

Monoclonal Antibodies, Immunogenicity, and Associated Infusion Reactions

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Abstract

The increasing use of monoclonal antibodies as treatment modalities for a number of immune mediated and malignant diseases has yielded great promise. In using this approach, however, we have encountered problems, in terms of infusion reactions. Two forms of reactions have been identified: acute and delayed; they appear to be related to the presence of antibodies to the monoclonal antibodies (against murine or human components). The reactions are largely **not** anaphylactic (IgE mediated), making it possible to re-treat patients using specific protocols. These protocols are detailed in this overview.

Key Words: Monoclonal antibody, inflammatory bowel disease, infusion reactions, infliximab.

Introduction

A NUMBER OF NEW BIOLOGIC THERAPIES that have become available over the last 15 years have revolutionized the treatment options for immune mediated inflammatory diseases (e.g., rheumatoid arthritis [RA], Crohn's disease [CD], and psoriasis). The most notable of these agents is infliximab, a chimeric (part-murine, part-human) monoclonal antibody that binds to tumor necrosis factor alpha (TNF- α) and neutralizes its biologic activity. Infliximab has been shown to be effective and safe in the treatment of moderately and severely active and fistulizing CD, RA, ankylosing spondylitis, uveitis, and pyoderma gangrenosum (1–12). Infliximab was approved for the treatment of CD in 1998 and for RA in 1999.

As is the case with any foreign-protein-derived agent, infusion of infliximab can lead to infusion

reactions, either acute or delayed. Overall, these reactions are rare, occurring in approximately 5–10% of all infusions, and they can, in most cases, be easily managed (13). Although the mechanisms underlying the development of infusion reactions are not completely understood, antibody formation against infliximab may play a role. The generation of antibodies to these monoclonal antibodies is currently an area of intense research. It has recently been shown that the formation of antibodies to infliximab is very likely to be associated with a greater risk of infusion reactions and that it may also limit infliximab's long-term efficacy (14, 15). However, new infusion techniques and approaches have been developed that may minimize such antibody formation and mitigate its potentially negative effects. Such methods should now be considered for all routine infliximab infusions in order to help maintain the efficacy of infliximab and reduce the potential side effects associated with antibody formation.

Immunologic Basis for Infusion Reactions

Many of the new biologic therapies now available for treatment of immune mediated inflammatory diseases are monoclonal antibodies. These antibodies are designed to block particular factors involved in the inflammatory pathway. This is accomplished by binding to and neutralizing/eliminating

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Adapted from a Grand Rounds presentation to the Department of Medicine, Mount Sinai School of Medicine, New York, NY on March 25, 2003, and updated as of February 2005.

nating individual cytokines or triggering the death of cytokine-producing cells. Like all immunoglobulins, these engineered antibodies are comprised of an Fab fragment that includes the antigen-binding domain and an Fc portion that binds complement and Fc receptors on phagocytic cells. Monoclonal antibodies are classified according to the amount of murine protein present in the molecule. When murine protein is present, it partially or fully makes up the antigen-binding domain of the antibody. There are four types of monoclonal antibodies that are used in clinical practice today (Table 1). Murine antibodies, such as OKT3, are comprised entirely of murine protein. Human antibodies, such as adalimumab, are devoid of all murine protein. Monoclonal antibodies rituximab and infliximab are examples of chimeric antibodies, of which 25% is murine and 75% is human. Humanized antibodies, of which CDP-571 is an example, are 15% murine (specifically the antigen-binding domain) and 85% human. Although distinct in their composition, all four subtypes have been utilized successfully as clinical therapies.

The human immune system typically reacts to these monoclonal antibodies as foreign antigens and responds by creating its own antibodies to different sites on the molecule. If murine protein is present in the monoclonal antibody, the immune system can react by producing anti-idiotypic, anti-allotypic, or anti-mouse antibodies. As would be expected, monoclonal antibodies comprised entirely of murine protein are more likely to elicit an immune response than completely human monoclonal antibodies. However, even completely human monoclonal antibodies can trigger an immune response, leading to the development of human anti-human antibodies (HAHA).

Two companies have developed an assay for antibodies to infliximab. This assay is able to measure anti-murine antibodies (to epitopes on the murine variable region of infliximab) as well as anti-allotypic antibodies to the human immunoglobulin G1 (IgG1) constant region. When this assay has been used in individuals receiving infliximab infusions, only anti-murine antibodies

have been found (16). These antibodies were originally known as human anti-chimeric antibodies (HACA) but now are more commonly known as antibodies to infliximab (ATI). Since infliximab itself interferes with the ATI assay in one assay system, the presence of these ATI can only be determined when infliximab is not detectable in the serum. When infliximab is found in the serum, the sample is considered indeterminate. It has been proposed that it may be reasonable to consider samples that are indeterminate for ATI as negative, because even if present, these ATI are overwhelmed relative to concentration of infliximab (16).

