-regulation of pro-inflammatory cytokines, which resulted in decreased joint destruction [13] and fewer leukocytes in joints [53]. Overall, anti-TNF therapies have been shown to slow the progression of RA [2]. Maini et al. [11] combined infliximab with methotrexate and showed a response to this combination therapy in patients who did not respond well, or at all, to

Fig. 1 Rheumatoid arthritis current treatment guidelines

methotrexate monotherapy. This led to the approval of other anti-TNF drugs and small molecules with different molecular structures (Table 4). Other anti-TNF drugs currently available are etanercept (Enbrel®, Amgen, Thousand Oaks, CA) [54], adalimumab (Humira®, Abbott Laboratories, North Chicago, IL) [55], golimumab (Simponi®, Janssen Biotech Inc., Horsham, PA) [56], and certolizumab (Cimzia®, UCB, Inc., Smyrna, GA) [2, 36]. All of these anti-TNF drugs have molecular structures that target and neutralize the same pro-inflammatory cascade. For example, etanercept is an immunoglobulin G (IgG) fusion protein that consists of the extracellular portion of the human TNF receptor 2 (TNFR2) and the Fc portion and binds to TNF- α as a decoy receptor. Adalimumab and golimumab are human monoclonal antibodies that, like infliximab, bind to TNF- α , preventing downstream inflammatory response. Certolizumab is a Fab fragment of an anti-TNF- α monoclonal antibody that binds to soluble and membrane-bound TNF- α . While anti-TNF drugs are highly effective for some (Table 3), the majority of patients do not respond adequately to such therapies and switch to alternative approved targeted therapies (AATTs) to try to achieve their treatment targets.

AATTs are therapies that target specific molecules, other than TNF- α and its receptor, that are involved in the inflammatory cascade. AATTs inhibit pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1 (IL-1), or inhibit specific enzymes such as JAKs. Examples that target IL-6

are tocilizumab (Actemra®, Genentech, Inc., South San Francisco, CA) and sarilumab (Kevzara®, Sanofi-Aventis, Bridgewater, NJ). Abatacept (Orencia®, Bristol-Myers Squibb, Princeton, NJ) [57] inhibits T cell activation, tofacitinib (Xeljanz®, Pfizer, Inc., New York, NY) and baricitinib (Olumiant®, Eli Lilly and Company, Indianapolis, IN) target different JAK family members.

ACR responses to anti-TNF therapies

The ACR20, ACR50, and ACR70 responses of patients with RA treated with anti-TNF drugs were reviewed by Chung et al. [49], and Scott [58] and are summarized in Table 3. Taken together, these data indicate ACR50 is an attainable target for patients with RA and can be maintained for at least 3 years [59]. Unfortunately, only 25–42% of patients reach the treatment target of ACR50 (Table 3). This agrees with the percentage of patients estimated to obtain ACR20, 50 and 70 responses to these drugs at week 24 of treatment: ACR20, 13–46%; ACR50, 11–38%; ACR70, 8–20% [48] (Table 3).

Time to reach adequate response

According to EULAR recommendations [8], the time period to determine a clinical response to treatment is 3 months, after

Table 3 ACR Responses of First-Line FDA-Approved Therapies for Rheumatoid Arthritis

