Optimizing Use of Tumor Necrosis Factor Inhibitors in the Management of Immune-Mediated Inflammatory Diseases

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ABSTRACT. The introduction of anti-tumor necrosis factor (TNF) therapies has dramatically improved the treatment of immune-mediated inflammatory diseases and provides treatment options for patients who do not respond to conventional disease-modifying antirheumatic drugs. However, the use of anti-TNF therapies still needs to be optimized. Dropoff rates, patients' lack of response, and toxicity are issues that need to be addressed to render these therapies more effective for more patients. (J Rheumatol 2010;37 Suppl 85:40–52; doi:10.3899/jrheum.091464)

Key Indexing Terms:
ANTI-TUMOR NECROSIS FACTOR DISEASE-MODIFYING ANTIRHEUMATIC DRUGS
IMMUNE-MEDIATED INFLAMMATORY DISEASES

Although many patients benefit from anti-tumor necrosis factor (TNF) therapy, there are significant numbers of patients who discontinue their use because of lack or loss of response, let alone side effects. High dropoff rates have been observed not only in clinical trials but also in clinical practice, including a significant number of patients (~20%–30%) who do not initially respond to therapy[1]. Issues such as patient compliance, immunogenicity, and possibly involvement of cytokines aside from TNF contribute to the high dropoff rates for inefficacy. Several predictors of response have been identified, which may aid physicians in identifying those patients who will most benefit from anti-TNF therapy. In addition, there is evidence that switching from one TNF inhibitor due to lack of efficacy does not preclude successful treatment with a secondary TNF inhibitor. However, it has been documented that patients who initially respond to an anti-TNF agent and subsequently lose their response (secondary nonresponders) tend to achieve better response rates receiving a second anti-TNF agent than those who do not respond at all to initial anti-TNF treatment (primary nonresponders). Some patients taking these agents may ultimately develop toxicities such as infection, autoimmunity, demyelinating disease, and malignancy. These observations indicate a need to optimize the use of anti-TNF therapies in the treatment of immune-mediated inflammatory diseases (IMID).

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Dropoff Rates from Different Studies

Currently available anti-TNF agents appear to have similar efficacy in RA, with at least a 20% improvement in disease activity observed in up to 70% of patients[2]. Despite good efficacy, there are significant discontinuation rates in patients treated with anti-TNF therapies due to either lack of efficacy or appearance of adverse events.

A study using data from the British Society for Rheumatology Biologics Register (BSRBR) analyzed the dropoff rates in patients with rheumatoid arthritis (RA; Table 1) under treatment with adalimumab, etanercept, or infliximab[1]. It was observed that slightly more than one-third of patients discontinued their primary anti-TNF therapy.

Similar dropoff rates were observed for RA patients within the Swiss Clinical Quality Management RA cohort receiving etanercept, infliximab, and adalimumab[3]. Lack of efficacy represented the largest single cause of treatment discontinuation, followed by adverse events. Discontinuation rates differed between anti-TNF agents, with infliximab, a chimeric antibody, having the shortest reten-

Table 1. Details of treatment with the first anti-tumor necrosis factor-α agent. Drop-off rates (discontinuations) for patients with rheumatoid arthritis (RA) from the British Society for Rheumatology Biologics Register (BSRBR). There was a 30% discontinuation rate for patients receiving adalimumab (12% due to lack of efficacy, 11% due to adverse events, and 7% for other reasons), a 29% discontinuation rate for patients receiving etanercept (10% due to lack of efficacy, 14% due to adverse events, and 5% for other reasons), and a 42% discontinuation rate for patients receiving infliximab (15% due to lack of efficacy, 17% due to adverse events, and 10% for other reasons). From Hyrich, *et al*, Arthritis Rheum 2007;56:13–20[1]; with permission from John Wiley and Sons, Inc.

	Total Cohort	Adalimumab	Etanercept	Infliximab
Total starts, no.	6739	876	2826	3037
Still taking agent April 30, 2005, no. (%)	4379 (65)	611 (70)	2004 (71)	1764 (58)
Mean/maximum duration of therapy, mo*	13/61	10/26	12/56	16/61
Mean/maximum duration of therapy, mo	15/61	11/26	13/60	18/61
Discontinuations, no. (%)	2360 (35)	265 (30)	822 (29)	1273 (42)
Stopped 1st agent for inefficacy, no. (%)	841 (12)	109 (12)	277 (10)	455 (15)
Switched to 2nd agent, no.	503	61	137	305
Stopped 1st agent for adverse event, no. (%)	1023 (15)	98 (11)	405 (14)	520 (17)
Switched to 2nd agent, no.	353	25	74	254

* First course only.

tion rate. Infliximab also demonstrated an increased risk of adverse events as compared to etanercept and adalimumab, mostly due to an increased risk of infusion or allergic reactions.

Data collected from longterm studies suggest discontinuation rates as high as 36%, 50%, and 61% at 6, 12, and 24 months, respectively, for RA patients receiving anti-TNF therapy[4]. Other studies, however, show more favorable outcomes[5]. Flendrie, *et al*[6] noted a 50% dropoff rate at 37 months. Zink, *et al*[7] found that one-quarter of patients discontinued therapy after 12 months. The dropoff rates in a study by Ostergaard, *et al*[8] were 30% at 52 weeks and 50% at 134 weeks. In the USA, Stern and Wolfe[9] revealed a 25% rate of discontinuation after 2 years of therapy. As dropoff rates may reflect different attitudes and actions of rheumatologists and patients, which may vary according to clinical settings, it is important to identify reasons underlying high dropoff rates in order to optimize the use of anti-TNF therapies in all patients.