Types of Infusion Reactions

Infusion reactions to infliximab or against any monoclonal antibody can be characterized as either acute or delayed. An acute infusion reaction occurs within 24 hours of an infliximab infusion, but most commonly within 10 minutes to 4 hours of the infusion. A delayed infusion reaction can occur from 24 hours to 14 days after an infusion of infliximab, but usually occurs after 5–7 days. Both types of reaction can be further characterized as mild, moderate or severe, depending on the accompanying signs and symptoms (Table 2).

Acute infusion reactions can also be characterized by whether they are anaphylactic or non-allergic based, i.e., IgE-mediated type I acute hypersensitivity (anaphylactic) or anaphylactoid. Symptoms of true allergic anaphylactic reactions include chest tightness, shortness of breath, flushing, hypotension, wheezing and urticaria. In fact, without bronchospasm or urticaria, an acute infusion reaction is unlikely to be a true type I mediated hypersensitivity reaction and should be considered non-allergic. The non-allergic types of reactions make up the overwhelming majority of acute infusion reactions.

To date, only one study has examined the pathogenesis of acute infusion reactions (13). In this study, performed at Mount Sinai, serum was obtained from eleven patients who had a total of fourteen acute infusion reactions. The level of tryptase, a mast cell enzyme elevated after an acute hypersensitivity reaction, was measured and found to be within the normal range in all cases. Levels of IgE were evaluated in six of these patients and were also found to be normal. It was concluded that these acute infusion reactions were not due to IgE-mediated hypersensitivity. This probably explains why most of the reactions were successfully managed by simply reducing the rate of infusion (13). If these had been IgE mediated anaphylactic reactions, re-infusion would have been impossible.

Delayed infusion reactions are characterized

TABLE 1
Classification of Monoclonal Antibodies

Type	% Murine	Example
Human	0%	adalimumab
Humanized	15%	CDP-571
Chimeric	25%	infliximab
Murine	100%	OKT-3