Drug	References	3 months						6 months					
		ACR20		ACR50		ACR70		ACR20		ACR50		ACR70	
Etanercept (Enbrel)	[23]	66 ^a (33) ^b	33 ^c	42 (0)	42	15 (0)	15	71 (27)	44	39 (3)	36	15 (0)	15
	[24]	–	–	–	–	–	–	73 (27)	46	48 (10)	38	21 (1)	20
Infliximab (Remicade)	[25]	–	–	–	–	–	–	58 (20)	38	28 (4)	24	11 (0)	11
	[26]	–	–	–	–	–	–	55 (19)	36	28 (5)	23	12 (0)	12
Adalimumab (Humira)	[27]	–	–	–	–	–	–	63 (30)	33	39 (10)	29	21 (3)	18
	[28]	–	–	–	–	–	–	62 (27)	35	36 (11)	25	18 (3)	15
Certolizumab pegol (Cimzia)	[29]	–	–	–	–	–	–	59 (14)	45	37 (8)	29	21 (3)	18
	[30]	–	–	–	–	–	–	–	–	35 (8)	27	–	–
Golimumab [#] (Simponi)	[31]	55 (33)	22	35 (10)	25	13 (4)	9	60 (28)	32	37 (14)	23	20 (5)	15
	[32]	–	–	–	–	–	–	–	–	38 (15)	23	–	–
	[33]	55 (45)	10	36 (18)	18	12 (8)	4	62 (49)	13	40 (29)	11	24 (16)	8
	[34]	35 (18)	17	16 (6)	10	10 (2)	8	34 (17)	17	18 (5)	13	12 (3)	9
	[35]	55 (33)	22	35 (10)	25	14 (4)	10	60 (28)	32	37 (14)	23	20 (5)	15
Abatacept (Orencia)	[36]	62 (37)	25	32 (8)	24	13 (3)	10	68 (40)	28	40 (17)	23	20 (7)	13
	[37]	54 (31)	23	18 (7)	11	6 (0)	6	–	–	–	–	–	–
	[38]	41 (18)	23	–	–	–	–	50 (20)	30	20 (4)	16	10 (2)	8
	[39]	38 (24)	14	9 (4)	5	2 (0)	2	61 (38)	23	30 (9)	21	10 (3)	7
Tocilizumab (Actemra)	[40]	–	–	–	–	–	–	55 (21)	34	35 (8)	27	16 (2)	14
	[41]	–	–	–	–	–	–	–	–	39 (10)	29	–	–
	[42]	74 (41)	33	53 (29)	24	37 (16)	21	–	–	–	–	–	–
	[43]	43 (38)	5	23 (13)	10	8 (3)	5	50 (30)	20	29 (16)	13	12 (5)	7
	[44]	62 (28)	34	32 (1)	31	27 (0)	27	59 (26)	33	44 (11)	33	22 (2)	20
Tofacitinib (Xeljanz)	[45]	55 (27)	28	29 (8)	21	11 (3)	8	50 (25)	25	32 (9)	23	14 (1)	13
	[46]	–	–	–	–	–	–	52 (28)	24	37 (12)	25	20 (3)	17

^a Percent response for maximum approved dose of medication plus methotrexate
^b Numbers in parentheses are percent response for methotrexate controls for each medication
^c Placebo adjusted value in percent (medication plus methotrexate minus methotrexate control)

which significant clinical improvement should be measurable (i.e., achieving LDA). Lack of response to treatment at 3 months indicates a low probability of achieving a clinical response after 1 year of the same treatment [25]. Therefore, the 3-month response rate is used as a surrogate marker of long-term outcome [16, 50]. This coincides with both ACR and EULAR guidelines, which recommend evaluating response to treatment at 3 months [7, 8] and to continue treatment for patients who respond to that therapy.

Switching bDMARD due to inefficacy: within and across mechanistic category

A thorough classification of patient populations that do not respond to anti-TNF therapy is important for a better understanding of the disease mechanism and is critical for finding the most efficient therapies for such individuals. Patients who do not respond to anti-TNFs (non-responders) can be classified into two groups of patients: those who are primary non-responders and those who initially respond but then exhibit

secondary loss of response. Primary non-responders may or may not show some initial response, but never reach their treatment target with anti-TNFs. If these patients do not respond to one anti-TNF therapy, they are not likely to respond to other anti-TNFs. This is probably because the chronic inflammation caused by their disease is not sufficiently driven by TNF- α -dependent biological processes. In contrast, loss of response occurs in people who respond initially to treatment, but the response diminishes over time and is often due to the development of neutralizing or anti-drug antibodies [1]. After a loss of response to one anti-TNF, switching to another anti-TNF may recover progress to the treatment target in secondary loss of response patients [60]. However, only a small number of primary non-responsive patients who switch to a second anti-TNF achieve a significant clinical response, and the clinical benefit for patients who cycle to a third anti-TNF is negligible [60]. Therefore, there is a clear unmet need for a PM approach to predict response to anti-TNF therapies before treatment initiation so that predicted primary non-responders can be offered AATs.