In an extended clinical study of etanercept, 39.8% of patients with early RA (ERA) and 34.6% of patients with long-standing RA (LRA) remained on therapy at 10 years (Figure 1)[10]. The most common reasons patients discontinued therapy were adverse events (ERA 13%, LRA 14%) or

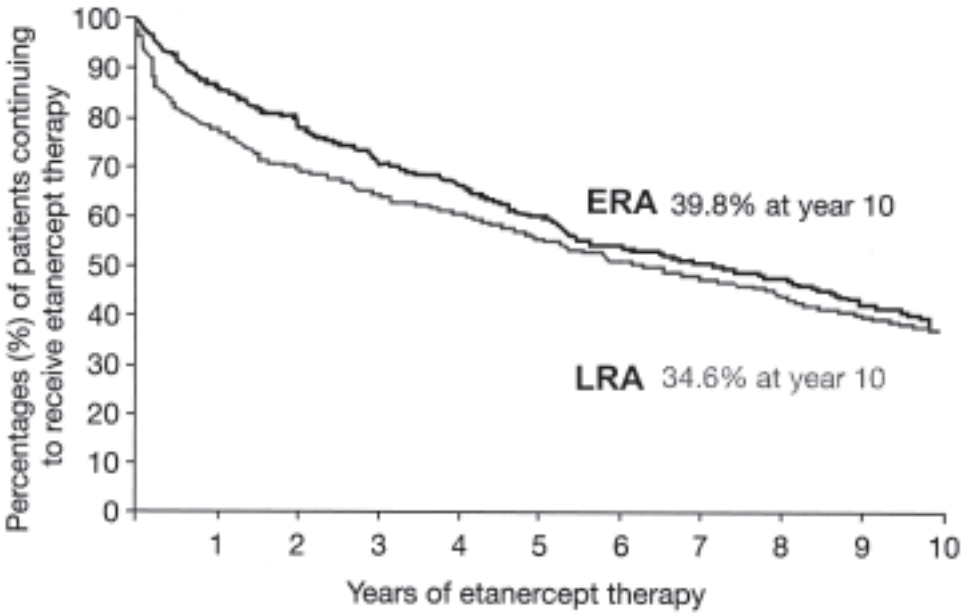

Figure 1. Continuation rates for etanercept over 10 years. At 10 years, 39.8% of patients with early RA (ERA) and 34.6% of longstanding RA (LRA) were continuing etanercept treatment[10]. From Weinblatt, *et al*, Arthritis Rheum 2008;58 Suppl:S540. With permission of John Wiley & Sons, Inc..

lack of efficacy (ERA 8%, LRA 13%). Patients enrolled in the ARMADA, DE019, STAR, DE005, and DE037 randomized, controlled trials for adalimumab (Figure 2) were followed for up to 7 years[11]. Entering year 7, 58% of patients continued therapy. These data show comparable durability of response for etanercept and adalimumab.

Why some patients do not respond. The efficacy of TNF inhibitors varies in different IMID, with some inhibitors having a clear benefit in some IMID and having little or no effect in others. In addition, about one-third of patients do not initially respond to treatment. Issues such as lack of patient compliance, immunogenicity, and involvement of cytokines aside from TNF may be responsible for a lack of response to anti-TNF therapy and high dropoff rates.

Compliance. The International Society for Pharmacoeconomics and Outcomes Research defines "medication compliance" or "adherence" as "the degree or extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen"[12]. Compliance is an enormous problem in the treatment of inflammatory bowel disease (IBD), with studies indicating that patients often take only 40%–80% of their prescribed dosage of medication[13]. This affects not only the course of the disease but also the healthcare system as a whole. Lack of compliance may be attributed to disease-, treatment-, or patient-related factors (Figure 3)[14].

Disease-related factors that may affect compliance include severity, extent, and duration of disease; frequency, intensity, and duration of flares; and type and severity of complications. For example, it has been observed that patients with ulcerative colitis (UC) for fewer than 10 years are more likely to take their medication as prescribed than patients with longer disease duration[15]. Patients with quiescent UC are more likely to be noncompliant than those with active disease[16]. There also exists a relationship between a more complicated disease course and better medication-taking behavior[17].

Treatment-related factors that may affect compliance include dose regimen, cost of treatment, and adverse reactions. An inverse relationship between daily dose regimen and medication persistence has been observed in patients with UC receiving maintenance mesalamine > 6 months[16]. The overall adherence rate was found to be 40%, and the median amount of medication dispensed per patient was 71% of the prescribed regimen. These findings are in agreement with other studies showing that 40%–60% of patients taking oral therapies for Crohn's disease (CD) are compliant.

In comparison to oral therapies, adherence rates are much higher in patients receiving either intravenous or subcutaneous therapies. Kane and Dixon[18] observed an adherence rate of 96% in a study of patients taking infliximab for CD. Compliance rates are equally high for patients taking infliximab, etanercept, or adalimumab to treat RA (78.0%, 72.8%, and 70.8%, respectively)[19], or to treat psoriatic arthritis (mean compliance 75.5%)[20].

Cost of anti-TNF therapies remains an important obstacle to medication adherence, with lack of coverage and high co-payments being the major contributors. For example, in a study of 326 Canadian patients diagnosed with IBD, Ediger, *et al*[21] reported that cost was the most commonly cited obstacle to adherence. Although one study determined that most patients pay less than $20/week for biologics, some patients have high out-of-pocket expenses, which may be associated with lower medication compliance[22].

Fear of adverse effects of medication may also have a negative effect on compliance. A study by Ediger, *et al*[22] estimated that 13% of patients with IBD cited adverse events as an obstacle to taking medication regularly as pre-