TABLE 2
Infliximab Infusion Reaction Protocol *

Type of Reaction Symptoms	Treatment Protocol	Prophylaxis
Mild Flushing, Dizziness, Headache, Diaphoresis, Nausea, Palpitations	Slow infusion rate to 10 mL/hr Infuse normal saline (500–1000 mL/hr) Diphenhydramine 25–50 mg IVPB Acetaminophen 650 mg Monitor VS every 10 min, until WNL Wait 20 min, then increase infusion rate to 20 mL/hr × 15 min, then 40 mL/hr, 80 mL/hr, 100 mL/hr, 125 mL/hr every 15 min, as tolerated	Pre-treat with diphenhydramine 25–50 mg and acetaminophen 650 mg PO 1.5 hours prior to infusion. (Five days of a second generation antihistamine can be substituted to decrease sedation.) Test dose @ 10 mL/hr prior × 15 min. Increase infusion rate to 20 mL/hr, 40 mL/hr, 80 mL/hr, 100 mL/hr, 125 mL/hr every 15 min, as tolerated.
Moderate Chest discomfort, SOB, Hypo/hypertension (>20 points SBP), Increased temperature, Palpitations, Urticaria	Slow infusion rate to 10 mL/hr or stop infusion Infuse normal saline (500–1000 mL/hr) Diphenhydramine 25–50 mg IV Acetaminophen 650 mg Monitor VS every 5 min until WNL Wait 20 min, then restart infusion at 10 mL/hr for 15 min Increase infusion rate to 20 mL/hr × 15 min., then 40 mL/hr, 80 mL/hr, 100 mL/hr, 125 mL/hr every 15 min, as tolerated	Pre-treat with diphenhydramine 25–50 mg and acetaminophen 650 mg PO 1.5 hours prior to infusion. (Five days of a second generation antihistamine can be substituted to decrease sedation.) Test dose @ 10 mL/hr prior × 15 min. Increase infusion rate to 20 mL/hr, 40 mL/hr, 80 mL/hr, 100 mL/hr, 125 mL/hr every 15 min, as tolerated.
Severe Hypo/hypertension (>40 points SBP), Increased temperature with rigors, Chest discomfort, SOB with wheezing, Stridor (if potential to lose airway, call EMS for transport to ER), Flushing	Stop infusion Infuse normal saline (500–1000 mL/hr) Maintain airway; oxygen if available Epinephrine (1:1000) 0.1–0.5 mL SQ (may repeat q 5 min × 3) Diphenhydramine 25–50 mg IVPB Hydrocortisone 100 mg IV or methylprednisolone 20–40 mg IV Monitor VS every 2 min until WNL If patient stabilizes, wait 20 min, then restart infusion at 10 mL/hr for 15 min Increase infusion rate to 20 mL/hr × 15 min, then 40 mL/hr, 80 mL/hr, 100 mL/hr, 125 mL/hr every 15 min, as tolerated If patient requires second dose of epinephrine, call EMS and transfer patient to ER for monitoring	Prednisone 50 mg PO q12 hours BID × 3 doses prior to infusion or Hydrocortisone 100 mg IV or methylprednisolone 20–40 mg IV prior to infusion. Pre-treat with diphenhydramine 25–50 mg and acetaminophen 650 mg PO 1.5 hours prior to infusion. (Five days of a second generation antihistamine can be substituted to decrease sedation.) Test dose @ 10 mL/hr prior × 15 min. Increase infusion rate to 20 mL/hr, 40 mL/hr, 80 mL/hr, 100 mL/hr every 15 min, as tolerated.
Delayed Rash / urticaria, Myalgias, Flu-like symptoms, Joint stiffness and pain, Headache	Acetaminophen 650–1000 mg PO QID Second generation antihistamine or diphenhydramine 50 mg QD-BID Medrol pack if severe joint pain	Pre-treat with diphenhydramine 25–50 mg and acetaminophen 650 mg PO 1.5 hours prior to infusion. (Five days of a second generation antihistamine can be substituted to decrease sedation.) Test dose @ 10 mL/hr prior × 15 min. Increase rate to infuse over 3 hours. Acetaminophen 650–1000 mg PO QID × 3 days post infusion. Second generation antihistamine × 7 days post infusion. Send home with Medrol dose pack if severe joint pain.

EMS = emergency medical services; ER = emergency room; IVPB = intravenous piggyback; VS = vital signs; SBP = systolic blood pressure; WNL = within normal limits; SQ = subcutaneous; SOB = shortness of breath.

* If patient experiences a second reaction during the infusion, follow steps for moderate reaction, but give IV hydrocortisone or methylprednisolone. Do not increase rate past where the patient had the reaction.

by a skin rash, diffuse joint pains, fatigue and myalgias, with or without fever. These reactions have been labeled “serum-sickness-like” and may actually represent mild type III (immune-complex-mediated) reactions. We previously proposed the term “delayed immune-mediated infusion reaction.” Regardless of the terminology, delayed infusion reactions must be differentiated from other states that may produce similar symptoms such as an inflammatory bowel disease (IBD) flare, extra-intestinal manifestations of IBD, a viral syndrome, or a lupus-like reaction.

Management of Infusion Reactions

The management of acute infusion reactions should focus on alleviating the patients’ associated signs and symptoms (i.e., fever, chest pain, and dyspnea). Such symptoms usually resolve with adjustment of the infusion rate and administration of intravenous fluids, acetaminophen, antihistamines and steroids. (Epinephrine is indicated when wheezing is present.)

A suggested infliximab infusion reaction treatment protocol, based upon the experience at Mount Sinai, has been published previously and is slightly modified here (Table 3). These modifications are based on continued clinical experience in treating and preventing infusion reactions. The importance of saline infusion in patients experiencing an infusion reaction cannot be understated. It is also extremely important to auscultate the lungs if the patients are complaining of chest pain and shortness of breath. The absence of wheezing virtually rules out a true anaphylactic reaction.

Severe anaphylactic reactions are rare, but if they occur, the infusion should be stopped immediately, normal saline should be infused, and vital signs should be monitored every 2 minutes. Epinephrine 0.1–0.3 cc should be administered subcutaneously and repeated two more times at five-minute intervals if needed. Intravenous diphenhydramine (25–50 mg) and steroids (either hydrocortisone 100 mg or methylprednisolone 20–40 mg) should also be given, as well as PO acetaminophen (650–1000 mg). The epinephrine and

diphenhydramine should be given before the steroids because of their faster onset of action. In these rare cases of anaphylaxis, the infusion should not be restarted. These patients may be eligible for desensitization or an experimental protocol using adalimumab (fully human anti-TNF antibody).