Table 4 FDA-Approved Therapies for the Treatment of Rheumatoid Arthritis

Biologic type	Drug name (brand name)	Year FDA-approved	Molecular construct	Mechanism of action	First or second line ^a	Route of administration
TNF inhibitors	Etanercept (Enbrel)	1998	IgG ^b fusion protein with TNF ^c receptor	Binds to TNF α	First line	SC ^d
	Infliximab (Remicade)	1998	Chimeric mouse human Ab ^c	Binds to soluble and membrane bound TNF α	First line	IV ^f
	Adalimumab (Humira)	2002	Human mAb ^g	Binds to TNF α	First line	SC
	Certolizumab pegol (Cimzia)	2008	Pegylated Fab of humanized TNF mAb	Binds to soluble and membrane bound TNF α	First line	SC
AATT ^h	Golimumab (Simponi)	2009	Human mAb	Binds to soluble and membrane bound TNF α	First line	SC, IV
	Anakinra (Kineret)	2001	Non-glycosylated recombinant human IL-1 ⁱ receptor antagonist	Binds to IL-1 receptor	First line	SC
	Abatacept (Orencia)	2005	Ig fusion with extracellular domain of CTLA ^j -4	CD-8 and CD-86 (CTLA-4)	First line	SC, IV
	Rituximab (Rituxan)	1997	Chimeric mAb	Targets cells with CD20 surface receptors	Second line	IV
	Tocilizumab or atlizumab (Actemra)	2010	Recombinant anti-human IL-6 ^k receptor mAb	Binds to IL-6 receptor	Second line	SC, IV
	Sarilumab (Kevzara)	2017	Recombinant anti-human IL-6 receptor mAb	Binds to IL-6 receptor	First line	SC
	Tofacitinib (Xeljanz)	2012	Small molecule	Binds to JAK ^l 1 and 3	First line	Oral
	Baricitinib (Olumiant)	2018	Small molecule	Binds to JAK1 and 2	Second line	Oral

^a First line: approved for inadequate responder to MTX; Second Line: approved for inadequate responder to anti-TNF

^b IgG = immunoglobulin G

^c TNF-tumor necrosis factor

^d SC = sub-cutaneous

^e ab = antibody

^f IV = intravenous

^g mAb = monoclonal antibody

^h AATT = alternative approved targeted therapy

ⁱ IL-1 = interleukin 1

^j CTLA = cytotoxic T lymphocyte-associated protein

^k IL-6 = interleukin 6

^l JAK = Janus kinase

New directions for treatment of RA

Currently, there is no way to determine which RA patients will respond to a targeted treatment. In clinical practice, it is common for non-responding patients to cycle among several anti-TNFs prior to switching to a drug with a different mechanism of action (MOA) [61]. There is a clear unmet need for a PM approach to predict response to anti-TNF therapies before treatment initiation to avoid harming patients, especially those who respond partially or not at all to therapy and continue to try various treatments while their disease progresses [4]. Meeting this need would require defining biomarker signals that predict a patient's response to therapy, so that medical treatment can be customized to each individual patient. This

PM approach is currently in use in oncology [4], where the therapies are prescribed to patients with specific genetic markers. There are also a few positive examples of PM approaches in RA where a number of different biomarkers are being utilized or have been explored. These include biomarkers for seropositivity [62], genetic risk loci such as HLA-DBR1, and the group of alleles referred to as shared epitope. In total, genetic approaches to identify biomarkers of response have been taken to address anti-TNF [63] and tocilizumab [64, 65] interventions. Many have attempted to utilize gene expression data to identify biomarkers of biologic therapeutic response [66], but these have been limited in the main by modest sample size. In addition, the production of antibodies against biological agents, such as those to anti-

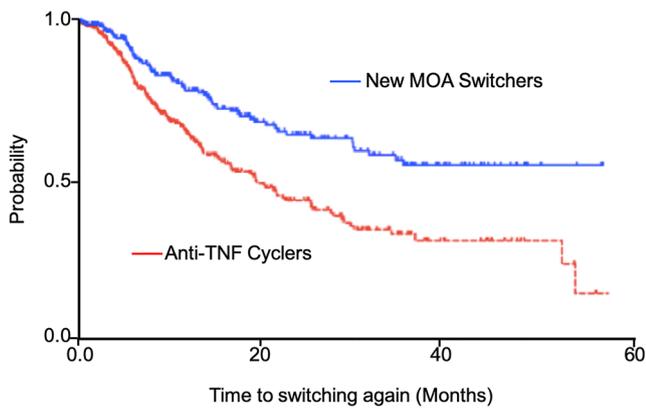


Fig. 2 Switching mechanism of action

TNFs, have been associated with loss of patient response to treatment [67]. Although disease-gene associations that may potentially lead to a greater understanding of RA have been established, there is yet a lack of a predictive classifier with meaningful clinical utility that can predict treatment response.

To adapt this approach to RA, an individual patient’s molecular signature of gene expression would be predictive of their response to a particular treatment [4]. Such a test to determine if a patient will respond to a particular therapy is currently under development [3].

Predicting a patient’s response to anti-TNF drugs is important because roughly 90% of patients with RA receive anti-TNF therapy as the first-line biological DMARD (bDMARD). Detecting patients who will not respond to anti-TNF therapy (primary non-responders) would allow more rapid achievement of treatment targets than current practice because clinicians can treat predicted primary non-responders with an AATT that they are more likely to respond to rather than cycling through the same ineffective MOA. As can be seen in Fig. 2, patients who cycle through anti-TNFs, rather than switching to another MOA, switch classes again much earlier than non-cyclers on AATTs, almost certainly for inefficacy. The data summarized in Table 5 shows that the response rate is higher when switching mechanism of action vs switching within the anti-TNF class.