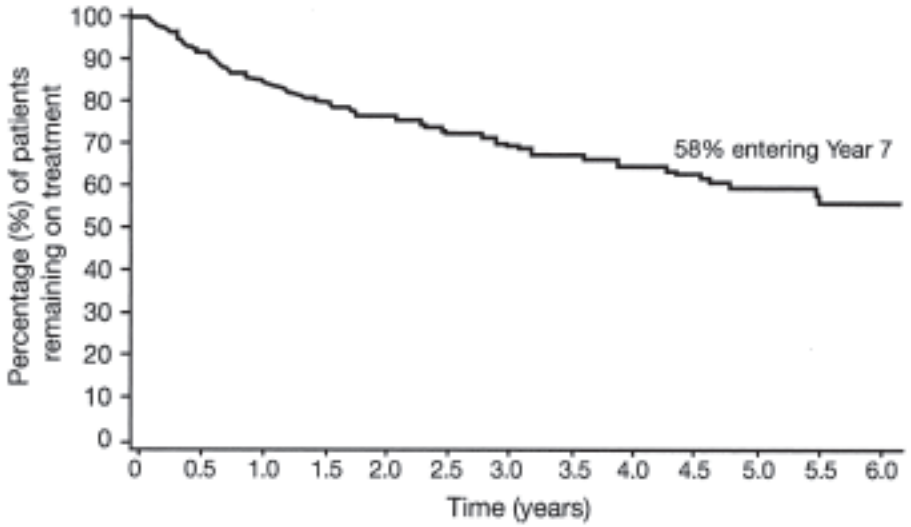

Figure 2. Retention among patients receiving adalimumab for 7 years; 58% of patients remained on therapy entering Year 7. From Weinblatt, *et al*, Arthritis Rheum 2007;56 Suppl:S163[11]; with permission of John Wiley & Sons, Inc.

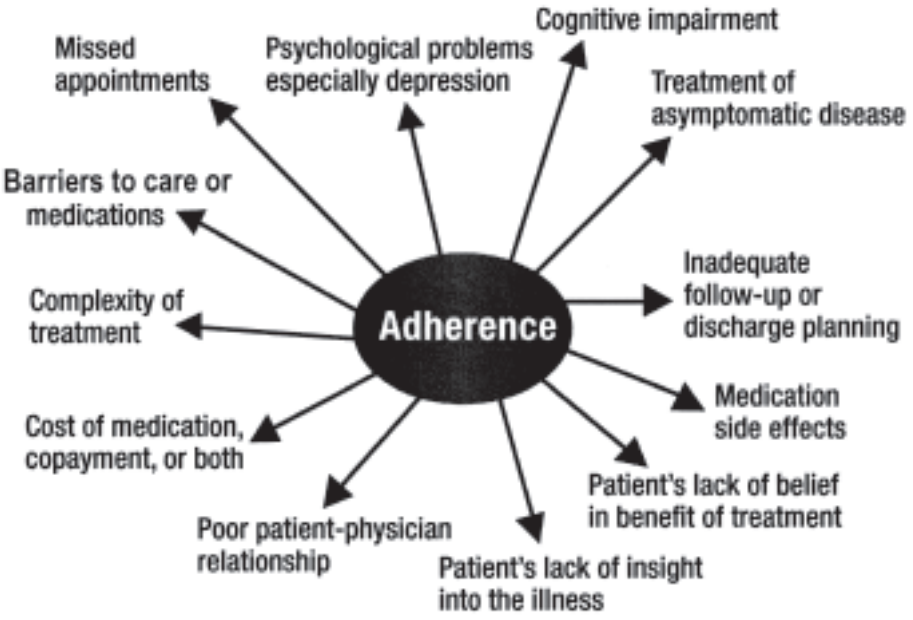

Figure 3. The multifactorial and complex nature of patient compliance[14].

scribed. Patients identify safety concerns as an important factor in determining adherence, and 74% of patients with UC consider lack of side effects to be very important when choosing treatment for their disease[23]. Physicians may contribute to lack of patient understanding by failing to sufficiently explain the potential adverse events and benefits of a medication[14].

Individual and psychosocial characteristics and the patient-physician relationship also have a strong influence on compliance. Noncompliance in UC patients is associated with age, full-time employment, symptomatic remission, history of taking > 4 concomitant medications, male gender, new patient status, psychiatric comorbidity, disease duration, variations in class of medication taken, and single (i.e., unmarried) status[24-28]. Although the data in the literature are inconclusive, individual patient perceptions and beliefs appear to influence the way that they adhere to prescribed therapies. Of particular importance is patient denial of illness and incomprehension for the need to continue taking medication during times of remission[24,25,27].

The role of the physician-patient relationship in determining nonadherence was evaluated in a prospective study involving 153 patients with IBD[25]. The study findings support the belief that adherence depends on effective patient-physician dialogue. Noncompliance was high at 41%, which is similar to the rate determined by other studies in the literature, with 33% of patients unintentionally nonadherent to medication and 15% intentionally nonadherent. Higher patient-physician discordance increased the risk of intentional nonadherence in all patients, as well as the risks of overall and unintentional nonadherence in psychologically nondistressed patients[25].

Therefore, interventions that facilitate adherence to medication are more effective if they address the patient's beliefs and perceptions, thereby motivating the patient to start and continue with the agreed treatment plan[28].

Immunogenicity. Immunogenicity — the ability of a substance to evoke an immune response, or the degree to which it can bring about this response — is not an intrinsic feature of a molecule but is defined by the interaction among the immunogenic molecule, the host immune system, and the biological context in which the interaction occurs. The clinical consequences of immunogenicity are adverse events (e.g., injection site/infusion site reactions), loss of efficacy over time, increased dosing requirement, and ultimately switching to another therapy.

Infliximab, a chimerical monoclonal antibody with 75% human peptide sequences and 25% mouse peptide sequences (Figure 4)[29], has been shown to be the most immunogenic of the anti-TNF inhibitors. Studies demonstrated the prevalence of anti-infliximab antibodies varying from 12% to 44% in patients with RA[30-33]. Antibody-positive patients were more likely to have higher rates of clearance, have reduced efficacy, to experience infusion reactions, to be significantly more often classified as nonresponders, and to require dose escalation to respond to therapy[30,33,34]. In some patients, concomitant use of methotrexate was associated with reduced development of antibody.