The vast majority of reactions are not IgE mediated and respond to stopping the infusion and providing hydration, diphenhydramine and acetaminophen. Patients in this group may have their infusion restarted slowly after 30 minutes. By slowing the rate of infusion, the opportunity for soluble immune complexes to form is greatly reduced. Development of an infusion reaction does not preclude further infliximab infusions. Pretreatment (prophylaxis) protocols were developed using previous desensitization protocols for 5-fluorouracil and vancomycin as templates. For prophylaxis in mild or moderate acute reactions, the patients should receive diphenhydramine (25–50 mg) and acetaminophen (650 mg) orally 1.5 hours prior to infusion. Alternatively, the patients can be given a second-generation non-sedating antihistamine for five days leading up to the infusion, in order to avoid the sedating effects of diphenhydramine. If a test dose of infliximab (10 mL/hr) is tolerated, the infusion rate should then be increased every 15 minutes to 125 mL/hour as tolerated and continued for at least 3 hours (Table 4). For severe acute (non-IgE mediated) reactions, in addition to an antihistamine and acetaminophen, the patients should receive prednisone 50 mg \times 3 doses over 24 hours prior to the infliximab infusion. Alternatively, intravenous hydrocortisone (100 mg) or methylprednisolone (20–40 mg) could be given 20 minutes before infusion, although this is probably less efficacious. A maximum infliximab infusion rate of 125 mL/hr should not be exceeded in these patients.

In our study, after receiving the appropriate medical prophylaxis, all of the patients who had mild or moderate acute infusion reactions tolerated re-treatment and completed re-infusion with infliximab when clinically indicated. One patient with a moderate infusion reaction early in the study was not re-treated because of our limited experience at

TABLE 3

Methods of Decreasing Antibody Formation to Infliximab

1. Use concurrent immunomodulator (6-MP, azathioprine, or methotrexate)
2. Induction (0, 2, and 6 week or 0 and 4 week) and maintenance (q 8–12 weeks) infusion regimen
3. Steroid pre-medication prior to infusion, if not on immunomodulator (i.e., intolerant)

6-MP = mercaptopurine

TABLE 4

Methods of Combating Antibodies to Infliximab

1. Add immunomodulator if patient is currently not taking
2. Increase the dose of infliximab by 5 mg/kg
3. Slow infusion rate (i.e., infusion over 4–6 hours instead of 2 hours)
4. Shorten the infusion interval (i.e., every 4–6 weeks)
5. Switch to another anti-TNF agent (e.g., adalimumab)

TNF = tumor necrosis factor

that time. Of the eight patients with severe infusion reactions, six tolerated re-infusion. Of the remaining two patients, one developed a second severe acute reaction on re-infusion, and no further attempts were made. The other patient was not re-treated. Although almost every patient tolerated re-treatment, prophylaxis did not always prevent further infusion reactions. This underscores the fact that in cases of severe acute infusion reactions, the risks and benefits of re-infusion need to be weighed carefully.

Because delayed infusion reactions are much less common, there are far less data available on their treatment and prophylaxis. Clinical experience suggests that these patients can be treated with acetaminophen (1,000 mg QID) and an antihistamine (either diphenhydramine 50 mg QD-BID or a second-generation antihistamine). A Medrol dose pack may be needed immediately following the infusion if there is no response to the acetaminophen and antihistamine.

Although most physicians will not re-infuse infliximab after a documented delayed reaction, we propose that it is possible. One should pre-treat with acetaminophen and either diphenylamine or a second-generation antihistamine (for 5 days prior to infusion). Type III immune reactions occur when the antigen/antibody complexes are soluble. By increasing the dose of infliximab (antigen excess), one can shift the curve to the left and decrease the formation of soluble immune complexes. In this case, one can double the dose of infliximab from 5 mg/kg to 10 mg/kg. One can also affect antigen/antibody complex formation by decreasing the interval between the infusions (which may elevate infliximab levels similarly, leading to antigen excess).

Anti-monoclonal Antibody Antibodies

The formation of antibodies to infliximab is not uncommon. The frequency in the literature varies widely, from 7–61%, but is generally 7–15% (7, 14). This broad range is at least partially attributable to the different infliximab dosing schedules used in the studies performed to date and to variations in concomitantly administered medications. It has recently been shown that formation of these antibodies to infliximab may lead to a greater risk of infusion reactions and also may limit the long-term efficacy of the drug (14–18). Several studies have demonstrated that an induction regimen followed by scheduled maintenance infusions decreases the likelihood of antibody formation (i.e., generates immunologic tolerance) (16–18). It has also been shown that the use of

concomitant immunomodulators prior to starting infliximab is effective in reducing antibody production (17).