The cost of anti-TNF cycling

For non-responders, prolonged anti-TNF treatment is costly and unnecessary and may be associated with potentially harmful side effects such as infusion or injection site reactions, infections, tuberculosis, malignancy, lupus-like syndromes, demyelinating syndromes, and/or the appearance of blocking auto-antibodies [1, 3, 26]. Hence, long-term treatment is not recommended for patients who do not respond to therapy [6]. Yet, it is common practice for primary non-responders to anti-TNF drugs to receive multiple anti-TNFs for prolonged periods, often years [61].

A randomized clinical trial compared the efficacy of a non-anti-TNF biologic with a second anti-TNF drug for patients who failed to meet their treatment targets on anti-TNFs [68]. After 24 weeks of treatment, patients who had previously responded insufficiently to an anti-TNF reported a better response on a non-anti-TNF therapy compared to a second anti-TNF (70% vs 52%, achieving a good or moderate EULAR response; 45% vs 28%, achieving low disease activity; 27% vs. 19%, achieving remission) [68]. However, when comparing only those subjects achieving EULAR good responses, the differences were more striking. At both 12 and 24 weeks of treatment, the proportion of EULAR good responders on the non-anti-TNF alternative was almost double than that on a second anti-TNF (after 24 weeks 39% on non-anti-TNF alternatives vs 21% on a second anti-TNF and after 12 weeks 28% on non-anti-TNF alternatives vs 13% on a second anti-TNF). This clinical trial, like others comparing second-line therapy options, could not include a true placebo arm. As a result, the reported response rate is likely an over-estimation of the actual response rate. Other studies [23, 24, 25] reported switching from an anti-TNF medication to the anti-CD20 therapy, rituximab (Rituxan), was associated with better clinical outcomes than switching to another anti-TNF therapy. Furthermore, switching to a treatment with AATT is more effective than cycling to another anti-TNF in patients with an inadequate response to the initial anti-TNF drug [27, 61]. Together, these data demonstrate that switching to AATT therapy after anti-TNF treatment failure improves clinical outcomes for patients with RA [26, 60, 68] and is more efficient in terms of healthcare

Table 5 Response rate comparisons for TNF-IR^a patients who switched to a second anti-TNF vs switching to a different mechanism of action

Reference	Endpoint	n	Country	% TNF	% AATT ^{a,b}	% Improvement in response rate
[67]	ΔDAS28-ESR > 1.6 at 6 months	728	Global	29.4	38.5 ^{a,b}	31
[26]	EULAR good at 6 months	300	France	21	39	86
[68]	EULAR good at 6 months	1328	UK	13.5	17.1 ^{a,b}	27

^a TNF-IR = inadequate responders to anti-TNF therapies

^b In studies 36 and 39 rituximab was prescribed as the only alternative mechanism of action, in study 38 the medication used was one of the AATTs in Table 4 prescribed by the rheumatologist

costs and medication compliance [61] than TNF-cycling. This is supported by ACR and EULAR guidelines, which recommend AATTs as an option to an anti-TNF as a first-line therapy, or as a second-line therapy after one anti-TNF has been tried, instead of switching to a second anti-TNF [61].

Summary and conclusions

ACR50 is a definition of meaningful clinical response in RA sufficient for most patients with moderate to severe disease activity to reach treatment targets. The time to assess whether a patient is responding adequately to a therapy is 3 months. In the pivotal trials that supported anti-TNF therapy approval, 58–73% of patients failed to reach ACR50 (Table 3). Approximately 90% of biologic-naïve RA patients with moderate to severe disease activity still receive such therapies as first-line biologic therapy [3].

Cycling patients through multiple anti-TNFs does not appear to significantly improve their clinical response rate and exposes them to disease progression and costly and ineffective treatments with potentially harmful side effects. By switching anti-TNF primary non-responders to an AATT as their first-line therapy, the likelihood of a meaningful response increases (Table 5). A PM test is required to achieve this goal and would allow rheumatologists to start treatment for biologic-naïve RA patients with medications more likely to produce a positive clinical response the first time. When this goal is achieved, it will usher in an era of PM for autoimmune diseases such as RA, leading to a significant increase in the number of patients achieving their treatment target on their first targeted therapy. The ultimate goal, however, remains to find a PM test that predicts for all approved therapeutic options and not just for anti-TNFs.

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Conflict of interest All authors are full-time employees of Scipher Medicine Corporation.

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