Adalimumab, like infliximab, is a monoclonal antibody (Figure 4) that blocks the TNF molecule directly. However, its completely human composition makes it less immunogenic. Some immunogenicity of adalimumab has been reported, possibly related to development of anti-idiotypical antibodies[32,35-37]. About 5% of RA patients develop neutral-

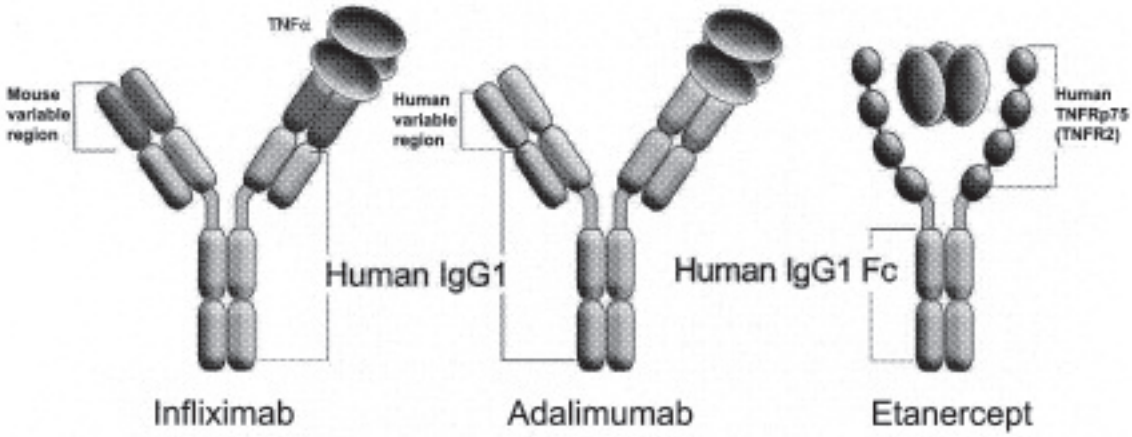

Figure 4. Structures of the tumor necrosis factor (TNF) inhibitors infliximab, adalimumab, and etanercept. Infliximab is a chimerical monoclonal antibody with 75% human peptide sequences and 25% mouse peptide sequences and is the most immunogenic. Adalimumab is a monoclonal antibody like infliximab; its completely human composition makes it less immunogenic. Etanercept, also completely human, is a dimeric fusion protein made up of 2 extracellular domains of the human TNFR2 receptor linked to the Fc portion of a type 1 human immunoglobulin and is less immunogenic than infliximab[29]. From Anderson PJ, Semin Arthritis Rheum 2005;34 Suppl 1:19-22[29]; with permission from Elsevier.

izing antibodies, which are not associated with increased adverse events but are associated with increased clearance and reduced efficacy of adalimumab[38]. Concomitant use of methotrexate reduces, and every-other-week dosing increases, the development of antibodies to adalimumab.

Etanercept, a dimeric fusion protein made up of 2 extracellular domains of the human TNFRII receptor linked to the Fc portion of a type 1 human immunoglobulin (Figure 4), is less immunogenic than infliximab. Anti-etanercept antibodies were detected in 2%–6% of patients with RA[39,40]. Detected antibodies were all non-neutralizing and had no apparent correlation to clinical response or adverse events; however, the longterm immunogenicity of etanercept is unknown[39,41].

Factors affecting immunogenicity of anti-TNF inhibitors include the degree of self-similarity, genotype of the host, formulation/dose, and host immunocompetence. The degree of self-similarity is of paramount importance in the development of immunogenicity. Chimeric antibodies containing murine particles offer greater capacity of inducing development of human anti-mouse antibodies (Figure 5); however, human anti-human antibodies (HAHA) (Figure 5) can be formed in the presence of humanized monoclonal antibodies[29]. HAHA bind to the unique antigen-binding site to which the immune system has not been tolerized. The consequences of developing immunogenicity include loss of effectiveness over time (with concomitant requirement for increased dosage) and induction of allergic reactions.

The genotype of the host plays an important role in determining whether a given substance will stimulate an immune response. Genetic control of immune responsiveness is controlled by genes mapping within the major histocompatibility complex region, therefore an individual lacking the genetic information required to synthesize T or B lymphocytes of a particular specificity will be unable to stimulate an immune response (hole in the repertoire).

The formulation and dose of a given anti-TNF inhibitor influences the development of immunogenicity. Whereas aggregation and the presence of adjuvants can increase immunogenicity, pegylation (as in the case of certolizumab pegol) can mask the molecule and hence reduce immunogenicity. There is evidence that aggregates existing in a commercial formulation, as well as aggregates induced by freeze-thawing and agitation stresses, can increase immunogenicity[42]. Low infliximab dose has been associated with production of anti-infliximab antibodies[43,44]. Maini, *et al*[45] observed an inversely proportional relationship between rate of antibody response and dosage, with 53%, 21%, and 7% of patients developing immunogenicity following treatment with 1, 3, and 10 mg/kg, respectively.

Other cytokines. Research over the past 2 decades has highlighted the important role of cytokines other than TNF in the pathogenesis of RA. Interleukin 1 (IL-1), IL-6, and IL-15 are potential therapeutic targets[46], as are IL-12 and IL-18[47]. With the development of the IL-1 inhibitor anakinra[48] and the IL-6 inhibitor tocilizumab for the treatment of RA[49], it follows that other cytokine inhibitors might be useful for those patients who do not respond to anti-TNF therapies.

Predictors of Response/Treatment Outcomes

In daily clinical practice, clinicians are faced with the challenge of predicting which patients will and which will not adequately respond to anti-TNF therapy. These therapies are expensive and are associated with harmful side effects. Therefore, it is important to foresee both pros and cons of using a particular anti-TNF agent in a particular patient. A