This concept of decreasing immunogenicity derives from the original trials of infliximab in RA. In the phase II trial (17) in which infliximab was given as a one-time dose, the frequency of ATI was 53%, 21%, and 7% (1, 3, 10 mg/kg) in patients receiving infliximab alone. When given in conjunction with methotrexate, the frequency of ATI was 15%, 7%, and 0% (1, 3, 10 mg/kg). Thus, concomitant administration of methotrexate and infliximab modulated the immune response to the monoclonal antibody. In the phase III trial (7), infliximab was given as an induction regimen (3 or 10 mg) at 0, 2, and 6 weeks, followed by a maintenance regimen of every 4 or 8 weeks. All patients were receiving concomitant methotrexate. Because of the maintenance regimen, most patients still had infliximab in their serum, and therefore only 60 of the 428 patients could be assessed for ATI. Of these 60 patients, only 5 (8%) were positive for ATI (if we consider indeterminate samples negative—which we do). Thus, a 3-dose induction regimen followed by maintenance infusions is less immunogenic than a one-time dose followed by episodic infusions.

In the largest study evaluating long-term infliximab for CD, the ACCENT I trial (2), patients received episodic (one dose of infliximab and then placebo) 5 mg/kg or 10 mg/kg every 8 weeks after a 0, 2, and 6-week induction regimen of infliximab. Because of the maintenance regimen, many patients still had infliximab in their serum and only 233 of 442 patients could be assessed for ATI. At week 54, 64 patients (14%) had ATI. Patients who received a 3-dose induction regimen of infliximab and then received maintenance infusions every 8 weeks were less likely to develop antibodies than were patients who received a single dose (28.1% vs. 6.3–9.1%). However, the rate of infusion reactions was the same for both groups. The rate of infusion reactions in the episodic group may have been artificially lower, however, because they received fewer infusions than the maintenance group. The frequency of ATI formation was also less in patients receiving both steroids and immunomodulators (6%) than in patients on immunomodulators alone (10%), patients on steroids alone (17%), and patients receiving neither (18%). It also appears that the 3-dose induction and maintenance regimen is slightly better than the addition of an immunomodulator for preventing antibody formation.

In a recently published study reevaluating the ACCENT I data, patients in the maintenance-scheduled treatment arm demonstrated higher re-

mission rates and higher quality-of-life scores than did patients receiving episodic treatment. These patients also had significantly fewer CD-related hospitalizations and surgeries (18).

In the ACCENT II trial (4), 17% of evaluable patients (n=44) developed antibodies to infliximab, 31% did not (n=80), and 52% (n=134) were inconclusive for the presence of antibodies. This trial also demonstrated that patients who were on steroids (13%) or immunomodulators (11%) were less likely to develop antibodies than patients on no medications at baseline (24%). Patients who were on both steroids and immunomodulators were the least likely to develop antibodies to infliximab (4%).

Another study, by Baert et al. (14), confirmed the finding that concomitant immunomodulator therapy was associated with a lower frequency of ATI (42% vs. 75%). However, this study showed that a three-dose induction regimen without a follow-up maintenance regimen did not decrease ATI formation and was actually slightly worse than episodic treatment.

Recently, a prospective trial by Farrell et al. (15) once again confirmed that concurrent immunomodulators (odds ratio [OR] = 0.19) and a second infusion within eight weeks of the first (OR = 0.13) significantly reduced ATI formation. In the placebo-controlled portion of their trial, they were able to show that patients who were pretreated with intravenous hydrocortisone developed lower levels of ATI (1.6 microg/mL vs. 3.4 microg/mL) than did those patients who received placebo. They also demonstrated that fewer hydrocortisone-treated patients developed ATI than did those who received placebo (26% vs. 42%), although this was not statistically significant (p=0.06). Interestingly, pretreatment with hydrocortisone had no effect on the number of infusion reactions.