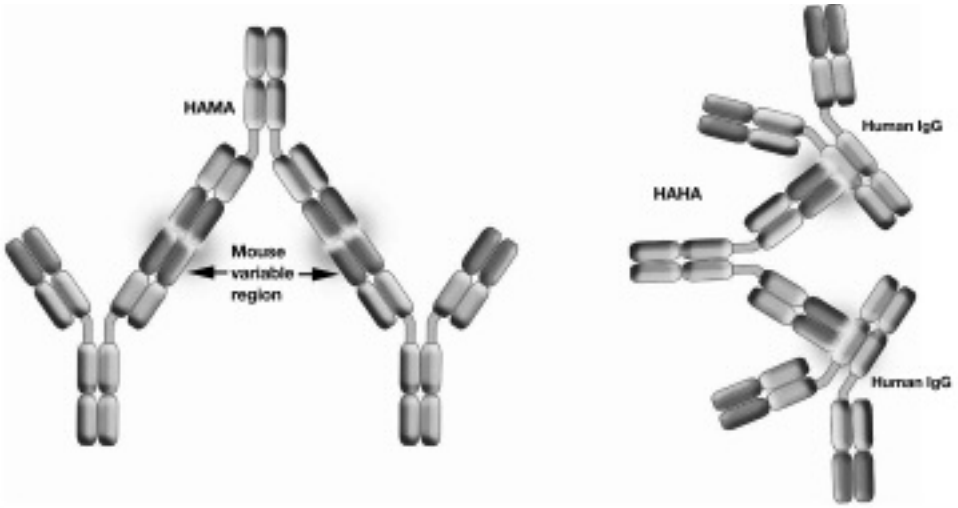

Figure 5. Development and binding of antibodies against anti-TNF inhibitors. HAMA: human anti-mouse antibodies; HAHA: human anti-human antibodies. From Anderson PJ, Semin Arthritis Rheum 2005;34 Suppl 1:19-22[29]; with permission from Elsevier.

patient's overall health status, habits (i.e., smoking), medical history, and presence of comorbidities, as well as preference (i.e., intravenous vs subcutaneous administration) should be taken into consideration. Several studies have analyzed patient characteristics and biochemical findings that point to those individuals who will most likely respond to treatment.

Hyrich, *et al*[50] analyzed data collected from the BSRBR on RA patients receiving etanercept or infliximab and achieving a minimum 6 months of followup. The findings of the study identified higher European League Against Rheumatism (EULAR) response or remission (defined as a Disease Activity Score < 2.6) at 6 months in patients who were male, nonsmokers, had lower baseline Health Assessment Questionnaire (HAQ) score, and were concurrently treated with methotrexate or nonsteroidal antiinflammatory drugs. There was no association with age, disease duration, rheumatoid factor, and previous number of DMARD, and no difference observed between etanercept and infliximab. A portion of these findings were supported in a study analyzing data from the South Swedish Arthritis Treatment Group (SSATG) on RA patients treated with etanercept, infliximab, or adalimumab[51]. Predictors of higher EULAR response or remission were concurrent methotrexate or DMARD use, lower baseline disease activity, and lower baseline HAQ score.

An observational cohort from southern Sweden showed that response to treatment at 6 and 12 weeks of therapy predicted continuation of anti-TNF therapy in RA patients[52]. It was also shown that remaining in a high disease activity state predicted drug discontinuation at both time points. Other predictors of discontinuation were identified in the Brigham RA Sequential Study and included higher physician global scores, higher Rheumatoid Arthritis Disease Activity Index scores, and higher number of TNF inhibitors previously used. Prior use of synthetic disease-modifying antirheumatic drugs (DMARD) and more years of cumulative methotrexate use were inversely associated with discontinuation of TNF inhibitor[53].

Disease duration and C-reactive protein (CRP) levels have been studied as predictors of response in patients with RA. Disease duration is a predictor of response, with better outcomes observed in adalimumab- or infliximab-treated RA patients with early disease compared to late disease[54,55]. CRP profiles serve as a predictor of infliximab and etanercept response patterns in patients with DMARD-resistant RA[56]. Failure at Week 2 following the first infliximab infusion to lower CRP levels predicted a nonresponse at Week 12. Success at 12 weeks in lowering CRP levels in nonresponders predicted a "late" response to treatment continued up to 24 weeks. Interestingly, nonresponse to infliximab did not correspond with nonresponse to etanercept. Patients who did not respond to infliximab and did not experience decreases in CRP levels at Week 12 responded to etanercept and showed a significant decrease in CRP levels.

Detectable trough serum levels of infliximab predicted clinical remission at 12 months in CD patients treated with scheduled maintenance infusions of infliximab[57]. Additionally, the median serum CRP levels were lower in patients with a detectable serum trough concentration, and a higher proportion of these patients achieved normal CRP levels. Greater CRP concentration, HLA-B27 positivity, younger age, and TNF antagonist naivety were the predictors of good clinical response and partial remission in patients with ankylosing spondylitis treated with adalimumab[58].

Preliminary data from several pharmacogenetic studies have identified genetic factors that may predict patient response. According to Miceli-Richard, *et al*[59], a single TNF locus haplotype (–238G/–308G/–857C) present on both chromosomes is associated with a lower response to adalimumab in patients with RA. Another study identified that a certain combination of alleles for TNF (–308 TNF1/TNF1) and IL-10 (–1087 G/G) was associated with good responsiveness to etanercept in RA patients[60]. In addition, a combination of alleles influencing IL-1 receptor antagonist (IL1Ra) and production of tissue growth factor-ß1 (A2 allele for IL1RN and rare C allele in codon 25 of TGFB1 gene) was associated with nonresponsiveness to etanercept. In luminal CD, 2 genetic predictors for response to infliximab were identified[61]: the Fas ligand –843 CC/CT genotype predicted a response to therapy, as did the caspase-9 93 TT genotype. The same Fas ligand –843 CC/CT genotype was a predictor of response in fistulizing CD.

Recently, Oliveira, *et al*[62] reported upregulation of 5 genes (*CALM1*, *CAMK2B*, *BIN1*, *CCL4*, and *MAP2K6*) in RA patients who responded to anti-TNF therapy. On the other hand, in the nonresponders these same genes were downregulated. It is important to note that these genes are involved in different pathways and cellular processes such as growth and cell cycle (*CALM1*), macrophage response to inflammatory stimuli (*CAMK2B*), acute inflammatory response (*CCL4*), tumor suppressor activity (*BIN1*), and apoptosis (*MAP2K6*). These data further demonstrated that gene expression profiling can be a useful tool in identifying RA patients likely to respond to anti-TNF-α therapy.

PRIMARY VERSUS SECONDARY NONRESPONDERS — DATA ON SWITCHING

Patients not responding to anti-TNF therapies can be divided into 2 groups. While primary nonresponders do not respond to initial anti-TNF therapies, secondary nonresponders initially respond but subsequently lose their responsiveness. Although all anti-TNF inhibitors exert their beneficial effects through blockade of TNF, there are differences in their site of action and molecular structure. In individual patients, these differences may explain the differential response to these agents, although there is no direct evidence to support this. Reports suggest that initiating therapy with a second anti-TNF agent in patients who have failed therapy with a first agent may be beneficial and is not associated with an increased rate of adverse events with the second agent[1].

Using the BSRBR, Hyrich, *et al*[1] studied a prospective cohort of 6739 RA patients who were newly prescribed an anti-TNF agent (876 starting adalimumab, 2826 starting etanercept, and 3037 starting infliximab). These patients were followed for a mean of 15 months. During the course of the study, 841 patients stopped taking the first drug due to lack of efficacy and 1023 stopped the first drug due to toxicity, of which 503 and 353, respectively, switched to a second anti-TNF agent. Patients who switched to a second anti-TNF drug had high rates of continuation (73%) on the new therapy. Patients who discontinued the first drug due to lack of efficacy usually discontinued the second drug due to lack of efficacy but not toxicity. Similarly, those who discontinued the first drug due to toxicity usually discontinued the second drug due to toxicity (Table 2). Observations by others regarding the benefit of switching anti-TNF therapy in primary nonresponders support these data[63], demonstrating that continuation of therapy was better in patients replacing the first anti-TNF inhibitor due to adverse events than in patients who showed lack of efficacy.

Nalysnyk, *et al*[64] conducted a metaanalysis of 31 studies evaluating 5306 primary nonresponders. They found that patients who switched due to primary failure exhibited lower response compared to those switching due to secondary failure or intolerance. Moreover, patients who failed 2 or more anti-TNF agents showed lower responses compared to those who failed only one anti-TNF agent. These observations suggest a decreasing benefit when switching TNF inhibitors.

Adalimumab was shown to be effective in patients with moderate to severe RA who previously failed treatment with infliximab, etanercept, or both[65]. More patients who experienced a loss of initial response to their previous TNF antagonist continued adalimumab treatment, compared with patients who had no response or were intolerant of a prior TNF antagonist. There was no additional risk observed in patients who switched from either etanercept or infliximab to adalimumab. Villeneuve and Haraoui[66] determined that patients who switch appear to improve regardless of the reason for discontinuing the first TNF inhibitor and that the efficacy of a second anti-TNF therapy is similar to that in

Table 2. Outcomes of treatment with a second biologic agent. Patients who switched from the first anti-TNF therapy because of lack of efficacy tended to stop the second anti-TNF therapy due to lack of efficacy. Similarly, patients who switched from the first therapy due to adverse events tended to stop the second therapy due to adverse events. In total, 13% of patients stopped the second anti-TNF therapy due to lack of efficacy, which is similar to the rate of discontinuation due to lack of efficacy for the first therapy (12%). 14% of patients stopped the second anti-TNF therapy due to adverse events, which is in line with adverse event-related discontinuation of the first anti-TNF therapy (15%). Values are the number (%) of patients. From Hyrich, *et al*, Arthritis Rheum 2007;56:13–20[1]; with permission from John Wiley and Sons, Inc.

		Outcome with 2nd Biologic Agent		
	n	Still Taking Agent at End of April 2005	Stopped for Inefficacy	Stopped for Adverse Event
Reason for switch				
Inefficacy	503	375 (74)	78 (16)	50 (10)
Adverse event	353	249 (71)	33 (9)	71 (20)
Total switches	856	624 (73)	111 (13)	121 (14)

patients previously naive to TNF inhibitors. Further, the safety profile of a given TNF inhibitor was not altered by the fact that a patient had previously used another TNF inhibitor, even if discontinuation was due to intolerance.

With the introduction of newer anti-TNF agents such as certolizumab pegol, clinicians have more choice when switching to a second or third anti-TNF therapy. Allez, *et al*[67] examined the efficacy and tolerability of adalimumab and certolizumab pegol following lack of efficacy or intolerance to 2 previous anti-TNF therapies in patients with CD. Clinical response was observed in 61% of patients at Week 6 and 51% of patients at Week 20. The probabilities of remaining under treatment at 3 months, 6 months, and 9 months were 68%, 60%, and 45%, respectively. Therefore, treatment with either adalimumab or certolizumab pegol as a third anti-TNF inhibitor demonstrates favorable efficacy and provides an option for patients when multiple therapies fail.

A study evaluating the efficacy and safety of golimumab in 461 RA patients who had previously been treated with 1 (n = 303), 2 (n = 115), or 3 (n = 43) anti-TNF therapies[68] confirmed the effectiveness of golimumab in this patient population. Golimumab was efficacious at both the high (100 mg) and low (50 mg) dose in 42.7% and 35.7%, respectively, of patients who discontinued due to lack of efficacy. Although these results are promising, more switching data on golimumab are required to definitively demonstrate its benefit.

The outcomes of the above studies suggest that patients who do not tolerate one anti-TNF therapy, who are primary nonresponders, or who are secondary nonresponders can benefit from switching to a second or even a third anti-TNF therapy[66]. The reasons may lie in the differences between the anti-TNF molecules, differences in their modes of administration, the pathophysiology of disease, stage of disease, differences in the pharmacokinetic profiles, and immunogenicity.

Toxicities of Anti-TNF

The establishment of global biologic registries results in the proper documentation and tracking of TNF inhibitor-related toxicities and provides longterm safety data for these therapies (Table 3)[69]. Registries such as the BSRBR monitor the longterm safety profiles of these drugs[70], whereas registries such as the Anti-Rheumatic Therapies In Sweden (ARTIS) compile patient data across multiple registries; i.e., the SSATG, the Stockholm Tumor Necrosis Factor-α Follow-up Registry (STURE), cancer registries, and tuberculosis (TB) registries. This allows clinicians to track the same patient and match the patient's diagnosis to risk factors and outcomes[71].

The most common documented toxicities caused by anti-TNF therapies include infections (including TB), autoimmunity, demyelinating diseases, and malignancies.