Response Effect of Anti-monoclonal Antibody Antibodies

Although antibodies are formed against infliximab, it is not fully confirmed that this has clinical significance. In addition to the increased risk of infusion reactions, there may be a link between antibody formation and decreased efficacy of the drug over time. In the study by Baert et al. (14), the presence of high levels of ATI (>8.0 µg/mL, an arbitrary cutoff value) prior to an infusion was predictive of a shorter duration of response (35 days vs. 71 days). These patients were also at higher risk for an infusion reaction (relative risk 2.4). Furthermore, once an infusion reaction occurred, the duration of clinical response to subsequent infu-

sions decreased. No attempt to alter dose or interval was made in this study. The study by Farrell et al. (15) showed that patients who had ATI were more likely to lose their initial response and develop an infusion reaction. Overall, ATI were seen in 36% of their patients (19 of 53). Of the patients who lost their response to infliximab, 73% (11 of 15) were positive for ATI. This is in stark contrast to the 21 continuous responders, none of whom developed ATI. Also, all seven of their patients with serious infusion reactions had ATI. This was not the case in ACCENT I, in which there was no correlation between antibody level and increased likelihood of reaction.

It is interesting to note that in the ACCENT I and ACCENT II trials, the presence of ATI did not affect outcome at one year in patients receiving maintenance dose infusions. Of the patients who lost response on a 5 mg/kg maintenance regimen, increasing the dose to 10 mg/kg re-established response in 90%. Likewise, in those patients on 10 mg/kg who lost response, 80% regained response when increased to 15 mg/kg. (18)

Summary

The new biologic therapies have revolutionized the treatment of a number of immune-mediated inflammatory diseases. However, their immunogenicity, through the development of antibodies to the monoclonal antibody, appears to be associated with an increased risk of infusion reactions and may reduce the long-term response to these new medications. One can decrease the risk of antibody development by: (a) using concurrent immunomodulator therapy, (b) using an induction regimen followed by maintenance infusions, (c) considering steroid premedication in those patients not currently on immunomodulators, or (d) increasing the dose or shortening the infusion interval of infliximab. Once present, the immunogenicity can be overcome, at least temporarily, by increasing the dose of infliximab or shortening the dosing interval. If infusion reactions do occur, and they do in only about 5–10% of infusions, they can easily be managed as outlined above.

References

1. Targan SR, Hanauer SB, van Deventer SJ, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med* 1997; 33:1029–1035.
2. Hanauer SB, Feagan BG, Lichtenstein GR, et al.; and ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomized trial. *Lancet* 2002; 359(9317):1541–1549.

3. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999; 340:1398–1405.
4. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004; 350:876–885.
5. Regueiro M, Valentine J, Plevy S, et al. Infliximab for treatment of pyoderma gangrenosum associated with inflammatory bowel disease. *Am J Gastroenterol* 2003; 98:1821–1826.
6. Elliott MJ, Maini RN, Feldman M, et al. Randomized double-blind comparison of chimeric monoclonal antibody to tumor necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. *Lancet* 1994; 344:1105–1110.
7. Maini R, St Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumor necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomized phase III trial. ATTRACT Study Group. *Lancet* 1999; 354:1932–1939.
8. Lipsky PE, van der Heijde DM, St Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med* 2000; 343(22):1594–1602.
9. Joseph A, Raj D, Dua HD, et al. Infliximab in the treatment of refractory posterior uveitis. *Ophthalmology* 2003; 110:1449–1453.
10. El-Shabrawi Y, Hermann J. Anti-tumor necrosis factor-alpha therapy with infliximab as an alternative to corticosteroids in the treatment of human leukocyte antigen B27-associated acute anterior uveitis. *Ophthalmology* 2002; 109:2342–2346.
11. Braun J, Brandt J, Listing J, et al. Treatment of active ankylosing spondylitis with infliximab: a randomized controlled multicenter trial. *Lancet* 2002; 359:1177–1193.
12. Chaudhari U, Romano P, Mulcahy LD, et al. Efficacy and safety of infliximab monotherapy for plaque-type psoriasis: a randomized trial. *Lancet* 2001; 357(9271):1842–1847.
13. Cheifetz A, Smedley M, Martin S, et al. The incidence and management of infusion reactions to infliximab: a large center experience. *Am J Gastroenterol* 2003; 98(6):1315–1324.
14. Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med* 2003; 348:601–608.
15. Farrell RJ, Alsahli M, Jeen YT, et al. Intravenous hydrocortisone premedication reduces antibodies to infliximab in Crohn's disease: a randomized controlled trial. *Gastroenterology* 2003; 124(4):917–924.
16. Sandborn W. Preventing antibodies to infliximab in patients with Crohn's disease: optimize not immunize. *Gastroenterology* 2003; 124:1140–1145.
17. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998; 41(9):1552–1563.
18. Rutgeerts P, Feagan BG, Lichtenstein GR, et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. *Gastroenterology* 2004; 126:202–413.