Table 3. Overview of current worldwide biological registers. From Hyrich KL, Rheumatoid Arthritis National Grand Rounds 2008;2:1–6[69]; with permission from the Rebecca MacDonald Centre for Arthritis and Autoimmune Disease.

Country	Register	Started	No. of Biologic-Treated Patients (Estimates)
Sweden	ARTIS	1998	> 6600
Spain	BIOBADASER	2000	> 6000
Denmark	DANBIO	2000	> 3500
Norway	NOR-DMARD	2000	> 2000
Finland	ROB-FIN	2000	> 1400
United Kingdom	BSRBR	2001	> 14000
Germany	RABBIT	2001	> 3500
Czech Republic	ATTRA	2001	> 1000
USA	RADIUS-2	2002	> 5000 (etanercept)
The Netherlands	DREAM	2003	> 1000
Australia	ARAD	2003	> 560
Russia	BIOROSS	2005	> 300

The degree of direct involvement of anti-TNF agents in the development of these toxicities and the mechanisms by which the toxicities are manifested remain incompletely understood.

Infections. With a prevalence of 6%–18% and an incidence rate of about 6 per 100 patient-years, serious infections (defined as life-threatening or requiring intravenous antibiotics or hospitalization) appear to be the most frequent adverse event reported with the use of anti-TNF therapies[72,73]. Studies have shown the risk of serious infection to be 2- to 3-fold higher in patients receiving TNF inhibitors, although it is somewhat challenging to identify the risk of serious infection associated with anti-TNF therapy beyond that already associated with severe disease[74]. According to BSRBR data, the risk of anti-TNF-associated infections is inconsistent over time, increasing 5-fold during the first 6 months on therapy and decreasing thereafter[75].

Opportunistic intracellular infections such as with *Listeria*, *Salmonella*, and *Legionella* pose a threat to patients under treatment with TNF inhibitors. Infliximab appears to be associated with the greatest risk of infection, possibly due to its long half-life and induction of monocyte apoptosis[76]. *Listeria* can be found in well water, sewage, contaminated food, and the intestinal tract of humans and animals; *Salmonella* can be found in contaminated food and the intestinal tract of humans and animals; and *Legionella* can be found in contaminated water[77]. Illness due to these infections can be manifested as bacteremia, sepsis, meningitis, and systemic complications, and may even result in death. Mortality rates of up to 30% have been reported[78]. Physicians and patients must be vigilant when unexplained fever persists.

Increased rates of TB in patients treated with anti-TNF therapies are of particular interest, especially in light of increased incidence of TB reported up to 12 months following discontinuation of anti-TNF therapies. Not only does the

rate of TB differ in anti-TNF-treated patients compared to the general population, but also the pattern of disease. In patients who developed TB, extrapulmonary TB was observed in 56% of patients compared to 40% observed in the general population, confirming immunosuppressed TB[79]. According to the BSRBR, extrapulmonary TB was identified in 67% of infliximab-treated, 63% of adalimumab-treated, and 43% of etanercept-treated patients with RA compared to 40% of the general population[75]. Together, these data indicate a need for vigilance and for continuous patient monitoring. Encouraging evidence, however, emerged from the Spanish registry showing that preventive measures can reduce the incidence of TB in patients treated with anti-TNF agents compared to that observed in the general population[80].

Two chronic viral infections are particularly relevant to the safe use of anti-TNF therapy: hepatitis B (HBV) and herpes zoster. The use of anti-TNF drugs has been reported in HBV-infected patients, with outcomes varying from apparent viral clearance to fatal hepatitis[81,82]. Infliximab and adalimumab are more often associated with HBV reactivation than etanercept. Duration of anti-TNF therapy prior to HBV reactivation ranged from a single dose to many months of treatment, and most patients who did not receive concomitant antiviral therapy demonstrated increased viral loads and developed hepatic dysfunction. With routine HBV screening prior to initiating therapy, the use of prophylactic antiviral drugs, and close laboratory monitoring during treatment, anti-TNF therapy may be used with an acceptable safety profile in HBV-infected patients[83].

Herpes zoster is a neurocutaneous disease characterized by a painful vesicular dermatomal rash resulting from reactivation of the varicella zoster virus (VZV). It is one of the most common adverse events reported in clinical trials of anti-TNF agents, with complications including postherpetic neuralgia, and the cause of substantial morbidity[84]. One study analyzing patient data from the German Rheumatoid Arthritis Observation of Biologic Therapy register (RABBIT) identified 39 cases of herpes zoster following treatment with infliximab or adalimumab (out of 3524 patients) and 23 cases following treatment with etanercept (out of 2588 patients)[84]. Monoclonal antibodies infliximab and adalimumab were associated with increased risk of herpes zoster, whereas the receptor fusion protein etanercept was not. Based on these data, careful monitoring of patients treated with infliximab or adalimumab for early symptoms of herpes zoster is recommended, as is vaccinating patients against varicella to prevent its reactivation as herpes zoster.

There were 281 cases of invasive fungal infections associated with anti-TNF therapies reported up to June 2007[85]. Of these cases, 226 (80%) were associated with infliximab, 44 (16%) with etanercept, and 11 (4%) with adalimumab. In the majority of cases (98%), the use of at least 1 other immunosuppressant medication was reported during the course of the fungal infection. The most prevalent fungal infection was histoplasmosis, followed by candidiasis and aspergillosis, with pneumonia being the most common pattern of infection. Of the cases for which outcome information was available, 29 fatalities (32%) were recorded, indicating the necessity of surveillance for fungal infections complicating biologic therapies.

Autoimmunity. A significant proportion of infliximab-treated patients develop autoantibodies; 40%–60% of patients develop antinuclear antibodies (ANA) and 10% develop anti-double-stranded deoxyribonucleic acid (DNA) antibodies[86,87]. In comparison, only 10% of patients treated with etanercept, adalimumab, or certolizumab pegol develop ANA. Bobbio-Pallavicini, *et al*[88] investigated the longterm effect of infliximab treatment on the development of ANA and anti-dsDNA antibodies in patients with RA. ANA levels at 30 weeks of therapy were detected in 50% of patients, and 80% showed detectable levels by 78 weeks. Anti-dsDNA levels showed a transient rise up to 17% at 54 weeks, which dropped to 0% at 78 weeks.

With the increasing use of anti-TNF therapies and longer followup periods, there are a growing number of reports of the development of autoimmune processes such as lupus, vasculitis, and psoriasis (Ps)[89]. Between January 1990 and December 2006, 233 cases of autoimmune diseases secondary to anti-TNF therapies in 226 patients were reported in the literature: vasculitis in 113, lupus in 92, interstitial lung diseases in 24, and other diseases in 4. Of these, 105 patients were treated with infliximab, 96 with etanercept, 21 with adalimumab, and 3 with other anti-TNF agents.

Data from the BSRBR estimated 40 cases of lupus out of 11,394 patients, and the Mayo Clinic cited 3 cases in the first 500 treated patients, suggesting a relatively low risk of developing drug-induced lupus due to anti-TNF therapy[90].

The mechanisms by which anti-TNF therapy induces lupus remain unclear but are likely to differ from classic drug-induced lupus. One potential mechanism is the ability of therapeutic anti-TNF-α antibodies to bind to cell-surface TNF-α and to thereby induce apoptotic cell death, resulting in the release of ANA and the induction of anti-dsDNA antibodies[91]. Another hypothesis is that TNF inhibitors suppress T-helper type 1 response, thereby favoring a T-helper type 2 response leading to systemic lupus erythematosus[92]. It is also possible that bacterial infections associated with the use of anti-TNF therapy stimulate polyclonal B-lymphocyte activation and autoantibody production[93].

Between January 1990 and December 2006, there were 113 reported cases of vasculitis secondary to anti-TNF therapy: 59 cases with etanercept treatment, 47 with infliximab, 5 with adalimumab, and 2 with other agents[89]. Cutaneous vasculitis was reported in the majority of the cases. Further, 63% of the cases were leukocytoclastic vasculitis, 17% were necrotizing vasculitis, and 6% were lymphocytic vasculitis. In a similar study conducted on patients developing vasculi-

tis between December 2004 and January 2005, 39 cases were identified with the following involvement: skin (n = 32), peripheral nervous system (n = 9), kidney (n = 7), central nervous system (n = 3), pleura (n = 2), pericardium (n = 2), lung (n = 1), gall bladder (n = 1), and heart (n = 1)[94].

Recently, cases of induction or exacerbation of Ps in conjunction with TNF inhibitor therapy have been reported. This is intriguing, given that this therapy is approved for treatment of the same condition. According to the BSRBR, out of 9823 RA patients receiving anti-TNF therapy, 25 cases of new-onset psoriasis were reported between January 2001 and July 2007[95]. Palmoplantar pustular Ps was observed in 40.5% of the cases, with plaque-type Ps in 33.1%, and other types comprising the remainder. More information and studies are needed to understand what cytokines and cell types drive the development of these lesions in order to treat this paradoxical side effect.

Demyelinating disease. Demyelinating disease is a rare but important toxicity associated with anti-TNF therapy. In a study of 500 patients with CD and under treatment with infliximab, only 1 case of new-onset demyelinating disease was reported[90]. Unlike other toxicities associated with anti-TNF therapy, neurological symptoms and magnetic resonance imaging changes linked to infliximab-induced demyelinating disease persist following termination of treatment[96]. It is important to note that patients with IBD are at high risk of developing demyelinating disease regardless of biologic therapy[97].

Cases of demyelinating syndromes and multiple sclerosis (MS)-like disease or reactivation of MS have also been reported, although rarely, in RA patients treated with anti-TNF agents, mainly etanercept[98-100]. Therefore, a history of MS is contraindicated in the use of anti-TNF agents.

Malignancy. TNF plays a role in apoptosis and tumor suppression; therefore, interference with these pathways can potentially lead to an increased risk of malignancies. However, the increased risk of malignancies observed in patients with IMID makes it difficult to estimate the real effect of anti-TNF therapy on the induction of malignancies in these individuals. For example, compared to the general population, patients with Ps show increased risk of squamous cell carcinoma, lymphoma, and smoking-related cancers[101,102]. CD patients show increased risk for colorectal, small bowel, colon, and extraintestinal cancers and lymphoma[103]. RA patients have twice the risk for lymphoma compared to the general population, mainly in relation to disease severity and disease duration[104].

Of the malignancies observed in IMID, the risk for patients developing lymphoma is 2 to 3 times higher than the general population but comparable to the risk of RA patients treated with DMARD. It has been hypothesized that this increased risk might possibly be related to use of immunosuppressants, altered lymphoid proliferation, immunologic defects, and ongoing chronic inflammation. Hepatosplenic T cell lymphoma is a rare cancer comprising 5% of peripheral T cell lymphomas. As of October 2006, there were 8 reports to the US Food and Drug Administration of hepatosplenic T cell lymphoma in patients receiving infliximab for CD (7 patients) and UC (1 patient)[105]. Six of the 8 cases were fatal. There were 3 reports of hepatosplenic T cell lymphoma with adalimumab treatment[106]. It is important to note that all 8 infliximab-treated patients and 2 of the 3 adalimumab-treated patients were receiving combination therapy with the immunosuppressants azathioprine and 6-mercaptopurine. Therefore there is a possible association between hepatosplenic T cell lymphoma and immunosuppression.

SUMMARY

The availability of TNF inhibitors has expanded the clinician's repertoire of therapies for treating IMID, especially in patients who do not respond to DMARD. However, at the moment, there remains a significant portion of patients who do not respond to anti-TNF therapy, lose response, or experience adverse events. Identifying predictors of response is an ongoing challenge facing clinicians involved in clinical trials as well as those who are faced with response-related problems in their daily clinical practice. Noncompliance can be addressed by providing the patient with information and support to maximize adherence to therapy. Loss of response due to immunogenicity can be overcome by switching to a second, a third, or even a fourth TNF inhibitor. By developing protocols to closely monitor the onset of adverse events, physicians can reduce the risk of toxic effects. Ultimately, the development of biologic therapies with different modes of action is needed to provide more varied treatment options.

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